GiveWell

INTERVENTION REPORT

Mass Distribution of Long-Lasting Insecticide-Treated Nets (LLINs)

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Table of Contents

In a nutshell

This page discusses the case for mass distribution of long-lasting insecticide-treated nets (LLINs) for protection against malaria. In general, we focus our discussion on work similar to that of the **Against Malaria Foundation**.

This intervention involves trying to achieve universal ownership of LLINs within a population, giving free new LLINs to the people who do not already have them. There is strong evidence that when large numbers of people use LLINs to protect themselves while sleeping, the burden of malaria can be reduced, resulting in a reduction in child mortality among other benefits.

LLINs cost under $10 each to purchase and distribute (including all costs), and this intervention is generally considered to be among the most cost-effective ways to save lives. Mass distribution of LLINs is in the same range of cost-effectiveness as **other priority programs** we have considered.

Previous versions of this report:

- **2015 report on insecticide treated nets**
- **2014 report on insecticide treated nets**
- **2012 report on insecticide treated nets**
- **2011 report on insecticide treated nets**
- **2009 report on insecticide treated nets**

What is malaria (the disease targeted by LLINs)?

Malaria is one of the leading causes of child deaths in Africa.[1] It is transmitted from person to person by infected mosquitoes.[2] It involves flu-like symptoms including fever.[3] As discussed below, there is evidence connecting malaria with death (particularly in children under 5), anemia, splenomegaly (enlarged spleen), other nutrition-deficiency-related indicators, and low birthweight.

It is also believed that malaria can cause permanent disability (hearing impairment, visual impairment, epilepsy, etc.).[4]

What is LLIN distribution and how does it target malaria?

An **insecticide-treated net (ITN)** is a net (usually a bed net), designed to block mosquitoes physically, that has been treated with safe, residual insecticide for the purpose of killing and repelling mosquitoes, which carry malaria.[5] A **long-lasting insecticide-treated net (LLIN)**[6] is an ITN designed to remain effective for multiple years without retreatment.[7] The World Health Organization recommends that LLINs be distributed for free to achieve universal coverage (one LLIN for every 1.8 people in the target population) of those at risk for malaria.[8] An LLIN distribution involves surveying people to determine the need for LLINs; delivering LLINs; and promoting the use of LLINs (to read our notes from visiting an ongoing LLIN distribution, see our **page on October 2011 site visits**).

What is the evidence regarding the general effectiveness of LLIN distributions?

Evidence from small-scale, high-quality studies

The best evidence for the effectiveness of LLIN distributions comes from randomized controlled trials of insecticide-treated net campaigns, which are reviewed in two **Cochrane** reviews (**Lengeler 2004a**; **Gamble, Ekwaru, and ter Kuile 2006**). We have separately found, examined, and summarized the papers reviewed in Lengeler 2004a.[9] The studies are mostly short-term, examining insecticide-treated nets (not necessarily LLINs) over a period of 6 months to 2 years.

Lengeler's (2004a) meta-analysis, examining 22 studies,[10] found:

- *Mortality* (5 studies): a statistically significant impact on all-cause mortality in children under 5, summarized as "5.53 deaths averted per 1000 children protected per year" with no clear dependence on one measure of the regional malaria transmission dynamics.[11] Two studies attempted to examine malaria-specific mortality and found smaller or similar-sized effects, which the review author attributes to the difficulty of attributing mortality to malaria.[12]

  > Note that the above figure ("5.53 deaths averted per 1000 children protected per year") is based on people who could be covered by the ITNs distributed, not on people who are confirmed to be using ITNs (i.e., the implication is that .00553 lives are saved for every child under five who *could be covered by a distributed ITN*, not that .00553 lives are saved for every child under five who is *confirmed to be using an ITN*).[13]

- *Anemia* (9 studies): statistically significant impacts on haemoglobin levels, about +1.3 g/L when insecticide-treated nets were compared to untreated nets and +5.7 g/L when insecticide-treated nets were compared to no nets.[14] (More on how to interpret these g/L figures at our **writeup on deworming**.)

- *Splenomegaly* (enlarged spleen) (5 studies): about 23% protective efficacy (which we presume means that the nets reduced splenomegaly by 23%) when insecticide-treated nets were compared to untreated nets and 30% protective efficacy when insecticide-treated nets were compared to no nets.[15]
- Effects that were usually statistically significant in individual trials, but were not combined into summary analysis, for severe malarial disease,[16] uncomplicated clinical episodes of malaria,[17] prevalence of malaria parasites,[18] high parasitemia (prevalence of malaria parasites in the blood),[19] and nutrition-related measures (weight for age, weight for height, mean mid-upper arm circumference but not height-for-age or unspecified other measures).[20]

Gamble et al. (2006) focused on the effects on pregnant women; it examined fewer studies than Lengeler (2004a) (6 vs. 22). It connected ITNs with statistically significant reductions in the risk of low birthweight and fetal loss (only in women with four or fewer previous pregnancies) and in placental malaria (overall), but not in anemia/haemoglobin measures.[21]

We focus here on Lengeler (2004a) because (a) it reviewed more studies; (b) it had a general-population focus and was thus more in line with the programs we seek to evaluate and the effects we seek to assess (particularly the effects on mortality).

What sorts of programs were carried out in small-scale studies?

We have examined and summarized the papers reviewed in Lengeler (2004a),[22] seeking to better understand the basic approaches of the programs that led to the results discussed above. We found:

- The details of the programs are often unclear.
- The programs' approaches varied; most consisted of free ITN distribution, or treatment of existing untreated nets with insecticide (effectively turning untreated nets into ITNs), but some involved promotion/marketing of nets and treatment.
- All of the studies examining child mortality involved distribution of ITNs to entire communities, not just to children under five. Only two studies distributed ITNs specifically to children under five.
- In most studies, coverage of ITNs was very low prior to the program (though there was often high coverage of untreated nets), and substantially higher afterward.

Many studies report intensive measures to ensure that people used their ITNs consistently and properly - measures well beyond what we would expect to be feasible in a larger-scale distribution (and well beyond the measures taken by the **Against Malaria Foundation**). Sample quotes:[23]

- "Each village was visited daily by a supervisor who checked the dilution of the permethrin and the progress of the installation."
- "Care was taken to place the nets over all beds in each selected house."
- "Mothers of the children in the study cohort were reminded weekly how to use the net. Nets which became torn or damaged were repaired or replaced. A survey was conducted every 4 weeks during the rainy season to determine whether the bed nets had been tucked in and the entry flaps placed correctly."
- "After distribution, study staff went door-to-door to ensure that nets were hung properly."
- "At mass meetings of the intervention group males, insecticide dipping procedures and net erection methods were demonstrated...Two months after bed net distribution, the teams revisited the trial families to give further encouragement."

Usage does not appear to have been near-universal. Most studies report usage rates in the range of 60-80%, though some report 90%+ usage.

- Only two studies specifically reported both *reported* usage and *actual* usage as determined by surprise visits to homes. In one, actual usage was 70-73% while reported usage was 85%; in the other, actual usage was 85% and reported usage was 97%.[24]

The author of Lengeler (2004a) has stated to us that few if any randomized controlled trials have been done since this review, and that few are likely to be done, since the efficacy of ITNs is well enough established that such studies could face challenges with ethics boards.[25]

How have larger-scale distributions compared to the programs addressed in these studies?

Funding for malaria control has increased substantially since 2004, making a large number of national scale-ups possible.[26]

As noted **above**, the studies discussed above may have differed substantially from what can be expected of an "average" ITN distribution. The review author notes this, stating, "the bulk of data in this review describe impact under ideal trial conditions (efficacy) rather than impact under large-scale programme conditions (effectiveness). While the difference between efficacy and effectiveness is likely to be small for certain medical interventions (such as vaccination or surgery), it can potentially be large for preventive interventions such as ITNs."[27]

In order to get a sense for how the large-scale performance of LLINs has compared with the promise of the smaller-scale studies discussed above, we have asked the following key questions:

1. How have officially delivered LLINs matched up with LLINs confirmed to be in use by actual households?
2. What has been the general pattern of LLIN usage, i.e., have people used their LLINs?
3. What has been the connection between LLIN usage and drops in malaria deaths and morbidity?

We feel that malaria scholars have used reasonably credible data to provide helpful answers to #1 and #2. We feel that #3 is substantially harder to answer due to issues with malaria data and the difficulty of isolating the impact of LLINs, though we have not thoroughly investigated the literature on this topic since 2013. Details follow.

From LLIN distribution to LLIN ownership

It appears to us that malaria control programs commonly use an "8%-20%-50%" model to estimate the percentage of *distributed* LLINs that *remain in the field* years later: they assume that 8% of LLINs distributed 0-12 months ago are no longer in the field (whether because of loss in the process of delivery, falling into disrepair, being given away, etc.), that 20% of LLINs distributed 12-24 months ago are no longer in the field, and that 50% of LLINs distributed 24-36 months ago are no longer in the field. The very limited evidence we have seen on this topic appears consistent to us with the idea that this model is the best available. Further discussion of this topic is available at **another page**, for the sake of brevity.

From LLIN ownership to LLIN usage

We used data from national surveys collected in the WHO World Malaria Report to analyze net usage rates in sub-Saharan Africa. We report results from the 2010 and 2012 editions of the World Malaria Report, which cover different survey years and may use slightly different methodologies (though it is difficult to know from the information available in the reports).[28] Our findings are below.

2010 World Malaria Report

In the 2010 World Malaria Report, net usage rates are determined by using national population surveys to compare (a) the percentage of the population that could theoretically be protected by **owned** ITNs based on an assumption that each ITN protects two people,[29] with (b) the percentage of the population that reports **using** an ITN.[30] The 2010 World Malaria Report finds 3 countries in sub-Saharan Africa with greater than 100% apparent usage (this could be a function of more than 2 people covered by each ITN in some cases,[31] combined with possible over-reporting of usage in surveys), 2 countries with very low apparent usage (Swaziland, 0%, and Nigeria, 40%), and 7 countries with apparent usage ranging from 69% to 85%.[32]

2012 World Malaria Report

The 2012 World Malaria Report tabulates results from national population surveys, and compares (a) the percentage of the population that could theoretically have access to an **owned** ITN in their household, assuming that each ITN within a household protects two people and does not protect anyone outside of the household,[33] with (b) the percentage of the population that reported **using** an ITN the previous night.[34] It finds slightly higher usage rates than the 2010 World Malaria Report. In 17 sub-Saharan African countries that conducted surveys from 2009-2011, the median net usage rate was 91%, with an interquartile range of 82%-98% usage.[35]

Over-reporting

It is possible that survey data overstates usage; in our discussion of small-scale studies **above**, we cite one study where actual usage (as assessed by spot visits to homes) was 70-73% while reported usage was 85%.[36] If we assume an equal amount of over-reporting in the national surveys as in the small-scale study, and apply this adjustment to the 2010 World Malaria Report data, actual net usage rates would range from 57% to 73%.[37] If this adjustment were applied to the 2012 World Malaria Report data, the interquartile range for net usage rates would be 68% to 84%.[38]

Bottom line

Broadly speaking, the net usage figures implied by surveys gathered in the World Malaria Report are similar to what was found in the small-scale studies discussed above (which had net usage rates generally in the 60%-80% range),[39] even after accounting for minor over-reporting. However, this data and our analysis of it could easily be unreliable.[40]

From LLIN usage to reduced malaria burden

Funding for malaria control has increased substantially since 2004, making a large number of national scale-ups possible. In 2012-2013, we looked into the question of whether the impact of LLINs on the burden of malaria can be directly seen in available data (outside the context of intensive small-scale studies). Our discussion is on a **separate page**, for brevity.[41] At the time, we concluded that it was difficult to link changes in the burden of malaria to particular malaria control measures.

However, we have not revisited this question since 2013 and are aware of recent studies (e.g., **Bhatt et al 2015**) that assess the large-scale impact of LLINs and conclude that there have been large effects attributable to LLINs.[42]

How might the effectiveness of ITNs vary across settings with different malaria transmission patterns?

Smithuis et al 2013a raises the possibility that ITNs do not provide consistent protection against malaria in areas with malaria transmission patterns that seem very different than the areas in which the Against Malaria Foundation (AMF) works.

Smithuis et al 2013a, a study published after the two reviews we discuss (**Lengeler 2004a**; **Gamble, Ekwaru, and ter Kuile 2006**), randomly assigned 20 villages (containing a sample of 8,175 children under 10 years old) in Western Myanmar to either a treatment group that received ITNs or a control group.[43] The study did not find statistically significant effects of ITNs on malaria infections, spleen rates, hemoglobin concentrations or weight for height over the study period (10 months) and it concluded that ITNs did not provide consistent protection

against malaria in the study area.[44] **Smithuis et al 2013a** does not claim to undermine the evidence of the impact of ITNs in Africa and attributes the lack of an impact in the study to differences in the transmission dynamics for malaria between Africa and Asia.[45]

The 5 small-scale, high-quality studies that originally established the impact of ITNs on child mortality (see **above**) all took place in sub-Saharan Africa in areas with stable malaria transmission (we do not know the details of what qualifies malaria transmission as "stable," but the description of malaria transmission in **Lengeler 2004a** seems to contrast with the "unstable malaria" described in **Smithuis et al 2013a**).[46] As of November 2015, AMF is planning to conduct its major distributions in sub-Saharan African countries.

We do not see **Smithuis et al 2013a** as providing a meaningful update on the potential effectiveness of AMF's activities because (a) AMF works in sub-Sarahan Africa, which we generally expect to have similar transmission dynamics to the 5 studies finding large positive effects of ITNs, and (b) **Smithuis et al 2013a** does not claim to undermine the evidence of the impact of ITNs in Africa. We do not know if malaria transmission dynamics differ substantially between sub-Saharan African countries or whether they may change over time within sub-Saharan Africa, but we would guess that we would have seen discussion of this topic in our review of the literature on the effectiveness of ITNs if it had been important to the expected effect of ITNs in sub-Saharan Africa.

Effects on mortality in individuals 5+ years old

We include our analysis of this question on **a separate page** for brevity. We conclude:

- We are aware of three organizations that estimate malaria mortality rates. All of them seem to agree that roughly 25% of all malaria mortality in sub-Saharan Africa occurs among individuals 5+ years old. (For simplicity, throughout this write up we refer to individuals 5 years old and over as "5-and-overs.")
- We believe that the mechanism by which bed nets would reduce malaria mortality among 5-and-overs is straightforward and plausible: bed nets would reduce malaria cases in this group, which would in turn reduce deaths. We checked this reasoning with three malaria researchers, and they agreed with this assessment.

- We are not aware of any randomized controlled trials (RCTs) that estimate the impact of bed nets on 5-and-over mortality. We have seen one RCT that finds that bed nets reduce 5-and-over malaria episodes. The malaria researchers we spoke to told us that they did not believe there was additional research we missed that directly addresses this question.
- Given the above, our best guess is that reducing malaria mortality among 5-and-overs is a meaningful impact of bed net distributions, but due to a lack of relevant evidence we are forced to make a variety of judgment calls when estimating the magnitude of this impact in our cost-effectiveness analysis (CEA) (see **our CEA** for more details).

Possible developmental effects

As noted **above**, ITN distribution appears to have benefits other than reduced mortality, such as reduced anemia (an effect size larger than what we have seen for **deworming**). In addition, **Bleakley 2010** makes a case that reducing the burden of malaria may have a lasting impact on children's development, and thus on their ability to be productive and successful throughout life.

