RTS,S/AS01 malaria vaccine current evidence, including efficacy, safety, feasibility and impact and update on R21/Matrix-M malaria vaccine

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Credit: WHO/Neil Thomas.

Objectives

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- To brief on the background of the RTS,S malaria vaccine and WHO recommendations
- To provide updates on the malaria vaccine pipeline and R21/Matrix-M malaria vaccine

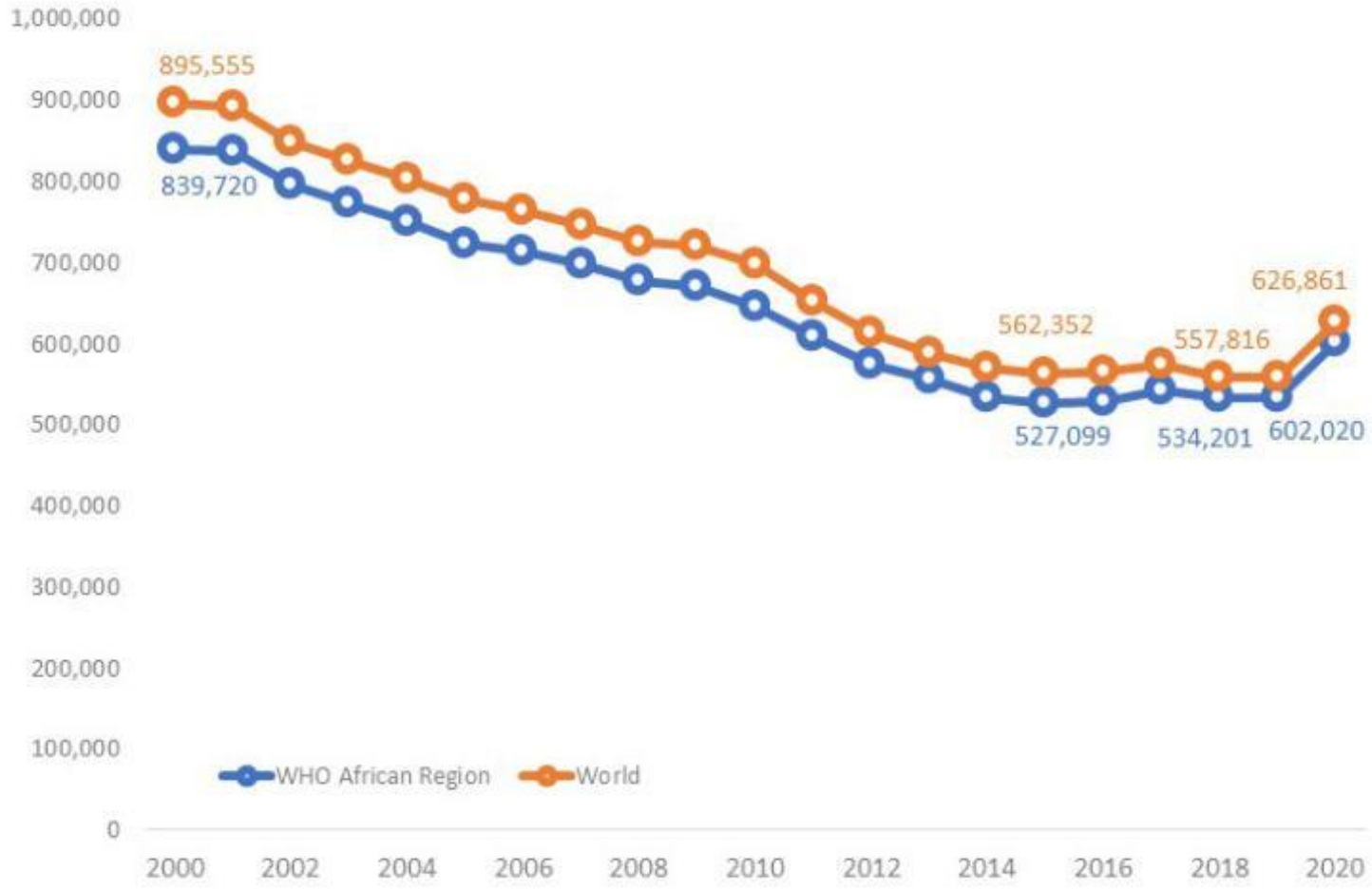
RTS,S/AS01 Malaria Vaccine

Credit: WHO/Neil Thomas.

