Anthrax Vaccine Dose Reduction & Route Change Study

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Centers for Disease Control and Prevention
Anthrax Vaccine Research Program

AVRP Clinical Trial

- Optimize use, assess altered route of administration, evaluate surrogate markers of protection, evaluate immunologic memory
- Randomized, double-blind, placebo controlled Phase IV
- Data Safety Monitoring Board
  - Dr. Stanley Plotkin, chair
- Inclusion
  - Healthy adult; 18-61 years old
- Exclusions - Specific allergies, immunosuppression, pregnancy
- Enrollment
  - 1564 civilian adults, 51% female
  - 25 office visits
    - 8 injections
    - 17 blood draws, 22 in-clinic exams, 8 patient diaries

- Marano N, Plikaytis BD, Martin SW, et al. Effects of a reduced dose schedule and intramuscular administration of anthrax vaccine adsorbed on immunogenicity and safety at 7 months. JAMA. 2008;300(13):1532-1543.

Schedule of Injections

Study Group	Label	Week 0	Week 2	Week 4	Month 6	Month 12	Month 18	Month 30	Month 42
8SQ	**4SQ**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**
8IM	**4IM**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**
7IM	**COM**	**AVA**	**S**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**	**AVA**
5IM		**AVA**	**S**	**AVA**	**AVA**	**S**	**AVA**	**S**	**AVA**
4IM		**AVA**	**S**	**AVA**	**AVA**	**S**	**S**	**S**	**AVA**
IM Placebo	**CNT**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**
SQ Placebo	**CNT**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**

