

**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.

**The Goal:** Vaccinate 40 million children against malaria in 2024.

## Background

- **New malaria vaccines could save many lives:** A new malaria vaccine (R21) has been recommended by the WHO and can be produced in enough volume to save the lives of hundreds of thousands of African children. One study estimates 6,300 lives saved per million children vaccinated.
- **Current rollout plans do not fit available supply:** Over 100 million doses could be produced over the next year, with 20 million already available, for a total of 120 million. But the WHO does not expect distribution to begin until the middle of next year, and the latest public materials from WHO and UNICEF indicate only a small fraction of available vaccines will be used. 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: Using every dose that's made next year:** Buying 120 million doses at \$3.90 per dose would cost \$468 million, with distribution costs adding several hundred million dollars more. At this price, the average cost of saving a child's life is projected to be less than \$4,000. Global institutions are obligated to set the shared expectation that all doses available will be distributed in 2024.

## Immediate Priorities

**Prequalification:** Before vaccines can be purchased, they must be prequalified by the WHO. WHO must set a public timeline for completion of prequalification of R21, and this deadline should be as soon as feasible without sacrificing safety.

**Funding:** Global stakeholders, particularly international aid bodies, NGOs, and Western governments, must prepare to provide the necessary resources and funding to enable the rapid, mass rollout of R21. Gavi must confirm the funding needed to provide these doses so that fundraising can begin if there are shortfalls.

**Setting global expectations:** The world must treat malaria as the emergency it is and set an expectation to vaccinate 40 million children in 2024.

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## **Background on malaria and estimates of R21 vaccine impact**

### **What is malaria?**

Malaria is a disease caused by parasites of the *Plasmodium* genus carried by mosquitoes. Common symptoms include fatigue, fever, chills, and headaches.<sup>1</sup> Some cases are profoundly painful: one survivor likened it to “being stung repeatedly by an electric shock gun”.<sup>2</sup>

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

*Plasmodium 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. Some reproductive forms of the parasite are then transmitted to mosquitoes that bite the infected person, beginning the life cycle once again.<sup>6 7</sup>

Existing methods of prevention and treatment include chemoprevention, mosquito control, bed nets, and artemisinin combination therapy, among others. Diagnosis of malaria alone has a median estimated cost of \$6.06, more than the cost of a dose of the R21 vaccine.<sup>8</sup> Vaccination combined with existing methods will further reduce the burden of malaria in Africa.

### **The two malaria vaccines: RTS,S and R21**

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 three years. The vaccines are 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”). Both were developed using multiple human challenge studies and protect against *Plasmodium falciparum*, the deadliest species of the malaria parasite.<sup>9</sup>

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<sup>1</sup> [Malaria](#), WHO, March 29, 2023.

<sup>2</sup> Coumba Makalou, “[What it feels like to have Malaria](#).” NothingButNets, June 5, 2007.

<sup>3</sup> [World malaria report 2022](#), WHO, December 2022, p. 15.

<sup>4</sup> [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](#) does not encompass all of Africa; it excludes Somalia and most countries in North Africa.

<sup>5</sup> [World malaria report 2022](#), WHO, December 2022, p. 17.

<sup>6</sup> See this [Works in Progress diagram](#) of the life cycle of malaria for a visualization.

<sup>7</sup> Stephen L. Hoffman, Carlos C. Campbell & Nicholas J. White, “[Malaria](#),” in *Tropical Infectious Disease: Principles, Pathogens and Practices* (3rd. Ed., 2011).

<sup>8</sup> Conteh et. al. (2021), [Costs and Cost-Effectiveness of Malaria Control Interventions: A Systematic Literature Review](#), *Value Health* 24(8).

<sup>9</sup> Sekhar & Kang (2020), [Human challenge trials in vaccine development](#), *Seminars in Immunology*, 50:101429.

**The two vaccines are closely related:** the creators of R21 describe it as “a next-generation RTS,S-like vaccine.”<sup>10</sup> Both target the parasite’s circumsporozoite protein (CSP) before it can enter the liver,<sup>11</sup> employ virus-like particles built from scaffolding derived from the hepatitis B virus,<sup>12</sup> and use similar adjuvants to enhance the natural immune response.<sup>13</sup> The surface of the R21 particle is covered with a greater density of the malaria protein (CSP) antigen than RTS,S.<sup>14</sup>

	RTS,S	R21
<b>Phase 3 efficacy in children age 5-17 months</b>	First 12 months: 56% efficacy First 48 months: 36% efficacy <sup>15</sup>	First 12 months: 78% efficacy <sup>16</sup> First 48 months: Unknown <sup>17</sup>
<b>Price (not including distribution cost)</b>	\$10.20 per dose <sup>18</sup>	\$3.90 per dose. <sup>23</sup>
<b>Doses available in 2024</b>	6 million <sup>19</sup>	>120 million <sup>20</sup>
<b>Doses for full vaccination</b>	Three doses spaced one month apart and a booster a year later. <sup>21</sup>	
<b>Recommended population</b>	Children over five months old. <sup>22</sup>	
<b>Vaccine storage</b>	Stable for three years at 2°-8°C. <sup>23</sup>	Stable for two years at 2°-8°C, and up to two weeks between 25°-40°C. <sup>24</sup>

<sup>10</sup> 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 for a multi-component approach to malaria vaccination](#), PhD thesis, St Cross College, Oxford University.

