

RTS,S MEDICAL AND SCIENTIFIC QUESTIONS & ANSWERS

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Disclaimer

The primary focus of this resource is to be an internal training tool for RTS,S malaria vaccine candidate, containing related data in the format of a Q&A for Medical Affairs personnel. Information presented here is not for external distribution.

Whilst this document can be inspirational for reactive responses to experts or medical enquiries, local regulations, the GSK Code of Practice, scientific engagement principles and/or medical information processes should be followed appropriately.

Please Note

- For media enquiries, please refer to the specific reactive Q&A for Media Enquiries and notify the Global Pipeline Communications team before you respond to a request for an interview so that they can help you to prepare (contact person: Aoife Pauley at aoife.x.pauley@gsk.com).
- The vaccine RTS,S/AS01 has completed phase 3 clinical program and positive regulatory assessment from the European Medicines Agency, but is not yet authorized for marketing in any country. The RTS,S vaccine is being developed in Public Private Partnership with PATH-MVI, as an additional tool to be added to the currently available malaria preventive interventions and for implementation through the national immunization programs in malaria endemic regions in sub-Saharan African countries.
- When referencing clinical data on RTS,S any statements should be prefaced by "In this study...", to make it clear that it is too early to make any general statement on the vaccine profile outside the context of the ongoing clinical trials.
- Have you found what you were looking for? If you have any suggestions for information which should be included in this tool please contact us at the following address: Carys Calvert at carys.calvert@gsk.com.

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BACKGROUND INFORMATION ON MALARIA AND RTS,S

GENERAL

1. How does RTS,S work?

The RTS,S malaria vaccine candidate aims to trigger the immune system to defend against the *P. falciparum* malaria parasite when it first enters the human host's bloodstream and/or when the parasite infects liver cells. This is the pre-erythrocytic part of the parasites lifecycle and explains why RTS,S is commonly referred to as a pre-erythrocytic vaccine. RTS,S is designed to prevent the parasite from infecting, maturing and multiplying in the liver, and from re-entering the bloodstream and invading red blood cells, at which point the infected person would begin to show symptoms of the disease^(a).

Although no correlate of protection has currently been established, both humoral and cellular immune responses are considered to contribute to protection against *P. falciparum*.^(b) To stimulate an immune response to the malaria parasite, a portion of the circumsporozoite protein (the surface protein that helps the malaria parasite invade human liver cells) was fused with the hepatitis B surface protein (HBsAg). This 'RTS' fusion protein is expressed together with 'free' HBsAg ('S') in yeast cells (*Saccharomyces cerevisiae*), allowing spontaneous formation of 'RTS,S' particles known to enhance immune responses to the antigen. The addition of one of GSK's proprietary Adjuvant Systems (AS01) aims to further improve the immune response to the antigen and thereby induce protection^(c,d).

a. Gordon et al. J Infect Dis 1995; 171:1576-85

b. White et al 2013 PLoS ONE 8(4): e61395

c. Cohen et al. Ann Pharm Françaises 2010;68:370-9

d. Cohen et al. in Parasitology, Springer-Verlag Berlin Heidelberg 2011, Chapter 7

2. Will the emerging drug resistance to malaria drugs have also an effect on the efficacy of RTS,S, or vice versa?

The mechanisms by which the RTS,S malaria vaccine candidate prevents malaria cases from occurring are completely different from those used by drugs to attack the malaria parasite. There is no reason to assume that resistance of the malaria parasite against malaria drugs would also have an effect on the efficacy of the RTS,S malaria vaccine candidate.

In addition, there are no data available to substantiate that RTS,S would accelerate the emergence of resistance of the malaria parasite against malaria drugs. There is also no biologically plausible mechanism that could explain how such effect might happen. If the number of malaria cases would be reduced following the introduction of the RTS,S vaccine, there would be less need to use anti-malaria drugs and therefore potentially less pressure for drug resistance to emerge.

3. What is the effect of RTS,S on different parasite strains?

RTS,S will only induce protection against malaria caused by *Plasmodium falciparum*. Neafsey et al investigated the genetic diversity of *P. falciparum* and the protective efficacy of RTS,S^(a). The authors conclude that their results suggest that among children 5 to 17 months of age, the RTS,S vaccine had greater activity against malaria parasites with the matched circumsporozoite protein allele than against mismatched malaria. The overall vaccine efficacy in this age category will therefore depend on the proportion of matched alleles in the local parasite population.

Since in the efficacy trial, less than 10% of parasites had matched alleles, it also means that the results of the Malaria-055 trial are representative of the vaccine efficacy in an environment where the malaria parasites with the matched circumsporozoite protein allele are relatively rare. Genetic diversity will be actively monitored in the phase 4 program to evaluate if widespread RTS,S use has the potential to change parasite genetic diversity.

a. Neafsey D et al. N Engl J Med 2015; 373:2025-2037

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CLINICAL DEVELOPMENT OF RTS,S

GENERAL

4. What additional trials of RTS,S planned in the future?

GSK and MVI are committed to further monitoring the safety and assessing the real-life effectiveness of RTS,S, its benefit/risk profile in infants and young children living in malaria endemic regions, and its compatibility with current immunisation schedules. The studies below have been agreed upon with European Medicines Agency as part of the approved Risk Management plan ^(a)

Malaria-073^(a), is a Phase IIIb study to further evaluate co-administration with measles, rubella and yellow fever vaccines.

Malaria-076^(b) is an open-labelled Phase IIIa study to follow-up children in three centres of the Malaria-055 (Nanoro, Korogwe and Kombewa) to further evaluate efficacy and safety over an additional 3 years (January 2014 to December 2016).

Phase IV studies are also being developed for pharmacovigilance and impact of the vaccine, as part of a post-approval plan to accompany first widespread implementation. Additional operational and health-economic studies are also planned. Currently, three studies are included in the post-approval program.

EPI-MAL-002^(c): A prospective epidemiological pre-licensure surveillance study to assess baseline incidence of adverse events of specific interest (AESI), of other adverse events leading to hospitalization and death and of meningitis in 40,000 infants and children below 3 or 5 years of age. Study started in 2015 in some centres in geographical areas with Health and Demographic Surveillance System.

EPI-MAL-003^(d): A post-approval safety-surveillance study in 40,000 infants and children vaccinated with RTS,S/AS01 in sub-Saharan Africa by public health sector. This study will also measure impact of the vaccine on malaria disease as measured by malaria diagnosed at health facilities.

EPI-MAL-005^(e): A study of malaria epidemiology running alongside the EPI-MAL-002 and 003 will measure changes over time in parasite prevalence among vaccinated and unvaccinated populations and monitor changes in usage of malaria prevention measures in areas where these other studies will take place.

EPI-MAL-010 ^(f): This study will use samples from the EPI-MAL-005 to monitor the genetic diversity in CS sequences in parasite populations pre- and post- introduction of RTS,S.

Malaria-094 ^(g), is a Phase IIb open-label study to evaluate efficacy in children of different timings of the fourth dose, as well to evaluate the efficacy of additional vaccine doses either as full dose or fractional (1/5th of standard) vaccine doses. Planned study start from the end of 2016.

a. Malaria-073, (GSK study ID 200596)

b. Malaria-076; GSK study ID 200599; [clintrials.gov NCT number NCT02207816](https://clinicaltrials.gov/ct2/show/study/NCT02207816)

c. EPI-MAL-002; GSK study ID 115055; [NCT02374450](https://clinicaltrials.gov/ct2/show/study/NCT02374450)

d. EPI-MAL-003; GSK study ID 115056

e. EPI-MAL-005; GSK study ID 116682; [NCT02251704](https://clinicaltrials.gov/ct2/show/study/NCT02251704)

f. EPI-MAL-010; GSK study ID 205071

g. Malaria-094; GSK study ID 204889

DESIGN OF THE LARGE PHASE III EFFICACY STUDY

5. What is the design of the Phase III efficacy trial?

This Phase III efficacy trial is a double-blind, randomized, controlled trial conducted in 11 clinical trial sites in seven countries in sub-Saharan Africa^(a). 15,460 participants aged 6-12 weeks or 5-17 months first received three vaccine doses, one month apart, of either the RTS,S malaria vaccine candidate or a comparator vaccine. In the younger age category, administration was done concomitantly with the EPI vaccines DTPw-HepB/Hib and OPV. In the older age category, no other vaccine was co-administered to avoid confounding factors. After a year and a half (18 months), participants received a fourth dose of either the RTS,S malaria vaccine candidate or a comparator vaccine to assess whether such a “booster” dose will provide benefit.

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All subjects were followed up over 32 months post dose 1. In addition, follow-up continued until Dec 31, 2013 leading to a median follow-up of 48 months for children and 38 months for infants post dose 1.

