



Phase 1b randomised controlled double blind trial to evaluate the Safety and Immunogenicity of 30 and 100  $\mu$ g GMZ2 candidate malaria vaccine in healthy Gabonese children aged 1 to 5 years

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## GMZ2 VACCINE

GMZ2 is a hybrid malaria vaccine composed of merozoite surface protein 3 (MSP3) and glutamate rich protein (GLURP). The vaccine is adjuvanted with Aluminium hydroxide.

## Primary objective

To evaluate the safety and reactogenicity of three doses of 30 and 100µg GMZ2, adsorbed on aluminium hydroxide, in comparison with three doses of the control vaccine (rabies vaccine), in healthy Gabonese children aged 1-5 years

Through:

1. Immediate reactogenicity; defined as any systemic adverse reactions occurring within 30 minutes after each injection,
2. Local and systemic reactogenicity measured from Day 0 to Day 14 after each dose,
3. Any unsolicited Adverse Event resulting in a visit to a physician between each injection and one month after the third dose,
4. Any Serious Adverse Event (SAE) occurring from the inclusion throughout the study.
5. Biological safety, one month after each vaccination, in reference with the baseline level.

## Secondary objectives

**To assess the humoral response** to the vaccine antigens GMZ2, GLURP and MSP3 by measuring total IgG by ELISA.

1. Anti-GMZ2 specific memory B-cell-responses and IgG-subtypes were assessed by ELISPOT and ELISA, respectively.
  - IgG responses at Days 0, 28, 56, 84, and 365.
  - IgG subclasses at Days 0 and 84.
2. Antigen-specific memory B-cells by ELISPOT at Days 0, 84, and 365.

## METHODES (1)

- The study was performed in Lambaréné, province of Moyen Ogooué in Gabon
- A total of 55 volunteers were screened
- 30 volunteers (15 males and 15 females) were enrolled
- Ten volunteers were randomized to each group to receive either three doses of 30  $\mu\text{g}$  or 100  $\mu\text{g}$  of GMZ2 or rabies vaccine
- The second and the third doses were administered 28 and 56 days after the first dose was given

# Inclusion process

## **Meetings with community members and leaders**

- Authorities in the villages and urban quarters

## **Prescreening**

- Meetings with potential participants in Lambaréné and surroundings
- Signature of the prescreening informed consent by potential who accepted to be screened

## **Screening for inclusion**

- Signature of the screening informed consent at the study site for inclusion

## Ethics aspects of the study

- Approval by the AMANET scientific coordinating committee (SCC)
- Review and approval by regional ethics committee (Comité d'Ethique Régional Indépendant de Lambaréné)
- Authorization by the Ministry of Health of Gabon
- Registered with the US public registry of clinical trials

## Database and analysis timings

- Data double-entered and any discrepancies resolved to produce the final database.
- Database was locked after all results are entered (including Elisa results) and all queries up to Day 84 have been resolved and the database finalised.
- A final copy of the clinical and immunological data were archived and a copy lodged with the Data Safety Monitoring Board (DSMB).
- The analysis plan was elaborated
- The analysis of the long-term follow up to Day 365 was supplied as an annex to the final statistical report.

# Analysis populations

## i) Per Protocol:

- Vaccination, blood sampling and visits number as well as the time-interval between vaccination and follow-up visits are respected, as they are defined in the protocol and in the flow chart.
- All participants who have not been compliant with the protocol were excluded from this analysis but were described in the final report.

## ii) Intention to treat:

- All 30 randomized participants were included in the analysis.
- **For safety endpoints**, all randomized subjects were included.
- **For immunological endpoints**, intention to treat and per protocol analysis were done.