<sup>11</sup> Laurens (2020), [RTS,S/AS01 vaccine \(Mosquirix™\): an overview](#), *Human Vaccines and Immunotherapeutics* 16(3).

<sup>12</sup> 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 Collins (2014), [R21, a novel particle based vaccine for a multi-component approach to malaria vaccination](#), PhD thesis, Oxford University; and [Collins et al. \(2017\)](#).

<sup>13</sup> The adjuvants in these vaccines are saponins, a chemical derived from the soapwort plant. R21 uses a simpler adjuvant, Matrix-M (a Novavax product), than RTS,S.

<sup>14</sup> [Collins et al. \(2017\)](#).

<sup>15</sup> RTS,S Clinical Trials Partnership (2015), [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.

<sup>16</sup> 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% v. 70%). At seasonal sites for 5–17-month-olds, efficacy was 79%, versus 75% at standard/perennial sites.

<sup>17</sup> 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.

<sup>18</sup> [Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping](#), UNICEF Supply Division, October 2023.

<sup>19</sup> Ibid.

<sup>20</sup> The Serum Institute [indicated](#) in October 2023 that they have “more than 20 million doses” on hand. An [October 2023 Serum Institute press release](#) stated that it “has already established production capacity for 100 million doses per annum, which will be doubled over the next two years,” for a total of 200 million doses per year by 2026. By comparison, Serum Institute produced [1.5 billion doses](#) of the Astra-Zeneca/Covishield vaccine in 2021.

<sup>21</sup> [Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping](#), UNICEF Supply Division, October 2023.

<sup>22</sup> [Malaria vaccines \(RTS,S and R21\)](#), WHO, October 17, 2023.

<sup>23</sup> [Mosquirix: Product Information](#), European Medicines Agency, October 2023, p. 12.

<sup>24</sup> [“A high efficacy malaria vaccine”](#) lecture by Adrian Hill, August 2023, c. 33:45.

The WHO recommended RTS,S in October 2021. R21 was recommended on October 2, 2023, but has not yet been prequalified by the WHO.<sup>25</sup> As is discussed below (See “When is WHO prequalification expected for R21?”), the prequalification process is required before global funders like Gavi and UNICEF can formally procure vaccines. Burkina Faso, Ghana, and Nigeria have already licensed R21.<sup>26</sup>

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,<sup>27</sup> but concerns about a potential meningitis risk led to WHO requiring further testing.<sup>28</sup> This took place from 2019-2021 and confirmed the vaccine’s safety. WHO approval came in 2021 and prequalification in 2022.<sup>29</sup>

R21 was developed in 2011 at the Jenner Institute at Oxford University by Katharine Collins.<sup>30</sup> The first clinical trials testing the vaccine began in 2015, including a phase I study evaluating R21 combined with Novavax’s adjuvant Matrix-M.<sup>31</sup> A phase 2b study concluded 2023,<sup>32</sup> and a phase 3 is slated for completion in early 2024,<sup>33</sup> with preliminary results available as of September 2023.<sup>34</sup>

The comparatively greater efficacy at 12 months and indications that R21 generates a stronger immunological response than RTS,S suggest R21 is likely a more potent vaccine.<sup>35</sup> It is possible, though not likely, that R21 proves less effective in the long term, as four-year follow-up data is not yet available. The WHO has stated that there is no sufficient evidence to conclude either vaccine is better than the other, as the two vaccines have not been tested in head-to-head trials.<sup>36</sup>

R21 and RTS,S are good vaccines, but they should not be the final vaccines developed. The WHO has compiled a database of 89 malaria vaccine candidates under clinical development.<sup>37</sup> Expanded distribution capacity developed now can only enhance the utility of future vaccines.

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<sup>25</sup> [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.

<sup>26</sup> Dattoo 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).

<sup>27</sup> [The RTS,S malaria vaccine](#), PATH, September 17, 2019.

<sup>28</sup> Meredith Wadman, [First malaria vaccine slashes early childhood mortality](#), *Science*, October 24, 2023.

