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Avoiding Another Lost Decade on Malaria Vaccines

RYAN DUNCOMBE · KARAM ELABD · JUSTIN SANDEFUR

Abstract

After decades of research and development, two new malaria vaccines entered routine administration this year, and are projected to save 180,000 children's lives by 2030. But under current plans, roughly 2.5 million children will die of malaria unvaccinated over the same period. What's stopping a faster rollout? Money is the obvious answer. Nigeria, home to a third of global malaria deaths, has a total health budget of $10 per capita, and qualifies for only limited international assistance to purchase a vaccine that costs more than $15 per child for even the generic R21 variety. Poorer countries like the Democratic Republic of Congo have received highly subsidized vaccines, but will struggle to ensure take-up for a four-dose regimen without additional expenditure on community outreach and cold-chain management. Despite these financing challenges, malaria vaccines appear highly cost effective, at around $4,200 per life saved, rivaling some of the best buys in global health. While policymakers must weigh malaria spending against other disease priorities, the advent of vaccines implies malaria can absorb more resources while maintaining higher cost effectiveness than ever before. The most ambitious rollout would exceed the malaria budget of Gavi, the Vaccine Alliance, by $2 to $3 billion over the next five years.

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Introduction

The history of humanity's fight against malaria is full of excruciatingly long lags between the discovery of a new malaria treatment and its widespread availability.

Peruvians introduced the Spanish to *quinquina* bark in the early 1600s. But as Sonia Shah recounts in her popular history of the disease, *The Fever*, the Spanish and later the Dutch took great pains to protect this new intellectual property, leaving quinine in short supply for centuries.

In the 1960s, Mao's government tasked Chinese scientists to scour ancient texts for clues about alternative drug remedies. A 4th-century reference to wormwood as a treatment for intermittent fevers led them to artemisinin. But it took almost a decade for that discovery to make it out of China, and another twenty years of wrangling between international agencies and pharmaceutical companies before artemisinin combination therapy became widely available in malaria-endemic countries.

Around the same time, research began on the first malaria vaccine candidates. But as Saloni Dattani, Rachel Glennerster, and Siddhartha Haria have detailed, research was "stalled over and over again" by a "lack of funding and urgency to address what had become a distant problem for the West." The first successful human challenge trials of the RTS,S vaccine were completed in 1997, and even then decades of practical and regulatory hurdles still lay ahead.

Since 2022, two malaria vaccines, RTS,S and R21, finally received "prequalification" from the World Health Organization. Both are now being administered in relatively small numbers, with financial backing from Gavi, the Vaccine Alliance. The newer vaccine, R21, is more affordable, just as effective at preventing malaria, and available in almost unlimited supply.

Yet under current plans as outlined by Gavi, we estimate it will take another decade before all children in malaria endemic countries have access to malaria vaccines. Most children alive today, even in places with high malaria burdens, will never be vaccinated.

What explains the delay?

Over the past several months, we've traveled to Nigeria, the Democratic Republic of Congo, Mozambique, and Malawi, and asked this question to government officials, staff at Gavi, the WHO, and the U.S. President's Malaria Initiative, as well as international NGOs like PATH which has been a central player in malaria vaccine rollout.

Supply remains well below countries' notional demand for vaccines. Until this summer, Gavi was rationing doses of both the RTS,S and R21 vaccines quite strictly. A tug of war emerged between African governments on the one hand – pushing for access to the newer, cheaper R21 vaccine, whose manufacturer claims it can produce north of a hundred million doses per year – and Gavi on the other,

who had made prior commitments to purchase RTS,S and sought to build a marketplace with multiple vaccine alternatives. The situation has improved in recent months, but as we'll see, the question of whether that supply constraint has lifted remains murky.

While supply constraints have eased, funding remains an obstacle. Gavi has stated publicly that "It is accurate to say that we are moving from a supply constrained environment to a resource constrained one." For the Nigerian government, even after subsidies from Gavi are accounted for, the price per child of malaria vaccines still exceeds total government spending on health each year, which is only about USD $10 per capita. And overcoming the last-mile problems of vaccine delivery will require additional resources too.

A somewhat banal but quantitatively important reason most kids alive will never receive the vaccine is because current plans restrict routine immunization to new infant cohorts – even though the WHO has given the green light for vaccinating children up to age five. But of course, expanding the eligible age range confronts financial barriers as well.

Talking to people on the frontlines of malaria vaccine rollout, we heard a daunting list of practical and logistical obstacles to introducing a new, 4-dose vaccine in some of the poorest places on the planet. We spend much of this essay on those. But we also encountered broad confidence that these challenges are familiar and surmountable with enough resources.

How much money are we talking?

In terms of financing, the picture that emerges can be broken into three basic stages. First, in the very short term, up to $500 million spent on strengthening the rollout of vaccine doses that Gavi has already purchased could have an extremely high return. It could mean the difference between lives saved and vaccines sitting unused in the warehouse. But that's just scratching the surface.

The second phase would be to buy more vaccines, beyond the doses Gavi has already committed to. There is scope to vaccinate somewhere around 87 million additional infants in the highest malaria burden countries by 2030. Accounting for the full cost of vaccines plus community mobilization, training, supply chain management, etc., we estimate the cost per life saved for this phase at around $4,200 – implying malaria vaccines could absorb another $2 billion in spending with extremely high returns by the standards of global health. Finally, a third phase would incorporate roughly 45 million kids alive today in the highest-malaria burden countries who will never be eligible for the vaccine because they're too old. The cost per life save increases for this group, and reaching them could absorb another $1 billion.

In short, while diminishing marginal returns do kick in eventually, the advent of vaccines has pushed that point out by a few billion dollars. That creates an historic opportunity for highly effective aid spending – and perhaps the chance to turn the tide of the war on malaria that has been stalled for the last decade or so.

But behind all these calculations are some very contentious policy choices, about which vaccine donors should back, which countries are first in line for financial assistance, and how fast the push to roll out malaria vaccines can realistically go.

I. Choosing the right vaccine

The question of which vaccine to prioritize has been a point of much contention in the policy sphere. For now, any viable scale up of malaria vaccines must embrace R21, the vaccine which is cheaper and in greater supply. Though a new technology transfer agreement allowing RTS,S to be produced in India could upend some of these calculations as soon as 2026.

The two current malaria vaccines appear similarly effective

To date, two vaccines have been recommended for use by the World Health Organization: the earlier, more expensive vaccine known as RTS,S, and the newer, significantly cheaper vaccine, R21.

In terms of efficacy, both vaccines are quite similar. R21 is essentially an improved version of RTS,S, and they have both undergone phase 3 clinical trials. In the closest thing to a head-to-head comparison – sites with perennial malaria, and ages 5 to 17 months, albeit in different years and different countries – RTS,S showed a 12-month vaccine efficacy against clinical malaria of 56%, while R21 achieved 75%. R21's efficacy was slightly lower in seasonal sites (68%), and for older children (18–36 months) across multiple outcomes.

