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ANALYSIS

WHO's rollout of malaria vaccine in Africa: can safety questions be answered after only 24 months?

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Key messages

- Phase III trials of the RTS,S malaria vaccine identified three safety concerns: higher risks of meningitis, cerebral malaria, and doubled female mortality
- These safety concerns are now being investigated in pilot implementation studies with 720 000 participating children in Ghana, Kenya, and Malawi, planned to last 4-5 years
- Owing to the urgency of improving malaria control, the World Health Organization intends to decide on extending the vaccine to other African countries after only 24 months using the prevention of "severe malaria" as a surrogate marker for overall mortality
- Severe malaria is not a good marker for all cause mortality; it is not even a good marker for malaria mortality, as data indicate that case fatality from severe malaria might be higher in the malaria vaccine group
- An early decision after 24 months might be biased in favour of the vaccine, which was more efficacious in the first year of follow-up in the phase III trials; the relative risks of both cerebral malaria and female mortality increased after the booster dose at 20 months
- We recommend that the pilot studies use "overall mortality" to assess vaccine performance and that study populations are followed for the full 4-5 years of the study before a decision on rollout is made

World malaria day on 23 April 2019 saw the start of the first routine malaria vaccine programme in Africa—a pilot study in Malawi. Ghana and Kenya have now followed. The RTS,S/AS01 malaria vaccine has been under development by GlaxoSmithKline for 30 years and is the first malaria vaccine to receive regulatory approval for human use. The pilot study aims to enrol 720 000 children in vaccination and control clusters over a two year period; it is planned to last about 50 months.

Media and leading medical journals have celebrated the news,[1-4] emphasising the potential to dramatically reduce child mortality. In the words of Tedros Adhanom Ghebreyesus, director general of the World Health Organization, "It has the potential to save tens of thousands of children's lives."[1 3]

Why then are pilot studies needed before rolling out the vaccine for all children? One reason is that achieving an efficacy of 36% in the phase III trials required a booster dose at 20 months after the primary series of three doses given at 5-17 months of age.[5] Giving a booster dose after 2 years of age is a challenge because the current vaccination programme is focused on vaccine delivery in infancy, so the pilot study is partly to examine whether boosters are logistically feasible. Furthermore, the European Medicines Agency (EMA) requested the pilot study to confirm or refute important safety concerns around meningitis, cerebral malaria, and sex specific, all cause mortality identified in the phase III trials.[6 7]

WHO advisory bodies and the EMA have said that these safety concerns might have arisen by chance. But we should be particularly careful about introducing new vaccines amid unresolved safety concerns, especially given recent use of a dengue vaccine in the Philippines that led to increased morbidity and mortality from dengue[8 9] as well as a resurgence of measles and polio secondary to a fall in public confidence in vaccination programmes.[10] Making a premature decision on a malaria vaccine that is ultimately found to have detrimental effects would be disastrous for the credibility of vaccination programmes (and all types of vaccines).

Safety concerns

The phase III randomised controlled trials recruited children in two age groups (6-12 weeks and 5-17 months). Vaccine efficacy was highest (36%) in the cohort of 5-17 month olds who received a booster dose, so the 5-17 month age group with a booster dose was selected for the pilot study.

The final phase III report, however, noted that, in the 5-17 month age group, significantly more children who received the malaria vaccine had meningitis than those in the control group (who received the rabies vaccine): 21 of 5948 in the RTS,S groups (with and without booster), and 1 of 2974 in the control group.[5] The difference was observed both before the time of the booster vaccine (16 of 5948 versus 1 of 2974, relative risk (RR) 8.0,

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95% confidence interval 1.1 to 60.3) and after the time of the booster vaccine (5 of 5400 versus 0 of 2702).