Bleakley 2010 analyzes a number of attempts to eliminate malaria in the Americas during the early-to-mid 20th century, focusing on the U.S., Brazil, Columbia, and Mexico. He concludes:

Relative to non-malarious areas, cohorts born after eradication [in malarious areas] had higher income as adults than the preceding generation. These cross-cohort changes coincided with childhood exposure to the campaigns rather than to pre-existing trends. Estimates suggest a substantial, though not predominant, role for malaria in explaining cross-region differences in income.[47]

There are good reasons to be cautious in using this study as evidence relevant to ITN distribution:

- The programs studied were very different from LLIN distribution campaigns: they focused on indoor residual spraying and other interventions, and did not involve bednets.[48]
- The context was very different from that of modern-day ITN distributions: the campaigns took place in the U.S.A. of the 1920s and Latin America of the 1950s, where the impact of malaria could have been very different from the consequences in the modern-day developing world (and the infections themselves may have been quite different as well).
- Bleakley 2010 is not an experimental study, but a retrospective one. That is, rather than setting out to answer a question by collecting new data, the author collected and analyzed a

large amount of pre-existing data, raising strong possibilities for **publication bias**. We believe it is unlikely that this paper would have been published in a major economics journal if it had simply concluded that there was no strong evidence for major benefits of malaria eradication. We are generally very hesitant to use papers of this nature in our work. This worry is enhanced by the use of multiple different outcomes and measures of malaria prevalence across the different countries studied, raising the possibility that the author could have selected those specifications that make the outcomes most interesting (in this case, positive for malaria eradication).

That said, we believe the paper merits some weight on the question of developmental benefits, because:

- GiveWell Senior Advisor David Roodman subjected **Bleakley 2010** to intense scrutiny, conducting a detailed review and reanalysis (see blog post **here** and detailed report **here**) and concluded: "the campaigns to eradicate malaria from Brazil, Colombia, and Mexico, and perhaps the American South as well, were followed by accelerated income gains for people whose childhood exposure to the disease was reduced. The timing of these events is compatible with the theory that rolling back malaria increased prosperity."
- It has a plausible strategy for separating the effects of malaria infection from effects of other things (such as poverty) that may correlate with malaria infection. Specifically, it exploits the fact that the eradication campaigns caused a relatively rapid drop in malaria infection rates (which was plausibly exogenous because of technological advancement in the creation of DDT) and that areas with higher initial malaria prevalence saw greater falls in malaria prevalence.[49] Thus, it seems possible that a connection between the fall in malaria prevalence and positive life impacts - coinciding with the timing of the campaign - could be attributed specifically to malaria eradication, and not to other factors.
- It uses graphs to illustrate a relationship between malaria prevalence and later-in-life income that, while varying across countries, shows that the correlation between baseline malaria rates and adult income was negative and fairly constant, then turned into "zero effect" (when adjusted using a set of controls), coinciding well with the timing of the eradication campaign. It seems difficult to explain this pattern except by attributing the change to the drop in malaria prevalence, though it is worth noting that the relationship in Colombia becomes positive, which is unexpected.[50]

- It addresses multiple alternate possible explanations for its observations, including a fairly robust set of controls, though they vary by country (because there is no consistent set of cross-country and cross-time data).[51]
- It covers a number of very large-scale campaigns. While randomized controlled trials allow for a cleaner connection between a program and its effects, a large-scale study like this seems likely to be less dependent on idiosyncratic aspects of a particular mini-program designed to be studied.

Bleakley 2010 also finds effects on school enrollment that vary by country.[52]

Possible productivity effects

We have seen little evidence that providing ITNs improves short-term productivity (i.e., improvements in productivity through more immediate channels than possible developmental effects).

We know of 2 RCTs examining the effect of ITNs on short-term productivity (**Fink and Masiye 2015** and **Sedlmayr 2014**).[53] **Fink and Masiye 2015** randomly assigned 516 farmers in Zambia to either a group that received subsidized ITNs, a group that received ITNs for free, or a control group, and found a major potential benefit of ITNs on productivity: it found that free ITNs increased the average annual harvest value for a farmer by $76, about 12% of the group's average annual harvest value at baseline.[54] However, baseline imbalance between the treatment and control groups in the outcome of interest poses a major threat to the study's validity.[55] We believe that it is difficult to adjust for the potential confounding suggested by this imbalance, so we are hesitant to place much weight on this study's findings.[56] We view this study as very weak evidence for the effect of ITNs on productivity. We have not examined **Sedlmayr 2014** as closely as **Fink and Masiye 2015**, but it appears to not have detected an impact of ITNs on productivity.[57]

Possible negative/offsetting impact

- **Possible development of insecticide resistance**. There appears to be consensus in the malaria community that the use of LLINs will contribute to the development of insecticide resistance. We discuss this issue in greater depth **on a page focused on insecticide**

resistance. In brief, we feel that resistance is a very serious concern, and would like to see substantially more data available to assess it. It also appears to us that the malaria control community has been devoting attention and investigation to this issue, has developed a reasonable knowledge base (if one that has plenty of room to grow), and still recommends the use of LLINs regardless of the resistance situation. A reasonable summary of the malaria community's perspective is available in **notes from our conversation with the WHO's Dr. Abraham Mnzava**.

- **Possible postponement of human immunity.** It has been argued that LLINs, by protecting children from mosquitoes, may not only reduce the short-term burden of malaria, but may also reduce opportunities for humans to acquire immunity, making them more susceptible to malaria over the long term.[58] A 2010 paper claims that this question has been "answered, with a clear indication that even seven years after initial exposure of infants to ITN, no increased mortality could be observed"[59] and cites three sources: **Binka et al. 2002**, **Diallo et al. 2004**, and **Lindblade et al. 2004**. All of these appear to be follow-ups on the **small-scale, high-quality studies** that originally established the impact of ITNs on child mortality, and all conclude that reductions in child mortality were sustained in the several years after the initial study.[60] These follow-ups account for 3 of the 5 studies that originally established an impact of LLINs on child mortality. We have emailed the authors of all five studies to ask whether there have been any follow-ups beyond the latest we're aware of; in 4 of 5 cases, it's been confirmed that no more follow-ups were done, and in the fifth case we have not heard back. A more recent trial, **Louis et al 2012**, measured mortality over a median follow-up time of about 8 years in children individually randomized to either receive ITNs at birth or at 6 months of age.[61] In line with the follow-ups, the study concluded that ITN protection in early infancy does not increase mortality later in life.[62] We attempted to vet the conclusions of one of the follow-ups (**Binka et al. 2002**), but we found the study difficult to interpret based on the information provided in the paper and our vet was inconclusive.[63]
- **Undermining private markets.** It is possible that giving away LLINs for free causes people to systematically expect that they will continue to receive LLINs for free, and thus causes people to be unwilling to pay for them. (More at a **2012 blog post**.)
- **Allergic reactions**. We have heard anecdotes of minor allergic reactions (e.g., itching skin) to LLINs. We have located no mention of this issue in the **Cochrane** reviews discussed **above** and have located very little information on it in general. We did discuss it with program staff during our **visit to an ongoing LLIN distribution** (we were told that this

issue affects few people and can be avoided by letting an LLIN hang for a few days before use). We believe this to be a very minor concern.

- **Equity concerns.** It is possible that LLIN distribution may cause conflicts if it is not perceived as fair and equitable. We have seen very little evidence on whether this is an issue. We feel that the **Against Malaria Foundation** takes **appropriate steps** to mitigate this concern.

- **Using bed nets for fishing in waterside, food-insecure communities.** A New York Times **article** describes people using insecticide treated bed nets for fishing instead of sleeping under the nets to protect themselves from malaria-carrying mosquitoes. We believe this problem is unlikely to apply to a meaningful portion of AMF's work, and we see it as a much smaller problem than people lacking nets for preventing malaria. For more detail, see our **response** to the article.

- **Fire hazard from bed nets.** Bed nets may pose a fire hazard, because of their flammability.[64] **Ergot et al 2014** interviewed people about bed net related fires in a district in Benin and conducted a search for studies on bed net related fires.[65] The study found reports of bed net related fires in several countries.[66] Some of the reported cases resulted in severe bodily harm or death.[67] The study found little data on the frequency of bed net related fires.[68] **Kalanzi et al 2014** examined admissions for bed net related burns to a national referral hospital in Kampala, Uganda.[69] The study found 45 patients admitted to the burns unit with bed net related burns from 2008 to 2011. 15 of the 45 patients died.[70] Hospital data may underestimate the true incidence of bed net related burns if many burn victims don't seek care. From the scant data available, bed net related burns do not seem like a large problem relative to the amount of people using nets.

Two key issues around LLIN distributions

Targeted vs. universal coverage

It appears that there has been a shift in emphasis over the last several years from *targeted coverage* (aiming primarily to cover children under five and pregnant women with ITNs) to *universal coverage* (aiming to protect everyone in a community with ITNs).

The 2004 Cochrane review discussing the impact of ITNs on under-5 mortality (discussed **above**) appears to advocate primarily for coverage of children under five,[71] and as of 2006 this seemed to be the focus of the Roll Back Malaria Partnership, the United Nations Millennium Development Goals, and the US President's Malaria Initiative as well.[72] However, in 2007 the World Health Organization issued a recommendation for universal coverage that appears to have been an explicit change in position.[73] As of 2016, the World Health Organization continues to recommend universal coverage.[74]

We did a brief investigation of the arguments for targeted vs. universal coverage, because we wondered whether the **Against Malaria Foundation**'s focus on universal coverage was justified. It seemed to us that if the main benefit of ITNs is in reducing mortality for children under five, then targeting children under five could achieve most of the benefits of universal coverage, for a fraction of the cost. On the other hand, there is a potential argument for universal coverage based on the possibility that universal coverage will be more likely to have community-level effects.[75]

Our investigation consisted of:

- Speaking with Christian Lengeler, the author of the **Cochrane** review of the evidence regarding ITN distribution discussed **above**. (This Cochrane review appears to us to be the most widely cited evidence of the efficacy of ITNs.[76]) We have published our notes from this conversation.[77]
- Speaking with two scholars that Professor Lengeler referred us to on this question, Dave Smith and Thomas Smith. We have published notes from each of these conversations.[78]
- Reviewing literature that these scholars referred us to.

Our conclusions are:

- The evidence for the efficacy of ITNs in the Cochrane review is based on studies of universal coverage programs, not targeted programs. In particular, all five studies relevant to the impact of ITNs on mortality involved distribution of ITNs to the community at large, not targeted coverage (see **above**). (We confirmed this in our examination of the individual studies cited in the Cochrane review.[79]) Thus, there is little basis from the Cochrane review for determining how the impact of ITNs divides between **individual-level effects** (protection of the person sleeping under the net, due to blockage of mosquitoes) and **community-level effects** (protection of everyone in communities where ITN coverage is high, due to reduction in the number of infected mosquitoes, caused either by mosquitoes' being killed by insecticide or by mosquitoes' becoming exhausted when they have trouble finding a host).
- The people we spoke to all believe that the community-level effect of ITNs is likely to be a significant component of their effect, though none believe that this effect has been conclusively demonstrated or well quantified.[80]
- There is some empirical evidence suggesting that the community-level impact of ITNs is significant.
  - We reviewed one study, **Hawley et al. 2003**, which examined data from a randomized study of ITNs and compared (a) households *not selected to receive ITNs* but *living near other households that had been selected to receive ITNs* to (b) households *not selected to receive ITNs* living *far from other households that had been selected to receive ITNs*.[81] Non-ITN households were divided into quartiles based on proximity to ITN households, and statistically significant trends were observed for child mortality, hemoglobin level and percentage anemic (e.g., non-ITN households showed more favorable performance on these measures as they got closer to ITN households), though the trends were not significant for two other measures of malaria burden.[82] For the set of non-ITN households closest to ITN households, malaria outcomes were similar to those for ITN households themselves.[83] We find this study credible, although we note that this was a separate analysis of data from a trial of ITN efficacy, so it may be susceptible to **publication bias**.
  - This study cites eight other studies arguing for significant community-level effects on malaria transmission and one study arguing against this idea. Of these nine, only two (both arguing for community-level effects) examine measures of malaria morbidity/mortality as opposed to simply transmission.[84] We have not examined these studies.

- Counter-evidence comes from the **Cochrane** review focused on pregnant women (which is not the main one we have discussed):

> The most recent trial from western Kenya by Njagi et al. is informative in this respect, as it is the only trial that compared the effects of ITNs versus no nets using simple randomisation by individual in an area with low ITN coverage (little or no mass effect) [24,29]. This trial and the community-randomised trial by ter Kuile et al. [27] were conducted simultaneously in contiguous areas with similar malaria transmission at baseline, and similar socioeconomic and educational status and ethnicity of the trial population. The effect estimates were similar between the two trials (in women not randomised to IPTp-SP), suggesting that ITNs may work equally well when provided to individuals as part of antenatal care in the second trimester or when provided to entire communities.[85]

The scholars we spoke with also pointed us to papers attempting to model malaria transmission mathematically.

- One such paper, Killeen et al. (2007), that we were pointed to by two of the scholars we spoke to and has been described as a particularly influential paper,[86] uses a relatively detailed model of mosquito behavior, which we have not independently vetted and assessed, in order to conclude that "high (80% use) but exclusively targeted coverage of young children and pregnant women (representing <20% of the population) will deliver limited protection and equity for these vulnerable groups. In contrast, relatively modest coverage (35%–65% use, with this threshold depending on ecological scenario and net quality) of all adults and children, rather than just vulnerable groups, can achieve equitable community-wide benefits equivalent to or greater than personal protection."[87]
- Smith et al. (2009) proposes a model for the relationship between ITN coverage and effective protection for the community. This model implies that each incremental increase in ITN coverage is more valuable to the community than the previous increase (e.g., going from 60% to 70% coverage would be more valuable than going from 50% to 60% coverage, which in turn would be more valuable than going from 40% to 50% coverage).[88]

We asked one scholar whether there were any prominent papers in this category making the opposite argument (that community-level effects are likely to be insignificant) and he replied that he did not know of any.[89]

We do not find the evidence for community-level impact to be conclusive, but we believe that the best interpretation of the available evidence suggests at least some community-level impacts, consistent with the consensus of the scholars we spoke to and the World Health Organization.

Free vs. cost-recovering distributions

There has been some debate about whether ITNs should be sold or given freely, with some arguing that selling them (even for highly subsidized prices) may improve the likelihood that they get to people who will use them. We believe that the weight of the (limited) available evidence supports giving out ITNs rather than selling them. Evidence implies that charging a fee has significantly reduced demand for the product, without leading to corresponding increases in utilization rates (and has not significantly impacted the costs of the program).

- One high-quality study evaluated the impact of user fees on net purchase and on utilization of the net. A program distributing nets at prenatal clinics in Kenya found that increased prices (from $0 to $0.75, the price at which they were sold) reduced demand by approximately 75%,[90] but were not associated with higher rates of utilization.[91]
- A review of high-quality studies on this general issue cites two other studies. One found that charging for deworming drugs significantly reduced demand while raising little revenue and failing to improve the targeting of recipients[92]; another found that charging for water disinfectant "led to a rapid drop-off in take-up, with no evidence of increased targeting to the most vulnerable" while slightly increasing utilization rates.[93]
- **D'Alessandro et al. 1995** reports that individuals in The Gambia given free nets in year one, who were then asked to pay for insecticide to retreat them in year two, saw a significant reduction in coverage and a rise in child mortality.[94]
- **Noor et al. 2007** reports that a program in Kenya began selling nets at subsidized prices starting in 2002.[95] Net coverage rates remained extremely low, at 25%,[96] so in 2004, Kenya sold more heavily subsidized nets.[97] In 2006, the program began distributing nets for free,[98] raising net coverage to 79% between 2006 and 2007.[99]
- As discussed **above**, there is a case that ITNs provide community-level protective benefits, so increasing the level of coverage in a community could be beneficial to everyone, not just ITN users. This gives some additional reason for giving out ITNs for free.