Malaria continues to cause unacceptably high levels of disease and death

World Health Organization

Global trends in malaria deaths, 2000–2020



Global (2020)

- 241 million cases
- 627 000 deaths

Highest Burden in Africa

- 95% of all cases and 96% of all deaths
- **479 000 child deaths in Africa** (= 80% of malaria deaths in Africa)

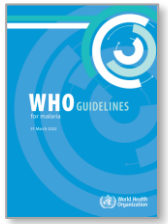
WHO recommendation on use of the first malaria vaccine

WHO recommends the RTS,S/AS01 malaria vaccine be used for the prevention of *P. falciparum* malaria in children living in regions with moderate to high transmission as defined by WHO

- RTS,S/AS01 malaria vaccine should be provided in a schedule of 4 doses in children from 5 months of age for the reduction of malaria disease and burden.
- Countries may consider providing the RTS,S/AS01 vaccine seasonally, with a 5-dose strategy in areas with highly seasonal malaria or areas with perennial malaria transmission with seasonal peaks.
- RTS,S/AS01 introduction should be considered in the context of comprehensive national malaria control plans.

Useful links

WHO malaria vaccine position paper
https://www.who.int/publications/i/item/who-wer9709-61%E2%80%9380



WHO Guidelines for malaria
PDF version:
https://www.who.int/publications/i/item/guidelines-for-malaria
MAGICapp Online platform:
https://app.magicapp.org/#/guideline/5701

Malaria Vaccine Implementation Programme
https://www.who.int/initiatives/malaria-vaccine-implementation-programme

NITAG Resource center
https://www.nitag-resource.org/

WHO recommendations for malaria vaccine schedule

Schedule

- First dose administered from 5 months of age
- Minimum interval of 4 weeks between doses
- 3-dose primary schedule
- 4th dose approx. 12 – 18 months after 3rd dose to prolong duration of protection
- Flexibility in schedule to optimize delivery: as an example, to align 4th dose with other vaccines in second year of life
- Children who begin their vaccination series should complete the 4 dose schedule.

Optional schedule for settings with highly seasonal malaria or perennial malaria with seasonal peaks

- Seasonal vaccination to maximize impact by timing vaccination to the period of highest malaria transmission
- Primary 3-dose series provided monthly (either from 5 months of age, or just prior to peak season), additional doses provided annually prior to peak season (up to 5 doses total)
- **Countries that choose a seasonal deployment strategy strongly encouraged to document their experience**

Product characteristics of WHO-prequalified RTS,S/AS01 malaria vaccine

Adjuvant AS01
liquid
(green ring)

Antigen RTS,S
lyophilized
(red ring)

Vials are clipped together to reduce the chance of reconstitution error

- Product overview on WHO list of pre-qualified vaccines: https://extranet.who.int/pqweb/content/mosquirix
- Injectable vaccine (intramuscular) consisting of two vials
- Once reconstituted, the vial contains TWO doses of vaccine (0.5mL/dose) which must be used within 6 hours or discarded at the end of the session, whichever comes first.
- Shelf life of 36 months at storage temperature between **+2°C and +8°C.** Freeze sensitive and light sensitive
- Vaccine Vial Monitor (VVM14)*
- Packing dimension of inner carton:
  - 100 vials (= 50 pairs, 100 doses) per pack
  - Volume : 9.92 cm^3/dose
- Co-administration: can be given concomitantly with Pentavalent (DPwP/Hep B/Hib), OPV, measles, rubella, yellow fever, rotavirus and pneumococcal conjugate vaccines

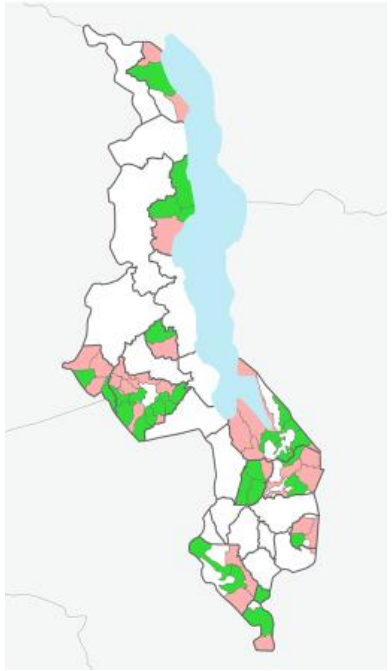
*VVM: label containing heat sensitive material registers cumulative heat exposure over time

Pilot implementations to understand the vaccine in routine use, (2019-2023)

