BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

MAM01: The Development of A Long-Acting Intervention to Prevent *P. falciparum* Malaria

ASTMH 2023

Kayla Andrews

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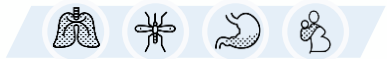
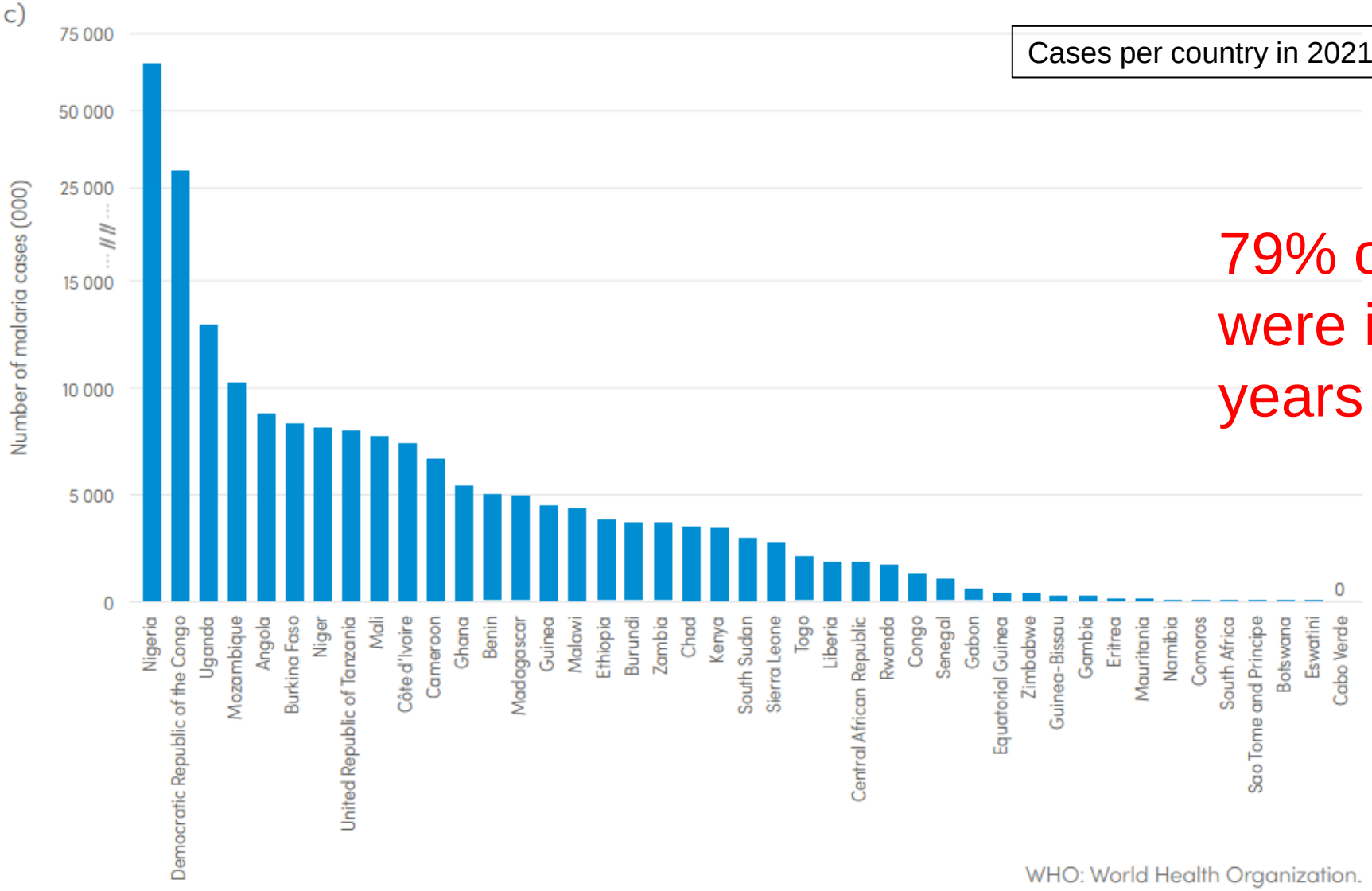


Gates MRI
WHO WE ARE

The institute is a non-profit medical research organization dedicated to the development and effective use of novel biomedical interventions addressing substantial global health concerns and for which the required development investment by traditional biopharmaceutical organizations is lacking or insufficient.

The institute works through collaborating partners and organizations, coordinating and driving the full spectrum of biopharmaceutical development activities, including pre-clinical development, full clinical development (from phase 1 through and including phase 3), and global regulatory interactions.

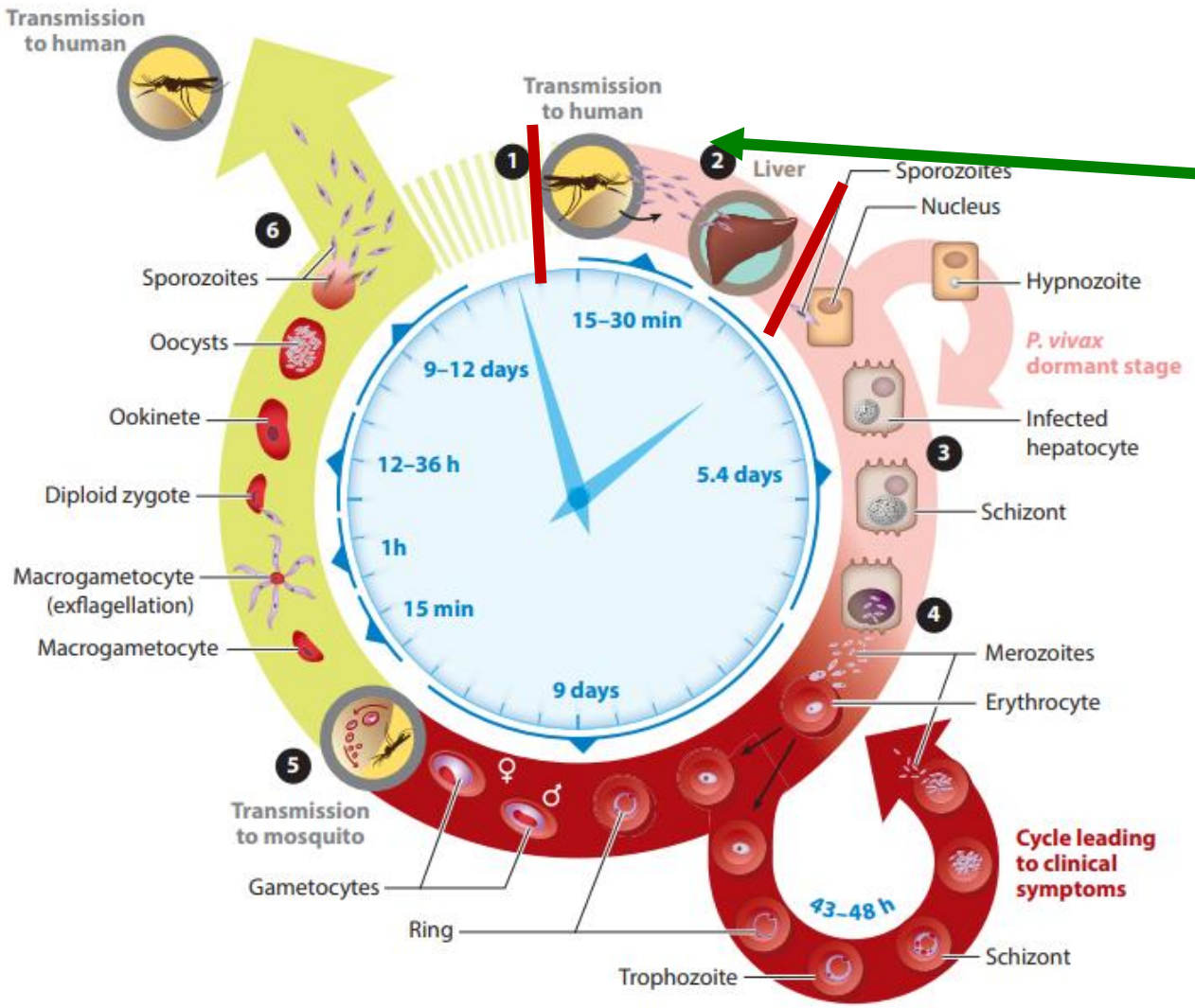
Malaria Incidence and Mortality in Africa 2000-2021*