Subsequent analyses of the 5-17 month population found that the RTS,S groups also had more cases of cerebral malaria: 43 of 5948 cases compared with 10 of 2974 cases among controls (RR 2.15 (1.08 to 4.27)).[11] This calculation was based on a clinical algorithm. A later review by two independent external experts reduced the total number of possible cerebral malaria cases from 53 to 37,[12] resulting in a new RR estimate of 0.93 (0.37 to 2.32) in the first 20 months of follow-up and 3.75 (0.86 to 16.39) after the booster dose.[12]

The published data also showed a trend towards a higher rate of death among patients hospitalised with severe malaria in those who received the vaccine (21 of 648) than in controls (6 of 388) (RR 2.10 (0.85 to 5.15)).[5 13]

Finally, we analysed the data released by GlaxoSmithKline[14] and found that female children who received the vaccine had significantly higher all cause mortality than controls in both age groups, the RR being 2.00 (1.18 to 3.39) in the 5-17 month age group, which is the focus of the pilot implementation study.[15] In its position paper, WHO emphasised that mortality was similar for male and female children in the control and vaccine arms.[11] But female recipients of the vaccine in the 5-17 month age group had 33% (2% to 74%) significantly higher mortality than the male recipients.[15] Notably, the excess mortality among recipients of the vaccine increased after the booster dose (table 1). This trend was particularly marked for female children (RR 3.40 (1.01 to 11.42)) after the booster dose (table 1).

WHO and GlaxoSmithKline have interpreted this sex difference in mortality as a possible chance finding or due to unnatural low mortality in the female control group.[11 16] But the statistical likelihood that particularly low mortality among female controls would have happened in both age groups must be slim.[15] Some researchers have proposed that the higher mortality in vaccinated female children was due to the rabies vaccine having beneficial non-specific effects leading to unnaturally low mortality in the female 5-17 month control group.[16 17] But this would not explain the higher mortality among female recipients of the malaria vaccine in the 6-12-week age group (table 1), in which the controls received meningococcal serogroup C conjugate vaccine.[5]

Other non-live vaccines and increased female mortality

Other vaccines have been associated with increased female mortality. In 1989, WHO recommended the high titre measles vaccine (HTMV) in areas with a high risk of measles infection. However, five randomised controlled trials subsequently showed that HTMV was associated with doubled female mortality.[18 19] WHO withdrew HTMV in 1992. Subsequent analyses showed that the increased female mortality was most likely due to the non-live diphtheria, tetanus, and pertussis (DTP) vaccine being given after HTMV.[18] Receiving DTP has consistently been associated with higher female mortality, including when given after a measles containing vaccine.[20 21] We have subsequently shown that other non-live vaccines—including the hepatitis B vaccine,[22] inactivated polio vaccine,[23] pentavalent vaccine,[24] and H1N1 influenza vaccine[25]—are also associated with higher female mortality. As a non-live vaccine, RTS,S fits this pattern, reducing the likelihood that the higher female mortality is a chance finding.

We don't know of any biological explanation for non-live vaccines being associated with female mortality, but two recent immunological studies showed that the influenza vaccine and non-live vaccines containing DTP were associated with immunological tolerance towards stimulation with unrelated pathogens.[26 27] A potential sex difference in this process is currently being explored.

Malaria vaccine pilot study

Given the safety concerns for meningitis, cerebral malaria, and female mortality, the EMA's risk management plan said that the vaccine should be evaluated for these potential risks, [6] and WHO's Strategic Advisory Group of Experts on immunisation (SAGE) recommended that this evaluation be carried out in large enough numbers to detect a possible sex difference in mortality and to provide evidence of a beneficial effect of the vaccine on overall mortality.[11] The pilot study was funded by Gavi, the Vaccine Alliance, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, Path, and Unitaid, and is sponsored by WHO and the national ministries of health in the three participating countries.

