{This draft is being circulated with a variety of internal and external reviewers (including WHO, GAVI, etc.) for comments and suggested edits prior to a public version being finalized the week of December 4th to use for informing media. (Updates will continue after that time). Please feel free to comment/make edits in this document, or if you would like your comments not to appear to other reviewers, make a copy or email thoughts to josh@1daysooner.org.}

Malaria Vaccination Talking Points

Key point: The world must commit to using in 2024 all malaria vaccine doses that can be produced. This would save hundreds of thousands of children's lives.

- **New Malaria Vaccines Could Save Many Lives**: A new malaria vaccine (R21) has been approved and can be produced in enough volume to save the lives of hundreds of thousands of African children.
- **Current Rollout Plans Do Not Fit Available Supply**: Over 100 million doses could be produced over the next year, with material for 20 million already available. But the WHO does not expect distribution to begin until the middle of next year, and the latest public forecast predicts only a small fraction of available vaccines will be distributed. This would leave tens of millions of children unvaccinated despite having shots available.
- **An Extraordinary Opportunity Requires an Extraordinary Response**: More than a billion COVID-19 vaccine doses were delivered in Africa within two years. A similar undertaking must be made to vaccinate African children for malaria.
- **Commit to the Goal: Use Every Dose That's Made This Year**: Each dose of R21 costs $3.90, and each one is predicted to save on average nearly a month of a child's life. Global institutions are obligated to set the shared expectation that all doses available will be distributed in 2024: that represents at least 120 million doses, enough to vaccinate 40 million children with an initial course.

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Frequently Asked Questions

What is malaria?

Malaria is a disease spread by parasites carried by mosquitoes. Common symptoms include fatigue, fever, chills, and headaches.[1] Some cases are profoundly painful: one survivor likened it to "being stung repeatedly by an electric shock gun".[2]

Worldwide, in 2021 there were roughly 247 million malaria cases, which caused 619,000 deaths.[3] 95% of malaria cases and 96% of deaths from malaria occur in Africa, almost entirely in sub-Saharan Africa.[4] About three quarters of people who die from malaria are children under the age of 5.[5]

What causes malaria?

Malaria is caused by microscopic parasites of the *Plasmodium* genus, four of which regularly infect humans. Of these, *P. falciparum* is responsible for the vast majority of deaths.

P. falciparum needs to infect both a human and a mosquito to complete the four stages of its life cycle. As it bites a human, a mosquito releases the parasites into the blood. Within minutes they travel to the liver, where they further mature for about 5.5-7 days. The parasite re-enters the bloodstream and invades red blood cells, reproducing and breaking out of infected cells cyclically every two days, leading to "waves" of fever. As the cycle continues, some reproductive forms of the malaria parasite are then transmitted to mosquitoes that bite the infected person, beginning the life cycle once again.[6] [7]

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[1] Malaria, WHO, March 29, 2023.
[2] Coumba Makalou, "What it feels like to have Malaria," NothingButNets, June 5, 2007.
[3] World malaria report 2022, WHO, December 2022, p. 15.
[4] World malaria report 2022, WHO, December 2022, p. 18. Nearly half of malaria cases in 2021 occurred in four countries (Nigeria, the Democratic Republic of the Congo, Uganda, and Mozambique). (Id., 17) Slightly more than half of all malaria deaths in 2021 occurred in four countries (Nigeria, the Democratic Republic of the Congo, the United Republic of Tanzania, and Niger). (Id. p. 16) Note that the WHO African Region excludes most countries in North Africa along the Mediterranean.
[5] World malaria report 2022, WHO, December 2022, p. 17.
[6] See this *Works in Progress* diagram of the life cycle of malaria for a visualization.
[7] Stephen L. Hoffman, Carlos C. Campbell & Nicholas J. White, "Malaria," in *Tropical Infectious Disease: Principles, Pathogens and Practices* (3rd. Ed., 2011).

Are there any effective malaria vaccines?

Yes. After more than six decades of struggle to create a working malaria vaccine, two have been approved by the World Health Organization in the last two years: RTS,S/AS01 (brand name Mosquirix, by GSK, "RTS,S" below) and R21/Matrix-M (developed by Oxford and manufactured by the Serum Institute of India, "R21"). The WHO approved RTS,S in October 2021 and prequalified it in July 2022. R21 was approved October 2, 2023 and has not yet been prequalified.[8]

The two vaccines are closely related: the creators of R21 describe it as "a next-generation RTS,S-like vaccine."[9] Both require three doses each spaced one month apart followed by a booster dose about a year later.[10] Both target the parasite's circumsporozoite protein (CSP) before it can enter the liver.[11] Both employ virus-like particles built from the same scaffolding derived from the hepatitis B virus.[12] Both use similar adjuvants to enhance the natural immune response.[13] Both were developed with multiple human challenge studies.[14]

What are the differences between the vaccines?

