

**A Phase I-II, Randomized, Controlled, Dose-
Ranging Study of the Safety, Reactogenicity, and
Immunogenicity of Intramuscular Inactivated
Influenza A/H5N1 Vaccine Given Alone or with
Aluminum Hydroxide to Healthy Adults
DMID 05-0127**

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Study Design

- Multicenter, Randomized, Double-blind
- Population: Healthy Adults; 18-49 years old
- Vaccine: Inactivated SV Influenza A/H5N1 (3.75, 7.5, 15 or 45 μ g/dose); each dosage level +/- 600 μ g/dose aluminum hydroxide (AIOH) adjuvant (sanofi pasteur)

Dosage Level (μ g of HA)	Volume	Number per group (+/- adjuvant)
3.75	0.25	60
7.5	0.5	60
15	0.5	60
45	0.5	120

Study Design

- **Procedures: 2 IM doses of vaccine given 1 month apart**
 - **Reactogenicity: Memory Aid during the week after each dose; in-clinic visits days 2, 8 & 28; SAE follow-up for 7 months**
 - **Immunogenicity: Sera for HAI and Neutralizing (Neut) antibody assays collected before and 1 month after each dose and 6 months after the second dose**

SAMPLE SIZE CALCULATION

- The study has $>80\%$ power for testing the primary immunogenicity hypotheses in the $45\mu\text{g}$ group if the response rate is 0.4 or greater in the no adjuvant group, and the absolute response rate in the adjuvant group is at least 50% greater (ratio ≥ 1.5).

RESULTS

- 600 subjects were enrolled
- 574 received 2 doses of vaccine
- 570 subjects had sera available for assay after receipt of 2 doses
- Study Status: 6 month visits completed late 2006. Safety and immunogenicity results available up to the day 28 visit after dose 2 for most subjects. Study remains blinded.

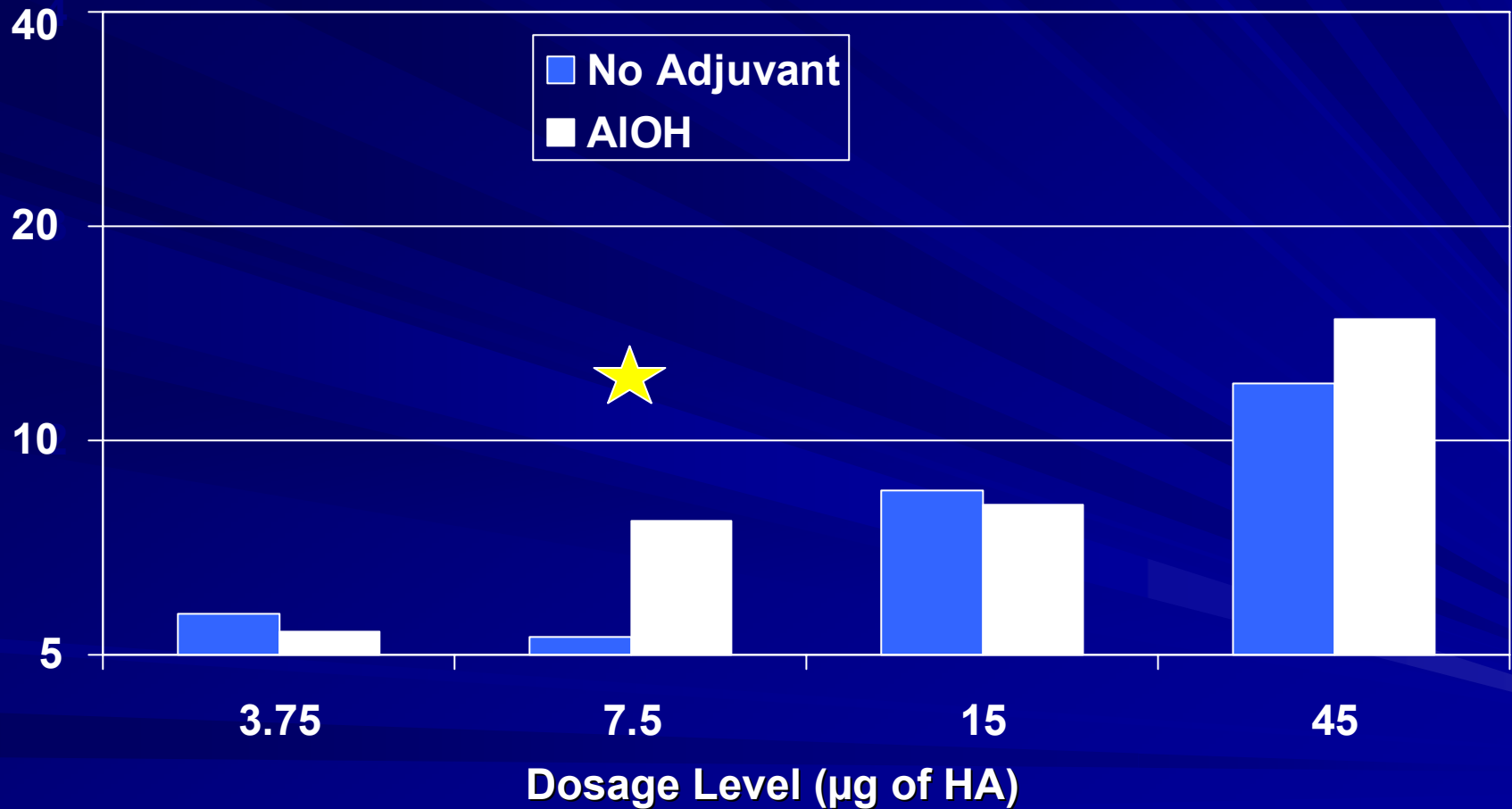
DEMOGRAPHIC CHARACTERISTICS (05-0127)

