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Historical global health R&D "hits"

Development, main sources of funding, and impact

Global Health and Development Department

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Editorial note

This report was produced by Rethink Priorities during December 2022 and January 2023. The project was commissioned and supported by Open Philanthropy, which does not necessarily endorse our conclusions.

The report focuses on the development story and impact of some global health R&D "hits" or "success stories" of the last two decades: injectable artesunate, rectal artesunate, Coartem Dispersible, long-lasting insecticidal nets, and dolutegravir. We did not classify these developments as hits ourselves, or compare them to any other treatments, but we were asked to look into them based on the expectation that they have saved or could save many lives, and could constitute some of the most successful treatments of the past couple of decades. We analyzed the steps that led to their development, with a particular focus on the roles different stakeholders played. Additionally, we estimated the number of deaths these products have averted to date and might avert in the future.

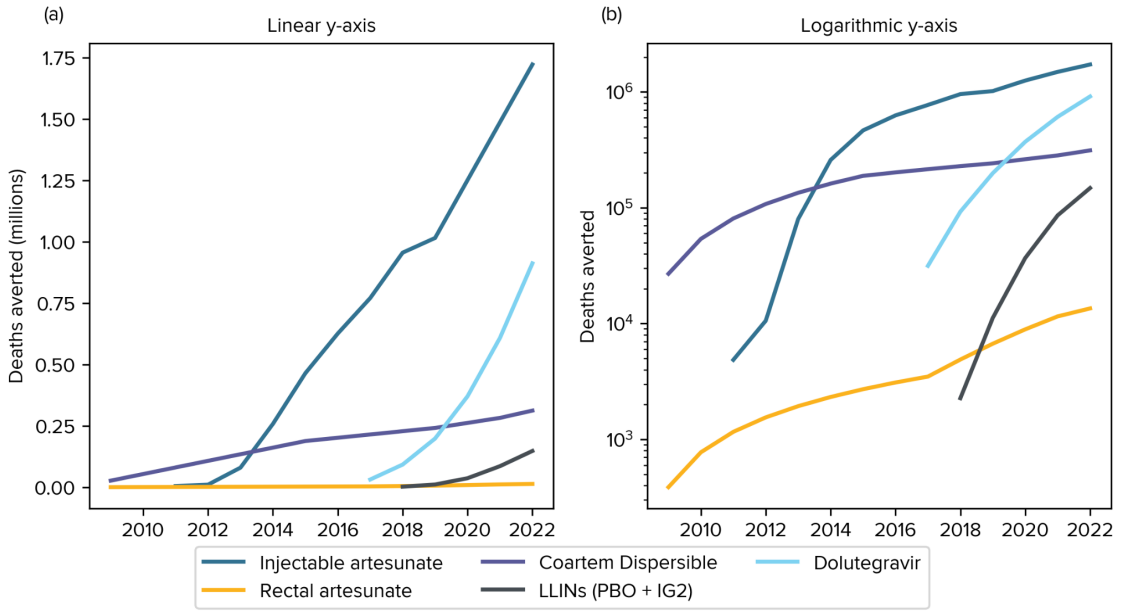
We have tried to flag major sources of uncertainty in the report and are open to revising our views as more information becomes available.

Executive summary

In this report, we attempted to reconstruct the development story behind five global health R&D hits of the last two decades, four types of antimalarial treatments and one antiretroviral used for HIV, and estimate the number of deaths each of them has averted to date and might avert in total. The latter ranges from a few tens of thousands (for rectal artesunate) to a few million (for injectable artesunate and dolutegravir).

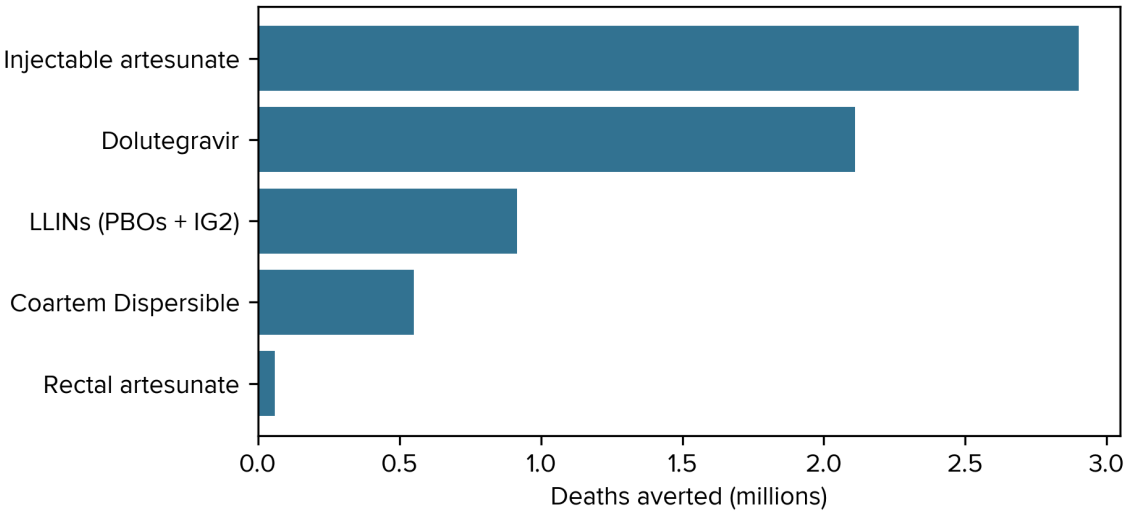
You can find below two plots (Figures 1 and 2) summarizing our models' estimates for the lives saved by each of these products since their introduction and until obsolescence (you can also find the plots and associated data here).

Figure 1: Cumulative number of deaths averted by each product since its introduction



Note. Panel (a) uses a linear y-axis to show deaths averted, while Panel (b) uses a logarithmic y-axis.

Figure 2: Total number of deaths averted by each product until obsolescence



In most of the examples studied, the drugs were developed through partnerships involving: (1) a pharmaceutical company that carried out the development of the product, (2) academics who ran the trials to show the product's effects and/or compare it to the standard of care, and (3) philanthropic and public actors that provided funding for various stages. Philanthropic funds were also used in some cases to support local manufacturers and help them get WHO approval. One notable exception is dolutegravir, for which the development seems to have been entirely funded by industry.

You can find here a table including the partners involved in the development of each of the products, and the cost and funders for different parts of the process where we were able to find the information. As noted above, philanthropic funds seem to have been pivotal to the development of all products except for dolutegravir. Even though the cost incurred by the pharmaceutical companies is unknown, and likely to be quite large, it seems as though these partnerships are quite frequent and necessary when developing products for diseases mainly affecting low and middle income countries.

For all cases in which philanthropic funding played a significant role, the funds needed seem to have been in the range of a few million dollars to the low tens of millions. It should be noted that the total funds these organizations invested toward R&D of products related to these diseases is likely much larger, including funds devoted to these particular drugs through unsuccessful initiatives we were not able to find, and funds devoted to the development of other drugs that were unsuccessful (or just less successful).

Injectable artesunate

Artesunate, given intravenously or by injection, is the recommended initial treatment for severe cases of malaria.

Artesunate was developed in the '70s with industry funds, and philanthropic funds supported the most important trials

Summary timeline

- **1977**: Artesunate developed at Guilin Pharmaceutical (Li et al., 2017)
- **1994-2001**: Small-scale study Newton et al. (2003) conducted, finding promising results and prompting the SEAQUAMAT trial
- **2003-2005**: Large, multicenter, open-label randomized SEAQUAMAT (2005) trial conducted, finding that treatment with injectable artesunate decreases mortality relative to treatment with quinine
- **2005-2010**: Large, multicenter, open-label randomized AQUAMAT (2010) trial conducted, confirming efficacy in children in Africa
- **November 2010**: WHO prequalification for injectable artesunate from Guilin Pharmaceutical (Injectable Artesunate Stakeholders' Meeting, 2011)
- **April 2011**: WHO recommends injectable artesunate as the first-line treatment for severe malaria (Injectable Artesunate Stakeholders' Meeting, 2011)

Artemisinin was isolated and named in the 1970s, and has since become a key antimalarial drug. Various artemisinin derivatives, including artemether, artesunate, dihydroartemisinin, and arteether, are also used as antimalarials. Artesunate, developed in 1977 at Guilin Pharmaceutical, is notable for being water-soluble, unlike earlier derivatives, which were

oil-soluble. Intravenous and intramuscular injections of artesunate, as well as oral formulations, were tested in malaria patients as early as 1978-1980 (Li et al., 2017, pp. 20-21).

Interest in artemisinin derivatives as first-line treatments for severe malaria, replacing quinine, goes back to at least 1987. In 1998, a Cochrane review included thirteen studies comparing parenteral[1] artemisinin derivatives to quinine in patients with severe falciparum malaria. This Cochrane review concluded that artemisinin derivatives seem to be "no worse" than quinine.[2] At the time, there was no particular interest in artesunate specifically; artemether seems to be the most commonly used artemisinin derivative in these studies, and the review finds no evidence that any of the artemisinin derivatives differ in effectiveness.

"No worse than quinine" was potentially still pretty good, because quinine can have severe side-effects; attempts to prevent those side-effects, such as slow administration and close monitoring, can be difficult or costly. Resistance to quinine may also have been a concern. So people continued to study artemisinin derivatives for severe malaria.

