Malaria Transmission Intensity Likely Modifies RTS,S Efficacy Due to a Rebound Effect in Ghana, Malawi, and Gabon

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MAJOR ARTICLE

Malaria Transmission Intensity Likely Modifies RTS, S/AS01 Efficacy Due to a Rebound Effect in Ghana, Malawi, and Gabon

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BACKGROUND

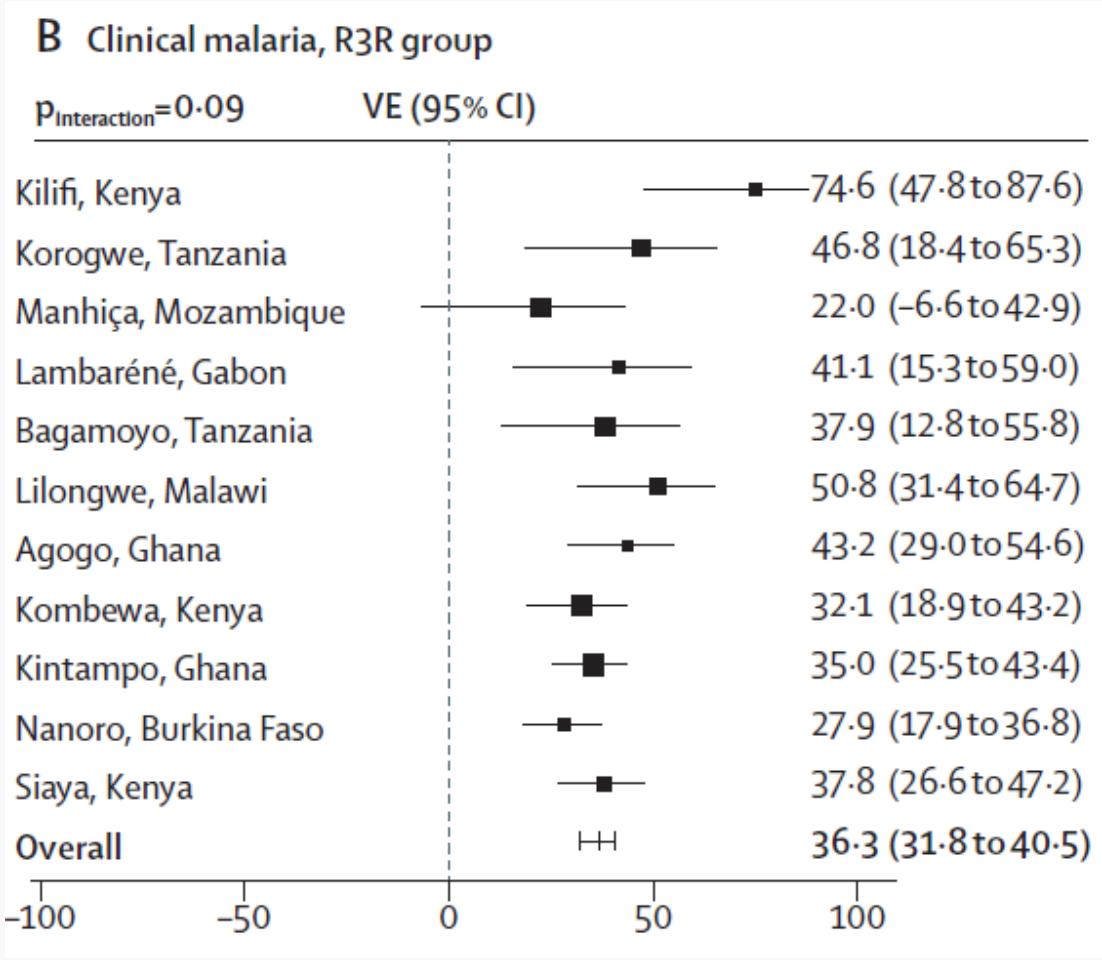
- RTS,S is the first vaccine against malaria *(P. falciparum)*
- Recommended for widespread implementation by WHO.
- Three doses (with a fourth booster dose 18 months after the third).
- Efficacious in children (5-17 months) but not infants (6-12 weeks) in clinical trials.