TABLE 1. Comparison of the two malaria vaccines

	RTS,S	R21
Phase 3 trial publication	The Lancet 2015	The Lancet 2024
Phase 3 trial start	2009	2021
WHO prequalification	2022	2023
Age range reported here	children 5–17 months	children 5–17 months
Age eligibility per WHO policy paper	≥5 months	≥5 months
Vaccine efficacy against clinical malaria in perennial (i.e. non-seasonal) sites in children aged 5–17 months		
12 months	56%	75%
32 months	44%	Ongoing
48 months	36%	Not tested
Vaccine efficacy against clinical malaria in seasonal sites[1]	60%	78%
Reduction in mortality (excluding accidents)	13%	Not tested
Price per dose (NB: WHO recommends 4 doses for both vaccines)	$9.81	$3.90
Production	GSK	Serum Institute
Production capacity	~8 million doses/year	~100 million doses/year

1 Note that the age ranges differ for the two vaccines for this measure, including children at 5–17 months for RTS,S and 5–36 months for R21.

Because RTS,S was developed earlier, we have more data on its longer term protection, all the way through to mortality outcomes. Pilot data from Ghana, Kenya, and Malawi showed that RTS,S "cut deaths among young children by 13% over nearly 4 years." That startling drop in mortality came despite the efficacy rate falling to 36% by the fourth year. For R21, on the other hand, the longest available phase 3 data is only at 12 months. However, that 12 month data, the lengthier phase 2 data available, and the vaccine's similar design to RTS,S all suggest it is more than likely that R21 offers at least comparable long-term protection.

Importantly, no head-to-head trials between the two vaccines have been conducted so far, and the WHO has stated there isn't enough evidence yet to definitively declare one vaccine superior to the other. For now, it seems safe to conclude that R21 is at least *no worse* than RTS,S in terms of efficacy.

Of the two, R21 is much cheaper and more readily available

While RTS,S and R21 look very similar in terms of the science – i.e., similar underlying makeup and proven efficacy – they look quite different in terms of the economics of price and supply.

R21 can be manufactured at 100 million doses per year, significantly exceeding RTS,S, which has a current capacity of 8 million doses per year. This disparity in manufacturing capacity, especially in the short term, is partially due to the Serum Institute's capacity, but it's also due to fundamental differences in the vaccine design that mean R21 only needs 1/5th the dose of RTS,S for the same efficacy. This difference in potential availability prompts the question: does RTS,S offer a significant enough advantage over R21 to justify its use?

It has been clear for at least a few months that supply is no longer the binding constraint, as noted here by Zacharia Kafuko and Jean-Vincent Lamien. That's most obviously true in the case of R21. The Serum Institute, which is producing the R21 vaccine, says openly that it's producing more than it can sell. As Serum's CEO Adar Poonawalla told TIME magazine:

> "We've made 100 million doses, and we're expecting about 20 to 25 million doses to go out this year. But getting countries ready in terms of preparedness, training their staff, accepting the cold chain, and getting parents in to bring their children to get vaccinated usually takes a little time. I'd really like to get to 50 to 60 million annual supply to the African continent in three years. We have the capacity, the demand, and the will of the people to want this vaccine, now we just need to get enough funding from Gavi and donors to be able to support that."

R21's advantage in terms of price and supply may narrow over time. GSK, the maker of RTS,S, has signed a technology transfer agreement with Bharat Biotech to produce the vaccine in India starting in 2026, expected to expand RTS,S capacity up to 25 million doses per year. At that point,

RTS,S' price is also projected to drop below the current $9.80 per dose, though the adjuvant, the part of a vaccine used to boost effectiveness, will still be manufactured in the West by GSK, and further price declines are also possible for R21 as well. For now, we focus on the current prices in our calculations below.

Models suggest that so far, R21 has averted one child death per $4,200

Similar efficacy and a lower price implies, of course, greater cost effectiveness. A recent review of cost-effectiveness ratios by Elabd and Duncombe finds that R21 has the potential to extend one disability-adjusted life year at a cost just slightly higher than bed nets, generally considered the most cost-effective intervention in malaria control, and already at much higher saturation.

To fully appreciate the cost effectiveness of malaria vaccines over the long term and across diverse geographic contexts, the results from clinical trials can be plugged into existing epidemiological models of malaria transmission. In the case of R21, that modeling also extrapolates the clinical trial results on malaria cases averted into longer-term impacts on deaths averted. For comparison purposes, we focus on the results from perennial settings[2] that broadly equate to areas of moderate-to-high malaria transmission.[3]

For RTS,S/ASO1, two independent groups have conducted cost effectiveness analyses: the Swiss Tropical and Public Health/Telethon Kids Institute and Imperial College. Median estimates from the two models for a 4-dose vaccination schedule were 417 to 448 malaria deaths averted per 100,000 fully vaccinated children,[4] and 9.2% and 18.6% malaria deaths averted in children under 5 years of age. The models assumed a price of $9.81 per dose, the median cost-effectiveness ratio, compared with no vaccine, ranged between $52 to $105 per clinical case averted, and $175 to $187 per DALY averted. This is considered positive and comparable with other new vaccines.

The Imperial College team also modeled the cost-effectiveness of the R21 vaccine. Vaccination avoids 629 malaria deaths for every 100,000 kids who complete 4 shots, a 33 percent reduction in malaria mortality among children under 5 years. At an assumed vaccine price of $3 per dose, they estimate a median incremental cost-effectiveness ratio, compared to no vaccine, of $7 per clinical case averted, $34 per DALY averted.

2 Areas with year-round (perennial) malaria transmission rates are considered more relevant in this context, and the RTS,S modeling analyses did not take seasonality into account (i.e. seasonal trends in rainfall and mosquito density were assumed to be constant throughout the year).

3 The modeling studies considered slightly different malaria transmission scenarios. In terms of parasite prevalence in children aged 2–10 years ($PfPR_{2-10}$), the RTS,S and R21 modeling groups assumed a $PfPR_{2-10}$ ranging between 10–50% and 3–65%, respectively. A vaccine's cost-effectiveness is generally considered to be less favorable in areas with lower transmission rates due to fewer malaria cases and deaths being averted for the same overall cost of a vaccine program.

4 Having received at least 3 vaccine doses.

TABLE 2. Model-based estimates of cost effectiveness

Vaccine	RTS,S (Swiss)	RTS,S (Imperial)	R21 (Imperial)
Dose price used in published model (USD)	$10	$10	$3
Malaria Deaths Averted (per 100,000 *full vaccinated children*)	417 (205–540)	448 (315–534)	629 (250–646)
Proportion of Deaths Averted in Children Under 5 (%)	9.2% (8.7–10.1)	18.6% (13.5–20.8)	33.6% (21.4–43.0)
Cost per Clinical Case Averted (USD)	$105 (87–160)	$52 (35–91)	$7 (4–48)
Cost per DALY Averted (USD)	$175 (146–412)	$187 (157–274)	$34 (29–139)
Additional calculations:			
Current dose price	$9.81	$9.81	$3.90
Cost per DALY Averted (USD) using current dose price	$175	$187	$44
Additional financial cost of rollout in MVIP countries	$2.75	$2.75	$2.75
Cost per DALY Averted (USD) using current dose price + MVIP rollout costs	$223	$239	$75
Implied cost per death averted, only vaccine cost	$9,592	$8,929	$2,480
Implied cost per death averted, including rollout	$12,230	$11,384	$4,229

The cost figures used in the published studies are probably too optimistic, in two regards. First, the price of R21 currently stands at $3.90, not $3. Second, these costs only cover the price of actual vaccine doses. In Ghana, Kenya, and Malawi, where the WHO's Malaria Vaccine Implementation Program piloted routine administration at large scale, the government and donors spent roughly USD $2.75 per dose to support retention and community engagement, over and above the cost of the vaccines themselves.[5]

Adding in these extra costs, we calculate that full implementation of R21 rollout would avert one child death for approximately $4,200. Again, that compares reasonably well to some of the most cost-effective philanthropic interventions in global health, e.g., seasonal malaria chemoprevention in Nigeria, which GiveWell estimates costs approximately $3,000 per death averted.