<sup>29</sup> Cassandra Willyard, [The slow roll-out of the world’s first malaria vaccine](#), *Nature Outlook*, December 19, 2022.

<sup>30</sup> Katharine Collins (2014), [R21, a novel particle based vaccine for a multi-component approach to malaria vaccination](#), PhD thesis, St Cross College, Oxford University.

<sup>31</sup> 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.

<sup>32</sup> [Safety, Immunogenicity and Efficacy of R21 Matrix-M in 5-17 Month Old Children in Nanoro, Burkina Faso](#) (NCT03896724)

<sup>33</sup> [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)

<sup>34</sup> Dattoo 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).

<sup>35</sup> Anti-NANP IgG titers appear significantly higher following R21 vaccination compared to RTS,S vaccination. Such titers correlate with reduced risk of clinical malaria and are the simplest measure of immune response currently available, though they do not represent a comprehensive correlate of protection. Direct comparison between R21 and RTS,S titers is hampered by substantial methodological variables between the two studies: [Dattoo et al.](#) (forthcoming, posted September 2023) and [RTS,S Clinical Trials Partnership \(2015\)](#).

<sup>36</sup> [Malaria vaccines \(RTS,S and R21\)](#), WHO, October 17, 2023.

<sup>37</sup> [WHO review of malaria vaccine clinical development](#), WHO, November 2022. Some candidates of note: ChAd63-MVA RH5 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 ([Silk et al. 2023](#)); Pfs230D1-EPA/Alhydrogel targets the parasite in mosquitoes rather than in human hosts, and thus is

## Estimating the number of children suitable for malaria vaccination

Suitable R21 and RTS,S vaccine recipients must live in areas where there is a risk of *P. falciparum* malaria and be at least five months old. Existing data on age and malaria risk from WHO and other international sources enable a rough estimate of the number of children meeting these criteria in 2024: **about 80 million**. How we arrived at this estimate:

- Approximately 91.7% of the population in Sub-Saharan Africa — 1.01 billion people — live at risk of contracting malaria, according to WHO estimates for 2021.<sup>38</sup> Malaria cases in sub-Saharan Africa in recent years are almost exclusively (>99%) caused by *Plasmodium falciparum*.<sup>39</sup>
- U.S. Census International Database 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.<sup>40</sup>
- Assuming half of this 163.78 million fall between 5 and 36 months old,<sup>41</sup> the ideal age range for vaccination, approximately 82 million should thus be suitable targets for a malaria vaccine in 2024. 2 to 4 million children are to be vaccinated with RTS,S,<sup>42</sup> so we round down to **about 80 million children who should be eligible for R21 and fall within the ideal age window for vaccination in 2024**.

This calculation is an estimate based on publicly available information and not intended to be highly precise.

## How many vaccine doses do we need?

Each child requires three R21 doses in the first calendar year followed by a booster a year later. Thus, covering the approximately 80 million children in 2024 who need a vaccine would require 240 million doses along with another 80 million doses in 2025 as boosters. The Serum Institute has said they can produce 100 million doses in 2024,<sup>43</sup> in addition to the 20 million it has on hand, **so the goal should be to use every single one of the vaccine doses that can be made available in 2024 — enough to cover at least 40 million children**.

Beyond the 80 million children who currently need the vaccine, each year about 30 million children are born who will require vaccination.

This estimate is substantially larger than that provided by UNICEF, as discussed below (see “What we don’t know about current malaria vaccination plans”).

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especially promising for eliminating malaria transmission, not just clinical disease ([Sagara et al. 2023](#)); and, various candidates attempting to utilize new mRNA technology ([Ganley et al. 2023](#), [Matarazzo & Bettencourt 2023](#)).

<sup>38</sup> [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.

<sup>39</sup> [World Malaria Report 2023](#), WHO, November 2023, pg. 12.

<sup>40</sup> [U.S. Census Bureau IDB](#), accessed November 27, 2023.

<sup>41</sup> R21 was tested and had high efficacy in children between 5 and 36 months old.

<sup>42</sup> 6 million doses of RTS,S are expected to be delivered in 2024. How many vaccinations occur will depend on how many of these doses are used as boosters and how many are used in the primary three-dose vaccination courses.

<sup>43</sup> [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.

## Number of lives saved through vaccination

Two different studies, neither of which has been peer-reviewed yet, imply that it is realistic to expect about 6,000 lives saved per million children vaccinated.

