An Antigen and Adjuvant System Dose Ranging Safety and Immunogenicity Study of the M72 Candidate Tuberculosis Vaccines in Healthy Filipino Adults

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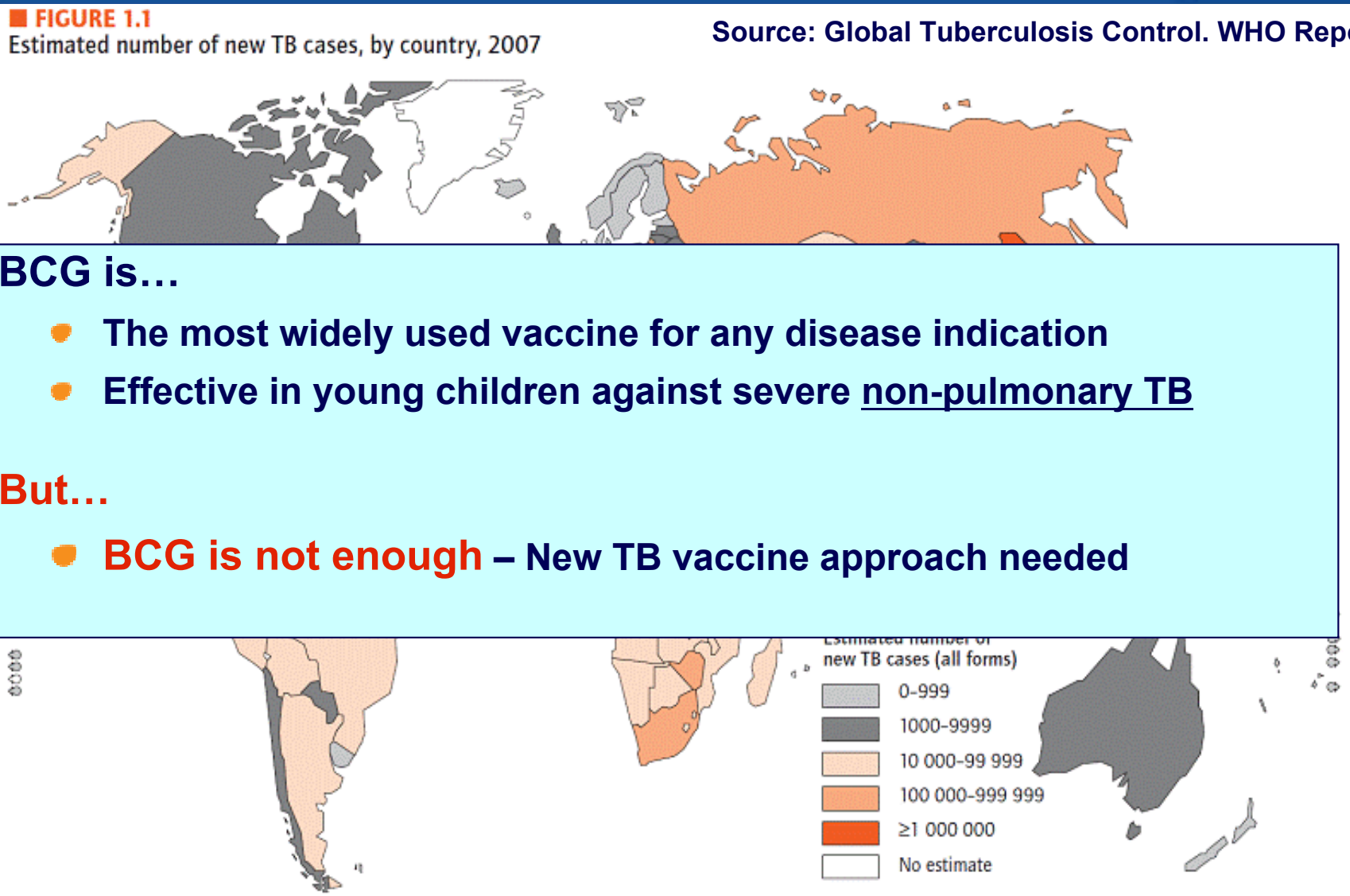
TUBERCULOSIS BURDEN



Source: Global Tuberculosis Control. WHO Report 2009.