A 2001 meta-analysis (AQMSG, 2001) of artemether vs. quinine in patients with severe falciparum malaria seems to have solidified the view that artemether and quinine are approximately equally effective. E.g., a 2008 Cochrane review says, "Trials examining whether the artemisinin derivative artemether is more effective than quinine have not shown a reduction in mortality (AQMSG 2001)"; Newton et al. (2003) cite AQMSG 2001 as proving that "parenteral artemether was as effective as quinine in terms of mortality but superior in terms of the number of serious adverse events associated with its use." Meanwhile, within the world of artemisinin derivatives, there was reason to think that artesunate might be more effective than artemether: artemether can only be given intramuscularly, and its intramuscular absorption was observed to be "erratic and partial" (Cochrane Collaboration, 2008, citing sources from 1997, 1997, and 2003), while artesunate can be given intramuscularly, intravenously, or rectally, and is rapidly absorbed and converted to its active form (dihydroartemisinin) (Newton et al., 2003).

Since artesunate should be better than artemether, and artemether is as good as quinine, by transitivity artesunate should be better than quinine. This seems to be the logic of the pivotal study Newton et al. (2003), conducted between 1994 and 2001, which was explicitly "a prelude to consideration of a large, multicenter mortality trial." The study observed lower mortality with intravenous artesunate than with intravenous quinine, though the difference did not reach statistical significance.[3] This difference, alongside faster parasite clearance and fewer side effects with artesunate than with quinine, was considered promising, and did lead to a **large, multicenter, open-label randomized controlled trial**: SEAQUAMAT, conducted from 2003 to 2005 and published in 2005. **SEAQUAMAT found a 35% reduction in mortality attributable to**

[1] That is, not given orally.
[2] Overall, artemisinin derivatives were "associated with better survival (mortality odds ratio 0.61, 95% confidence interval 0.46 to 0.82)," but when restricted to the trials with "adequate" blinding, the difference was "barely statistically significant (odds ratio 0.72, 95% CI 0.54 to 0.96)" (McIntosh and Olliaro, 1998, pp. 1-2).
[3] "Mortality was 12% with artesunate and 22% with quinine treatment (relative risk, 0.53; 95% confidence interval, 0.23–1.26; P = .22)" (Newton et al., 2003, p. 7).

treatment with intravenous artesunate rather than intravenous quinine. The Newton et al. and SEAQUAMAT studies were both **funded by the Wellcome Trust**.[4]

The SEAQUAMAT results shifted the consensus in favor of artesunate, at least for the SEAQUAMAT study population, which was South Asian and mostly adult. For example, the 2008 Cochrane review concludes "Intravenous artesunate is the drug of choice for adults with severe malaria, particularly if acquired in Asia," and the WHO's 2010 guidelines for the treatment of malaria say "Intravenous (IV) artesunate should be used in preference to quinine for the treatment of severe P.falciparum malaria in adults. Strong recommendation, high quality evidence." Regarding treatment of severe malaria in children, the guidelines say, "For children (especially in the malaria endemic areas of Africa) the following antimalarial medicines are recommended as there is insufficient evidence to recommend any of these antimalarial medicines over another: artesunate IV or IM; quinine (IV infusion or divided IM injection); artemether IM (should only be used if none of the alternatives are available as its absorption may be erratic)." **Further studies, notably AQUAMAT in 2010, resulted in the recommendation of artesunate being expanded to all severe malaria patients. The AQUAMAT trial was also Wellcome-funded, with grants totalling ~£4.2 million**; see here for a breakdown by grant.

Around the same time that the Newton et al. trial was being conducted, researchers at the Walter Reed Army Institute of Research (WRAIR) were interested in developing an intravenous artemisinin treatment for severe malaria. This project is described in the 2001 annual report of Medicines for Malaria Venture (MMV), an organization that supports the development and delivery of antimalarial drugs (MMV, Annual Report 2001).[5] As mentioned above, it was known at the time that intramuscular absorption of oil-soluble artemisinin derivatives could be slow and unreliable. **WRAIR was interested in developing an IV treatment of either artesunate or artelinic acid**, another water-soluble artemisinin derivative. **MMV supported this project from 2002 through 2005, with grants totalling ~$1.9 million** (year-by-year numbers here). By 2002, the WRAIR team had concluded that "IV artesunate should be developed to international standards" (MMV, Annual Report 2002, p. 19). Sadly, no particular progress seems to have followed, and by 2005 the project is listed as "discontinued" due to "lack of a pharmaceutical partner and formulation difficulties" (MMV, Annual Report 2005, p.11).

From 2007 to 2009, **MMV supported a phase II trial of IV artesunate for severe malaria, in partnership with the European and Developing Countries Clinical Trials Partnership (EDCTP)**. MMV **granted a total of ~$900,000 to the project** (year-by-year numbers here); we have not been able to find out how much funding was contributed through EDCTP.[6] The resulting paper, published in 2012, compares a 3-dose regimen of IV artesunate to "the conventional 5-dose regimen," and concludes that the simpler 3-dose regimen is noninferior.

[4] We have only found records of Wellcome grants since 2000, so we have no records of grants to the Newton et al. trial, and have only identified one grant of ~£250,000 in support of the SEAQUAMAT trial, which we doubt was the full amount spent. See here for all the relevant Wellcome Trust grants we have identified.

[5] MMV was not formally involved as a grantor until the following year; see pp. 29-30.

[6] Fact of dubious relevance: the average clinical trial grant value during the relevant era of EDCTP was about €3.19 million (Technopolis Group, 2014, p. 31).

From the initial development of artesunate in 1977 until ~2018, Guilin Pharmaceutical was the main creator and supplier. Guilin improved its method of producing artesunate in 1983,[7] and constructed an artesunate production line in 1987 (Li et al., 2017, p. 21). Starting in 2009, **Guilin worked with MMV on a Good Manufacturing Practice assessment, with the aim of WHO prequalification**. **MMV provided a total of ~$120,000 to the project** (year-by-year numbers here); we have not been able to find out the cost to Guilin. In 2009, MMV described the motivation for the project as follows: "Intravenous artesunate is an important option for patients with severe malaria, as they are often unconscious or likely to vomit an orally administered medication" (MMV, Annual Report 2009, p. 27). This suggests that they were viewing IV artesunate as a substitute for oral artemisinin-based combination treatment (ACT) later in treatment, rather than as a substitute for initial treatment with quinine. By contrast, in their 2010 Annual Report, after announcing that Guilin had achieved WHO prequalification, they added "The approval has also been quite timely as it coincided with clinical study findings published in late 2010 demonstrating that IV artesunate is superior to quinine in reducing mortality due to severe malaria by an additional 22%" (p.6), citing the AQUAMAT trial.

Overall division of credit

Tentatively, we would identify the Wellcome Trust's funding of the Newton et al., SEAQUAMAT, and AQUAMAT trials as the most important R&D funding leading to injectable artesunate, because those trials constitute the evidence base for this specific use of artesunate, a drug that had existed and been used as an antimalarial for years without being broadly noticed as a great improvement over quinine as an initial parenteral treatment for severe malaria. **The initial private investment in developing artesunate, in the 1970s at Guilin Pharmaceutical, is also a crucial part of the story**. MMV and its funders deserve credit for the existence of a WHO-prequalified injectable artesunate.

We estimate that injectable artesunate has averted ~0.79 million-1.25 million deaths since its introduction

Summary

- Our topline estimate is that the introduction of **injectable artesunate likely averted between 785,716 and 1,246,897 deaths** since its mainstream introduction in 2011, compared to a counterfactual of receiving quinine (the standard of care before the introduction of injectable artesunate).
    - This is 1.7-1.9x of the number of deaths that MMV, which also compares its figures to quinine, estimates it averted (450,000 ~ 650,000).
- A **five-year speedup model** would mean between **798,310 and 1,266,884 deaths averted**.
- We came to a range of around **96~153 AS vials procured per death averted** compared to the quinine counterfactual.
    - Sense check compared to other methods:
        - Unitaid report: **135~194 vials procured per death averted**.
        - MMV estimates: **154~167 per death averted**.
- You can find our model here.

[7] "Because the stability of free-dried sodium artesunate powder for injection was poor, the SIPI attempted to overcome the substance's unstable hygroscopic property with a double-ampule preparation. An ampule containing a sodium bicarbonate solution would be injected into an ampule of artesunate microcrystals to dissolve them before use. In June 1983, Shi Guangxia from [Guilin Pharmaceutical] successfully produced artesunate microcrystals using a 'wet method.' This preparation method received the national invention patent in 1988" (Li et al., 2017, p. 21).

Method

- We took age stratification data for malaria deaths from Our World in Data (Roser and Ritchie, 2019).
- We took yearly procurement figures from this Unitaid report (Annex F, p. 58).
- We modeled a 54% reduction of medicines that have a therapeutic effect based on various causes of wastage, taken from this USAID health system e-handbook (Ch. 8, p. 3, Figure 1).[8] We used that as the upper estimate for medication wasted and we additionally modeled a 27% wastage as a lower bound (crudely halving the above figure), driven by our uncertainties around the USAID methodology (which we could not find), as well as the fact that these figures (for all drugs) likely would not be generalizable to malaria specifically.
- We computed the vials needed per patient using a best estimate of 1 vial / 25 kg body weight of the patient. We made various assumptions here, including:
    - Assuming patients who received injectable artesunate and patients who died from malaria look similar in terms of demographics.
    - Modeling all 70+ age group in the 50-75 kg group
    - Modeling 5-69 group as 15% at 25~50 kg, 60% at 50~75 kg, and 25% at 75+ kg
        - This was based on this population pyramid, which suggested ~13% is between the age of 5-14. We took this group to be within the 25~50 kg range. While many people above age 14 will still be <50 kg, we are also mindful that a portion of the 5-14 age group may be below 25 kg. Given the dominance of child deaths in the African region, we do not think differences in assumptions here will strongly change our topline figure.
        - Assuming the average adult weight in Africa is ~60 kg.
    - Modeling all patients under 5 as in the <25 kg group.
    - Assuming vials with unfinished medication are thrown away as per guidelines and standard practice in high income countries (HICs)
- This gives us an average vial per patient figure, which we then use to find a figure for patients reached given our procurement figures.
- We then estimate the absolute risk reduction compared to quinine based on Dondorp et al. (2010) and Sinclair et al. (2014), which is approximately 2.5%, and we use that to estimate the number of deaths averted counterfactually by injectable artesunate per year.
- To compute the total number of patients saved by injectable artesunate to date, we modeled 2011 as year 1, partly because pre 2010 procurement figures are a few orders of magnitude below 2011 onwards, and partly because WHO prequalification happened in November 2010.
- Lastly, we work out the average number of vials needed per death averted, which we can use to sense check our estimates against other methodology.