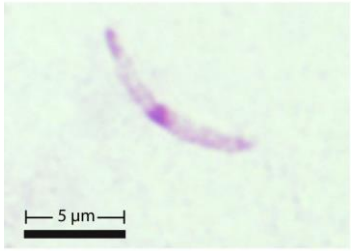
79% of all deaths were in children < 5 years old.

* WHO World Malaria Report 2022

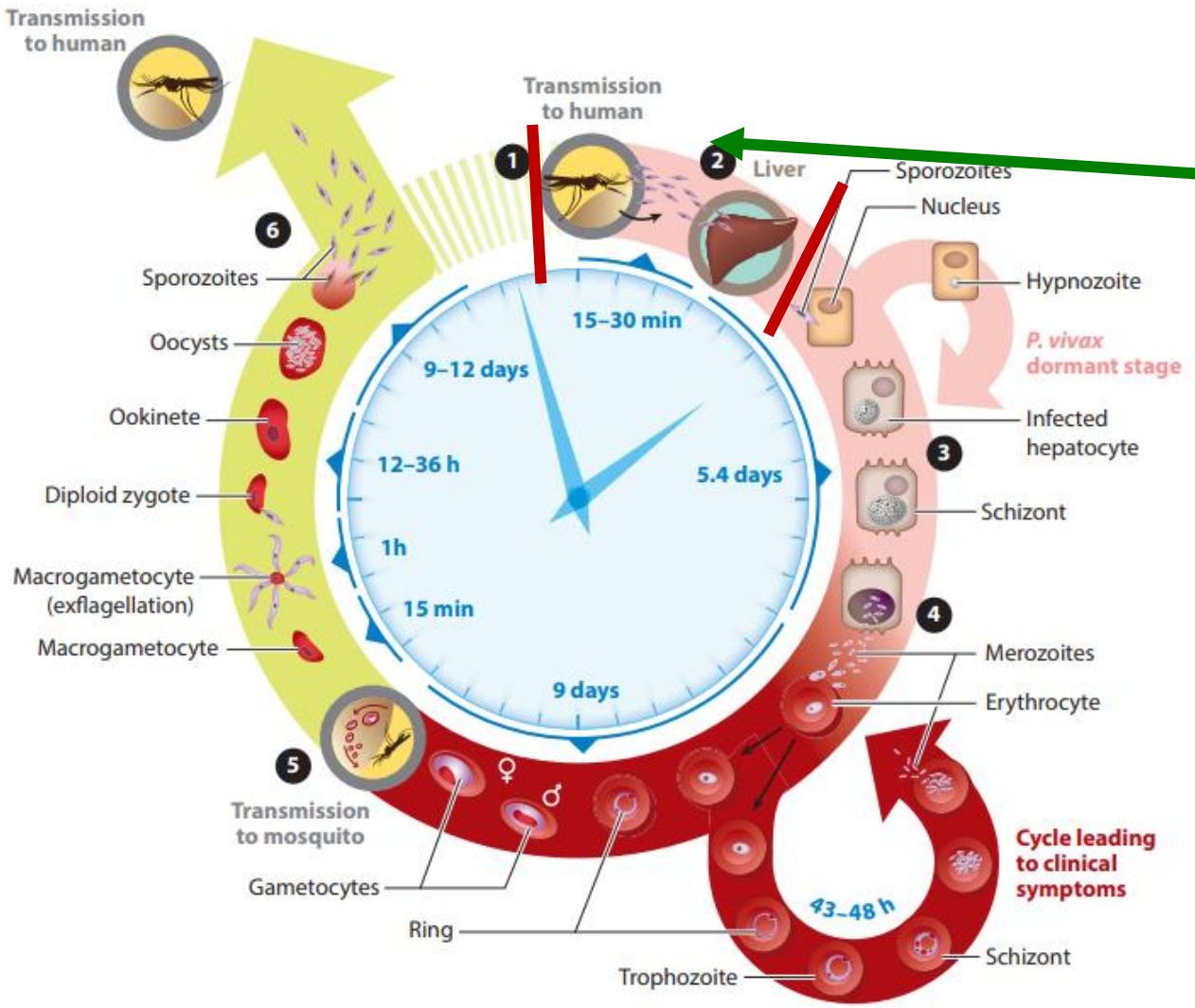
What Are We Trying To Prevent With a mAb?



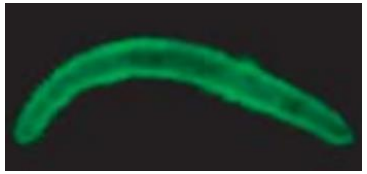
5 min to 1 hour window to stop sporozoites from entering hepatocytes



CSP is the target for preventative mAbs



Sporozoite is coated with CSP



High-risk populations to consider for mAb

Infants and children

Reduce *Plasmodium falciparum* malaria burden by preventing clinical cases and severe malaria in children 3 months to 10 years old during the high transmission season.

Initial FOCUS of MAM01

Pregnant women

Reduce *Plasmodium falciparum* malaria burden in women by preventing infection and placental malaria in primigravids and reduce fetal risks from placental malaria in all pregnancies.

High-risk workers

Protect workers (forest workers, farm hands, miners) during visits into malarious regions and reduce the re-introduction of newly acquired parasites into the village when they return.

Crisis situations

Prevention/prophylaxis of *Plasmodium falciparum* malaria in crisis scenarios and reduce the febrile disease burden on the health system. Reduce re-introduction in previously cleared geographies.

Travelers or short-term workers to malarious regions

Prophylaxis of *Plasmodium falciparum* malaria by protecting immunologically naïve, uninfected persons from malaria infection. Dual market opportunity for high-risk travelers or military personnel.

Potential Indications of a Preventative mAb

Infants and children

Reduce *Plasmodium falciparum* malaria burden by preventing clinical cases and severe malaria in children 3 months to 10 years old during the high transmission season.

