Malaria vaccines

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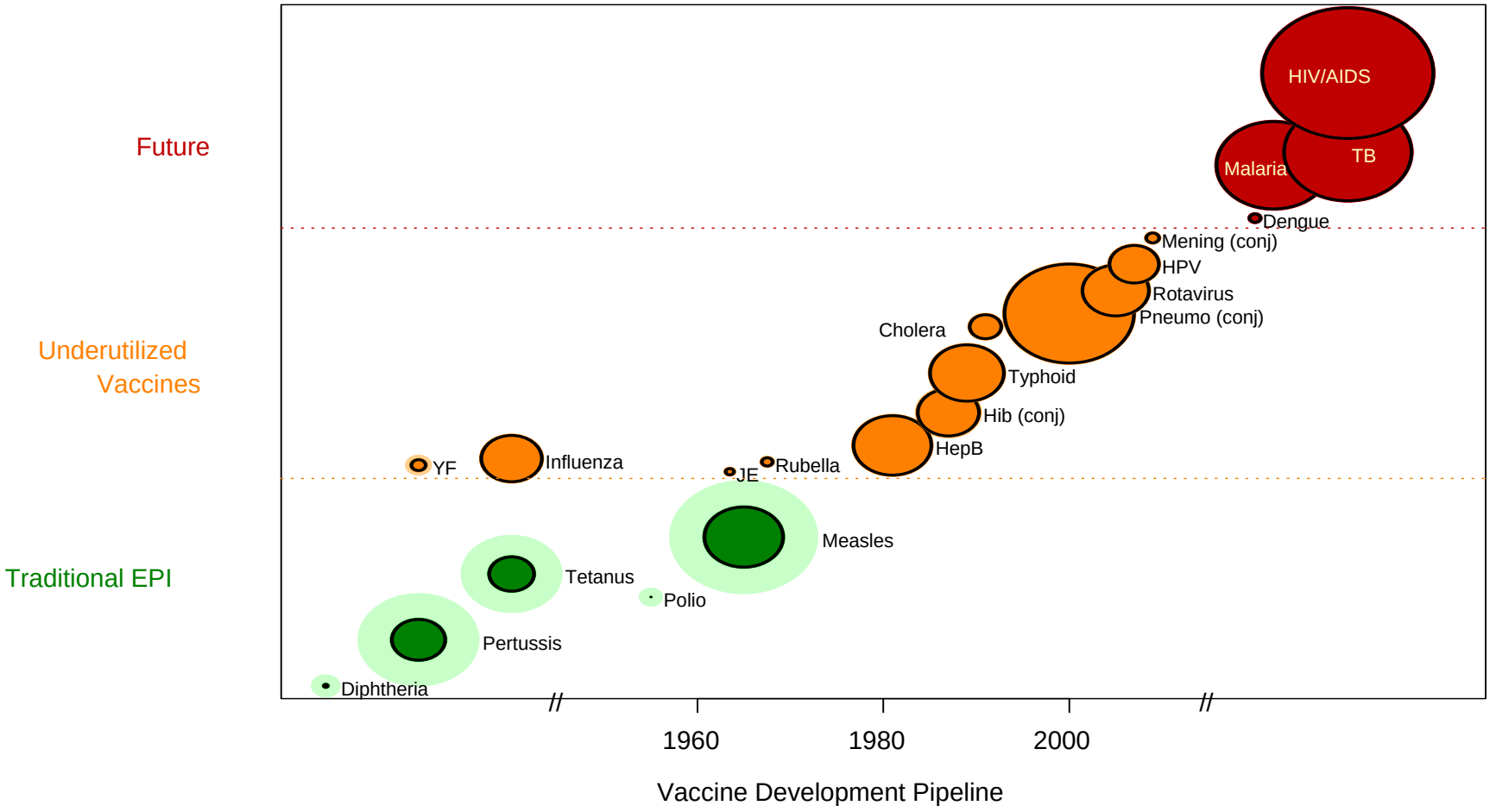
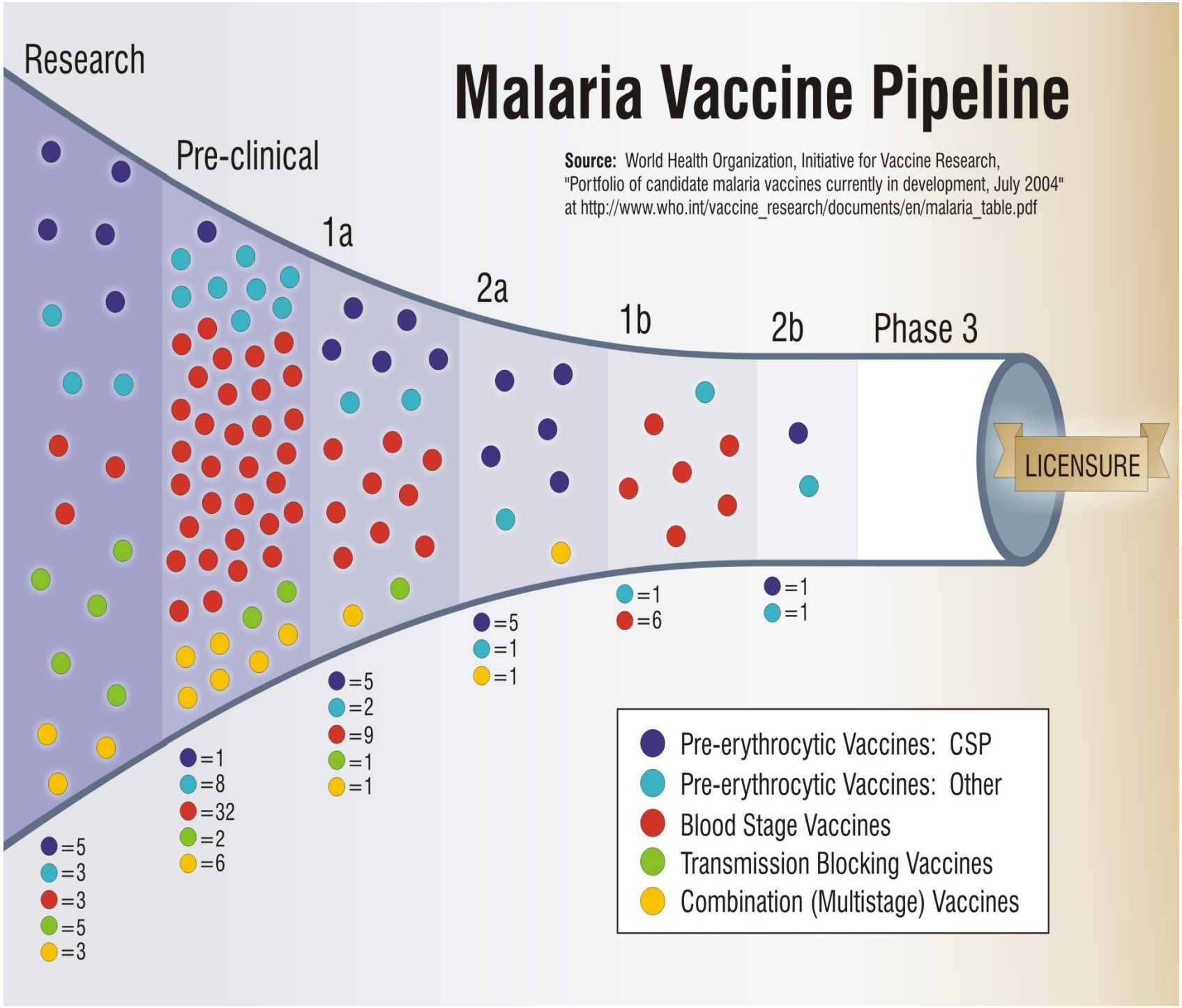
WORLD MALARIA REPORT 2015

