

SAGE Meeting Outcomes

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Speaker key:

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DW	Prof. Dyann Wirth
DM	Dr Daniel Madandi
MA	Dr Mary Hamel
KO	Dr Kate O'Brien
PA	Paul Adepoju
CP	Carmen Paun
AM	Annalisa Merelli
BR	Bianca Rothier
AB	Ashvin Barshinge
DM	Donato Paolo Mancini
GV	Gretchen Vogel

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MH Hello, everyone. This is Margaret Harris in WHO headquarters, Geneva, welcoming you to our press briefing on the outcomes of the Strategic Advisory Group of Experts on Immunization meeting today, which was held last week. And, of course, today is October 2nd, 2023.

We will start with opening remarks from our Director-General, Dr Tedros Adhanom Ghebreyesus, and he will be joined by Dr Hanna Nohynek, the Chair of SAGE, that's the Strategic Advisory Group of Experts. And after that we'll also hear from Prof. Dyann Wirth, who is the Chair of the Malaria Policy Advisory Group.

After that, I will open the floor to questions and we have a panel of technical experts, both here in the room and online, able to answer your questions. To the right of Dr Tedros we have Dr Katherine O'Brien, who is the Director of our Immunization, Vaccines and Biologicals Department. Next to Dr O'Brien is Dr Joachim Hombach, who is the Executive Secretary for the SAGE.

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And to Dr Tedros' left we have Dr Daniel Madandi, who is the Director of the Global Malaria Programme. Next to Dr Madandi, we have Dr Mary Hamel, who is our Senior Technical Officer for WHO. We've got a lot of exciting news for you here and so, without further ado, I'll hand over to Dr Tedros.

TAG Thank you, Margaret. Good morning, good afternoon and good evening. Today is a great day for health, a great day for science, and a great day for vaccines.

I offer my warmest congratulations to Dr Katalin Karikó and Dr Drew Weissman, who today won the Nobel Prize in Physiology or Medicine for their work in developing the technology that led to mRNA vaccines against COVID-19.

As they have for so many other diseases, safe and effective vaccines against COVID-19 played a vital role in bringing the pandemic under control, and safe and effective vaccines are also giving us new hope of bringing one of the oldest diseases known to humanity under control, malaria.

Almost exactly two years ago, WHO recommended the broad use of the world's first malaria vaccine, called RTS,S. Today, it gives me great pleasure to announce that WHO is recommending a second vaccine, called R21/Matrix-M, to prevent malaria in children at risk of the disease. This recommendation is based on advice from two expert groups, the Strategic Advisory Group of Experts on Immunization and the Malaria Policy Advisory Group.

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Both groups reviewed evidence from trials of the R21 vaccine, which showed that in areas with seasonal transmission it reduced symptomatic cases of malaria by 75% in the 12 months following a three-dose series of the vaccine.

A fourth dose, given a year after the third, was shown to maintain protection. This efficacy is similar to the RTS,S vaccine when given seasonally. The trials showed the vaccine to be safe and safety monitoring will continue as the vaccine is rolled out.

At a cost of between US\$2 and US\$4 a dose, it's comparable with other recommended malaria interventions and other childhood vaccines. As a malaria researcher, I used to dream of the day when we would have a safe and effective vaccine against malaria. Now, we have two.

Since 2000, malaria deaths have fallen by more than half and we have succeeded in eliminating malaria from many parts of the world, but globally progress has stalled. Nearly half the world's population remains at risk of malaria. In 2021, there were an estimated 247 million cases of malaria and 619,000 deaths. 95% of cases and deaths are in Africa and most deaths are in children under five.

Demand for the RTS,S vaccine far exceeds supply, so the R21 vaccine is a vital additional tool to protect more children faster and to bring us closer to our vision of a malaria-free world. WHO is now reviewing the vaccine for prequalification, which is WHO's stamp of approval and will enable Gavi and UNICEF to buy the vaccine from the manufacturers.