## ATP and ITT populations

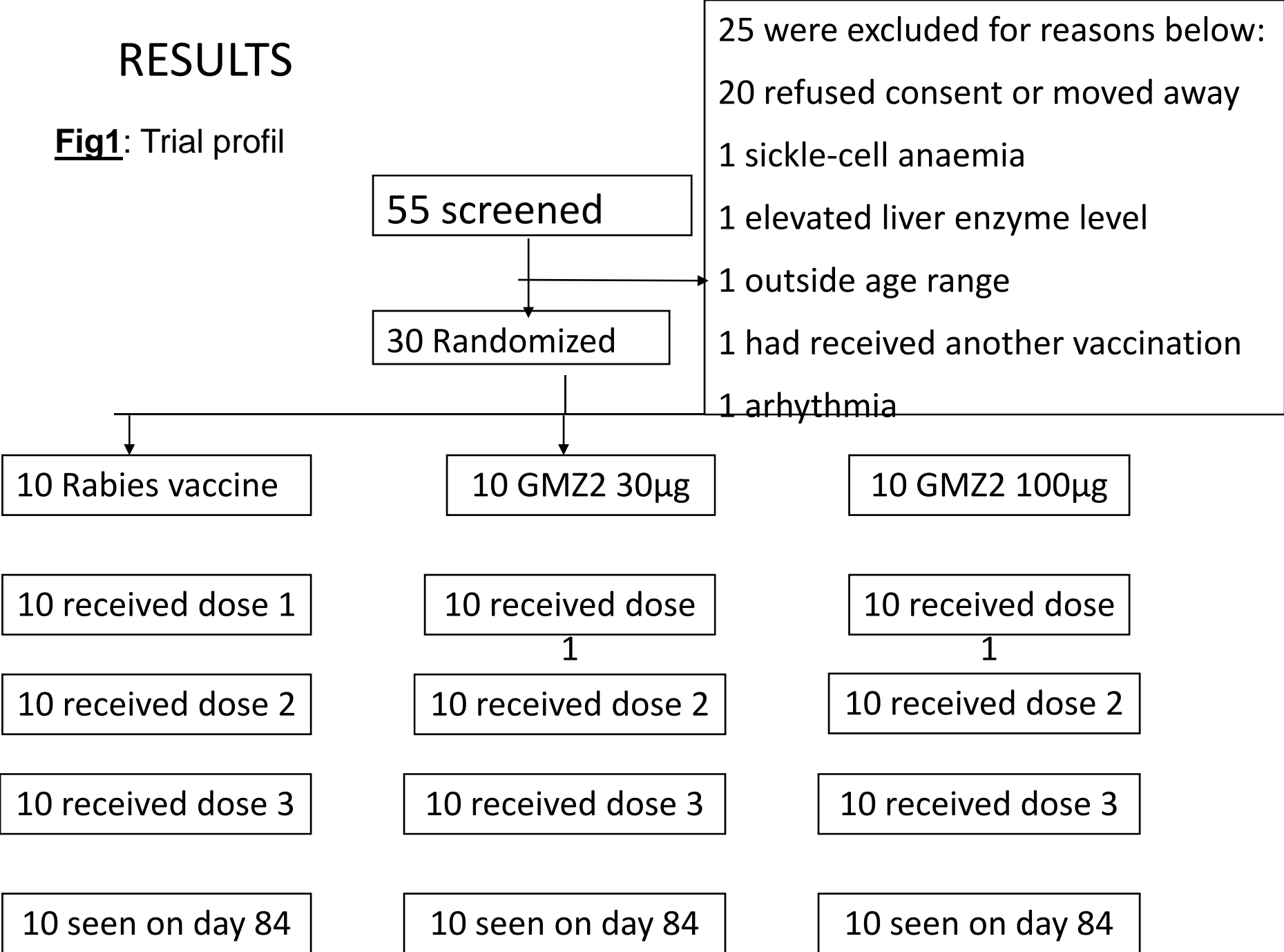
- The ATP population includes 29 subjects who received three doses of vaccine, and did not receive forbidden medication or vaccination.

One boy aged 2 years in the GMZ2 30 µg group, excluded from ATP after receiving tetanus vaccine 21 days after received the third dose of GMZ2.

- The ITT population includes all randomized subjects.