A recent study (in preprint) by authors at Imperial College, co-authored by members of the Oxford R21 team, projected that for every million children vaccinated by R21 age 5-17 months in Sub-Saharan Africa, about 6,320 deaths and 1.9 million cases of malaria would be averted over the next 15 years (children can contract malaria multiple times).<sup>44</sup> If the study's conclusions are accurate, **vaccinating 40 million children would save more than 200,000 lives.**<sup>45</sup>

A recent WHO study found that RTS,S vaccination reduced childhood mortality for all non-accidental causes by 13% for every child vaccinated.<sup>46,47</sup> If R21 has a similar impact, we would expect it to save around 6,000 lives per million children vaccinated, similar to the estimates modeled in the Imperial and Oxford paper (see “Number of lives saved through vaccination”).<sup>48</sup> Because the data behind the 13% figure number has not been made public, the 6,000 lives-saved projection is necessarily a rough estimate. Contrariwise, R21 may be more effective than RTS,S given its stronger efficacy and immune response in trials (see “The two malaria vaccines: RTS,S and R21” above).

## Cost estimates of R21 vaccination

Based on analysis of RTS,S distribution costs and the current per-dose cost of R21, fully vaccinating children could cost as little as **\$25 per full course in early years**, and prices will decrease as vaccination campaigns scale. Based on impact calculations (see the following section), this translates into a projected cost of **less than \$4,000 per life saved initially, and less than \$3,000 per life saved over time.**

UNICEF has secured R21 doses at a price of \$3.90 each.<sup>49</sup> Vaccination cost entails more than just the cost of the doses, however. Recent analysis of the RTS,S rollout suggests the cost of delivery and administration for RTS,S at pilot sites was between \$1.04 and \$2.46 in three countries. A substantial

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<sup>44</sup> Schmit et al. (forthcoming), [The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study](#), ll. 312–329; 344–353, *The Lancet* (preprint), 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.

<sup>45</sup> Note that lives saved per million saved will be lower for children vaccinated at age 18-36 months because they have fewer years at peak risk of death.

<sup>46</sup> Meredith Wadman, [First malaria vaccine slashes early childhood mortality](#), *Science*, October 24, 2023.

<sup>47</sup> The originally published [preprint](#) from July 2023 indicates a 9% reduction in mortality among eligible children (excluding injuries) and a 32% reduction in severe malaria. The [Science article](#) cited above as well as a [GAVI article](#) published in October and November 2023, respectively, are based on findings from the same study shared at the Annual Meeting of the American Society of Tropical Medicine and Hygiene, but with updated values of 13% mortality reduction and a 22% reduction of severe malaria. The authors of the study presumably altered or updated their analysis, but we do not currently have access to an updated preprint. We use 13% as the more relevant and recent figure.

<sup>48</sup> 74 out of 1000 children born in Sub-Saharan Africa die before the age of 5, 27 of whom die in the first month of life and would not be protected by a malaria vaccine ([Levels and trends in child mortality](#), United Nations Inter-Agency Group for Child Mortality Estimation Report 2022). Subtracting 27 from 74 yields 47 deaths out of 1000 children; reducing this by 13% would save about 6110 children per million children vaccinated. This number is somewhat liberal given that children can die after the first month of life but before vaccination, but that it is in the same range as the Imperial and Oxford estimate is encouraging.

<sup>49</sup> [Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping](#), UNICEF Supply Division, August October 2023.

portion of this (between 33% and 71%) was due to non-recurring startup costs. The recurring/steady state cost of delivery was between \$0.29 and \$0.89 per dose.<sup>50</sup>

Applying these costs to R21, doses in initial campaigns would run from \$4.94 to \$6.36 at first, and then \$4.19 to \$4.79 thereafter. RTS,S distribution costs are likely higher than R21 because RTS,S comes in slightly larger packaging (increasing transportation and storage costs) and has much stricter cold chain requirements.<sup>51</sup>

For simplicity, assume that at the high end, initial full vaccination of children thus costs \$25, and this falls to about \$18 in the medium-term. Vaccinating one million children in 2024 would cost \$25 million (including the subsequent 2025 booster), and save an estimated 6,320 from death by malaria — about \$3,956 per life saved. At \$18 per course, it would cost \$2,848 per life saved.

The above are very rough estimates and should not be taken as precise predictions. Distribution costs are highly variable, and will likely be higher in areas with less infrastructure. Nevertheless, it is clear that through R21, the deaths of many children can be prevented at an astonishingly low cost.