- *P. falciparum* transmission is tied to ecology

BETWEEN-SITE VARIATION

Efficacy against clinical malaria varied from 22% to 75%

There is some evidence that efficacy decreases as background malaria incidence increases (Olotu et al. *NEJM.* 2013)

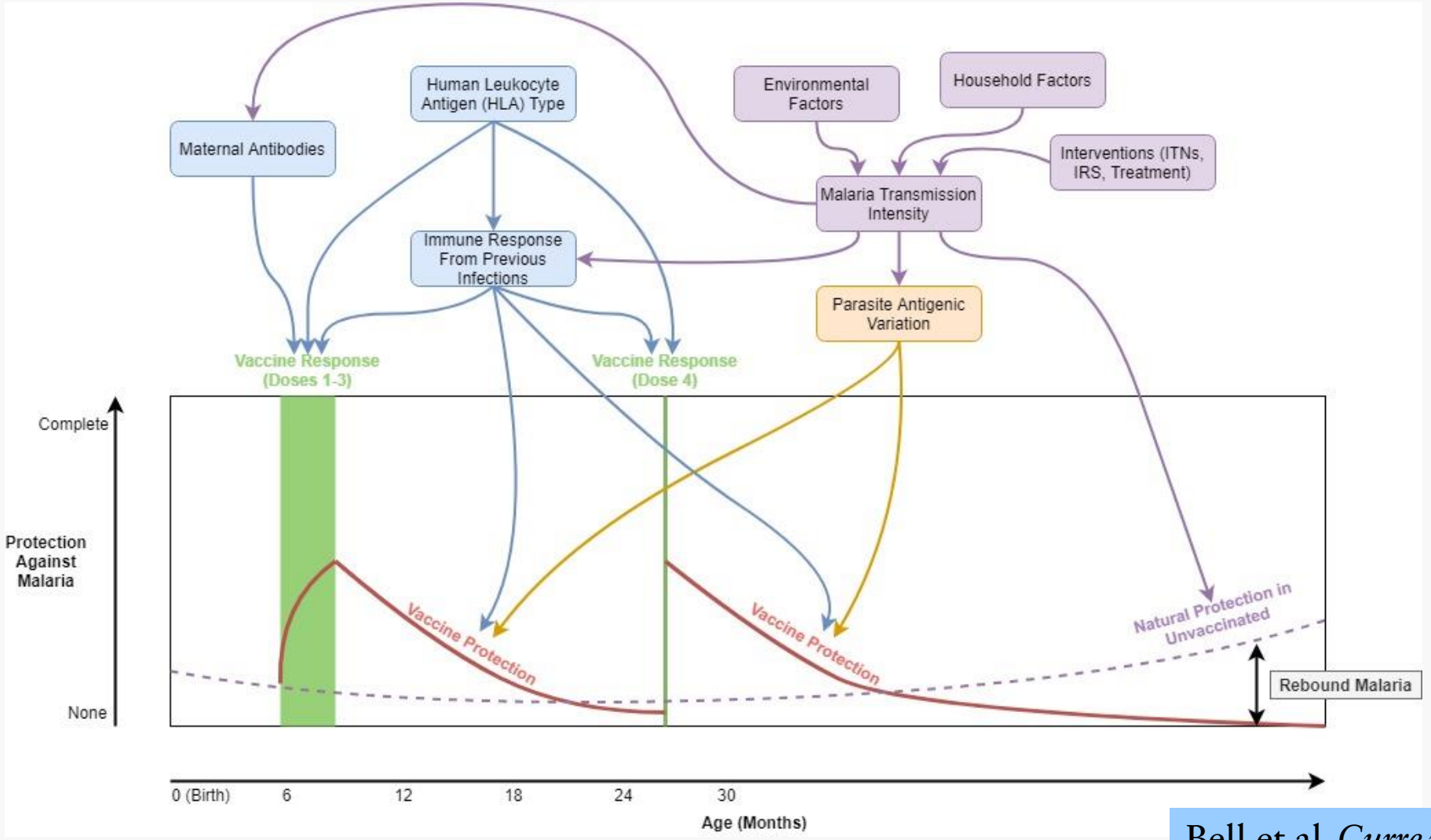


Efficacy and safety of RTS,S/AS01 malaria vaccine with or without a booster dose... *Lancet*. 2015.