Gender – N (%)	
Male	252 (42)
Female	348 (58)
Ethnicity – N (%)	
Non-Hispanic	565 (94)
Hispanic	35 (6)
Race – N (%)	
American Indian/Alaskan Native	2 (0)
Asian	34 (6)
Hawaiian/Pacific Islander	1 (0)
Black/African American	65 (11)
White	480 (80)
Multi-Racial	11 (2)
Other/Unknown	7 (1)
AGE: Mean (STD)/ Median(STD)	32.8 (9.0) / 30.2

SAFETY & REACTOGENICITY

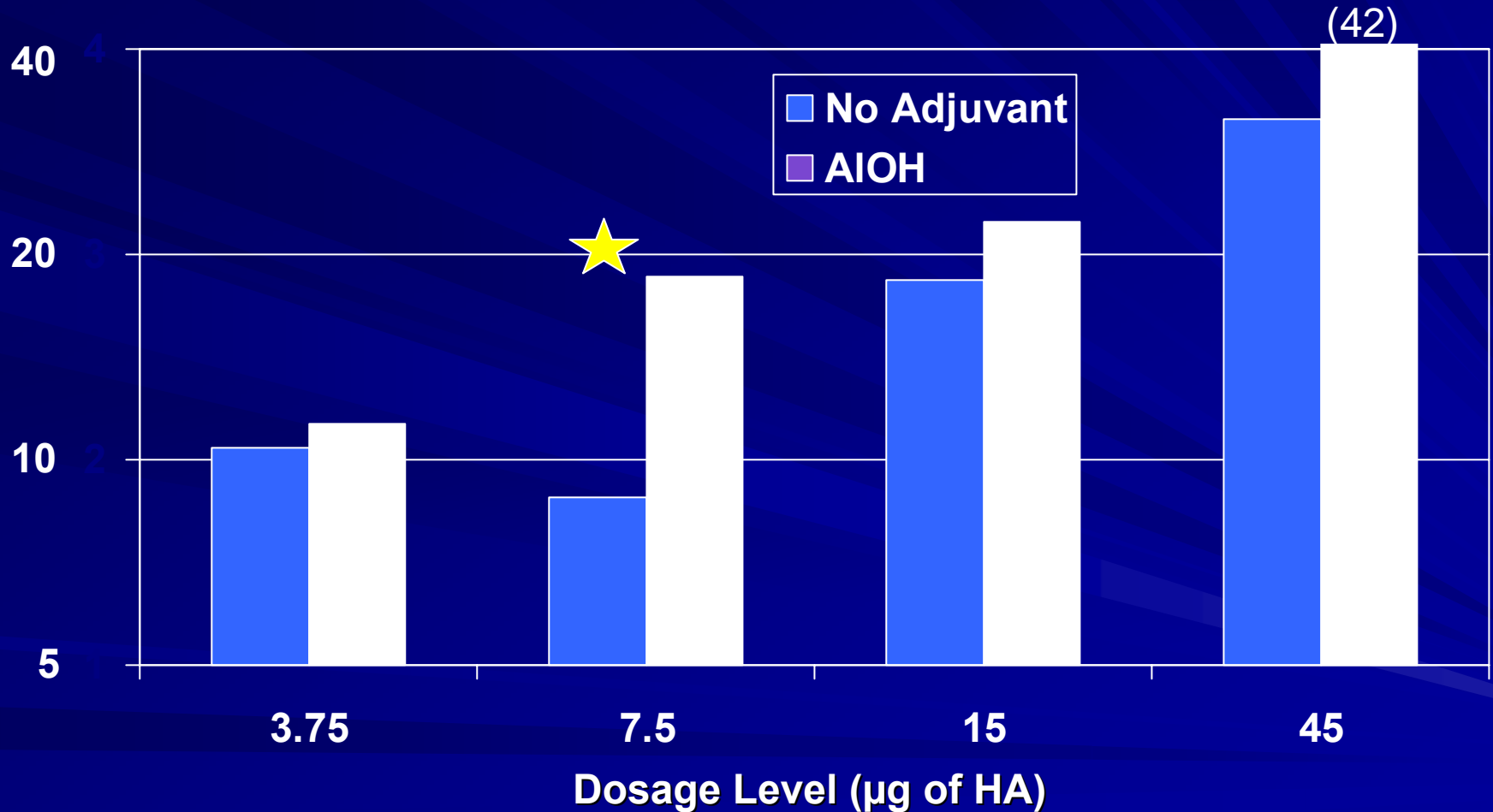
- **5 unrelated SAEs reported as of January 2007**
- **Pain +/- tenderness at the injection site reported by 32-77% after dose 1, and 25-66% after dose 2.**
- **Systemic reactions reported by 16-26% after the first dose and 9-22% of subjects after dose 2.**
- **Most reactions were mild and peaked on day 0 or day 1 after vaccination.**