Interim Analysis

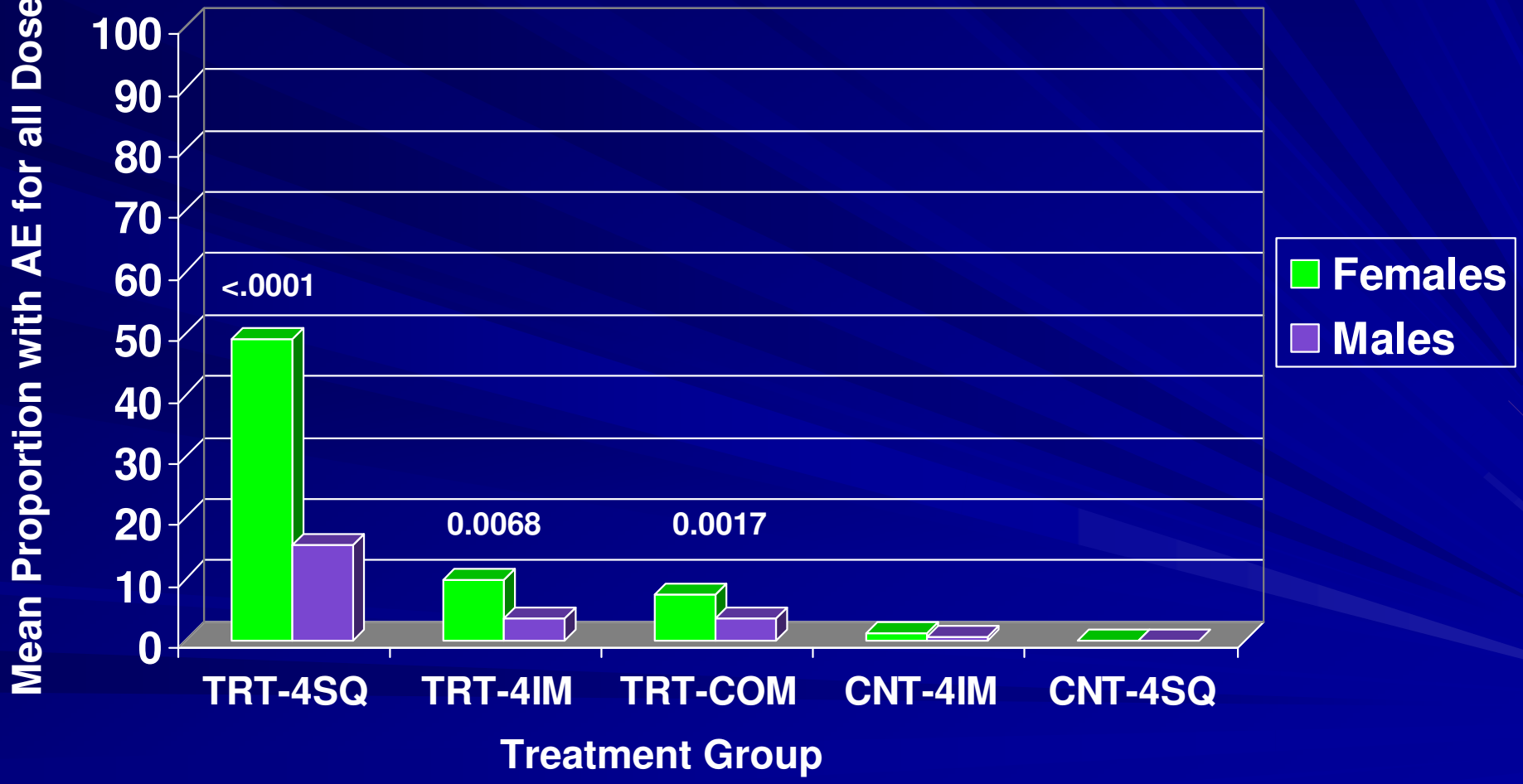
Reactogenicity AEs

- Injection Site AEs
  - Dichotomous endpoints
    - warmth, tenderness, itching, pain, arm motion limitation, erythema, induration, edema, nodule, and bruise
  - Ordinal endpoint
    - Pain upon injection (assessed immediately following each injection)
- Systemic AEs
  - Dichotomous endpoints
    - fatigue, muscle ache, headache, fever, and tender/painful axillary adenopathy
- AEs were assessed during clinic exams and self-reported using AE diaries and phone follow-up
  - Clinic Exams
    - Pre-vaccination
    - 15 to 60 min after each dose
    - 1 to 3 days after each dose
    - 28 days (+/-7 days) after doses 3 and 4

Injection Site AEs

Warmth

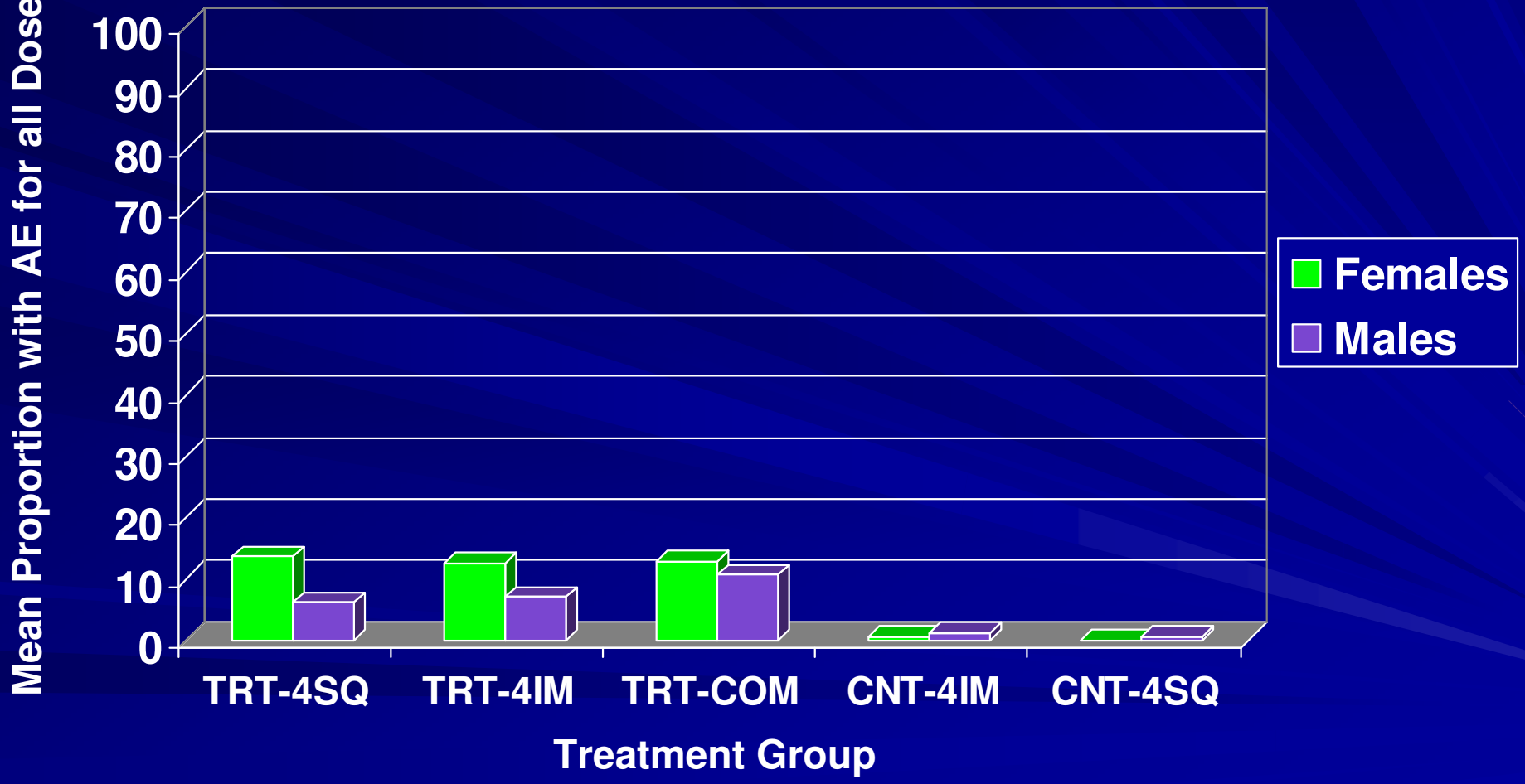
Sig. diff. between TRT-4IM vs TRT-4SQ (p=<.0001) and F vs M (p=<.0001)
Gender by treatment Interaction is sig.