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At least 28 countries in Africa plan to introduce a WHO-recommended malaria vaccine as part of their national immunisation programmes. The RTS,S vaccine will be rolled out in some African countries early next year and the R21 vaccine is expected to become available to countries by the middle of next year.

R21 was not the only vaccine that SAGE reviewed at its meeting last week. It also recommended a new vaccine against dengue, called Qdenga, for children aged six to 16 years living in areas where dengue is a significant public health problem.

SAGE also recommended a new vaccine against meningitis, called Men5CV, or the pentavalent, which has been shown to protect against five subgroups of bacteria that cause the disease.

And it recommended that for most COVID-19 vaccines, a single dose is sufficient for primary immunisation, given most people have had at least one prior infection. In addition, SAGE issued advice on the use of vaccines to prevent antimicrobial resistance, as well as for polio, cholera, mumps and smallpox.

To say more, I'm delighted to welcome the Chair of SAGE, Dr Hanna Nohynek, the Chief Physician at the Department of Health Security at the Finnish Institute for Health and Welfare. Hanna, thank you for your leadership at this exciting time for vaccines and the fight against malaria. And in your own language, kiitos. Over to you.

00:07:35

HN Thank you, DG Tedros. I'm very happy to be here today. We did have an extremely intense five-day meeting last week and we actually made seven policy recommendations and provided advice on various other items, as you now described.

Let me take those three new vaccines. Two of them are of major importance to Africa, the R21 malaria vaccine and the five-valent conjugate meningococcal vaccines. Both vaccines will allow to further expand on the incredible success of the RTS,S malaria and the MenA vaccines.

And the third new vaccine, as you mentioned, is against dengue. That was also discussed lengthily. This is the first dengue vaccine with the potential for wider use. As you know, many countries are facing devastating dengue outbreaks and we expect a general worsening of the situation with the climate change.

But let me go deeper a bit more on those three vaccines. The first one that you mentioned in the joint session SAGE and Malaria Policy Advisory Group reviewed all the available evidence of the novel malaria vaccine R21/Matrix-M.

The vaccine is similar to the RTS,S/AS01 malaria vaccine and there is currently no evidence that one vaccine performs better than the other. SAGE and MPAG recommended that either R21/Matrix or RTS,S vaccine be used for the prevention of the falciparum malaria for children living in malaria endemic areas, prioritising areas of moderate and high transmission but also considering vaccination in low-transmission settings.

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Vaccine introduction should be done in the context of comprehensive malaria control efforts and the vaccine can be used following a seasonal or age-based schedule, as already described for RTS,S.

The availability of the second malaria vaccine is expected to close the gap between supply and demand, enabling broader and possibly unconstrained access. Malaria vaccines introduced widely have the potential to save tens of thousands of young lives each year.

Then, to move on to the five-valent meningococcal conjugate vaccine, which you also mentioned. SAGE took a moment to celebrate the success from the rollout of the MenA vaccine and highlighted the prospect to terminate meningitis epidemics with the use of this new five-valent vaccine.

SAGE recommended that all countries in the African meningitis belt introduce the novel pentavalent meningococcal conjugate vaccine targeting serogroups A, C, Y, W and X into their routine immunisation programmes in a single-dose schedule at nine to 18 months of age. And in the high-risk settings catch-up with pentavalent should be conducted.

Countries that have not yet introduced the MenAC vaccine should do so now and not wait until the pentavalent is available, so as to avoid the resurgence of *Neisseria meningitidis* due to this serogroup A surge.

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Then, to move on with dengue. SAGE reviewed the extensive data from a second generation live-attenuated quadrivalent dengue vaccine that was studied in children four to 16 years of age across Asia and Latin America.

The trial has demonstrated efficacy against all four serotypes of the virus in baseline seropositive children from four to 16 years of age in endemic countries, and against serotypes 1 and 2 in baseline seronegative children. However, there remains uncertainty as to the performance against serotype 3 and 4, including a residual risk of enhanced disease in seronegative persons.