How cost-effective is LLIN distribution?

Two general notes on the limitations to cost-effectiveness analysis such as this:

- Such analysis will usually draw its main estimates of program effects from small-scale, high-quality studies (our analysis here is no exception). These studies may be unrepresentative of real-world conditions, on account of being carried out in optimal locations and with unusual amounts of funding and intensity.
- We believe that **cost-effectiveness estimates such as these should not be taken literally**, due to the significant uncertainty around them. We provide these estimates (a) for comparative purposes and (b) because working on them helps us ensure that we are thinking through as many of the relevant issues as possible.

We provide a spreadsheet[100] that estimates the (a) cost per life saved, (b) cost per person protected per year, and (c) cost per child under 14 protected per year (since ITN protection may yield non-mortality-related benefits similar to those of **deworming**).

Our analysis is relatively simplified and unlikely to capture all of the key issues. Some key assumptions and choices made in our model:

- We build the model on the **Cochrane review**'s conclusion that each effective year of protection for children under five results in 0.00553 lives saved.[101]
- We include an adjustment to account for the fact that child mortality rates are lower today than they were at the time of the studies on ITNs.[102] This adjustment assumes that ITNs avert the same *proportion* of under-5 deaths that they averted at the time of the studies. This could be incorrect.[103]

  LLINs are assumed to last 2.22 years on average, consistent with the **decay model discussed above**.[104]

- Our estimate does not include the **possible concerns discussed above** around negative/offsetting impact (delaying the development of immunity, causing allergic reactions, etc.) with the exception of insecticide resistance. We believe that these are minor concerns.
- Our estimate does not include all of the possible benefits of malaria control; it focuses on the benefits of saving lives and on possible **developmental effects**. Other potential benefits

including averting malaria morbidity, benefits to the health system of a reduced malaria burden, etc.

Bottom line

LLIN distribution is one of the most cost-effective ways to save lives that we've seen. See **our cost-effectiveness models page** for the most up-to-date version of our cost-effectiveness analysis of LLIN distribution.

Is there room for more funding in LLIN distribution?

See the **relevant section of our AMF review** for the most recent information on the global funding gap for LLINs.

Our process

2013

In 2013, we only conducted further investigation into issues that (a) could significantly affect our perception of the effectiveness of mass distributions of LLINs and that (b) we could reasonably expect to learn more about in a limited amount of time.

We conducted further research on the following issues:

- **Evidence from small-scale, high-quality studies** (assessed as up-to-date in September 2013)[105]
- **From LLIN distribution to LLIN ownership** (assessed as up-to-date in September 2013)
- **From LLIN ownership to LLIN usage**[106]
- **From LLIN usage to reduced malaria burden** (assessed as up-to-date in September 2013)
- **Possible negative/offsetting impact** (updates to insecticide resistance and delayed immunity only)[107]
- **How cost-effective is LLIN distribution?**[108]
- **Is there room for more funding in LLIN distribution?**[109]

Major questions that may merit further research in the future include:

- What is the impact of insecticide resistance on the current effectiveness of LLINs?
- Do LLINs reduce all-cause mortality for people older than age 5?
- What is the evidence that LLINs have long-term impacts on children?
- Has the proportion of deaths averted by LLINs in under-5-year-olds changed over time because of improvements in general health?

2014

In 2014, we did not reassess the evidence for LLINs. We only updated the **room for more funding section** of this page.

2015

We investigated a small number of high priority research questions based on our impression of the likelihood that they could substantively change our view of LLINs:

- **Possible postponement of human immunity**. We found **Louis et al 2012**, a RCT comparing mortality rates in children that received ITNs at birth to children that received ITNs at 6 months of age, and looked more closely at one of the follow-ups of the RCTs that originally established the impact of ITNs on child mortality (**Binka et al. 2002**). See our discussion in the section **here**.

- **Insecticide resistance**. We only did a cursory review of new literature that might update us on the importance of insecticide resistance. We primarily scanned new literature to see whether there were any studies that directly measured human outcomes (e.g., malaria cases) and found that insecticide resistance potentially led to negative effects on those outcomes (e.g., more malaria cases), but we did not find any such studies. Details on our search for studies are in this footnote.[110]
- **Possible productivity effects**. We found 2 RCTs examining the effect of ITNs on productivity (**Fink and Masiye 2015** and **Sedlmayr 2014**). See our discussion of these studies **here**.

We also searched Google Scholar for well-identified studies on the effectiveness of bed nets.[111] In addition to the studies we had already found through our investigation of high-priority research questions, we also found two studies on bed net related burns (**Ergot et al 2014** and **Kalanzi et al 2014**), which we discuss **here**, and a cluster RCT on ITNs in Myanmar (**Smithuis et al 2013a** and **Smithuis et al 2013b**), which we discuss **here**.

We also added our response to a New York Times article on the problem of using bed nets for fishing in waterside, food-insecure communities **here**.

2017

In this update, we prioritized reviewing research in two areas that we believed were most likely to substantially affect our cost-effectiveness analysis:

- **Effects on mortality in individuals 5+ years old**: we reviewed relevant evidence and spoke with malaria researchers about this topic. We published **a new page** covering our conclusions.
- **Insecticide resistance**: we updated **our page** on this topic but did not significantly change our conclusions since our last update in 2016. See the **process section** of that page for more details.

We briefly reviewed other potentially relevant papers that we became aware of since our last intervention report update. To learn about potentially relevant papers, we have set up Google Scholar alerts so that we are notified when new studies cite the key papers discussed in this intervention report (e.g. **Lengeler 2004a**). We also learn about relevant research papers through a variety of other channels, including speaking with researchers and charities focused on malaria.

Finally, we:

- Added a reference to GiveWell Senior Advisor David Roodman's analysis of **Bleakley 2010**, a key source on the potential developmental effects of LLINs (see blog post **here** and detailed report **here**).
- Added a note that our analysis of **the macro literature** on effectiveness of LLINs may be outdated.

Sources

Document	Source
Against Malaria Foundation. Recently approved distributions and others being assessed	**Source** (**archive**)
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Binka et al. 2002	**Source** (**archive**)
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Cohen and Dupas 2007	**Source**
D'Alessandro et al. 1995	**Source** (**archive**)
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Uncited supplementary materials

Document	Source
GiveWell. Country-level charts of ITN coverage vs. malaria mortality	**Source**
GiveWell. Tabulation of ITN coverage vs. malaria mortality	**Source**
Hoffman, Vivian, Christopher Barrett and David Just. 2009. Do free goods stick to poor households? Experimental Evidence on Insecticide Treated Bednets. World Development 37: 607-617	**Source**
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Trape, Francois et al. 2011. Malaria morbidity and pyrethroid resistance after the introduction of insecticide-treated bednets and artemisinin-based combination therapies: a longitudinal study	**Source** (**archive**)
World Health Organization. Profiles: 31 high-burden countries (2009)	**Source**

1. "In 2015, malaria was the fourth highest cause of death, accounting for 10% of child deaths in sub-Saharan Africa." **World Health Organization. World Malaria Report (2015)**, Pg x.

2. "Human infection begins when the malaria vector, a female anopheline mosquito, inoculates plasmodial sporozoites from its salivary gland into humans during a blood meal. The sporozoites mature in the liver and are released into the bloodstream as merozoites. These invade red blood cells, causing malaria fevers. Some forms of the parasites (gametocytes) are ingested by anopheline mosquitoes during feeding and develop into sporozoites, restarting the cycle." **Jamison et al. 2006**, Pg 413.

3. "Most malaria infections cause symptoms like the flu, such as a high fever, chills, and muscle pain. Symptoms tend to come and go in cycles. Some types of malaria may cause more serious problems, such as damage to the heart, lungs, kidneys, or brain. These types can be deadly." **WebMD. Malaria: Topic overview**

4. See **Jamison et al. 2006**, Pg 416, Table 21.3 for estimates of cases of hearing impairment, visual impairment, epilepsy, etc. caused by malaria.

5. "Using mosquito nets as a protection against nuisance insects was practiced in historical times (Lindsay 1988). During World War II, Russian, German, and US armies treated bed nets and combat fatigues with residual insecticide to protect soldiers against vector-borne diseases (mainly malaria and leishmaniasis) (Curtis 1991). In the late 1970s, entomologists started using synthetic pyrethroids: their high insecticidal activity and low mammalian toxicity made them ideal for this purpose.

   In the 1980s, studies of ITNs showed that pyrethroids were safe and that ITNs had an impact on various measures of mosquito biting (such as the proportion of mosquitoes successfully feeding on humans and the number of times a mosquito bit humans in one night). These studies showed that pyrethroids worked by both repelling and killing mosquitoes. In addition, researchers determined optimal doses of various insecticides with different materials (Curtis 1991; Curtis 1992a; Curtis 1996; Lines 1996; Rozendaal 1989a). The cost-effectiveness of ITNs has also been demonstrated (Goodman 1999; Hanson 2003)." **Lengeler 2004a**, Pg 2.

6. See "Abbreviations" - **World Health Organization. World Malaria Report (2015)** Pg ix.

7. - "Re-treating ITNs semiannually or just before the annual peak in transmission is essential for effective vector control and is proving a major logistical and financial challenge. Fortunately, new types of nets with a long-lasting insecticidal property are now available, and re-treatment will soon cease to be an issue." **Jamison et al. 2006**, Pg 421.
   - "Sumitomo Chemical's Olyset net uses the latest research and technology to achieve a breakthrough in the global fight against malaria. Permethrin is incorporated inside the Olyset fibres to create a bed net guaranteed to last at least five years.* It is tear-proof, wash-proof, and never requires treatment.

     > The pyrethroid insecticide permethrin is a synthetic molecule similar to natural pyrethrin, which comes from a species of chrysanthemum. Because it poses minimal toxic risk to humans, Olyset is particularly valuable where babies and small children are concerned." **Sumitomo Chemical. Olyset net**

8. "WHO recommendations for malaria vector control are the following:
   Insecticide-treated nets

1. As high coverage rates are needed to realize the full potential of vector control, WHO recommends that in areas targeted for malaria prevention, and for which ITNs are selected as the vector control method, they should be made available to all people at risk, i.e. universal access (21). Because of the operational advantages of LLINs over ITNs, and the fact that the vast majority of nets being procured and distributed today are indeed LLINs, the remainder of this section will refer to LLINs rather than ITNs. In order to meet the target of universal access, it is currently proposed that 1 LLIN should be distributed for every 2 persons. At the household level, the distribution of 1 LLIN for every 2 members of the household will entail rounding up in households with an odd number of members (e.g. 3 LLINs for a household with 5 members, etc.) Because of this rounding up, the achievement of 1 LLIN for every 2 people at household level requires an overall ratio, for procurement purposes, of 1 LLIN for every 1.8 people in the target population (17).
2. LLINs should be provided either free of charge or be highly subsidized. Cost should not be a barrier to their availability to all people at risk of malaria, especially those at greatest risk such as young children and pregnant women (21) and those in rural communities with least ability to purchase outright or provide a supplemental co-payment.
3. Universal access to LLINs is best achieved and maintained by a combination of delivery systems. The basic concept is a combination of 'catch up' and 'keep up'. Catch up involves mass distribution campaigns which can rapidly achieve universal coverage of LLINs. However, it is essential to complement such campaigns with continuous 'keep up' delivery systems, particularly routine delivery to pregnant women through antenatal services and to infants at immunization clinics. It should also be noted that targeted distribution to infants and pregnant women will fall short of the quantity needed to maintain universal coverage, and other strategies involving further campaigns may be required (21).
4. In order to be protected, individuals must not only own LLINs but also use them. Behaviour change interventions including information, education, communication (IEC) campaigns and post-distribution "hang-up campaigns" are strongly recommended, especially where there is evidence of their effectiveness in improving LLIN usage (21).
5. Only LLINs recommended by the WHO Pesticide Evaluation Scheme (WHOPES) should be procured by national programmes and partners for malaria control. At present there are 13 recommended products (22). Detailed guidance on good practice in the handling and use of pesticides, and on quality control in procurement, can be found on the WHOPES website (23). Independent quality control of products (including insecticides) should be undertaken before shipment, to ensure that substandard products are not delivered to countries. The suppliers of pesticide should bear the cost of analysis, including the cost of sending samples to an accredited or recognized laboratory for analysis on behalf of countries that do not have adequately equipped or staffed national quality control laboratories (9).
6. It is now recognized that the lifespan of LLINs is variable, among settings and among products. Therefore, all large-scale LLIN programmes (including those implemented by NGOs) should make efforts to monitor LLIN durability in local settings, using standard methods published in 2011 (24). The collection of local data on the comparative durability of alternative LLIN products, using rigorous and auditable methods, is expected to enable procurement decisions to be made on the basis of price per year of protection rather than unit price per net; this in turn is expected to bring rapid and potentially substantial cost savings. This is important because LLINs represent a large proportion of the global malaria control budget (18). Efforts are also under way to develop more varied and sophisticated methods for testing the durability of LLINs under simulated laboratory conditions." **World Health Organization. World Malaria Report (2012)** Pgs 4-5.

9.

GiveWell. Summary of ITN RCTs

10.

"The remaining 22 trials, including 1 trial that is currently unpublished, met the inclusion criteria for this review. These trials are described below." **Lengeler 2004a**, Pg 6.

11. "The summary rate difference, which expresses how many lives can be saved for every 1000 children protected, was 5.53 deaths averted per 1000 children protected per year (95% CI 3.39 to 7.67; Analysis 1.2). I performed a regression analysis of the natural logarithm of the rate difference on the entomological inoculation rate and could not find a trend ($r^2 = 0.52$, $F = 3.2$ on 1,3 degrees of freedom, $P = 0.2$). In contrast to protective efficacies, the risk differences seemed to have a tendency towards a higher effect with a higher entomological inoculation rate. This apparent paradox is because the baseline mortality rates are higher in areas with high entomological inoculation rates." **Lengeler 2004a**, Pg 9. (Note on the entomological inoculation rate: "The intensity of malaria transmission in an area is the rate at which people are inoculated with malaria parasites by infected mosquitos. It is expressed as the annual entomological inoculation rate (EIR), which is the number of infectious mosquito bites received by an individual in 1 year." **World Health Organization. Guidelines for the Treatment of Malaria, 3rd ed. (2015)** Pg 129.)

12. "The impact of ITNs on malaria-specific death rates was looked at only briefly because of the problems using verbal autopsies in determining malaria deaths. In the two trials for which the data were available, the percentage reduction in malaria-specific mortality was similar or smaller than the percentage reduction in all-cause mortality: 14% (versus 23%) for Gambia (**D'Alessandro et al. 1995**), and 22% (versus 18%) for Ghana (**Binka et al. 2002**). One interpretation is that malaria-specific death rates were not reflecting the true impact of ITNs on mortality (since a much higher specific impact would have been expected)." **Lengeler 2004a**, Pg 9.

13. "The summary rate difference, which expresses how many lives can be saved for every 1000 children protected, was 5.53 deaths averted per 1000 children protected per year (95% CI 3.39 to 7.67; Analysis 1.2)." **Lengeler 2004a**, Pg 8. We have confirmed with the author that this figure is based on an "intention to treat" analysis, e.g., "protected" refers to children in the treatment group, not to children who were confirmed to own or use ITNs.