Commitment to support continued vaccination in MVIP areas

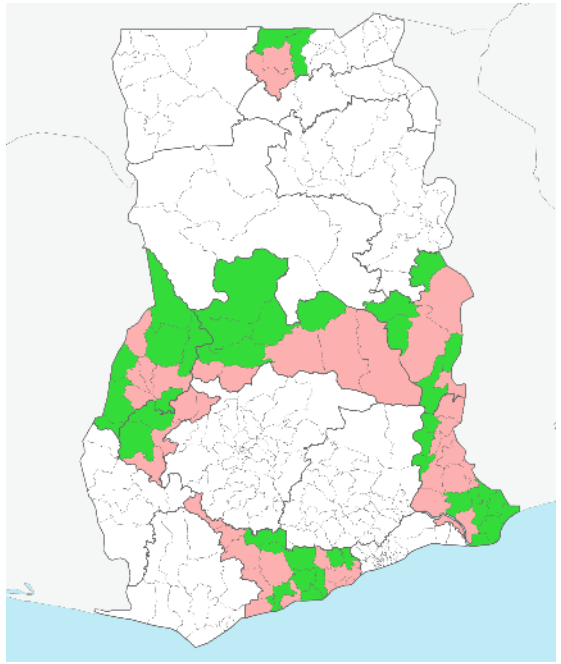
- Pilot vaccinating areas
- Pilot comparator (non-vaccinating) areas—following WHO recommendation will expand vaccination