Note: control groups were dropped from the model due to low cell counts

Arm Motion Limitation

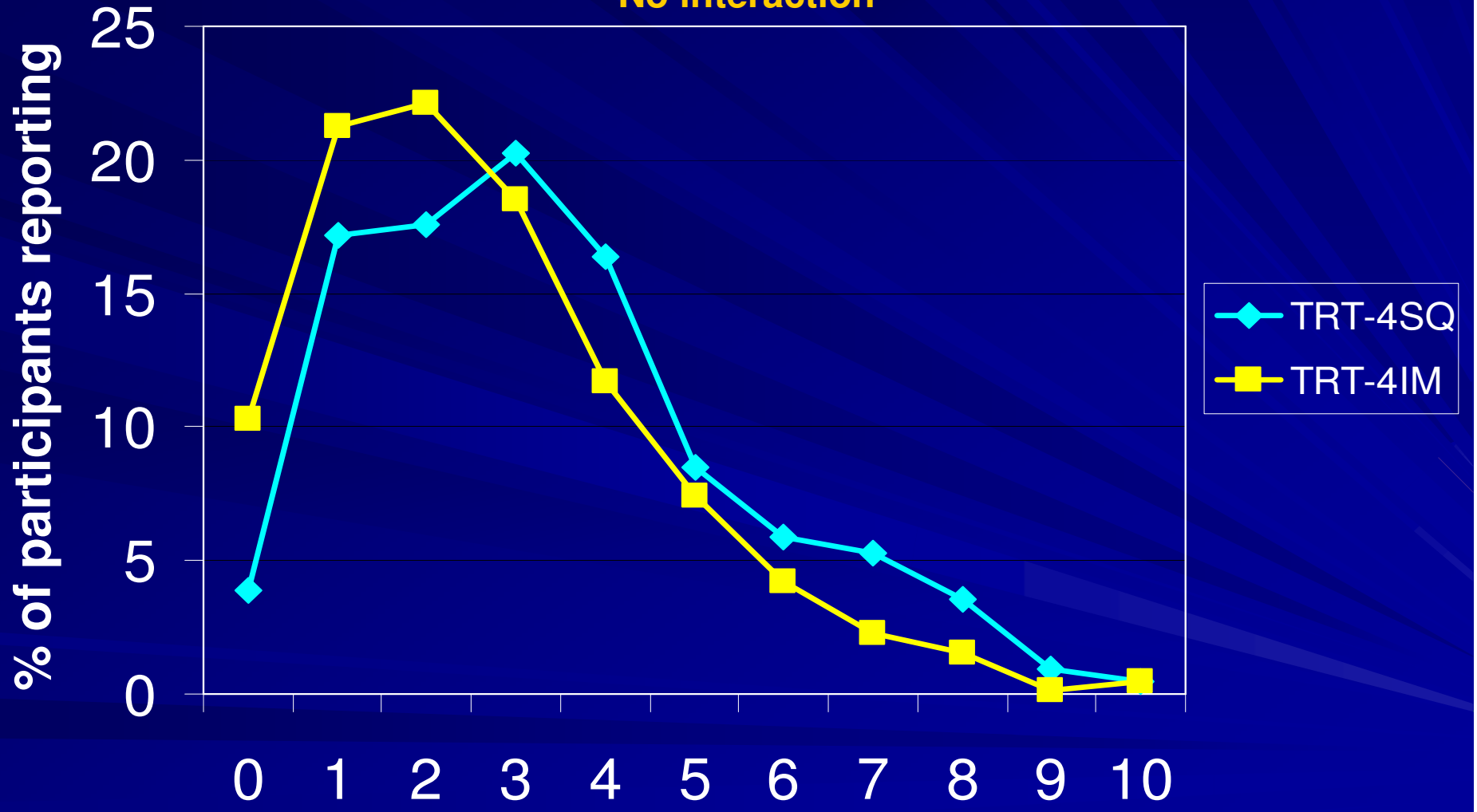
No sig. diff. between TRT-4IM vs TRT-4SQ (p=0.9481)
Sig. diff. between F vs M (p=0.0469)
No interaction