## **The current plans for malaria vaccine rollout**

### **How many doses are currently planned to be delivered in 2024?**

RTS,S vaccine deployment is expected to continue, with GSK committed to delivering 6 million doses in 2024 and 8 million in 2025.<sup>52</sup>

R21 rollout plans are unclear. Previous public forecasts by GAVI and UNICEF imply a range of 15-35 million doses delivered in 2024, though they may be out of date. The WHO has said it expects rollout to begin in mid-2024,<sup>53</sup> but details are lacking, and this timing may be dependent on having completed prequalification by the end of 2023. UNICEF announced a deal in October 2023 to secure supply of R21 with the Serum Institute of India from 2024–2028, but has not disclosed the number of doses covered by the deal.<sup>54</sup>

UNICEF and the WHO have stated they expect R21 to fill the gap in vaccine supply such that demand will be met in 2024.<sup>55</sup> Thus, we can estimate the R21 doses based on older public statements and

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<sup>50</sup> Baral et al. (2023), [Cost of introducing and delivering RTS,S/AS01 malaria vaccine within the malaria vaccine implementation program](#), *Vaccine*, February 17, 2023.

<sup>51</sup> R21 is stable from 25–40°C (77–104°F) for up to two weeks, whereas RTS,S must be stored between 2–8°C (36–46°F) up until administration. See [Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping](#), UNICEF Supply Division, October 2023, page 3.

<sup>52</sup> [Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping](#), UNICEF Supply Division, October 2023.

<sup>53</sup> Donato Paolo Mancini, [Oxford vaccine developer criticises WHO's mid-2024 target for malaria shot](#), *Financial Times*, October 6, 2023.

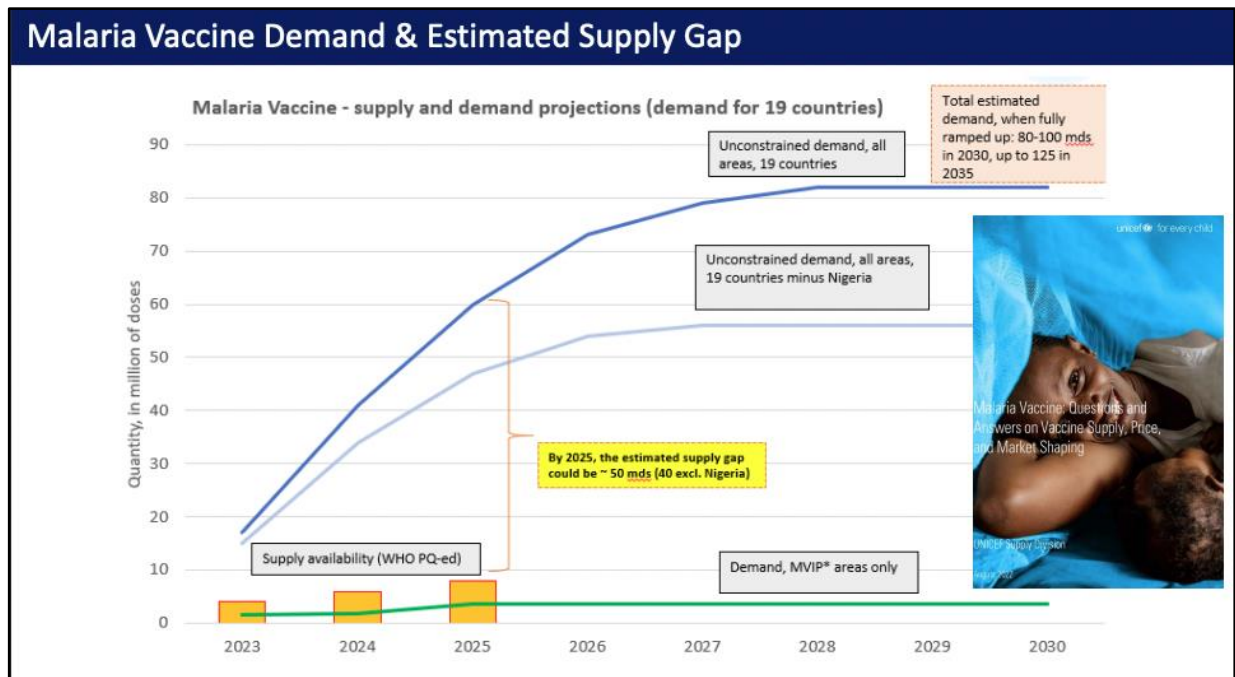
<sup>54</sup> [UNICEF signs deal to deliver new malaria vaccine in breakthrough for child survival](#), UNICEF press release, October 11, 2023.

<sup>55</sup> [Update on malaria vaccines](#), WHO, October 2023: “UNICEF expects to begin delivering the R21/Matrix-M vaccine in mid-2024, with immunizations beginning in the same period. As a result, beginning in 2024, the cumulative supply availability of the two WHO-recommended malaria vaccines is expected to meet the high demand.” [Malaria Vaccines: Questions and Answers on](#)



documents from UNICEF and Gavi about malaria vaccine demand, although these offer a contradictory picture.