In their April 2019 meetings, SAGE and the WHO Malaria Policy Advisory Committee (MPAC) approved a framework for policy on RTS,S.[28] The study protocol has not been made available, but the framework says that different districts in each country will be randomly allocated to receive malaria vaccine or no malaria vaccine (no placebo or control vaccine is being used).[28] To assess the risk of meningitis and cerebral malaria, between four and eight sentinel hospitals in each country will conduct inpatient surveillance. The plan is to capture information on deaths by means of "resident village reporters" and to supplement this information with adverse events data reported by the routine pharmacovigilance systems.[28]

The pilot study is expected to last about 50 months to be able to provide the mortality data. But SAGE and MPAC plan to make a decision about the broader use of RTS,S after only 24 months, for two reasons. First, given increasing drug resistance, further control measures against malaria are urgently needed. Second, GlaxoSmithKline might have problems maintaining the production line if the decision is delayed.[28]

Thus, at the meeting in April, SAGE and MPAC agreed that a recommendation could be made in the absence of mortality data.[28 29] They consider the vaccine's effect on severe malaria to be an acceptable surrogate indicator for mortality.[29]

A registration of a smaller study to evaluate the feasibility, safety, and impact of the introduction of RTS,S in pilot programmes in Ghana, Kenya, and Malawi based on 15 800 households was registered in March 2019 (NCT03806465). In January 2020 the registration was updated to specify that with 120 000 participants enrolled at each site each year, the pilot study will have "80% power to detect, at the 5% significance level, a decrease of at least 10% in overall mortality in each country" and "an increased risk of mortality in girls of 1.035, compared with the 1.9-fold increase in risk among girls receiving RTS,S/AS01 in the RTS,S phase III trial." Written informed consent is not obtained. What participants are told about the outstanding safety concerns is unclear.

Concerns

The decision to use severe malaria as a surrogate marker for all cause mortality seems strange. The case fatality for severe malaria for RTS,S recipients was double that for controls in phase III trials,[13] and malaria deaths accounted for only 20-25% of all deaths in the previous trials.[15] Hence, even though RTS,S might slightly reduce the risk of severe malaria, recipients might

be at higher risk of dying (from malaria and overall).[15] Each pilot study country is estimated to have around 2040 deaths before 24 months of follow-up (240 000 children recruited over two years with an average follow-up of one year per person with a mortality rate of 8.5 per 1000 person years), so there should be no need for a surrogate marker. The mortality data collected from village reporters and through the routine pharmacovigilance system, however, might not be complete—both types of data collection might have major quality problems.[30 31]

Importantly, the decision to make a recommendation about the wider scale use of RTS,S after just 24 months might bias the decision in favour of the malaria vaccine.

Firstly, at the 24 month mark of a study in which participants were recruited over two years 75% of the follow-up time will be in the first year after the enrolment, where the vaccine efficacy against clinical malaria was 50.4% in the phase III trials.[32] Subsequently, vaccine efficacy fell dramatically.[32]

Secondly, an assessment after just two years will include virtually no observation time after the booster dose of RTS,S given 20 months after first dose. This is problematic because cerebral malaria[12] and the excess in female mortality compared with controls seemed to increase after the booster dose (table 1, table 2). This might be related to the booster dose of the non-live malaria vaccine being given after the measles vaccine; other non-live vaccines have been associated with negative effects when given after measles vaccine.[33-37]

Finally, the pilot study is designed to have 90% power to rule out the possibility that the female-male mortality ratio is 20% higher among malaria vaccine recipients than in controls. Because the effectiveness of malaria vaccination declines over time[5 38] and malaria infection might lead to higher case fatality in those who receive the vaccine, the excess mortality might become apparent only after longer follow-up, particularly for females (table 1, table 2).

Conclusion

The idea that the malaria vaccine "will go global in two years' time" has already been sold to the public.[39] With its very large sample size, the pilot study could conceivably confirm some of the safety concerns in the first 24 months. If there is a substantial difference in the female-male mortality ratio between malaria vaccine recipients and controls, for example, the pilot study will presumably be stopped by the Data Safety and Monitoring Board.