So, SAGE recommends that the vaccine be considered for introduction in settings with high dengue disease burden and high transmission intensity to maximise the public health impact in predominantly seropositive children six to 16 years of age.

We also heard about the progress and challenges of Immunization Agenda 2030 and proposed actions by the partnership. The action agenda has six trajectories which are catch-up and strengthening of immunisation programmes, equity promotion, regarding control of measles, making the case for investment into immunisation, accelerate the introduction of WHO-recommended vaccines and advancing vaccination in adolescence.

Other main themes were the continued work on the Big Catch-up, work with countries strengthening primary health care and the ever-increasing challenges posed by the humanitarian emergencies which the climate change is also contributing to.

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We also discussed the further simplification of COVID vaccines recommendations and prospects of the novel XBB vaccines. In brief, SAGE recommended a simplified single-dose regime for primary immunisation for most COVID-19 vaccines, which would improve acceptance and uptake and provide adequate protection at a time when most people have had at least one prior infection and also simplified recommendations on revaccination of priority-use populations.

When monovalent XBB vaccines are not available, which is the case for many countries actually, any available WHO Emergency Use Listed or prequalified vaccines, bivalent variant-containing or monovalent index virus vaccines may be used since they continue to provide benefits against severe disease in high-risk groups.

SAGE noted with great concern the increased frequency of severe cholera outbreaks and the majority supply shortage of the oral cholera vaccine. SAGE re-emphasised the option of using a one-dose vaccination schedule to vaccinate pregnant women and high risk and noted data supportive to using oral cholera vaccine under the control temperature conditions.

Then, to move on, in addition SAGE updated its recommendations on the use of the mumps combination vaccines, MMR, and revised its recommendation on the composition on the WHO vaccine reserve and the use of vaccines preventive in laboratory workers and outbreak response teams, as well as for reactive vaccination in case of highly unlikely outbreak.

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SAGE also provided advice on the most effective use of polio vaccine in outbreak situations with a co-circulation of vaccine-derived type 2 and wild viruses. And lastly, SAGE emphasised the importance that current and future vaccines can play to curb antimicrobial resistance and advised that any clinical vaccine trials may aim at collecting relevant data.

This, in a nutshell, is what came out with during those five days of meeting and I'll be very happy to turn over to Dyann to explore more on what we discussed on the malaria vaccine. Over to you, Dyann.

DW Thank you, Hanna. It is a pleasure to be here. As we all know and Dr Tedros has pointed out, progress towards malaria elimination in Africa has stalled but we now have two safe, effective vaccines to prevent malaria among young children, new tools in our fight against malaria to be used with existing tools to enhance the impact on disease burden.

It is important to note that a vaccine is a completely different mode of action than the existing tools for vector control, diagnosis and treatment. A vaccine recruits the human immune system to fight the parasite as soon as it enters the body. A vaccinated person is poised to fight off the infection at its earliest stage.

Both malaria vaccines, R21 and RTS,S are safe and effective, and when implemented broadly are expected to have high public health impact. The vaccines have not been tested in direct head-to-head comparison studies and so there is no technical evidence to support claims that one malaria vaccine has improved performance over the other but every indication is that they will be very similar.

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Given the similarity of the vaccines and that RTS,S is efficacious in high, moderate and low transmission settings, it is likely that R21 will also be efficacious in all malaria-endemic settings. However, as the R21 vaccine is rolled out, it will be important for countries and WHO to monitor its long-term effectiveness, safety and impact.

With ongoing threats to our existing tools, drug-resistant parasites, insecticide-resistant mosquitoes, innovation is needed not only to create new tools but to better tailor our current tools to achieve maximum impact. The malaria parasite is a formidable foe and, while we are excited by this recent development, major battles remain.