14.
- "Anaemia: expressed in mean packed cell volume (PCV); it is equivalent to the percentage haematocrit. Results given in g/decilitre were converted with a standard factor of 3:1, that is, 1 g/decilitre equals 3%PCV." **Lengeler 2004a**, Pg 4.
- " The nine trials that measured anaemia were conducted in areas of stable malaria; six trials compared treated to untreated nets (Appendix 13), and three trials compared treated nets to untreated nets (Appendix 14). Overall, the packed cell volume of children in the ITN group was higher by 1.7 absolute packed cell volume per cent compared to children not using nets. When the control group used untreated nets, the difference was 0.4 absolute packed cell volume per cent." **Lengeler 2004a**, Pg 9.
- 0.4 packed cell volume converts to (0.4/3 * 10) = 1.3 g/L using the conversion factor provided (and multiplying by 10 to convert from g/dL to g/L). Similarly, 1.7 packed cell volume converts to (1.7 / 3 * 10) = 5.7 g/L.

15. "Four out of the five trials that measured splenomegaly were carried out in areas with stable malaria (Appendix 15 and Appendix 16). Because the exception was one trial carried out in Thailand whose weight is very small (only 2.6% in the relevant comparison) (Thailand (Luxemberger)), I did not carry out a subgroup analysis. Splenomegaly was significantly reduced for both types of controls: there is a 30% protective efficacy when controls were not using nets, and a 23% protective efficacy when the control group used untreated nets." **Lengeler 2004a**, Pg 9.

16. "Only one trial examined severe malarial disease as an outcome Kenya (Nevill). The trial used passive and hospital-based case ascertainment, and observed a 45% (cluster-adjusted 95% CI 20 to 63) reduction in the frequency of severe malaria episodes following the introduction of ITNs (Appendix 4)." **Lengeler 2004a**, Pg 8.

17. "Uncomplicated clinical episodes:

The trial results are available in Appendix 5 for no nets controls and in Appendix 6 for untreated nets controls. A summary of the main findings for protective efficacies is available in Appendix 7; confidence intervals were not calculated as this analysis includes both cluster and individually randomized controlled trials. No risk or rate differences were calculated because the denominators were not uniform and the sensitivity of the reporting systems of the different trials is likely to have varied considerably. Three findings can be highlighted.

- The effect of ITNs on uncomplicated clinical episodes of malaria is shown by large effect estimates in all trials. Overall, the reduction in clinical episodes was around 50% for all subgroups (stable and unstable malaria; no nets and untreated nets) and for both P. falciparum and P. vivax.
- The protective efficacy is higher (at least 11% for P. falciparum) when the control group had no nets. This was expected and it was the reason to create two separate comparisons. In areas with stable malaria (entomo- logical inoculation rate > 1) the differences in protective efficacies against uncomplicated malaria was 11% (50% no nets versus 39% untreated nets). In areas with unstable malaria (entomological inoculation rate < 1), the differences were bigger: 23% (62% no nets versus 39% untreated nets) for P. falciparum, and 41% (52% no nets versus 11% untreated nets) for P. vivax.
- In areas of unstable malaria (entomological inoculation rate < 1), the impact against P. falciparum episodes seemed to be higher than the impact against P. vivax episodes."

Lengeler 2004a, Pg 9.

18.

"Parasite prevalence:

The results are available in Appendix 8 for no nets and in Appendix 9 for untreated nets controls. The results for both groups are summarized in Appendix 10; confidence intervals were not calculated as this analysis includes both cluster and individually randomized controlled trials. Two points can be highlighted from these results.

- In areas of stable malaria, impact on prevalence of infection (measured through cross-sectional surveys) was small: 13% reduction when the control group did not have any nets and 10% reduction when the control group had untreated nets.
- In areas with unstable malaria, the results are of limited value because there was only a single trial in each subgroup (treated versus no nets; and treated versus un-treated nets).

Lengeler 2004a, Pg 9.

19.

"High parasitemia:

The results are shown in Appendix 11 for no nets and Appendix 12 for untreated nets controls. This outcome was only assessed for trials in areas of stable malaria, where parasitaemia does not necessarily lead to a clinical episode, and where parasitaemia cut-offs are useful to define disease episodes. Five trials measured this outcome: four used 5000 trophozoites/ml as the cut-off, while the fifth trial used an age-specific cut-off (Kenya (Phillips-Howard)). The protective efficacy was 29% for the two trials in which the control group did not have nets, and was 20% for the three trials in which controls had untreated nets." **Lengeler 2004a**, Pg 9.

20.

"Three trials carried out with ITNs have demonstrated a positive impact on anthropological measurements in children sleeping under treated nets.

In Gambia (**D'Alessandro et al. 1995**), mean z-scores of weight-for-age and weight-for-height were higher in children from treated villages (-1.36 and -0.98, respectively) than in those from untreated villages (-1.46 and -1.13, respectively). The differences were statistically significant after adjustment for area, age, differential bed net use, and gender (P = 0.008 and P = 0.001, respectively). There was no statistically significant difference in me significant an z-scores for height-for-age.

In the trial carried out in Kenya (Kenya (Nevill)), infants sleeping under ITNs in the intervention areas had statistically significantly higher z-scores for weight-for-age than control infants not under treated nets (analysis of variance allowing for season, gender, and age: F = 21.63, P = 0.03). Mean mid-upper arm circumference z-scores were also statistically significantly higher among infants in the intervention communities (analysis of variance allowing for survey, gender, and age: F = 19.0, P = 0.005) (Snow 1997).

In Kenya (Kenya (Phillips-Howard)), protected children under two years of age had a statistically significantly better weight-for- age z-score than unprotected children (P < 0.04). No other statistically significant differences were measured for other parameters or other age groups, although all z-score differences between intervention and control groups were in favour of the protected group." **Lengeler 2004a**, Pgs 9-10.

21.

"Six randomized controlled trials were identified, five of which met the inclusion criteria: four trials from sub-Saharan Africa compared ITNs with no nets, and one trial from Asia compared ITNs with untreated nets. Two trials randomized individual women and three trials randomized communities. In Africa, ITNs, compared with no nets, reduced placental malaria in all pregnancies (risk ratio (RR) 0.79, 95% confidence interval (CI) 0.63 to 0.98). They also reduced low birthweight (RR 0.77, 95% CI 0.61 to 0.98) and fetal loss in the first to fourth pregnancy (RR 0.67, 95% CI 0.47 to 0.97), but not in women with more than four previous pregnancies. For anaemia and clinical malaria, results tended to favour ITNs, but the effects were not significant. In Thailand, one trial randomizing individuals to ITNs or untreated nets showed a significant reduction in anaemia and fetal loss in all pregnancies but not for clinical malaria or low birthweight." **Gamble, Ekwaru, and ter Kuile 2006**, Pg 1.

22.

GiveWell. Summary of ITN RCTs

23.

GiveWell. Summary of ITN RCTs

24.

GiveWell. Summary of ITN RCTs, Sheet 1, cells Q14-R14, Q21-R21.

25.

"To the best of my knowledge there have been no more RCTs with treated nets. There is a very strong consensus that it would not be ethical to do any more. I don't think any committee in the world would grant permission to do such a trial." **Christian Lengeler, author of Cochrane Review of insecticide-treated bed nets, phone conversation with GiveWell, November 2, 2011**

26.

See **World Health Organization. World Malaria Report (2015)** figure 4.1 on Pg 36.

27.

"The results presented in this review are from randomized controlled trials where the intervention was deployed under highly controlled conditions, leading to high coverage and use rates. The one exception is Gambia (**D'Alessandro et al. 1995**), which was a randomized evaluation of a national ITN programme in which the intervention deployment was not as good as in the other trials. Therefore, the bulk of data in this review describe impact under ideal trial conditions (efficacy) rather than impact under large-scale programme conditions (effectiveness). While the difference between efficacy and effectiveness is likely to be small for certain medical interventions (such as vaccination or surgery), it can potentially be large for preventive interventions such as ITNs.

Some of the consequences of moving from a scientific trial towards a large-scale programme is illustrated by the results of the two mortality trials carried out in The Gambia. The first trial was carried out under well-controlled implementation conditions, with a high coverage rate in the target population (Gambia (Alonso)). Unfortunately it was not randomized and

hence not included in the present analysis. The second one was the evaluation of a national impregnation programme carried out by primary health care personnel and which faced some operational problems (leading, for example, to a lower than expected insecticide dosage) and a lower coverage rate (around 60%) of the target population (Gambia (D'Alessandro)). The difference of impact between the two studies is important: the first trial achieved a total reduction in mortality of 42%, while the protective efficacy in the second trial was 23%. It is not clear whether the difference in the baseline mortality rate (42.1 versus 24.3 deaths per 1000 in the control group) played a role in this difference of impact." **Lengeler 2004a**, Pg 10.

28.
Possible methodological differences between the reports include:

- The 2012 World Malaria Report is explicit that its calculation of net usage is: (# of people who report using bed nets) / (# of people with access to owned bed nets in their household, assuming that each net can cover 2 people and that a net does not cover anyone outside of the household). The 2010 World Malaria Report does not provide detailed information about its net usage calculation. It is possible that its calculation of net usage is: (# of people who report using bed nets) / (# of owned bed nets * 2). If this difference exists, it would partly explain the higher apparent usage in the 2012 World Malaria Report because the denominator in the 2012 report would be smaller than the denominator in the 2010 report.
- The surveys included in the 2012 World Malaria Report seem to survey reported usage by asking whether individuals slept under an ITN *the previous night* (see **World Health Organization. World Malaria Report (2012)** Annex 5, Pg 212). It is unclear what period of time spent sleeping under an ITN is asked about in the surveys included in the 2010 World Malaria Report.

29.
"In reviewing household surveys that provide the most recent results available on ITN coverage for 27 malaria-endemic countries between 2003 and 2009, it was evident that relatively low proportions of households own an ITN (median 16%, lower quartile 5%, upper quartile 45%); only 7 surveys were conducted during the massive expansion of ITN programmes from 2008 to 2010. However, within all surveys, a high proportion of available nets appear to be used (approximately 80%) assuming that one net can cover two people (Fig. 4.6a). Some countries such as Madagascar (2008) and Rwanda (2008) have higher rates of use than others. These results are consistent with previous analyses which suggest that the main constraint to enabling persons at risk of malaria to sleep under an ITN is lack of availability of nets (3)." **World Health Organization. World Malaria Report (2010)** Pg 23.

30.
World Health Organization. World Malaria Report (2010) Table 4.2, Pg 19.

31.
"In some cases the percentage of people living in households in which all members sleep under a net exceeds the percentage of households with enough nets to cover all occupants. Evidently in some households more than two people are sleeping under one net."
World Health Organization. World Malaria Report (2010) Pg 23.

32.
World Health Organization. World Malaria Report (2010) Table 4.2, Pg 19.

33.
"The proportion of the population with access to an ITN in the household (Footnote 2: Assuming 2 persons per ITN and the number of persons with access to an ITN cannot be greater than the number of persons sleeping in the household.) ranged from 2%-18% in initial surveys to 28-64% in the most recent surveys." **World Health Organization. World Malaria Report (2012)** Pg 25.

34.
World Health Organization. World Malaria Report (2012) Annex 5, Pg 212.

35.

"In surveys from 17 countries in sub-Saharan Africa conducted during 2009–2011, the median proportion of the population using an ITN among the population with access to one was 91% (IQR 82%–98%). However, this includes households using nets beyond their assumed capacity of two persons per net and those households using nets at or below their full capacity. For example, in 21% of Rwandan households surveyed in 2010, a greater proportion of the population slept under an ITN than the proportion which had access to one, while in the remaining 79% of households approximately 71% of persons with access to an ITN slept under one. This same phenomenon resulted in the fraction of the population sleeping under an ITN to be higher than the fraction deemed to have access to one in the Rwanda 2007 survey (Figure 4.4). People use nets that are available at high rates; however, more work needs to be done to ensure that all persons with nets available to them use their nets to full capacity." **World Health Organization. World Malaria Report (2012)** Pg 25.

36.

GiveWell. Summary of ITN RCTs, Sheet 1, cells Q14-R14, Q21-R21.

37.

- As stated above, the 7 'mid-range' countries discussed range from 69-85% reported usage.
- The study discussed has 85% reported usage and 70-73% directly measured usage, for a 82%-86% ratio of directly measured usage to reported usage.
- Applying the 82%-86% ratio to the 77%-94% reported usage results in a range of 57% (69%*82%) to 73% (85%*86%) implied actual usage.

38.

- As stated above, the interquartile range for reported usage rates in 17 sub-Saharan African countries was 82%-98%.
- The study discussed has 85% reported usage and 70-73% directly measured usage, for a 82%-86% ratio of directly measured usage to reported usage.
- Applying the 82%-86% ratio to the 82%-98% reported usage rates results in a range of 67% (82%*82%) to 84% (98%*86%) implied actual usage.

39.

GiveWell. Summary of ITN RCTs.

40.

- It does seem possible that the surveys used for the above analysis are less prone to over-reporting than the surveys done in the small-scale studies, because the latter were likely done in the context of ITN promotion programs whereas the analysis above relies on large-scale surveys covering a large number of topics (a sample of the full surveys are available via **Measure DHS. Malawi DHS 2010**). On the other hand, the intensiveness of the interventions in the small-scale studies may have meant more accurate data collection and/or a higher ratio of actual (correct) usage to reported usage.
- Additionally, evidence from a recent study (**Gobena et al. 2012**) that directly observes net usage, rather than relying on self-reported survey data, has found very low usage rates (about 33% usage) in Ethiopia. However, we have not vetted this study and have not found other recent studies that use direct observation to measure usage rates.

41.

42.

"We found that Plasmodium falciparum infection prevalence in endemic Africa halved and the incidence of clinical disease fell by 40% between 2000 and 2015. We estimate that interventions have averted 663 (542–753 credible interval) million clinical cases since 2000. Insecticide-treated nets, the most widespread intervention, were by far the largest contributor (68% of cases averted)." Abstract, **Bhatt et al 2015**.

43.

- "Initially, 22 villages were informed about the study- procedures and were invited to participate, but after further discussions two villages declined to join. Finally 20 villages (clusters) were paired, and for each pair one was selected randomly (using a computer generated random number) to receive impregnated bed nets (ITNs), while the other acted as the control village." **Smithuis et al 2013a**, Pg. 4

- "The data were aggregated for each village to obtain cluster-level infection rates. In total 8,175 children under 10 years of age were followed up for 10 months, which included the main malaria transmission period." **Smithuis et al 2013a**, Abstract

44.

"Results: In aggregate, malaria infections, spleen rates, haemoglobin concentrations, and weight for height, did not differ significantly during the study period between villages with and without ITNs, with a weighted mean difference of −2.6 P. falciparum episodes per 1,000 weeks at risk (95% Confidence Interval −7 to 1.8). In areas with a higher incidence of malaria there was some evidence ITN protective efficacy. The economic analysis indicated that, despite the uncertainty and variability in their protective efficacy in the different study sites, ITN could still be cost-effective, but not if they displaced funding for early diagnosis and effective treatment which is substantially more cost-effective.
Conclusion: In Western Myanmar deployment of ITNs did not provide consistent protection against malaria in children living in malaria endemic villages. Early diagnosis and effective treatment is a more cost effective malaria control strategy than deployment of ITNs in this area where the main vector bites early in the evening, often before people are protected by an ITN." **Smithuis et al 2013a**, Abstract

45.

"There is no doubt concerning the consistent and large benefits provided by ITNs in Africa which fully justifies current deployment initiatives. In contrast, the epidemiology of malaria in Asia is extremely heterogeneous. Transmission is highly seasonal and unstable and intensities vary greatly over short distances, and also show great variation from year to year. It is not surprising that ITNs are relatively ineffective in areas of unstable malaria where the principal malaria vectors bite outdoors early in the evening, before people go in or near their ITN." **Smithuis et al 2013a**, Pg. 12

46.

