Malaria Vaccine Impact on Drug-susceptible and Resistant Cases and Deaths: A Modeling Study

Alisa Hamilton[1], Fardad Haghpanah[1], Mateusz Hasso-Agopsowicz[2], Isabel Frost[2], Gary Lin[1], Emily Schueller[1], Eili Klein[1,3], Ramanan Laxminarayan[1,4,5]

[1]One Health Trust (formerly the Center for Disease Dynamics, Economics & Policy), [2]World Health Organization, [3]Johns Hopkins University, [4]Princeton University, [5]University of Washington

Background

- ~627,000 people died of malaria in 2020. 96% of global malaria deaths occurred in sub-Saharan Africa, and 80% of these were among children under five[1].
- Gains towards malaria elimination could be reversed by the spread of resistance to artemisinin combination therapies (ACTs) or partner drugs.
- Chloroquine resistance spread rapidly in Africa in the 1980s and 90s, with treatment failure rates (TFRs) reaching ~80%[2]. ACT resistance could spread as quickly[3].
- Vaccines effectively prevent both resistant and susceptible infections, reducing pathogen-associated antimicrobial use and selection pressure for resistance[4].

RTS,S, S/AS01 and Vaccine Efficacy

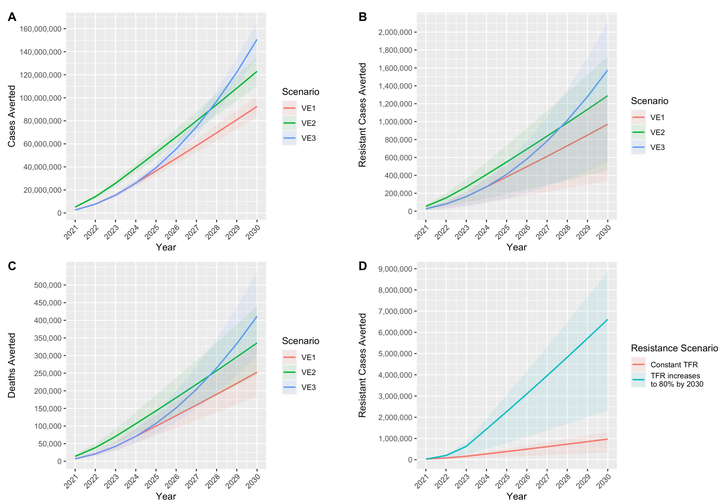
- RTS,S is the only vaccine candidate to receive WHO approval in 2021.
- Pre-erythrocyte vaccine, targeting the infectious stage of *Plasmodium falciparum*, specifically the circumsporozoite protein (CSP).
- The rate at which vaccine efficacy (VE) wanes depends on various ecological, parasite, and human host factors factors[5].
- In the Phase III trial, RTS,S showed ~36% efficacy at 48 months follow up[6].

Objective

Estimate cases, drug- resistant cases, and deaths averted from 2021 to 2030 with a vaccine similar to RTS,S administered yearly to infants in the WHO Africa Region under different VE scenarios.

Scenario	Vaccine Efficacy	Justification
1	VE remains constant at 40% for 4 years, dropping to 0% in year 5	Phase III trial of RTS,S[6]
2	VE begins at 80%, dropping 20 percentage points each year until reaching 0% in year 5	7-year follow-up study of RTS,S[7]
3	VE remains constant at 40% for the entire study period	Difficulty generalizing exactly how VE will change over time and at scale
4	Scenario 1 with TFRs increasing linearly to 80% by 2030 (worst-case scenario)	Example of chloroquine resistance in Africa[2] and modeling studies of ACT resistance[3]

Figure 2. Cumulative Burden Averted by Vaccine Efficacy Scenario, WHO Africa Region

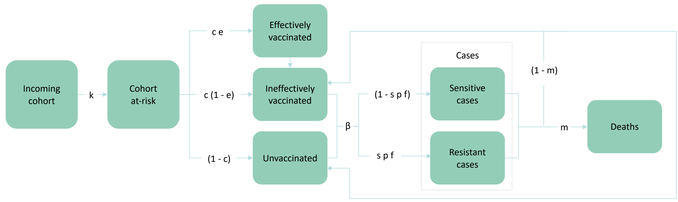


A) Cumulative cases averted from 2021-2030 for scenarios 1-3. B) Cumulative resistant cases averted from 2021-2030 for scenarios 1-3. C) Cumulative deaths averted from 2021-2030 for scenarios 1-3. D) Cumulative resistant cases averted for scenarios 1 and 4 (worst-case resistance scenario).

Methods

Discrete model of patient infection states in which a new cohort of one-year-olds is introduced each year and followed over several years. Infants enter as effectively vaccinated, ineffectively vaccinated, or unvaccinated. A proportion without an effective vaccine becomes infected with a drug-sensitive or drug-resistant parasite. After vaccinated individuals lose immunity, they enter the ineffectively vaccinated state. A proportion of cases lead to death each year, and the remainder return to either ineffectively vaccinated or unvaccinated states.