Malaria continues, as Dr Tedros pointed out, to be a leading cause of illness and death for many people around the world but the African region bears the brunt of the disease, with approximately 95% of the cases and 96% of the deaths. Every year, more than a half million children die from malaria and the vast majority of these deaths are in African children.

As we all know, Member States have committed to reducing malaria case incidence and mortality rate by at least 90% by 2030 compared to a 2015 baseline but progress toward both targets is substantially off-track. We expect that over a short period of time every endemic country could have the opportunity to integrate malaria vaccines into their national malaria control strategies.

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Impact can be maximised by combining the WHO-recommended malaria prevention interventions, such as malaria vaccine, insecticide-treated nets and seasonal malaria chemoprevention. Decisions on the appropriate mix of effective interventions should be driven by local data and in the local context.

At this moment, when the Nobel Prize has been awarded for the groundbreaking work on messenger RNA vaccines, I think it's also important to recognise the nearly 50 years of research that led us to the achievement we're celebrating today.

We stand on the shoulders of giants like Dr Ruth Nussenzweig, whose discoveries led to these vaccines, and the cadre of scientists in academia, government, industry, NGO and importantly communities who carried them through their various phases of development. This is a very exciting moment for the world's response to malaria and for broader efforts to improve child health and survival. With that, I turn it back to Dr Tedros.

TAG Thank you. Thank you, Dyann. Thank you so much, indeed. And thank you, Hanna. Thank you to both of you for your leadership and we're very, very grateful for your commitment and dedication and leadership. Now, I would like

Margaret to take it from here and I hope, Dyann and Hanna, you will stay with us for Q&A. Thank you. Margaret, back to you.

00:20:55

MH Thank you very much, Dr Tedros and Prof. Wirth and Dr Nohynek. I now open the floor to questions from the journalists. There are over 230 of you online and so please keep the questions quite tight.

I would also like to let you know that the press release is now in your inboxes and the SAGE meeting highlights are linked in that press release and that is live on our website, so all that wealth of technical information that you've already heard will be reinforced in those materials.

We will also provide recordings. I understand that some feeds dropped off but we will provide the full recordings. Now, the first question goes to Paul Adepoju, from The Lancet. Paul, please unmute yourself and ask your question.

PA Thank you very much. This is Paul Adepoju, for The Lancet. My question goes to Dr Tedros, I think, but others may also take the question, which is considering these major milestones how much dent do you think the combined effect of these new vaccines could have on the current trends of malaria has, for instance conditions like the resistance and drug insensitivity issues that continue to be the major challenges with the vaccines not preventing new cases? How much impact do you think these new vaccines or the current state of vaccines could have on preventing disease resistance? Thank you very much.

MH Thank you. I might actually start with Dr Madandi. Are you ready for that question or would you prefer me to start with Prof. Wirth?

00:22:42

DM You can start with Prof. Wirth.

MH Okay. Over you Prof. Wirth first, and then I thought you might like to add.

DW Thank you for that question and I may also call on Dr Daniel or Dr Hamel to join in the answer to this. I think that introduction of the vaccine is focused on young children, so it's not going to be broadly introduced into the entire population, and so we expect the greatest impact to be on young children.

Since drug use is throughout the population, we don't anticipate an immediate effect on drug resistance but we feel that by reducing overall malaria cases and thus the presence of parasites exposed to drug, that there will be an add-on effect of reducing resistance but there won't be a direct effect. Mary or Daniel, anything to add?

MH Dr Hamel?

MA Thank you for that. WHO did commission an assessment looking at antimicrobial resistance with the introduction of the vaccine and, as Prof. Wirth said, the impact won't be immediate but with time, because most of those presenting to clinics in areas that are malarious areas are young

children and they often get anti-malarial drugs as well as antibiotics when they come in, with time the modelling does suggest that there could be considerable impact with the broad use of the vaccine.

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I think maybe your question went a little beyond that as well. Noting that we do have our current malaria prevention tools at risk from insecticide resistance, drug resistance, what is the added advantage of the vaccine? We certainly think that it's important to have this different way of approaching malaria.