Neither the volunteers nor the investigators know which vaccine is being administered in order to ensure there is no bias when interpreting the results (double-blind).

Researchers monitor cases of clinical malaria that are characterized by fever and the presence of malaria parasites in the blood, as well as the incidence of severe malaria and other relevant public health endpoints. Different case definitions have been used through a range of parasite levels; these are described in a separate document. To measure the vaccine's efficacy, occurrence of clinical and severe malaria cases will be compared between infants and children who received the RTS,S malaria vaccine candidate and those who received the comparator vaccine. In addition, researchers will continue to monitor safety and potential side effects as well as effect of RTS,S on growth and assess the safety and immunogenicity in HIV-infected and malnourished children.

a. *Leach A, et al. Malaria Journal 2011; 10: 224.*

b. *gsk.com-clinical trial register study ID 110021 (Malaria-055)*

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EFFICACY

PHASE III (MALARIA-055) EFFICACY RESULTS

6. What is the efficacy of RTS,S in infants 6-12 weeks old at first vaccine dose?

Key messages:

- Over the first year after vaccination, RTS,S reduced the number of malaria cases in infants by a third.
- Vaccine efficacy as highest shortly after vaccination, but could be enhanced by a 4th dose
 - Vaccine efficacy waned over time, but the VE against clinical malaria remained statistically significant over the 3 years follow up period and was enhanced by a 4th dose.
- Vaccines were given in co-administration with routine EPI vaccines (DTPw-HepB-Hib, OPV)
- Efficacy results were achieved in context of good access to health care and on top of existing malaria interventions, such as insecticide-treated bed nets used by 86% of study participants, demonstrating that RTS,S can provide protection in addition to that provided by existing malaria control interventions.

More detailed information:

The co-primary objective of the trial demonstrated a vaccine efficacy of 31% (97.5%CI: 24;38) over the first 12 months after dose 3 (ATP cohort) against the first episode of clinical malaria. ^(a) These results are not aligned with phase II results where efficacy against first episode of clinical malaria over 12 months was 62% [95% CI: 36 to 77] ^(d)

In the Phase III efficacy trial, VE was similar between the According-to-protocol and Intention-to-treat populations. ^(a,b,c)

The difference in VE between study sites was not statistically significant. ^(b)

VE waned over time, and although it remained statistically significant for clinical malaria until study end, no efficacy was observed during the last study period (month 21 to study end) in the absence of a booster dose. No significant protection was seen against severe malaria beyond the first year of follow-up, whether with or without a fourth dose ^(d)

Vaccine efficacy (as described in European SmPC ^(e))	clinical malaria (95% CI)	severe malaria (95% CI)	hospitalisation caused by malaria 95% CI)
Over 12 months follow-up from dose 3 (ATP* cohort, N = 6003)	33% (26; 39)	37% (5; 58)	32% (7; 50)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6003)	27% (20; 32)	15% (-20; 39)	17% (-7; 36)
3 doses only (ATP* cohort, N=5997)			
Over 30 months follow-up from dose 3	20% (13; 27)	11% (-22; 35)	10% (-15; 30)
Over 36 months follow-up** from dose 3	18% (11; 25)	13% (-17; 35)	13% (-9; 31)
3 doses + 4th dose (ATP* cohort, N=5997)			

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Over 30 months follow-up from dose 3	28% (22; 34)	17% (-14; 40)	25% (3; 42)
Over 36 months follow-up** from dose 3	27% (21; 32)	21% (-7; 42)	27% (7; 43)

*ATP: Subjects who received all vaccinations According-To-Protocol procedures within specified intervals, with period at risk starting 14 days after dose 3, N= total number in all 3 study groups

** All subjects were followed up over 32 months post dose 1. In addition, follow-up continued until Dec 31, 2013 leading to a median follow-up of 38 months for infants post dose 1.

VE was not demonstrated against all-cause mortality, malaria mortality, hospitalized pneumonia, septicaemia or prevalent anaemia, nor was there a detectable effect on nutritional status or growth. Case fatality rate for malaria and all-cause mortality was low ^(b). This may, in part, be explained by the very high standard of care throughout the trial and low mortality.

- The RTS,S Clinical Trial Partnership. NEJM 2012; 367: 2284-95.*
- RTS,S Clinical Trial Partnership. PloS Medicine 2014; doi/10.1371/journal.pmed.1001685*
- The RTS,S Clinical Trial Partnership. The Lancet, 2015. dx.doi.org/10.1016/S0140-6736(15)60721-8*
- Asante, KP. et al, Lancet Infect Dis 2011; 11:741-9.*
- European Medicines Agency, ema.europa.eu/ema/*

7. What is the efficacy of a fourth dose?

The phase III efficacy trial has evaluated a fourth dose of RTS,S/AS01 given 18 months after the primary series of 3 doses.^(a)

- Protection against clinical malaria was prolonged in both children and young infants by a fourth dose.
- The increased risk for severe malaria in the older age-category as compared to the control group was reduced by the administration of a fourth dose of RTS,S/AS01.
- The proportional increase in efficacy against clinical malaria associated with a fourth dose was similar in children and young infants but efficacy after the fourth dose remained lower in those who received their primary vaccination when aged 6-12 weeks rather than at the age of 5-17 months.
- The incremental vaccine efficacy against clinical malaria provided by the booster dose (i.e., VE of the fourth dose in addition to the protection provided by the primary vaccination course) was (ATP cohort):
 - In children: 29% over the first year after dose 4 and 21% up to study end.
 - In infants: 24% over the first year after dose 4 and 20% up to study end.

a. *RTS,S Clinical Trial Partnership. The Lancet, 2015. dx.doi.org/10.1016/S0140-6736(15)60721-8*

8. What is the efficacy of RTS,S in children 5-17 months old at the first vaccine dose?

Key messages:

- **Over the first year after vaccination, RTS,S reduced the number of malaria cases in children by half.**
- **Vaccine efficacy was highest shortly after vaccination, but could be enhanced by a 4th dose**
 - Vaccine efficacy waned over time, but the VE against clinical malaria remained statistically significant over the 4 years follow up period and was enhanced by a 4th dose.
- Efficacy results were achieved in context of good access to health care and on top of existing malaria interventions, such as insecticide-treated bed nets used by 78% of study participants, demonstrating that RTS,S can provide protection in addition to that provided by existing malaria control interventions.

More detailed information:

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The co-primary objective of the trial demonstrated a vaccine efficacy of 56% (97.5% CI: 51-60) over the first 12 months after dose 3 (ATP cohort) against the first episode of clinical malaria in the first 6000 children.^(a) These efficacy results are aligned with phase II POC results where the vaccine efficacy against the first episode of clinical malaria in 5-17 months over 12 months was 39 % [95% CI: 20-54].^(d)

In the Phase III efficacy trial, VE was similar between the According-to-protocol and Intention-to-treat populations as well as across case definitions (>0 to >5000 parasites/μl). ^(a,b,c)

Vaccine efficacy was similar in children vaccinated at 5-11 months of age or 12-17 months of age. ^(c) Vaccine efficacy varied between the 11 study sites.^(b) This heterogeneity was statistically significant over the first 20 months of follow-up (range 41-70%) ^(b), but not when compared over the entire study period. ^(c)

Vaccine efficacy waned over time (p<0.01). ^(b) However, efficacy remained statistically significant for clinical malaria over the entire study period. ^(c)

Vaccine efficacy (as described in European SmPC ^(e))	clinical malaria (95% CI)	severe malaria (95% CI)	hospitalisation caused by malaria (95% CI)
Over 12 months follow-up from dose 3 (ATP* cohort, N=6880)	51% (47; 55)	45% (22; 60)	48% (35; 59)
Over 18 months follow-up from dose 3 (ATP* cohort, N=6885)	46% (42; 49)	36% (15; 51)	42% (29; 52)
3 doses only (ATP* cohort, N=6918)			
Over 30 months follow-up from dose 3	34% (29; 39)	2% (-28; 25)	18% (1; 32)
Over 46 months follow-up** from dose 3	26% (21; 31)	-6% (-35; 17)	12% (-5; 26)
3 doses + 4th dose (ATP* cohort, N=6918)			
Over 30 months follow-up from dose 3	46% (42; 50)	32% (10; 50)	40% (26; 52)
Over 46 months follow-up** from dose 3	39% (34; 43)	29% (6; 46)	37% (24; 49)

*ATP: Subjects who received all vaccinations According-To-Protocol procedures within specified intervals, with period at risk starting 14 days after dose 3, N= total number in all 3 study groups

** All subjects were followed up over 32 months post dose 1. In addition, follow-up continued until Dec 31, 2013 leading to a median follow-up of 48 months for children post dose 1.