Taking these numbers at face value, the R21 vaccine is two- to three-times more cost effective per death averted compared to RTS,S. While it is important to exercise caution when comparing estimates of cost-effectiveness between interventions evaluated by different methods (time intervals, differences in concurrent regional health interventions, and standards of care, etc.), the R21 vaccine clearly presents a compelling case for a highly cost-effective addition to existing malaria prevention strategies.

5 See Table 3. We focus here on the financial cost to countries of rollout, excluding the cost of vaccines themselves, and of the staff time and other in-kind government contributions to rollout. The figure of $2.75 is a simple average of the financial cost per dose across the three countries in MVIP.

Why not wait for better, next-generation vaccines?

"Gates hates this vaccine." That's the answer we heard multiple times, sometimes phrased gently and sometimes stated outright, when we asked academics, public health officials, and NGOs why the world has been so slow to embrace R21.

When pressed about why the Gates Foundation, which has poured billions of dollars into vaccines in poor countries, would oppose an effective vaccine against one of the world's biggest killers, answers got a bit conspiratorial: Bill Gates doesn't like generics, or Gates program officers put so much money into developing RTS,S they refuse to be beaten by R21. Behavioral biases are powerful and people (even those who care alot about evidence and are convinced they are being objective) tend to trust studies and product they have been involved in evaluating and know better.

A less conspiratorial explanation is that Gates is looking for better alternatives. The foundation's website emphasizes the need to look beyond RTS,S and R21 to new innovations:

> "[W]e cannot end malaria with the vaccines and other tools we have today, which is why our foundation is helping to fund the development of monoclonal antibodies, a single injection of which could give a person a full season's worth of protection against malaria, as well as self-replicating RNA vaccines that have the potential to be manufactured quickly and in large quantities."

Many are also worried about the practicality of a 4-dose vaccine – which both R21 and RTS,S are – and hoping for a simpler alternative.

It's evident that the search for more effective malaria vaccines continues, and, despite the potential of RTS,S and R21, it's worth understanding what's on the horizon. Other vaccine candidates aim to tackle malaria from different angles than R21 and RTS,S. Blood-stage vaccines like RH5 focus on preventing invasion of the parasites into red blood cells. Recently published results from a pediatric phase 2b trial demonstrated 55% efficacy[6] – not superior to R21 or RTS,S, but RH5 is intended to complement a pre-erythrocytic sporozoite vaccine, and is being evaluated together with R21 moving forward. This multistage vaccine strategy might not be game-changing, but it could add further to the efficacy and durability of R21 by targeting different stages of the parasite's life cycle.

However, the journey from idea to implementation is still lengthy, and Dr. Halido Tinto, Principal Investigator for the R21 trials, and others have suggested that a multistage malaria vaccine may still be a long ways away, as this must go through extensive testing to ensure the vaccines are compatible and still effective when combined. At the current pace, a multistage vaccine won't be expected to reach phase 3 until 2030 at the very earliest. Even after testing is completed, additional hurdles

6 In a seasonal setting in 5–17 month-olds. Three doses were administered with one month between each dose. Efficacy was measured as prevention against clinical malaria through 6 months post-vaccination.

remain for this new generation of vaccines, from securing regulatory approvals, (which delayed RTS,S for several years) scaling up manufacturing, or even, as the current situation demonstrates, preparing for funding and roll out of approved vaccines.

In the meantime, the case for leaving RTS,S and R21 on the shelf and waiting for better alternatives is weak.

Economists who study investment under uncertainty often talk about the "option value" of *not* investing right now, and waiting for a better moment. But this logic relates to irreversible capital investments that look nothing like the decision to vaccinate children. For DRC or Nigeria today, choosing to proceed with R21 now does not require large irreversible investments to be amortized over a long time horizon. It requires current expenditure – from government budgets and donor contributions – to vaccinate children alive today or who will be born in the next two to three years. The options for these cohorts are RTS,S, R21, or nothing at all.

R21 isn't perfect. But it's good enough to save lives at a reasonably low cost. In rough terms, 130,000 kids in Nigeria die of malaria each year, and results from clinical trials and the large-scale pilots in Ghana, Kenya, and Malawi suggest the vaccine could save at least 40,000 of those kids.[7] Each year of delay is an arena-full of children lost in just one country. There's little reason to believe saving fewer lives today will enable us to save more in the future. The risk of regret from underspending on vaccine rollout today – thousands of children lost to a vaccine-preventable disease who we could've saved – far outweighs any risk of regret from spending too much.

II. Getting kids to come back for all four shots

In September, one of us tagged along with PATH, an international NGO, to visit routine immunization days at clinics in Kisantu, Democratic Republic of Congo – the district chosen as the first site where Congo will roll out the R21 vaccine.

The launch of R21 was allegedly just two weeks away, but there were no preparations in sight. Billboards lined the main street through Kisantu promoting other public health campaigns, but there was no mention of malaria vaccines. UNICEF was due to print flyers, but they were behind schedule. Clinic staff told us they'd received no information about the vaccine. Unbeknownst to them, R21 doses arrived in DRC in June, but had not been distributed to the provinces.

7 The World Malaria Report presents a mid-point estimate of 580,000 malaria deaths globally in 2022, of which 31.1% are in Nigeria, and 72% of which are among under-5s in the West Africa region, yielding 130,000 deaths. The Imperial College model cited in Table 2 shows that R21 would avert roughly one-third of these deaths. An alternative computation is to note that Nigeria's annual birth cohort is about 7.6m, with an under-5 mortality rate of 107 per 1,000 live births, or 770,000 infants. Ignoring neonatal mortality of 34 per 1,000 live births (likey before malaria vaccination) and applying the MVIP 13% reduction in all-cause mortality would yield 72,000 children to be spared by nationwide R21 rollout in Nigeria, falling to 37,000 if we exclude all deaths under age 1.

As we watched infants get their routine shots, PATH's John Bawa mulled around in the background looking worried. Bawa had helped run the WHO's malaria vaccine implementation program mentioned earlier – the program that vaccinated over 2 million children in Ghana, Kenya, and Malawi starting in 2019 and reduced all-cause child mortality by 13 percent. He was in DRC to see the country's preparations for the malaria vaccine rollout, and help advise them on how to replicate those results. But it was clear from our visits in Kisantu that the DRC still had a long way to go.

Is it better to go big and fast or slowly and carefully?

If Congolese officials began with just one or two provinces, Bawa thought PATH and other organizations could support community mobilization to drum up demand, and help manage the supply chain to avoid stockouts. On a small scale then, maybe DRC could post the kinds of numbers his native Ghana had achieved.

That methodical approach would take time and money. As noted above, Ghana, Kenya, and Malawi spent roughly USD $2.75 per dose on vaccine introduction beyond the cost of the vaccines themselves.[8] The results were still not perfect. Coverage for the first dose was 96 percent, falling to 87 percent for the second, 78 percent for the third, and just 39 percent for the fourth. Matching those numbers for just two of DRC's 26 provinces would be a challenge, and in the meantime, the other 24 would have to wait.

So why not go to all provinces right away, accept that rollout wouldn't be perfect, but try to reach a much bigger population? Stuck in traffic on our car ride back to Kinshasa, Bawa tried and failed to dial into a meeting called by the director of Congo's essential immunization program about the R21 rollout, getting updates instead from PATH colleagues. The director was endorsing an ambitious national rollout, starting with two provinces in the short term, then proceeding quickly to the other twenty-four.