Figure 1. Model Diagram



Parameters and Sources

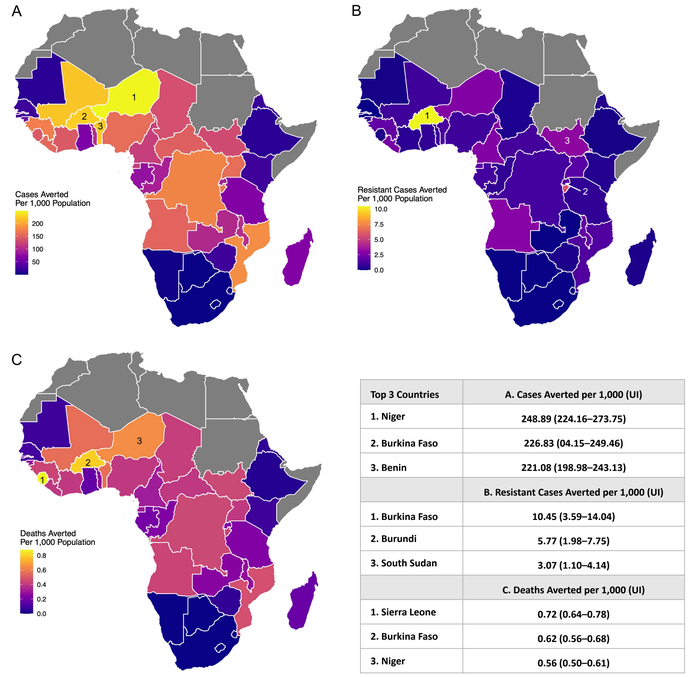
Parameter	Symbol	Definition	Value (Range)	Source
At-Risk	k	Proportion of a country's population considered at-risk in malaria endemic countries	Country-specific	World Malaria Report
Coverage	c	Proportion of one-year-olds receiving a vaccine	70%	WHO expert consultation
Efficacy	e	Proportion of vaccinated children protected from disease	Scenario 1: 40% (years 1-4), 0% (years 5+)	Expert consultation RTS,S trial results
			Scenario 2: 80% (year 1), 60% (year 2), 40% (year 3), 20% (year 4), 0% (years 5+)	
			Scenario 3: 40% all years	
Incidence rate	β	Age-stratified annual incidence rate	Country-specific	World Population Prospects Global Health Observatory IHME
Treatment seeking rate	s	Proportion of children under 5 with fever in the past 2 weeks for whom malaria treatment was sought	69.3% (59.4 - 74.2%) in sub-Saharan Africa (applied to all countries)	World Malaria Report
Treatment received rate	p	Proportion of children who received ACTs among those who sought treatment	75.7% (32.2 - 90.6%) in sub-Saharan Africa (applied to all countries)	World Malaria Report
Treatment failure rate	f	Proportion of cases for which treatment fails. Estimated using ACT TFRs from studies of *P. falciparum* in African countries	Country-specific	Malaria Threats Map
Case fatality rate	m	Proportion of cases that will result in death	0.256% (±20%) for low-transmission countries	World Malaria Report Global Health Observatory
			Estimated total deaths/estimated total cases (±20%) for high-transmission countries. Country-specific	

Results

- The highest burden averted was observed when VE remained 40% for the entire study period (Scenario 3), resulting in a reduction of ~28% in all outcomes.
- Scenario 2, in which VE began at 80% and dropped 20 percentage points each year, resulted in a reduction of ~23% in all outcomes.
- Scenario 1, in which VE remained 40% for 4 years and dropped to 0% in year 5, resulted in a reduction of ~17% in all outcomes.
- In the worst-case resistance scenario, over 6.5 million resistant cases were projected to be averted with an effective vaccine compared to ~1 million if TFRs remained constant.

Scenario	Cases (Uncertainty Interval)	Resistant Cases (UI)	Deaths (UI)
Baseline (No Vaccine)	**538M (484M-592M)**	**6M (2M -8M)**	**1.5M (1M-2M)**
	Cases Averted (UI)	**Resistant Cases Averted (UI)**	**Deaths Averted (UI)**
1	**93M (83M-102M)**	**990,000 (346,000-1M)**	**253,000 (184,000-330,000)**
2	**123M (111M-135M)**	**1M (459,000-2M)**	**336,000 (244,000-439,000)**
3	**151M (136M-166M)**	**1.5M (562,000-2M)**	**411,000 (299,000-538,000)**
4 (worst-case)	**93M (83M-102M)**	**7M (2M-9M)**	**253,000 (184,000-330,000)**

Figure 3. Burden Averted per 1,000 Population by Country (Scenario 1)



Top 3 Countries	A. Cases Averted per 1,000 (UI)
1. Niger	**248.89 (224.16–273.75)**
2. Burkina Faso	**226.83 (04.15–249.46)**
3. Benin	**221.08 (198.98–243.13)**
	B. Resistant Cases Averted per 1,000 (UI)
1. Burkina Faso	**10.45 (3.59–14.04)**
2. Burundi	**5.77 (1.98–7.75)**
3. South Sudan	**3.07 (1.10–4.14)**
	C. Deaths Averted per 1,000 (UI)
1. Sierra Leone	**0.72 (0.64–0.78)**
2. Burkina Faso	**0.62 (0.56–0.68)**
3. Niger	**0.56 (0.50–0.61)**

Conclusions

Swift and widespread deployment of an effective malaria vaccine in Africa, alongside other prevention and control interventions, could substantially reduce health and economic burden caused by drug-resistant malaria.

Limitations

- Used TFRs as proxy for resistance. Small sample sizes in Malaria Threats Map.
- Used the same incidence and mortality rates for sensitive and resistant infections. Resistance and mortality are highly dependent on drug type, stage of disease, and treatment duration.
- Did not account for increased partial immunity after an infection or herd immunity.

Needed for Future Modeling Studies

- Better surveillance data on treatment adherence and treatment failure at the country level
- Longitudinal studies of vaccine efficacy (R21/Matrix-M)

References

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