# RESULTS

**Fig1:** Trial profil



# Mean age and mean BMI of the participants

## Mean age of the participants:

No statistically difference in the three groups

- Rabies vaccine group: 41.4 (22.3 - 57.2) months
- GMZ2 30 µg group: 42.0 (25.9 - 67.1) months
- GMZ2 100 µg group: 41.3 (21.4 - 67.9) months

## Mean BMI of the participants:

- Rabies vaccine group: 14.6 (11.4 - 18.6)
- GMZ2 30 µg group: 13.7 (11.0,20.8)
- GMZ2 100 µg group: 13.3 (9.6,17.0)

Adverse events D0 to D28:

Solicited / Unsolicited

Grade: mild / moderate / severe

Duration

Frequency

Outcome

Relationship to vaccine

## **Solicited Local reactions 30 minutes to 14 days after vaccine dose**

- Pain on touch/painful when limb is moved, swelling, induration, erythema, pruritus were the most common local reactions at the injection sites.
- Induration was the most important (50.5 % of local reactions) and was mostly met in GMZ2 vaccine groups (71.4 % of induration).
- All these reactions were of mild intensity, short duration and well tolerated by the participants in the three vaccine groups
- All these reactions disappeared after 3 days.

# Solicited systemic reactions 30 minutes to 14 days after dose

- The most important solicited systemic reactions were:
  - \* lost of appetite (37.5%)  
mainly in both GMZ2 vaccine groups (30 µg and 100 µg).
  - \* and fever (25%)
- mild intensity and tolerated by the participants.
- No serious adverse events

However There were 4 Grade 3 events:

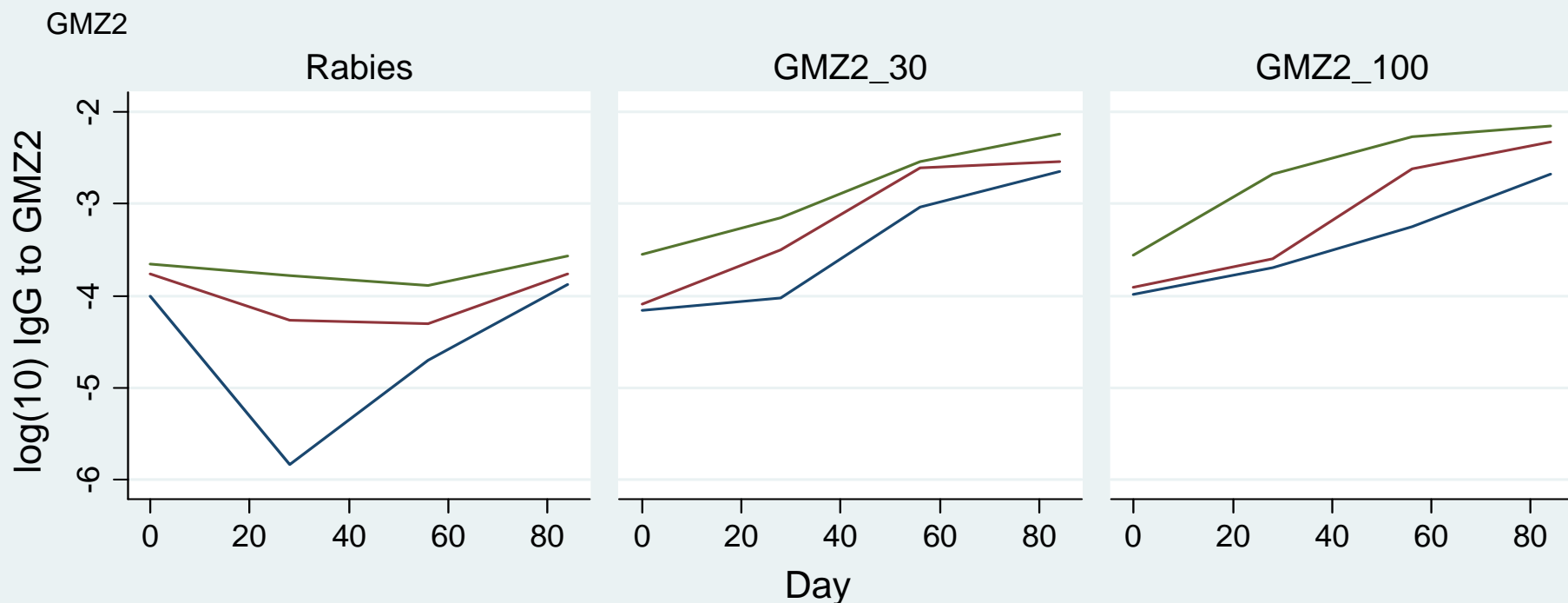
- Fever intensity grade 3 after the second dose of GMZ2 30 $\mu$ g (1 and 2 days after dose 2).
- Fever intensity grade 3, 4 and 5 days after dose 2 of rabies vaccine.
- Loss of appetite grade 3, 4 days after dose 2 of GMZ2 30 $\mu$ g.
- Fever intensity grade 3, 7 days after dose 2 of GMZ2 100 $\mu$ g vaccine.