The wisdom of going fast may hinge on an unknown parameter: What happens to kids who don't finish all their shots?

The advantages of speed and scale are self-evident. But back in DRC, John Bawa felt the wisdom of the approach hinged on the retention rates the Congolese health system could achieve with a rapid scale up, and – bracing for the possibility that lots of kids wouldn't return for later doses – how much protection would be conferred to kids who only got 1 or 2 doses before dropping out.

There is, to our knowledge, no rigorous experimental answer to that question.

8 See Table 3. We focus here on the financial cost to countries of rollout, excluding the cost of vaccines themselves, and of the staff time and other in-kind government contributions to rollout. The figure of $2.75 is a simple average of the financial cost per dose across the three countries in MVIP.

We spoke with Dr. Halidou Tinto, who led the Burkina Faso arm of the R21 clinical trial. He acknowledged the practical importance of the question, but said he could not think of a way to do an ethical trial on a one- or two-dose regimen at this stage, given the proven efficacy of 3- and 4-dose regimens. He also noted that there was uncertainty on the other end: nobody has really answered how many doses vaccinated infants will need later on to keep up their immunity through, say, age five.

Non-experimental results from a small sample in Western Kenya show that unvaccinated children were three times more likely to be infected with malaria compared to children with a single dose of the RTS,S vaccine. But conversely, those latter children were still six times more likely to be infected compared to those who finished their vaccine course. It's unclear how much one can infer from these associations, as both are likely confounded by other risk factors.

A randomized trial in Ghana and Kenya provides cleaner evidence on the impact of two versus three doses of RTS,S, but only over a period of 5 months. Two treatment arms both received an RTS,S dose at baseline and another one month later. At the second month, one arm received a third dose while the other was delayed until month seven.[9]

When both arms were evaluated after six months (i.e., before the second arm had received its third dose), there were positive impacts in both groups, but there was some loss from the delay. Relative to the pure control arm, the first group that got three doses saw about 130 to 140 clinical malaria cases averted per 1,000 children vaccinated, while that number was about 100 averted cases in the arm that hadn't gotten the third dose yet.

Note that these results were not the main focus of the trial. While outcomes for both groups appear significantly different from zero, they are likely indistinguishable from each other, and the study was not designed with power in mind for this specific test.

A separate concern about incomplete vaccinations is around perceived rather than actual efficacy. In the best circumstances, malaria vaccines do not provide complete immunity. A risk we've heard in the field is that incomplete doses followed by continued bouts of malaria and malaria deaths could lead to a loss of faith in the vaccine, and a vicious cycle of low take-up leading to low efficacy leading to even lower take-up, and so on.

In a hypothetical scenario, do you save more lives from fully vaccinating 100,000 kids with 4 doses, or rushing and vaccinating 200,000 kids, many of whom only come back for 2 shots each? How about 1,000,000 kids with 2 shots? The answer appears unclear, and urgently policy relevant in places like DRC.

9 The trial's main focus was on the size of the dose not the number of doses, known as fractional dosing – which is another relevant dimension for economizing on malaria vaccine costs, but distinct from the challenge of getting kids to come back to the clinic.

Finally, it's worth noting that we heard somewhat different answers in Nigeria compared to DRC. During our interviews with health officials in Nigeria, questions about the feasibility of rolling out R21 were repeatedly met with concerns about the cost of the vaccines, including co-financing requirements under Gavi. As an "accelerated transition" country for Gavi, Nigeria faces much higher co-financing requirements compared to DRC, and the national rollout of R21 appears to be in limbo over these financing questions. When pressed on the narrow question on rollout though, multiple officials in the Ministry of Health and international donor agencies were adamant that Nigeria's current routine immunization system and its experience with COVID vaccines gave them confidence that rollout would succeed if vaccine doses were made available.

III. Vaccinating older kids

So far we've focused on the cost-effectiveness of R21, and the practical challenges of a speedy rollout. But even going fast will only get to a fraction of kids who are theoretically eligible for malaria vaccines, because current plans focus almost exclusively on infants, leaving current cohorts of young children entirely unvaccinated.

Fortunately, malaria vaccines are suitable for both infants and older children. The WHO position paper on malaria vaccines states: "At the time of vaccine introduction, catch-up vaccination can be considered in children up to 5 years of age." The formal WHO recommendation on the R21 vaccine is for children 5 months and older.

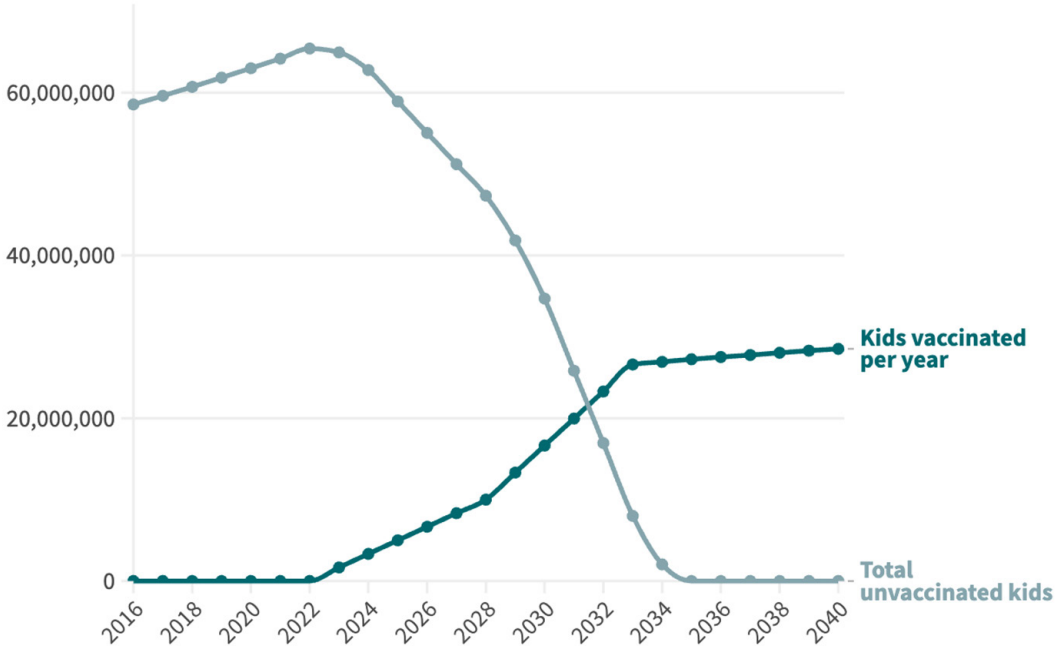
Older kids are less likely to die of malaria, but are still subject to considerable morbidity and mortality risk. Nevertheless, for the time being, no country has plans to actually vaccinate older children, focusing instead on gradual introduction of RTS,S and R21 into the routine immunization calendar for infants.

Current plans will take about a decade to reach full vaccine coverage

Gavi has not published a detailed rollout plan, but has made various statements about the scale and pace of its plans.[10] Taken at face value, those statements imply an immunization trajectory over the next several years that would ramp up gradually, leveling off in about 8 to 10 years from now (see Figure 1).