IMPACTS OF ENVIRONMENT, HOST GENETICS AND ANTIGEN DIVERSITY ON MALARIA VACCINE EFFICACY

Aim 1	• Determine the effect of environmental and behavioral factors on RTS,S efficacy.
Aim 2	• Determine the relative longevity of strain specific vaccine efficacy provided by RTS,S.
Aim 3	• Determine the effect of host genetic polymorphisms on RTS,S efficacy.
Aim 4	• Determine the effect of combinations of environmental, behavioral, host genetic and parasite genetics on RTS,S vaccine efficacy.

POTENTIAL MECHANISMS OF VACCINE EFFICACY VARIATION



Bell et al. *Current Epi Rep*. 2021.

ONE EXPLANATION: DELAYED MALARIA AND DEVELOPMENT OF NATURAL IMMUNITY IN THE CONTROL GROUP

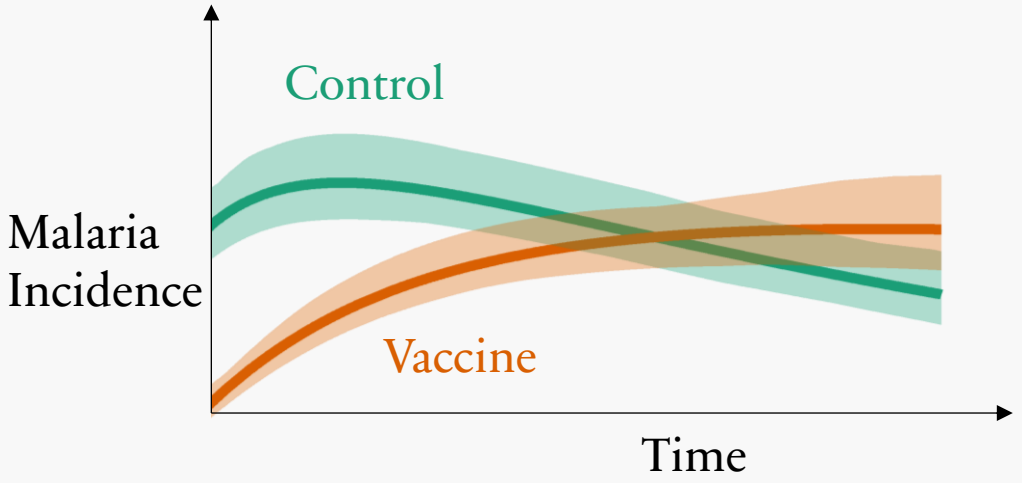
RTS,S reduces malaria incidence in vaccinated individuals initially.

- Vaccine-derived **immunity** wanes over time, resulting in "rebound" or "delayed" malaria cases.

Infections increase naturally acquired immunity, especially in the control group.

- Infections occur at a rate positively correlated with background incidence.

Incidence in vaccine group **rises** while incidence in the control group **falls**, and lines can even cross.