Note: control groups were dropped from the model due to low cell counts

Pain Upon Injection

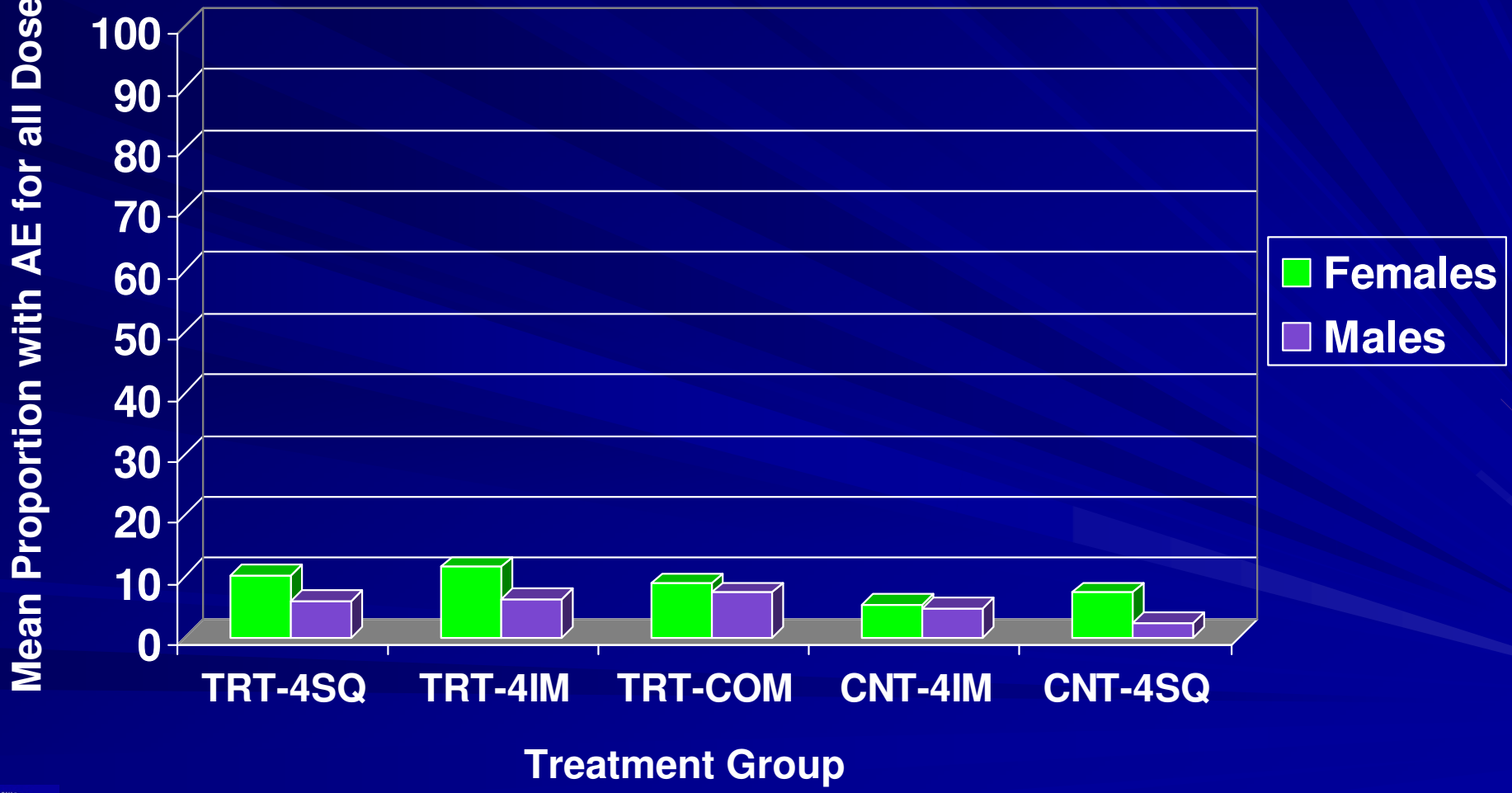
Sig. diff. between TRT-4IM vs TRT-4SQ (p=<.0001) and F vs M (p=<.0001)
No interaction