Multi-Dose Settings

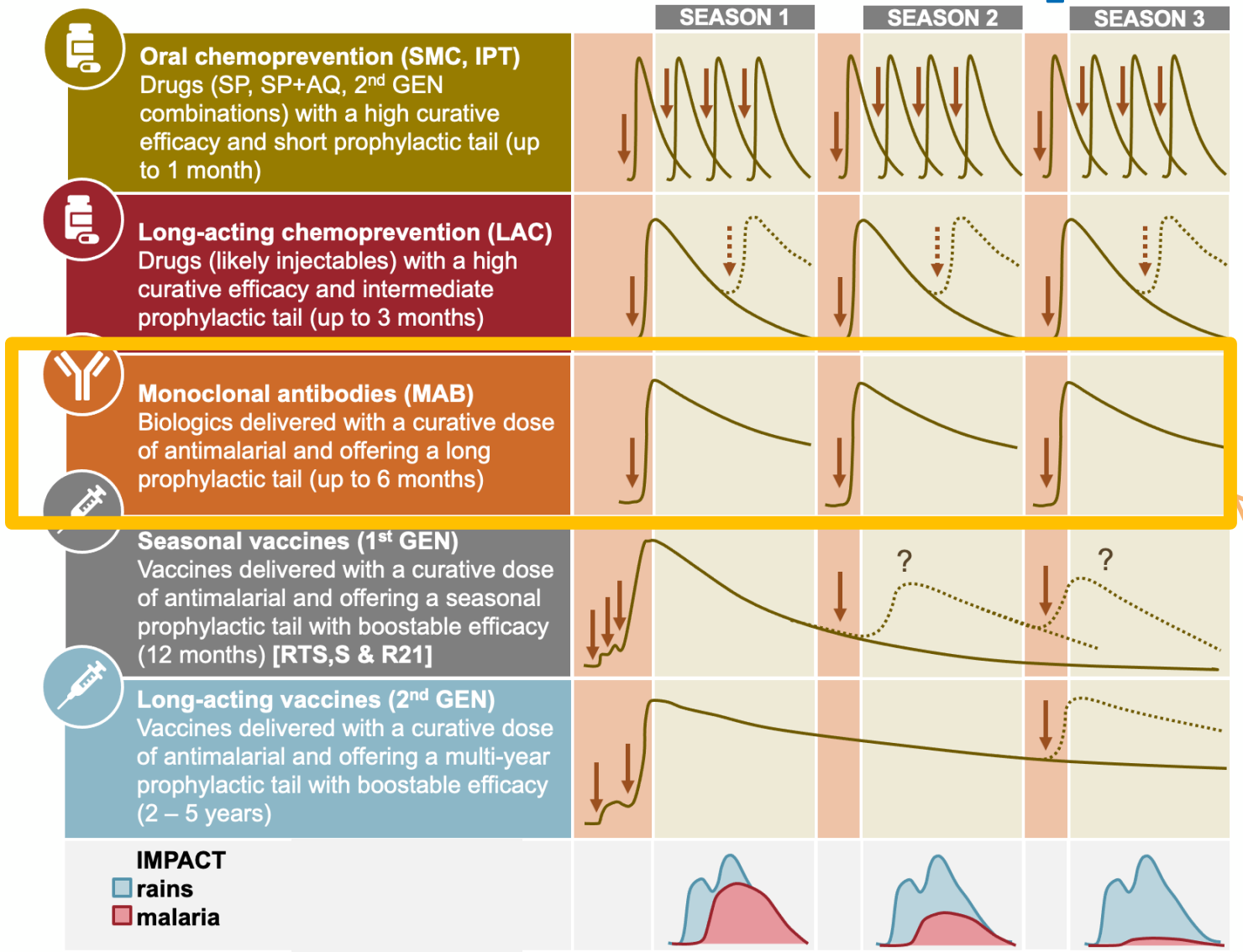
- Seasonal
  4-6m protection
  All 3m - <60m
- Perennial
  12m protection
  All 3m - <60m
- Seasonal and Perennial
  12m protection
  All 60m - <120m
- High-risk conditions (e.g., sickle cell) requiring chronic prophylaxis

Single Dose Settings

(**S**ingle **U**se **M**onoclonal **A**ntibody **C**hemoprevention)

- Severe Anemia (PDMC)
  4-6m protection
  High Risk 3m - <60m
- Severe Acute Malnutrition
  4-6m protection
  High Risk 3m - <60m
- Other Severe Malaria or 4-6m protection
  High Risk 3m - <60m
- Children and Adults
  Outbreak scenarios

Seasonal Malaria Chemoprevention Tools

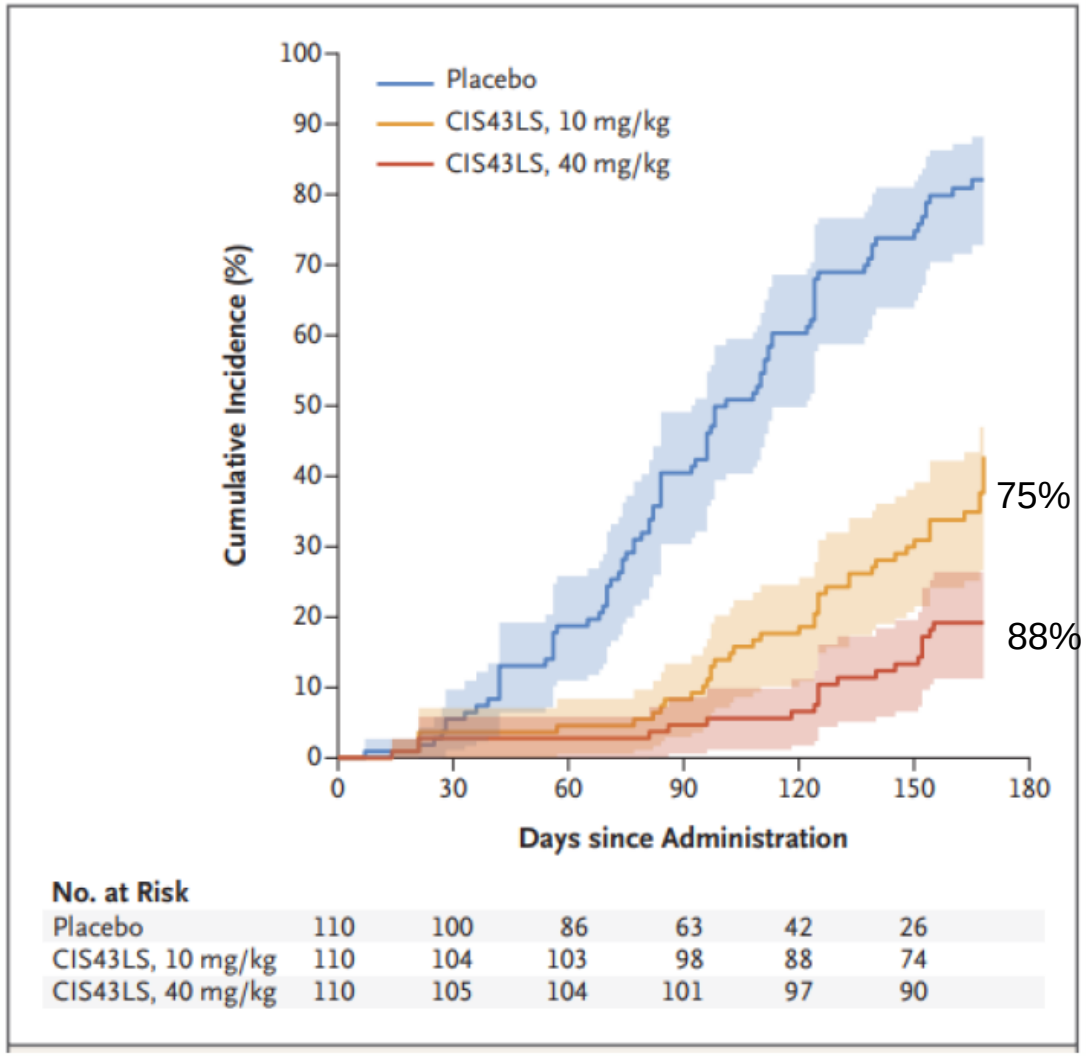


Monoclonal antibodies offer:

- One touchpoint with HCS / year
- Longer duration of protection than SMC
- Potential for less resistance (as compared to SMC)