BCG is…

- The most widely used vaccine for any disease indication
- Effective in young children against severe <u>non-pulmonary TB</u>

But…

- **BCG is not enough** – New TB vaccine approach needed

- 9.2 million new cases of clinical TB/year
- 3.2 million new TB cases/year in South-East Asia- second most affected region in the world

- In the Philippines (TB endemic region)
  - Incidence rate: 255,000/year
  - Prevalence rate: 500/100,000 population

OBJECTIVES OF GSK TB VACCINE DEVELOPMENT

- Prevention of primary tuberculosis in children, adolescents and adults
- Protection against disease induced by reactivation of latent infection
- Boosting pre-existing immune response induced by BCG and/or Mtb

GSK's TB VACCINE

Scientific rationale behind the development of the TB vaccine:

- Although no immuno-correlate of protection identified, T cells expressing "Th1" cytokines (IFNγ/TNFα) are associated with protection.

GSK's TB Vaccine is made up of:

- **The M72 ANTIGEN** which is a fusion of 2 proteins, Mtb32A and Mtb39A that:
  - Are specifically expressed in BCG and Mtb
  - Contain human CD4+ and CD8+ T cell epitopes
  - Induce proliferation and production of IFNγ by T cells from PBMCs in TB infected donors

- **GSK proprietary Adjuvant Systems (AS)**
  - Which induce type I cell-mediated immune response
  - Contain MPL and QS21 either in Oil-in-water-based emulsion (AS02) or liposome formulation (AS01)
  - Different formulations are available:

    $AS01_B$ and $AS02_A$ – 50 μg each of MPL, QS21

    $AS01_E$ and $AS02_D$ – 25 μg each of MPL, QS21

BACKGROUND AND AIM OF THE STUDY

BACKGROUND:

- **In a previous study in PPD-negative adults[1]:**
  - 40 μg doses of M72/AS01$_B$ and M72/AS02$_A$ were well tolerated and highly immunogenic
  - There was a trend towards stronger Th1 responses with M72 when adjuvanted with AS01 as compared to AS02
    - Higher level of antigen-specific CD4+ T cells expressing CD40L and/or IL-2 and/or TNF-α and/or IFN-γ

*I. Leroux-Roels *et al.* TB Vaccines for the World, Atlanta (2008)

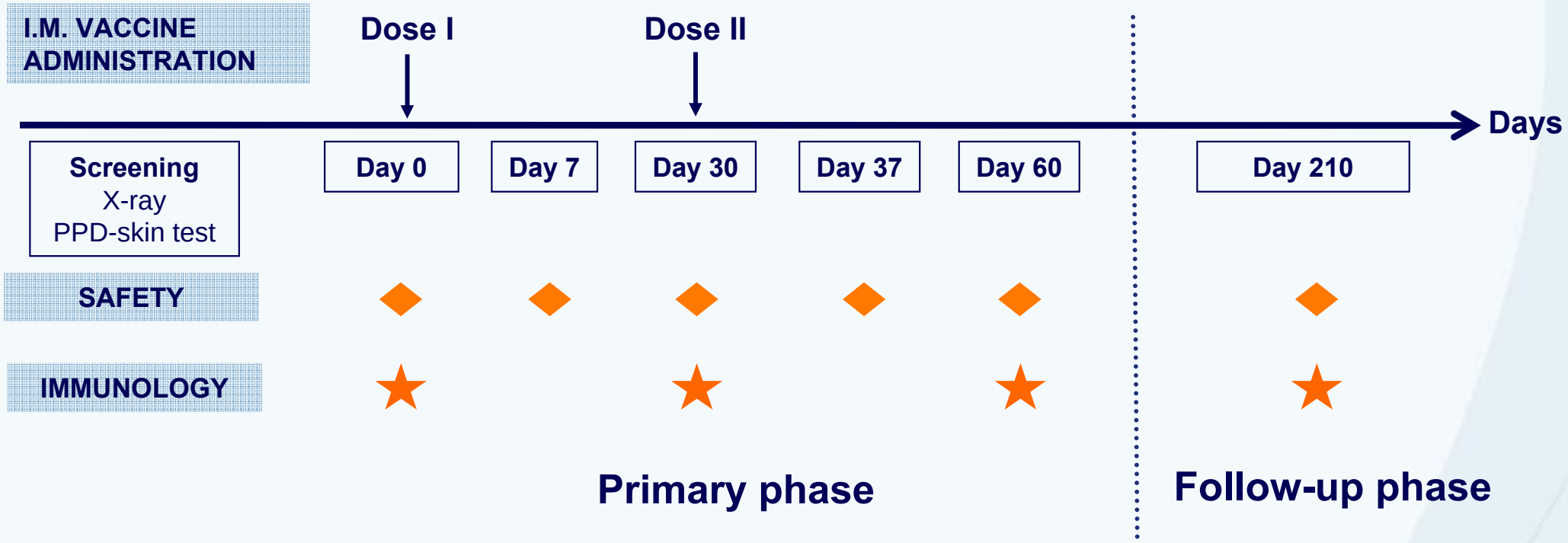
AIM:

- **To evaluate the safety and immunogenicity of a dose range of the M72 antigen in several Adjuvant Systems:**
  - M72(40 μg)/AS01$_B$
  - M72(20 μg)/AS01$_E$
  - M72(10 μg)/AS01$_E$
  - M72(10 μg)/AS02$_D$
- **To select one vaccine for further development**

METHODS

- **Study design:** observer-blind, randomized, controlled phase I/II study
- **Study population**: 180 HIV-negative adults (M/F); aged 18-45 years, weakly PPD reactive (3 mm ≥PPD induration ≤10 mm)
- **Study groups:**

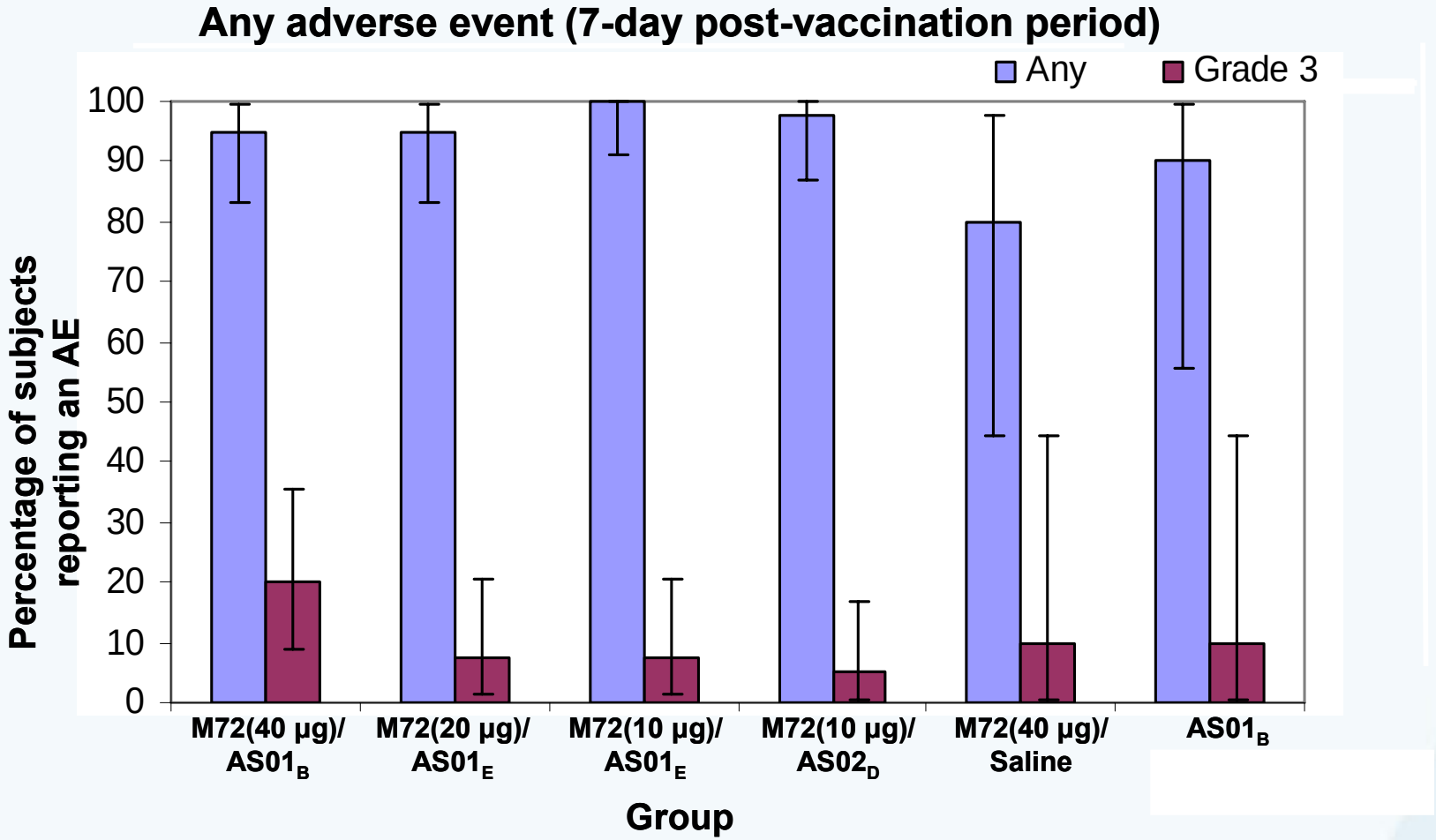
M72 (40 µg)/AS01$_B$ (N= 40)	M72 (10 µg)/AS02$_D$ (N = 40)
M72 (20 µg)/AS01$_E$ (N = 40)	M72 (40 µg)/Saline (N = 10)
M72 (10 µg)/AS01$_E$ (N = 40)	AS01$_B$ (N = 10)