Malawi



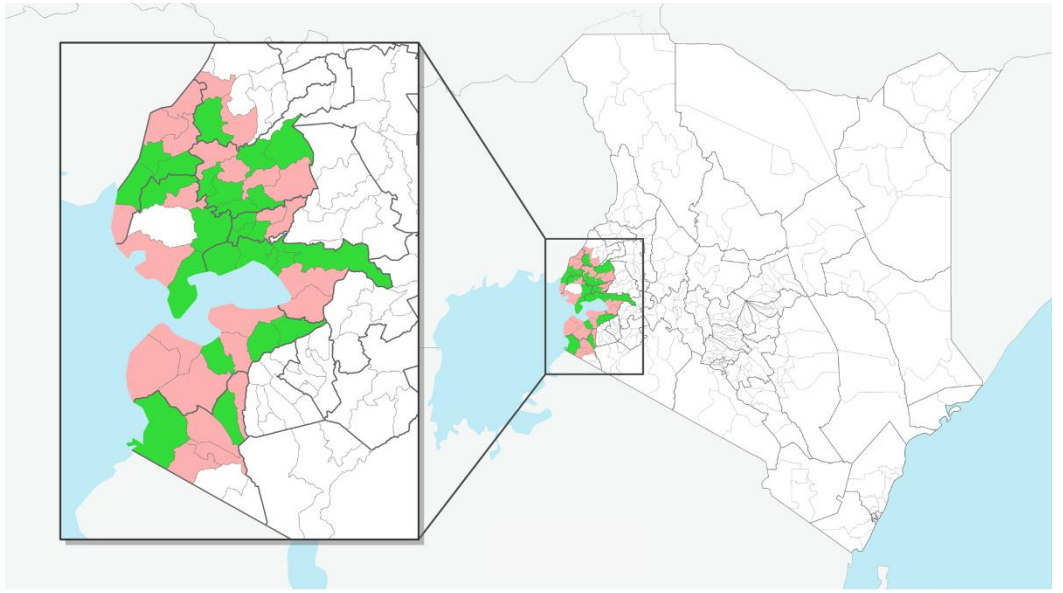
11 districts

Ghana



81 districts in 7 regions

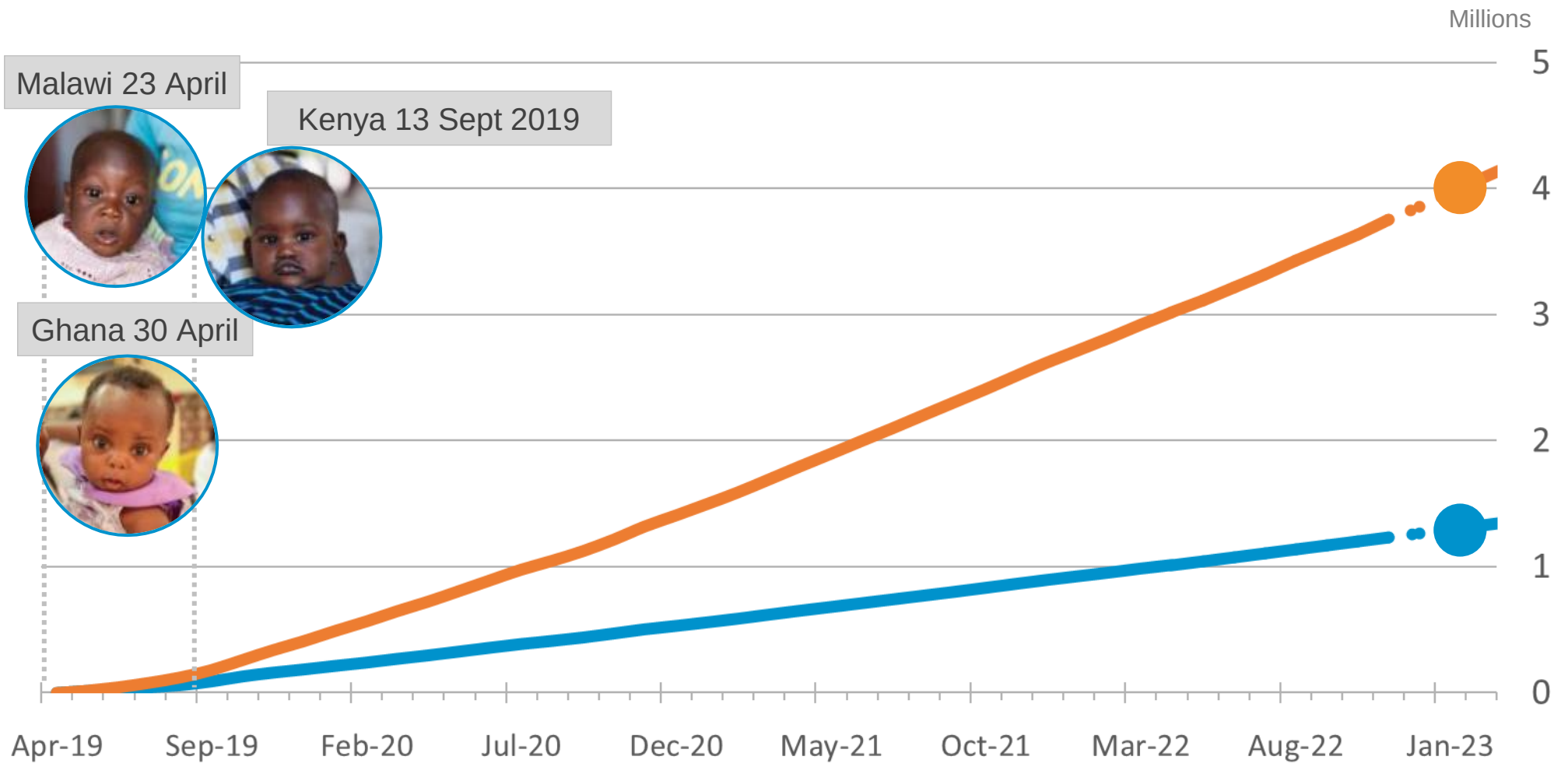
Kenya



51 sub-counties in 8 counties

The Malaria Vaccine Implementation Programme (MVIP) continues to progress well

World Health Organization



As of December 2022

>3.8 million vaccine doses **administered**

>1.2 million children received **at least one dose**

Estimates as of December 2022 - based on monthly MOH/EPI administrative data reports until November 2022 (for Kenya and Ghana) and September 2022 (for Malawi) and MVIP team projections for subsequent months

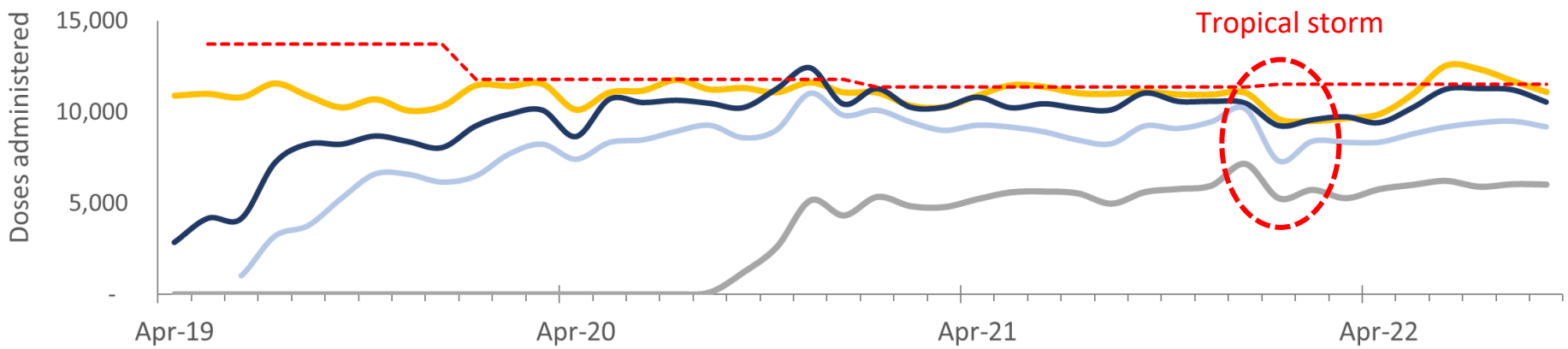
Immunization coverage in MVIP areas: monthly administrative data reports (through Nov 2022)