The African Region continues to shoulder the heaviest malaria burden. However, here too we have seen impressive gains: since 2000, malaria mortality rates have fallen by 66% among all age groups, and by 71% among children under five.

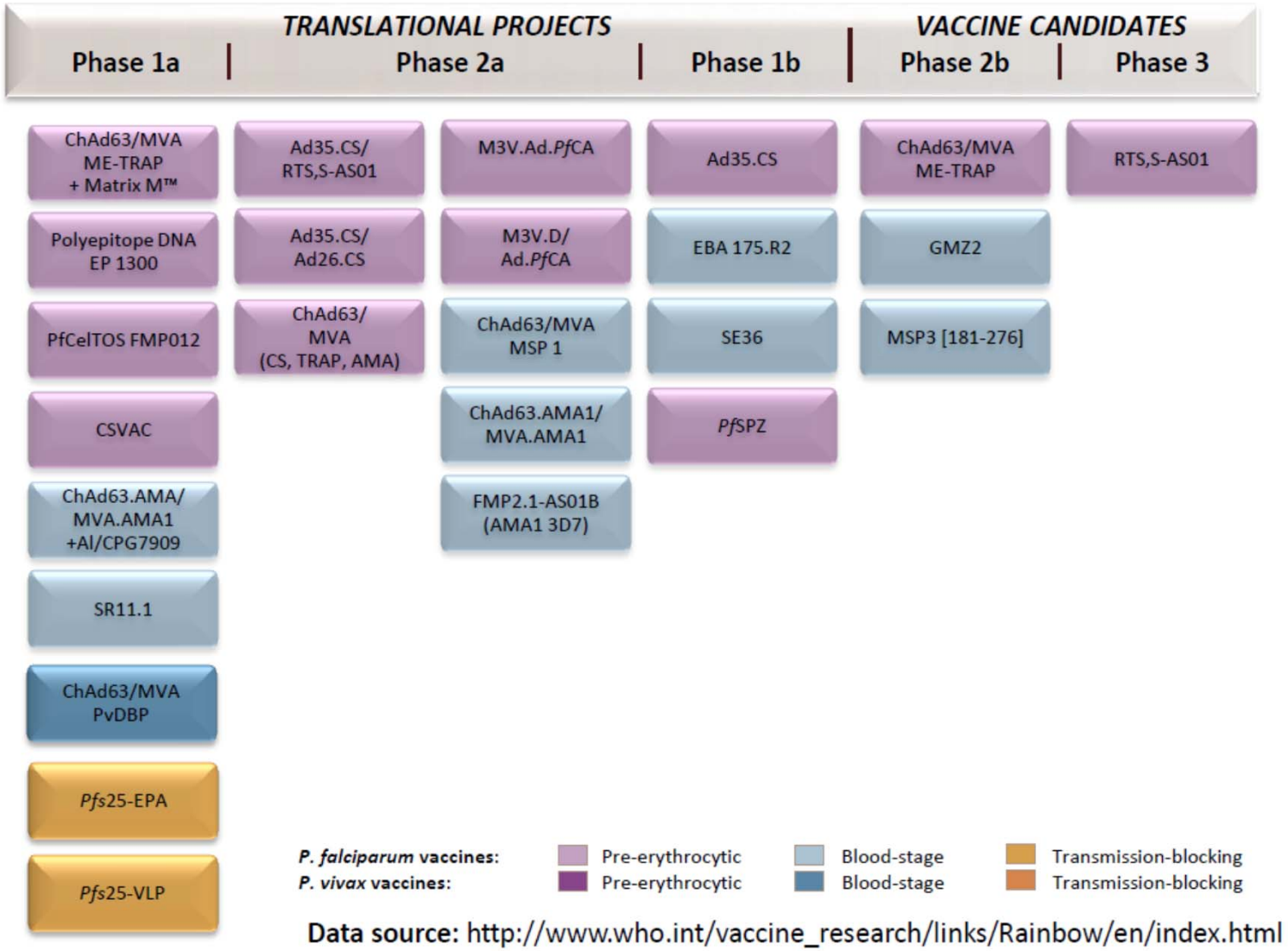
But our work is far from over. About 3.2 billion people remain at risk of malaria. In 2015 alone, there were an estimated 214 million new cases of malaria and 438 000 deaths. Millions of people are still not accessing the services they need to prevent and treat malaria.

WHO-IVR August 2006




Malaria Vaccine Pipeline
Source: World Health Organization, Initiative for Vaccine Research, "Portfolio of candidate malaria vaccines currently in development, July 2004" at http://www.who.int/vaccine_research/documents/en/malaria_table.pdf
Research
Pre-clinical
1a
2a
1b
2b
Phase 3
LICENSURE
=5
=3
=3
=5
=3
=1
=8
=32
=2
=6
=5
=2
=9
=1
=1
=5
=1
=1
=1
=6
=1
=1
Pre-erythrocytic Vaccines: CSP
Pre-erythrocytic Vaccines: Other
Blood Stage Vaccines
Transmission Blocking Vaccines
Combination (Multistage) Vaccines