In children not receiving a booster dose, a negative VE against severe malaria was observed during the follow-up period between month 21 and study end. (-44% [95% CI: -119 to 4]). ^(c) This temporary increase in incidence of severe malaria in children receiving a primary schedule of RTS,S (73 severe malaria cases out of 2,057 children) as compared to controls (48 out of 2,051) could be a chance finding, but could also be compatible with a rebound effect, ie age shift. Such rebound effect has been noted after withdrawal of other malaria preventive interventions, eg seasonal malaria chemoprophylaxis (SMC).

Vaccination with RTS,S/AS01 also significantly reduced overall hospital admissions, severe anaemia and the need for blood transfusion, with these protective effects being more marked in those who received a 4th dose.

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VE was not demonstrated against all-cause mortality, malaria mortality, hospitalized pneumonia, septicaemia or prevalent anaemia, childhood nutritional status or growth.. This may, in part, be explained by the very high standard of care throughout the trial and low mortality ^(b,c)

- a. *The RTS,S Clinical Trial Partnership. NEJM 2011, 365: 1863-75.*
- b. *RTS,S Clinical Trial Partnership. PLoS Medicine 2014; doi/10.1371/journal.pmed.1001685*
- c. *The RTS,S Clinical Trial Partnership. The Lancet, 2015. dx.doi.org/10.1016/S0140-6736(15)60721-8*
- d. *Lusingo, J, PLoS ONE 2010, 5(11): e14090. Doi:10.1371/journal.pone.0014090.*
- e. *European Medicines Agency, ema.europa.eu/ema/*

LONG-TERM EFFICACY

9. Does the vaccine efficacy wane over time? How long does RTS,S protection last?

In the Phase III efficacy trial, vaccine efficacy was highest shortly after vaccination and remained significant against clinical malaria over the 3-to-4 years follow-up period. Vaccine efficacy was enhanced by a fourth dose., ^(a,b)

Estimation of duration of vaccine efficacy is complex as the children in the control group were exposed to more episodes of malaria (especially in higher transmission areas) and thus acquired natural immunity more rapidly.

Malaria-076, is an open-label study to follow-up children from three sites from Malaria-055 to further evaluate efficacy and safety over an additional 3 years (January 2014 to December 2016). ^(c)

Detailed analysis from Malaria-055 (Data on file):

An analysis by periods showed a progressive decline in the efficacy against clinical malaria. Although the study groups were well matched during the first 6-month period this was no longer the case subsequently as children in the control group experienced more clinical malaria than children in the RTS,S/AS01 group, and thereby may have acquired natural immunity, making the vaccine appear less effective by comparison.

VE against all episodes of clinical malaria (ITT cohort)	6-12 weeks old category		5-17 months old category	
Months 0 to 8	44% ^(a)		60% ^(a)	
Months 9 to 14	23% ^(a)		41% ^(a)	
Months 15 to 20	12% ^(a)		28% ^(a)	
Months 0 to 20	27% ^(a,b)		45% ^(a,b)	
	Primary	+ 4th dose	Primary	+ 4th dose
Months 21 to 32	8% ^(b)	28% ^(b)	16% ^(b)	37% ^(b)
Months 33 to study end	3% ^(b)	12% ^(b)	3% ^(b)	12% ^(b)
Months 0 to 32	20% ^(b)	28% ^(b)	35% ^(b)	44% ^(b)
Months 0 to study end	18% ^(b)	26% ^(b)	28% ^(b)	36% ^(b)

ITT cohort: Intention-To-Treat subjects received at least one dose of vaccine, with period at risk starting the day of the first dose

These results are in alignment with previous Phase II studies which have investigated the long-term efficacy and safety of RTS,S. Sacarlal *et al* ^(d) reported clinical benefit for up to 42 months after the initial vaccination of children 1-4y of age. Olotu *et al* ^(e) reported a waning of vaccine efficacy in children 5-17 months of age from an initial 43.6% to zero per cent four years after vaccination and indicated possible rebound. However, over this 4-year period, 650 clinical cases were averted per 1000 vaccinees. A multivariate statistical analysis on pooled data from seven clinical studies reported by Bejon *et al* ^(f) indicated that vaccine efficacy varied significantly according to time since vaccination from 36% to zero per cent after 3 years across different transmission settings and adjuvants used.

- a. *RTS,S Clinical Trial Partnership. PLoS Medicine 2014; doi/10.1371/journal.pmed.1001685*

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- b. RTS,S Clinical Trial Partnership. *The Lancet*, 2015. [dx.doi.org/10.1016/S0140-6736\(15\)60721-8](https://doi.org/10.1016/S0140-6736(15)60721-8)
- c. GSK study ID 200599; [clintrials.gov NCT number NCT02207816](https://clinicaltrials.gov/ct2/show/study/NCT02207816)
- d. Sacarlal J, et al. *J Infect Dis* 2009; 200: 329-36.
- e. Olotu A, et al. *NEJM* 2013; 368:1111-20
- f. Bejon P. et al. *Lancet ID* 2013; 13: 319–27

PUBLIC HEALTH IMPACT/PARTIAL EFFICACY

10. With the decline in malaria, why invest in a malaria vaccine which has only moderate efficacy instead of in current malaria control interventions

Despite major efforts in control measures over the past decade one child dies every minute due to malaria, mainly in sub-Saharan Africa. Moreover, the remarkable progress achieved the last decade is threatened by the spread of insecticide resistant mosquitoes and drug resistant parasites and also sustainability. ^(a) A vaccine that would allow to further reduce the remaining malaria disease burden by 30-50% would still provide a significant public health benefit. The use of other malaria interventions (mainly ITNs and ACTs) has been optimized in the pivotal RTS,S phase III efficacy trial according to the national guidelines and recommendations for malaria treatment and prevention. The clinical efficacy of RTS,S as measured in the trial therefore actually reflects the protection provided by RTS,S in addition to the protection provided by the other interventions.

As an example of the success of vector control combined with bednets and effective drug treatments, Zanzibar's control program has exceeded expectations, but we need to keep in mind that Zanzibar is an island, isolated from mainland, and that considerable resources from outside donors are needed to maintain their multipronged control strategy. Another example of success has been Rwanda, which achieved remarkable reductions in malaria incidence between 2005 and 2008. However in 2009, due to a delay in ITNs availability, the malaria incidence increased again until new bednets became available and were distributed, demonstrating the challenges to sustaining success in an environment where a prevention program had significantly reduced the disease threat. A mix of existing and new tools is needed to further reduced the burden of malaria. Even a moderately effective malaria vaccine, as an additional tool for a comprehensive toolbox, could help to achieve improved and sustained malaria control.

- a. *World Malaria Report*, WHO 2014
- b. Greenwood B, et al. *Parasite Immunol*, 2009, 31, 582-86

11. What does partial or moderate efficacy mean in real terms?

Partial or moderate efficacy means that a vaccine is effective less than 100 percent of the time, and does not prevent all cases of the disease. Taking into account the important disease burden of malaria mainly in African children under five years of age ^(c), even a vaccine with moderate efficacy could still provide considerable public health benefit.

The importance of considering public health impact estimates is clearly illustrated by the example of the rotavirus vaccine trial in Malawi and South Africa^(a). Despite the higher efficacy of the vaccine in South-Africa (77% vs. 49% in Malawi), more severe rotavirus gastroenteritis cases are prevented in Malawi (67 episodes/1,000 person years at risk vs. 42 in South-Africa), and this due to the much higher disease burden in Malawi (131 episodes/1,000 infants/year vs. 54 in South-Africa).

RTS,S reduces the chance of a child to develop clinical malaria by 50%. This reduction can be either all-or-nothing, (ie 50% of children are fully protected) or partial, ie everyone is protected to 50%. The results from our clinical trials indicate that the latter is the mechanism of the RTS,S malaria vaccine candidate. This is not overly surprising given that even people living in malaria endemic regions develop only partial immunity against malaria, despite being exposed regularly to infection by the malaria parasites.

In the case of the Phase III efficacy trial, RTS,S reduces the chance of a child to develop clinical malaria by half in children and by a third in infants over the first year after primary vaccination. In terms of public health impact, this translates into for every thousand vaccinees, an average of over 500 clinical malaria cases was prevented in infants and over 1000 in children over the 3-4 years of the study. Impact was further enhanced by a 4th dose preventing over 3000 and 6000 cases in infants and children living in areas of high malaria transmission ^(b).

- a. Madhi S. et al. *NEJM* 2010; 362: 289-98.

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b. RTS,S Clinical Trial Partnership. The Lancet, 2015. dx.doi.org/10.1016/S0140-6736(15)60721-8

c. Malaria Fact sheet n°94, WHO 2015 (<http://www.who.int/mediacentre/factsheets/fs094/en/>)

12. What is the estimated public health impact of RTS,S in view of its moderate efficacy?

Due to the significant burden of malaria in sub-Saharan Africa, even a vaccine with moderate efficacy could still provide substantial public health benefit in malaria endemic regions when implemented in addition to existing malaria interventions such as bednets.