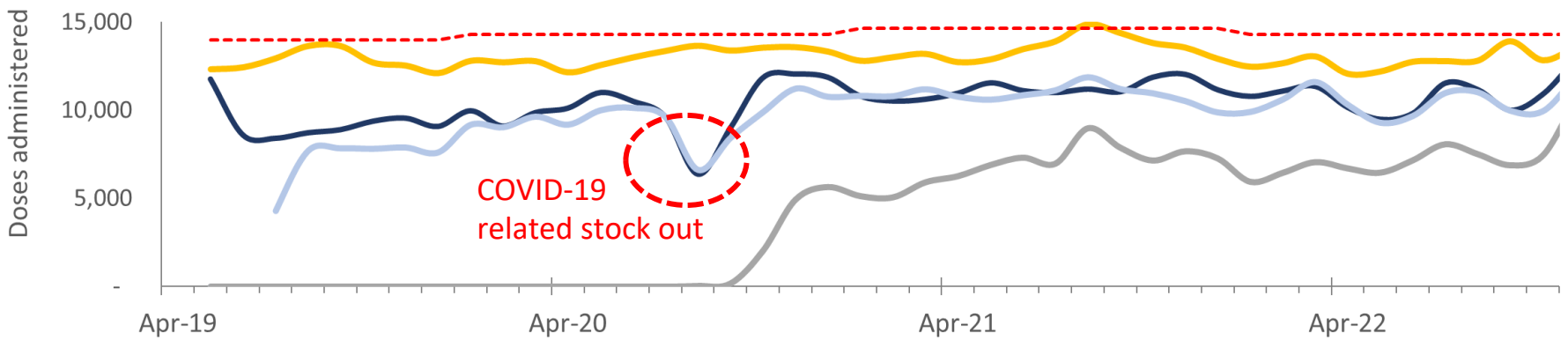
Malawi	2021	2022#
Penta-3	97%	94%
RTS,S-1	93%	89%
RTS,S-3	81%	76%
RTS,S-4		*69%

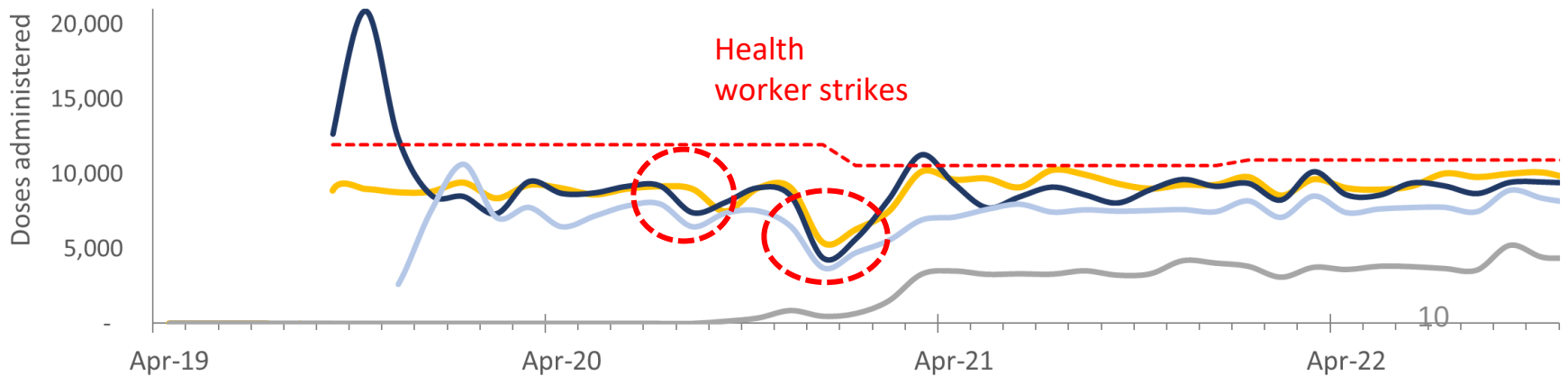
Ghana	2021	2022
Penta-3	92%	90%
RTS,S-1	76%	76%
RTS,S-3	74%	73%
RTS,S-4		*72%

Kenya	2021	2022
Penta-3	87%	87%
RTS,S-1	82%	84%
RTS,S-3	67%	73%
RTS,S-4		*54%

Data from Jan to Sept (or Nov) 2022
* Among children who received RTS,S-3







Summary findings from the MVIP: 24 months after first vaccination (April 2019 – April 2021)