Sense check

A sense check using the Unitaid report (p. 36) of the "Improving Severe Malaria Outcomes" (ISMO) project gave an estimate of the impact.[9] That report gives us a **range of 135~194 vials procured per death averted** compared to if all those patients received quinine instead, which is comparable to our estimate of **96~153 vials per death averted**.

[8] Therapeutic benefit, lack of adherence by patients, irrational prescribing, expiration, improper storage, theft, poor quality, high prices. In this case we excluded "poor quality" and "high prices" as reasons for wastage that we thought would not be relevant in the case of injectable artesunate

[9] This sense check happened after completion of the BOTEC and did not affect the figures used in the BOTEC.

Taking two recent MMV news releases (MMV, 2017; MMV, 2017) at face value gives us a range of **154~167 vials per death averted**.

Key uncertainties

We think the USAID estimates around wastage and drugs that do not lead to therapeutic effect is a key uncertainty for our estimates. We also have not modeled resistance to injectable artesunate, quinine, or other antimalarials, nor the likelihood of success of other non-antimalarial interventions (e.g. the malaria vaccine). We found this resource to be a useful compilation of antimalarial resistance, though given time constraints we did not review this literature. We think the extent to which introduction of injectable artesunate slows down resistance to other antimalarials is likely to be the main driver of differences not captured in the model, but resistance is unlikely to change our results if we use a speedup model, e.g. if we assume that resistance will develop at a similar rate regardless of date of introduction.

We estimate that injectable artesunate might avert ~1.8 million-4 million deaths in total

Unfortunately, we were unable to devote much time to projections of future lives saved. We estimated future lives saved using a quick method:

- To obtain a lower bound, we assume that in five years, there will be resistance to this product or a better product on the market, such that injectable artesunate will only continue to avert deaths for the next five years. We obtain the number of deaths averted per year using the average of past deaths averted between years four and eight of the product's distribution,[10] and apply a 0.9x correction factor, considering further development in countries with high malaria rates.
- To obtain an upper bound, we assume that injectable artesunate will continue to avert deaths for the next 10 years. We obtain the number of deaths averted per year using the average of past deaths averted between years four and eight of the product's distribution.
- Given that we only had information on this product until 2019, we have included 2020 to date as projections as well, using the method described above.
- Using those assumptions, we obtain a **total number of deaths averted between ~1.8 million and ~4 million**.

If we had more time to estimate the future lives saved, we would consider a variety of factors for the calculation. Please refer to Appendix A for more information on this.

[10] During years one through three, distribution was ramping up, so we do not think we should include them. We believe that data from the last year (year nine) might be incomplete, so we averaged years four through eight.

Rectal artesunate

Rectal artesunate suppositories can be given to patients with severe malaria in settings where injectable or IV artesunate is not immediately available, to buy time for the patient to be transferred elsewhere for full treatment.

Rectal artesunate was initially developed by WHO-TDR and Mepha Pharma, and supported by additional philanthropic and public actors

Summary timeline

- **1985**: First study of rectal administration of an artemisinin derivative (de Carvalho et al., 2020)
- **1996**: WHO-TDR and Mepha Pharma develop rectal artesunate suppositories (de Carvalho et al., 2020)
- **1996-97**: WHO-TDR conducts clinical trials (de Carvalho et al., 2020)
- **2000-06**: Gomes et al. (2009) study conducted
- **2006**: WHO recommends pre-referral rectal artesunate (Unitaid, 2018)
- **2012**: MMV begins work on WHO-prequalified rectal artesunate (MMV, Annual Report 2012)
- **2015**: Strides Arcolab and Cipla submit rectal artesunate for WHO-PQ consideration (MMV, Annual Report 2015)
- **2018**: Rectal artesunate from Strides and Cipla WHO-prequalified (WHO, 2018; WHO, 2018)

See above for more information about the development of artesunate and the wider evidence base on its efficacy for severe malaria. In this section, we discuss the development of its rectal suppository form.

The WHO's Special Programme for Research and Training in Tropical Diseases (WHO-TDR) facilitates research on "infectious diseases of poverty," including malaria. Around 1993, WHO-TDR's malaria programs shifted their focus from supporting basic scientific research on malaria to supporting clinical and field trials in malaria-endemic countries (Gomes and Kuesel, 2015). As part of this new focus, they became interested in rectal artesunate as a possible pre-referral treatment for severe malaria; in 1996 they began working with a manufacturing partner, Mepha Pharma (now called Acino), on rectal artesunate suppositories, and in 1996-7 they conducted clinical trials (de Carvalho et al., 2020).

WHO-TDR supported a large, randomized, placebo-controlled trial of pre-referral rectal artesunate in Bangladesh, Ghana, and Tanzania, which was conducted between 2000 and 2006 and published as Gomes et al. (2009). This study is the best existing evidence about the effectiveness of pre-referral rectal artesunate; a Cochrane review that was last updated in 2019 considers only this study. Overall, it found a **nonsignificant effect on mortality, and a significant effect on mortality among patients who still hadn't reached a clinic by six hours after initial treatment with rectal artesunate**. Later interpretations of this paper's data have focused on breakdowns by patient age, and have found a **significant decrease in mortality among children under six**, but indications of increased mortality among older children and adults. Broadly speaking, scientists do not seem to seriously believe that rectal artesunate is actively harmful for older children and adults, but these findings have nonetheless led to rectal artesunate mostly being recommended for children under six (see for example the WHO's 2015 guidelines).

The only indication of WHO-TDR's spending on rectal artesunate that we have been able to find is in the 2000-01 budget, which requests $6.5 million to establish a special fund for rectal artesunate and "expedite registration and field trials [...] in six countries in Africa and south-east Asia." As of a 2002 update, no progress was reported under that special initiative, with the note "Insufficient Funding." **The 2002 update does report four clinical trials of rectal artesunate under the general TDR operations budget** (planned cost $8.6 million, across research on severe malaria, drug policies, ITNs, and four diseases other than malaria). When the Gomes et al. trials (in three countries) were published, they cited **funding from the Global Malaria Programme, the Sall Family Foundation, the European Union, the UK Medical Research Council, USAID, Irish Aid, the Karolinska Institute, and the University of Oxford Clinical Trial Service Unit, in addition to WHO-TDR**.

The WHO recommended pre-referral rectal artesunate for severe malaria as early as the first edition of "Guidelines for the treatment of malaria," published in 2006 (Unitaid, 2018). Between 2009 and 2014, about three million rectal artesunate suppositories were procured by African countries via UNICEF, PMI, GPRM, and MSF (Unitaid, 2018; see annex 1). During this time, there were two manufacturers of rectal artesunate suppositories: WHO-TDR's initial partner Mepha Pharma, later called Acino; and Bliss GVS Pharma. Neither product was SRA-approved or WHO-prequalified. In 2014, it became more difficult to purchase products without these approvals using donor money; furthermore, in 2015 Acino stopped producing rectal artesunate suppositories (de Carvalho et al., 2020; Unitaid, 2018). It therefore became important to find new, qualified manufacturers of rectal artesunate suppositories.

In 2012, MMV was interested in finding manufacturers for rectal artesunate and helping with the approval process. By 2015, MMV had partnered with two Indian pharmaceutical companies, Cipla and Strides Arcolab, and both companies had applied for WHO prequalification for their rectal artesunate suppositories. In 2016, Cipla's product received a temporary approval which allowed it to be purchased with donor funds; in 2017, Strides' product received the same; in 2018, both products became WHO-prequalified. MMV reports spending about $1 million on this process overall.

Overall division of credit

Despite its lower prominence more recently, **we would tentatively say the WHO-TDR deserves the most credit of the philanthropic/public organizations involved in the development of rectal artesunate, followed by MMV and its funders**. WHO-TDR did most of the initial work of identifying rectal artesunate as a promising pre-referral option, working with a manufacturer, funding clinical trials, and funding the beginning of a large trial measuring mortality, while MMV deserves credit for the existence of WHO-prequalified rectal artesunate, and thereby for the renewed use of rectal artesunate after 2014/15. **Private funding from pharmaceutical manufacturing partners, and other public funders such as those listed above who supported the Gomes et al. trial, also played a role**.

We estimate that rectal artesunate has averted ~13,000 deaths since its introduction

See our model here.