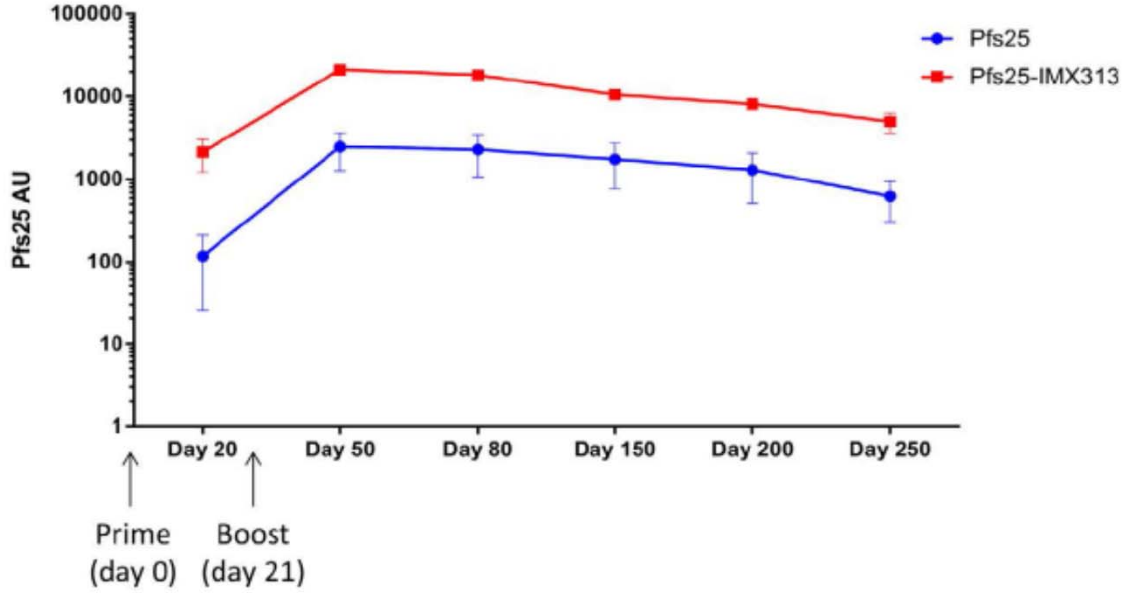
Global malaria vaccine pipeline



Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

March 14th 2016

Enhancing immunogenicity and transmission-blocking activity of malaria vaccines by fusing Pfs25 to IMX313 multimerization technology



Li, Y. *et al.* Enhancing immunogenicity and transmission-blocking activity of malaria

Antibody levels against GLURP R2, MSP1 block 2 hybrid and AS202.11 and the risk of malaria in children living in hyperendemic (Burkina Faso) and hypo-endemic (Ghana) areas