Proof of concept for CSP mAbs achieved

- CIS43LS and L9LS have shown 3-4 months of protection against Pf infection in African adults and older children
- LS modification: methionine to leucine (L) and asparagine to serine (S) (M428L/N434S) in Fc domain resulting in half-life of 60-80 days
- Does not require the body to mount a response to a vaccine. ***Immediately effective, single dose.***



Kayentao et al., DOI: 10.1056/NEJMoa2206966

Making CSP mAbs into an impactful product

- Optimize potency
- Optimize developability to reduce manufacturing costs

- Unlike vaccines where the correlate of protection is complex, we predict the correlate is the circulating concentration of the antibody at the time of infection

- **Variable Cost = dose of mAb,** which is based on the weight of person dosed, potency (e.g. EC80), and desired duration of protection

MAM01: Potential long-acting, 1st generation anti-CSP prophylactic mAb drug candidate

MAM01

- Engineered fully human IgG1 mAb with “LS” mutation to extend in vivo half life
- Targets NANP repeats and NVDP in minor & major central repeat region of *Plasmodium falciparum* Circumsporozoite protein (CSP)
- Binding of antibody to *Pf*CSP shown to limit parasite motility and prevent malaria infection in animal models, human challenge & field studies.
- Optimized for highest productivity and yield in CHO cells to minimize costs of production to target the WHO preferred product characteristics for access in LMICs
- Formulated to 150mg/mL; suitable for IV, IM or SC administration

Learn more at poster LB-8413 Saturday Session

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MAM01 Mechanism of Action: *In vivo* inhibition of Parasite Motility and Displacement

Yevel Flores-Garcia[1], Shamika Mathis-Torres[1], Minah Park[1], Kayla Andrews[2], Jared Silverman[2], Fidel Zavala[1]
[1]Bloomberg School of Public Health, Malaria Research Unit, Johns Hopkins University, Baltimore, MD, United States
[2]Bill & Melinda Gates Medical Research Institute, Cambridge, MA, United States

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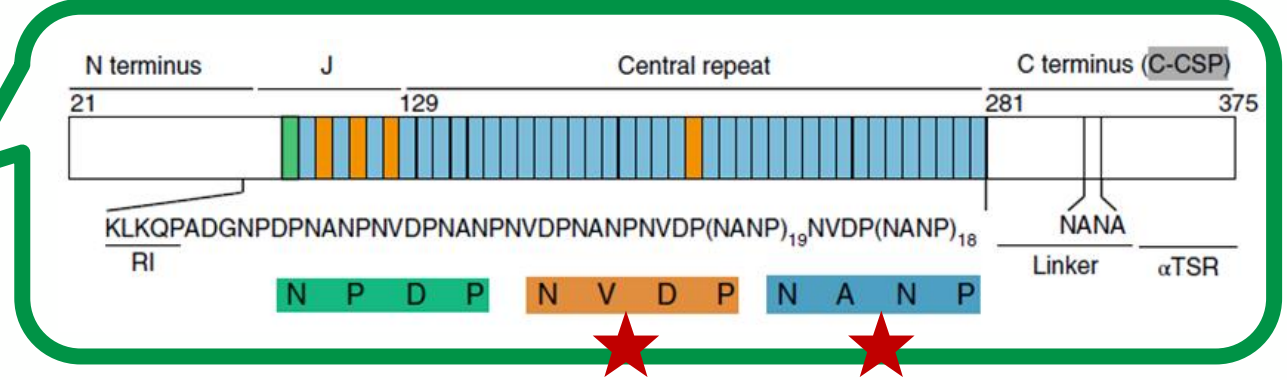
MAM01 binds CSP



- CSP coats the sporozoite surface (green image above)
- MAM01 targets the minor and major repeat region of *Pf*CSP, the validated target of the RTS,S vaccine & the minor NVDPNANP containing repeats of PfCSP
  - MAM01 has been shown to preferentially bind **NANP** tetrapeptides and has demonstrated cross-reactivity between **NANP** & **NVDP** tetrapeptides
  - There are 35-41 **NANP** tetrapeptide repeats in each *Pf*CSP
- In preclinical experiments, MAM01 was equally active against parasites expressing the full repeat region, eight **NANP** repeats, or the **NVDPNANP**-containing minor repeat region
  - Suggests peptide cross-reactivity has functional potential

Learn more at poster LB-8200 Friday Session

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Peptide Cross-Reactivity has Functional Potential for MAM01 Efficacy

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Yevel Flores-Garcia[1], Shamika Mathis-Torres[1], Minah Park[1], Kayla Andrews[2], Jared Silverman[2], Fidel Zavala[1]
[1]Bloomberg School of Public Health, Malaria Research Unit, Johns Hopkins University, Baltimore, MD, United States,
[2]Bill & Melinda Gates Medical Research Institute, Cambridge, MA, United States

Learn more at poster LB-8419 Saturday Session

CHSI DUKE CENTER FOR HUMAN SYSTEMS IMMUNOLOGY

Prophylactic malaria monoclonal antibody MAM01 showed extensive binding breadth to circumsporozoite protein repeat region epitopes

Kan Li[1,2], Shyam Sutariya[1,2], Derrick Goodman[1,2], Kayla Andrews[6], Jared Silverman[6], Robert A. Seder[7,8], S. Moses Dennison[1,2], Georgia D. Tomaras[1,2,3,4,5]

[1]Center for Human Systems Immunology, Duke University, Durham, NC, USA, [2]Department of Surgery, Duke University, Durham, NC, USA, [3]Department of Integrative Immunobiology, Duke University, Durham, NC, USA, [4]Department of Molecular Genetics and Microbiology, Duke University, Durham, NC, USA, [5]Duke Human Vaccine Institute, Duke University, Durham, NC, USA, [6]Bill & Melinda Gates Medical Research Institute, Cambridge, MA, USA, [7]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rockville, MD, USA, [8]Vaccine Research Center, Bethesda, MD, USA

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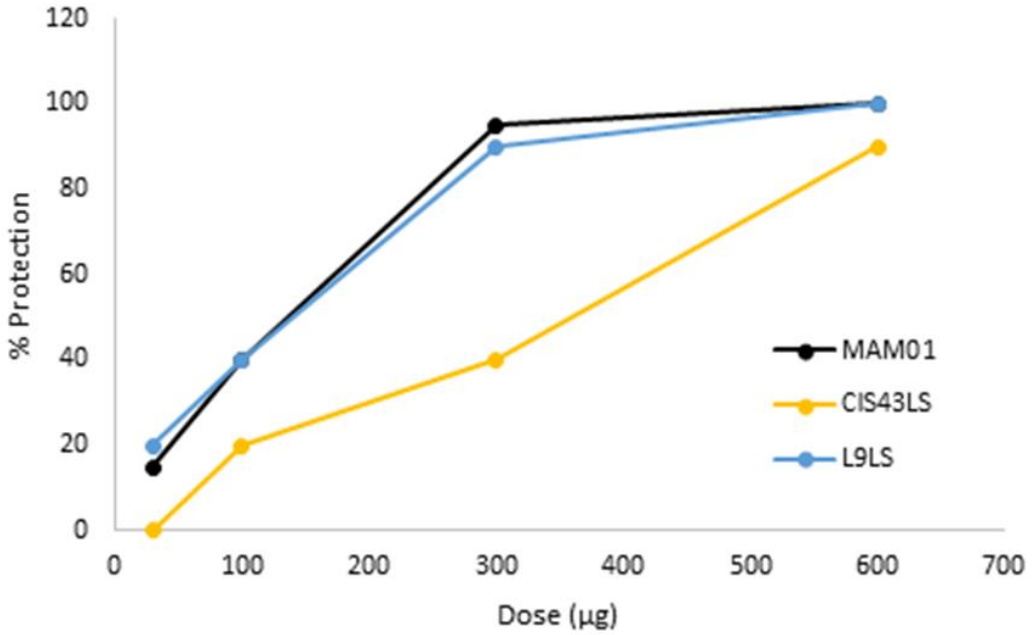
Comparing 1st Generation CSP mAbs in mouse models