1. **Feasibility:** Vaccine introduction is feasible, with good uptake and coverage through the routine systems, no impact on uptake of other vaccines, insecticide-treated bed nets (ITNs), care-seeking behavior

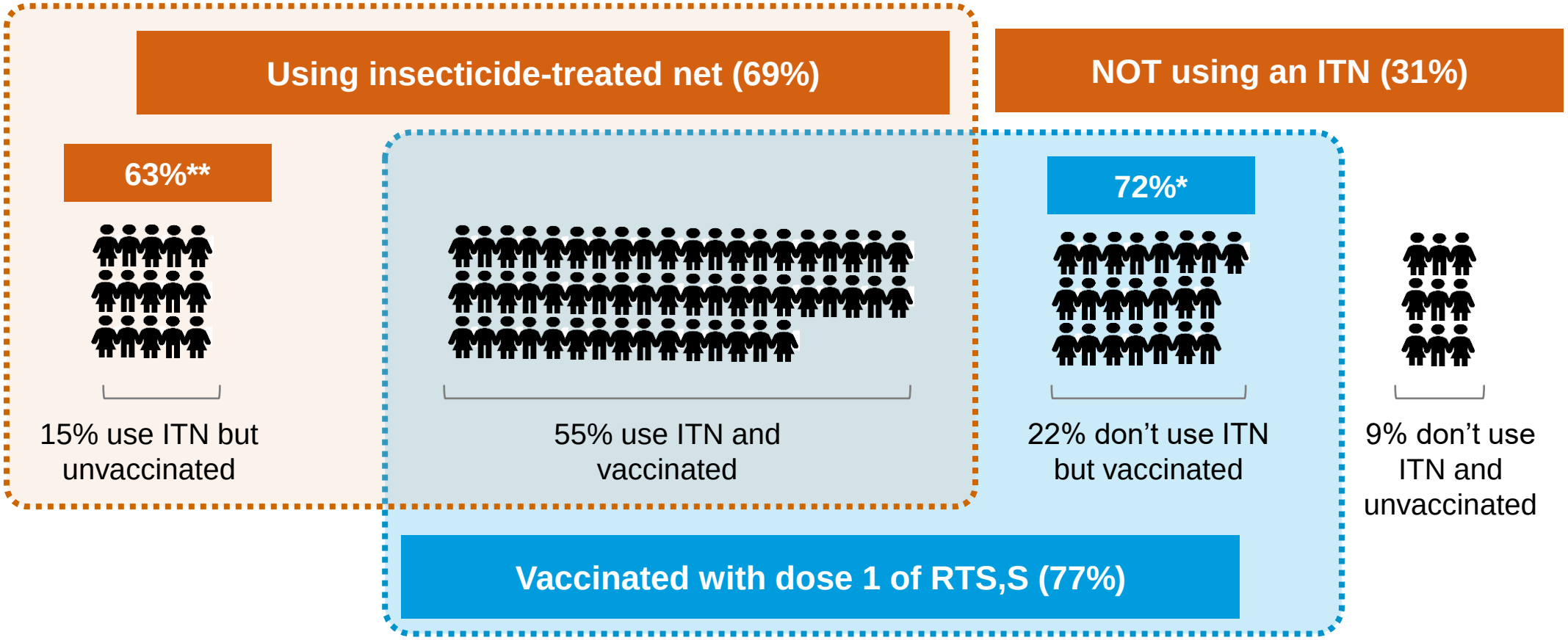
2. **Safety:** Vaccine is safe; no safety signals identified after over 3 million doses provided

3. **Impact:** Vaccine introduction resulted in a substantial reduction in severe malaria and all cause mortality in children age-eligible to receive the vaccine, even when introduced in areas with good ITN use and access to care
    - 32% (95% CI 8, 46%) reduction in hospitalized severe malaria
    - During 24 and 36 months after vaccine introduction, data show a reduction in all-cause mortality

4. **Equity:** the vaccine is reaching children who are not using other forms of prevention such as insecticide-treated nets, increasing access to malaria prevention interventions to > 90%

Adding a malaria vaccine to current interventions increases access and reduces gaps in malaria preventive tools