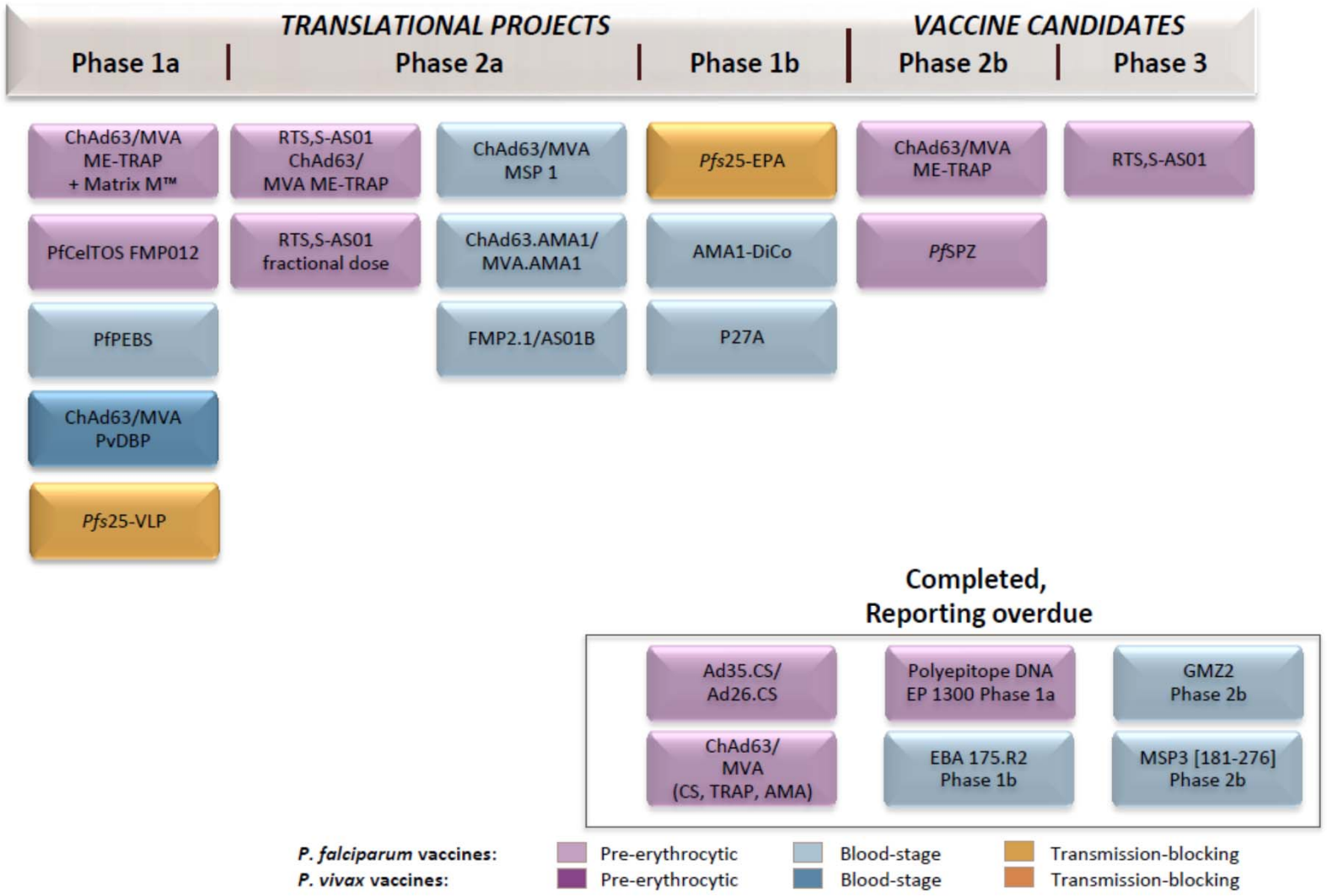
Bright Adu[1†], Mariama K. Cherif[2,3†], Samuel Bosomprah[4], Amidou Diarra[3], Fareed K. N. Arthur[5], Emmanuel K. Dickson[1], Giampietro Corradin[6], David R. Cavanagh[7], Michael Theisen[8], Sodiomon B. Sirima[3], Issa Nebie[3*] and Daniel Dodoo[1*]

Conclusion: These findings support further development of GLURP R2 and MSP1 block 2 hybrid, perhaps as a fusion vaccine antigen targeting malaria blood stage that can be deployed in areas of varying transmission intensity.

Adu *et al. Malar J (2016) 15:123*
DOI 10.1186/s12936-016-1146-4

Malaria Journal

Global malaria vaccine pipeline



Data source: http://www.who.int/vaccine_research/links/Rainbow/en/index.html

March 14th 2016

Phase III multicenter efficacy trial of RTS,S/AS01

Double-blind, randomized, controlled trial.

11 centers in 7 African countries.