The results from the phase III efficacy trial indicate that RTS,S “if used correctly, has the potential to prevent millions of cases of malaria” ^(b):

- Over 4 years of follow-up, an average of 1774 clinical malaria cases were prevented for every 1000 young children vaccinated with 4 doses of RTS,S in the clinical phase III efficacy trial. The cases averted ranged from 205 to 6565 per 1000 vaccinees, being greater in areas of higher malaria transmission. ^(b)

Cases averted per 1000 children vaccinated (median 48 months follow-up) ^(b)	3 doses	+ 4 th dose
	n (LL ; UL) range across sites	n (LL ; UL) range across sites
Clinical malaria	1363 (995 ; 1797) 215 to 4443	1774 (1387 ; 2186) 205 to 6565
Severe malaria	8 (-9 ; 26)	19 (4 ; 35)

- Although vaccine efficacy was lower in infants, meaningful public health impact might still be provided in areas with high disease burden. In the phase III study site with highest malaria incidence, over 3000 clinical malaria cases were prevented over 3 years of follow-up for every 1000 infants receiving 4 doses of RTS,S. ^(b)

Cases averted per 1000 infants vaccinated (median 38 months follow-up) ^(b)	3 doses	+ 4 th dose
	n (LL ; UL) range across sites	n (LL ; UL) range across sites
Clinical malaria	558 (158 ; 926) -172 to 2178	983 (592 ; 1337) -30 to 3406
Severe malaria	8 (-13 ; 28)	12 (-6 ; 32)

Modelling predicts that four doses of RTS,S could prevent roughly 484 malaria deaths per 100,000 vaccinated young children over an initial 15-year period when introduced on top of existing control programs. ^(c)

- Model predictions were made based on the final phase 3 efficacy results ^(b) by four different groups. Estimations were generated assuming a vaccination program starting in 2017 across a range of estimated parasite prevalence among 2-to-10 year-olds ($PfPR_{2-10}$) and access to treatment of 45%. Vaccination was done at the ages of 6, 7.5 and 9 months (90% coverage for 3rd dose) and a 4th dose at age 27 months (72% coverage, i.e., 80% of dose 3). ^(c)
- Over a 15-year period in settings of $PfPR_{2-10}$ of 10-65%, 4 doses of RTS,S would:
 - Avert 484 (189-859) malaria-related deaths per 100,000 vaccinated children
 - Avert 116,480 (31,450-160,410) clinical cases
- Public health impact of RTS,S is projected to be greatest in settings of $PfPR_{2-10} \geq 10\%$, although positive even at $PfPR_{2-10}$ of 5-10% and reasonably predicted by using the mean $PfPR_{2-10}$ in a country.
 - The impact by prevalence setting can be visualized on Malaria maps through the gsk web platform www.gskmodelsonweb.be/models/66#/models/66

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- Other influencing factors on the modelling estimates of overall public health impact were: vaccine efficacy profile, vaccine coverage in real-life settings, changes in insecticide resistance, or anti-malarial resistance, changes in access to treatment.

a. *Madhi S. et al. NEJM 2010; 362: 289-98.*

b. *RTS,S Clinical Trial Partnership. The Lancet, 2015. [dx.doi.org/10.1016/S0140-6736\(15\)60721-8](https://doi.org/10.1016/S0140-6736(15)60721-8)*

c. *Penny et al, Lancet 2015 ; [dx.doi.org/10.1016/S0140-6736\(15\)00725-4](https://doi.org/10.1016/S0140-6736(15)00725-4)*

13. Why is RTS,S only partially or moderately efficacious?

We currently do not know why the RTS,S malaria vaccine candidate is only moderately efficacious, but it is not overly surprising given that even people living in malaria endemic regions develop only partial immunity against malaria, despite being exposed regularly to infection by the malaria parasites.

A pre-erythrocytic malaria vaccine like the RTS,S malaria vaccine candidate should help the body's immune system kill sporozoites before they can infect a significant proportion of red blood cells and cause disease. However, only one sporozoite escaping the vaccine induced defence mechanisms is sufficient to start a blood stage infection resulting in clinical disease. Vaccine efficacy against clinical disease refers to the reduction in the risk of a child becoming infected and experiencing malaria disease and reflects the reduction of the number of malaria episodes for any child vaccinated.

In the phase III efficacy study, for every thousand vaccinees RTS,S was able to prevent more than thousands of clinical malaria cases in some of the trial sites over the four years of the study thus demonstrating the substantial public health benefit which can be provided by a vaccine with moderate efficacy on top of other control measures such as bednets.

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SAFETY

GENERAL SAFETY

14. What is the overall safety profile of RTS,S across the Phase II and Phase III programme?

More than 11,000 children have been vaccinated with RTS,S/AS01 in the Phase II and Phase III trials and, to date, the vaccine was shown to have an overall acceptable tolerability and safety profile^(a,b,c,d).

The most commonly reported adverse reactions were fever (27%), irritability (14%) and injection site reactions such as pain (16%) and swelling (7%)

- Very few of these reactions were of severe intensity.

The most serious adverse reaction was febrile convulsions (within 7 days post-vaccination) (0.1%)

- Within 7 days after the first 3 doses, the incidence of febrile convulsion per 1000 doses was:
 - in the children category (aged 5-17 months at time of first dose): 1.04 in the RTS,S group and 0.57 in the control, for a risk ratio of 1.8 (95% CI, 0.6 to 4.9)
 - In the infants category (aged 6-12 weeks at time of first dose): no increased risk of febrile convulsion was observed after the 3 first doses, which is coherent with the peak of incidence of febrile convulsion (18 months of age)
- Within the 7 days after the 4th dose, the incidence of febrile convulsions per 1000 doses was:
 - in the children category: 2.5 in the R3R group, 1.2 in the R3C group, and 0.4 in the C3C group
 - in the infants category: 2.2 in the R3R group, 0.0 in the R3C group, and 0.5 in the C3C group
 - Over 30 days post vaccination, the overall rates of febrile convulsions were similar between groups
 - Adverse reactions reported are listed according to the following frequency^(e):
 - Very common $\geq 1/10$
 - Common $\geq 1/100$ to $< 1/10$
 - Uncommon $\geq 1/1000$ to $< 1/100$

System Organ Class	Frequency	Adverse reactions
Metabolism and nutrition disorders	Common (very common following booster)	decreased appetite
Psychiatric disorders	Very common	irritability
Nervous system disorders	Common	somnolence
	Uncommon	febrile convulsions (within 7 days post-vaccination)
Gastrointestinal disorders	Common	diarrhoea
	Uncommon	vomiting
General disorders and administration site conditions	Very common	fever, injection site reactions (including swelling, erythema and pain)

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	Uncommon	injection site induration
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Clinical data in more than 4200 children who received a booster dose of Mosquirix shows that, following booster vaccination, decreased appetite was reported more frequently (very common) compared to the rates observed during primary vaccination.

- Vekemans J, et al. Human Vaccines 2011; 7: 1309-16.*
- The RTS,S Clinical Trial Partnership. NEJM 2011, 365: 1863-75.*
- The RTS,S Clinical Trial Partnership. NEJM 2012, 367: 2284-95.*
- The RTS,S Clinical Trial Partnership. The Lancet, 2015. [dx.doi.org/10.1016/S0140-6736\(15\)60721-8](https://doi.org/10.1016/S0140-6736(15)60721-8)*
- Mosquirix SmPC July 2015; European Medicines Agency, ema.europa.eu/ema/.*

PHASE III (MALARIA-055) SAFETY RESULTS

15. Does RTS,S change the pattern of severe malaria, and increase the risk of more severe forms of malaria like cerebral malaria?

In the Phase III efficacy study, in children aged 5-17 months at first dose, the incidence of severe malaria decreased over time in all groups. ^(a,b)

Whilst three doses of RTS,S reduced severe malaria by a third over 18 months of follow-up, ^(a) efficacy waned and after this period —unless a 4th vaccine dose was given— a trend to higher incidence of severe malaria was observed as compared to control children of the same age predominantly in sites with a high level of malaria transmission ^(b). Such shift of disease to an older age has also been described for other malaria interventions ^(c). This possibility needs to be explored in further studies eg the extended surveillance of study participants in three of the Malaria-055 centres, Malaria-076. ^(c)

In infants, no significant protection was seen against severe malaria beyond the 1st year of follow-up, whether with or without a fourth dose. There was no indication of increased incidence as compared to controls during the entire study period ^(b).