10 Specifically, the calculations above are based on three public statements from Gavi. First, "In July 2023, 18 million doses of RTS,S available for 2023–2025 were allocated to 12 countries." Second, "In the 2026–2030 period, Gavi will help vaccinate at least 50 million children with the recommended four doses of malaria vaccines." And third, "[a]nnually, at least 40–60 million doses of malaria vaccine will be needed by 2026, growing to 80–100 million doses each year by 2030."

FIGURE 1. Malaria vaccine rollout, Gavi baseline scenario
It will take until about 2035 before all kids under 3 are vaccinated



Notes: Kids vaccinated per year is based on Gavi's published plans, i.e., to reach 50 million kids from 2026–2030 and double that number in the following five years. The number of unvaccinated kids is based on total age cohorts in the top-20 countries by malaria prevalence.

Sources: Gavi vaccine rollout plans, UN population projections, WHO malaria incidence.

If all goes to plan, the number of kids left unimmunized will follow a similar path, in reverse. For the sake of argument, assume all of Gavi's doses go to the 20 countries with the highest incidence of malaria in the world. (According to the World Health Organization, this includes Benin with the highest incidence, followed in order by Burkina Faso, Mali, Liberia, Mozambique, Guinea, Central African Republic, the DRC, Sierra Leone, Nigeria, Niger, Uganda, Burundi, Cote d'Ivoire, South Sudan, Angola, Equatorial Guinea, Cameroon, Togo, and Gabon). Collectively, these countries contain just over 100 million kids under the age of five.

Getting to a point where all kids under age 5 are vaccinated will take about a decade. And notably, that's achieved mostly through letting kids age out of eligibility, unvaccinated.

Gavi estimates that its vaccination plans will avert 180,000 child deaths by 2030. But over that same period, nearly 2.5 million additional children are likely to die of malaria, per the World Malaria Report. The Imperial College model of R21 effectiveness cited above suggests ⅓, or about 800,000 of those deaths could be averted.[11]

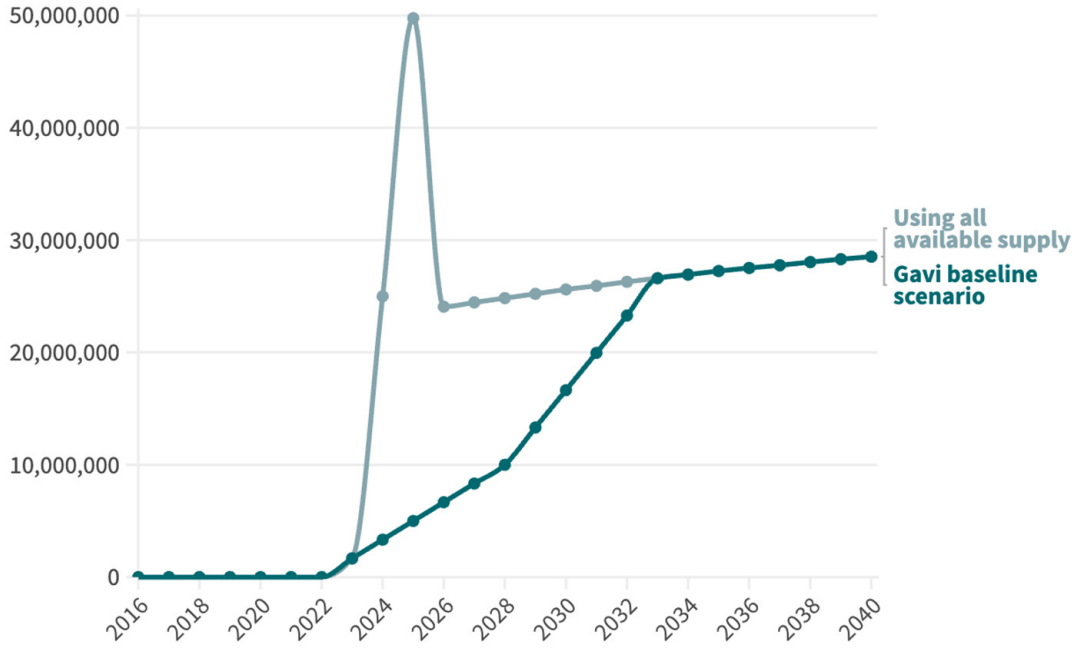
11 An alternative calculation yields a similar number: taking the total number of under-5 deaths in the 20 countries included here (and ignoring neonatal deaths that would likely occur before malaria vaccination), and applying the MVIP reduction in all-cause mortality of 13% yields about 1 million deaths potentially averted. Subtracting 180,000 already counted by Gavi yields 820,000 vaccine preventable malaria deaths by 2030.

Why not vaccinate older kids too?

In the long term, vaccinating all infants means vaccinating everyone. In the short term though, that ignores cohorts alive today who would benefit from the vaccine according to WHO recommendations.

The alternative is to frontload the roll-out. Based on the Serum Institute's stated capacity, frontloading would hit supply constraints in the short term. Serum's 100 million doses this year could cover 25 million kids, and its plan to produce 200 million doses in 2025 would cover 50 million kids. That's not quite as much as the world could hypothetically absorb, but it's close.

FIGURE 2. Kids vaccinated per year
Gavi plans to ramp up vaccination slowly. Clearing the backlog of unvaccinated kids would suggest the opposite



Notes: The Gavi baseline scenario is based on Gavi's published plans, i.e., to reach 50 million kids from 2026–2030 and double that number in the following five years. The more ambitious scenario is based on Serum Institutes stated supply capacity, initially covering all unvaccinated under-3s, then all infants in each new cohort.

In the most optimistic scenario, after two years of maxing out Serum's production capacity, supply would no longer be a limitation. The backlog of eligible children would be cleared, and Gavi could settle into its long-run plan of vaccinating new infant cohorts in line with routine immunization calendars.

The gap between the Gavi baseline scenario and this more ambitious plan is not small. Cumulatively, it could deploy nearly 600 million additional doses between now and 2033 (the area between the two lines in Figure 2). While delivering all those vaccines is a daunting logistical prospect, these extra doses either already exist or can be produced with current manufacturing capacity if financing is available.

Setting aside practical limitations for a moment to focus on what is mathematically feasible: immediately deploying all available vaccine supply would accelerate the point at which the world's most malaria-endemic countries reach full coverage by nearly a decade, shifting the timeline forward from around 2036 to as soon as 2027. In principle, expanding the age range would make an additional 145 million children eligible for vaccination over the course of the next dozen years. Again, this is not about vaccinating the same kids sooner; that would be 145 million kids who would otherwise age out of eligibility before receiving the vaccine, and suffer the consequences of repeated malaria infection in the meantime.

Vaccinating older children would, however, reduce the number of malaria deaths averted per shot.

While most malaria deaths occur among children under 5, malaria mortality risk falls with age within that under 5 group. Estimates vary on how steep that gradient is though. Data from seven sentinel surveillance sites in Africa show an age gradient that is much flatter for malaria than it is for other causes of death. The risk of dying from malaria remains high well after infancy, and falls off only after 2 or 3 years in most sites. Separate evidence from Kenya found malaria-specific mortality from verbal autopsies was about three times higher during infancy compared to years 1 to 4. Within those age bands, there was a downward age-gradient in malaria mortality risk in the first year of life, but no further decline from ages 1 to 4.