- "Five cluster randomized controlled trials examined child mortality from all causes (Appendix 3). They were all conducted in areas with stable malaria in sub-Saharan Africa: (Burkina Faso (Habluetzel); Gambia (D'Alessandro); Ghana (Binka); Kenya (Nevill); Kenya (Phillips-Howard))." **Lengeler 2004a**, Pg. 8
- "There is no doubt concerning the consistent and large benefits provided by ITNs in Africa which fully justifies current deployment initiatives. In contrast, the epidemiology of malaria in Asia is extremely heterogeneous. Transmission is highly seasonal and unstable and intensities vary greatly over short distances, and also show great variation from year to year. It is not surprising that ITNs are relatively ineffective in areas of unstable malaria where the principal malaria vectors bite outdoors early in the evening, before people go in or near their ITN." **Smithuis et al 2013a**, Pg. 12

47.

Bleakley 2010.

48.

- "The federal government's large-scale efforts against malaria in the south began with World War I (WWI). In previous wars, a significant portion of the troops were made unfit for service because of disease contracted in or around encampments. The PHS, working now with a strong knowledge base on malaria control and greatly increased funding, undertook drainage and larviciding operations in southern military camps, as well as in surrounding areas. After WWI, the IHB and PHS expanded the demonstration work further. By the mid-1920s, the boards of health of each state, following the IHB/PHS model, had taken up the mantle of the malaria control in all but the most peripheral areas of the region (Williams 1951). The south experienced a drop in malaria mortality of more than 60 percent in the decade of the 1920s." **Bleakley 2010**, Pgs 5-6.
- "In the early 1950s, the World Health Organization (WHO) proposed a worldwide campaign to eradicate malaria. While the WHO mostly provided technical assistance and moral suasion, substantial funding came from USAID and UNICEF. The nations of Latin America took up this task in the 1950s. While individual nations had formal control of the design and implementation of the programs, their activities were comparatively homogeneous as per the dictates of their international funders. The central component of these programs was the spraying of DDT, principally in the walls of houses. Its purpose was not to kill every mosquito in the land, but rather to interrupt the transmission of malaria for long enough that the existing stock of parasites would die out. After that, the campaigns would go into a maintenance phase in which imported cases of malaria were to be managed medically.

The Latin American countries analyzed in the present study (Mexico, Colombia, and Brazil) all mounted malaria eradication campaigns, and all saw large declines in malaria prevalence. Panel A of Figure 1 shows malaria cases per capita in Colombia. (Comparable time-series data were not available for the US, Brazil, or Mexico. Nevertheless, there is little doubt that malaria declined in all four countries immediately following these campaigns.) A decline of approximately 80 percent is seen in the graph. Throughout Latin America, the campaign ultimately proved inadequate to the task, and, in many areas, malaria partially resurged two decades later. But in almost all parts of the hemisphere, malaria never returned to its levels from before the application of DDT." **Bleakley 2010**, Pg 6

49.

"How realistic is the assumption that areas with high infection rates benefited more from the eradication campaign? Mortality and morbidity data indicate drops of 50 to 80 percent in the decade after the advent of the eradication efforts. Such a dramatic drop in the region's average infection rate, barring a drastic reversal in the pattern of malaria incidence across the region, would have had the hypothesized effect of reducing infection rates more in highly infected areas than in areas with moderate infection rates. Data on malaria cases by Colombian departments allow us to examine this directly. The decline in malaria incidence as a function of intensity prior to the eradication campaign is found in panel B of Figure 1. The basic assumption of the present study, that areas where malaria was highly endemic saw a greater drop in infection than areas with low infection rates, is borne out. (Similar results are seen for US and Mexican states. Data for Brazilian states were not available.)

Finally, the timing of the eradication campaign should induce variation in childhood malaria infection that has a marked pattern across year-of-birth cohorts. The present study considers the effects of childhood malaria infection on later-life outcomes, so it is useful to characterize childhood exposure to an eradication campaign. This is shown in Figure 2. Consider a campaign that starts in year zero and takes effect instantaneously. Cohorts born after this date will be exposed to the campaign for their entire childhood. On the other hand, those cohorts who were already adults in year zero will have no childhood exposure to the campaign, while the "in-between" cohorts will be partially exposed during childhood, as shown in Figure 2. I exploit this timing in two ways. First, in Section III, I compare the "born after" cohorts to the "already adult" cohorts by taking differences across these cohort groups. Second, in Section IV, I use the functional form of childhood exposure in estimation using data for all cohorts. (I discuss some alternative functional forms in Section IV.B.)

These four factors (the external origin of the campaigns, the quick reduction of malaria that followed, the use of nonmalarious areas for comparison, and the differential incidence of eradication benefits across cohorts) combine to form the research design of the present study." **Bleakley 2010**, Pgs 8-9.

50.

See **Bleakley 2010**, Figure 4, Pg 26.

51.

See **Bleakley 2010**, Appendix III, Pg 40, for the full list of controls by country.

52.

"Mixed results are found for years of education, in contrast with consistently positive effects of malaria eradication on income and literacy. Furthermore, in no country can the change in income be accounted for by the change in years of schooling. These facts are in no way discordant with the economic theory of schooling, which compares returns with opportunity costs. Childhood health plausibly raises both, leaving an ambiguous effect on the optimal time to spend in school. This combination of results, interpreted with simple price-theoretic reasoning regarding the education decision, show that we should be cautious in using changes in time in school as a sufficient statistic by which development and health policies are evaluated." **Bleakley 2010**, Pg 35.

53.

- "Even though this paper is to our knowledge the first one using experimental data to evaluate the productivity effects of malaria, several studies have analyzed agricultural output in the context of nutrition and other diseases." **Fink and Masiye 2015**, Pg. 152

- "This cluster randomized trial evaluates the economic impact of a private sector malaria control program. In collaboration with 81,597 smallholder contract farmers in 1,507 clusters, I investigate whether the distribution of free insecticide-treated mosquito nets at the outset of malaria season increased cotton output sufficiently to be commercially viable for the implementing agribusiness." **Sedlmayr 2014**, Abstract

54.

- **Fink and Masiye 2015** randomly assigned groups of farmers in Zambia to a group that received subsidized ITNs, a group that received ITNs for free or a control group.
  - Sample: "The sampling frame for the study was provided by Dunavant Zambia. Dunavant has nine regional offices, which distribute farming inputs and acquire cotton through local sheds and distributors. Each distributor handles between 10 and 50 farmers in his community. At the time the study was launched, Dunavant was working with 96 distributors in the study area. In order to reduce the risk of local spillovers, we restricted the sample to distributors operating in spatially separated areas, with a minimum distance of 3 km between any two locations. This left us with a final sample of 49 distributors and their respective villages. On average, each of the 49 distributors was working with about 20 farmers, a listing of which was provided to the study by Dunavant. We randomly selected 11 farmers from each distributor, and visited them for a baseline interview in December 2009. Only the 11 farmers selected for the study were allowed to receive the free or subsidized nets; with an average village size of about 50 households, this means that the program covered about 20% of the average village population. Out of 539 farmers invited to participate in the study, 516 farmers (95.7%) were enrolled in the study, and completed the baseline interview in December 2009." **Fink and Masiye 2015**, Pg. 154
  - Randomization: "In order to accelerate the distribution of bed nets, bed net loan programs were randomized prior to the collection of baseline data at the distributor level. Randomization was done using a simple random number draw generated by Stata. Out of the 49 eligible distributors, 15 were assigned to the control group (30%), and 15 distributors (30%) were selected for the free net program. Since we were particularly interested in the loan group and wanted to assess differences in uptake with and without subsidy, a slightly larger number of distributors (20% of distributors in each loan program) were randomized into the net loan programs. The spatial distribution of treatment assignment is illustrated in Fig. 3. All farms in the net program arms were informed about the programs at the end of the baseline interview, and given 48 h to decide on the number of nets they wanted to receive. Ordered nets were delivered within 10 days of the baseline survey, between December 20 and December 31, 2009." **Fink and Masiye 2015**, Pg. 155
  - Loan program subsidized nets: "As part of the experiment, farmers were randomly selected for bed net programs, which allowed them to obtain long-lasting insecticide treated nets (LLITNs) through agricultural loan program schemes at differentially subsidized prices." **Fink and Masiye 2015**, Pg. 151
- The study found that free ITNs increased the average annual harvest value by $76 (about 12% of the group's average annual harvest value at baseline).
  - Presumably, the 14.7% corresponds to the increase in harvest value as a proportion of the average annual harvest value in the group receiving free ITNs at endline, but we're not sure. "The point estimates from our preferred specification suggest that the returns to bed nets in the study sample were large: on average, we find that access to free bed nets (three nets for a typical household) increased agricultural output by US$ 76, which corresponds to 14.7% of the average annual harvest value." **Fink and Masiye 2015**, Pg. 152
  - Table 1, "Total harvest value 2009 (US$)", "Free nets": 613.8. 76/613.8 = ~12%.
  - Harvest value: "To measure total farm production, detailed harvest information was obtained from all crops, and then converted into monetary values using the median 2009 market prices reported among farmers who sold the respective crops. In theory, one may wish to use farm-specific crop prices to account for differences in market access or production quality; in practice, this is unfortunately not feasible since a large number of farms do not sell specific crops at all, but rather use it for their own consumption.(8)" **Fink and Masiye 2015**, Pg. 157
  - Statistically significant ($p < 0.05$): Table 3, "Panel C: Differences in outcomes with full set of covariates", "Free nets", "Total harvest value", **Fink and Masiye 2015**, Pg. 159

- We calculate a 95% confidence interval of 1% to 28% for this increase.
  - Table 3, “Free nets”, “Panel C: Differences in outcomes with full set of covariates”: 75.60 (35.85).
  - Lower bound of the 95% CI: 75.6-1.96*35.85 = 5.33
  - Upper bound of the 95% CI: 75.6+1.96*35.85 = 145.87
  - Average annual harvest value = (75.6/0.147) = 514.28
  - 5.33/514.28 = ~1%
  - 145.87/514.28 = ~28%
- The study did not find a statistically significant increase in total harvest value for the loan group (45.82, SE: 42.83, Table 3, Panel C, **Fink and Masiye 2015**, Pg. 159)

55.

- “In order to facilitate a rapid distribution of bed nets, treatments were randomly assigned at the cluster level prior to the collection of baseline data in the experiment. The non-stratified cluster-level randomization resulted in a rather unbalanced sample, with treated farmers on average both larger and more productive than farmers in the control group. To address these imbalances, we focus on analyzing changes in production outcomes between the 2009 (pre- intervention) and the 2010 (post-intervention) farming seasons.” **Fink and Masiye 2015**, Pg. 152
- Total harvest value 2009 (US$). Free nets (N = 155): 613.8 (SD: 476). Loans (N = 185): 649.0 (SD: 589.1). Control (N = 153): 453.2 (SD: 304). Table 1, **Fink and Masiye 2015**, Pg. 155

56.

- “While a large number of meta-reviews in the medical literature suggest that results from imbalanced trials controlling for baseline characteristics do on average not yield different results from fully balanced trials (Berger, 2010; Knottnerus and Tugwell, 2012; Riley et al., 2013), there is clearly a concern that observable differences may be correlated with other unobservable characteristics such as malaria knowledge or farming skills. To deal with these concerns, we follow the approach proposed by Glennerster and Takavarasha (2013) as well as by Bennett et al. (2014) and estimate both models where we control for lagged dependent variables and models where we use differences in outcome measures between the 2009 (pre-intervention) and 2010 (intervention) seasons as the dependent variable. These models exclusively identify changes in the outcome measures over time, and thus directly eliminate confounding or omitted variable bias concerns due to time-invariant farm-specific differences prior to the intervention. The resulting estimates will yield unbiased program impact assessments as long as the random treatment assignment is not correlated with changes in unobservable characteristics between baseline and endline conditional on initial values, which seems reasonable given the relatively short time period analyzed.” **Fink and Masiye 2015**, Pg. 156
- Their preferred analysis regresses the change in harvest value from baseline to endline on an indicator for assignment to treatment and several covariates, including, for example, plot size at baseline, household wealth, and education.
  - “The point estimates from our preferred specification suggest that the returns to bed nets in the study sample were large: on average, we find that access to free bed nets (three nets for a typical household) increased agricultural output by US$ 76, which corresponds to 14.7% of the average annual harvest value.” **Fink and Masiye 2015**, Pg. 152
  - Table 3, “Panel C: Differences in outcomes with full set of covariates”, “Total harvest value”, “Free nets”: 75.6, **Fink and Masiye 2015**, Pg. 159
  - “Specifications in Panel C control for lagged dependent variables as well as for plot sizes used for cotton, maize and other crops in 2009, family members under 5, family members 5–14, family members 60 and older, household wealth, mosquito nets at baseline, ownership of chickens, goats and sheep, farmer age, education and marital status.” **Fink and Masiye 2015**, Pg. 159
  - See Equations 2, 3, and 4. “…Tj is a vector of indicator variables capturing the distributor-level treatment assignment…” **Fink and Masiye 2015**, Pg. 157
  - It is not clear if the preferred regression includes harvest value at baseline as a covariate. The note in Table 3 states “Specifications in Panel C control for lagged dependent variables” (**Fink and Masiye 2015**, Pg. 159), which suggests that it does, but Equation 4 (**Fink and Masiye 2015**, Pg. 157) suggests that it doesn’t.

- They also regress harvest value at endline on an indicator for assignment to treatment and harvest value at baseline and run their preferred regression on subsamples (a) excluding the least productive farmers, (b) excluding the most productive farmers and (c) excluding the least and most productive farmers.
  - "Specifications in Panel B control for lagged dependent variables only." **Fink and Masiye 2015**, Pg. 159
  - See Equation 3. "…Tj is a vector of indicator variables capturing the distributor-level treatment assignment…" **Fink and Masiye 2015**, Pg. 157
  - "In order to make sure these results are not driven by individual farmers or clusters, we run a series of robustness checks in Table 4, based on the fully adjusted specifications shown in Panel C of Table 3. In column 1 of Table 4, we exclude households with heads who did not receive any schooling. In column 2, we restrict our analysis to farms with a medium degree of crop diversification (3–5 crops) to ensure that the year-over-year changes are not affected by differential exposure to price and crop risk. In order to deal more directly with pre-existing differences in productivity, we exclude the 20% least productive farmers in the baseline season from the regressions in column 3; in column (4) we exclude the most productive farmers in 2009, and last, in column 5, we exclude both the least and the most productive farmers from the analysis." **Fink and Masiye 2015**, Pg. 160
- These analyses all find that free ITNs increase harvest value compared to the control group.
  - Panels B, C. Table 3, "Total harvest value", "Free nets", **Fink and Masiye 2015**, Pg. 159
  - "Excluding bottom 2009 productivity quintile", "Excluding top 2009 productivity quintile", "Excluding clusters in top or bottom quintile in 2009", Table 4, "Free nets", **Fink and Masiye 2015**, Pg. 161
- Still, we believe that it is difficult to adjust for the potential confounding suggested by baseline imbalance in the outcome of interest and we don't find these regression analyses particularly convincing.

57.

"This cluster randomized trial evaluates the economic impact of a private sector malaria control program. In collaboration with 81,597 smallholder contract farmers in 1,507 clusters, I investigate whether the distribution of free insecticide-treated mosquito nets at the outset of malaria season increased cotton output sufficiently to be commercially viable for the implementing agribusiness. But despite large health effects in farming households, I do not detect any impact on deliveries to the agribusiness. I conclude that the independent and sustained distribution of free mosquito nets by Zambia's cotton industry is unlikely to materialize without subsidies. The results can be partially reconciled with previous research on the labor decisions of smallholder farmers, and tend to side with the minority of the observational literature that questions the role of malaria as a central and immediate cause of poverty." **Sedlmayr 2014**, Abstract

58.