EVALUATING THE DELAYED MALARIA AND CONTROL-GROUP-IMMUNITY THEORY

Using phase III trial data from three sites in Malawi, Gabon, and Ghana:

Among infants who received the control vaccine

- Fit a random forest model to predict malaria incidence using ecological variables* (from the time they reach 5 months of age)

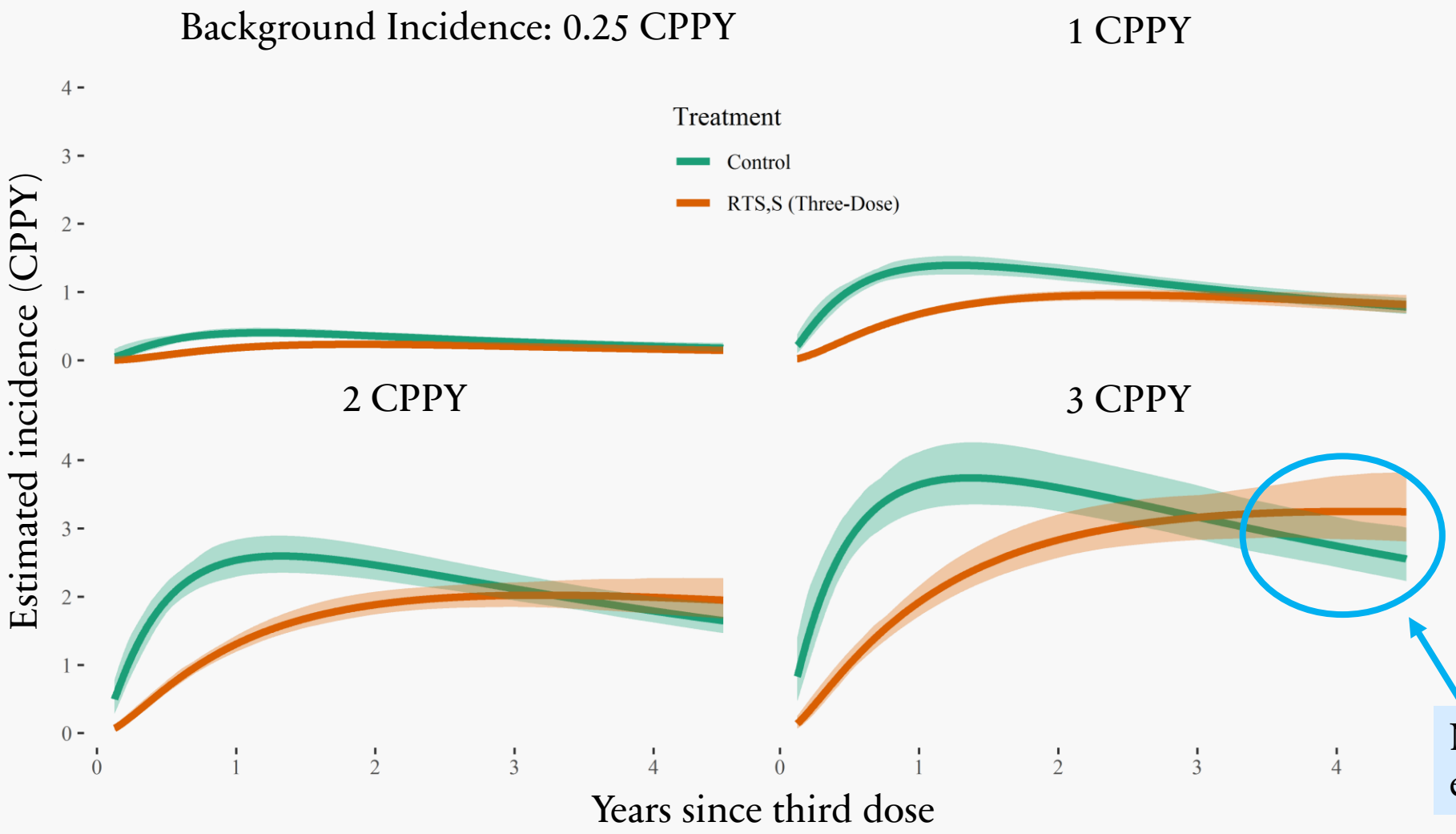
Among all children (analysis population)

- Apply the random forest model to predict background malaria incidence
- Create a regression interacting treatment, time, and predicted background malaria incidence.