The mathematical modelling, the estimates are that by adding the vaccine to the current tools that are in place tens of thousands of children's lives will be saved every year, so quite substantial but it will be really important not to substitute one intervention for the other. We don't want to roll out the vaccine and pull back on bed nets, which are also lifesaving. Adding these interventions on top of each other is where we're really going to get high impact.

MH Thank you very much, Dr Hamel. The next question goes to Carmen Paun, of Politico. Carmen, unmute yourself and ask your question.

CP Thank you so much for that, Margaret. I just wanted to hone in a bit on the comparison between the two vaccines for malaria because you said right now they're comparable. But with the RTS,S we heard efficacy level around 30-something percent and with this one we hear around 75%. So, you can explain to us why given these very different numbers, in very layman terms of course, you say that actually the vaccines so far, based on the evidence you have, are similar in terms of efficacy? Thank you.

00:26:23

MH I think it's another one for you Prof. Wirth and Dr Hamel.

DW Yes. I'll start but then turn it back to malaria, I think it's very important to understand that the data collected on the RTS,S vaccine on the time of its approval was from over 800,000 subjects who had received the vaccine in various conditions and the vaccine efficacy, as we know from the work on RTS,S, varies depending on how it is used.

The testing of the R21 vaccine has been much more limited, with only a few thousand subjects receiving the vaccine and much of the primary data is from its use in seasonal applications.

When RTS,S is used in seasonal applications, it has a similar efficacy to that reported for R21. However, as the RTS,S vaccine data is available for a much broader range of applications and transmission into situations, there the vaccine has somewhat less efficacy. I think Mary will expand on this with some additional details.

MA Thanks, Dyann. I understand that this is confusing because there are a lot of numbers and it's really important when you have a vaccine that has waning efficacy and a disease that you can get over and over, that you compare like with like. It's really crucial. And I think everybody will understand that if I say COVID vaccine has 90% efficacy at nine weeks after follow-up and

63% after a year, everyone understands that but you would not compare the next vaccine at nine weeks to an efficacy point after a year.

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This is where we have to be very careful with malaria vaccines. What we know, where both vaccines were tested in similar settings and delivered in similar ways, that is that they were delivered right before the high transmission season when vaccine efficacy was highest, both vaccines have about 75% efficacy, so that's great.

We cannot compare so easily when we look at the vaccine in an age-based strategy, the way it is usually given through the child immunisation programme, because the two vaccines have been tested in very different settings.

This is why we say that the data to date does not allow us to say that one vaccine performs better than the other. What we know is both vaccines are efficacious. What we expect is both vaccines will be highly impactful once they're rolled out across sub-Saharan Africa and other areas where malaria is a public health risk.

MH Thank you very much, Dr Hamel and Prof. Wirth. The next question goes to Annalisa Merelli, from STAT. Annalisa, can you unmute yourself and ask your question.

AM Hi. I apologise. There's a barking dog in the background. My question was whether there's any consideration to be made in terms of recommending one or the other vaccine, depending on locations or any other elements that might affect whether or not one or the other vaccine is more indicated.

MH Prof. Wirth do you want to start and Dr Hamel after?

00:30:33

DW I think that is a question for Dr O'Brien, for Kate O'Brien, unless Mary would rather answer.

MH That sounds fine.

KO Thanks so much for the question. The key issue here is I think, first of all, both Prof. Wirth and Dr Hamel have explained that there's really no choice to be made based on the current evidence around performance of the two vaccines but there are some differences between the vaccines about how a country might choose which one to actually implement in a programme.

The key characteristics that differentiate the vaccines, first of all I think we really want to emphasise the supply situation and I think, as you all know, we have only 18 million doses of RTS,S vaccines through the end of 2025, with work going on to increase that supply. With R21 coming in and commitments from the manufacturer with having over 100 million doses per year that they're previewing of being available, this is a very big step towards access and full supply to meet the demand.