"From 1995 onwards, coinciding with the results from the main African ITN trials, a vigorous debate arose about the possibility that the short-term mortality improvements observed in trials of 1–2 years' duration could be offset by increased mortality at older ages — a "delayed mortality" effect (4, 5). The underlying hypothesis was that immunity to malaria would develop more slowly under reduced transmission, leading to a longer period of susceptibility. No direct evidence was available at the time either to support or to refute this hypothesis." **Lengeler 2004b**

59.

Kilian, Wijayanandana, and Ssekitoleeko 2010.

60.

- " A 17% efficacy in preventing all-cause mortality in children aged 6–59 months was previously reported from a cluster-randomized controlled trial of insecticide-treated mosquito nets (ITNs) carried out in the Kassena-Nankana District of northern Ghana from July 1993–June 1995. A follow-up until the end of 2000 found no indication in any age group of increased mortality in the ITN group after the end of the randomized intervention. These results should further encourage the use of ITNs as a malaria control tool in areas of high endemicity of Plasmodium falciparum." **Binka et al. 2002**. This appears to be a followup on Binka et al. 1996 (cited in our **GiveWell. Summary of ITN RCTs**)
- "OBJECTIVES: To determine the impact of insecticide-treated curtains (ITC) on all-cause child mortality (6-59 months) over a period of six years. To determine whether initial reductions in child mortality following the implementation of ITC are sustained over the longer term or whether 'delayed' mortality occurs … A rural population of ca 100 000 living in an area with high, seasonal Plasmodium falciparum transmission was studied in Burkina Faso. Annual censuses were conducted

from 1993 to 2000 to measure child mortality. ITC to cover doors, windows, and eaves were provided to half the population in 1994 with the remainder receiving ITC in 1996. Curtains were re-treated or, if necessary, replaced annually. FINDINGS: Over six years of implementation of ITC, no evidence of the shift in child mortality from younger to older children was observed. Estimates of the reduction in child mortality associated with ITC ranged from 19% to 24%." **Diallo et al. 2004**, abstract. This appears to be a followup on Habluetzel et al. 1997 (cited in our **GiveWell. Summary of ITN RCTs**).

- "A total of 130,000 residents of 221 villages in Asembo and Gem were randomized to receive insecticide-treated bednets at the start of phase 1 (111 villages) or phase 2 (110 villages) ... Mortality rates did not differ during 2002 (after up to 6 years of bednet use) between children from former intervention and former control households born during phase 1 (HR, 1.01; 95% CI, 0.86-1.19)." **Lindblade et al. 2004**, abstract. This appear to be a follow-up on Phillips-Howard et al. 2003 (cited in our **GiveWell. Summary of ITN RCTs**

61.

"Between 2000 and 2002, a birth cohort was enrolled in 41 villages of a malaria holoendemic area in north-western Burkina Faso. All neonates (n = 3387) were individually randomised to ITN protection from birth (group A) vs. ITN protection from age 6 months (group B). Primary outcome was all-cause mortality." **Louis et al 2012**, Pg. 733

62.

- "The main findings from our large and representative study conducted in a malaria holoendemic area of rural SSA thus clearly show that ITN use in early infancy is not a risk factor of public health importance for excess mortality. However, it has to be considered that this study has only tested the specific hypothesis related to reduced exposure in early infancy. Thus, other aspects of immunological rebound associated with decreasing transmission intensity may still play a role in endemic areas where ITNs are used for malaria prevention." **Louis et al 2012**, Pg. 738
- "After a median follow-up time of 8.3 years, 443/3387 (13.1%) children had migrated out of the area and 484/2944 (16.4%) had died, mostly at home. Long-term compliance with ITN protection was good. There were no differences in mortality between study groups (248 deaths in group A, 236 deaths in group B; rate ratio 1.05, 95% CI: 0.889–1.237, P = 0.574)." **Louis et al 2012**, Pg. 733

63.

- We chose **Binka et al. 2002**, because it seemed like the most straightforward of the follow-ups to investigate.
- **Binka et al. 2002** reported “no indication in any age group of increased mortality in the ITN group after the end of the randomized intervention.” (Abstract)
- The authors seem to have reached this conclusion based on judging the mortality rate differences in the follow-up period as minimal.
  - “There was no indication in any group that the benefits of reducing malaria exposure for the 2- year period of the trial were lost during the subsequent follow-up period. In particular, in the age group 6-11 months of age at baseline, the cohort analysis found a significant protective efficacy during the 2-year period of the trial (confidence interval not overlapping with 0, see Table) but there was minimal difference between the control and ITN groups in mortality in this age group during the subsequent [5.5] years of follow-up (Table).” **Binka et al. 2002**, Pg. 597
- However, the mortality rate differences in the follow-up period do not strike us as small enough to demonstrate that mortality did not increase at older ages. Instead, the study seems to provide weak evidence of an increase in mortality at older ages.
  - For children less than 2 years old at the start of the trial (the cohort in which mortality declined in the trial period), we calculate a difference in deaths per 1,000 people of -16.4 (95% CI: -28.4 to -4.6) over the trial period and 5.4 (95% CI: -4.6 to 15.3) over the follow-up period (these calculations probably underestimate the width of the confidence intervals, because we did not account for clustering). See **Calculations for Binka et al 2002 (Google spreadsheet)**.
- It still seems possible that this increase did not offset earlier reductions in mortality by much, but we could not calculate a confidence interval for this offset from the information provided in the paper, so we do not know if the study had sufficient

statistical power to reject the hypothesis with high confidence that delayed mortality offset earlier reductions in mortality by some non-negligible amount.

64.

- "WHO-RBM publication following an experts meeting on 'Specifications for netting materials' addresses the issue of flammability in these terms as early as 2001. A chapter specifically entitled “Fire safety” explains: “Several specifications and test methods exist. Flammability is not the sole concern since toxic gases are also produced when burning [...]. No fire retardant is normally added to polyester. Polyester is Class 1 in the American test; to raise the specification to Class 3 would require the use of retardant and this would double the price of the net. No member of the committee had heard so far of an accident involving burning polyester nets. It was recommended that an investigation into whether fire safety properties are stable over time should be undertaken' [25]." **Ergot et al 2014**, Pg. 4
- "Of the 91 interviewees, 35 did not mention bed nets catching on fire or responded to a specific question, stating they had never heard about bed nets catching on fire. Of the remaining 56 persons, 22 stated that bed nets can catch on fire but limited their comments to generalities without referring to specific facts. By contrast, 34 people illustrated their point by referring to events they heard about or experienced, with some providing several supporting accounts (up to four in the same interview). Eleven of these accounts involved a vague memory of a fact heard in their communities or on the radio. However, 39 accounts reported by 30 persons were geographically located and situated in time, with details describing the circumstances surrounding the onset of the accident and/ or its consequences. These accounts indicated 27 situations where people were burned by their bed nets, for which 12 people died. Eight of the interviewees personally knew a victim of fires attributed to bed nets catching fire." **Ergot et al 2014**, Pg. 2

65.

"Methods: This anthropological study is based on an inductive qualitative approach, including 91 semi-structured interviews conducted from July 2011 to March 2012 in a health district in Southern Benin.
Results: Fifty-six persons stated that bed nets can catch on fire but do not always refer to specific facts. However, 34 of the 56 people narrate specific events they heard or experienced. 39 accounts were geographically located and situated in time, with various details. In 27 situations, people were burned, for which 12 people reportedly died.
Discussion: The disparity between these results and the dearth of bibliographic documentation in the initial search prompted a more in-depth literature review: 16 contributions between 1994 and 2013 were found. Bed net fires were noted in 10 countries, but it is impossible to ascertain the frequency of such events. Moreover, bodily harm can be significant, and several cases of death attributed to bed net fires were noted." **Ergot et al 2014**, Abstract

66.

"The disparity between these results and the dearth of bibliographic documentation in the initial search prompted a more in-depth literature review: 16 contributions between 1994 and 2013 were found. Bed net fires were noted in 10 countries, but it is impossible to ascertain the frequency of such events. Moreover, bodily harm can be significant, and several cases of death attributed to bed net fires were noted." **Ergot et al 2014**, Abstract

67.

"Bodily harm can be significant, and several cases of death attributed to bed net fires were noted. Therefore, it is important to do everything possible to limit the harm suffered by individuals and their families." **Ergot et al 2014**, Pg. 5

68.

"It is impossible to ascertain the frequency of such events based on current knowledge. Only the evaluation in Uganda [17] and the trial in Thailand [18] estimated frequency: 2.5% and 1.2%, respectively. But the Thai study is old and dealt with cotton bed nets, while the Spencer study investigates Permanet® bed nets but used in a specific context: a refugee camp." **Ergot et al 2014**, Pg. 5

69.

"Data were collected from burns unit admission records at Mulago National Referral Hospital in Kampala, Uganda for the years 2008–2011 inclusive. Retrospective analyses on the characteristics of patients admitted with bed net related burns within this period were conducted." **Kalanzi et al 2014**, Abstract

70. "Methods: Data were collected from burns unit admission records at Mulago National Referral Hospital in Kampala, Uganda for the years 2008–2011 inclusive. Retrospective analyses on the characteristics of patients admitted with bed net related burns within this period were conducted.
Results: A total of 45 patients were admitted to the burns unit with bed net related burns during the study period. Most burns occurred among individuals who were 0–1 years old (33.3%) and 26–35 years old (24.2%) and the majority were male (71%). Bed net related burns at Mulago Hospital are severe, as evidenced by the fact that 15 of 45 patients died (crude mortality rate = 33%) and that 26 patients (57.8%) had total body surface area burn percentages that were greater than 20%. The average length of stay in hospital for patients with bed net related burns was 30.4 days." **Kalanzi et al 2014**, Abstract

71. "An approximate extrapolation to the current population of children under five years of age at risk for malaria in sub-Saharan Africa (14% of approximately 480 million population at risk, or 67 million children) indicates that approximately 370,000 child deaths could be avoided if every child could be protected by an ITN." **Lengeler 2004a**, Pg 10.

72. "The Roll Back Malaria Partnership, the United Nations Millennium Development Goals, and the US President's Malaria Initiative have set a target of at least 80% use of ITNs by young children and pregnant women (the people most vulnerable to malaria) by 2010." **Killeen et al. 2007**, Pg 1258. Note that this paper was "received December 22, 2006."

73.
- "This Position Statement from the WHO Global Malaria Programme (WHO/GMP) describes a shift in guidance on malaria prevention through the use of insecticide- treated nets (ITNs).

  > The WHO/GMP calls upon national malaria control programmes and their partners involved in insecticide-treated net interventions to purchase only long-lasting insecticidal nets (LLINs). LLINs are designed to maintain their biological efficacy against vector mosquitoes for at least three years in the field under recommended conditions of use, obviating the need for regular insecticide treatment.
  >
  > In order for their full potential to be realized, LLINs should be deployed as a vector control intervention. WHO/GMP, therefore, recommends full coverage of all people at risk of malaria in areas targeted for malaria prevention with LLINs." **World Health Organization. Insecticide-treated mosquito nets: A WHO position statement (2007)** Pg 1.

- "GMP now recommends universal coverage with Long Lasting Insecticidal Mosquito Nets. Wherever any of the earlier documents refers to targeted coverage of risk groups only, please refer to superseding guidance on this matter now provided in the 2007 GMP position statement *Insecticide-treated mosquito nets: a position statement* [the source quoted directly above]." **World Health Organization. Publications on insecticide-treated materials: Guidelines**

74. " Long-lasting insecticidal nets (LLINs) have played an important role in the remarkable success in reducing malaria burden over the past decade. They are a core prevention tool, and widely used by people at risk of malaria.
WHO recommends that:
1. Universal coverage remains the goal for all people at risk of malaria.
2. In order to maintain universal coverage, countries should apply a combination of mass free distributions and continuous distributions through multiple channels, in particular antenatal and immunisation services." **World Health Organization. Malaria Control**

75. There is a distinction between individual-level effects (protection of the person sleeping under the net, due to blockage of mosquitoes) and community-level effects (protection of everyone in communities where ITN coverage is high, due to

reduction in the number of infected mosquitoes, caused either by mosquitoes' being killed by insecticide or by mosquitoes' becoming exhausted when they have trouble finding a host).

76.

Examples:

- The World Health Organization position statement discussed immediately previously cites this review as its main source: "On the basis of five community-randomized trials, a Cochrane review concluded that, when full coverage is achieved, ITNs reduce all-cause child mortality by an average 18% (range 14–29%) in sub- Saharan Africa (5). The general implication of this is that 5.5 lives could be saved per year for every 1000 children under 5 years of age protected. It was also concluded that ITNs reduce clinical episodes of malaria caused by Plasmodium falciparum and *P. vivax* infections by 50% on average (range 39– 62%), as well as reducing the prevalence of high-density parasitaemia." World Health Organization. Insecticide-treated mosquito nets: A WHO position statement (2007) Pg 3.
- The **Disease Control Priorities Report** also cites this review as its main source for ITN efficacy: "We drew estimates of the effectiveness of ITNS from a recent meta-analysis of WHO/TDR-sponsored trials conducted in Sub-Saharan Africa [**Lengeler 2004a**]." **Jamison et al. 2006**, Pg 423.

77.

Christian Lengeler, author of Cochrane Review of insecticide-treated bed nets, phone conversation with GiveWell, November 2, 2011

78.

- **Dave Smith, University of Florida Associate Professor of Zoology, phone conversation with GiveWell, November 4, 2011**.
- **Thomas Smith, Swiss Tropical Institute Head of the Biostatistics and Computational Sciences Unit, phone conversation with GiveWell, November 8, 2011**

79.

GiveWell. Summary of ITN RCTs

80.

- "When you're moving from protecting only children to protecting everybody, you multiply your costs by a factor of five, but you also get at least twice as much effect and we know that from both modeling and empirical impact assessments … I don't think we will ever really have the reply to that question [about the relative magnitude of community-level effects]. Though one thing you can do is mathematical modeling. There are different groups in the world who are doing modeling for the effect of increasing coverage of ITNs, and they will be able to give you some sort of answer … The two people who occur to me are Thomas Smith at the Swiss Tropical Institute and Dave Smith at the University of Florida's Emerging Pathogens Institute." **Christian Lengeler, author of Cochrane Review of insecticide-treated bed nets, phone conversation with GiveWell, November 2, 2011**
- "There are empirical studies that show that there seems to be a community-level impact of ITNs. There are theoretical studies that show that there ought to be a community-level effect. What I don't think there is is any attempt to estimate the magnitude of the community-level effect from empirical data. We've done this with mathematical models, but haven't completed the linkage with empirical data that could help with this estimate." **Thomas Smith, Swiss Tropical Institute Head of the Biostatistics and Computational Sciences Unit, phone conversation with GiveWell, November 8, 2011**.
- "The argument for ITNs has always been that ITN coverage is a public good. Some of the good accomplished is not internalized to the person using the net. Some people argue that there's a negative externality as well - unprotected people are getting bitten by the mosquitoes that would have bitten the protected people - but I don't think you can make that argument with ITNs … What I do is analysis of data using mathematical models. In general, the leading models say that the more people use the nets, the bigger the positive externalities are … If you're talking about the marginal dollar for more nets,

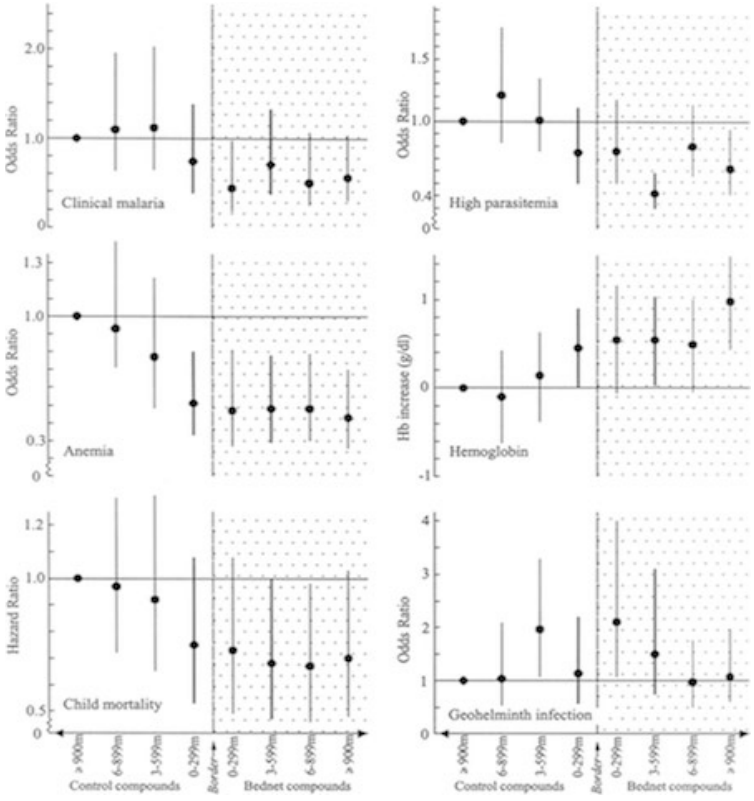
there's a lot more uncertainty on the cost-effectiveness of that than we'd like. The only data that we have is bad data. Improved surveillance would be helpful." **Dave Smith, University of Florida Associate Professor of Zoology, phone conversation with GiveWell, November 4, 2011**

81.