In a post-hoc analysis of the Phase III efficacy trial, severe malaria cases* were classified according to disease syndrome. There was a trend for more cases of cerebral malaria (defined as hospitalization with parasitaemia > 5000 parasites/μL and Blantyre coma score ≤ 2, without excluding co-morbidities) in RTS,S/AS01 recipients (11.7% in R3R and 10.8% in R3C groups) than in controls (4.3%) in the older age category. Numbers were low and there is no direct mechanism for a pre-erythrocytic vaccine to predispose to sequestration of infected red blood cells. Syndrome changes according to the age and shift of disease onset linked to the efficacy of the vaccine may explain the imbalance in markers and syndromes. Further assessment is planned in the Phase IV studies.

Time period	Syndrome	RTS,S group (N=5948)		Control group (N=2974)
M0-M20	All Cases	205		158
	Cerebral	16		5
	Cerebral + Anaemia	6		1
	Anaemia	25		29
	Other	157		123
	Missing	1		0
Time period	Syndrome	R3C (N=2719)	R3R (N=2681)	C3C (N=2702)
M21-SE	All Cases	103	76	76
	Cerebral	9	11	2
	Cerebral + Anaemia	0	1	2
	Anaemia	18	11	17

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	Other	75	53	54
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* Severe malaria secondary case definition = *P. falciparum* asexual parasitaemia at a density of > 5000 parasites per cubic millimetre with one or more markers of disease severity, including cases in which a coexisting illness was present or could not be ruled out.

The administration of a booster dose of RTS,S/AS01 prolonged the efficacy of the vaccine. ^(b) This finding suggests that if a decision is made to implement RTS,S/AS01 in an age category similar to that of the older children recruited to this trial, then strong consideration should be given to inclusion of a booster dose, especially in higher transmission areas and the possible impact of administration of further booster doses will need to be explored.

a. RTS,S Clinical Trial Partnership. *PloS Medicine* 2014; doi/10.1371/journal.pmed.1001685

b. RTS,S Clinical Trial Partnership. *The Lancet*, 2015. dx.doi.org/10.1016/S0140-6736(15)60721-8

c. GSK study ID 200599; *clintrials.gov* NCT number NCT02207816

CO-ADMINISTRATION

16. Can RTS,S be co-administered with other childhood vaccines?

Mosquirix™ can be given concomitantly with any of the following monovalent or combination vaccines including diphtheria (D), tetanus (T), whole cell pertussis (Pw), acellular pertussis (Pa), hepatitis B (HepB), *Haemophilus influenzae* type b (Hib), oral polio (OPV), measles, yellow fever, rotavirus and pneumococcal conjugate vaccines (PCV). ^(a)

- If RTS,S/AS01 is to be given at the same time as another injectable vaccine, the vaccines should always be administered at different sites. ^(a)
- Concomitant administration of rotavirus and pneumococcal conjugate vaccines with RTS,S/AS01 may reduce the antibody response to the circumsporozoite (CS) antigen of RTS,S. The impact of this observation on the level of protection induced by RTS,S/AS01 is currently unknown. ^(a)
- The co-administration of Mosquirix™ with PCV increases the risk of fever within 7 days post-vaccination ^(a)

RTS,S/AS01 vaccine formulations were evaluated in co-administration with the following licensed vaccines^(c,d): DTPw/Hib (*TETRActHib*), DTPa/Hib (*Infanrix Hib*), DTPw-HepB/Hib (*Tritanrix-HepB/Hib*), OPV (*Polio Sabin*), measles (*Rouvax/Attenuated Live Measles Vaccine*), yellow fever (*Stamaril*), rotavirus (*Rotarix*) and pneumococcal conjugated (*Synflorix*) vaccines.

The non-inferiority of the immune response was demonstrated for D, T, Pw, Pa, Hib, polio and pneumococcal antigens (except for pneumococcal serotype 18C); although there was a trend for lower antibody geometric mean concentrations (GMCs) for these antigens when compared to the control group. These observations were considered as not clinically significant. ^(a)

In a clinical study in infants aged 8-12 weeks, fever was reported more frequently in infants receiving PCV in co-administration with Mosquirix, DTPa/Hib and OPV simultaneously (26%), as compared to infants receiving only Mosquirix, DTPa/Hib and OPV (14%). However, the frequency of grade 3 fever (defined as axillary temperature > 39.0°C) was low (≤ 1%). ^(a,d)

Another study, **Malaria-073**^(e), is a Phase IIIb randomized, open-label, controlled study to evaluate the non-inferiority of immune response and the safety of the RTS,S/AS01, when administered as primary vaccination with or without co-administration of yellow fever (*Stamaril*®), measles and rubella (*MR-VAC*™) vaccines at 6, 7.5 and 9 months of age to children living in sub-Saharan Africa.

a. Mosquirix Global Datasheet v03, February 2015

b. Leach A, et al. *Malaria Journal* 2011; 10: 224.

c. Agnandji S, et al. *J Infectious Diseases* 2010, 202(7):1076–1087

d. Malaria-063, *ClinicalTrials.gov* NCT01345240 (GSK study ID 113681)

e. Malaria-073, (GSK study ID 200596)

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SAFETY IN SPECIFIC POPULATIONS

17. What data has been generated on RTS,S in HIV-infected children?

Limited data are available from use of Mosquirix™ in HIV-infected children. ^(c)

Data from clinical studies suggest that HIV-infected children are more likely to experience local and systemic reactogenicity (injection site pain and injection site erythema, fever, somnolence, irritability, decreased appetite) ^(a) compared to the general population of children vaccinated ^(b). Over the entire follow-up period, incidences of SAEs and deaths and viral load were similar in HIV-infected children vaccinated with RTS,S/AS01 or a control licensed vaccine.

No significant effect of RTS,S was observed on growth parameters, CD4+ T-cell percentage, absolute CD4 + T-cell counts, HIV viral load and WHO AIDS clinical classification.

Immunogenicity, safety and efficacy of RTS,S was evaluated in children aged 6 weeks to 17 months diagnosed with HIV (WHO stage 1 and 2) in two phase III studies, Malaria-055^(a) and Malaria-058^(b),

In **Malaria-055**, children with known HIV/AIDS disease stage I and II (WHO AIDS staging) were eligible. It should be noted that HIV testing was not a study procedure; this analysis included therefore all children known to be HIV infected at enrolment or subsequently diagnosed on clinical suspicion, with the limitation that HIV testing practices differed from one centre to another. A first sub-analysis of safety and immunogenicity of a primary course of RTS,S/AS01_E in HIV-infected children was conducted in 2012 ^(a). At study end, 1.0% of the children and infants had a confirmed HIV positive status and a few additional children and infants (9 in total) had an SAE coded as retroviral infection that was not confirmed by PCR or HIV antibody test (suspected HIV positive status). Six children were known to be HIV infected at enrolment, the others were identified HIV-infected during study conduct. Therefore, most of the children included in this analysis were not under treatment at the time of RTS,S/AS01_E vaccination. The adherence to treatment during the length of the study is unknown.

- Based on 125 children with confirmed HIV-infection, RTS,S elicited a lower anti-CS antibody response in HIV-infected children (GMC=193 EU/ml) as compared to children of unknown HIV infection status (GMC=492 EU/ml). ^(c)
- The overall safety information from dose 1 to study end showed that HIV-infected children in the three groups R3R, R3C and C3C experienced similar incidence of SAEs (92%, 85% and 88% respectively) and fatal SAEs (29%, 28% and 31% respectively).

Malaria-058, enrolled 200 children in Kenya, aged 6 weeks to 17 months, who were diagnosed with WHO stage 1 or 2 HIV disease in the context of high treatment coverage (anti-retrovirals and co-trimoxazole). These children were randomized to receive RTS,S/AS01 (99 children) or rabies control vaccine(101 children). This study looked specifically at safety of the vaccine in these children in terms of both reporting of safety events and monitoring of disease progression markers. The study also evaluated vaccine efficacy against clinical and severe malaria.