The estimate of lives saved to date relies on:

- Efficacy data from the Gomes et al. trials. We chose to use the mortality data from the Ghana and Tanzania trials, which are the most relevant to subsequent use because they took place in Africa and only included children.
- Procurement estimates for 2009-2018, short-term procurement forecasts for 2021 and 2022, and a linear interpolation for procurement in 2019 and 2020.
- Observed usage rates from CARAMAL, an observational study of the rollout of rectal artesunate in the DRC, Nigeria, and Uganda. Despite computing the usage rate somewhat optimistically (e.g. using the number of units distributed, rather than number of units procured[11]), **we found that only 9% of the rectal artesunate suppositories were ultimately used**. This does not necessarily seem implausible to us, considering the challenges of pre-referral treatment – the suppositories need to be kept in stock specifically in the most remote and least-supplied settings, and used only for initial presentation of cases of severe malaria, and they have a shelf life of only 4-6 months. Still, this usage rate may not be in line with other estimates. One cost-effectiveness study we are aware of assumes a wastage rate of 25%; in our model, assuming a usage rate of 75% would lead to estimates of about 100,000 lives saved to date and 480,000 lives saved in total.

We estimate that rectal artesunate might avert ~60,000 deaths in total

The estimate of lives saved in total relies on:

- Efficacy data from the Gomes et al. trials, as above.
- An assumption about the maximum or steady-state procurement of rectal artesunate. We have chosen a value in line with CHAI's projections through 2024; we do not anticipate a large expansion of rectal artesunate usage in the foreseeable future, since uptake was already slow and recently lost momentum due to negative results from the CARAMAL study; see here for the WHO's 2022 information note urging countries to pause the adoption and/or expansion of pre-referral rectal artesunate.
- An assumption about the number of years of benefit to attribute to rectal artesunate. Our model currently uses a value of 25 years. This is mostly arbitrary, but we did deliberately choose a relatively large value, due to rectal artesunate's status as essentially the only pre-referral treatment for severe malaria. Unlike some other drugs considered in this project, it is not a replacement for an earlier, less effective drug, and we do not have reason to expect it to soon be replaced in turn, so we are giving it many years of credit.

Coartem Dispersible

Coartem is an artemisinin-based combination therapy, or ACT; ACTs are the first-line treatment for uncomplicated malaria. Coartem Dispersible is a formulation of Coartem that was developed especially for children.

Coartem Dispersible was developed through a collaboration between Novartis and MMV

Summary timeline

- **1977**: Artesunate developed at Guilin Pharmaceutical (Li et al., 2017)

[11] At least some, but not all, of the procured-but-not-distributed units were distributed after the implementation period, so the number procured is an overestimate for our purposes, while the number distributed is an underestimate.

- **1972-1975**: Aretemether developed (Faurant, 2011)
- **1976**: Lumefantrine developed (Cui and Su, 2009)
- **1991**: First major randomized controlled trial (RCT) comparing artemether to quinine (Hien et al., 1996)
- **1992**: Coartem combination first comes into medical use, developed by Novartis (Faurant, 2011)
- **2004**: WHO prequalification for Coartem (WHO, 2023)
- **2006**: Artemether-lumefantrine recommended as a first line treatment for uncomplicated malaria (WHO, 2006)
- **2007**: Coartem Dispersible developed by Novartis in partnership with MMV (not all of R&D happened that year) (MMV, Annual Report 2007)
- **2009**: WHO prequalification for Coartem Dispersible (WHO, 2023)
- **2009-2021**: ~450 million treatments of Coartem Dispersible distributed (MMV, 2021)

Coartem is a combination of two medications: artemether and lumefantrine. Both were developed by the Chinese government under Project 523, initially to aid with the Vietnam War efforts (Cui and Su, 2009). After artemisinin was developed, its chemical instability was identified as an issue. The development of artemether was one attempt at rectifying this.

WHO-TDR and the United States focused on arteether instead of artemether. This was due to concerns around methanol toxicity that might arise from metabolic byproducts, and because arteether was more lipophilic and thus more suitable for injectable preparations (WHO, 1986, p. 19). However, given increasing malaria resistance in South East Asia (SEA) and lack of progress on arteether, Asian researchers decided to proceed with trials on artemether in SEA and Africa (White et al., 2015), including an **RCT comparing artemether to quinine in Vietnamese adults** (Hien et al., 1996), and a **smaller RCT comparing artemether to chloroquine in Gambian children** (White et al., 1992).

We could not find details around the motivation for the development of lumefantrine, nor details around how it was chosen to be used alongside artemether as a combination drug, though it was noted that a slower-acting drug would be helpful in eliminating any residual parasites that were not killed by artemether. Lumefantrine, a slower-acting drug with an elimination half-life of about four days, fits this bill; it helps eliminate residual parasites that artemether does not eradicate, while the rapid effect of artemether means that many fewer parasites are exposed to lumefantrine alone at the end of treatment (Djimdé and Lefèvre, 2009). By 1992, supported by studies conducted by China's Academy of Military Medical Sciences (AMMS), the artemether/lumefantrine combination had been licensed in China. Novartis, (then called Ciba) began collaborations with AMMS to help develop Coartem for use in other parts of the world (FDA, 2009, p. 8).

While efficacy of Coartem has consistently been around 95% against uncomplicated malaria caused by *Plasmodium falciparum* (Bassat et al., 2011; Assefa et al., 2010; Achan et al., 2009; Tun et al., 2018), quinine was a much more established drug. Combined with the limited availability of new ACTs, despite Coartem receiving WHO prequalification in 2004, this meant quinine was often used as the first-line treatment in practice, even if country guidelines did not reflect this (Achan et al., 2009). However, by 2006 the WHO recommended the use of artemether-lumefantrine as one of the first-line treatments for uncomplicated malaria, in part due to concerns around the spread of drug resistance (WHO, 2006).

An additional problem with Coartem, despite its effectiveness, was that the method of delivery to children involved crushing pills, which lead to practical difficulties: the crushing process

risked losing portions of the drug, and the bitter taste meant kids would spit out the drug, both of which lead to subtherapeutic dosing (Premji, 2009). **Coartem Dispersible was developed by Novartis in partnership with MMV** as a response to these issues (Abdulla and Sagara, 2009). Coartem Dispersible was MMV's first supported product, and **most of the R&D seems to have happened in 2007** (MMV, Annual Report 2007). Without going through detailed financial statements, we have been unable to find specific funding figures.

In a 2008 study, Coartem Dispersible was found to have similar efficacy to Coartem (Abdulla et al., 2008). Since then, MMV estimates that 450 million treatments of Coartem Dispersible have been distributed.

We have gone through the MMV portfolio and included all the grants awarded by MMV related to Coartem Dispersible that we could find in our funding spreadsheet (you can also find some additional notes in Appendix B). Unfortunately, they do not provide a more detailed breakdown of the nature of the grants, usually just listing them under "Clinical project development." **The total Coartem Dispersible funding coming from MMV over the years amounts to ~$7.4 million**.

We were unable to find how much Novartis spent on the development of Coartem Dispersible, and we are unaware of other sources of funding that contributed to the development of the drug.

Overall division of credit

It is difficult to meaningfully attribute credit here due to the paucity of data around exactly what was funded, and how much input other parties may have had. We have a prior that we should weigh any funding that happens before the influx of private investment greater than the private sector funding itself — the intuition is that the private sector is more likely to be funding something if it believes it will benefit in expectation, whether in the form of profit,[12] positive PR, or because it is instrumentally valuable in some other way. **This would mean MMV and its funders deserve most of the credit (in 2021, MMV was ~43% funded by the Bill and Melinda Gates Foundation, and 20% funded by the UK Foreign Office**; no other funding source was responsible for >10% of MMV's funding).

We estimate that Coartem Dispersible has averted ~219,000-347,000 deaths since its introduction

Summary

- Our topline estimate is that the introduction of **Coartem Dispersible**, a drug used for pediatric, uncomplicated, malaria, has **likely averted between 219,000 and 347,000 deaths** since its introduction in 2009, compared to a counterfactual of receiving crushed tablet formulations of Coartem.
    - Our largest uncertainty is around the exact percentage of children who have access to Coartem, fail to get a therapeutic dose, and subsequently progress to severe malaria.
    - We did not incorporate the 5 kg requirement for the drug - many neonates are resistant to malaria due to maternal antibodies, and we thought the effort of attempting to model this would not meaningfully change the estimates.

[12] In this case, Novartis provides Coartem, including Coartem Dispersible, "largely at no profit," but it is unclear what other benefits they may derive from the current arrangement.

    - MMV estimates Coartem dispersible has saved 926,000 lives (MMV, 2021). We haven't been able to review their calculations but think the main difference might come from the choice of counterfactual. In our analysis, the benefit of Coartem Dispersible is limited to: the subset of all children under five with uncomplicated malaria cases who are given Coartem → would only take Coartem if it was dispersible → is susceptible to severe malaria → actually progresses to severe malaria → dies from severe malaria.
- A **five-year speedup model** would mean between **104,000 and 165,000 deaths averted**.
    - We used five years based on MMV's contributions over a five-year period from start to completion of clinical testing.
- You can find our model here.

Method

- We used MMV's estimate of the number of treatments distributed.
- We discounted the number of treatments distributed by the amount of medication wasted (for more information on how we obtained our wastage figure, see the method for the injectable artesunate method above).
- We compared the marginal benefit of Coartem Dispersible to its non-dispersible version.
    - We did this by taking into account the % of patients who would benefit from just a change in formulation, the % of patients susceptible to severe malaria, the % of patients who would progress to severe malaria, and the case fatality rate (CFR) of severe malaria.[13]
    - We relied on the literature to estimate an absolute benefit of ~5.7% (0.4-11%) additional children reached when using Coartem Dispersible, compared to its previous non-dispersible version.
    - We used three different methods to obtain the CFR of severe malaria and averaged across them for a final estimate of ~1.9%.
- We then modeled a five-year speedup based on MMV grants awarded.
- Given that this model is more complex than the others, relying on more studies and assumptions, we have included a longer explanation of the methodology in Appendix C for interested readers.