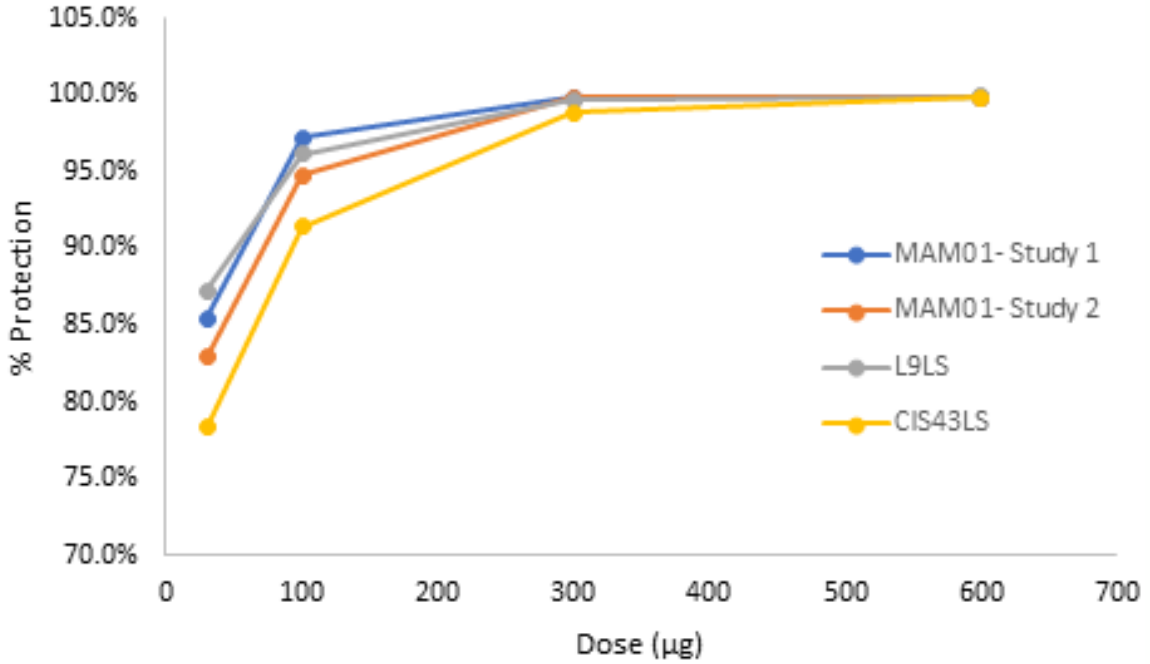
Bite parasitemia dose response comparison *(P. falciparum)*



- PK/PD study with engineered *P. berghei*
- Equipotent to L9LS and more active than CIS43LS (on a dose basis)

Learn more at poster LB-8026 Thursday Session

Liver burden dose protection comparison *(P. berghei)*



MAM01 was highly protective against *Pf* mosquito bite challenge in the parasitemia model with humanized mouse and *P. falciparum* infection

Learn more at poster LB-8208 Friday Session

Proposed label claim for infants and children

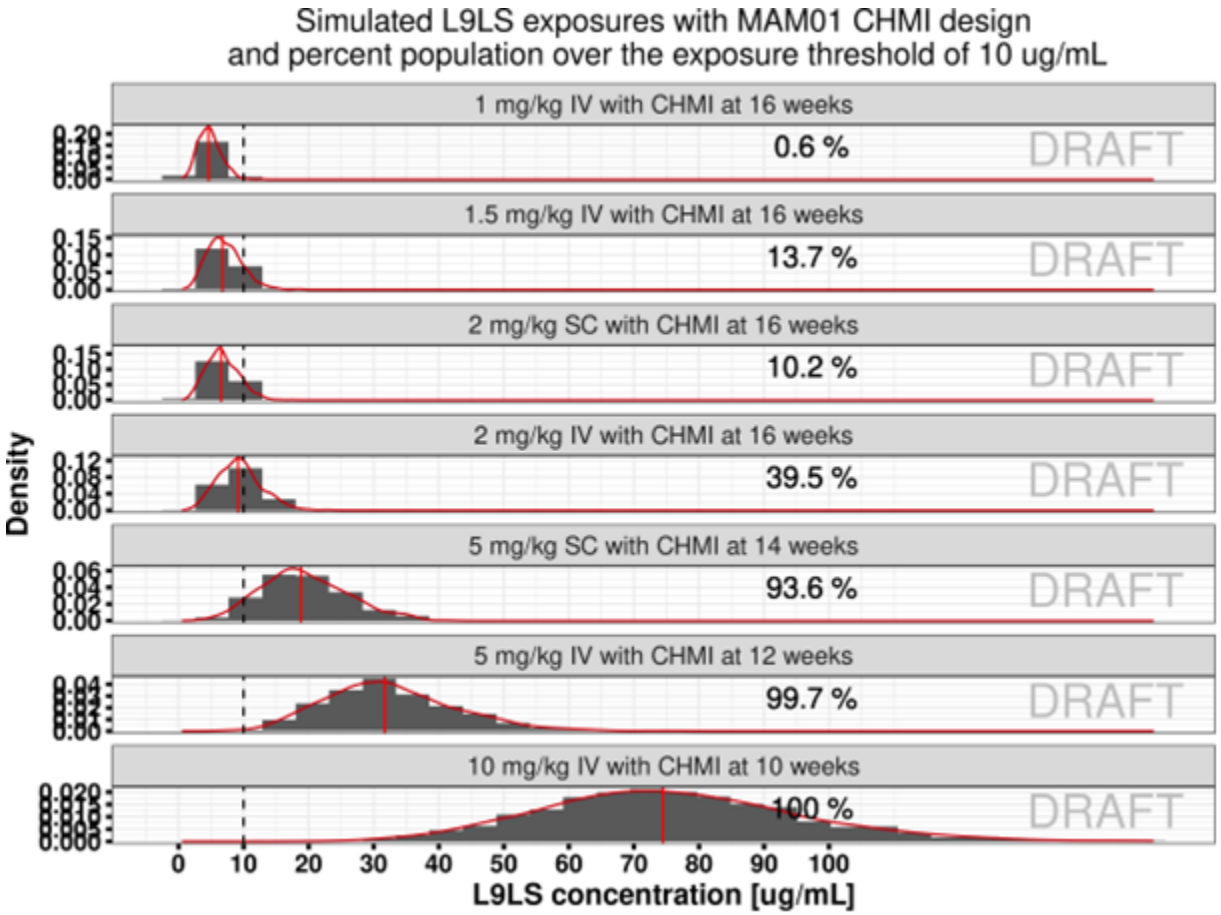
Supported by data from two populations:

- Children aged 3 months to 5 years in **moderate to high transmission settings**
  - Duration of protection will be determined from Phase 2 trial
  - Seasonal settings as an alternate product for SMC-SPAQ or vaccination
  - Consideration for annual use in perennial settings
    - If the MAM01 pediatric data support