But if no serious safety signal is found in the first 24 months, the pilot study should run for the full follow-up time to properly assess the three safety concerns before any decisions are made about broader use of RTS,S in Africa. There is no room for wishful thinking. Decision making must be grounded in robust evidence.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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Tables

Table 1| Mortality risk ratios for RTS,S recipients and controls by sex and length of follow-up. Data from 11 sites in seven countries in Africa.[14]

Period of follow-up by sex and age group	% deaths (deaths/n)		Risk ratio (RTS,S/controls) (95% CI)
	RTS,S vaccinated (with and without booster)	Controls	
Male, 0-20 months:			
5-17 months	0.9% (27/2981)	1.3% (19/1471)	0.70 (0.39 to 1.26)
6-12 weeks	1.8% (40/2234)	1.9% (21/1079)	0.92 (0.55 to 1.55)
All			0.82 (0.55 to 1.20)*
Male, 21 months to study end:			
5-17 months	0.6% (18/2954)	0.7% (10/1452)	0.88 (0.41 to 1.91)
6-12 weeks	0.5% (10/2194)	0.5% (5/1058)	0.96 (0.33 to 2.81)
All			0.91 (0.49 to 1.70)*
Female, 0-20 months			
5-17 months	1.6% (47/2967)	0.9% (14/1503)	1.70 (0.94 to 3.08)
6-12 weeks	2.1% (44/2124)	1.2% (13/1100)	1.75 (0.95 to 3.24)
All			1.73 (1.13 to 2.64)*
Female, 21 months to study end:			
5-17 months	0.7% (20/2920)	0.2% (3/1489)	3.40 (1.01 to 11.42)
6-12 weeks	0.6% (12/2080)	0.3% (3/1087)	2.09 (0.59 to 7.39)
All			2.75 (1.15 to 6.57)*
All, 0-20 months:			
5-17 months	1.2% (74/5948)	1.1% (33/2974)	1.12 (0.75 to 1.69)
6-12 weeks	1.9% (84/4358)	1.6% (34/2179)	1.24 (0.83 to 1.83)
All			1.18 (0.89 to 1.57)*
All, 21 months to study end:			
5-17 months	0.6% (38/5874)	0.4% (13/2941)	1.46 (0.78 to 2.74)
6-12 weeks	0.5% (22/4274)	0.4% (8/2145)	1.38 (0.62 to 3.09)
All			1.43 (0.87 to 2.35)*

* All estimate was calculated as the meta estimate of those for the individual age groups using Stata's "meta" command. GlaxoSmithKline data reported events for the first 20 months until the time of booster vaccination and for the full study period. The number of enrolled children in the period after the booster dose (21 months to study end) was calculated by subtracting the number of deaths in the first 20 months from the total events. The control group received three comparator vaccines at the start and then a comparator vaccine for the booster dose.

Table 2| Female:male mortality ratios for RTS,S recipients and controls

Period of follow-up	Female:male mortality ratio (95% CI)		Ratio ratio of F/M mortality ratio for RTS,S vs controls (95% CI)
	RTS,S vaccinated (with and without booster RTS,S)	Controls	
0-20 months:			
5-17 months	1.75 (1.09 to 2.80)	0.72 (0.36 to 1.43)	2.43 (1.05 to 6.61)
6-12 weeks	1.16 (0.76 to 1.79)	0.61 (0.31 to 1.21)	1.90 (0.85 to 4.25)
All			2.14 (1.20 to 3.82)*
21 months to study end:			
5-17 months	1.12 (0.60 to 2.12)	0.29 (0.08 to 1.06)	3.86 (0.92 to 16.3)
6-12 weeks	1.27 (0.55 to 2.92)	0.58 (0.14 to 2.43)	2.19 (0.42 to 11.44)
All			3.02 (1.02 to 8.94)*

* All estimate was calculated as the meta estimate of those for the individual age groups using Stata's "meta" command. GlaxoSmithKline data reported events for the first 20 months until the time of booster vaccination and for the full study period. The number of enrolled children in the period after the booster dose (21 months to study end) was calculated by subtracting the number of deaths in the first 20 months from the total events. The control group received three comparator vaccines at the start and then a comparator vaccine for the booster dose.