We estimate that Coartem Dispersible might avert ~350,000-750,000 deaths in total

We estimated future lives saved using a quick estimate:

- To obtain a lower bound, we assumed that there will be resistance to this product or a better product in the market no earlier than 2030, such that Coartem Dispersible will continue to avert deaths for the next five years. We obtained the number of deaths averted per year using the average of past deaths averted, and applied a 0.9x correction factor, considering further development in countries with high malaria rates.
- To obtain an upper bound, we assumed that Coartem Dispersible will continue to avert deaths for 15 years. We obtained the number of deaths averted per year using the average of past deaths averted.
- Given that we only had information on this product until 2021, we have included 2022 as a projection as well, using the method described above.

[13] Despite the high uncertainty, we have attempted to approach estimating the CFR of severe malaria and of untreated complicated malaria via different methods to minimize the model's dependence on highly uncertain variables.

- Using those assumptions, **we obtained a total number of deaths averted between ~350,000 and ~750,000**.

Long-lasting insecticidal nets

Insecticide-treated bed nets help prevent malaria, both by providing a physical barrier between people and mosquitoes, and by killing mosquitoes that come into contact with the nets. Long-lasting insecticidal nets, or LLINs, are insecticide-treated bed nets that are designed to remain effective for several years.

The development of LLINs was largely funded by the LLIN manufacturers, with philanthropic support for key trials

Summary timeline

Pyrethroid and PBO nets

- **1947**: PBO synthesized (Tozzi, 1999)
- **1960s**: First-generation pyrethroids developed (Mastsuo, 2019)
- **1970s**: Second-generation pyrethroids, the ones currently used in LLINs, developed (The Guardian, 2007)
- **1970s**: Pyrethroids applied to bednets (Lengeler and Snow, 1996)
- **1994**: Field trial of the first LLIN (Sumitomo, 2006)
- **2001**: First WHO approval of an LLIN, the Olyset net (WHO, 2001)
- **2003**: Second WHO approval of an LLIN, the PermaNet 2.0 (WHO, 2004)
- **2005**: WHO and UNICEF recommend a gradual switch to LLINs (WHO and UNICEF, 2005)
- **2007**: First pyrethroid-PBO net, the PermaNet 3.0, commercially available (Vestergaard, 2023)
- **2009**: WHO approval of the PermaNet 3.0 (WHO, 2020)
- **2014-16**: Randomized controlled trial comparing pyrethroid-PBO to pyrethroid-only nets conducted (Protopopoff et al., 2018)
- **2017**: WHO recommends pyrethroid-PBO nets in regions with pyrethroid resistance (WHO, 2017)

IG2 nets

- **2014-16**: Experimental hut trials of IG2 nets (BASF, 2017)
- **2018**: WHO prequalification of IG2 nets (WHO, 2023)
- **2019**: Rollout of IG2 nets started for two RCTs comparing IG2 nets to pyrethroid nets in Benin and Tanzania, and non-randomized scale-up across 13 African countries (conversation with IVCC).

Pyrethroid and PBO nets

Pyrethroids

Pyrethroids are a family of organic compounds which are used as insecticides. They were first developed at Rothamsted Experimental Station, an agricultural research center in the UK. The first generation of pyrethroids, developed in the 1960s, are no longer widely used because they are unstable in air and sunlight. In the 1970s, second-generation pyrethroids were developed, including permethrin, cypermethrin, and deltamethrin, the three pyrethroids currently used in WHO-recommended LLINs (Mastsuo, 2019; The Guardian, 2007).

Rothamsted Experimental Station was (and still is) mostly funded by the UK government; in particular, it worked closely with the Agricultural Research Council and the Ministry of

Agriculture, Fisheries, and Food (Rothamsted Research, 2023). That is, the development of pyrethroids was funded by the public sector, but in pursuit of British agricultural productivity, rather than public health per se.

Pyrethroid-treated nets

Pyrethroids were applied to bednets as early as the 1970s (Lengeler and Snow, 1996), and from that point until 2007, essentially all insecticide-treated nets used pyrethroids. A full account of the development of insecticide-treated nets (ITNs) and the trials establishing their efficacy is beyond the scope of this report.

Pyrethroid LLINs

The pyrethroids on the ITNs that were available in the 1980s and 1990s wore off relatively quickly. The nets were supposed to be redipped in insecticide every six months or so, but in practice this often was not done. Long-lasting insecticidal nets, which last three to five years without retreatment, addressed this issue. The first LLIN, the Olyset net, was developed at Sumitomo Chemical Co; Sumitomo's first field trial of the Olyset net began in 1994 (Sumitomo, 2006). By 2001, both the Olyset net and another early LLIN, the PermaNet 1.0 from Vestergaard Frandsen, were commercially available (Guillet et al., 2001). The WHO Pesticide Evaluation Scheme (WHOPES) recommended the Olyset net in 2001, and recommended the PermaNet 2.0 in 2003. At the time, WHOPES recommendations for insecticidal products served a purpose similar to the current WHO Prequalification for medications – it was a signal that international donor funds could and should be used to purchase these nets. By 2005, the WHO and UNICEF recommended that all usage of ITNs be "gradually" replaced by usage of LLINs (WHO and UNICEF, 2005).

A 2004 report on the commercial landscape of LLINs estimates the R&D cost of developing LLIN technology at $1 million-$4 million (RBM, 2004), based on personal communications with two relevant companies. Since these seem to be estimates for expenditure by individual companies, **we estimate that the overall R&D costs for the first generation of LLINs were at least $3 million-$12 million**, since three distinct approaches to creating LLINs were seriously pursued.[14]

PBO

Piperonyl butoxide, or PBO, is a synergist for pyrethroids; that is, PBO is not itself an effective insecticide, but it interrupts insects' defenses against pyrethroids, such that the combination of PBO and a pyrethroid is more effective than the pyrethroid alone (NPIC, 2017). PBO was first synthesized in 1947 at Dodge & Olcott, an American company, as part of a larger push in the United States to improve insecticide options.[15]

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[14] Pyrethroids can be incorporated into the fibers that are used to make the net (pursued by e.g. Sumitomo); applied to the net during manufacturing (pursued by e.g. Vestergaard Frandsen); or applied to the finished net (pursued by e.g. Bayer Environmental Science) (RBM, 2004).

[15] "At that time pyrethrum [the natural insecticide from which pyrethroids were later developed] was considered to be the strategic insecticide for the control of mosquitoes and other insect vectors. Japan was the major producer of pyrethrum, with East Africa under active development. The possibility of imports being disrupted in a future war was regarded as a serious risk, as existing supplies of the insecticide were barely adequate for public health uses.
Research and development was therefore directed towards the following goals.

- Developing more efficient methods of applying insecticides to control flying insects.
- Searching for chemical substitutes for pyrethrum with the same valuable properties of rapid 'knockdown', kill and complete safety to humans.

Pyrethroid-PBO LLINs

The first LLIN that incorporated PBO was the PermaNet 3.0 from Vestergaard Frandsen, which was made commercially available in 2007 (Vestergaard, 2023) and approved by WHOPES in 2009 (WHO, 2020). At the time, there was no consensus on whether PBO significantly increased the efficacy of LLINs, and early trials of the PermaNet 3.0 (Tungu et al., 2010; Corbel et al., 2010) remained inconclusive. In a 2015 review, the WHO concluded that there was inadequate evidence to recommend a switch to PBO nets (WHO, 2015).

The pivotal study leading to significant uptake of PBO nets was Protopopoff et al. (2018), a randomized controlled trial that **found significantly lower malaria prevalence in groups that received pyrethroid-PBO LLINs compared to groups that received pyrethroid-only LLINs**. These findings led to the WHO's 2017 recommendation of PBO nets in regions where mosquitoes show resistance to pyrethroids (WHO, 2017).

The Protopopoff et al. trial was **funded by the Joint Global Health Trials funding scheme, a collaboration of the UK's Department for International Development, the Medical Research Council, and the Wellcome Trust**. According to a 2019 review of the funding scheme, the **trial received £2,551,857** (Technopolis Group, 2019).

IG2 nets

Interceptor® G2 nets are a type of LLIN combining a pyrethroid and pyrrole insecticide. They were developed to combat insecticide resistance (IVCC, 2023). We have reconstructed the story of the development of Interceptor® G2 nets almost exclusively based on our conversation with three representatives from the Innovative Vector Control Consortium (IVCC)[16]: Chris Larkin, Mathias Mondy, and Tom McLean.

The development of Interceptor® G2 nets was made possible through a Product Development Partnership. The **agrochemical company BASF developed a formulation of the active ingredient chlorfenapyr** (a previously known insecticide) that was suitable for bed nets **and funded that molecule's development**. Academic partners ran initial trials in 2014-2016 (BASF, 2017) to prove the formulation worked (the following ones are linked on IVCC's website: N'Guessan et al., 2016; Bayili et al., 2017; Camara et al., 2018), and these trials were funded by IVCC, which in turn received grants from a wide range of funders (The Bill & Melinda Gates Foundation, UKaid, and The Swiss Agency for Development and Cooperation). The product **received WHO prequalification in 2018** (WHO, 2023).