- In **hospital settings** as an alternative to PDMC

Simulations to guide dose selection in Phase 1 & CHIM

We predicted a range of exposures for each arm which correspond to timing of CHMI for part 1

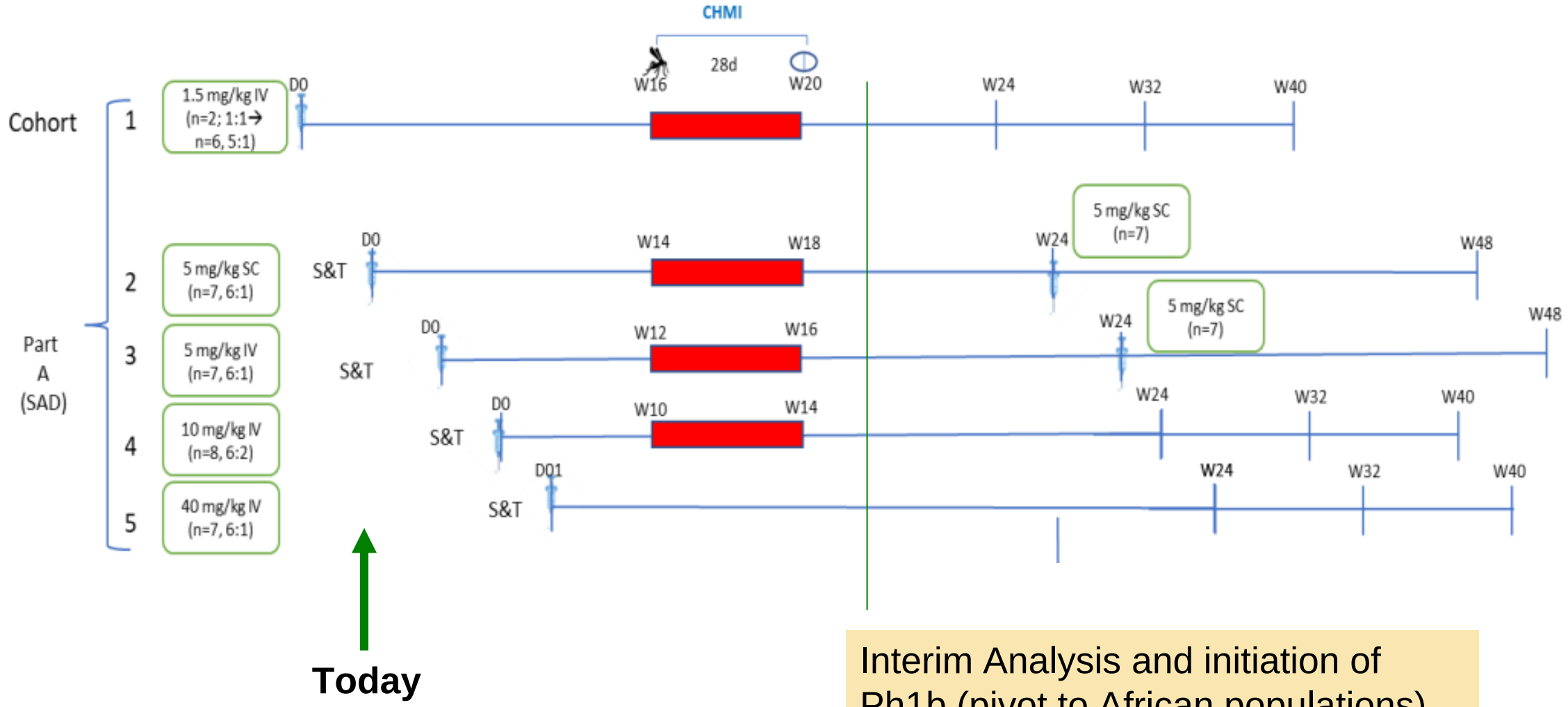


Caveat: translating the PK from Western adults to African children:

- Adults to children to infants
- Theoretical differences in FcRn expression in African populations affecting mAb recycling
- Any impact from an upregulated inflammatory response

Phase 1 FIH SAD/CHMI

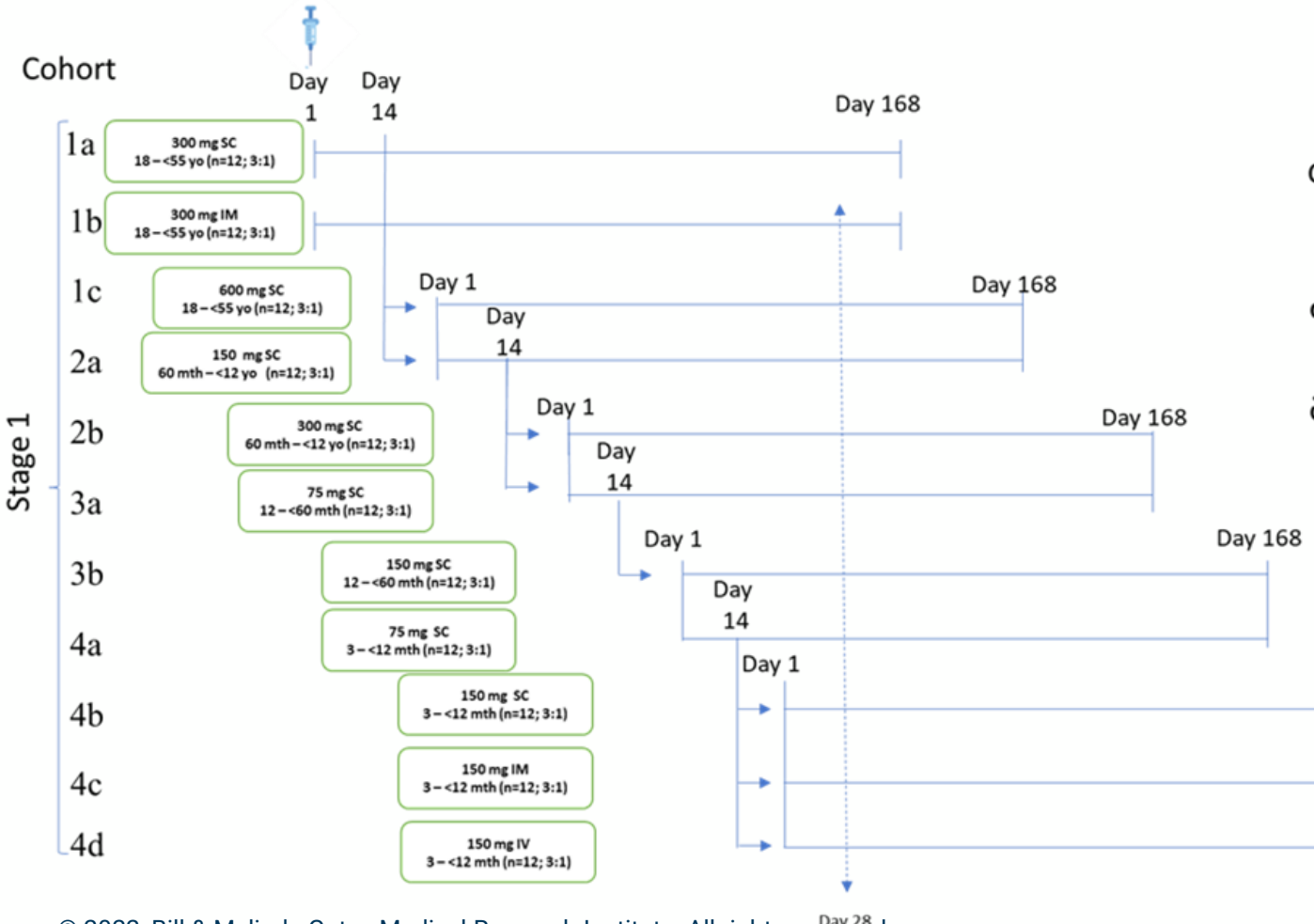
University of Maryland Center for Vaccine Development & Global Health