Even in the case of routine infant immunization, typically beginning at 5 months or later, much of the period of vaccine protection in trial data falls outside the first year of life. Taking the Kenyan data cited above as an illustration, and assuming (unrealistically, but conservatively for our purposes) that malaria mortality falls to zero after age 5, back of the envelope calculations suggest raising the age limit for first doses to 3 years old could reduce effectiveness against mortality by more than a third, raising the cost per death averted to $6,600. Another practical concern is that the uncertainty about uptake created by raising the age limit would also increase wastage from doses delivered to rural clinics that go unused, pushing the cost per life saved even higher.

IV. The funding gap

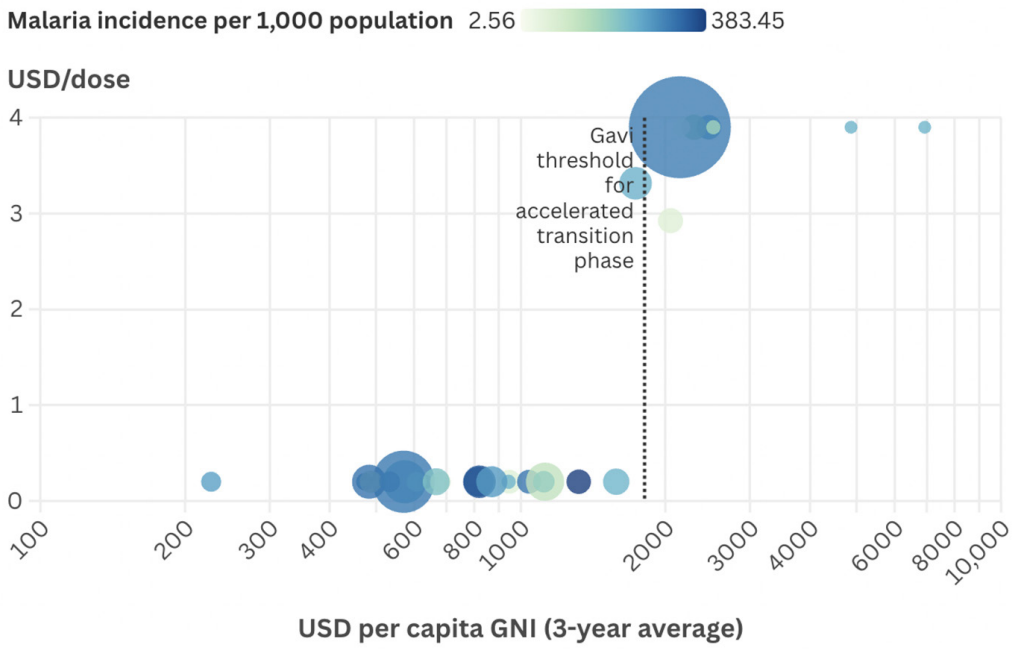
Over the summer as we worked on this piece, Gavi sent letters to multiple African countries approving orders of RTS,S and R21 sufficient to cover up to 85 percent of infants in high malaria burden areas.

Gavi has a multi-tiered pricing system for countries, based on income. In broad terms, low-income countries are eligible for Gavi vaccines at a cost to the country of $0.20 per dose. Countries with a per capita GNI above $1,810 enter a "preparatory transition" and then an "accelerated transition" phase, upon which they are required to pay 35 percent of the cost of all doses, increasing annually up to 100 percent after eight years.

Because of these co-financing requirements and because RTS,S is significantly more expensive than R21, multiple African countries which had originally placed orders for RTS,S have asked to switch to R21. While initially resistant, Gavi seems to have partially overcome this impasse by allocating the cheaper R21 doses to countries in the transition phase with percentage-based co-pays, as well as to larger countries like DRC, and the more expensive RTS,S to poorer countries whose co-pay is capped at 20 cents per dose.

FIGURE 3. Cost per dose of R21 per Gavi formula

Under the Gavi co-financing policy, the cost faced by countries increases with income



Note: Bubbles are proportional to a country's share of global malaria deaths.

The big sticking point in this grand bargain is that the one country with the single largest malaria burden in the world – Nigeria, accounting for 31 percent of global malaria deaths – is hovering just outside the income eligibility limits for significant Gavi assistance. Compounding the problem, although Nigeria's per capita GNI of $2,143 over the past three years only exceeds the Gavi threshold of $1,810 by a small margin, it has been above the line for several years, so is expected to cover almost the entire cost of new vaccines.

Nigeria's Minister of Health, Dr. Mohammed Pate who was previously chosen to run Gavi before pulling out to return to Abuja, has balked at the total cost, and the Nigerian government and Gavi appear to be at something of an impasse.

Angola is in a similar situation: per Gavi, Angola transitioned to "fully self-financing" in 2018. But amidst the global economic downturn during the pandemic, Angola's GNI actually dipped back down into eligibility for Gavi.

Finally, as discussed in detail above, Gavi's current allocation only covers infants, and the proposal to expand coverage to current cohorts of children would require more funds.

There is still a funding gap for the basic cost of vaccine commodities – and, in particular, for vaccine rollout

How much more money would be required to accelerate the rollout of R21 to reach all eligible children?

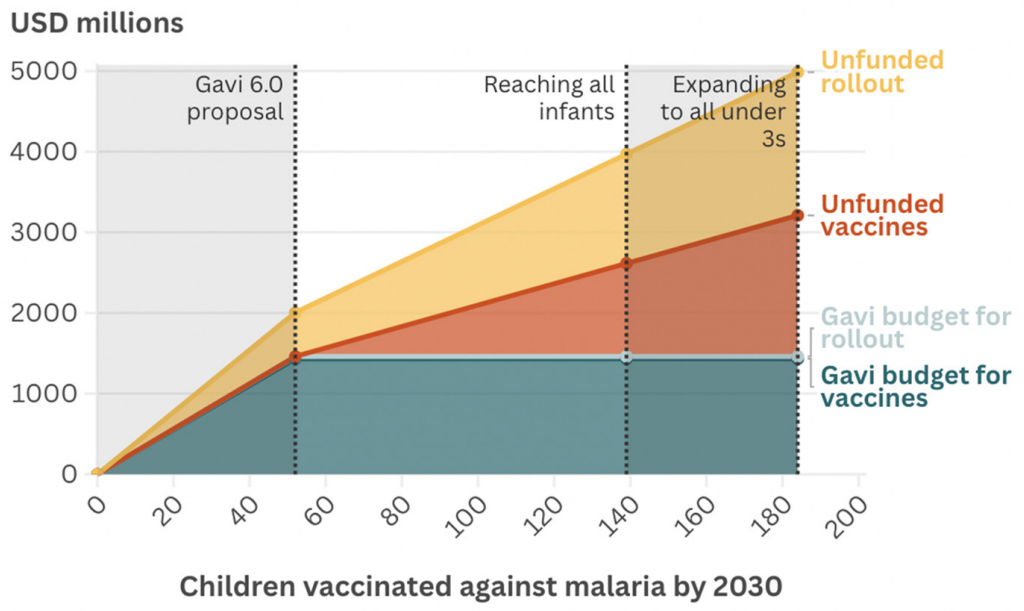
According to the official prospectus from its new fundraising round, Gavi plans to spend just under $1.5 billion on malaria vaccines between now and 2030. That money is slated to vaccinate 52 million children. That works out to about $28 per child for a 4-dose course, which is somewhere in the mid-range between the price of R21 ($3.90/dose) and RTS,S ($9.81/dose).

Gavi does not specify how much of that money will go to supporting rollout, as opposed to buying vaccines. But in the case of the malaria vaccine, the "vaccine introduction grant" which Gavi typically makes whenever countries start a new vaccine is anticipated to be between $0.70 and $0.80 per infant in the birth cohort. So for our thought experiment here, that's a fairly modest sum on the order of $20 million across 20 countries.