All these adverse events were considered not related to vaccination.

- As unsolicited adverse events only One malaria case was diagnosed in rabies vaccine group

For all abnormal biological values the child was well and not investigated further

# Geometric mean concentration to GMZ2, GLURP and MSP3 in each vaccine group plotted against time



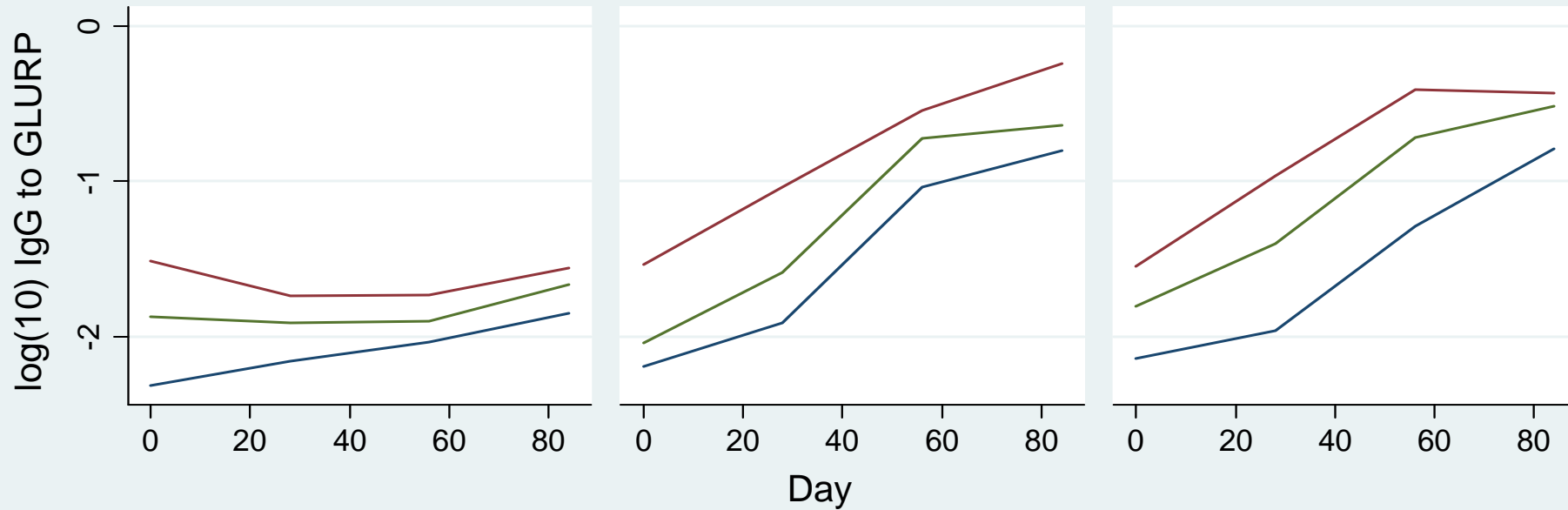
The graph showing the log(10) IgG to GMZ2 shows that IgG to GMZ2 concentration increases over time for GMZ2 30 $\mu$ g and GMZ2 100 $\mu$ g conversely to the rabies vaccine control.