**UNICEF: 34 million R21 doses?** — A December 2022 presentation by UNICEF contract specialists suggests that UNICEF believes that absent supply constraints, in 2024 there would be demand for approximately 40 million malaria vaccine doses from 19 countries. (At least 28 countries have now expressed interest to Gavi in rolling out the RTS,S vaccine.)<sup>56</sup>



**Figure 1.** [UNICEF Procurement: Comprehensive supply for impactful and cost-efficient health programmes](#), November/December 2022, slide 12.

**Gavi: <15 million doses?** — A December 2022 document by Gavi indicated that given the R21 vaccine in the pipeline, supply was expected to begin meeting demand between 2026 and 2028.<sup>57</sup> The document included a chart from 2021 predicting total vaccine demand for 2024 would be under 20 million doses in total (including RTS,S). 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.

**How are vaccines distributed through GAVI?**

Most African countries cannot afford to purchase vaccines without assistance, so they rely on GAVI, the Vaccine Alliance, to help buy them. GAVI procures vaccines through UNICEF, which pays the vaccine manufacturer, and then transfers the vaccines to African countries, which manage distribution (sometimes

[Supply, Price, and Market Shaping](#), UNICEF Supply Division, October 2023, p. 2: With the advent of R21, “UNICEF expects sufficient supply availability to meet countries’ needs in 2024 and beyond as per WHO recommendations.”

<sup>56</sup> [First malaria vaccine supply allocations May 2023: Explanation of process and outcomes](#), WHO, May 2023.

<sup>57</sup> [Market Shaping Roadmap: Malaria Vaccines](#), Gavi, December 2022. See also [Malaria vaccine market shaping roadmap](#), Gavi, April 2023, p. 3.

with the assistance of regional partners or other NGOs). 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. UNICEF and Gavi cannot purchase a vaccine unless it has been prequalified by the WHO.<sup>58 59</sup> For R21, once prequalification is complete, according to Gavi, "it is expected... that final steps to make doses available and ready for shipment will take a few months."<sup>60</sup>

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.

### **When is WHO prequalification expected for R21?**

WHO's prequalification process ensures production of medical products meets safety and efficacy standards. WHO prequalification typically is targeted to happen around 270 days after recommendation,<sup>61</sup> which would be roughly July 2024 for R21.<sup>62</sup> 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. It may be impossible to meet WHO's mid-2024 rollout timeline without completing prequalification by the end of 2023.

### **Problems with current plans for R21 distribution**

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

As noted above, the UNICEF supply and demand projections at best would cover vaccination of around 11 million children. What UNICEF forecasts for delivery (34 million R21 doses)<sup>63</sup> is 86 million doses fewer than what the Serum Institute of India says it can provide (at least 120 million). 86 million doses would be enough to vaccinate about 29 million more children with the primary course. Based on the modeling done by researchers and Imperial and Oxford (see "Number of lives saved through vaccination" above), vaccinating 29 million more children in 2024 would avert over 180,000 deaths.<sup>64</sup>

<sup>58</sup> UNICEF has stated that its purchase of R21 doses is conditional on prequalification ([UNICEF signs deal to deliver new malaria vaccine in breakthrough for child survival](#), UNICEF press release, October 11, 2023). 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.

<sup>59</sup> [WHO RECOMMENDATION OF WORLD'S SECOND MALARIA VACCINE – SEPTEMBER 2023](#), Gavi press release, October 2, 2023. "Similarly, the R21 vaccine still awaits WHO prequalification, which is a precondition to global rollout. Once a vaccine is prequalified it can then be offered through Gavi programmes."

<sup>60</sup> [1st MALARIA VACCINE SHIPMENTS: Frequently Asked Questions \(FAQs\)](#), Gavi, 2023.

<sup>61</sup> 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 recommended October 2021 and prequalified July 2022, about 270 days later.

<sup>62</sup> 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 announced was "mid-2024," which differed from earlier discussions for rollout in the first quarter of 2024.

<sup>63</sup> As noted in a previous section ("How many doses are currently planned to be delivered in 2024?"), UNICEF has not actually stated how many doses it has agreed to procure from the Serum Institute. We assume that since UNICEF says it anticipates malaria vaccine demand to be met that it purchased enough R21 to meet the malaria vaccine demand figures it published in late 2022, the most recent publicly available.

<sup>64</sup> 632 deaths averted per 100,000 children vaccinated multiplied by 290 is 183,280.

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.<sup>65</sup>

This deficit is not just a problem for 2024. UNICEF projects vaccine demand in 2025 to reach 60 million doses and 75 million doses in 2026 (see Figure 1 in the previous section). Because about 30 million children are born each year at risk of malaria, the deficit between available supply and current plans may represent more than 100,000 avoidable deaths each year.