R21 replicated the creation of RTS,S with more modern technology. As a result, the surface of R21 is covered with a greater density of the malaria protein (CSP) for the immune system to react to.[15] Similarly, the immune-amplifying adjuvant used by R21 is simpler than the one for RTS,S, so it's easier to make. These two factors likely contribute to the five-fold lower dose, stronger immune response, and simpler manufacturing at scale of the R21 vaccine.[16]

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[8] As is discussed in depth below, prequalification by the WHO is required before global funders will pay for the vaccine.
[9] Katharine Collins et al. (2017), Enhancing protective immunity to malaria with a highly immunogenic virus-like particle vaccine, *Scientific Reports* 2017;7:46621. See also Katharine Collins (2014), R21, a novel particle based vaccine fora multi-component approach to malaria vaccination, PhD thesis, St Cross College, Oxford University.
[10] Malaria vaccines (RTS,S and R21), WHO, October 17, 2023.
[11] Matthew B. Laurens, RTS,S/AS01 vaccine (Mosquirix™): an overview, *Human Vaccines and Immunotherapeutics* 16(3), 2020.
[12] For details on manufacturing standards related to production of R21, see Mukhopadhyay et al. (2022), Production of a high purity, C-tagged hepatitis B surface antigen fusion protein VLP vaccine for malaria expressed in Pichia pastoris under cGMP conditions, *Biotechnology & Bioengineering* 119(10). See also Katharine Collins (2014), R21, a novel particle based vaccine fora multi-component approach to malaria vaccination, PhD thesis, St Cross College, Oxford University..
https://pubmed.ncbi.nlm.nih.gov/28422178/
[13] Both amplify the immune response with a substance ("adjuvant") related to the soapwort plant (saponins). R21 uses a simpler saponin-based adjuvant, Matrix M (a Novavax product), than RTS,S, which uses a saponin-based adjuvant mixed with the liposomal compound MPL.
[14] Sekhar, A., & Kang, G. (2020). Human challenge trials in vaccine development. Seminars in Immunology, 50, 101429. https://doi.org/10.1016/j.smim.2020.101429
[15] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5395940/
[16] Datoo et al. (forthcoming, posted online September 2023), A phase III randomised controlled trial evaluating the malaria vaccine candidate R21/Matrix-M™ in African children, *The Lancet* (preprint).

	RTS,S	R21
Phase 3 efficacy: age 5-17 months	First 12 months: 56% efficacy First 48 months: 36% efficacy[17]	First 12 months: 78% efficacy[18] First 48 months: Unknown[19]
Immune response[20]	Anti-NANP IgG: 318 EU/mL[21]	Anti-NANP IgG: 11,438 EU/mL[22]
Price	$10.20 per dose[23]	$3.90 per dose.[24]
Doses available in 2024	6 million[25] [26]	>120 million[27]
Approved population	Children 6 weeks to 17 months[28]	Children 5-36 months
Vaccine storage	Stable for 3 years at 2°-8°C.[29]	Stable for two years at 2°-8°C, and stable for up to two weeks between 25°–40°C.[30]