There's also a question of price. Since most countries, the vast majority of countries that will be introducing this vaccine are Gavi-eligible countries, the

differentiation in price is significant for those countries that are soonest to leave Gavi support.

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For those that are in a group where they will continue to have Gavi support, the amount that a country pays per dose of vaccine is not determined by the price of the vaccine that Gavi is paying for it but there is a difference at this early stage on the price of the two vaccines.

There are a couple of other attributes that may be considered by a country. The second attribute is what is the nature of the vaccine? What does the vial actually look like? And there are some differences between the amount of cold chain space and the presentation of the vials, with RTS,S requiring reconstitution, so two vials, one that is freeze-dried and one that has a liquid that is used to make up the vaccine at the time of vaccine, whereas that is not the case for the R21 vaccine. So, some of those are programmatic characteristics.

Then, I think the final thing that might be under consideration for some countries is that on the RTS,S vaccine there is a very, very broad safety database on the vaccine, with millions of doses having been administered and extensive information around safety.

We also view the R21 vaccine as a safe vaccine but we have to acknowledge that, as Prof. Wirth indicated, we're in the thousands of children who have been vaccinated, not the tens of thousands, hundreds of thousands or millions of children. And so it will be important to continue to monitor the safety as the R21 vaccine we expect would be rolled out, again dependent on completing the WHO's prequalification.

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Maybe that explains a little bit about what a country might be looking at to prefer one vaccine over the other and the kinds of attributes, but they are not attributes that are on the basis of the expected performance of the vaccine.

MH Thank you very much, Dr O'Brien. We now go to Bianca Rothier, from Globo TV, Brazil. Bianca, please unmute yourself and ask your question.

BR Hi, Margaret. Many thanks. My question is the difference between the two vaccines. As far as I remember, the one approved two years ago was not cost-effective to be applied in Brazil because the mosquito found in the Amazon is not the same as found in Africa. So, how about this new one? Do you recommend the R21 to be used in Brazil? Thanks a lot.

MH Thanks, Bianca. I think that question has been fully answered but I did get a question in the chat about the prices, so maybe I'll go to Mary to talk about the prices, or Dyann.

DW I think this is a question for Mary.

MH Okay. Go ahead.

MA The price of the vaccine. We don't know right now what the price is. This is a contract that will be between Gavi and the manufacturer but the manufacturer has made public statements that the price will come under \$4

per dose and the mathematical modelling that looks at cost-effectiveness of this vaccine shows that it's cost-effective at \$2, \$3 or \$4 per dose in areas of low, moderate and high transmission. So, that's quite good news. I think I might have to pass over about the type of parasite I think you're speaking of in Brazil and whether it is vivax or falciparum.

00:36:15

DM Maybe I can jump in.

DW Yes.

DM I think R21 is valid for Plasmodium falciparum, whereas in Brazil we do have Plasmodium vivax as a vector for malaria. So, the most appropriate vaccine for Africa, where we have Plasmodium falciparum, is this one, R21 and RTS,S. But, for Brazil, this one is not necessary targeting the Plasmodium vivax.

MH Thank you very much for those answers. The next question we go to India, to Ashvin Barshinge, from the Observer Times. Ashvin, please unmute yourself and ask your question.

AB The is Ashvin Barshinge, from Observer Times, India. My question is, is it necessary now that the WHO has the WHO Sustainable Development Goals for vaccination to prevent high-risk viruses from the lives of human beings? Thank you.

MH It's the same question but go ahead.

DW For Mary, I think. Sorry, to Kate O'Brien.

MH Can you repeat it? We had a bit of a problem hearing. Sorry, could you repeat that question? Your question was about how it will accelerate the SDGs. Is that correct? I think that's a bit broad but perhaps Dr O'Brien could tackle it.