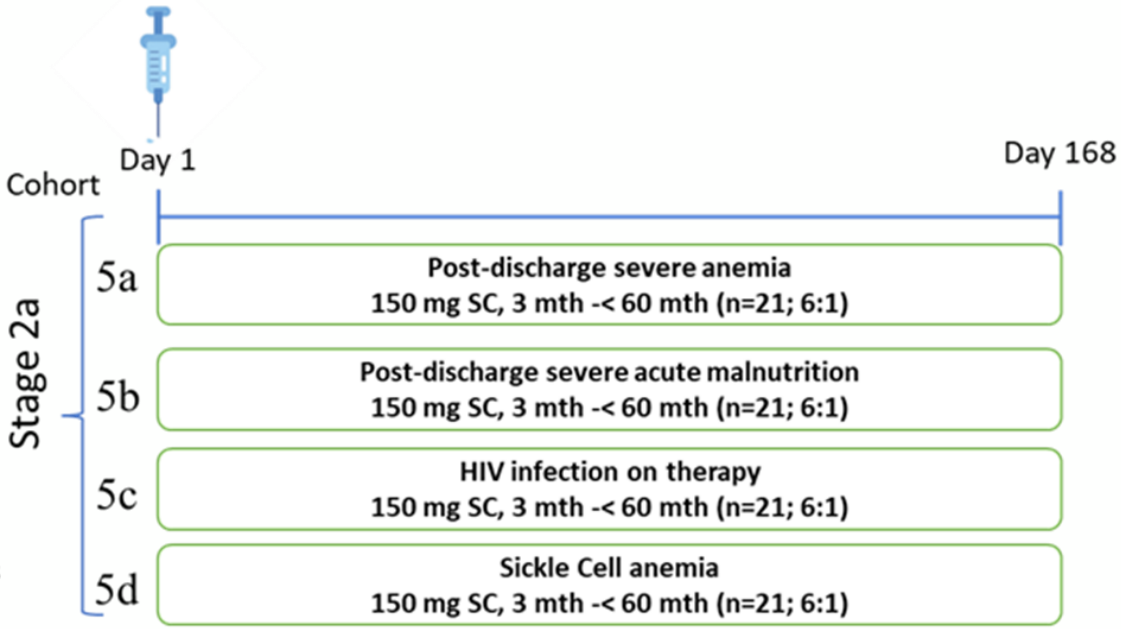
Interim Analysis and initiation of Ph1b (pivot to African populations).

Phase 1b and African pediatric populations – high perennial transmission

Age de-escalation



High-risk

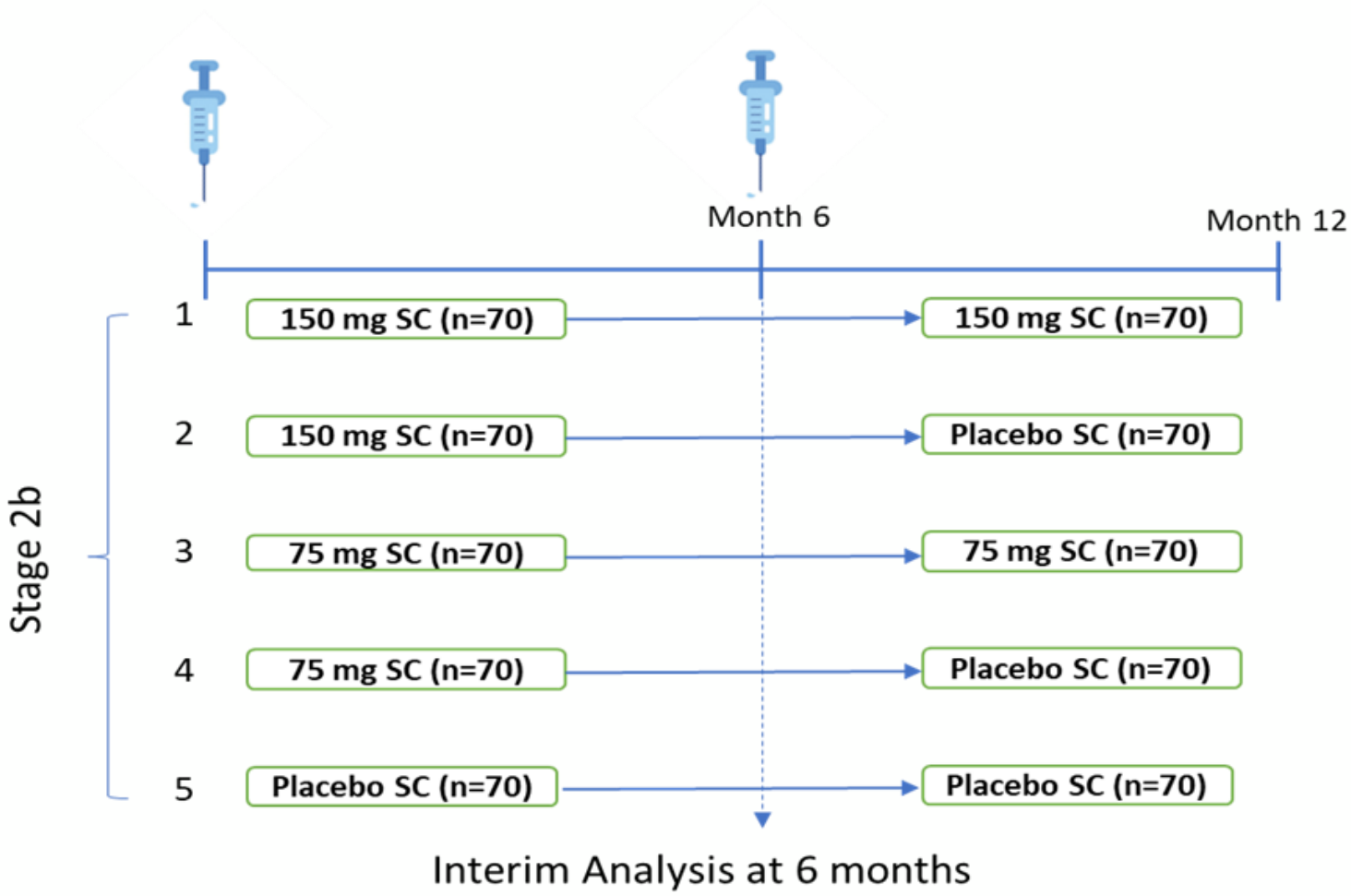


- safety and PK for 6 months of two doses bracketing target range
- for high-risk children, given with standard of care prophylaxis

Phase 2 (POC in children 6 mos – 5 years)

Assess duration of protection and EC80

- Multicenter trial
- Healthy children in moderate-high perennial settings
- Clearance of pre-existing parasitemia
- Primary endpoint: infection by microscopy
  - Preventive efficacy 6, 12 months
  - time to first infection



Summary

- With the Phase 1 and Phase 2 data, we will
  - Establish safety, PK and duration of efficacy data for MAM01:
  - Estimate EC80 and compare to CHMI predictions
  - Build robust population PK model
  - Establish weight bands for under 5 populations
- Predict dose that will give us desired duration of protection at the lowest cost
  - Goal to hit WHO target cost for malaria monoclonals
  - Offer sustained chemoprevention for 6 months or more with a single touchpoint with the health care system and no adherence risk