[17] RTS,S Clinical Trials Partnership, Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial, *The Lancet* 367: 2284, 2015.
[18] Datoo et al. (forthcoming, posted online September 2023), A phase III randomised controlled trial evaluating the malaria vaccine candidate R21/Matrix-M™ in African children, *The Lancet* (preprint), ll. 339–343. Efficacy differs based in part on age and seasonality. Malaria in some parts of Africa is seasonal, corresponding with rainy seasons that allow for mosquitos to proliferate. In other parts of Africa, it is a perennial threat. R21 was slightly more effective overall in 5–17-month-olds than 18–36-month olds (78% versus 70%). At seasonal sites for 5-17-month-olds, efficacy was 79%, versus 75% at standard/perennial sites.
[19] Initial results from the phase 2b R21 study in Burkina Faso did not include a four-year followup, and only recently concluded; results have not yet been posted. The phase III preprint includes data from followup at 18-months at seasonal sites, where VE was 74% for first-time malaria episodes at 72% for multiple episodes, including 18-36-month olds, in whom vaccine protection is notably less strong (Datoo et al., forthcoming, ll. 70–7; 339–347). R21 trials may have timed vaccinations optimally with malaria season at seasonal sites, which could lead to greater efficacy than in real-world scenarios, but the gap between seasonal and standard sites is relatively small.
[20] IgG is a type of antibody the immune system produces to disable pathogens. NANP is the part of the malaria protein that the antibody binds to. So this number indicates the amount of antibodies that bind effectively in a unit of blood. Anti-NANP IgG titers have correlated with reduced risk of clinical malaria and are the simplest measure of immune response currently available, though they may not represent truly robust "correlates of protection" in the formal immunology sense. The immune response differences between the two vaccines should not be overstated. Unlike RTS,S, immune response data for the R21 phase 3 is not yet available, and while the 35-fold difference in antibody amount does imply the R21 response is stronger, it is not 35-times stronger. In an immunology context, having 35x the antibodies is a much smaller difference than having 35x the effect.
[21] Datoo et al. (2021), Efficacy of a low-dose candidate malaria vaccine, R21 in adjuvant Matrix-M, with seasonal administration to children in Burkina Faso: a randomised controlled trial, *The Lancet* 397.
[22] In children 5-17 months 28 days after the third dose was administered.
[23] Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping, UNICEF Supply Division, August 2022.
[24] Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping, UNICEF Supply Division, August 2022.
[25] Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping, UNICEF Supply Division, August 2022.
[26] GSK welcomes WHO recommendation for broad roll-out of its RTS,S/AS01e (RTS,S) malaria vaccine, GSK press release, October 6, 2021.
[27] The Serum Institute has indicated that they have 20 million doses on hand, can currently produce 100 million doses annually, and intend to expand their production capacity to 200 million doses annually by 2026 <to confirm>). <FT article and Serum press release>. Thus it is realistic to expect a minimum of 120 million doses available during 2024. <By comparison, Serum Institute produced <__> million doses of the AZ COVID vaccine in 2021>.
[28] <EMA approval.>
[29] Mosquirix: Product Information, European Medicines Agency, October 2023, p. 12. A 2020 article suggests modifications could allow the vaccine to tolerate 1 month at 45 °C. Fortpied et al. (2020), The thermostability of the RTS,S/AS01 malaria vaccine can be increased by co-lyophilizing RTS,S and AS01, *Malaria Journal* 19(202).
[30] "A high efficacy malaria vaccine" lecture by Adrian Hill, August 2023, c. 33:45.

	RTS,S	R21
Development history	RTS,S was first created by GSK in 1987. Phase 3 testing concluded in 2014 and the European Medical Association approved the vaccine in July 2015,[31] but concerns about a potential meningitis related safety signal led to WHO requiring further testing.[32] This took place 2019-2021[33] and confirmed the vaccine's safety. WHO approval came in 2021[34] [35] and prequalification in 2022.[36]	R21 was developed in 2011 at the Jenner Institute at Oxford by Katharine Collins.[37] The first clinical trials testing the vaccine began in 2015, including a phase I study evaluating R21 combined with Novavax's adjuvant Matrix-M.[38] A phase 2b was concluded 2023,[39] and a phase 3 is slated for completion in early 2024,[40] with preliminary results available as of September 2023.[41] The vaccine was approved by the WHO in 2023 but has not yet received WHO prequalification.[42]

Roughly, how many people need to be vaccinated?

About 80 million. Existing data on age and malaria risk from WHO and other international sources enable a rough estimate of total potential vaccine recipients. Approximately 91.7% of the population in Sub-Saharan Africa — 1.01 billion people — are at risk of contracting malaria, according to WHO estimates for 2021.[43] U.S. Census population projections for Sub-Saharan Africa indicate that approximately 178.6 million people are children under the age of five as of 2023; 91.7% of this is 163.78 million.[44] Assuming half fall between 5 and 36 months old,[45] approximately 82 million should thus be eligible for a malaria vaccine.