00:38:14

KO Yes. Let me start. I think we got the gist of the question, which is really about the role of vaccines, especially for high-risk pathogens, in achieving the SDGs. I think one of the things to really recognise here is that 14 of the 17 SDGs have in some way a linkage to vaccines and immunisation.

And we've lived through this incredible emergency phase of COVID-19, where a lesson that every country around the world learned is that along with preparedness of systems, along with all of the elements of surveillance that are necessary and treatments and diagnostics, at the heart of responding to emergency situations and pathogen-derived emergency situations there is extremely often a vaccine, whether it's a vaccine we already have or whether it's a new vaccine.

Of the seven public health emergencies of international concern that WHO has ever declared, six of them have had at the heart of the response vaccines. So, I think the answer to this is that as we go forward into this rather uncertain world and a world that is being impacted dramatically by climate change affecting the transmission of pathogens, affecting the habitats of animals and vectors and changing the way humans are affected by the world in which we in

live, vaccines will increasingly, we expect, take a more and more central role in the ability to respond.

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And those are things that drive the success of many of the SDGs because certainly I think there is broad agreement that preventing disease is far in preference to having to address the consequences of disease.

We also know that the return on investment of vaccines is extremely high. For every dollar invested in vaccines, there's a return on investment, depending on what you include, of somewhere between \$25 and \$40 and, in some calculations up to \$50 of return on investment.

So, I think these are some of the critical elements as we are all looking towards how to continue to accelerate the SDGs, given the hit that they've taken over the course of these past pandemic years.

MH Thank you very much, Dr O'Brien, and thank you for that important question. The next question goes to Donato Mancini, from the Financial Times. Donato, please unmute yourself and ask your question.

DM Hi, everyone. Good afternoon. Thanks for taking my question. Congrats on this wondrous news. I'm sure you've done modelling on this. When do you expect supply to meet demand? And are you able to give us a bit more detail on perhaps age ranges, types of country, geographic clustering of countries? Essentially, can you tell us as much as you can about it? Thank you.

MH Thank you. Kate, would you like to start?

KO I can start and I think my colleagues probably want to jump in. Donato, you snuck in there several questions in a multiphase sentence, so we'll get started on this.

00:41:25

Just in terms of supply, I've mentioned previously that for RTS,S we have 18 million doses through 2025 and with the tech transfer ongoing, at which point we do expect the supply to increase of RTS,S.

For R21 vaccine, we don't have firm previews but the manufacturer has stated that they expect to be able to produce 100 million doses per year with some ramp-up required but meeting that 100 million doses in 2024 and into 2025.

So, we would expect in 2024, given what we know about the, so far, 18 countries that have been approved through the Gavi processes for support, both for the vaccine itself and for the assistance to deploy the vaccine, that we will, by the end of 2024, and probably before that, not be in a supply-constrained environment.

But we do expect more countries to be applying and for countries to be considering, as has been discussed in many of the opening statements, about exactly how to deploy the vaccine in concert with the existing interventions, which all need to stay in place and those need to accelerate also.

I think the short answer is that the supply outlook is very positive, even in 2024, and it will continue to improve through '25, '26 and onwards. I'll turn back to Mary or to Daniel to add any elements about the age, although just

noting that the age for the R21 vaccine deployment is exactly the same age recommendation as for the RTS,S recommendation.

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DM To add to what Kate said, definitely the demand will be high once this information is disclosed for having this vaccine recommended by WHO. The restriction with RTS,S was the shortage of vaccine compared to the demand but now, with the capacity of producing several doses from the manufacturer information, clearly countries will likely be submitting their requests to use this vaccine.

And for good reason because from statistics that we do have, each minute a child dies of malaria. This is a huge, huge burden to the health system, to the entire population. We hope that having this new tool added to the tools that we do have, we can't miss this opportunity. Especially, countries will make sure that they apply for this vaccine. The demand will be high, so the invitation is to the supplier to produce according to the demand and partners, of course, to support.

MH Thank you, very much. I'm looking at Dr Hamel. Have you got anything to add?