"In late 1996, the villages in Asembo were randomized into ITN (intervention) and control villages ... for two years, 1997 and 1998, people in half of the villages (intervention villages) in Asembo had access to properly treated bed nets and half (control villages) did not. Periodic spot checks during this period showed that few (<3%) nets were sold or moved outside the study area, although adherence to net use, measured as the proportion of study participants directly seen to be sleeping under nets during early morning observational surveys, was usually approximately 70% ... Although the study area is divided into villages with approximate boundaries as shown in Figure 1A, these are social constructs that do not reflect variation in population density ... The 300-meter interval for the main exposure variables was based upon the observation that this distance range divides the number of compounds of each type into approximately equal quartiles (Table 1). All distance calculations were done on the basis of intent to treat; all compounds in ITN villages were assumed to have ITNs and all compounds in control villages were assumed to lack ITNs." **Hawley et al. 2003**, Pg 121.

82.

"... Compounds in control villages that are ≥900 meters from the nearest ITN village served as the comparison group for these analyses. A total of seven dichotomous variables were created that contained all other compounds. For control villages, we created three variables for compounds that were 0–299, 300–599, or 600–899 meters from the nearest ITN compound. For ITN villages, we created four variables for compounds 0–299, 300–599, 600–899, and ≥900 meters from the nearest control compound. The intent of this analysis was to allow us to illustrate spatial patterns of effect in a straightforward way; however, the cost of this approach was some loss in statistical power. These distance categories approximate compound distribution by quartiles as shown in Table 1 ... The effect of the primary geographic exposure variable, distance to nearest compound of different type, is illustrated in Figure 2, which shows the effect of each of seven different exposure categories on five malaria-related outcomes, as well as geohelminth infection. For geohelminth infection, no effect of ITN use or distance is apparent. In contrast, a protective effect of living in ITN villages (stippled area of Figure 2) is apparent at all distance categories for all-cause mortality of children 1–59 months of age and for high-density parasitemia, anemia, and hemoglobin level ... The overall pattern of effects is similar for all five malaria-related outcomes: protective effects are observed within the ITN compounds, with a similar level of protection seen in control compounds located within 300 meters of intervention compounds; these effects are statistically significant for the morbidity measures most sensitive to changes in transmission levels: anemia and hemoglobin level ... Results of tests of trend reflect the patterns visible in Figure 2 for clinical malaria (odds ratio [OR] = 0.92, 95% confidence interval [CI] = 0.75, 1.12, P = 0.38), high-density parasitemia (OR = 0.89, 95% CI = 0.78, 1.01, P = 0.08), moderate anemia (OR = 0.78, 95% CI = 0.69, 0.89, P = 0.0001), hemoglobin level regression coefficient (OR = 0.18, 95% CI = 0.06, 0.31, P = 0.0048), and child mortality (hazard ratio = 0.94, 95% CI = 0.90, 0.98, P = 0.002). For all of these malaria-related outcomes, trends are in the direction indicating greater protection in compounds closer to intervention villages, with strongly significant trends seen for mortality, anemia, and hemoglobin level. For geohelminth infection, no trend was observed (OR = 1.09, P = 0.47)."



Hawley et al. 2003, Pgs 123-125.

83.

"This community effect on nearby compounds without nets is approximately as strong as the effect observed within villages with ITNs." **Hawley et al. 2003**, Pg 121.

84.

"studies from various parts of Africa and Papua New Guinea indicate the presence of a beneficial community effect (we propose use of this term rather than the less descriptive mass effect) on malaria transmission [references 1-6], severe malaria [reference 7] and mortality [reference 8] in children. One study, in contrast, yielded no evidence for either beneficial or harmful community-wide effects. [reference 9]" **Hawley et al. 2003**, Pg 121.

We looked up reference 9 and confirmed that it discusses only transmission: "In The Gambia, the use of permethrin-treated bed nets has led to a reduction in morbidity and mortality from malaria in children. However, no clear evidence has been found for a 'mass-killing effect' on the mosquito vectors as a result of this intervention. Two further entomological studies to investigate this phenomenon have been carried out. In one study, 20 villages were paired so that bed nets in one member of each pair were treated with permethrin. In the other, a cross-over design was used in which treated and untreated bed nets were exchanged between 2 villages. Longevity, biting rate and resting density of the malaria vector population and sporozoite rates were assessed in both studies. Malaria vectors were equally abundant and long-lived, and as likely to be infective, in villages with treated bed nets as in those with untreated nets. However, a clear reduction in the density of the indoor-resting population of mosquitoes in rooms with treated bed nets was found, probably reflecting the excito-repellency of the insecticide. This study confirmed that, in The Gambia, the protection against death and morbidity from malaria seen in children using treated bed nets must be due primarily to personal protection rather than to a 'mass-killing effect' on the mosquito vector population at a village level." Quinones et al. 1998, abstract.

85.

Gamble, Ekwaru, and ter Kuile 2006, Pg 14.

86.
"An important paper that had some influence in the political debate about mass distribution (as opposed to distribution to infants and pregnant women only) was: **Killeen et al. 2007**." **Thomas Smith, Swiss Tropical Institute Head of the Biostatistics and Computational Sciences Unit, email to GiveWell, November 8 2011**.

87.
Killeen et al. 2007, Pg 1246. The paper includes a spreadsheet with the full specification of its model.

88.
See **Smith et al. 2009**, Table 1, Pg 514. Note that the higher the existing level of ITN coverage (column headings), the lower the additional amount of ITN coverage needed (figure in the cell minus figure in the column heading) to reach the specified target. For example, at a PfPR of 50% and a goal of reducing it to 1% (10th row, 4th-6th columns), one would need to go from 0% to 71% effective coverage (71% absolute change), or from 10% to 77% coverage (67% effective change), or from 20% to 81% effective coverage (61% effective change).

89.
"Holden Karnofsky: Do you know of any papers or scholars arguing the opposite, that community-level effects are negligible and/or that universal coverage has little value-added above and beyond covering pregnant women and children under five?

Thomas Smith: I don't." **Thomas Smith, Swiss Tropical Institute Head of the Biostatistics and Computational Sciences Unit, phone conversation with GiveWell, November 8, 2011**.

90.
"This is very consistent with the results based on net sales; they suggest that demand for ITNs is 75 percent lower at the current cost-sharing price in Kenya (50Ksh or $0.75) than it would be under a free distribution scheme." **Cohen and Dupas 2007**, Pg 11. See also Figure 1, Pg 11.

91.
Cohen and Dupas 2007, Pg 15, Figure 2.

92.
"When a school-based NGO deworming program in western Kenya introduced cost sharing, the take-up of deworming medication fell sharply and revenue failed to outpace administrative costs, despite the health and education benefits of the program. User fees did not help target treatment to the sickest children. As deworming pills are delivered directly into children's mouths, there was no gap between take-up and usage, so pricing had no potential psychological impact on use through sunk costs." **Kremer and Holla 2009, "Pricing and Access: Lessons from Randomized Evaluations in Education and Heath" in What Works in Development?: Thinking Big and Thinking Small, ed. by Jessica Cohen, William Easterly**, Pg 95.

93.
"Two-stage pricing randomization has also been used to test the two potential routes by which pricing could affect use in a door-to-door marketing campaign for water disinfectant on the outskirts of Lusaka, Zambia. As with deworming and nets, pricing led to a rapid drop-off in take-up, with no evidence of increased targeting to the most vulnerable. Pricing had no statistically significant psychological effect on use. The authors of the study argue that there was some screening effect since those who were more willing to pay for the disinfectant were more likely to have chlorine in their water at later random checks than those who received it for free." **Kremer and Holla 2009, "Pricing and Access: Lessons from Randomized Evaluations in Education and Heath" in What Works in Development?: Thinking Big and Thinking Small, ed. by Jessica Cohen, William Easterly**, Pg 99.

94.
"In 1993 a cost-recovery programme was introduced and villages given free insecticide during the first year of the study were asked to pay 5.00 Dalasi (US$0.50) per bednet treated. Unfortunately this led to a dramatic drop in coverage and a return of child mortality rates in these villages to their pre-intervention values." **D'Alessandro et al. 1995**, Pg 483.

95.
"In January 2002 the UK Department for International Development (DFID) awarded PSI-Kenya US$33 million over 5 y to socially market partially subsidised ITN within the existing retail sector... A two-tier pricing system of 350 Kenya Shillings (KES) (equivalent to US$4.7) in urban settings versus KES100 (US$1.3) in rural settings was implemented." **Noor et al. 2007**, Pg 1342.

96.
Noor et al. 2007, Pg 1344, Table 1.

97.
"The programme began in October 2004, and during the first 6 mo Supanet ITNs were bundled with separate Powertab net treatment tablets (for every 6 mo) and distributed to MCH attendees. In May 2005 an additional US$37 million was committed by DFID to PSI to procure and distribute Supanet-branded long-lasting insecticidal nets (LLINs), Olyset and Permanet. These public sector nets were heavily subsidized pretreated nets (KES50; US$0.7) and branded with the MoH logo." **Noor et al. 2007**, Pg 1342.

98.
"During round four of the GFATM awards in April 2004, Kenya's application was successful and US$17 million was approved to procure and distribute 3.4 million LLINs (Olyset and Permanet brands) free of charge to children under the age of 5 y. This represented, at the time, the largest successful award for free distribution of LLINs in Africa." **Noor et al. 2007**, Pg 1342.

99.
Noor et al. 2007, Pg 1344, Table 1.

100.
See **our cost-effectiveness models page** for the most up-to-date version of our cost-effectiveness analysis of LLIN distribution

101. Note that this figure is based on people who could be covered by the ITNs distributed, not on people who are confirmed to be using ITNs (i.e., the review discussed **above** implies that .00553 lives are saved for every child under five who *could be covered by a distributed ITN*, not that .00553 lives are saved for every child under five who is *confirmed to be using an ITN*).

- "The summary rate difference, which expresses how many lives can be saved for every 1000 children protected, was 5.53 deaths averted per 1000 children protected per year (95% CI 3.39 to7.67; Analysis 1.2)." **Lengeler 2004a**, Pg 8. We have confirmed with the author that this figure is based on an "intention to treat" analysis, e.g., "protected" refers to children in the treatment group, not to children who were confirmed to own or use ITNs.

Our use of this figure entails a couple of implicit simplifications:

- We do not model variations in the transmission setting (prevalence and behavior of mosquitoes, presence of cattle, etc.). Note that the review we are using states that its ".00553 lives saved per child protected" figure does not appear sensitive to one measure of transmission dynamics.
  - “The summary rate difference, which expresses how many lives can be saved for every 1000 children protected, was 5.53 deaths averted per 1000 children protected per year (95% CI 3.39 to 7.67; Analysis 1.2). I performed a regression analysis of the natural logarithm of the rate difference on the entomological inoculation rate and could not find a trend (r 2 = 0.52, F = 3.2 on 1,3 degrees of freedom, P = 0.2). In contrast to protective efficacies, the risk differences seemed to have a tendency towards a higher effect with a higher entomological inoculation rate. This apparent paradox is because the baseline mortality rates are higher in areas with high entomological inoculation rates." **Lengeler 2004a**, Pg 8.
- Our use of this figure also implies that each person-year of protection provides an equivalent protective effect - e.g., going from 80% to 81% coverage has the same effect as going from 0% to 1% coverage. The information we have (discussion **above**) suggests that ITNs are actually more effective at *higher* levels of coverage (because part of their effect is on community-level transmission of malaria); this in turn implies that distributing ITNs in an area where coverage is already reasonably high should be *more* cost-effective than distributing ITNs in an area of low prior coverage, as in the **small-scale studies**. However, we are not confident in this dynamic and do not model it.

102.
See penultimate section of **our 2012 blog post on the subject** for more on the motivation behind this adjustment.

103.

- The deaths averted by ITNs may be the same deaths that could be averted by, for example, vitamin A supplementation (as noted **above**, many of the deaths averted by ITNs are not specifically attributable to malaria). So perhaps other improvements in general health are independently averting all the deaths that ITNs could avert in their absence; under this model it's possible that ITNs don't avert any deaths at all.
- On the flipside, there may be increasing returns to improved general health: perhaps there are children who previously (at the time of the studies) would have been in such poor health that they would have died even with ITNs, but now can have their deaths averted by ITNs.

104.
We assume that this decay model accounts for a substantial amount of the extent to which LLINs are lost, not delivered, or discarded. We provide a less optimistic estimate where LLINs are assumed to last 1 year on average (note that the **evidence** on ITN effectiveness is generally limited to a time frame of one year); we provide a more optimistic estimate where LLINs are assumed to last 3 years on average (this could be warranted if **Against Malaria Foundation** distributions result in fewer lost/undelivered/discarded LLINs).

105.

- We searched Google Scholar for all recent articles that cite Lengeler 2004a and assessed the relevance of these articles for our review.
- We searched Google Scholar for all recent articles that cite the key randomized controlled trials in Lengeler 2004a and assessed the relevance of these articles for our review.
- We did a general search for recent RCTs and reviews related to bed nets and mortality on Google Scholar. Search terms included "malaria bed nets," "malaria mortality," "bed nets mortality," "malaria randomized controlled," "bed nets randomized controlled," etc.

106.
We updated this section to include analysis from the 2012 World Malaria Report and searched Google Scholar for recent evidence on bed net usage. Recent net usage evidence did not lead to any significant changes in our report, but it raised the question of whether studies that directly observe bed net usage might find significantly less usage than studies that rely on usage surveys.

107.

- For our process on updating the insecticide resistance page, see the **process section of the insecticide resistance page**.
- The delayed immunity page was assessed as up-to-date in September 2013.

108.

- We updated our cost-effectiveness analysis to account for (a) concerns about insecticide resistance and (b) changes in our estimate of net costs due to falling global net prices and changes in our estimate of non-net distribution costs.
- We further emphasized the uncertainty involved in doing cost-effectiveness analysis.

109.
We conducted research on this topic and spoke with two net gap experts (see **Notes from a conversation with Marcy Erskine, 9/18/2013** and **Notes from a conversation with Melanie Renshaw, 10/17/2013**) to bring our estimate of the bed net funding gap up to date.