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[31] The RTS,S malaria vaccine, PATH, September 17, 2019.
[32] Meredith Wadman, First malaria vaccine slashes early childhood mortality, *Science*, October 24, 2023. "The lengthy, expensive RTS,S pilot program came at a cost, [Mary] Hamel acknowledged. It 'really did contribute to a delay in widespread use of the vaccine,' she told the audience. But without it, 'I really believe that questions would have lingered' about the vaccine's safety, effectiveness, and impact—and the feasibility of reaching kids. The pilot program and its critical data, she added, have 'forged a pathway for future malaria vaccines.'"
[33] Cassandra Willyard, The slow roll-out of the world's first malaria vaccine, *Nature* Outlook, December 19, 2022. The study was intended to last until 2023.
[34] Cassandra Willyard, The slow roll-out of the world's first malaria vaccine, *Nature* Outlook, December 19, 2022.
[35] Cassandra Willyard, The slow roll-out of the world's first malaria vaccine, *Nature* Outlook, December 19, 2022.
[36] Cassandra Willyard, The slow roll-out of the world's first malaria vaccine, *Nature* Outlook, December 19, 2022.
[37] Katharine Collins (2014), R21, a novel particle based vaccine fora multi-component approach to malaria vaccination, PhD thesis, St Cross College, Oxford University.
[38] There were two phase I safety/immunogenicity studies conducted by the Jenner Institute beginning in late 2015, assessing AS01B (NCT02600975) and Matrix-M (NCT02572388) as adjuvants.
[39] Safety, Immunogenicity and Efficacy of R21 Matrix-M in 5-17 Month Old Children in Nanoro, Burkina Faso (NCT03896724
[40] A Phase III randomized controlled multi-centre trial to evaluate the efficacy of the R21/Matrix-M vaccine in African children against clinical malaria (NCT04704830)
[41] Datoo et al. (forthcoming, posted September 2023), A phase III randomised controlled trial evaluating the malaria vaccine candidate R21/Matrix-M™ in African children, *The Lancet* (preprint).
[42] Oxford R21/Matrix-M™ malaria vaccine receives WHO recommendation for use paving the way for global roll-out, Serum Institute of India, October 2, 2023.
[43] World malaria report 2022, WHO, December 2022, Annex 4G. Sum of all countries in the WHO African Region (AFRO) in the spreadsheet (Algeria, which is in AFRO but is not Sub-Saharan, is not listed) plus Somalia.
[44] U.S. Census Bureau IDB, accessed November 27, 2023.
[45] There are 60 months of life before turning five years old; 31 are from five months (inclusive) to 36 months. This is an estimate used for simplicity as ages in reality are not uniformly distributed.

Each child requires three R21 doses in the first calendar year followed by a booster a year later. To vaccinate all eligible children in 2024 would require 246 million doses along with another 82 million doses in 2025 as boosters. After the "backlog" of currently unvaccinated children are protected, the roughly 30 million born each year would require 120 million doses.

What will be the impact of vaccination?

Methods to estimate the impact of vaccinating the most vulnerable children yield estimates that range from about 6,000-9,500 deaths averted per million children fully vaccinated. This implies vaccinating 40 million children would save about 240-380 thousand lives and vaccinating all 82 million eligible children would save about 495-775 thousand lives. If each dose costs $3.90 to purchase and about a dollar to distribute, that implies a cost per life saved of $2,100-$3,300, which equates to about a dollar per week of a child's life.

- **Imperial Preprint**: A recent study (in preprint) by authors at Imperial College projected that for every million children vaccinated by R21 age 5-17 months in Sub-Saharan Africa, about 6,000 deaths and two million cases of malaria would be averted over 15 years (children can contract malaria multiple times).[46] The vaccine is somewhat less impactful when given to children 18-36 months.[47]
- **WHO Study**: A recent study by the WHO found that RTS,S vaccination reduced all-cause childhood mortality by 13% for every child vaccinated (not just deaths from malaria).[48] 74 out of 1000 children born in Sub Saharan African die before the age of 5.[49] If R21 can reduce the all-cause death rate in this group by 13%, it would save about 9,500 lives per million children vaccinated.[50]

What is the current plan for malaria vaccination in 2024?

RTS,S vaccine deployment is expected to continue, with GSK committed to delivering 6 million doses, enough to boost 1.5 million previously vaccinated children and vaccinate 1.5 million new children.[51]

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[46] Schmit et al., The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study (preprint), ll. 312–329; 344–353, Lancet, October 2023. Modeled efficacy depended on the intensity and seasonality of malaria in given areas. In areas with seasonal malaria transmission, 663 deaths per 100,000 fully vaccinated children could be averted.

[47] <details tk>

[48] https://www.science.org/content/article/first-malaria-vaccine-slashes-early-childhood-deaths

[49] https://data.unicef.org/resources/levels-and-trends-in-child-mortality/

[50] Meredith Wadman, First malaria vaccine slashes early childhood mortality, *Science*, October 24, 2023.

[51] Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping, UNICEF Supply Division, October 2023.