Accelerating the rollout and incorporating older children will, of course, cost a lot more.

FIGURE 4. Ballpark total cost for R21 scale up

Gavi plans to vaccinate 52m children by 2030 for $1.4 billion. Back of the envelope calculations suggest vaccinating all infants would cost another $2 billion, and all children under 3 another $1 billion



Sources: Authors calculations based on Gavi 6.0 business case, MVIP rollout costs, age-specific population of 20 countries with highest malaria incidence.

Our calculations imply there are roughly 87 million additional infants in the 20 countries considered here, who could be vaccinated by 2030 over and above Gavi's current plans. Incorporating all children under age 3 who adds another 45 million children, mostly in the next one to two years. Assuming, in line with Gavi's offer to countries, that take-up would peak at around 85 percent, the cost of four doses of R21 for that number of children would be about $2 billion for commodities alone.

But as we've discussed, achieving vaccine uptake and retention rates similar to those witnessed in malaria vaccine pilots to date may require spending the same kind of resources on community mobilization and supply chain management that those pilots have spent.

In extremely rough terms, taking the MVIP budget as a template, this implies an additional cost of $2.75 per child. Deducting the tiny amount Gavi is already planning to spend on vaccine rollout leaves a funding gap here of about $1 billion.

Dividing rollout scenarios into three groups as shown in the graph – Gavi's current plans, expanding to cover all infants, and expanding to cover all under-3s – two things are worth noting in the picture:

- The slope decreases slightly after the current phase, i.e., unit costs fall rather than rise, contrary to what one might expect. This reflects the assumption of a shift to R21.
- Not shown in the graph, but worth noting: the lives saved per dollar likely decline with expansion, particularly in the third phase. As noted above, lower malaria mortality among older kids could reduce cost effectiveness by as much as half.

Stepping back though, the basic message of this back-of-the-envelope calculation is that malaria vaccines have the capacity to absorb huge sums of additional resources beyond Gavi's current budget, including as much as $2 billion in additional spending before we see clear reasons for diminishing marginal returns to kick in.

The total price tag for malaria vaccine rollout – or more realistically, the total amount countries could absorb with potentially high returns in terms of lives saved – comes to something on the order of $4 to $5 billion between now and 2030, of which Gavi is on track to raise about a third.

Malaria vaccines are no substitute for other malaria control tools, like nets and frontline drugs

A concern we've heard multiple times is that in an era of flat or even declining foreign aid budgets, spending on malaria vaccines will involve zero-sum reallocations away from bed nets or malaria drugs. Or in terms of the global aid architecture, any increased contribution to the "Gavi 6.0" replenishment to finance vaccines might be deducted from planned contributions to the Global Fund.

As noted above, preliminary analysis suggests that R21 may rival the cost effectiveness of even the best alternative anti-malaria interventions. Nevertheless, such trade offs would obviously undermine the impact of vaccine rollout.

The clinical trials of both RTS,S and R21 were conducted in the presence of a full suite of standard, complementary malaria control measures available at the time. So formally speaking, we don't even know how effective these vaccines are if people aren't sleeping under bed nets, clinics don't have rapid diagnostic tests, and patients don't have access to artemisinin combination therapy drugs to respond to malaria cases when they arise.

Allowing R21 expenditures to cannibalize the budget for bed nets, however, would be a self-defeating choice. The case for accelerating vaccine rollout is a case for putting additional money into malaria control as a whole. In economics terms, technological advances have pushed out the point at which malaria funds start to hit diminishing returns, justifying greater total spend on the disease.

So in a normative sense vaccines should be delivered alongside bed nets, etc., but in a positive sense, is crowding out a concern?

Preventing vaccines from cannibalizing other malaria spending is possibly facilitated by the fact that in most countries, and at the global level, vaccines and other malaria control programs are divided institutionally. The "essential program on immunization" or EPI is often a separate unit from the "national malaria control/elimination program", NMCP or NMEP, both with earmarked budgets and donor commitments. And globally, Gavi supports vaccines, while the Global Fund and the President's Malaria Initiative (among others) support other malaria control efforts. Nevertheless, there are rumors that some donors, such as the UK, are now viewing their Gavi and Global Fund malaria contributions as a single fixed sum, to be distributed across two institutions. This would defeat the economic logic described above of new tools justifying new spending.

In short, vaccines must be a complement, not a substitute for existing malaria control measures.

Building up African manufacturing capacity should improve vaccine access (not slow it down)

During the early stages of the COVID-19 pandemic, the world made grand plans for equitable distribution of vaccines through the COVAX facility. As soon as those vaccines arrived on the market, rich countries snapped them up, COVAX collapsed, and Africa was locked out. By late 2021 G20 members had received fifteen times more doses per capita than African nations.

That experience has led to renewed calls for Africa to build pharmaceutical manufacturing capacity on the continent. The African Union has set a target for 60 percent of the region's vaccine needs to be produced internally by 2040. In a recent op-ed, Olusoji Adeyi, Prashant Yadav, Raj Panjabi, and

Wilfred Mbacham have called for using the R21 vaccine rollout as a vehicle to achieve this goal of African manufacturing.

There are potential trade offs here. Gavi has committed $1 billion to the new African Vaccine Manufacturing Accelerator, which will provide incentives for production on the continent. As Adeyi et al note:

> "Admittedly, the fastest way to scale the production of a new vaccine is to manufacture it at a single site. We recognize the economies of scale in vaccine production and understand the practicalities of technology transfer to new production sites. At the same time, merely reducing production costs and accelerating timelines to production does not address the strategic goals of achieving sustainable African end-to-end manufacturing."

But promoting African manufacturing need not slow down the overall pace. For instance, Adeyi et al also recommend:

- Technology transfer and transparent access to intellectual property for African vaccine manufacturers
- And redirected investment spending by institutions like the U.S. Development FInance Corporation and World Bank International Finance Corporation into the pharmaceutical sector – essentially crowding in non-health money to support vaccines.

Similarly, Nigeria recently waived tariffs on certain inputs into medical supply manufacturing, which also threads this needle by promoting domestic manufacturing without hindering short-term access to vaccines.

Given realistic timescales, there is no real tension between placing large orders in the short term for India's Serum Institute to produce R21 while simultaneously investing in new manufacturing capacity in Africa.

Finally, as African leaders choose where to prioritize domestic manufacturing capacity, it is worth noting that manufacturing malaria vaccines is potentially a non-strategic choice from a national security perspective. Unlike COVID vaccines, nobody outside Africa is competing for R21. Malaria is often considered an "orphan" disease, because it primarily affects poor people in the developing world. Arguably, that's why it took so long to develop a vaccine: diseases affecting poor people offer pharma companies little commercial payoff to R&D investments. But the silver lining here is that African nations looking to buy R21 from India should have little fear of getting outbid by other countries. The U.S. and Europe will not be looking to buy R21. Even India, where R21 is currently produced, is unlikely to demand large supplies of the vaccine, as its malaria rate – particularly for *p falciparum* which RTS,S and R21 protect against – is insufficient to justify the cost of mass immunization. In short, Africa accounts for around 95 percent of malaria deaths, so wherever

R21 is produced, Africa is going to be the primary market, and thus African leaders may be better off investing in domestic capacity of commodities where there is more international competition on the demand side.

