Draft Target Product Profiles for mRNA *P. vivax* malaria vaccines

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To cover

1) Malaria 101: *Plasmodium* life cycle & different types of malaria vaccines

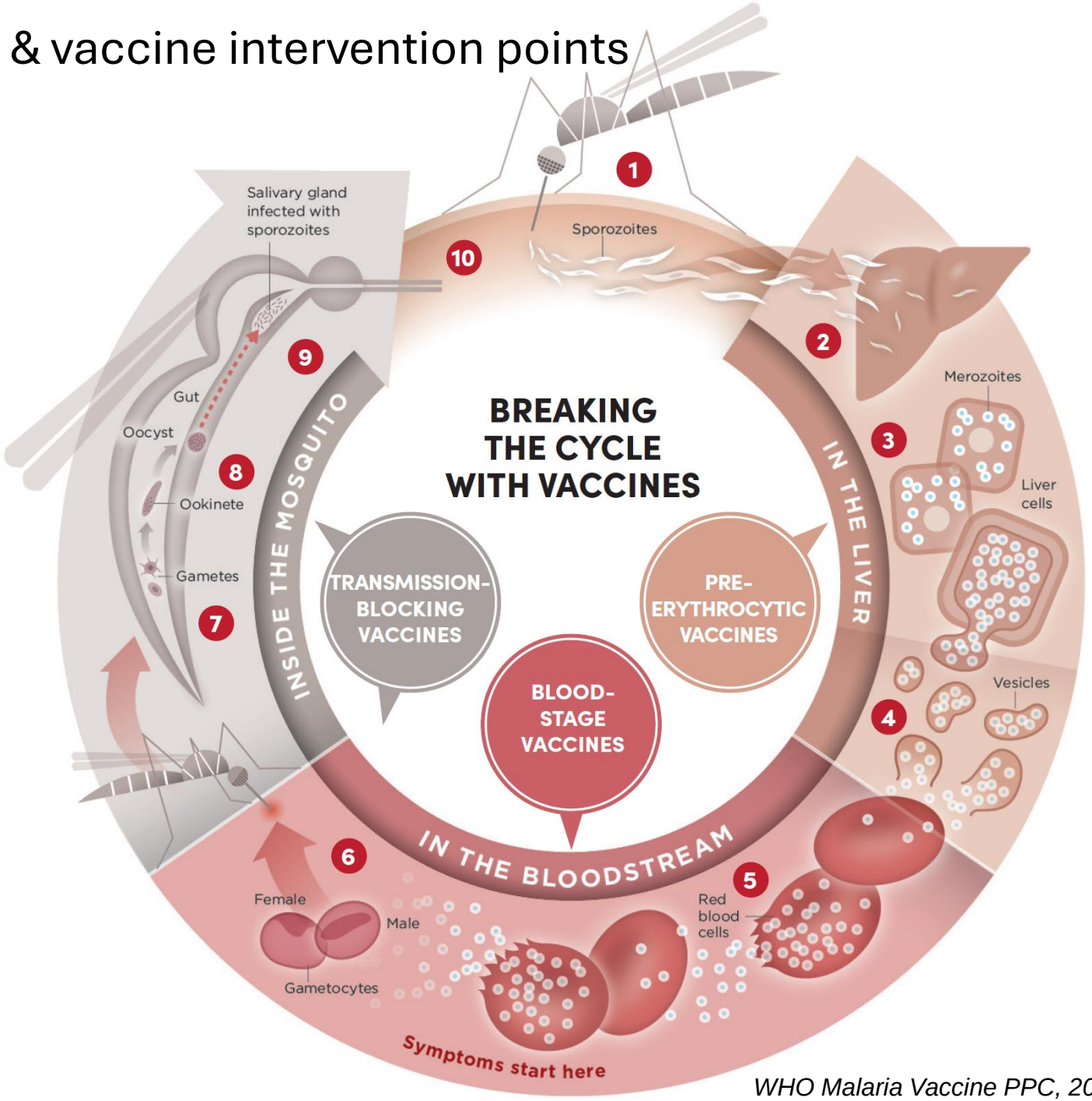
2) WHO strategic priorities of malaria vaccines

3) Current WHO endorsed malaria vaccines (*P. falciparum*)

4) *P. vivax* malaria versus *P. falciparum* malaria

5) Draft TPPs for different types of *P. vivax* mRNA vaccines

Malaria life cycle & vaccine intervention points



WHO Malaria Vaccine PPC, 2022

II. WHO strategic priorities for malaria vaccines

	Pre-erythocytic vaccines	Blood-stage vaccines	Transmission-blocking vaccines
Strategic goal 1: Prevent blood-stage infection at the individual level	✓ (**primary**)	✓	-
Strategic goal 2: Reduce morbidity and mortality at the individual level	✓	✓ (**primary**)	-
Strategic goal 3: Reduce transmission at the community level	✓	✓	✓ (**primary**)

III. Current WHO's endorsed malaria vaccines (*P. falciparum*)

WHO recommends the programmatic use of RTS,S/AS01 & R21/Matrix-M for the prevention of *P. falciparum* malaria in children, prioritizing areas of moderate and high transmission.