Plans for R21 rollout are unclear. The WHO has said it expects rollout to begin in mid-2024.[52] The most recent publicly available forecast (December, 2022) indicates that fewer than 20 million total malaria vaccine doses (including RTS,S) will be delivered in 2024 and less than 80 million per year by the end of 2027.[53] Because that forecast does not discuss R21, it is hard to imagine such a small fraction of Serum Institute's available capacity being distributed, and an updated forecast would likely have a higher number.

What has to happen for a new vaccine to be distributed in sub-Saharan Africa?

Most African countries cannot afford to purchase vaccines without assistance, so they rely on GAVI, the Vaccine Alliance, to help buy them. GAVI gives vaccines to the countries, which manage distribution (sometimes with the assistance of regional partners or other NGOs). GAVI in turn procures vaccines through UNICEF, which pays the vaccine manufacturer. UNICEF cannot purchase a vaccine unless it has been prequalified by the WHO.[54]

When is WHO prequalification expected for R21?

WHO prequalification typically is targeted to happen 270 days after approval,[55] which would be roughly July 2024 for R21. [56] But the R21 prequalification process has been rumored to be on an accelerated timeline with some insiders expecting it may occur before the end of 2023.

How does GAVI's purchase of the vaccines work?

GAVI purchases vaccines and provides them to countries based on its forecast of their demand. That is, countries develop plans to distribute vaccines internally and then provide requests to GAVI to purchase doses on their behalf, which GAVI aggregates into a market shaping forecast. GAVI has a cost-sharing formula so that poorer countries pay a smaller proportion of a vaccine's cost than GAVI-eligible countries with higher incomes.

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[52] Malaria vaccines (RTS,S and R21), WHO, October 17, 2023.

[53] Market Shaping Roadmap: Malaria Vaccines. GAVI, December 2022. See also Malaria vaccine market shaping roadmap, Gavi, April 2023.

[54] COVID vaccines were an exception, but they went through a more rapid WHO emergency use listing process that was a substitute for prequalification. See the WHO's Regulation and Prequalification of COVID-19 vaccines web page.

[55] Aisling Leow, James Hu, and Tom Hird, An overview of WHO Prequalification: Process, usage, and potential improvements, Rethink Priorities, July 24, 2023. For reference, RTS,S was approved October 2021 and prequalified July 2022, about 270 days later.

[56] Donato Paolo Mancini, Oxford vaccine developer criticises WHO's mid-2024 target for malaria shot, *Financial Times*, October 6, 2023. FT notes that the WHO target was "mid-2024".

What are the deficiencies of the current plan to deploy malaria vaccines?

The difference between what Serum Institute says it can supply (at least 120 million doses) and GAVI forecasts for delivery (20 million doses) represents a difference of about 33 million children vaccinated or about 200,000 extra kids' deaths if the Imperial pre-print projection can be relied upon.[57] If the Serum Institute can meet their goal of 200 million doses per year in 2024, this death toll from undistributed supply would be about 400,000.

Moreover, a plan to begin rollout in mid-2024 is likely to leave many children vaccinated in 2024 unprotected during the peak malaria season in their country.[58]

Finally, this is not just a problem for 2024. The public GAVI market shaping forecast indicates only a maximum of 30 million doses in 2025 and 45 million in 2026.[59] This would represent an annual average of about <___K>[60] extra kids' deaths preventable by distributing available vaccine doses.

What are some of the challenges to vaccinating more children in 2024?

- **Vaccination Is Normally Slow**: Vaccines typically take about ten years from starting human testing to regulatory approval and another 10-15 years to achieve broad distribution.[61] Malaria vaccine development has taken decades. Thus it is difficult institutionally and psychologically to immediately begin a sprint to deployment, especially when sprinting is far outside the norm.
- **There's Not Much Money**: African countries must spend very limited resources to fight a variety of diseases. Philanthropic funding for global health is similarly overburdened. Beyond the almost one billion dollars needed to purchase R21 vaccine doses, more will be required to pay for distribution. These budgets cannot be shifted at a moment's notice, and without new sources of funding spending on one priority means shorting another.
- **Four Doses Are Tough:** Most vaccines require fewer than four doses, and the timing for the current malaria vaccines does not fit well with the existing schedule for vaccinating children. This is not impossible: RTS,S vaccination rates are high in countries where it is available,[62] and parents are very experienced with malaria and

[57] And <xx> based on the WHO RTS,S study.