Systemic AEs

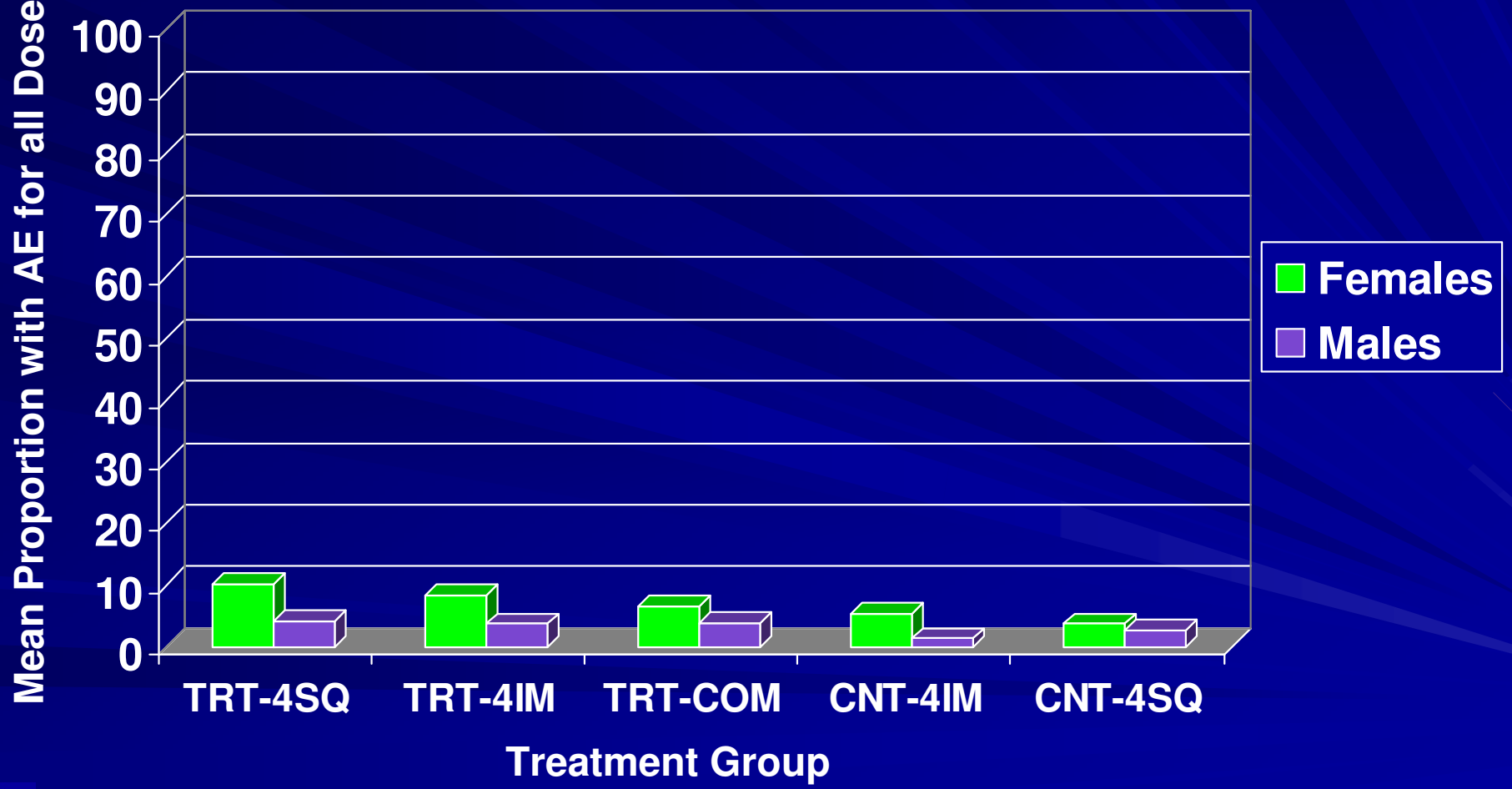
Fatigue

No sig. diff. between TRT-4IM vs TRT-4SQ (p=0.7159)
Sig. diff. between F vs M (p=0.0391)
No interactions



Headache

No sig. diff. between TRT-4IM vs TRT-4SQ (p=0.3631)
Sig. diff. between F vs M (p=0.0001)
No interactions



Serious Adverse Events (SAEs)

- Standard reporting
- Blinded assessments by independent Medical Monitor
- Interim analysis
  - 51 reports of SAEs in 47 participants
  - None were assessed as causally related to study agent
- Since study start:
  - 231 reports of SAEs in 187 participants
  - 9 events in 7 persons assessed as “possibly” related to the investigational agent

"Possibly" Related SAEs*

- Tear of shoulder supraspinatus tendon
- Generalized reaction night of 6th vaccine
- Bilateral pseudo tumor cerebri with bilateral disc edema
- New onset of generalized seizures, hydrocephalus consistent with aqueductal stenosis
- New onset bilateral arthralgia
- 2 events of invasive breast cancer**
- November 2006 secondary review of VAERs and DoD data found no obvious trend for AVRP "possibly" related SAEs among persons receiving AVA

*blinded analysis

**occurred after November 2006, not included in VAERS review

Reactogenicity Summary

- TRT-4IM group experienced
  - Local AEs at lower frequencies, lower severity and for shorter durations
- Route of administration did not significantly influence the occurrence or duration of systemic AEs
- Women reported significantly more AEs than men
  - Differences between men and women for systemic events were statistically similar across treatment groups
    - Even among the control groups
- Related AEs
    - 9 Serious Adverse Events – "possibly"

AVRP Interim Analysis: Reactogenicity Conclusions

- IM administration is associated with significantly fewer and less severe injection site AEs
- No serious AEs reported during the first 7 months were assessed as causally related to AVA

Immunogenicity Analyses

Conrad P. Quinn, Ph.D.
Chief, Microbial Pathogenesis and Immune Response Laboratory

Immunogenicity

- **Serological data**
  - Non-inferiority of anti-protective antigen IgG (anti-PA) antibody responses at week 8 and month 7
- **Month 7 is the critical evaluation point**
  - Completion of study priming series
- **Primary endpoints**
  - Anti-PA IgG geometric mean concentration (GMC)
  - Geometric mean titer (GMT)
  - Proportion with a 4-fold rise in titer
- **Non-inferiority criteria**
  - Upper bound of the 95% confidence intervals for the ratio of the 4-SQ group to the test groups' GMC and GMT were <1.5
  - Analogous upper bound for the differences in proportions of four-fold response was <0.10