REACTOGENICITY

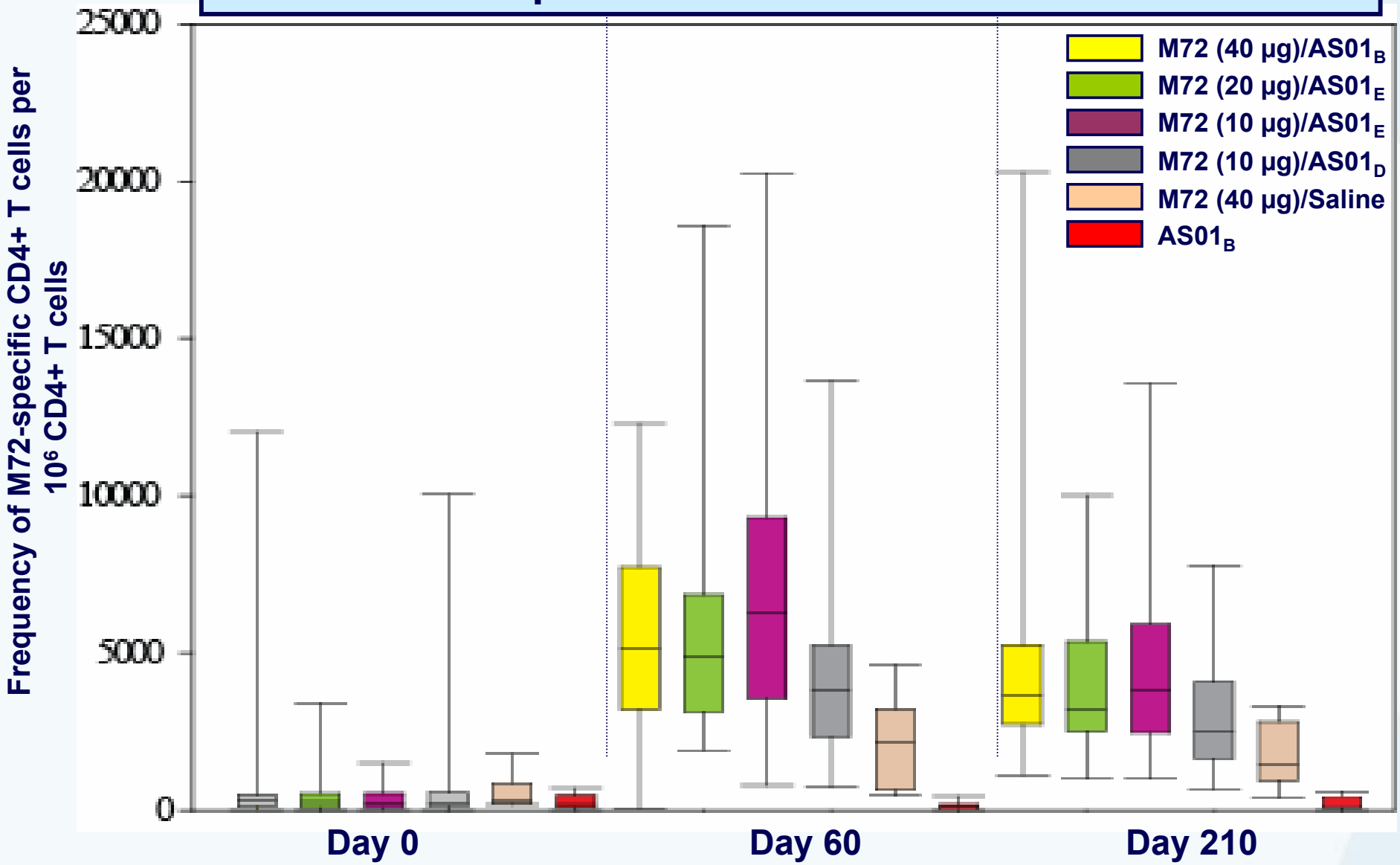
Vaccines were generally well tolerated

- No vaccine related SAEs.
- AEs were reported comparably in all vaccine and control groups.
- Transient, mild to moderate AEs reported.
- Grade 3 AEs were infrequent and resolved or reduced in intensity in 1–2 days.



IMMUNOGENICITY – CMI

Robust and persistent vaccine induced M72-specific CD4+ T cell responses in all candidate vaccines