Once the product was developed and the trials showed it works and remains effective against resistant mosquitoes, epidemiological studies (specifically two big cluster randomized trials in Benin and Tanzania) were carried out to determine the effectiveness of Interceptor® G2 nets compared to the previous standard, pyrethroid nets. The results showed that these new nets prevent about twice as many infections as a traditional net. In parallel to the two RCTs, the product was piloted and scaled-up in a non-randomized way in 13 African countries. The **cost of the epidemiological studies and the scale up was ~$63 million and was covered by IVCC, who in turn received funding from The Global Fund for Aids TB and Malaria, Unitaid, and the Bill & Melinda Gates Foundation**. The rollout of the nets started in early 2019, and they

- Developing 'pyrethrum extenders'- chemicals which could be added to existing pyrethrum formulations to improve their efficiency. Later such compounds which had little or no intrinsic action on their own were called synergists." (Tozzi, 1999)

[16] IVCC is a Product Development Partnership bringing together a variety of stakeholders to improve vector control strategies.

were able to distribute ~35 million nets in those countries over three years. **IVCC, in collaboration with academics at Imperial College London, estimates that 20,000 deaths were averted by Interceptor® G2 nets in the three years that followed the rollout in early 2019**.

Overall division of credit

Pyrethroids and PBO were both developed in the context of supporting the strategic interests of developed country governments – pyrethroids in the UK as part of a push for increased agricultural productivity, and PBO in the US as part of a push for reduced dependence on imported insecticides. **Development and early testing of pyrethroid and pyrethroid-PBO LLINs were funded by the LLIN manufacturers, though we note that one key manufacturer, Vestergaard Frandsen, is a "social enterprise" which aims to maximize humanitarian benefits as well as profits.** The development of IG2 nets was also funded by the manufacturer, but the early trials of IG2 nets were funded through IVCC. **Later trials establishing the efficacy of pyrethroid-PBO nets and of IG2 nets were enabled by philanthropic and public organizations, most prominently DFID and IVCC**.

We estimate that PBO and IG2 nets have averted ~115,000-146,000 deaths since their introductions

Summary

- We estimate that **~100,000-130,000 deaths have been averted by PBO nets to date since their introduction in 2018**.
- We estimate that **~13,000-16,000 deaths have been averted by IG2 nets to date since their introduction in 2018**.
    - sense-check: **IVCC**, in collaboration with academics at Imperial College London, **estimates that 20,000 deaths were averted by IG2 nets** in the three years that followed the rollout in early 2019.
- We estimate that 4,400,000 deaths have been averted by pyrethroid nets to date since their introduction in 2004 (though we use a suboptimal counterfactual of untreated nets, so are overestimating lives saved by pyrethroid LLINs).
- You can find our model here.

Method

We found head-to-head comparisons of pyrethroid LLINs to PBO LLINs and Dual-AI LLINs in terms of effectiveness. We only used studies that looked at clinical endpoints, (instead of e.g., mosquito deaths), though this means we leaned on two studies (Shepard et al., 2021 and Mosha et al., 2022) for our figures.

We estimated ITN coverage based on the Malaria Atlas Project and a document from the Alliance for Malaria Prevention, which additionally provided breakdowns based on the type of net. We considered a sense-check based on WHO data, but it was too time consuming to try and compile, so we disregarded it.

Using the market share breakdowns of the respective types of LLINs, along with malaria mortality rates, and relative effectiveness of the nets, we estimated how many marginal lives were saved by PBO and IG2 nets compared to a world with only pyrethroid LLINs.[17]

[17] This is an oversimplification, and there are many uncertainties around exactly how the distribution of various LLINs works. Some of these include the following: Do Dual-AI LLINs replace regular ITNs,

We unfortunately ran out of time to look deeply into pyrethroid LLINs. We think the majority of the marginal benefit between pyrethroid ITNs and pyrethroid LLINs comes down to the benefit of not needing retreatment of pyrethroids, without which the ITNs would be comparable to untreated nets. Unfortunately, there is a wide range of figures around attrition rates related to pyrethroid retreatment, from 96% over two years (Solomon et al., 2018), to 4% per year (Pulkki-Brännström et al., 2012), which makes comparison between LLIN and non-LLIN ITNs difficult.

Due to difficulties around assessing the marginal value of pyrethroid LLINs to non-LLIN pyrethroid ITNs, we were unable to come up with a topline figure for the estimated value of all LLINs. Comparing all pyrethroid ITNs against untreated nets instead yields a total of ~4.4 million deaths averted to date. Interested readers can find the methodology used to obtain this estimate in Appendix D.

We estimate that PBO and IG2 nets might avert ~690,000-910,000 deaths in total

We estimate that PBO and dual AI LLINs like IG2 might avert between 690,000 and 910,000 deaths in total, compared to the counterfactual of pyrethroid nets.

We did not have time to build a detailed model of future lives saved. Here we estimate total lives saved using a quick method:

- Very roughly, we estimate that pyrethroids alone maintained significant efficacy for about 30 years (~1990 through ~2020); we assume that adding PBO as a synergist might extend the effective lifespan of pyrethroids by half, so we attribute 15 years of benefit to PBO nets; we assume that nets with a new active ingredient will have approximately the lifespan of pyrethroids, so we attribute 30 years of benefit to IG2 nets.
- We assume that the number of lives saved per year in recent years, and/or in near future projections, is close to the maximum yearly benefit that these technologies will attain.
- These assumptions imply about 570,000-750,000 lives saved by PBO nets in total, and about 120,000-160,000 lives saved by IG2 nets in total.

pyrethroid LLINs, PBO nets or some combination? How is resistance affecting each of the three classes of nets?

Dolutegravir

Dolutegravir is an antiretroviral medication, used in combination with other antiretrovirals to treat HIV.

The development of dolutegravir was funded by industry, but its widespread use in LMICs was made possible through nonprofit and philanthropic partnerships

Summary timeline

- **2000**: Discovery of integrase inhibitors (Bailly and Cotelle, 2015)
- **2007**: First integrase inhibitor, raltegravir, approved by the FDA (Bailly and Cotelle, 2015)
- **2006-2012**: Dolutegravir developed by ViiV Healthcare and Shionogi Pharmaceuticals (Bailly and Cotelle, 2015)
- **2013**: Dolutegravir approved by the FDA (FDA, 2013)
- **2014**: Dolutegravir licensed to the Medicines Patent Pool (MPP, 2022)
- **2016**: Tentative approval of generic dolutegravir (CHAI, 2016)
- **2016**: Initial rollout of dolutegravir in Kenya, Nigeria, and Uganda (UNAIDS, 2017)
- **2017**: Tentative approval of generic TLD (a dolutegravir-based fixed-dose combination) (MPP, Annual Report 2017)
- **2017**: Major pricing agreement for TLD announced, large-scale rollout of TLD begins (UNAIDS, 2017)

Dolutegravir is an integrase inhibitor, a relatively new class of antiretroviral drugs used to treat HIV. The discovery of integrase inhibitor molecules was first published in 2000, and the first integrase inhibitor approved by the FDA was raltegravir in 2007, developed by Merck (Bailly and Cotelle, 2015). Another first-generation integrase inhibitor, elvitegravir, was developed by Japan Tobacco and Gilead Sciences. **Dolutegravir was developed by ViiV Healthcare and Shionogi Pharmaceuticals, between about 2006 and 2012** (Bailly and Cotelle, 2015). Ownership of dolutegravir was consolidated under ViiV in 2012. As far as we are aware, **this development was a purely industry-funded process, with no public or philanthropic funding involved**. The clinical trials leading to the approval of dolutegravir were also funded by ViiV (Dow and Bartlett, 2014). Dolutegravir was approved by the FDA (first global approval) in 2013 (FDA, 2013).

ViiV Healthcare is an HIV-focused pharmaceutical company, majority-owned by GSK. ViiV/HIV R&D spending numbers may be available from GSK reports, but probably not broken down any further. We have not had time to explore this.

Formulation and pricing for LMICs

The WHO recommends a combination of TDF (tenofovir disoproxil fumarate) + 3TC or FTC (lamivudine or emtricitabine, respectively) + DTG (dolutegravir) as the preferred first-line antiretroviral therapy for adults and adolescents (see table 4.3 here). A fixed-dose combination of TDF + 3TC + DTG, TLD for short, is manufactured for LMICs, and is now taken daily by ~20 million people across ~100 LMICs (MPP, 2022). This particular formulation doesn't seem to be available in HICs (see for example the notes to table six in these US guidelines).

Development of this formulation: In 2014, ViiV Healthcare and the Medicines Patent Pool (MPP) signed a voluntary licensing agreement for dolutegravir, and Mylan, a generic pharmaceutical manufacturer, in turn licensed dolutegravir from the MPP. Mylan, as well as some of the MPP's other generic manufacturing partners, developed the fixed-dose combination of TLD. Mylan's TLD was tentatively approved by the FDA in August 2017 (MPP, 2022; MPP, Annual Report 2017).

Pricing: In September 2017, a pricing agreement for TLD was announced at the UN (press release here). Formally, it was announced by the governments of South Africa and Kenya, in partnership with UNAIDS, the Clinton Health Access Initiative, the Gates Foundation, Unitaid, DFID, PEPFAR, USAID, the Global Fund, Mylan Laboratories, and Aurobindo Pharma. The agreement allowed public-sector purchasers in LMICs to buy TLD from Mylan and Aurobindo for about $75 per patient per year.