Acknowledgements

- **Bill & Melinda Gates Medical Research Institute** – Scott Miller, Jared Silverman, Charles Wells, Hong Liu, Neelima Sharma, Monicah Otieno, Micha Levi, Aparna Anderson, James Huleatt, Joleen White, Todd Bowser, Aurelia Haller, Ross Dikas, Upendra Argikar
  - **Clinical**: Grace Fitzgerald, Danielle Slaughter, Jill Steeley, Christine Redmond, Chrissy Fleming, Lisa Hampton, Judy Loughry, Poonam McFarland, Alex Brown, Noel Taylor, Sophe Ap, Chris Mucci, Deborah Roby, Rakib Ouro-Djobo, Leann Frankel, partners at FHI Clinical, the University of Maryland School of Medicine Center for Vaccine Development and Global Health, and the Walter Reed Army Institute of Research
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- **Atreca** - Daniel Emerling, Kate Williams
- **Just-Evotec Biologicals** – Randal Ketchem, Dean Pettit, Bruce Kerwin, Caren Tidwell, Jen Smith-Yuen
- **Duke University** – Kan Li, Shyam Sutariya, Derrick Goodman, Moses Dennison, Georgia D. Tomaras
- **Oregon Health and Science University** – Thomas Martinson, Maya Aleshnick, Payton Kirtley, Brandon Wilder
- **Johns Hopkins University** – Yevel Flores-Garcia, Shamika Mathis-Torres, Minah Park, Fidel Zavala

WHO Preventative Chemotherapy Malaria Policies

	Where	Who	What	How
Perennial malaria chemoprevention (PMC)	Areas of moderate to high perennial malaria transmission	Children (12-24 mo) at high risk of severe malaria	• Sulfadoxine-pyrimethamine (SP) or artemisinin-based combination therapies (ACTs)	Expanded Programme on Immunization (EPI)
Seasonal malaria chemoprevention (SMC)	Seasonal malaria transmission	Children in age groups at high risk of severe malaria (<10 years)	• SP plus amodiaquine (SP+AQ) • Schedule dependent on local epi	Door-to-door delivery or fixed-point delivery
Intermittent preventive treatment of malaria in school-aged children (IPTsc)	Areas of moderate to high perennial malaria transmission	School aged children 5-15 years	• SPAQ or SP + piperaquine, SP +artesunate (AS), ACTs	Schools or community-based approaches
Post-discharge malaria chemoprevention (PDMC)	Areas of moderate to high malaria transmission	Children admitted to the hospital with severe anemia <9 years	• SP, Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DHAP)	Community or facility-based delivery
RTS,S/AS01 **R21/Matrix-M** NEW	Malaria-endemic areas, prioritizing areas of moderate and high transmission but also considering vaccination in low transmission settings	Children 5 months+	Three doses at monthly intervals and subsequent annual single doses just prior to the high transmission season; 5 dose seasonal strategy	Expanded Programme on Immunization (EPI) if possible

Moderate to high perennial malaria transmission settings are defined as areas with P. falciparum parasite prevalence greater than 10% or an annual parasite incidence greater than 250 per 1000.

WHO Guidelines for Malaria, June 2022

WHO Malaria Guidelines Updated June 2022

Greater flexibility given to National Malaria Control Programs

No longer specified:

- strict age group
- transmission intensity thresholds
- # of doses
- # of cycles
- specific drugs

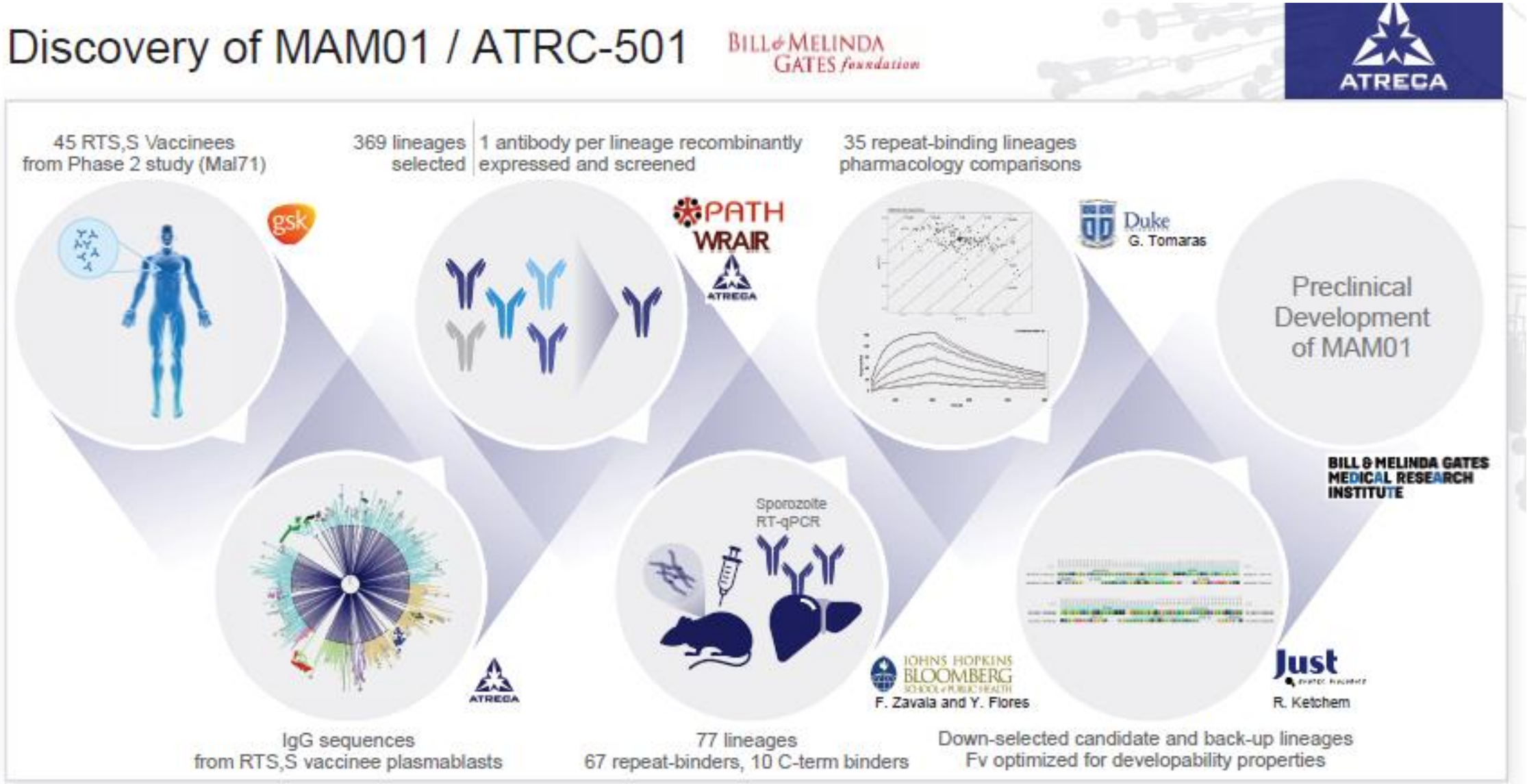
Unknowns acknowledged:

- Adherence
- Extent of seasonal variation in transmission and intensity
- Availability of drugs
- Duration of protection
- Coverage achieved
- Preventative efficacy
- Frequency of dosing

Call for:

Local data for sub-national tailoring to determine implementation.

History of MAM01



An antibody drug engineered for prevention of malaria in global populations

c/o Daniel Emerling and Kate Williams, Atreca