MA Yes, I could add a little bit, thank you, just to build on the point about such high demand. This vaccine, Gavi has reported that this is the vaccine that has had the highest demand of any new vaccine that has come in. In the first year, after opening applications, 18 countries have already been approved for Gavi support to introduce the vaccine and 28 have said that they want to introduce the vaccine.

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Right now, the applications have come from sub-Saharan Africa. There are areas outside of sub-Saharan Africa that would qualify to be able to get the vaccine from which children would benefit.

There's an excess of 25 million children living in areas of moderate to high transmission and when you expand out from there to areas that are lower transmission you would add more children as well. So, really a huge demand and fortunately we now have the promise of sufficient vaccine to meet that demand.

MH Thank you very much for all those answers. We've got time for one more question and that goes to Gretchen Vogel, from Science magazine. Gretchen, please unmute yourself and ask your question.

GV Thanks very much. If you could just explain, you mentioned a couple of times that the WHO still needs to issue a prequalification. Could you explain the difference between this recommendation and what still needs to happen before prequalification and the difference between these two announcements?

MH I think that's Dr O'Brien, who is very familiar with this.

KO This is a great question. There are two distinct processes that happen. The first is the policy recommendation and that's what you're hearing about

today, in other words a review of evidence on safety, efficacy, programmatic suitability, performance of the vaccines that we review.

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And that's the recommendation that has been provided, accepted by the Director-General after a recommendation coming to him from the SAGE and MPAG group, having reviewed all of this evidence.

There is a distinct and separate review process that is undertaken that is a review from a regulatory perspective and although some of the data is similar data that is reviewed in both processes, there's a slightly different lens that is taken.

The regulatory process is also evaluating the safety and the efficacy of the vaccine but also the quality manufacturing aspects. It's a distinct group of external experts who is responsible for that review, and that review has a lot of engagement with the manufacturer, particularly around the steps involved in the manufacturing of the vaccine, assuring that lot-to-lot the same vaccine is produced in every round of production and that all of the measures of quality are in place.

That is a process that has been initiated many months ago and there is an ongoing review in that process and we do expect that that will come to completion in the relatively near future, but that's really determined by the pace with which manufacturers are responding to questions that are asked of them around the evidence on safety efficacy and the quality of manufacturing.

So, that will be the next step and achieving that step will allow for, as was explained, UNICEF, as a UN agency, to procure the vaccine under the funding that would come from Gavi.

00:48:26

MH Thank you very much, everybody. We're running up against a hard stop, so I'll hand it back to Dr Tedros for final remarks.

TAG Thank you. Thank you, Margaret. Again, I would like to thank Dr Hanna Nohynek, the Chair of the Strategic Advisory Group of Experts on Immunization and also to Prof. Dyann F Wirth, the Chair of the Malaria Policy Advisory Group for your leadership.

Thank you so much for joining us today and thank you also for the good news. And as I said earlier, as a malariologist today is a happy day because I have two vaccines. And I think the interest of some of the members of the media is whether we will have enough in terms of scale.

I think the addition of the second vaccine is addressing the supply chain that we had. As Kate said earlier, I think with the addition of the second vaccine, especially starting from the third quarter of 2024, we will have a good amount of vaccines from the two, so we can make it available to all countries who need the vaccines.

And, as you can imagine, this will have a significant impact on children, especially children in Africa. As you know, the highest burden of malaria is in Africa. Out of the ten high-burden countries, nine of them are in sub-Saharan

Africa and one, of course, India, is the only country actually which is outside the African continent.

00:50:16

So, this is good news to those countries who have been really struggling with malaria. 247 million cases a year is a lot but when you learn to live with a disease, although it's a killer, then that's the problem. But I hope this will change the game.

So, thank you so much again to Hanna and Dyann and all colleagues who have worked on this, my two directors, Kate and Daniel, and all colleagues who have participated, including the other members of the two committees. Thank you also to members of the press who have joined today. See you next time.