[58] <Discussion of peak malaria season>

[59] https://www.gavi.org/sites/default/files/document/Malaria-Roadmap-Public-Summary.pdf

[60] [(Total doses needed (77.5*4+120+120) minus current rollout plan (20+30+45))/3]*6,000

[61] See SAVAC Stakeholders Meeting video at 1:20:30. See also Plotkin's Vaccines, 7th edition, Chapter 4 ("The Vaccine Industry"), table 4.3.

[62] <better source but here's the quote from the imperial modeling paper>: "Pilot implementation of this regimen through the Malaria Vaccine Implementation Programme (MVIP) in Ghana, Kenya and Malawi has subsequently demonstrated the feasibility of delivery. To date, high demand has been demonstrated with 89%, 76% and 83% uptake of the 1st dose, 76%, 73%

motivated to protect their children. But it is not as easy as distributing most new vaccines.

- **The Process Is Very Complicated**: Institutionally, vaccination in poor countries requires a series of interlocking steps (described above) between the manufacturer, regulator, payor, facilitator, and nation-state distributor. Each of those institutions in turn may have multiple departments who share responsibility for a decision. This creates significant friction and delay (particularly if each step must be completed sequentially before the next can begin). Practically, giving out hundreds of millions of doses of a vaccine across dozens of countries requires educating and enabling tens of thousands of providers located across many poor and inaccessible areas.
- **Vaccinologists Are Human**: While the many heroes who spent decades developing malaria vaccines are motivated primarily by saving lives, there are human factors that inhibit rapid and seamless cooperation. Much blood and treasure was spent advancing RTS,S over many years, which can make it hard to immediately shift towards driving forward a different vaccine (even if that vaccine is based almost entirely on RTS,S). Moreover, while many people contributed to R21's development, the senior scientist overseeing the work was Oxford professor Adrian Hill, who a book about Operation Warp Speed described as "a polarizing figure who spent years fighting malaria and being abrasive to his peers."[63]

What should be the goal of malaria vaccination in 2024?

Each vaccine dose saves almost a month of healthy life at a cost of $3.90.[64] At that price, no dose should go unused in 2024. This means that if the Serum Institute can produce 120 million doses, forty million children should be vaccinated, and if they can make 220 million, seventy-three million should be.

Because there are many different institutions that will need to work together to achieve this and none can force the issue on their own, it is critical that all commit to a common expectation of distributing all possible doses and to identify the obstacles to achieving that outcome. Even if the target cannot be hit in 2024, sharing information about the critical path and causes of failure will save lives in 2025 and beyond.

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and 72% uptake of the 3rd dose and 50%, 52% and 36% uptake of the first booster dose in Malawi, Ghana and Kenya respectively in 2022.4"

[63] Gregory Zuckerman, *A Shot to Save the World: The Inside Story of the Life-or-Death Race for a COVID-19 Vaccine*, Portfolio (2021).

[64] <$50/DALY per Imperial and $3.90 per dose equates nearly a month per dose>

What steps could help achieve a better outcome?

From 2021-2023 more than a billion COVID vaccine doses were distributed in Africa,[65] showing that rapid rollout can be achieved. The following are some of the policy steps that could enable optimal malaria vaccination in 2024.

- Public WHO Commitment to ensuring all doses produced are distributed before the end of 2024, including a commitment to achieve the 120 million doses target and identify obstacles and enablers for a 220 million stretch goal.
- A New GAVI Forecast of malaria vaccine demand that articulates what would be needed to achieve a 120 million dose target/220 million stretch goal. Additionally a transparent process is needed for regular updating of the forecast in response to African government requests.
- Parallelized Deployment Planning: Currently, African countries may not feel empowered to begin planning for R21 distribution until they are guaranteed funding from GAVI, and GAVI's plans are slowed down while waiting for prequalification. Just as Operation Warp Speed achieved rapid COVID vaccine development by parallelizing normally sequential processes, African distribution planning needs to be enabled now rather than beginning only with prequalification and purchase. This may require both a push from experts and advocates within African countries and a pull from new funders willing to work with GAVI to provide bridge funding that can be wholly or partially returned once GAVI is able to pay.
- African Demonstration Projects: Nigeria, Burkina Faso, and Ghana approved R21 prior to the WHO, and Burkina Faso both conducted clinical trials of RTS,S and R21 and have led early rollout of RTS,S. Making Burkina Faso (or another African country) the first one with a clear and funded plan to vaccinate all its eligible population (about 5 million in total) would set a valuable precedent for other countries and global institutions to follow.
- Advanced Market Commitment to Subsidize Distribution: Because the costs of distribution may be unpredictable and funds may be scarce, one potential way to help countries provide vaccination would be to create a fund that pays countries for each vaccine dose that is distributed in 2024 (possibly with a diminishing subsidy in later years).
- U.S. Technical Assistance: U.S. government help was important to the rollout of COVID vaccines over the last two years. USAID and the CDC can play a role in providing technical assistance to help African countries plan their R21 vaccination campaigns. This would be especially useful as a public-private partnership in tandem with new