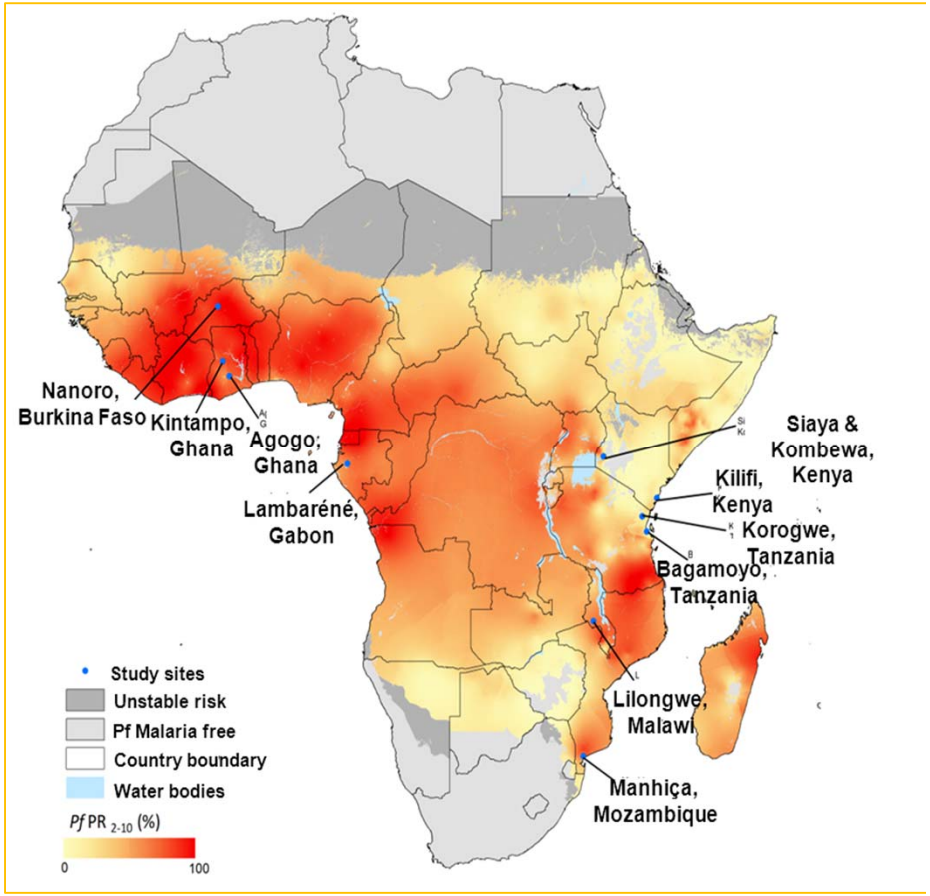
Wide range of malaria transmission intensities by site: 0.03-4.27 clinical episodes per infant during first 12 months of follow-up.

15,459 children enrolled in two age categories:

- Children aged 5–17 months (8,922)
- Infants aged 6–12 weeks (6,537)

Infants received the study vaccine co-administered with routine vaccines.

High access to malaria diagnostics and treatment (ACT).



Leach A., et al. Malaria J 2011; 10:224 ; PLoS Medicine 2014; 11(7): e1001685; Hay SI, Guerra CA, Gething PW et al. A World Malaria Map: Plasmodium falciparum Endemicity in 2007. PLOS Med 2009;6:e1000048

MALARIA-055 PRI:
(Month 32 and extension)

MALARIA-055 PRI Month 32 & Extension

- The trial was conducted across a range of transmission settings in presence of high insecticide-treated bednet (ITN) use
  - Malaria incidence ranged in controls (secondary case definition 1): 0.03 (Kilifi) to 4.27 (Siaya) in infants in the first year of follow-up
  - ITN use remained high throughout the trial (78% in 5-17M and 86% in 6-12W at Month 14, 79% in 5-17M and 86% in 6-12W at Month 32, 74% in 5-17M and 82% in 6-12W at end of extension)
  - High quality was maintained throughout the trial

- <u>Vaccine efficacy against clinical malaria (ATP - primary case definition):</u>
- In the 5-17M: Vaccine efficacy (VE) over a median FU 46 months post Dose 3 was:
  - VE against all episodes of clinical malaria over 46 months (M2.5-SE) without a boost was **26.2% [95% CI:20.8 to 31.2]**
  - VE against all episodes of clinical malaria over 46 months (M2.5-SE) with a boost was **39.0% [95% CI:34.3 to 43.3]**
  - There is a significant variation of VE against clinical malaria for a schedule with boost between sites (interaction p=0.03)

- In the 6-12W : Overall, VE over a median FU 36 months post Dose 3:
  - VE against all episodes of clinical malaria over 36 months (M2.5-SE) without a boost was **18.2% [95% CI: 11.4 to 24.5]**
  - VE against all episodes of clinical malaria over 36 months (M2.5-SE) with a boost was **26.7% [95% CI: 20.5 to 32.4]**