*16 geospatial datasets, 3 household surveys, trial data

Bell et al. *JID*. 2022.

MODELED INCIDENCE BY VAX GROUP OVER TIME AND BACKGROUND INCIDENCE: 3 DOSES

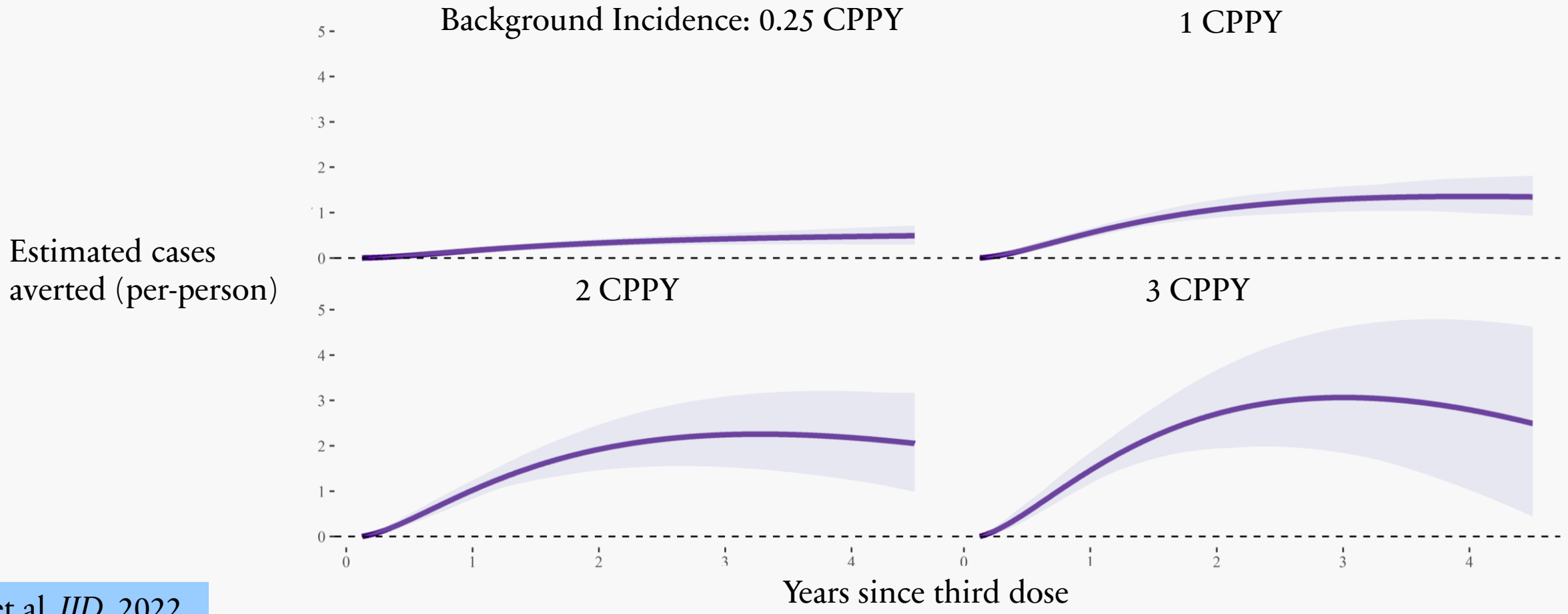


Major take-away: Incidence in the vaccine group rises above the control group incidence in the highest transmission settings around 3 years after the third dose.

Bell et al. *JID*. 2022.

CUMULATIVE CASES AVERTED: 3 DOSES

Major take-away: Delayed malaria does not erase initial gains.



Bell et al. *JID*. 2022.

CONCLUSION: UPDATED WHO GUIDANCE ON MALARIA VACCINES (OCT '23)

- Should be provided in a schedule of **4 doses**.
- A 5th dose may be considered in areas where there is a **significant malaria risk**.
- Seasonal vaccine schedules may be considered.

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