[65] Africa CDC COVID-19 Vaccine Dashboard, accessed November 21, 2023.

philanthropic funding to support distribution efforts or other technical assistance from groups like PATH.[66]

What are intermediate advocacy targets in the short-term to help achieve the goals above?

- African Governmental Support and Planning: Malaria vaccination cannot succeed without African governments leading the way. Therefore it is critical to build expert networks and advocacy campaigns within each affected nation to ensure that the countries are motivated and enabled to (a) plan for and implement vaccination campaigns and (b) make the case to western governments, international institutions, and the global public to treat this issue with urgency.[67]
- Prequalification: While reassuring statements have been made privately to some insiders, the WHO should set a public target for when to conclude the prequalification process, with a goal aimed ideally before the end of 2023.
- WHA Resolution: The World Health Assembly begins May 27th, 2024.[68] Member countries have a mechanism to propose resolutions for all member states to vote on.[69] A resolution calling for a malaria dose distribution commitment would serve as a useful rallying point for countries around the world and ensure a WHO commitment if successful.
- U.S. Government Inquiry: As a member of the WHO Executive Board and major funder, U.S. government inquiries (possibly via the President's Malaria Initiative or HHS's Office of Global Affairs) can drive global attention and engagement for the issue.
- Fundraising: An extraordinary vaccine deployment process will require additional resources. Drawing funding from existing sources runs the risk of pulling funding from current priorities and robbing Peter to pay Paul. A fundraising campaign that brings in new sources of funding to global health would help mitigate this risk.
- Attention: Setting a broad expectation of using all available vaccines will require persistent and pervasive public messaging across Europe, the Americas, and Africa. This will require a range of strategies for a range of audiences but promoting African experts and public health officials is one attractive tactic.

What Lessons Can Be Drawn from the African COVID Vaccine Experience?

The response to Covid-19 showed that a fast and large-scale vaccine roll-out was feasible in low-to-middle-income countries. The COVAX mechanism is an initiative of GAVI, WHO,

[66] https://www.givewell.org/research/grants/PATH-malaria-vaccines-January-2022
[67] Because 50% of malaria deaths occur in Nigeria, the Congo, Tanzania, and Niger, these countries are especially important to mobilize. Uganda and Mozambique are other countries with great malaria disease burden.
[68] https://apps.who.int/gb/gov/en/dates-of-meetings-eb_en.html
[69] <https://apps.who.int/gb/bd/pdf_files/BD_49th-en.pdf#page=182>

CEPI and UNICEF that played a key role in making the vaccine available in 92[70] eligible countries. From 2021 to 2022, 1 billion doses were delivered through COVAX[71]. The first Covid-19 vaccine to receive WHO prequalification received it in October 2023[72]. For Covid-19, WHO used its Emergency Use Listing procedure, which allowed large-scale distribution before prequalification. The Emergency Use Listing procedure requires that "the disease may cause an outbreak, epidemic or pandemic", and that "there are no products available capable of eradicating or preventing the disease"[73]. These criteria might not apply for malaria.

Lessons from existing vaccination campaigns

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Are There Other Ways to Control Malaria besides Vaccination?

Malaria diagnosis can be established with rapid diagnostic tests (RDT) and examination of a blood smear by microscopy.[74] Severe malaria is treated with artesunate, an IV artemisinin-based therapy, while uncomplicated malaria is treated with artemisinin combination therapy (ACT).[75,76] WHO maintains a list of malaria treatments tailored to the species of malaria circulating in different regions and countries around the world.[77] In Southeast Asia, drug resistance has developed among plasmodium parasites, including resistance to artemisinins and ACT partner drugs.[78] Vector and parasite drug resistance are both challenges to malaria treatment[79] that malaria vaccines may help address.