- The anti-CS antibody GMC was 329 EU/mL, one month after the third dose of RTS,S.
- The incidence of SAEs was similar (41% in the RTS,S group and 37% in the rabies vaccine group) over 14 months post dose 1. There were 9 fatal SAEs, 5 in the RTS,S group and 4 in the rabies vaccine group.
- Over one year of follow-up, the VE of RTS,S against all episodes of clinical malaria was 37% (95% CI: -27; 69).

a. *Malaria-055, ClinicalTrials.gov NCT00866619 (GSK study ID 110021)*

b. *Malaria-058, ClinicalTrials.gov NCT01148459 (GSK study ID 112745)*

c. *Mosquirix European SmPC 2015; ema.europa.eu*

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HEALTH ECONOMICS/COST EFFECTIVENESS

GENERAL

18. What is the estimated cost for RTS,S delivery?

Costs estimated for RTS,S delivery are similar to other vaccines recently introduced in sub-Saharan Africa.^(a)

Although comparability with other antigens is limited given differences in vaccine properties, deployment strategies, immunization rate, etc., costs estimated by Galactinova *et al* for RTS,S delivery are similar to other vaccines recently introduced in the region.^(a)

- Financial vaccine delivery costs estimated to \$0.90 to \$1.91 per fully vaccinated child across the 6 countries (Burkina Faso, Ghana, Kenya, Senegal, Tanzania, and Uganda)
- Levels of support currently awarded by Gavi for new vaccine introduction: \$0.80 per child for vaccines delivered to infants and \$2.40 per girl for HPV vaccine
- Costs are higher if vaccine is delivered outside of routine schedule and if new visits would be required.

a. Galactinova *et al*, *Vaccine* 2015, [dx.doi.org/10.1016/j.vaccine.2015.10.0797](https://doi.org/10.1016/j.vaccine.2015.10.0797)

19. What is the estimated cost-effectiveness of RTS,S?

Adding Mosquirix™ to current malaria control interventions is highly cost-effective.^(b)

Model predictions were made by four modelling groups based on the final phase 3 efficacy results.^(a) Estimations assumed a vaccination program starting in 2017 across a range of estimated parasite prevalence among 2-to-10 year-olds ($PfPR_{2-10}$) and access to treatment of 45%. Vaccination was done at the ages of 6, 7.5 and 9 months (90% coverage for 3rd dose) and a 4th dose at age 27 months (72% coverage, i.e., 80% of dose 3).^(b)

The Incremental Cost-effectiveness ratios (ICER) estimates for vaccination of young children living in regions with a $PfPR_{2-10}$ of 10-65% from the age of 6 months with 4th doses (at a price of US\$ 5 per dose) was US\$87 (\$43-240) per DALY averted.^(b)

These estimates are higher than for LLINS, but similar to estimates for IRS however, not directly comparable due to studies conducted in different settings. In comparison, average incremental costs per DALY averted for other interventions (2009 prices) was for LLINs \$27 (\$8.15-\$110), for IRS \$143 (\$135-\$150), for IPT \$24 (\$1.08-\$44.24)^(c)

a. RTS,S Clinical Trial Partnership. *The Lancet*, 2015. [dx.doi.org/10.1016/S0140-6736\(15\)60721-8](https://doi.org/10.1016/S0140-6736(15)60721-8)

b. Penny *et al*, *Lancet* 2015

c. White *et al*. *Malaria J*. 2011;10:337

20. What is the economic burden of malaria?

Malaria consumes an important part of the household income in Africa and pushes them further into poverty.

- Malaria consumes 4-13% of annual family income in Tigray region in Ethiopia (GMAP financing strategy document) and 2.7-3.9% in Tanzania^(a).
- In the Maputo district of Mozambique, one third of households incurred catastrophic payments related to malaria and this rate was 9-12.5% in 2 districts with highest malaria burden in South Africa^(b).
- The estimated national cost of malaria in children <5 years expressed in US\$ (2009) was 37.8 M in Ghana, 109.04 M in Kenya and 131.94 M in Tanzania.^(c)

a. Somi M. *et al Trop Med Int Health* 2007; 12: 1139-47

b. Castillo-Riquelme *et al, Trop Med Int Health* 2008, 13: 108-122

c. Sicuri *et al, Malaria J* 2013;12:30

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21. What is the economic impact of malaria prevention and control?

Malaria prevention and control triggers a stronger economic growth by reducing also the disease burden on poor households.

- Malaria has lifelong effects on cognitive development and education levels through the impact of chronic malaria-induced anemia and school absenteeism due to illness. ^(a)
- Countries with high malaria incidence had their economic growth reduced by 1.3% annually compared with similar countries without malaria. ^(a)
- Malaria promotes poverty by effects on household behaviour that limit economic growth (e.g. demography, education and human capital), and by macroeconomic effects such as adverse effects on trade, tourism and direct investment. ^(b,c)

a. Gallup JL. and Sachs JD. *Am J Trop Med Hyg.* 2001; 64(1-2 Suppl): 85-96

b. Sachs & Malaney, *Nature* 415, 680-685

c. Conley, McCord, & Sachs, 2007, *Africa's lagging demographic transition: evidence from exogenous impacts of malaria ecology and agricultural technology*, National Bureau of Economic Research, Cambridge, MA, USA, Working paper 12892

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PRICING AND FINANCING

GENERAL

22. How much will the vaccine cost?

It is too early for GSK to confirm the price of RTS,S during this development phase. In January 2010, GSK committed to setting a price which covers costs of manufacturing the vaccine and a small return of 5% to be reinvested in R&D for next generation malaria vaccines or for other treatments for diseases of the developing world. GSK also committed to evaluate any possibility that would allow limiting the cost of manufacturing^(a).

a. Witty A. *New Strategies For Innovation In Global Health: A Pharmaceutical Industry Perspective*. *Health Affairs* 2011; 30: 118-26.

23. Will Gavi support implementation of RTS,S as for other vaccines?

RTS,S is expected to be available through usual procurement process including UN agencies (UNICEF) with support from Gavi. Gavi has included malaria vaccine in their Vaccine Investment Strategy ^(a) and is now looking into its role (and that of Global Fund against AIDS, Tuberculosis and Malaria) into financing of Pilot introduction projects as recommended by WHO.

a. *Gavi Vaccine Investment Strategy*, 2013.

24. How will you ensure that cost of the vaccine will not be a barrier to access?

The partnership believes that no child should be deprived of a malaria vaccine because their parents can't afford it. If countries decide to implement the vaccine, it should reach those who need it most: children living in malaria endemic regions in Africa. Two things need to happen so that cost will not be a barrier to access: First, in most African countries current childhood vaccines are provided to children for free. GSK and MVI trust that this would also apply for a malaria vaccine.

Second, funding mechanisms exist today to ensure that childhood vaccines are made available to African communities, with limited financial contributions from the countries. GSK and MVI hope that similar mechanisms will be put in place for a malaria vaccine.

25. What is the intellectual property on RTS,S?

GSK owns patents that cover RTS,S and the adjuvant system. MVI and GSK are committed to making the vaccine available to those who need it most: infants and young children in malaria endemic regions in sub-Saharan Africa, and have agreed global access terms to that effect.

26. How will you ensure that the vaccine, once approved, will reach those who need it?

If the vaccine is recommended for use and approved by regulatory authorities, MVI and GSK are committed to doing all they can to make the vaccine available to those who need it most: infants and young children in malaria endemic regions in sub-Saharan Africa. Indeed, the partners engaged early on—and continue to engage—with the WHO to help ensure they have all the information required to issue a policy recommendation and pre-qualification, and thus pave the way for procurement by UN and other agencies. In addition, the partners are engaging with malaria endemic African countries to ensure processes and systems are in place for decision making regarding the potential introduction of a malaria vaccine. Price should not be a barrier to access. MVI and GSK will collaborate closely with multilateral organisations such as GAVI, UNICEF, and others to allow these organisations to purchase the vaccine in large volumes at affordable prices.

27. Will RTS,S be made available as part of a tiered pricing structure?

RTS,S is currently being developed solely for use in sub-Saharan Africa since burden of malaria caused by *P. falciparum* is mostly occurring in sub-Saharan African children under 5 years of age. Tiered pricing (where prices are aligned to a country's ability to pay) is not applicable because this vaccine will not be made available in higher income countries.

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28. How much will development of the vaccine cost and who is paying?

GSK has invested more than \$365 million to date and expects to invest a further \$200 to \$250 million until development is completed. Between 2001 and the end of 2014, MVI, supported by grants from Bill & Melinda Gates Foundation (BMGF), invested more than \$200 million to advance the RTS,S project.

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LICENSURE, INDICATION, IMPLEMENTATION

REGULATORY PROCESS, INDICATION

29. When will Mosquirix™ be approved for use in Africa?

In July 2015, the European Medicines Agency (EMA) gave a positive scientific opinion on the benefit-risk of RTS,S – now known as Mosquirix – in children aged 6 weeks to 17 months. ^(a) The positive opinion from the EMA is the first step in the regulatory and policy process toward making Mosquirix available as an addition to existing tools currently recommended for malaria prevention.

In November 2015, WHO recommended 3-5 large pilot implementation projects in sub-Saharan Africa with moderate-to-high malaria transmission to understand how to best use RTS,S to protect young children against malaria. The pilot projects should evaluate the additional contacts with the health care system needed to deliver the four doses to children from the age of 5 months. ^(b)

This will be followed in 2016 by a technical variation to EMA and application for WHO pre-qualification.