110.

- We searched Google Scholar for studies published since 2014 containing "insecticide resistance" and "review". We scanned the first 5 pages of results and identified 3 high-level reviews related to insecticide resistance: **Mnzava et al 2015**, **Strode et al 2014** and **Quiñones et al 2015**. None of these studies seemed to find potential negative effects of insecticide resistance on human outcomes.
    - "In recent years, there has been an increase in resistance of malaria vectors to insecticides, particularly to pyrethroids which are widely used in insecticide-treated nets. The Global Plan for Insecticide Resistance Management in malaria vectors (GPIRM), released in May 2012, is a collective strategy for the malaria community to tackle this challenge. This review outlines progress made to date and the challenges experienced in the implementation of GPIRM, and outlines focus areas requiring urgent attention. Whilst there has been some advancement, uptake of GPIRM at the national level has generally been poor for various reasons, including limited availability of vector control tools with new mechanisms

of action as well as critical financial, human and infrastructural resource deficiencies. There is an urgent need for a global response plan to address these deficits and ensure the correct and efficient use of available tools in order to maintain the effectiveness of current vector control efforts whilst novel vector control tools are under development. Emphasis must be placed on enhancing national capacities (such as human and infrastructural resources) to enable efficient monitoring and management of insecticide resistance, and to support availability and accessibility of appropriate new vector control products. Lack of action by the global community to address the threat of insecticide resistance is unacceptable and deprives affected communities of their basic right of universal access to effective malaria prevention. Aligning efforts and assigning the needed resources will ensure the optimal implementation of GPIRM with the ultimate goal of maintaining effective malaria vector control." **Mnzava et al 2015**, Abstract

- "Background: Pyrethroid insecticide-treated bed nets (ITNs) help contribute to reducing malaria deaths in Africa, but their efficacy is threatened by insecticide resistance in some malaria mosquito vectors. We therefore assessed the evidence that resistance is attenuating the effect of ITNs on entomological outcomes.
Methods and Findings: We included laboratory and field studies of African malaria vectors that measured resistance at the time of the study and used World Health Organization–recommended impregnation regimens. We reported mosquito mortality, blood feeding, induced exophily (premature exit of mosquitoes from the hut), deterrence, time to 50% or 95% knock-down, and percentage knock-down at 60 min. Publications were searched from 1 January 1980 to 31 December 2013 using MEDLINE, Cochrane Central Register of Controlled Trials, Science Citation Index Expanded, Social Sciences Citation Index, African Index Medicus, and CAB Abstracts. We stratified studies into three levels of insecticide resistance, and ITNs were compared with untreated bed nets (UTNs) using the risk difference (RD). Heterogeneity was explored visually and statistically. Included were 36 laboratory and 24 field studies, reported in 25 records. Studies tested and reported resistance inconsistently. Based on the meta-analytic results, the difference in mosquito mortality risk for ITNs compared to UTNs was lower in higher resistance categories. However, mortality risk was significantly higher for ITNs compared to UTNs regardless of resistance. For cone tests: low resistance, risk difference (RD) 0.86 (95% CI 0.72 to 1.01); moderate resistance, RD 0.71 (95% CI 0.53 to 0.88); high resistance, RD 0.56 (95% CI 0.17 to 0.95). For tunnel tests: low resistance, RD 0.74 (95% CI 0.61 to 0.87); moderate resistance, RD 0.50 (95% CI 0.40 to 0.60); high resistance, RD 0.39 (95% CI 0.24 to 0.54). For hut studies: low resistance, RD 0.56 (95% CI 0.43 to 0.68); moderate resistance, RD 0.39 (95% CI 0.16 to 0.61); high resistance, RD 0.35 (95% CI 0.27 to 0.43). However, with the exception of the moderate resistance category for tunnel tests, there was extremely high heterogeneity across studies in each resistance category (chi-squared test, p,0.00001, I2 varied from 95% to 100%).
Conclusions: This meta-analysis found that ITNs are more effective than UTNs regardless of resistance. There appears to be a relationship between resistance and the RD for mosquito mortality in laboratory and field studies. However, the substantive heterogeneity in the studies' results and design may mask the true relationship between resistance and the RD, and the results need to be interpreted with caution. Our analysis suggests the potential for cumulative meta-analysis in entomological trials, but further field research in this area will require specialists in the field to work together to improve the quality of trials, and to standardise designs, assessment, and reporting of both resistance and entomological outcomes." **Strode et al 2014**, Abstract
- "Scale-up of the main vector control interventions, residual insecticides sprayed on walls or structures and/or impregnated in bed nets, together with prompt diagnosis and effective treatment, have led to a global reduction in malaria transmission. However, resistance in vectors to almost all classes of insecticides, particularly to the synthetic pyrethroids, is posing a challenge to the recent trend of declining malaria. Ten International Centers of Excellence for Malaria Research (ICEMR) located in the most malaria-endemic regions of the world are currently addressing insecticide resistance in the main vector populations, which not only threaten hope for elimination in malariaendemic countries but also may lead to reversal where notable reductions in malaria have been documented. This communication illustrates the current status of insecticide resistance with a focus on the countries where activities are ongoing for 9 out of the 10 ICEMRs. Most of the primary malaria vectors in the ICEMR countries exhibit insecticide resistance, albeit of varying magnitude, and spanning all mechanisms of resistance. New alternatives to the insecticides currently available are still to be fully developed for deployment. Integrated vector management principles need to be

better understood and encouraged, and viable insecticide resistance management strategies need to be developed and implemented." **Quiñones et al 2015**, Abstract

- We also searched the Malaria Journal for studies published since 2014 with titles that contained "resistant" or "resistance." We scanned the titles of the studies appearing in the search results and identified two studies as warranting further investigation because they evaluated human outcomes: **Tokponnon et al 2014** and **Lindblade et al 2015**. Neither study found negative effects of insecticide resistance on human outcomes.
  - "Background: The widespread use of insecticide-treated nets (LLINs) leads to the development of vector resistance to insecticide. This resistance can reduce the effectiveness of LLIN-based interventions and perhaps reverse progress in reducing malaria morbidity. To prevent such difficulty, it is important to know the real impact of resistance in the effectiveness of mosquito nets. Therefore, an assessment of LLIN efficacy was conducted in malaria prevention among children in high and low resistance areas.
    Methods: The study was conducted in four rural districts and included 32 villages categorized as low or high resistance areas in Plateau Department, south-western Benin. Larvae collection was conducted to measure vector susceptibility to deltamethrin and knockdown resistance (kdr) frequency. In each resistance area, around 500 children were selected to measure the prevalence of malaria infection as well as the prevalence of anaemia associated with the use of LLINs.
    Results: Observed mortalities of Anopheles gambiae s.s population exposed to deltamethrin ranged from 19 to 96%. Knockdown resistance frequency was between 38 and 84%. The prevalence of malaria infection in children under five years was 22.4% (19.9-25.1). This prevalence was 17.3% (14.2-20.9) in areas of high resistance and 27.1% (23.5-31.1) in areas of low resistance (p = 0.04). Eight on ten children that were aged six - 30 months against seven on ten of those aged 31–59 months were anaemic. The anaemia observed in the six to 30-month old children was significantly higher than in the 31–59 month old children (p = 0.00) but no difference associated with resistance areas was observed (p = 0.35). The net use rate was 71%. The risk of having malaria was significantly reduced
    (p Conclusion: The results of this study showed that the resistance of malaria vectors seems to date not have affected the impact of LLINs and the use of LLINs was highly associated with reduced malaria prevalence irrespective of resistance." **Tokponnon et al 2014**, Abstract
  - "Background: Insecticide-treated bed nets (ITNs) are the cornerstone of malaria control in sub-Saharan Africa but their effectiveness may be compromised by the spread of pyrethroid resistance among malaria vectors. The objective of this investigation was to assess the effectiveness of ITNs to prevent malaria in an area of Malawi with moderate pyrethroid resistance.
    Methods: One deltamethrin ITN was distributed in the study area for every two individuals in each household plus one extra ITN for households with an odd number of residents. A fixed cohort of 1,199 children aged six to 59 months was seen monthly for one year and at sick visits to measure malaria infection and use of ITNs. Insecticide resistance among malaria vectors was measured. The effect of ITN use on malaria incidence was assessed, adjusting for potential confounders using generalized estimating equations accounting for repeated measures.
    Results: There were 1,909 infections with Plasmodium falciparum over 905 person-years at risk (PYAR), resulting in an observed incidence of 2.1 infections per person-year (iPPY). ITNs were used during 97% of the PYAR. The main vector was Anopheles funestus: mortality in WHO tube assays after exposure to 0.05% deltamethrin was 38% (95% confidence interval (CI) 29–47), and resistance was due to elevated oxidase enzymes. After adjusting for potential confounders, the incidence of malaria infection among ITN users was 1.7 iPPY (95% CI 1.5-2.1) and among non-bed net users was 2.6 iPPY (95% CI 2.0-3.3). Use of ITNs reduced the incidence of malaria infection by 30% (rate ratio 0.7; 95% CI, 0.5-0.8) compared to no bed nets.
    Conclusion: ITNs significantly reduced the incidence of malaria infection in children in an area with moderate levels of pyrethroid resistance and considerable malaria transmission. This is the first study to show that ITNs provide protection in areas where pyrethroid-resistant An. funestus is the major malaria vector. Malaria control programmes should continue to distribute and promote ITNs in areas with low to moderate pyrethroid resistance; however, insecticide resistance may intensify further and it is not known whether ITNs will remain effective at higher levels of resistance.

There is an urgent need to identify or develop new insecticides and technologies to limit the vulnerability of ITNs to insecticide resistance." **Lindblade et al 2015**, Abstract

- We looked at abstracts and presentations from a symposium entitled "Quantifying the Impacts of Insecticide Resistance on Malaria Control" at the 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene held in November of 2014. We did not see any evidence of negative effects of insecticide resistance on human outcomes. These abstracts and presentations are not yet publicly available.
- The summaries of the evidence on insecticide resistance that we have seen seem to suggest that there is not yet direct evidence of negative effects of insecticide resistance on human outcomes.
  - "To date, resistance has been directly implicated in operational control failure of pyrethroids only in An. funestus in South Africa [57]." **Strode et al 2014**, Pg. 28
  - "57. Hargreaves K, Koekemoer LL, Brooke BD, Hunt RH, Mthembu J, et al. (2000) Anopheles funestus resistant to pyrethroid insecticides in South Africa. Med Vet Entomol 14: 181–189." **Strode et al 2014**, Pg. 31
  - "We carried out a systematic review of all relevant studies on human outcomes, but it became clear very quickly that there was an almost total absence of evidence to draw any conclusions on the impact of pyrethroid resistance on the efficacy of nets in decreasing disease transmission." **Strode et al 2014**, Pgs. 2-3
  - "While there has been some limited evidence linking the operational failure of pyrethroid-based IRS to resistant vectors [14-16], there are as yet no epidemiologic data demonstrating that pyrethroid resistance reduces the effectiveness of ITNs to prevent malaria infection. Several studies of ITN efficacy or effectiveness conducted in pyrethroid-resistant areas have shown continued ability of ITNs to protect against malaria transmission when properly deployed [17-19]." **Lindblade et al 2015**, Pg. 2
  - "ITNs significantly reduced the incidence of malaria infection in children in an area with moderate levels of pyrethroid resistance and considerable malaria transmission. This is the first study to show that ITNs provide protection in areas where pyrethroid-resistant An. funestus is the major malaria vector. Malaria control programmes should continue to distribute and promote ITNs in areas with low to moderate pyrethroid resistance; however, insecticide resistance may intensify further and it is not known whether ITNs will remain effective at higher levels of resistance. There is an urgent need to identify or develop new insecticides and technologies to limit the vulnerability of ITNs to insecticide resistance." **Lindblade et al 2015**, Abstract
  - "The widespread use of insecticide-treated nets (LLINs) leads to the development of vector resistance to insecticide. This resistance can reduce the effectiveness of LLIN-based interventions and perhaps reverse progress in reducing malaria morbidity. To prevent such difficulty, it is important to know the real impact of resistance in the effectiveness of mosquito nets. Therefore, an assessment of LLIN efficacy was conducted in malaria prevention among children in high and low resistance areas…The results of this study showed that the resistance of malaria vectors seems to date not have affected the impact of LLINs and the use of LLINs was highly associated with reduced malaria prevalence irrespective of resistance." **Tokponnon et al 2014**, Abstract
  - We briefly looked at the studies cited in these quotes from **Mnzava et al 2015**: "However, the effectiveness of these core malaria interventions is threatened by increases in the distribution and strength (intensity) of insecticide resistance in these mosquitoes [2-4]" (**Mnzava et al 2015**, Pg. 1) and "There is emerging evidence that insecticide resistance is already compromising the effectiveness of malaria control efforts [3,9,10]" (**Mnzava et al 2015**, Pg. 2). Most of the studies seem to be examining entomological outcomes (i.e., not human outcomes).
  - We read the abstract, the introduction and the discussion of **Quiñones et al 2015** and these sections did not discuss evidence related to human outcomes for compromised efficacy for ITNs or ITN control failures where insecticide resistance was implicated.
- We also found the protocol for a multi-country study "to quantify the potential loss of epidemiological effectiveness of ITNs and IRS due to decreased susceptibility of malaria vectors to insecticides." The results of this study are not yet available.
  - "Background: Progress in reducing the malaria disease burden through the substantial scale up of insecticide-based vector control in recent years could be reversed by the widespread emergence of insecticide resistance. The impact of

insecticide resistance on the protective effectiveness of insecticide-treated nets (ITN) and indoor residual spraying (IRS) is not known. A multi-country study was undertaken in Sudan, Kenya, India, Cameroon and Benin to quantify the potential loss of epidemiological effectiveness of ITNs and IRS due to decreased susceptibility of malaria vectors to insecticides. The design of the study is described in this paper. Methods: Malaria disease incidence rates by active case detection in cohorts of children, and indicators of insecticide resistance in local vectors were monitored in each of approximately 300 separate locations (clusters) with high coverage of malaria vector control over multiple malaria seasons. Phenotypic and genotypic resistance was assessed annually. In two countries, Sudan and India, clusters were randomly assigned to receive universal coverage of ITNs only, or universal coverage of ITNs combined with high coverage of IRS. Association between malaria incidence and insecticide resistance, and protective effectiveness of vector control methods and insecticide resistance were esti- mated, respectively. Results: Cohorts have been set up in all five countries, and phenotypic resistance data have been collected in all clusters. In Sudan, Kenya, Cameroon and Benin data collection is due to be completed in 2015. In India data collection will be completed in 2016. Discussion: The paper discusses challenges faced in the design and execution of the study, the analysis plan, the strengths and weaknesses, and the possible alternatives to the chosen study design." **Kleinschmidt et al 2015**, Abstract

111.

- In late October, we searched Google Scholar for studies (a) published since 2013, (b) citing **Lengeler 2004a** and (c) containing in their title one of “randomized”, ”randomised”, ”experimental”, ”experiment”, ”effect”, ”impact”, ”evidence”, or ”effectiveness”
- In late October, we searched Google Scholar for studies (a) published since 2013, (b) citing **Lengeler 2004a** and (c) containing in their title one of ”bed nets” (without quotes), “bed nets” (without quotes), “insecticide net” (without quotes), or “insecticide nets” (without quotes)
- In late October, we searched Google Scholar for studies (a) published since 2013, (b) containing in their title one of “insecticide+net” (without quotes), “insecticide+nets” (with quotes), “bed+net” (without quotes), “bed+nets” (without quotes) and (c) containing in their title one of “randomized”, ”randomised”, ”experimental”, ”experiment”, ”effect”, ”impact”, ”evidence”, or ”effectiveness”