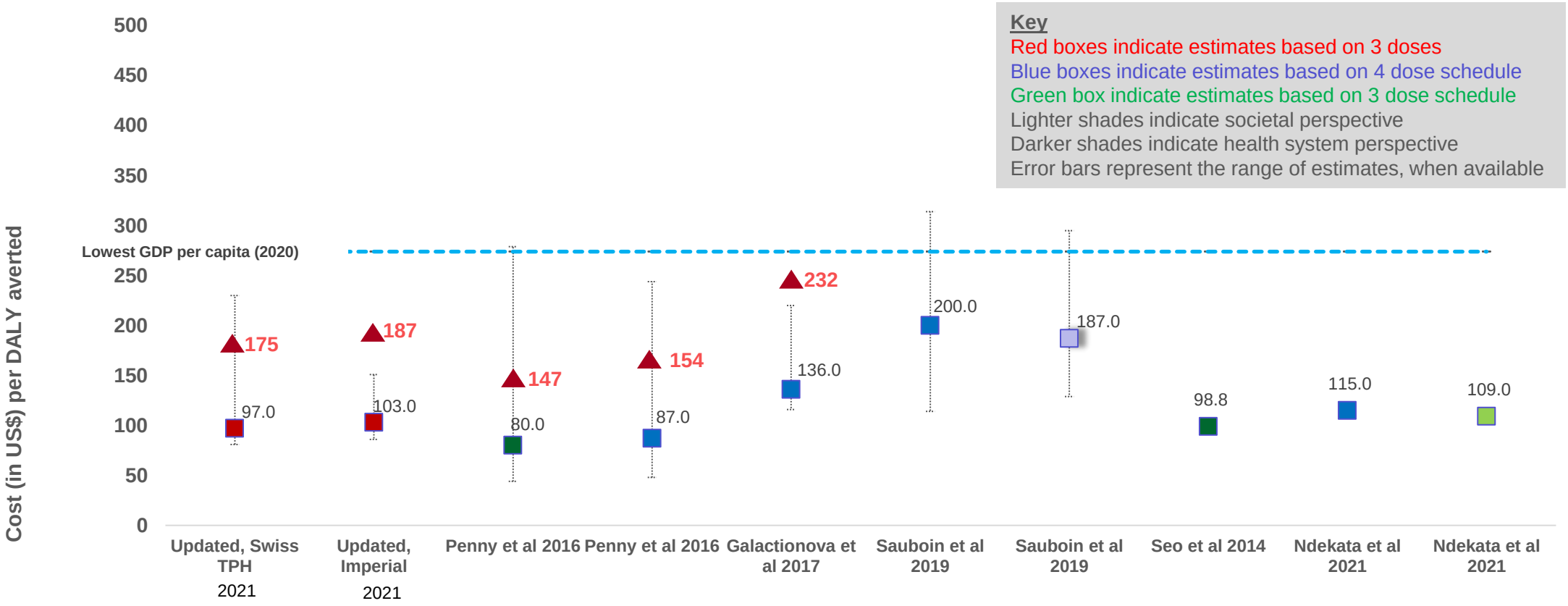
Ghana Midline Feasibility Household Survey Children 12-23 months (conducted in November 2020, `18 months after introduction)



Source: HHS data from KHRC Ghana

Cost effectiveness of RTS,S

Modelling predictions indicate a significant public health impact across a wide range of settings, and a high level of cost effectiveness. The 2021 updated analysis estimated **approximately 400 deaths averted per 100,000 fully vaccinated children.** Cost effectiveness continues to be robust even at 10 USD per dose.



- **Estimates in▲ red represent vaccine price of $10 per dose**. All other estimates in the slide assume a baseline vaccine price of $5 per dose.
- Most studies evaluate RTS,S cost effectiveness at a range of vaccine prices ($2 -$10). Cost effectiveness improves with lower assumed vaccine price.

PATH

Updates on the R21/Matrix-M Malaria Vaccine and malaria vaccine pipeline

Credit: WHO/Neil Thomas.

Candidate vaccines in advanced clinical development

World Health Organization

Recommended vaccine: RTS,S/AS01

Pre-erythrocytic (*P. falciparum*) candidates:

- **RTS,S/AS01 pre-erythrocytic (phase 4)**
  - Fractional dose, seasonal vaccination
- **R21 Matrix-M (phase 3)**
  - Anti-sporozoite subunit vaccine
- **PfSPZ Vaccine (phase 2)**
  - Whole sporozoite (radiation attenuation)
- **PfSPZ CVac (phase 2)**
  - Whole sporozoite (chemically attenuated) with chemoprophylaxis
- rCSP (full length) subunit (phase 1, ongoing)
- FMP013/FMP014 self-assembling nanoparticle (phase 1, ongoing)
- VLPM01 virus-like particle (phase 1, 2020), DNA ChAd63 PfCSP PfAMA1 ME-TRAP (phase 1, 2020), GAP genetically attenuated whole sporozoite vaccine (phase 1, 2019), ChAdOx1 MVA LS2 (phase 1, 2017), PfAMA1 (phase 1, 2015)

Blood stage (*P. falciparum*)