Role of CHAI: Around 2010, CHAI signed an agreement with ViiV "to collaborate with the goal of bringing innovative formulations of medicines for the treatment and prevention of HIV/AIDS to people living with HIV in developing countries." After FDA approval of ViiV's dolutegravir (Tivicay), CHAI worked with ViiV to agree on a manufacturer for generic dolutegravir. They settled on Aurobindo Pharma, who filed an FDA application for generic dolutegravir in 2015 (CHAI, 2015).
Later in 2015, CHAI and Aurobindo announced an agreement to make generic dolutegravir available for $44 per patient per year. As part of the same agreement, Aurobindo announced plans to file an FDA application for TLD.
After the FDA's tentative approval of Aurobindo's generic dolutegravir in 2016, CHAI, along with Unitaid, WHO, USAID, and the Ministries of Health in Kenya, Nigeria, and Uganda, was involved in an initiative to offer dolutegravir in those countries. The project was later described as helpful preparation for a wider rollout of the TLD combination treatment.

Role of Gates Foundation: The Gates Foundation seems to have been the driving force behind the 2017 pricing agreement with Mylan and Aurobindo. In particular, Reuters reports that Gates agreed to guarantee minimum sales volumes of TLD. The commitment seems to have been made through the Strategic Investment Fund (Mylan, Aurobindo) and is described by Reuters as "a multi-million dollar guarantee," but we have not been able to find the amount of the commitment or the amount that was ultimately spent on the commitment.

Likewise, we are not sure how much money was spent by Unitaid (which funds the MPP), CHAI, etc., in their early coordinating and licensing efforts. The announcements and descriptions we have found do not mention costs to these kinds of organizations, and their annual reports do not break down their spending in a way that we found helpful. CHAI's later work on rolling out dolutegravir and TLD was funded by Unitaid as part of "Optimal ARV," initially announced in 2016 as a three-year project with a grant of $34 million, now ongoing with a total grant value of $70 million. We are also aware of a $3 million grant in 2017 from the Gates Foundation directly to CHAI in support of dolutegravir rollout.

Overall division of credit

To our knowledge, private funding was purely responsible for the initial development and approval of dolutegravir, and its availability in HICs. Nonprofit coordination efforts, such as through the MPP and CHAI, and funding commitments, such as from Unitaid and the Gates Foundation, seem to be responsible for its current widespread use in LMICs.

We estimate that dolutegravir has averted ~900,000 deaths since its introduction in LMICs

See our model here.

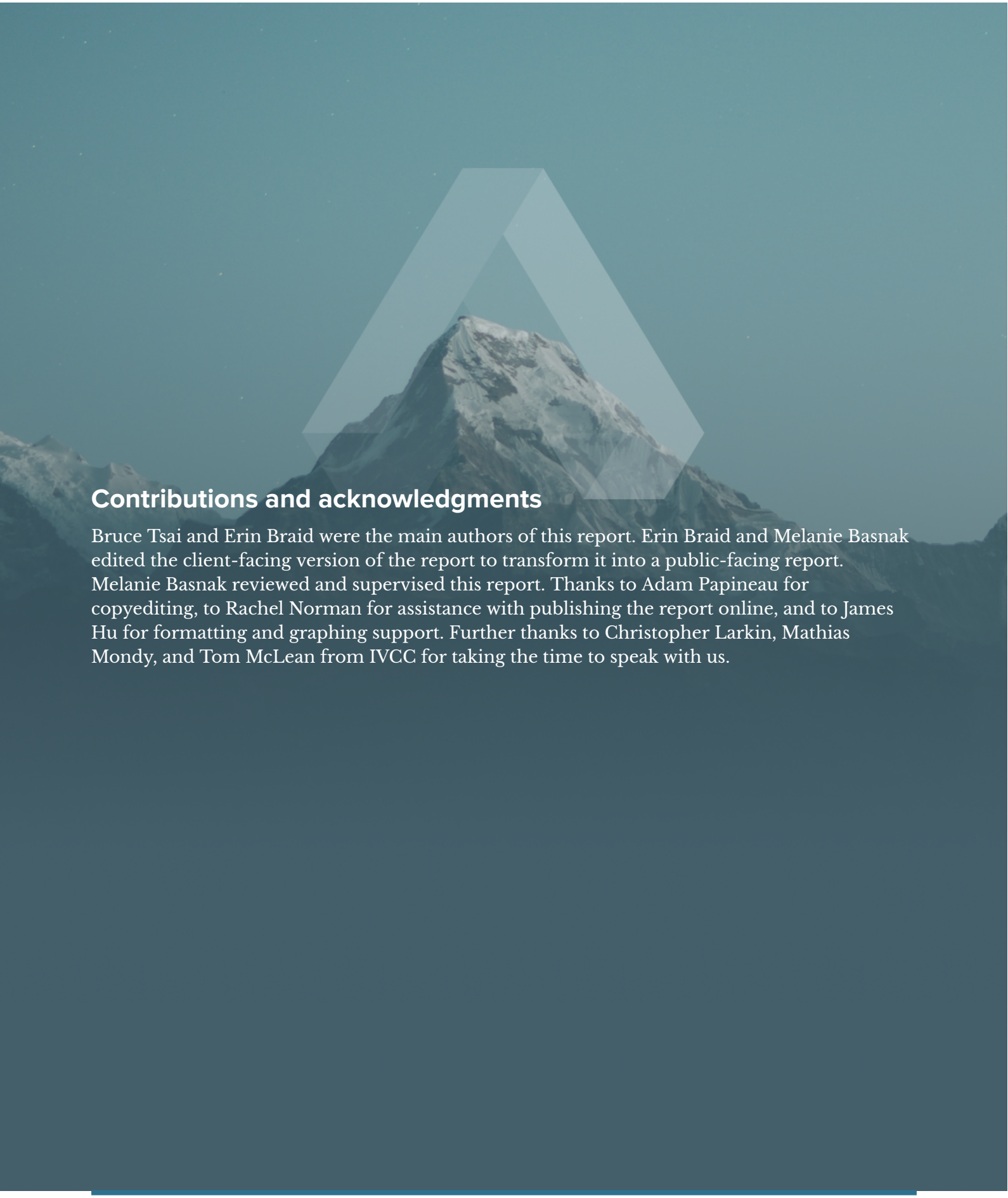
To quantify the benefits of the switch to dolutegravir, we have relied on estimates from Zheng et al. (2018), which models the cost-effectiveness of switching from efavirenz-based antiretroviral therapy (ART), the previous standard of care, to dolutegravir-based ART, specifically Tenofovir, Lamivudine, and Dolutegravir (TLD), which is the formulation discussed above. Zheng et al. **consider both the direct benefits to patients taking TLD instead of the previous regimen, and the indirect benefits via lower transmission**.

- Direct benefits: From the five-year survival rates modeled by Zheng et al., **we infer that treating patients with TLD instead of efavirenz-based ART increases annual survival rates by about 1.5 percentage points**. This figure seemed very high to us, but we note that it is comparable to the findings of Phillips et al. (2017), who write that "A transition to use of a dolutegravir as a first-line regimen in all new ART initiators is the option predicted to produce the most health benefits, resulting in a reduction of about 1 death per year per 100 people on ART over the next 20 years in a situation in which more than 10% of ART initiators have NNRTI resistance" (10% NNRTI resistance being a level observed in "several countries in sub-Saharan Africa" as of 2017 and expected to increase).
- Indirect benefits: In addition to their own better health outcomes, patients with better-controlled HIV due to better ART are also less likely to transmit HIV to others. **We infer from Zheng et al.'s model that a patient on TLD instead of efavirenz-based ART causes about 0.0028 fewer new cases of HIV per year. In our model, the deaths averted due to averted transmission turn out to be a much less significant factor than the deaths directly averted by treatment efficacy**, so our topline estimate is not very sensitive to changes in assumptions about e.g. the treatment received by people counterfactually infected with HIV.

We estimate that dolutegravir might avert ~2.1 million deaths in total

For a rough estimate of the total lives saved attributable to dolutegravir, we estimate the maximum yearly benefit of dolutegravir, and then assume the approximate number of years before a comparable drug would have been developed and used in the absence of dolutegravir.

- Maximum yearly benefit: Currently, about 26.8 million people in LMICs are treated for HIV. Considering that about 20 million of those people are using dolutegravir, that that number has been growing quickly, and that there is a continued push to expand dolutegravir use in LMICs, 26.8 million seems like a reasonable approximation of eventual yearly users.
- Years until counterfactual replacement: Both before and after the development of dolutegravir, there has been an ongoing research pipeline aimed at finding new and improved antiretroviral drugs. To roughly estimate the time between the actual development and use of dolutegravir, and the hypothetical development and deployment of a comparable drug in a world without dolutegravir, we looked at the next approval of a new integrase inhibitor following the approval of dolutegravir. Dolutegravir was approved in 2013, and the next approval of a new integrase inhibitor was in 2018 (bictegravir, in the fixed-dose combination Biktarvy), so use a figure of five years.



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Appendices

Appendix A: Projections on future lives saved

Future projections of the impact of any anti-malarial drug will depend on the number of expected malaria deaths in the future, the effectiveness of the drug, and the effectiveness of the counterfactual. Malaria deaths can be broken down into the incidence of infections times the mortality rate of infections.

Factors that affect the incidence of malaria include vector-related variables, such as the prevalence of conditions that are conducive to mosquitos, such as housing conditions (eaves, ceilings, window screens), stagnant water for mosquito larvae, WASH infrastructure, etc.

It may be easiest to just use a proxy measure such as a human development index, GDP per capita, and make the assumption that these issues are negatively correlated with the countries' development.

Modeling potential habitat ranges for various vector species will also require considering environmental factors, such as any changes in temperature and rainfall patterns in the future, as well as predator/prey interactions, though Target Malaria's analysis suggests that at least for *Anopheles gambiae*, this is likely not a major consideration.