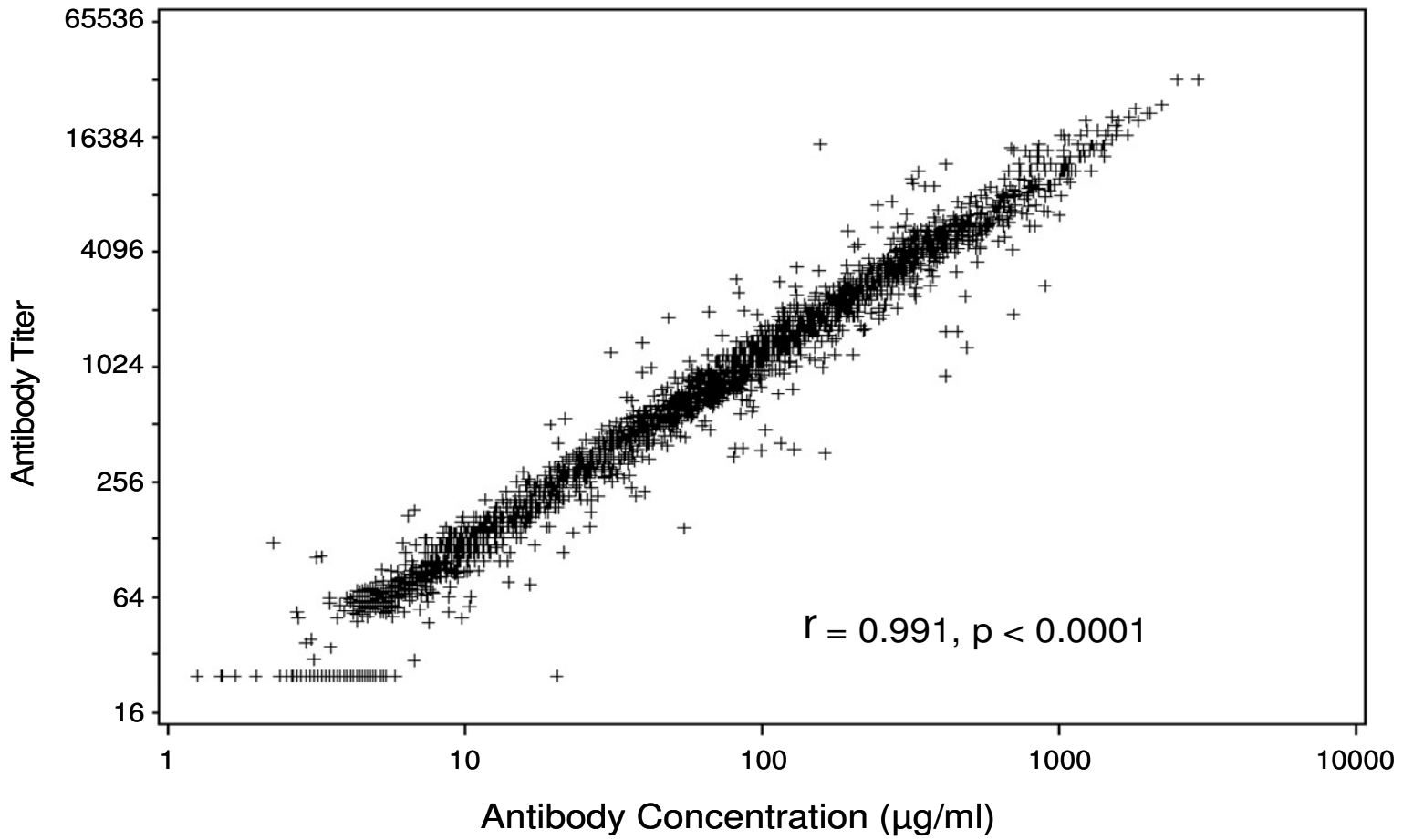
Geometric Mean

- A measure of central tendency
- Widely used in statistical analyses
- Particular application in immunology
  - Positively skewed distributions
  - Long ‘tails’ of larger values
  - Only applicable tool for log-normally distributed dilutional titers
  - Provides unbiased estimates

Anti-PA IgG

- 'Protective Antigen' serological responses evaluated since 1945
- PA pivotal to *Bacillus anthracis* infection
- PA central to anthrax
- Vaccines that protect against anthrax contain all or part of PA

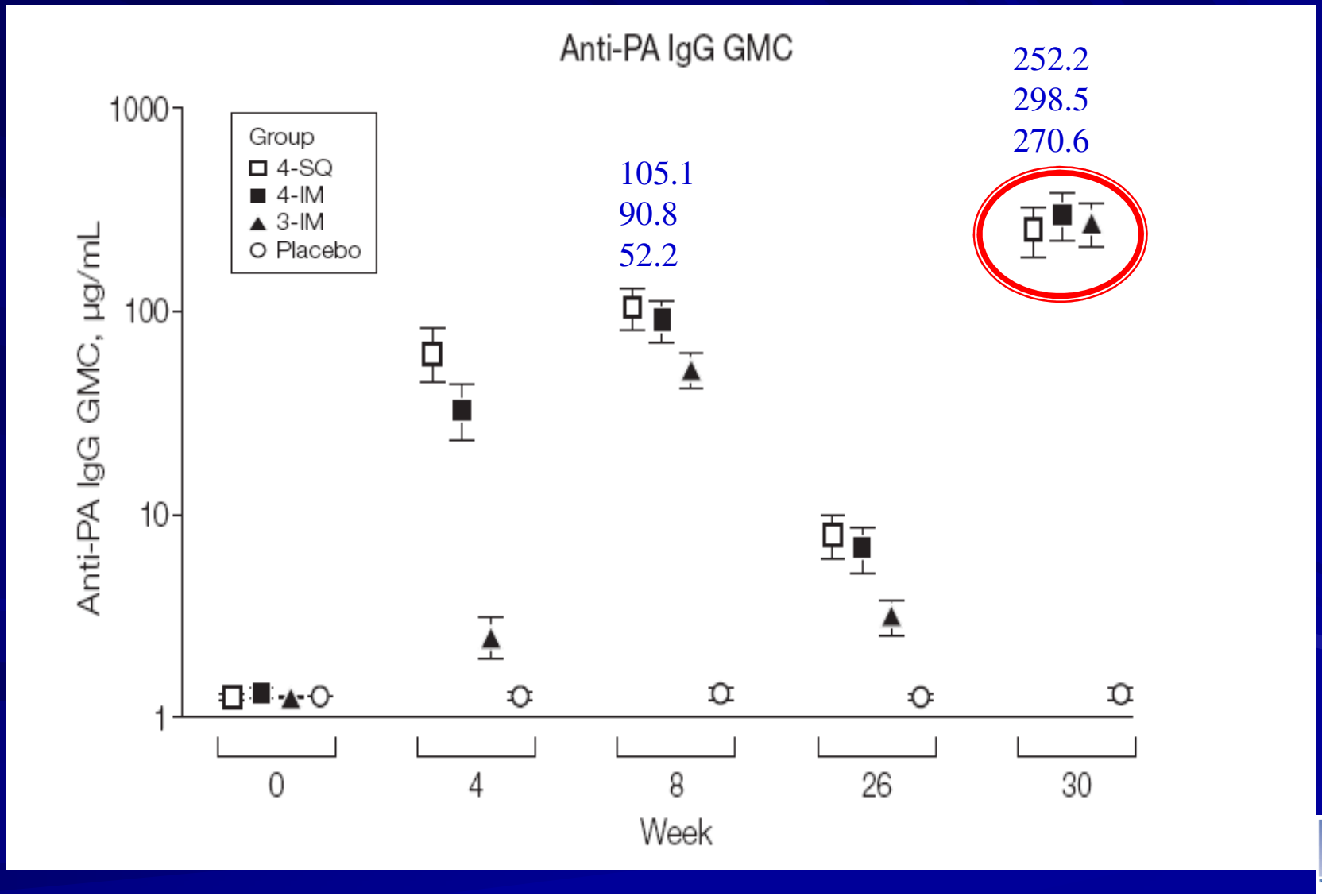
Anti-PA Titer and IgG Concentration Are Highly Correlated