MALARIA-055 PRI Month 32 & Extension

- Vaccine efficacy against severe malaria (ATP - primary case definition):
  - In the 5-17M, VE against severe malaria over 46 months (M2.5-SE) without a boost was -5.8% [95% CI: -35.0 to 17.0]
    - An observation was that in the 5-17M without boost there is trend towards an increased risk of severe malaria relative to controls after the Month 20
  - In the 5-17M, VE against severe malaria over 46 months (M2.5-SE) with a boost was 28.5% [95% CI: 6.3 to 45.7]
  - In the 6-12W, VE against severe malaria over 36 months (M2.5-SE) without a boost was 12.7% [95% CI:-17.2 to 35.0]
  - In the 6-12W, VE against severe malaria over 36 months (M2.5-SE) with a boost was 20.7% [95% CI: -7.3 to 41.6]
- Vaccine efficacy against incident severe anemia (ATP - case definition 1):
  - In the 5-17M, VE against severe anemia over 46 months (M2.5-SE) without a boost was 20.6% [95% CI: -32.7 to 52.9]
  - In the 5-17M, VE against severe anemia over 46 months (M2.5-SE) with a boost was 61.2% [95% CI: 26.5 to 80.6]
  - In the 6-12W, VE against severe anemia over 36 months (M2.5-SE) without a boost was 12.8% [95% CI:-50.9 to 49.9]
  - In the 6-12W, VE against severe anemia over 36 months (M2.5-SE) with a boost was 31.5% [95% CI: -23.1 to 62.6]

MALARIA-055 PRI Month 32 & Extension

- Summary of the effect of the booster on vaccine efficacy (ATP - primary case definition):
- In the 5-17M
  - The incremental VE of a booster dose over a primary schedule alone against clinical malaria (M21-SE) was 21.3% [95% CI: 14.2 to 27.8]
  - The incremental VE of a booster dose over a primary schedule alone against severe malaria (M21-SE) was 27.4% [95% CI: -5.1 to 50.1]
- In the 6-12W
  - The incremental VE of a booster dose over a primary schedule alone against clinical malaria (M21-SE) was 19.5% [95% CI: 11.5 to 26.8]
  - The incremental VE of a booster dose over a primary schedule alone against severe malaria (M21-SE) was 26.4% [95% CI: -17.6 to 54.4]

MALARIA-055 PRI Month 32 & Extension

- Impact (ITT – secondary case definition 1):
- In the 5-17M for a schedule without a boost, over 32 months of FU post Dose 1 :
  - 1221 cases of clinical malaria [95% CI: 973 to 1483] were averted per 1000 vaccinees; range across site: 132 cases [95% CI: 12 to 253] to 3847 cases [95% CI: 2389 to 5501]
  - 12 cases of severe malaria [95% CI: -2 to 27] were averted per 1000 vaccinees
- In the 5-17M for a schedule with a boost, over 32 months of FU post Dose 1 :
  - 1475 cases of clinical malaria [95% CI: 1234 to 1733] were averted per 1000 vaccinees; range across site: 126 cases [95% CI: 40 to 219] to 4656 cases [95% CI: 3173 to 6308]
  - 20 cases of severe malaria [95% CI: 7 to 34] were averted per 1000 vaccinees
- In the 6-12W for a schedule without a boost, over 32 months of FU post Dose 1 :
  - 526 cases of clinical malaria [95% CI: 200 to 819] were averted per 1000 vaccinees; range across site: -50 cases [95% CI: -540 to 378] to 1853 cases [95% CI: 337 to 3333]
  - 5 cases of severe malaria [95% CI: -13 to 24] were averted per 1000 vaccinees
- In the 6-12W for a schedule with a boost, over 32 months of FU post Dose 1 :
  - 873 cases of clinical malaria [95% CI: 573 to 1158] were averted per 1000 vaccinees; range across site: -25 cases [95% CI: -206 to 150] to 2921 cases [95% CI: 1406 to 4344]
  - 9 cases of severe malaria [95% CI: -8 to 28] were averted per 1000 vaccinees

MALARIA-055 PRI Month 32 & Extension

- Immunogenicity :
- In the 5-17M:
  - The anti-CS GMT in RTS,S/AS01$_E$ recipients were 621 EU/mL* one month post Dose 3 (R3R+R3C)
  - The anti-CS GMT in RTS,S/AS01$_E$ recipients were 34 EU/mL [95% CI: 31 to 39] before booster dose (Month 20) and 318 EU/mL [95% CI: 295 to 343] EU/mL one month post booster dose of RTS,S/AS01$_E$ (R3R group)