Mortality rate will depend on:

- rate of resistance to treatments
- the rate of improvement and dissemination of other interventions, such as new antimalarials or insecticides

- other comorbidities, such as HIV co-infection
- access to healthcare services

Mortality rate needs to be considered for nontreatment, the existing gold-standard, as well as other alternatives (but at least the second-line treatment). For example, in a scenario where a particular variable means resistance to the second-line treatment grows without affecting the effectiveness of the gold standard, the expected lives saved of the gold standard goes up.

You can find here a draft template that could be used as a starting point to model this.

Appendix B: Some notes on Novartis's contribution to the development of Coartem dispersible

We have also included notes from Novartis' annual reports, though these do not provide many details that might help us meaningfully attribute credit.

2008 (p. 73):
"Focusing on children in Africa, the group most vulnerable to malaria, Novartis has developed a more convenient formulation of Coartem as a powder that can be dissolved in milk, water or other liquids."

2007 (p. 77):
"During 2007, Novartis and partners completed clinical testing of a new dispersible formulation of Coartem, aiming to increase convenience of administration and improve palatability for young children."[18]

2006 (p. 87):
"Novartis also is pushing ahead with initiatives such as joint development of a new pediatric formulation of Coartem with MMV."

2005 (p. 53):
"Scale-up of Coartem production capacity completed. Development of pediatric formulation of Coartem and field support to Zambia ongoing."

2004 (p. 64):
"In 2005, Novartis also will continue with the development of a new pediatric formulation of Coartem, in collaboration with Medicines for Malaria Venture (MMV), a nonprofit foundation dedicated to developing affordable new antimalarials."

Appendix C: Full methodology for the Coartem Dispersible BOTEC

- We used MMV's estimate of the number of treatments distributed.
- We modeled a 35-54% reduction in terms of medication wastage, based on this USAID health system e-handbook (Ch. 8, p. 3, Figure 1). The 54% reduction excludes "poor quality" and "high prices" as contributions towards wastage for this context. We think this is our best guess at a point estimate. We additionally modeled a ~50% reduction

[18] In this report, Novartis lists UNICEF, Crown agents, Mission Pharma, MSF, as "alternative providers" for Coartem (tablet), and Wellcome Trust as a grantor for other malaria treatments. With more time we would investigate to see whether any of these organizations played a role in the development of Coartem Dispersible.

scenario as an upper bound for the number of lives saved. This is driven by our uncertainties around the USAID methodology (which we could not find), as well as the extent to which these figures (for all drugs) are generalizable to malaria specifically.

- We translated this directly to the total number of malaria cases treated.
- We relied on the literature to estimate an absolute benefit of ~5.7% (0.4-11%) additional children reached when using Coartem dispersible (CD), compared to its previous non-dispersible version (ND).
    - Data is sparse, with minimal randomized studies that compare the two head-to-head. Abdulla et al. (2008) showed no significant difference (0.4%) in dropout and adherence rates, even when assuming "lost to followup" and "withdrew consent" to be 100% due to medication issues.
    - A few studies looked at adherence to ND, but given the lack of comparison to CD, we did not feel comfortable using these figures. For example, many causes of nonadherence are applicable to both CD and ND (such as stopping treatment due to "feeling better" or due to concerns around too many doses).
    - Lemma et al. (2011) provided more specific breakdowns on reasons patients gave for nonadherence, and we included the ones that we felt were likely to benefit from switching to CD ("refused to take," "bitter," and "too big to swallow"), as well as the patients that they excluded due to "spitting/vomiting with no readministering." This came to a total of ~11% (of patients who we think would be likely to receive a therapeutic dose when on CD compared to ND.
    - We crudely took the average of the two as we did not feel comfortable disregarding either figure.
- We then tried to work out the % that would progress to severe malaria, as well as the case fatality rate (CFR) of severe malaria, to work out the % that would be harmed in expectation if Coartem dispersible were not developed. Next are the details on how we did this.
    - Estimating the % that would progress to severe malaria
        - Our best guess is that 10% of all who receive Coartem for uncomplicated malaria, but do not benefit from it, will progress to severe malaria. However, we are highly uncertain about this figure.
        - First we take the group who we expect to counterfactually benefit from dispersible Coartem, and try to work out how many of them would be susceptible to severe malaria.
            - We reached our estimate of 54% by approximating the area under a graph in White et al. (2014).
        - Then we try to work out the proportion of U5s with uncomplicated malaria who both have access to Coartem, fail to get a therapeutic dose, and subsequently progress to severe malaria. It was unsurprisingly difficult to find meaningful data on this.
            - Our best guess for this figure is 18%.
            - 18% comes from Camponovo et al. (2017), which gives us an estimate of the total number of severe cases. If we divide this by the total number of cases, it gives us a proportion of total malaria cases that are severe (1.8%).
            - This is not the exact figure we are looking for, as it includes all patients (including those successfully treated by antimalarials).
            - We have crudely assumed that 90% of these patients do in fact receive antimalarials and get better, mainly based on the effectiveness of Coartem. This means that after excluding those who benefit from antimalarials our estimate will be 10x higher.

- Some other ways this number might be wrong: we might expect higher rates of severe malaria in children, who have not yet grown resistant to malaria. We might expect higher rates of severe malaria in children who spit out or don't use Coartem tablets than the average malaria patient. On the other hand, we might expect lower rates of severe malaria in children who have access to Coartem in the first place than those who do not.
- Ultimately, changing this figure by 2x will only change our final topline estimate of CFR of untreated uncomplicated malaria by about 0.8% in absolute terms.

- This gives us the proportion we might expect to progress to severe malaria, once we take into account the 54% who are susceptible to severe malaria.

- Estimating case fatality rate of severe malaria
  - Method 1
    - Our estimated CFR via method 1 is ~0.14.
    - We took our estimates for the proportion of malaria cases that end up progressing to severe malaria via Camponovo et al. (2017).
    - This method leans heavily on Camponovo et al. (2017), which estimates the admission rate for severe malaria in Africa, which gives us some indication of the true total rate and proportion of severe malaria, as well as an implied CFR for severe malaria based on total number of malaria deaths which we know from other sources. We did not spend much time evaluating the methodology of this paper, as we could not find anything else that would give us similar information.
    - This figure is for severe malaria generally, and not specific to U5s. We did not discount for this as we did not think additional time spent here would lead to any significant changes to our estimates.
  - Method 2
    - Our estimated CFR via method 2 is ~0.007.
    - We attempted another independent methodology, deferring to WHO estimates of the % of patients who received treatment with ACTs, of those who seek care, which is the relevant denominator for our purposes.
    - We multiplied this by the effectiveness of ACTs - we use Coartem as our estimate here.
    - We then accounted for the existence of second-line treatments, assuming that 90% of places where people do go to seek help have at least one antimalarial.[19]
  - We averaged these two methods for a topline CFR of ~0.07 for all severe malaria.[20]

[19] Sheet will say 0.6, as this is crudely assuming complete overlap between access to ACT and non-ACT antimalarials (i.e., of the 20% remaining, 0.6 of that will have a non-ACT antimalarial, which represents the marginal benefit).

[20] We also included a few sources in the literature of mortality in the hospital, but this was difficult to weight appropriately with methods 1 and 2, mainly because it's unclear how much of the difference in value reflects a true discrepancy between hospital mortality and out-of-hospital mortality that's already incorporated in the figures, versus differences in methodology that aren't captured by methods 1 and 2. We've left the (unused) option that includes these estimates, weighted by the % of patients that do arrive in hospital. Due to the discounting by our current estimate of ~10% of all cases of malaria progressing to severe malaria, views on the above do not meaningfully affect the topline figure of ~2.3%.

        - We then discounted this by only taking into account the ~10% of cases that would progress to severe malaria for a CFR of 0.007 for those who received Coartem but did not get therapeutic effect.
        - Lastly, we included an estimate from a RAND report, based on two studies and expert opinion which suggested the CFR of untreated uncomplicated malaria to be at 0.03.
        - We averaged our estimate of CFR in untreated malaria (1.6%) and the RAND figures (3%) for a final topline CFR of 0.0186, or 1.9%. We wanted to include the expert opinion figure given we did not have an opportunity to meet and hold our own expert interviews.
- We used five years as our estimate for speedup. This was based on grants awarded by MMV starting in 2003, leading to completion of clinical testing in 2007.
    - This gives us our estimate of 104,000-165,000 lives saved.

Appendix D: Estimated lives saved by pyrethroid ITNs compared to untreated nets

Most studies looking at the impact of pyrethroid ITNs compared to untreated nets are very old. Some studies suggest that untreated nets provide half the protective effects of treated nets. However, other studies suggest that this figure is closer to 10%. It is also likely that the untreated net leads to nearby children who do not have access to a bednet to take the malaria risk for the protected individual. This is in contrast to treated nets, which have a protective effect at the community level (i.e., those who do not have bed nets will also face a lower, instead of higher risk of malaria). Data collection for net distribution in the ’80s and ’90s are also sparse. We take crude estimates of seven million lives saved from 2004 to 2020 for two billion nets distributed, and obtain a lives-saved:nets-distributed ratio of 1:286. We subtract the estimates of ITNs distributed between the years 2018 and 2020 based on Alliance for Malaria Prevention data, for a total of 598 million nets distributed. At the same lives-saved:nets-distributed ratio, this comes to a total of ~2.1 million lives saved. We subtract this from seven million, and then subtract 10% from this as the counterfactual of untreated nets, for (7–2.1)×0.9, or around 4.4 million lives saved.