GLURP

Rabies

GMZ2\_30

GMZ2\_100

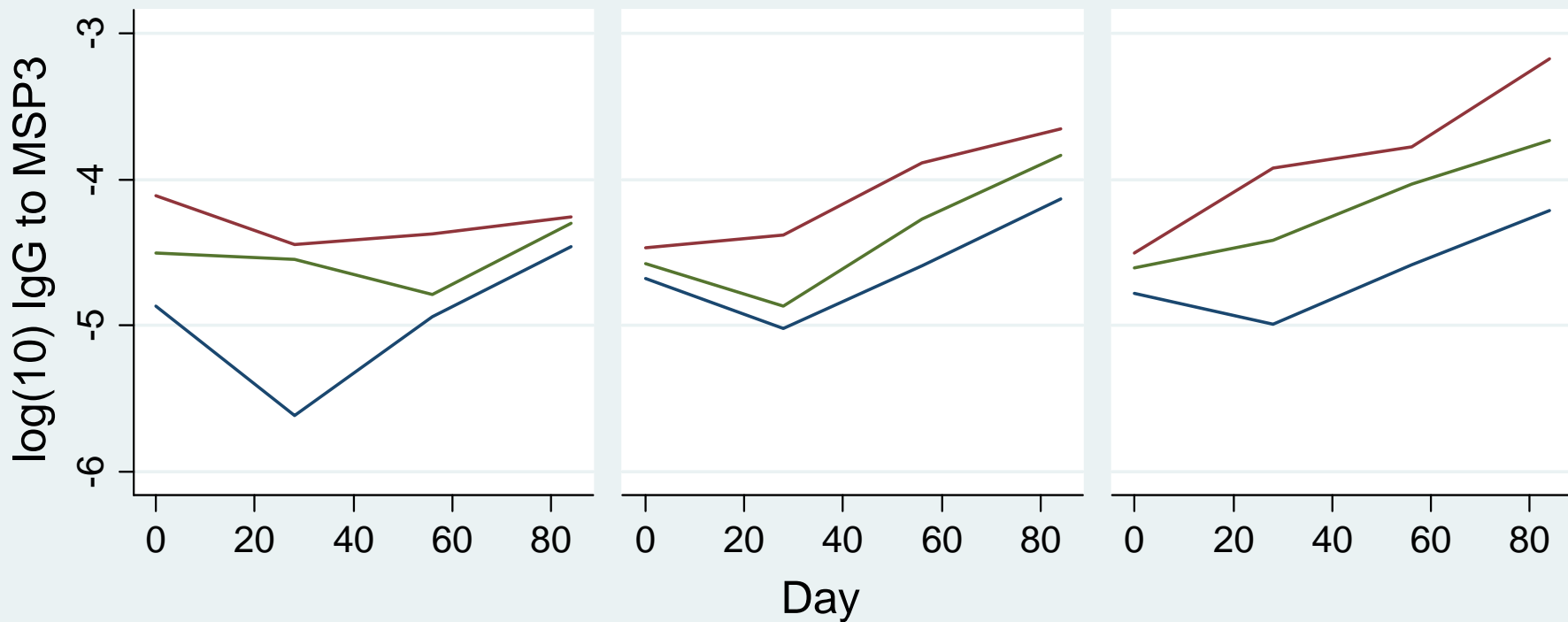


MSP3

Rabies

GMZ2\_30

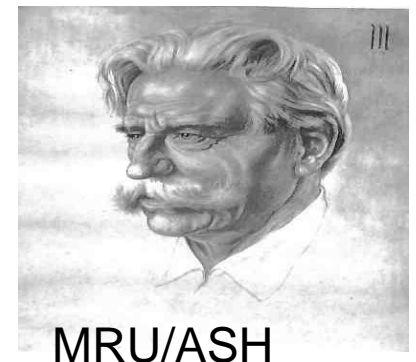
GMZ2\_100



# Conclusion

- The clinical and biological results suggest that three doses of 30 and 100 µg GMZ2, adsorbed on aluminum hydroxide administered on days 0, 28 and 56 are well tolerated by children exposed to *P. falciparum* infections in this perennial malaria transmission area of Central Africa.
- GMZ2 vaccine induces an increase of IgG to GMZ2, GLURP and MSP3. The effect being pronounced for GMZ2 and GLURP
- There is a good correlation between GLURP/GMZ2 for each vaccine group and at day 84.
- A clear difference between the two GMZ2 vaccine regimens and the rabies vaccine control regardless of ITT or ATP analysis.

# MANY THANKS



MRU/ASH