### **Challenges to vaccination more children in 2024**

- **Vaccination campaigns are normally slow:** Vaccines typically take about ten years from starting human testing to regulatory approval and another 10-15 years to achieve broad distribution.<sup>66</sup> Malaria vaccine development has taken decades. Thus, there is institutional and psychological inertia weighing against an immediate sprint to deploy vaccines, 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. We estimate that about \$1 billion will be needed to purchase and distribute R21 vaccine doses. 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: vaccination rates for RTS,S have been high in communities where it has been introduced,<sup>67</sup> and parents are very experienced with malaria and 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 distributors (including national and sub-national agencies and political bodies). 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, as well as coordinating with many country's public institutions such as Ministries of Health, Finance, Interior, and others that may have relevant authorities.

<sup>65</sup> Malaria is mostly seasonal, and tends to peak during the rainy season when mosquitoes are most active. Rainy seasons can vary in timing throughout Sub-Saharan Africa, but some of the areas of highest malaria prevalence in West Africa exhibit peak malaria transmission between [July and November](#).

<sup>66</sup> See [SAVAC Stakeholders Meeting video](#) at 1:20:30. See also *Plotkin's Vaccines*, 7th ed., Chapter 4 ("The Vaccine Industry"), table 4.3.

<sup>67</sup> Mumtaz et al. (2023), [Acceptance, availability, and feasibility of RTS, S/AS01 malaria vaccine: A review](#), *Immunity, Inflammation & Disease*, 11(6): e899; Schmit et al. (forthcoming), [The public health impact and cost-effectiveness of the R21/Matrix-M malaria vaccine: a mathematical modelling study](#), *The Lancet* (preprint), October 2023. "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% 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."

- **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. Tremendous effort 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."<sup>68</sup>

### What lessons can be drawn from the rollout of RTS,S?

- **Regulatory speed matters:** In 2015, the European Medicines Agency approved the RTS,S vaccine.<sup>69</sup> In 2016 WHO recommended pilot program implementation, and in 2019 RTS,S launched in Ghana, Kenya, and Malawi.<sup>70</sup> RTS,S was first recommended for widespread use by WHO in October 2021.<sup>71</sup> The six-year delay between the EMA's approval and WHO greatly slowed the rollout of RTS,S and shows how regulatory uncertainty and delays can be massively consequential.
- **Advance financing affects rollout:** In 2019, GAVI reduced the risk of investment in RTS,S vaccine, allowing production to begin while evidence was collected to support implementation plans and policies.<sup>72</sup> A similar agreement between the manufacturer and GAVI to support production of R21 while WHO prequalification is sought in parallel could accelerate R21 deployment.
- **Community engagement is important:** Interviews with health service managers and frontline health workers in Ghana in 2019 aimed to understand lessons learned during RTS,S vaccine implementation, which was the first malaria vaccine deployment. Community engagement early in RTS,S deployment was important to the success of the vaccine.<sup>73</sup>
- **MVIP sets a strong path to follow:** During the Malaria Vaccine Implementation Programme pilot programs, supportive supervision visits for sites with low uptake improved vaccine coverage. Updating communications materials for health care workers on guidance when children do not receive doses on schedule was also important. Planning early for R21 implementation will improve gaps encountered during the four dose RTS,S schedule.<sup>74</sup> Because R21 is expected to be available in larger volumes, it may be used by larger countries to avoid the need to switch products.<sup>75</sup>
- **Four-dose distribution works:** While there were challenges, RTS,S deployment showed that implementation of a four-dose vaccine works with careful planning and that scaling up distribution is possible.

<sup>68</sup> Gregory Zuckerman, *A Shot to Save the World: The Inside Story of the Life-or-Death Race for a COVID-19 Vaccine*, Portfolio (2021).

<sup>69</sup> [Mosquirix](#), European Medicines Agency, 2015.

<sup>70</sup> [UNICEF Procurement: Comprehensive supply for impactful and cost-efficient health programmes](#), WHO, December 2022.

<sup>71</sup> [Malaria vaccines \(RTS,S and R21\)](#), WHO, October 2023.

<sup>72</sup> [1st Malaria Vaccine Shipments: Frequently Asked Questions \(FAQs\)](#), Gavi, 2023.

<sup>73</sup> Grant et al. [Challenges and lessons learned during the planning and early implementation of the RTS,S/AS01E malaria vaccine in three regions of Ghana: a qualitative study](#), Malaria Journal, April 2022.

<sup>74</sup> [Learning lessons from the pilots: overcoming knowledge gaps around the malaria vaccine schedule in support of vaccine uptake](#), WHO, October 2022.

<sup>75</sup> [1st Malaria Vaccine Shipments: Frequently Asked Questions \(FAQs\)](#), Gavi, 2023.