Vaccine	Type	Target	Regimen	Efficacy (Phase III)	End point	Follow-up duration	Reference
RTS,S/ AS01	Pre-erythrocytic	Children (5-17 month)	3 doses	56%	Clinical malaria	12 month	NEJM; 365(20): 1863-1875
R21/ Matrix-M	Pre-erythrocytic	Children (5-36 month)	3 doses	68% - 75%	Clinical malaria	12 month	Lancet; 403: 533-544
RTS,S/ AS01	Pre-erythrocytic	Children (5-17 month)	3 doses	28%	Clinical malaria	48 month	Lancet; 386: 31-45

Differences between *P. vivax* malaria and *P. falciparum* malaria

P. vivax malaria relative to *P. falciparum* malaria	Consequence on *P. vivax* vaccine development
1. Lower severity, mortality	Higher bar for efficacy & safety
2. Lower transmission intensity	Priority weighed more towards community protection (elimination) than reducing morbidity/mortality.
3. Presence of hypnozoites	Late-stage clinical trials may need to consider a) longer follow-up & booster after the primary series b) administration of anti-hypnozoite drug
4. Older demographics at risk: teenagers and adults	None-EPI

Draft TPPs for *P. vivax* mRNA vaccines

1) Pre-erythrocytic vaccines

2) Blood-stage vaccines

3) Transmission-blocking vaccines

4) Considerations for multivalent vaccines

1) Draft TPP for *P. vivax* pre-erythrocytic vaccines

WHO Strategic goal 1: Prevent blood-stage infection at the individual level

Parameters	Target product profile	Minimum acceptable product profile
Target Population	Individuals at high risk	same
Safety	Comparable to WHO-recommended vaccines in use in LMICs	same
Doses	1 dose (primary); Additional annual booster okay	2 doses (primary); Additional annual booster okay
Route	IM	Not IV
Stability & Storage	24 months at 2-8 ºC	6 months at -20 ºC 30 days at 2-8 ºC (Covid-19 mRNA vaccine)
Efficacy & Duration	90% reduction of clinical malaria* over 12 months	75% reduction of clinical malaria over 12 months (R21/Matrix-M)

* Ideally, reduction of infection would correspond more directly to Strategic Goal 1, but measuring infection requires ACD which may not be feasible in large-scale trials.

P. vivax pre-erythrocytic vaccine endpoints

WHO Strategic goal 1: Prevent blood-stage infection at the individual level

Efficacy assessment		
Preclinical / Phase I	Phase II	Phase III
in vitro parasite growth	I. Blood infection* II. Time to reach threshold blood parasitemia (human challenge study)	I. Blood infection* (active detection) II. Clinical malaria* (passive detection)

* need to take relapses in to consideration

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2) Draft TPP for *P. vivax* blood-stage vaccines

WHO Strategic goal 2: Reduce morbidity and mortality at the individual level

Parameters	Target product profile	Minimum acceptable product profile
Target Population	Individuals at high risk	same
Safety	Comparable to WHO-recommended vaccines in use in LMICs	same
Doses	1 dose (primary); Additional annual booster okay	2 doses (primary); Additional annual booster okay
Route	IM	Not IV
Stability & Storage	24 months at 2-8 ºC	6 months at -20 ºC 30 days at 2-8 ºC (Covid-19 mRNA vaccine)
Efficacy & Duration	90% reduction of clinical malaria over 12 months	75% reduction of clinical malaria over 12 months (R21/Matrix-M level)

P. vivax blood-stage vaccine endpoints

WHO Strategic goal 2: Reduce morbidity and mortality at the individual level

Efficacy assessment		
Preclinical / Phase I	Phase II	Phase III
in vitro parasite growth	I. Clinical malaria II. Parasite amplification rate (human challenge study)	Clinical malaria

3) Draft TPP for *P. vivax* transmission-blocking vaccines

Strategic goal 3: Reduce transmission at the community level

Parameters	Target product profile	Minimum acceptable product profile
Target Population	Individuals at high risk	same
Safety	Comparable to WHO-recommended vaccines in use in LMICs	same
Doses	1 dose (primary); Additional annual booster okay	2 doses (primary); Additional annual booster okay
Route	IM	Not IV
Stability & Storage	24 months at 2-8 ºC	6 months at -20 ºC 30 days at 2-8 ºC (Covid-19 mRNA vaccine)
Efficacy & Duration	__ % reduction in _____ over __ months	__% reduction in _____ over __ months

Possible *P. vivax* transmission-blocking vaccine endpoints

Strategic goal 3: Reduce transmission at the community level

Efficacy assessment		
Preclinical / Phase I	Phase II	Phase III
Mosquito infection or density (oocysts) by feeding assay	Mosquito infection or density (oocysts) by feeding assay	Clinical incidence / prevalence /sero-conversion in human population* (Cluster Randomized Trial)

* need to take relapses in to consideration

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Lastly, multi-stage multivalent vaccines to address all WHO strategic goals

Strategic goal 1: Prevent infection (individual)
Strategic goal 2: Reduce disease (individual)
Strategic goal 3: Reduce transmission (community)

Parameters	Target product profile	Minimum acceptable product profile
Efficacy (individual)	90% reduction of clinical malaria over 12 months	75% reduction of clinical malaria over 12 months (R21/Matrix-M)
Efficacy (community)	__ % reduction in _____ over __ months	__% reduction in _____ over __ months

Thoughts & suggestions welcome

Malaria vaccines: preferred product characteristics and clinical development considerations. Geneva: World Health Organization; 2022 (*WHO Malaria Vaccine PPC, 2022*).