The last step will be the application for marketing authorisation to national health authorities in sub-Saharan Africa. EMA's positive scientific opinion will be the basis for these applications that are a mandatory step on the way toward the implementation of Mosquirix through African national immunisation programmes.

The timing or duration of these steps is yet to be established. Based on experiences with other vaccines, it is likely to take a couple of years.

a. *Mosquirix SmPC July 2015; European Medicines Agency, ema.europa.eu/ema/*

b. *WHO Q&A on malaria vaccines Nov 2015 who.int/immunization/research/development/malaria_vaccine_qa/en/*

c. *SAGE news release Oct 23 2015 who.int/mediacentre/news/releases/2015/sage/en/*

30. What data was included in the file submission to the European Medicines Agency?

Data from the Phase III vaccine trials programme conducted at 13 African research centres in eight African countries (Burkina Faso, Gabon, Ghana, Kenya, Tanzania, Mozambique, Malawi and Nigeria) including over 16,000 infants and young children have been included to support the filing. This includes data from the pivotal efficacy trial, safety in HIV+ children and infants, and co-administration of the RTS,S vaccine candidate with other paediatric vaccines. Data and reports from the clinical development including phase I and phase II trials are also presented in the application, as relevant for the assessment of the claimed indications of prevention of malaria and hepatitis-B diseases.

Quality data from commercial manufacturing of RTS,S, and a substantial amount of nonclinical data were also included.

The main clinical study is the phase III efficacy study Malaria-055. Malaria-055 is a large controlled, randomized, observer-blind, multi-centre study aiming to evaluate, in over 15,000 infants and children, the efficacy, safety and immunogenicity of RTS,S/AS01_E against malaria disease caused by *P. falciparum* infection, across diverse malaria transmission settings in SSA ^(a). Study results including co-primary endpoints and efficacy and safety over 3-4 years and the effect of a booster dose have been published ^(b,c,d,e). Three centres of the Malaria-055 will follow-up children to further evaluate efficacy and safety over an additional 3 years in the Malaria-076, an open-label study (January 2014 to December 2016) ^(f)

The concomitant use with other vaccines was evaluated in two other studies besides the Malaria-055:

- Malaria-050: safety, immunogenicity and efficacy when given with DTPw-HepB/Hib, measles and yellow fever vaccines ^(g)
- Malaria-063: safety/immunogenicity when given with *Infanrix* /Hib + OPV, *Synflorix* and *Rotarix* ^(h)
- The characterization of immune responses to the candidate vaccine was mainly done in phase II trials; vaccine lot-to-lot consistency was evaluated in two phase III trials:
- Malaria-061 lot-to-lot consistency with respect of the anti-CS response in children 5-17 months ⁽ⁱ⁾
- Malaria-063 lot-to-lot consistency with respect of the anti-HBs response in infants 6-12 weeks ^(h)

Safety and immunogenicity in special populations have been assessed in:

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- Malaria-055: subgroup analysis in HIV seropositive children, low-for-weight children and pre-term infants
- Malaria-058 trial ⁽ⁱ⁾, 200 children 6 weeks to 17 months with a known HIV seropositive status.
 - a. Leach A, et al. *Malaria Journal* 2011; 10: 224.
 - b. The RTS,S Clinical Trial Partnership. *NEJM* 2011, 365: 1863-75.
 - c. The RTS,S Clinical Trial Partnership. *NEJM* 2012, 367: 2284-95.
 - d. RTS,S Clinical Trial Partnership. *PloS Medicine* 2014; doi/10.1371/journal.pmed.1001685
 - e. RTS,S Clinical Trial Partnership, *The Lancet*, 2015. dx.doi.org/10.1016/S0140-6736(15)60721-8
 - f. GSK study ID 200599; *clintrials.gov* NCT number NCT02207816
 - g. Agnandji ST, et al. *J Infect Dis* 2010;202:1076-87
 - h. Malaria-063, study ID 113681; NCT01345240
 - i. Malaria-061, study ID 113398; NCT01323972
 - j. Malaria-058, study ID 112745; NCT01148459

31. What is the regulatory process?

An application was submitted to the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP), to obtain a scientific opinion using a specific procedure called *Article 58* of the EU medicines legislation. This procedure allows the EMA to assess the quality, safety and efficacy of a candidate vaccine or medicine for a disease of major public health interest, but intended exclusively for use outside the European Union while being manufactured in the European Union. This assessment is done by the EMA in collaboration with WHO, and requires products to meet the same standards as vaccines or medicines intended for use in the European Union.

The positive opinion from the EMA in July 2015 ^(a) is the first step in the regulatory and policy process toward making Mosquirix available as an addition to existing tools currently recommended for malaria prevention. Next, GSK will seek WHO prequalification for Mosquirix™, in order to allow United Nation agencies, such as UNICEF, to purchase the vaccine in partnership with developing countries. This positive opinion would also be the basis for Marketing Authorisation Applications to National Regulatory Authorities (NRAs) in sub-Saharan Africa.

In addition to regulatory processes, the pathway to implementation also requires policy recommendations by international and national public health authorities. ^(b)

- a. Mosquirix SmPC July 2015; European Medicines Agency, ema.europa.eu/ema/
- b. WHO Q&A on malaria vaccines Nov 2015 who.int/immunization/research/development/malaria_vaccine_qa/en/

32. For whom is Mosquirix™ indicated?

Following review by the European Medicines Agency ^(a), Mosquirix™ is indicated for active immunisation of children aged 6 weeks up to 17 months against malaria caused by *Plasmodium falciparum* and against hepatitis B. The use of Mosquirix should be based on official recommendations considering *Plasmodium falciparum* malaria epidemiology in different geographical areas.

Mosquirix should not be used for the prevention of hepatitis B in settings where prevention against malaria caused by *P. falciparum* is not sought. The safety and efficacy of Mosquirix in children younger than 6 weeks and older than 17 months of age (at first dose) has not been established. Data regarding the efficacy of Mosquirix are limited to children from sub-Saharan Africa.

In November 2015, WHO recommended 3-5 large pilot implementation projects in sub-Saharan Africa with moderate-to-high malaria transmission to understand how to best use RTS,S to protect young children against malaria. The pilot projects should evaluate the additional contacts with the health care system needed to deliver the four doses to children from the age of 5 months. ^(b)

- a. Mosquirix SmPC July 2015; European Medicines Agency, ema.europa.eu/ema/
- b. WHO Q&A on malaria vaccines Nov 2015 who.int/immunization/research/development/malaria_vaccine_qa/en/

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AVAILABILITY, IMPLEMENTATION

33. Why should the international community start preparing now, if RTS,S will not be rolled out for several years and there is no guaranteed funding for its purchase?

We have learned from other interventions that if planning for a decision is not started years in advance, the intervention may ultimately, and unfortunately, remain unused for years after its availability. The planning and decision-making process - as well as the generation or collection of needed data - takes time and careful evaluation. The goal for the RTS,S malaria vaccine candidate is to minimise, to the extent possible, delays between regulatory approval, possible recommendations for use, and initiation of uptake.

In November 2015, WHO recommended 3-5 large pilot implementation projects in sub-Saharan Africa with moderate-to-high malaria transmission to understand how to best use RTS,S to protect young children against malaria. ^(a) Continued partnership with global organisations for malaria control and immunisation as well as funders will be needed to support the introduction and implementation of Mosquirix™ in countries who have adopted the vaccine. A shared risk approach from development to access is necessary to make sure that this vaccine candidate is available to those that need it.

- The regulatory post-marketing requirements are significant, given the not-for-profit nature of this vaccine. PATH and GSK are working together to identify potential sources of funding for these studies. The Gates Foundation continues to support RTS,S through PATH that is funded to help ensure informed decision-making by malaria-endemic countries; partial funding for the baseline PhIV study.
- African countries will need support to develop different methods for post-marketing surveillance eg sentinel sites to further evaluate safety and impact and in parallel, preparing for vaccine implementation.
- Gavi has included malaria vaccine in their Vaccine Investment Strategy. ^(b) They are now looking into their role (and that of Global Fund against AIDS, Tuberculosis and Malaria) in supporting pilot introduction projects recommended by WHO.
- By beginning the process now of gathering data and establishing systems to aid in decision-making, countries can determine the appropriate role of a malaria vaccine in their malaria control and EPI programs without undue delay.

a. WHO Q&A on malaria vaccines Nov 2015: who.int/immunization/research/development/malaria_vaccine_qa/en/

b. Gavi Vaccine Investment Strategy, 2013, www.gavialliance.org/about/strategy/vaccine-investment-strategy/

34. When will RTS,S be made available for implementation?

In November 2015, WHO recommended 3-5 large pilot implementation projects in sub-Saharan Africa with moderate-to-high malaria transmission to understand how to best use RTS,S to protect young children against malaria. ^(a) The pilot projects should evaluate the additional contacts with the health care system needed to deliver the four doses to children from the age of 5 months as well as potential impact on mortality. WHO estimates that the pilot implementation programme will generate critical evidence to enable decision-making about the potential wider scale use of this vaccine in 3-5 years' time. ^(a)

A WHO policy recommendation is the global equivalent of a national public health authority's (e.g. Ministry of Health's) decision about use of vaccines. Many countries appreciate guidance from the WHO policy recommendation process on which vaccines they should consider for introduction in their national immunization programmes. Similarly, donor agencies, such as the GAVI Alliance, require a WHO recommendation for use before funding procurement of vaccines for developing countries.