Many antimalarials are well tolerated, but side effects of these medications vary depending on the medication.[80] Artesunate, for instance, can cause agitation, coma, or

[70] 92 low- and middle-income economies eligible to get access to COVID-19 vaccines through COVAX
[71] COVAX: 1 billion vaccines delivered | UNICEF Supply Division
[72] BIMERVAX | WHO - Prequalification of Medical Products
[73] Coronavirus disease (COVID-19): Use of Emergency Use Listing procedure for vaccines against COVID-19
[74] "Webinar Thursday, July 20, 2023 - Review of Malaria Diagnosis and Treatment in the United States," accessed November 12, 2023.
[75] Borimas Hanboonkunupakarn and Nicholas J. White, "Advances and Roadblocks in the Treatment of Malaria," *British Journal of Clinical Pharmacology* 88, no. 2 (February 2022): 374–82, https://doi.org/10.1111/bcp.14474.
[76] US CDC, "CDC - Malaria - Diagnosis & Treatment (United States) - Treatment (U.S.) - Artesunate," June 26, 2023.
[77] "Country Antimalarial Drug Policies by WHO Regions," accessed November 8, 2023, https://www.who.int/teams/global-malaria-programme/case-management/treatment/country-antimalarial-drug-policies-by-who-regions.
[78] Hanboonkunupakarn and White, "Advances and Roadblocks in the Treatment of Malaria."
[79] Rosauro Varo, Carlos Chaccour, and Quique Bassat, "Update on Malaria," *Medicina Clinica* 155, no. 9 (November 13, 2020): 395–402, https://doi.org/10.1016/j.medcli.2020.05.010.
[80] "Medicines for the Prevention of Malaria While Traveling - Atovaquone-Proguanil," n.d.

confusion.[81] Attempts have been made to study the long term effects of antimalarials, especially those with neurologic effects such as mefloquine.[82]

Malaria infection during pregnancy is associated with miscarriage and stillbirth, and "one in ten maternal deaths in malaria endemic countries are estimated to result from *Plasmodium falciparum* infection."[83] While evidence shows malaria treatment during pregnancy is safe and efficacious, WHO has yet to recommend malaria treatment with ACTs during the first trimester of pregnancy.[84] Chemoprevention during pregnancy is challenging, such that "alternative strategies to prevent malaria in pregnancy are needed."[85]

Malaria can also cause a relapse years after treatment if treatment is inadequate.[86] Limitations on access to diagnostic testing, vector and parasite drug resistance, side effects of antimalarial prevention medications and treatment, and the need for new strategies to prevent malaria during pregnancy all mean that the R21 vaccine will be an important tool to address these challenges.

Are there other promising vaccine candidates in the pipeline?

While the two existing WHO-approved vaccines are very valuable, research is ongoing with the goal of finding vaccines that are even more effective, and ideally that require fewer doses. The WHO has compiled a database of 89 malaria vaccine candidates under clinical development,[87] and of particular interest are:

- ChAd63-MVA RH5, which was recently shown to be safe and immunogenic in a phase 1b trial, and targets the malaria parasite at the blood stage of its life cycle.[88]
- mRNA vaccines (the technology used in the Pfizer/BioNTech Covid-19 vaccine) to target the malaria parasite, which can be easier to produce.[89]

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[81] "Artesunate (Intravenous Route) Side Effects - Mayo Clinic," accessed November 12, 2023, https://www.mayoclinic.org/drugs-supplements/artesunate-intravenous-route/side-effects/drg-20489625.
[82] "Summary | Assessment of Long-Term Health Effects of Antimalarial Drugs When Used for Prophylaxis | The National Academies Press," accessed November 12, 2023, https://nap.nationalacademies.org/read/25688/chapter/2.
[83] Makoto Saito et al., "Deleterious Effects of Malaria in Pregnancy on the Developing Fetus: A Review on Prevention and Treatment with Antimalarial Drugs," *The Lancet. Child & Adolescent Health* 4, no. 10 (October 2020): 761–74, https://doi.org/10.1016/S2352-4642(20)30099-7.
[84] Saito et al.
[85] Saito et al.
[86] "Webinar Thursday, July 20, 2023 - Review of Malaria Diagnosis and Treatment in the United States," accessed November 12, 2023, https://emergency.cdc.gov/coca/calls/2023/callinfo_072023.asp.
[87] WHO review of malaria vaccine clinical development
[88] https://www.cell.com/med/fulltext/S2666-6340(23)00226-X
[89] https://www.nature.com/articles/s41590-023-01562-6
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10166207/

- Pfs230D1-EPA/Alhydrogel which targets the parasite in mosquitoes rather than in human hosts, and thus is especially promising for eliminating malaria transmission, not just clinical disease.[90]

[90] https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(23)00276-1/fulltext