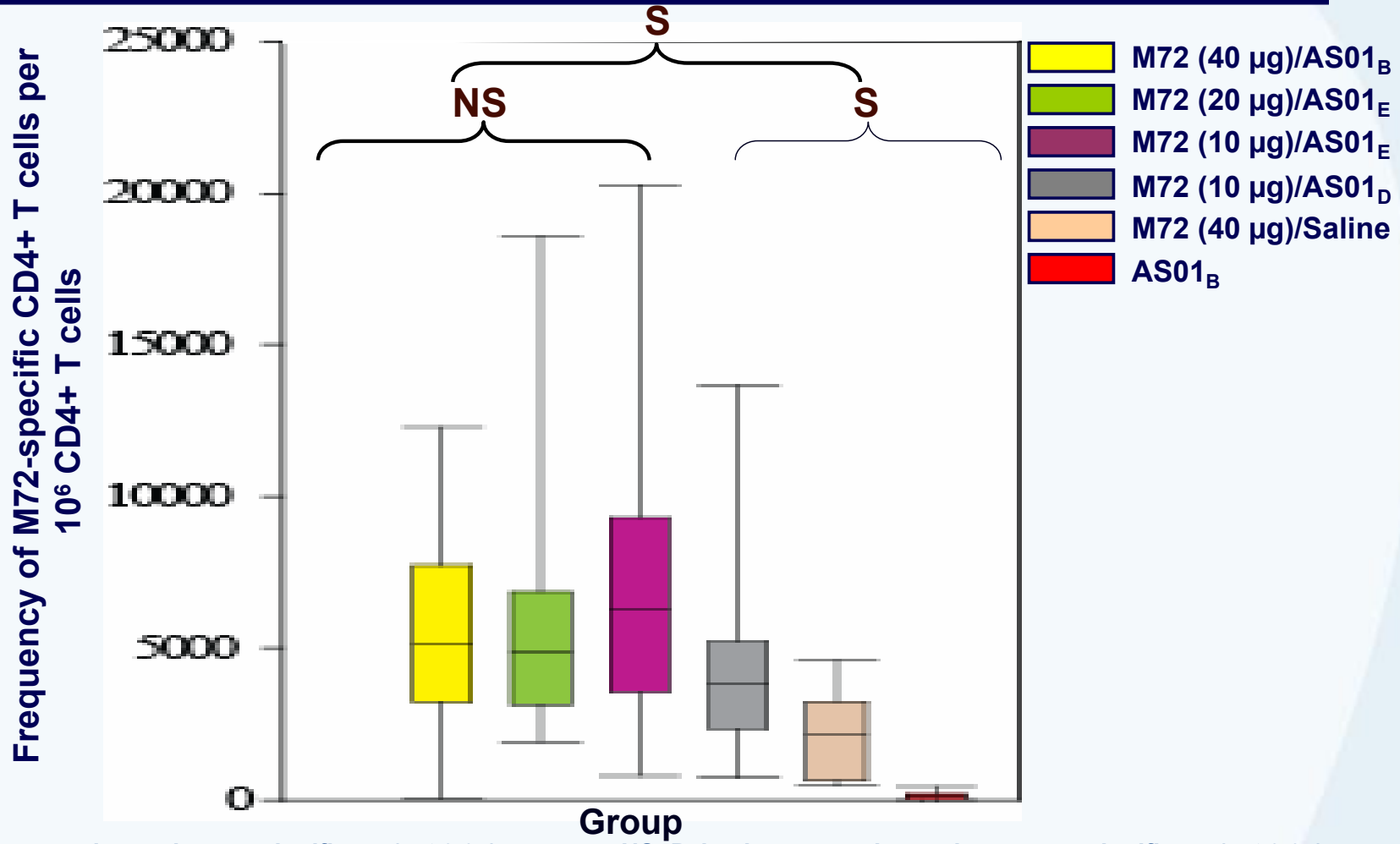
Frequency of M72-specific CD4+ T-cells expressing at least two markers among CD40-L, IL-2, IFN-γ and TNF-α (ICS)

Pair-wise comparisons of CMI at Day 60

Comparable responses with M72 (40 µg)/AS01$_B$, M72 (20 µg)/AS01$_E$ & M72 (10 µg)/AS01$_E$ which were superior to the other groups.

Responses with M72 (10 µg)/AS02$_D$ were superior to the control groups.

Same trend observed at 6 months post-vaccination.



S: Pair wise comparisons that are significant ($p \leq 0.05$)

NS: Pair wise comparisons that are not significant ($p \leq 0.05$)

Frequency of M72-specific CD4+ T-cells expressing at least two markers among CD40-L, IL-2, IFN-γ and TNF-α (ICS) at Day 60

CONCLUSIONS

In these PPD-reactive individuals:

- All vaccines tested were well tolerated with comparable reactogenicity as compared to the controls.
- A robust and sustainable antigen-specific CD4+ T cell responses were observed post vaccination with the different antigen and Adjuvant System combinations.
- No CD8+ T cell responses were observed at the time points evaluated (data not shown).
- A vigorous and persistent humoral immune response was observed (data not shown).
- The lowest concentration of antigen (10 μg of M72) and Adjuvant System ($AS01_E$) will be developed further.

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