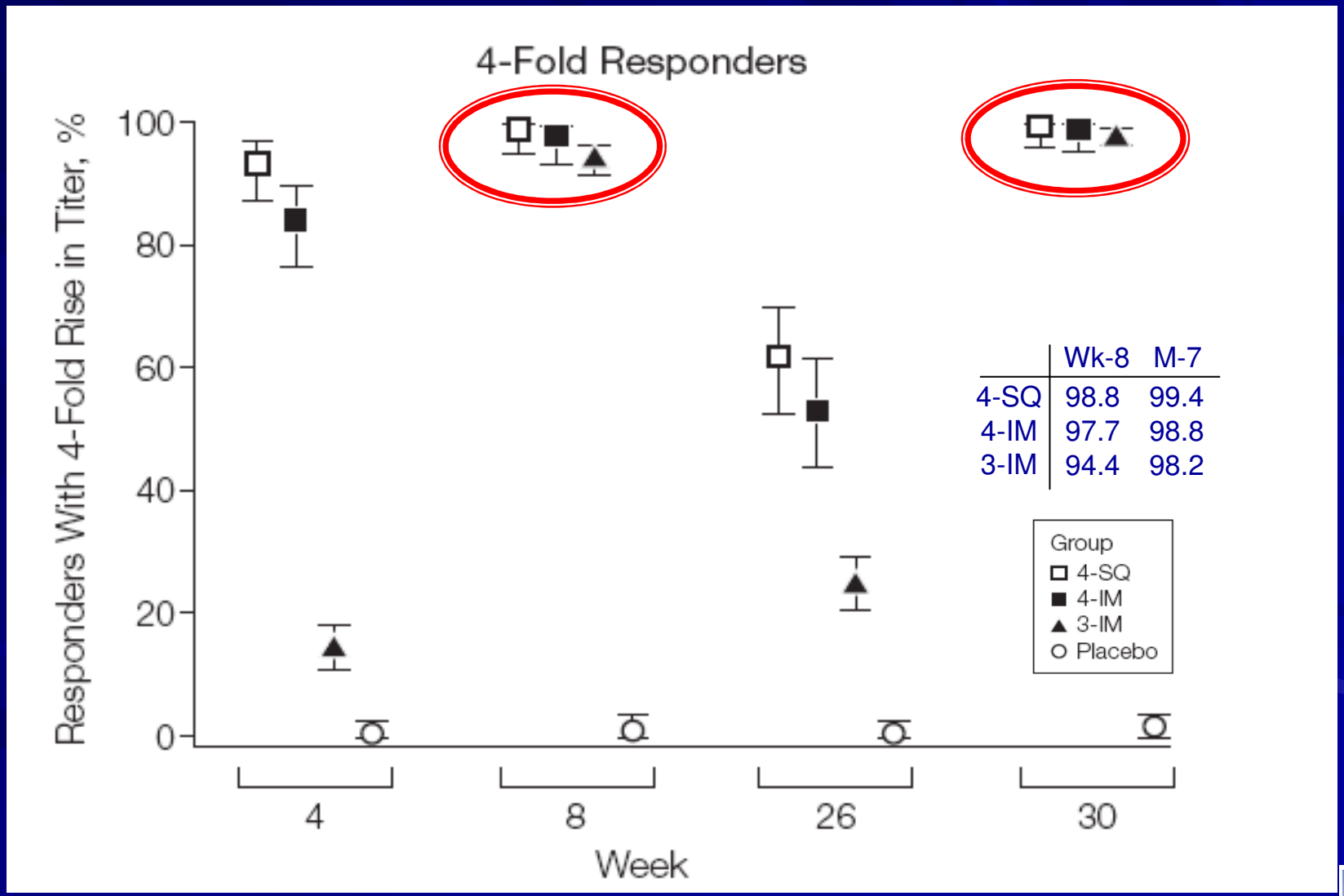
Immunogenicity Results

- At month 7
  - All groups non-inferior to the licensed regimen for all endpoints
- At week 8
  - 4-IM group was non-inferior to the 4-SQ regimen for all three primary endpoints
  - 3-IM group was non-inferior for proportion of participants with 4-fold rise in titer
- LTx Neutralization Efficacy & Median IgG Are Highly Correlated