The last step will be the application for marketing authorisation to national health authorities in sub-Saharan Africa. EMA's positive scientific opinion ^(b) will be the basis for these applications that are a mandatory step on the way toward the implementation of Mosquirix through African national immunisation programmes.

a. WHO Q&A on malaria vaccines Nov 2015 who.int/immunization/research/development/malaria_vaccine_qa/en/

b. Mosquirix SmPC July 2015; European Medicines Agency, ema.europa.eu/ema/

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35. Will RTS,S be available outside of sub-Saharan Africa?

Five different species of *Plasmodium* parasites cause malaria in different regions of the world. *Plasmodium falciparum*, which is targeted by the RTS,S malaria vaccine candidate, is considered to be the most deadly malaria parasite, and is the predominant species causing malaria in sub-Saharan Africa.

The vast majority of estimated cases (80%) and deaths (90%) occur in sub-Saharan Africa. The great majority of malaria deaths caused by the *Pf* parasite occur in children under the age of five (77%). Therefore the current priority is to make RTS,S available in this population as soon as possible.

In Asia and many parts of Latin America, *Plasmodium vivax* (*Pv*) is prevalent, although *Pf* is present with some hot spots. The impact of the RTS,S malaria vaccine candidate on clinical malaria outside Africa could therefore be more limited and would require further investigation. The potential age- and geographic extensions of RTS,S are still under discussion and would also require external funding.

36. Will the implementation of the RTS,S malaria vaccine candidate in malaria endemic areas replace the current malaria control interventions?

Mosquirix is being considered as a complementary intervention, i.e. one that would be deployed in addition to fully scaled-up access to and use of other malaria preventive measures, prompt diagnostic testing and effective anti-malarial medicines. The efficacy data published for Mosquirix were generated on top of the use of these existing interventions.

Results to date indicate that the RTS,S malaria vaccine candidate has the potential to reduce the risk of malaria by 30-50% among infants and young children living in malaria endemic areas in sub-Saharan Africa on top of existing malaria interventions (mainly bednets). Taking into account the disease burden of malaria in this region, with one child dying every minute^(a), even a vaccine with moderate efficacy could provide substantial public health benefit. However, given the efficacy profile of the vaccine candidate to date, it will be important to also continue using other malaria control interventions (such as long-lasting insecticide treated bednets, indoor residual insecticide spraying, rapid diagnosis and appropriate treatment of malaria cases with artemisinin-based combinations therapies) according to national recommendations.

a. World Malaria Report, WHO 2014 (<http://www.who.int/malaria/publications/>)

37. Does GSK plan to make RTS,S eventually available as a travellers vaccine?

Current routine practice is to help protect travellers visiting malaria endemic regions with prophylactic anti-malaria drugs, shortly before, during, and for a short period after travel. The effectiveness of such prophylactic treatment is considered to be very high, and a vaccine with partial efficacy, although capable of providing substantial public health benefits to populations living in malaria endemic areas, would not be considered acceptable to replace the currently recommended practice of chemoprophylactic treatment for travellers.

PRODUCT CHARACTERISTICS

38. What will the product presentation of RTS,S be? What is the pack size?

The RTS,S candidate vaccine presentation is a two-dose presentation with two vials clipped together, lyophilized RTS,S in one vial and the liquid adjuvant AS01 in the other vial. There is no preservative in either RTS,S or the AS01 adjuvant. The product is stable for 3 years at +2-8°C. RTS,S must be reconstituted with AS01 prior to administration. After reconstitution, the product is stable for 6 hours.

Each pack will contain 100 vials (50 pairs of RTS,S/AS01) and equals 100 doses. This is similar to the standard for GSK vaccines in 3mL vials supplied by UNICEF. The pack dimension of the inner carton will be Length: 18cm; width 14.9cm; height 3.7cm for a total volume of 9.92cm³/dose.

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PARTNERS IN THE DEVELOPMENT OF THE RTS,S MALARIA VACCINE CANDIDATE

GENERAL

39. Who is responsible for the development of RTS,S?

The clinical development of the RTS,S malaria vaccine candidate is being implemented by the Clinical Trials Partnership Committee, a collaboration of leading African research institutes, their Northern academic partners, MVI and GSK. The trial sites were selected for their track record of world-class clinical research, strong community relations and commitment to meeting the highest international ethical, medical, clinical and regulatory standards. With support from the Malaria Clinical Trials Alliance (MCTA) the partnership ensured capacity building at clinical trial sites to prepare them for the conduct of high-quality trials. This included building of infrastructure, provision of equipment such as laboratory equipment and X-ray machines, establishment of quality systems and staff training.

MVI is involved in the technical design of the trials, conducts ongoing training for trial sites, participates in oversight of the trials, and funds the sites' conduct of the trials. GSK takes the lead in the clinical development and assumes all the clinical trial sponsorship responsibilities according to the GCP guidelines. GSK takes also the lead in the interactions with regulatory agencies and is responsible for the manufacturing and distribution of the RTS,S malaria vaccine candidate once regulatory approvals and recommendations for use have been obtained.

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ADJUVANTS

GENERAL

40. What is an Adjuvant? Why does GSK use an Adjuvant System in the RTS,S malaria vaccine candidate?

An adjuvant is a substance which enhances the immune response against a vaccine antigen. Adjuvants, such as aluminium salts, have been used in vaccine formulations to enhance the immune response of vaccines for more than 80 years.

GSK's proprietary Adjuvant Systems (AS) utilise a combination of two or more different adjuvants to enhance and guide the immune responses against the antigens contained in the vaccine. Phase I and Phase II clinical trials evaluated different Adjuvant Systems for the RTS,S malaria vaccine candidate and demonstrated that the enhanced antibody and cellular immune responses observed with AS01 also resulted in a trend towards improved vaccine efficacy against malaria infection and disease while maintaining an acceptable safety profile. This most promising AS01 adjuvanted formulation of the RTS,S malaria vaccine candidate was selected for further testing in the ongoing Phase III studies.

41. What is the composition of the AS01 adjuvant contained in the malaria vaccine candidate?

GSK's proprietary AS01 Adjuvant System contains MPL, QS-21 and liposomes.

MPL (monophosphoryl lipid A) is derived from the cell wall lipopolysaccharide of *Salmonella Minnesota* strain R595. It is the first and only toll-like receptor (TLR) ligand currently approved in a human vaccine^(a).

QS-21 is a saponin extracted from the bark of the *Quillaja saponaria* tree, also known as the soap bark tree or Soapbark, an evergreen tree native to warm temperate central Chile. QS-21 is a purified fraction of saponin, and has been shown to enhance both antibody- and cell-mediated immune responses^(b). QS-21 is registered by Agenus Inc. as Stimulon®. Agenus Inc. (Nasdaq: AGEN) is a US based biotechnology company (www.agenusbio.com). QS-21: Quillaja saponaria Molina, fraction 21 is in-licensed from Antigenics Inc, a wholly owned subsidiary of Agenus Inc., Lexington, MA, USA.

Liposomes are artificial vesicles that comprise an aqueous core enclosed in one or more phospholipid layers^(c). They have been developed and studied for over 30 years as a way to deliver drugs to cells. Liposomes alone are usually inert carriers. Over the last 20 years, this principle has been applied to vaccines in order to deliver antigens and other adjuvants to antigen-presenting cells^(d,e).

MPL and Liposomes used in AS01 are property of GSK.

- a. Mata-Haro V, et al. The vaccine adjuvant monophosphoryl lipid A as a TRIF-biased agonist of TLR4. *Science* 2007;316:1628-32.
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- c. Garçon N, et al. GlaxoSmithKline Adjuvant Systems in vaccines: concepts, achievements and perspectives. *Expert Rev Vaccines* 2007;6:723-39.
- d. Alving CR, et al. Effectiveness of liposomes as potential carriers of vaccines: applications to cholera toxin and human malaria sporozoite antigen. *Vaccine* 1986;4:166-72.
- e. Alving CR, et al. Liposomes as carriers of peptide antigens: induction of antibodies and cytotoxic T lymphocytes to conjugated and unconjugated peptides. *Immunol Rev* 1995;145:5-31.