- Rh5 (phase 2a, 2019)
  - Reticulocyte-binding protein homologue 5
- SE36 (formerly BK-SE36) (phase 1, 2020)
- CAP chemically attenuated whole parasite (phase 1, 2018)
- GMZ (phase 1, 2016), P27A synthetic peptide (phase 1, 2015)

Sexual stage / transmission blocking (*P. falciparum*)

- Pre-fertilisation - **Pfs230 (phase 2, 2020)** and Pfs48/45
- Post-fertilisation – **Pfs25 (phase 2, 2020)** and Pfs28

***P. vivax* (phase 1/2a)**

- PvDBP (phase 2, ongoing) – blood stage duffy-binding protein
- Pvs25 (phase 1, ongoing) - sexual-stage protein vaccine
- PvCSP (phase 2, ongoing)
- PvSPZ (phase 2a, 2017) - irradiated sporozoites

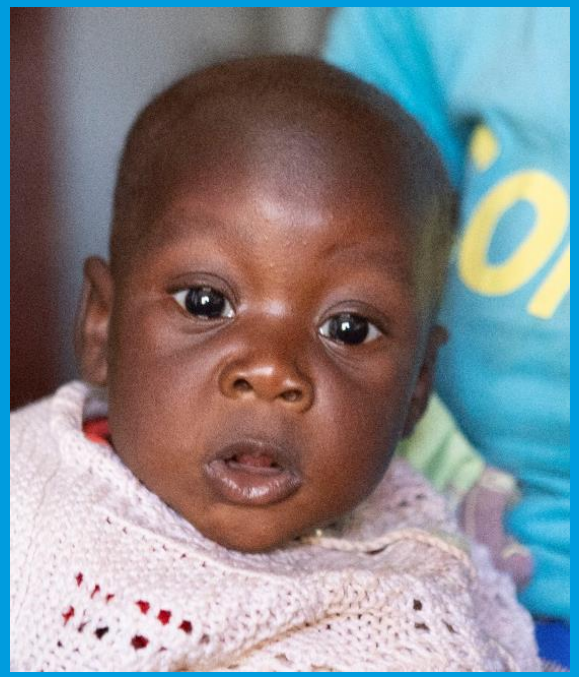
Malaria in pregnancy

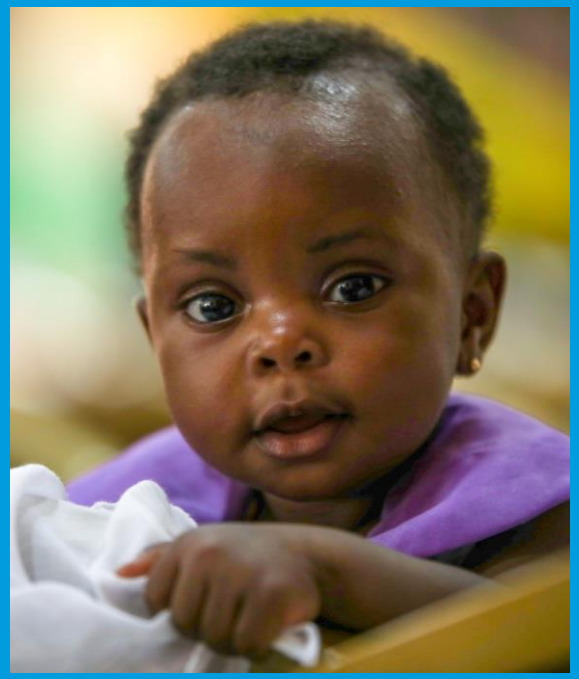
- Two VAR2CSA antigen-based vaccines currently in phase 1
  - PRIMVAC (phase 1, 2019) and PAMVAC (phase 1, 2017)

R21/Matrix-M

- Phase II trial (N=350) showed high efficacy when provided seasonally (~75%) *
  - Similar to RTS,S/AS01 when provided seasonally
- Currently in Phase III trials
  - 5 sites, children 5-36 M of age, 4-dose schedule
    - 2 highly seasonal sites (Mali and Burkina Faso) with vaccine provided seasonally (0,1,2 prior to high transmission season; 12M prior to second season)
    - 3 in low or low/mod transmission sites (Kenya, Tanzania, Burkina Faso) where vaccine given in age-based schedule from 5 months of age (0,1,2,M with 4th dose given 12M after D3)
- WHO preparing to review (efficacy, safety, programmatic suitability)
  - May have recommendation for seasonal vaccination strategy before perennial use
- Developers also seeking pre-qualification
- If found recommended for use, could be important means to increase supply/meet demand

Datoo *et al;* Lancet, 2022





Temps pour des questions
Any questions?