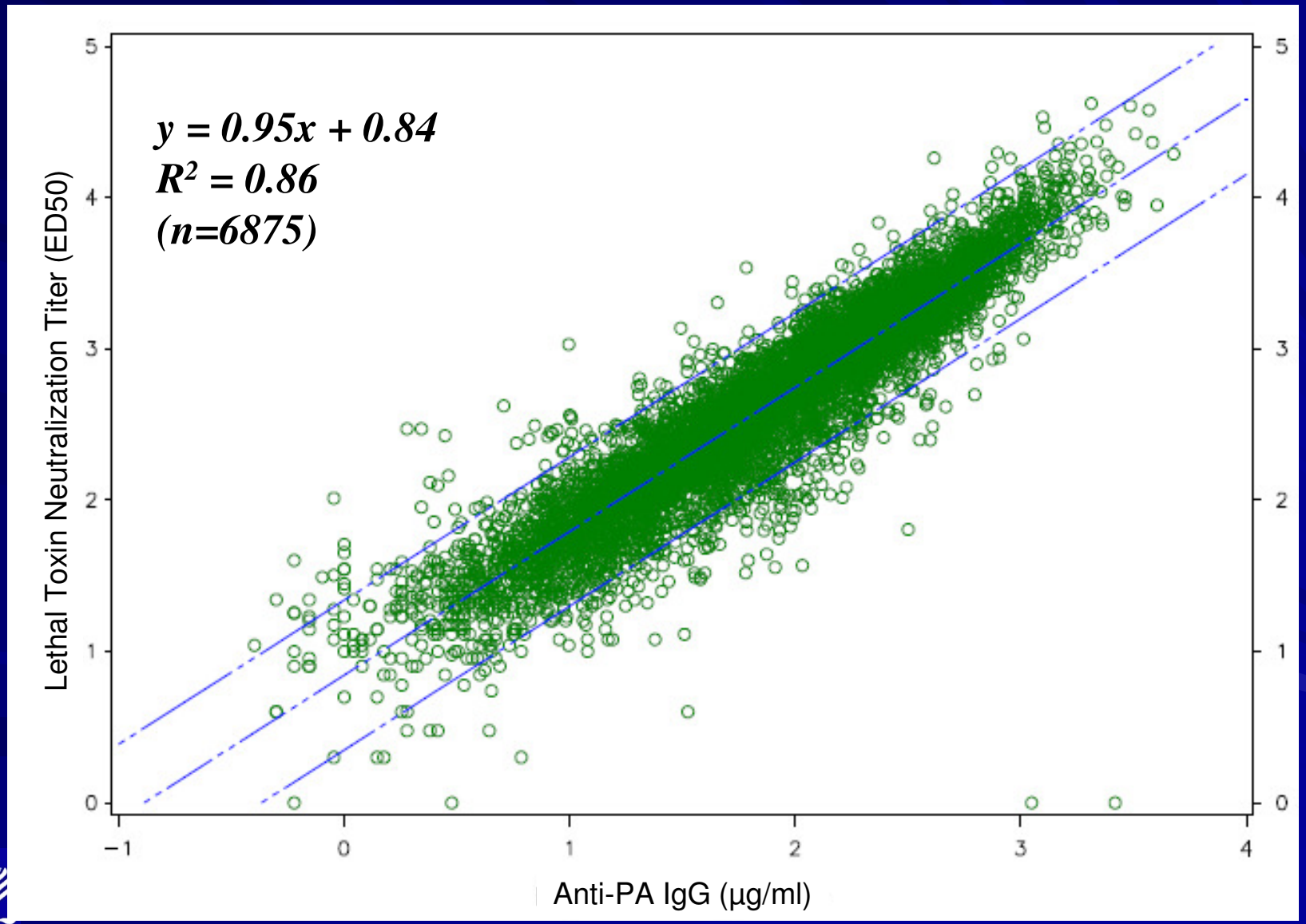
Anti-PA IgG GMC is Non-inferior At Month 7



Proportion of 4-Fold Responders is Non-inferior At Week 8 & Month 7



LTx Neutralization Efficacy & Median IgG Are Highly Correlated



AVRP Month 7 Analysis: Serologic Conclusions

- **Month 7 GMC**
  - Primary decision time point
  - High levels anti-PA IgG in all groups
    - <0.5% non-responders; GMC >200µg/ml anti-PA IgG; >98% 4-fold responders; ≥95% @ ≥50µg/ml anti-PA IgG
  - Non-inferiority achieved; all primary endpoints
  - 4-SQ, 4-IM and 3-IM regimens provide equivalent immunological priming

- **Week 8 GMC**
  - High levels anti-PA IgG in all groups
    - <0.5% non-responders; GMC >50-100µg/ml anti-PA IgG; ≥95% 4-fold responders; >60-82% @ ≥50µg/ml anti-PA IgG
  - Non-inferiority achieved; proportion of 4-fold responders
  - Significantly higher in females in 4-IM and 3-IM groups but not in the 4-SQ group (p=0.12)
  - General decrease in antibody response with increase in age
  - These differences not evident at Month 7

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