- In the 6-12W:
  - The anti-CS GMT in RTS,S/AS01$_E$ recipients were 211 EU/mL* one month post Dose 3 (R3R+R3C)
  - The anti-CS GMT in RTS,S/AS01$_E$ recipients were 5.9 EU/mL [95% CI: 5.2 to 6.7] before booster dose (Month 20) and 170 EU/mL [95% CI: 154 to 188] EU/mL one month post booster dose of RTS,S/AS01$_E$ (R3R group)

* Data from previous analysis

MALARIA-055 PRI Month 32 & Extension

- Safety :
- In the 5-17M between study start and end of extension (M0-SE):
  - The occurrence of SAE was similar in the three groups: 24% (R3R), 25% (R3C), 28% (C3C)
  - Fatal SAE: 2.0% (R3R) , 1.7% (R3C), 1.5% (C3C)
  - Meningitis remains a signal for the 5-17 months age group
  - The number of meningitis cases between M0-SE was: 11 (R3R) vs 10 (R3C) vs 1 (C3C)
  - The number of meningitis cases post booster (M21-SE) was: 2 (R3R) vs 3 (R3C) vs 0 (C3C)
  - The occurrence of generalized convulsive seizures post booster (7 days) was: 2.5 per 1000 doses (R3R)

- In the 6-12W between study start and end of extension (M0-SE):
  - The occurrence of SAE was similar in the three groups: 27% (R3R), 28% (R3C), 28% (C3C)
  - Fatal SAE: 2.3% (R3R) , 2.5% (R3C), 1.9%(C3C)
  - No meningitis signal in the 6-12 weeks age group
  - The number of meningitis cases between M0-SE was: 5 (R3R) vs 7 (R3C) vs 6 (C3C)
  - The number of meningitis cases post booster (M21-SE) was: 0 (R3R) vs 2 (R3C) vs 3 (C3C)
  - The occurrence of generalized convulsive seizures post booster (7 days) was: 2.2 per 1000 doses (R3R)

RTS,S/AS01 prevented a substantial number of cases of clinical malaria over a 3-4 year period in young infants and children when administered with or without a booster dose. Efficacy was enhanced by the administration of a booster dose in both age categories. Thus, the vaccine has the potential to make a substantial contribution to malaria control when used in combination with other effective control measures, especially in areas of high transmission.

What next for the malaria RTS,S vaccine candidate?

On Oct 23, the Strategic Advisory Group of Experts on Immunization (SAGE) and the Malaria Policy Advisory Committee (MPAC) announced their much-anticipated recommendations for the world's first malaria vaccine candidate known as RTS,S/AS01. Their decision is not to recommend widespread deployment of the vaccine based on existing evidence, but instead to assess the feasibility of delivering the vaccine and its impact in real-world settings. This decision was perhaps unexpected given the fact that earlier this year the European Medicines Agency reviewed the same safety and efficacy data, and approved the vaccine's use in young children.

Research Centers and Partners

Albert Schweitzer Hospital, Lambarene, Gabon

Centro de Investigação em Saúde de Manhiça, Manhiça, Mozambique

Ifakara Health Institute, Bagamoyo, Tanzania

Institut de Recherche en Science de la Santé, Nanoro, Burkina Faso

KEMRI/CDC Research and Public Health Collaboration, Kisumu, Kenya

KEMRI-Walter Reed Project, Kombewa, Kenya

KEMRI - Wellcome Trust Research Program, Kilifi, Kenya

Kintampo Health Research Center, Kintampo, Ghana

National Institute for Medical Research, Korogwe, Tanzania

School of Medical Sciences, Kumasi, Ghana

University of North Carolina Project, Lilongwe, Malawi

University of Tübingen, Germany

Prince Leopold Institute of Tropical Medicine, Belgium

University of Copenhagen, Denmark

University of Barcelona, Spain

Swiss Tropical and Public Health Institute, Switzerland

London School of Hygiene and Tropical Medicine, UK

US Centers for Disease Control and Prevention, USA

University of North Carolina at Chapel Hill, USA

Walter Reed Army Institute of Research, USA

Participants and families

Study staff

PATH Malaria Vaccine Initiative

GlaxoSmithKline

Malaria Clinical Trials Alliance

Bill & Melinda Gates Foundation

THANK YOU