Nevertheless, the goal of manufacturing R21 on the African continent is worthwhile. National and multilateral policymakers can potentially avoid life-and-death trade-offs by focusing on policies that facilitate vaccine production on the continent – tech transfer, FDI, and easing barriers to imported inputs – rather than constraining imported vaccine access in the short term.

V. Policy recommendations for specific actors

It's not easy to find 2 billion dollars between the sofa cushions. So where is all the extra spending needed to accelerate the malaria vaccine rollout supposed to come from? Here are a few ideas, tailored to specific actors.

Gavi, the Vaccine Alliance:

- **Prioritize the cheaper, equally effective R21 over RTS,S.** Gavi has taken pains to shield countries from the higher cost of RTS,S. But Gavi's own budget is finite. The point remains that to maximize lives saved with scarce resources, it is hard to justify spending money on RTS,S rather than R21 in the short term.
- **Let Nigeria and Angola back in.** As shown above, two of the countries with the largest total malaria burden in the world are currently eligible for limited or no assistance from Gavi. That jeopardizes the world's ability to make a serious dent in malaria deaths with these new vaccines. Gavi should be prepared to bend the rules.

The Global Fund for AIDS, Tuberculosis, and Malaria:

- **Don't fight the new technology; fund vaccine rollout.** Global Fund officials have expressed fear that malaria vaccines are going to crowd out their funding for other malaria control measures. It shouldn't. But rather than resort to Luddism, the Global Fund needs to get on board with scientific progress. Vaccine procurement is normally Gavi's job, but vaccine rollout is arguably closer to the traditional role and capabilities of the Global Fund – working with governments and third parties on the ground to actually implement. There's a huge financing gap on rollout. Global Fund should fund it.
- **Relax malaria funding caps for Nigeria and DRC.** The Global Fund allocates money for different diseases (HIV, TB, malaria) based on country needs, but with a maximum share of the global pie for any single country. The net effect is to cap Nigeria and DRC, the two countries with the biggest malaria burden in the world. It might be time to rethink those caps.

Bilateral donors:

- **Fund Gavi.** As the main multilateral vehicle for vaccine funding, Gavi is currently in fundraising mode. The new malaria vaccines strengthen the case for rich-country donors like the U.S. and U.K. to go big on their Gavi contributions.
- **Expand total malaria funding.** There is a temptation to reallocate money from other malaria control measures to fund malaria vaccines. But new innovation in the malaria space is pushing out the point of diminishing marginal returns. Technology progress justifies more investment, not less. Donors should avoid a zero sum situation where they reallocate from the Global Fund's budget for malaria drugs or bed nets to fund malaria vaccines through Gavi (as the U.K. is rumored to be contemplating).
- **If necessary, reallocate from outside global health.** If donors need to reallocate money from other parts of the aid budget, look outside the health verticals like Gavi and Global Fund to some of your lower-impact bilateral programs in middle-income countries. The time is ripe to prioritize lives saved over diplomatic vanity projects in countries that don't need the money.

A short-term window for highly effective philanthropic support

Gavi raises funds in five-year cycles. In June 2024 it launched the replenishment drive for Gavi 6.0, which will cover 2026 to 2030. It is probably safe to presume that until that replenishment drive is done, we're not going to see bold new financial commitments from Gavi to buy more vaccines. Even where current doses suffice, resources for community awareness campaigns and supply chain management are lacking, which limits the speed of rollout in two ways: directly, by lowering take-up and retention once vaccines are introduced in a given geography, and indirectly, by discouraging countries from making vaccines available on a national scale in the first place.

That creates an opportunity in the next 0 to 5 years for someone – either a current Gavi donor accelerating their pledge, or philanthropies stepping into the breach – to work in collaboration with Gavi to expedite vaccine rollout. Donors, and especially private philanthropies, can't do this alone. Governments must demand the vaccine and lead the rollout, which will be a monumental logistical undertaking. They will require technical assistance, which Gavi and NGOs like the Clinton Health Access Initiative, PATH, and others can provide – but only with external financing.

Several features make this an attractive use of philanthropic money:

1. **Vaccines are high-impact and scalable.** There are few more cost-effective philanthropic endeavors than paying for vaccinations. Clinical trial data, modeling, and data from large-scale pilots in Ghana, Kenya, and Malawi, suggest the rollout of the R21 vaccine could avert one child death per $4,200 spent. Relatively few other philanthropic causes rival that level of cost-effectiveness, and among those, even fewer could credibly absorb $2 to $3 billion over

the near term. There may be no other way to save so many lives with such a high degree of certainty with "only" cash.

2. **There is low risk of duplication and fungibility.** One reason that philanthropists might normally eschew vaccines as a focus for their giving is that they might assume, somewhat reasonably, that because vaccines are so cost-effective, someone else will surely pick up the tab. Hence any donation to vaccine rollout will displace money that would otherwise be forthcoming from governments and official donors. But that appears not to be the case for the short-term rollout of malaria vaccines. Gavi, the vaccine alliance, is the conduit for the bulk of official foreign aid for vaccines, and they are busily raising all the money they can for its 2026–2030 cycle. But even if the Gavi replenishment goes well, it will likely not suffice to procure enough RTS,S or R21 for millions of children in the most malaria-endemic countries in the world over the next decade, and will almost certainly not provide the necessary resources to make sure all kids actually get their shots.
3. **There's a sustainable institutional model.** In the long-run, access to lifesaving public health interventions should not hinge on the year-to-year whims of philanthropic program officers. Philanthropic donors often worry, quite rightly, about trying to fix perennial problems with two- to three-year grant cycles. Shouldn't we be investing in systems, not patches? In that sense, the shortfall for malaria vaccine rollout is a unique exception. Arguably, the world *has* invested in a robust system for the international community – spanning governments, philanthropies, and corporations – to provide free access to life-saving vaccinations to billions of people around the world. But due to the timing of the vaccine approval and the vagaries of fundraising cycles, Gavi is resource constrained. Philanthropic intervention at this point would not aim to bypass or undermine the multilateral system, but to help a system designed to evolve slowly respond quickly to a new opportunity.
4. **It's a one off commitment with no recurring liability.** Closely related to sustainability, donors also worry about getting locked into supporting a given cause in perpetuity. Again, this concern is mitigated by the time-bound nature of the current funding gap for malaria vaccines. Gavi has a plan in place for the longer term, having agreed with its board to finance malaria vaccine access for all infants in malaria-endemic countries within the next decade. Several hundred thousand lives hang in the balance in the meantime.

As we've tried to elaborate here, some key questions remain unanswered though. What share of children can countries realistically expect to show up for – and complete – vaccine series in an accelerated rollout scenario? If children drop off after 1 or 2 doses, will vaccine efficacy decline more or less than proportionally? And given the large number of unvaccinated children above 1 year old, should donors and governments be prepared to bear the higher cost of vaccinating older children? In addition to funding procurement and vaccine rollout, short term expenditures on answering these questions would likely pay a high social return.

Right now, we're mostly losing the fight against malaria. Roughly 600,000 people, mostly children, die of the disease annually. And in the past decade, despite billions of dollars spent on malaria control, that number has gone up, not down (though the rate of malaria deaths has gone down slightly).

After decades of frustrating setbacks and procedural delays, science has given us new tools to prevent those deaths. The R21 vaccine is effective, cheap, and available right now. Actually getting R21 shots in the arms of millions of kids in some of the poorest countries in the world will be a Herculean task. But the payoff could be one of the biggest public health victories in recent history.

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