## The Goal: deliver every dose that can be produced in 2024

### Vaccinating 40 million children

R21 vaccination purchases an average of about a week of a child's life for every dollar spent.<sup>76</sup> At that price, **no dose that can be produced should go unused in 2024**. If the Serum Institute can produce 120 million doses by the end of 2024, then the expectation must be that forty million children will be vaccinated with the initial three-dose course.

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. The bar must be set high.

### Steps to catalyze more rapid mass rollout of R21

From 2021 to 2023, more than a billion COVID vaccine doses were distributed in Africa,<sup>77</sup> showing that rapid rollout of a novel vaccine is achievable. The following are some of the policy steps that could enable optimal malaria vaccination in 2024.

- **Finish prequalification in a timely manner:** Prequalification is the current bottleneck preventing GAVI and UNICEF from purchasing R21 doses. WHO must set a public deadline for completion of prequalification, and this deadline must be as soon as feasible without sacrificing safety. UNICEF's October 2023 malaria vaccine Q&A document noted that prequalification by late 2023 and in-country availability of R21 doses by Q2 2024 represented the "best case scenario."<sup>78</sup> If prequalification is not finished soon, the WHO's current mid-2024 estimate for R21 rollout may not be realistic. Replicating the COVID vaccine tactic of a group call by the WHO for African regulators to ask questions about prequalification would also likely be valuable.
- **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** for malaria vaccine demand that articulates what would be needed to achieve a 120 million dose target. Additionally, a transparent process is needed for regular public updating of the forecast in response to African government requests, which should be allowed on a rolling basis similar to that used for COVID-19 vaccines.
- **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

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<sup>76</sup> Current life expectancy in Sub Saharan Africa is 61 years, or about 3,200 weeks, per [United Nations: World Mortality in 2019](#).

<sup>77</sup> [Africa CDC COVID-19 Vaccine Dashboard](#), accessed November 21, 2023.

<sup>78</sup> [Malaria Vaccines: Questions and Answers on Supply, Price, and Market Shaping](#), UNICEF Supply Division, October 2023.

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.

- **Demonstration rollout programs in select African countries:** Nigeria, Burkina Faso, and Ghana approved R21 prior to the WHO's recommendation, 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 would set a valuable precedent for other countries and global institutions to follow.
- **Advanced Market Commitments (AMCs) 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).
- **Western technical assistance:** The 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, as can European Union institutions. This would be especially useful as a public-private partnership in tandem with new philanthropic funding to support distribution efforts or other technical assistance from groups like PATH.<sup>79</sup>
- **Confirm the resources needed for purchase and distribution of doses:** Western funders must commit to provide the financial resources needed to enable the vaccination of 40 million children in 2024.

### **Intermediate advocacy targets to help achieve maximum vaccine coverage**

- **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.<sup>80</sup>
- **WHA resolution:** The World Health Assembly begins May 27th, 2024.<sup>81</sup> Member countries can propose resolutions for the Assembly to vote on.<sup>82</sup> 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.

<sup>79</sup> [PATH — RTS,S Malaria Vaccines in Pilot Comparison Areas \(January 2022\)](#), GiveWell, January 2022.

<sup>80</sup> 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 major malaria disease burden.

<sup>81</sup> [WHO | Dates of Constitutional Meetings](#)

<sup>82</sup> [Basic documents: forty-ninth edition \(including amendments adopted up to 31 May 2019\), Rule 12](#), WHO, 2020.

- **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 promising tactic.

### **What Are 1Day Africa and 1Day Sooner doing?**

1Day Africa and 1Day Sooner publicly launched our campaign to accelerate R21 vaccine deployment in December 2023. Our campaign aims to make progress on three different fronts:

1. Persuade international institutions — primarily WHO, UNICEF, and Gavi – to set a public expectation that at least 40 million children will be vaccinated in 2024.
2. Collaborate with and support civil society groups within African countries to advocate for and enable comprehensive R21 malaria vaccination on a country-by-country basis.
3. Recruit resources (funding and technical assistance) from the West — including governments, NGOs, and philanthropies — to give African countries and global institutions what they need to make these plans work.

### **What are 1Day Africa and 1Day Sooner?**

[1Day Sooner](#) is a US-based nonprofit that aims to accelerate the development and deployment of life-saving medical research and policy interventions. A core focus of 1Day Sooner is human challenge studies, a form of clinical research where adult volunteers are deliberately exposed to a pathogen, often to test a vaccine (as was done with R21 and RTS,S during their early stages of development).

[1Day Africa](#) is the African chapter of 1Day Sooner. 1Day Africa focuses on global vaccine equity and building scientific capacity for medical research and production on the continent.