GEOMETRIC MEAN SERUM HAI ANTIBODY LEVELS 1 MONTH AFTER DOSE 2



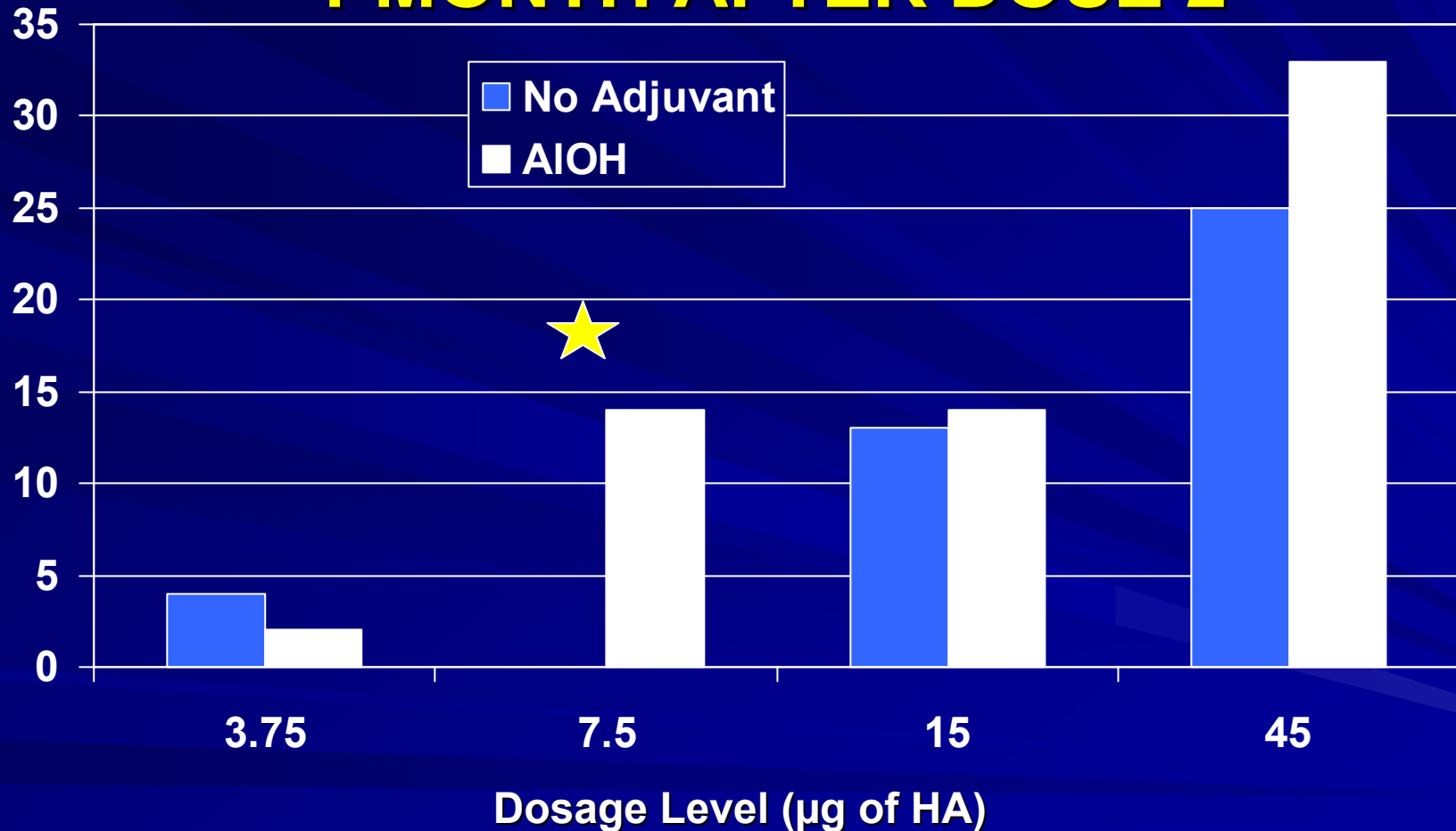
7.5 with adjuvant significantly greater than 7.5 without adjuvant

GEOMETRIC MEAN SERUM NEUT ANTIBODY LEVELS 1 MONTH AFTER DOSE 2



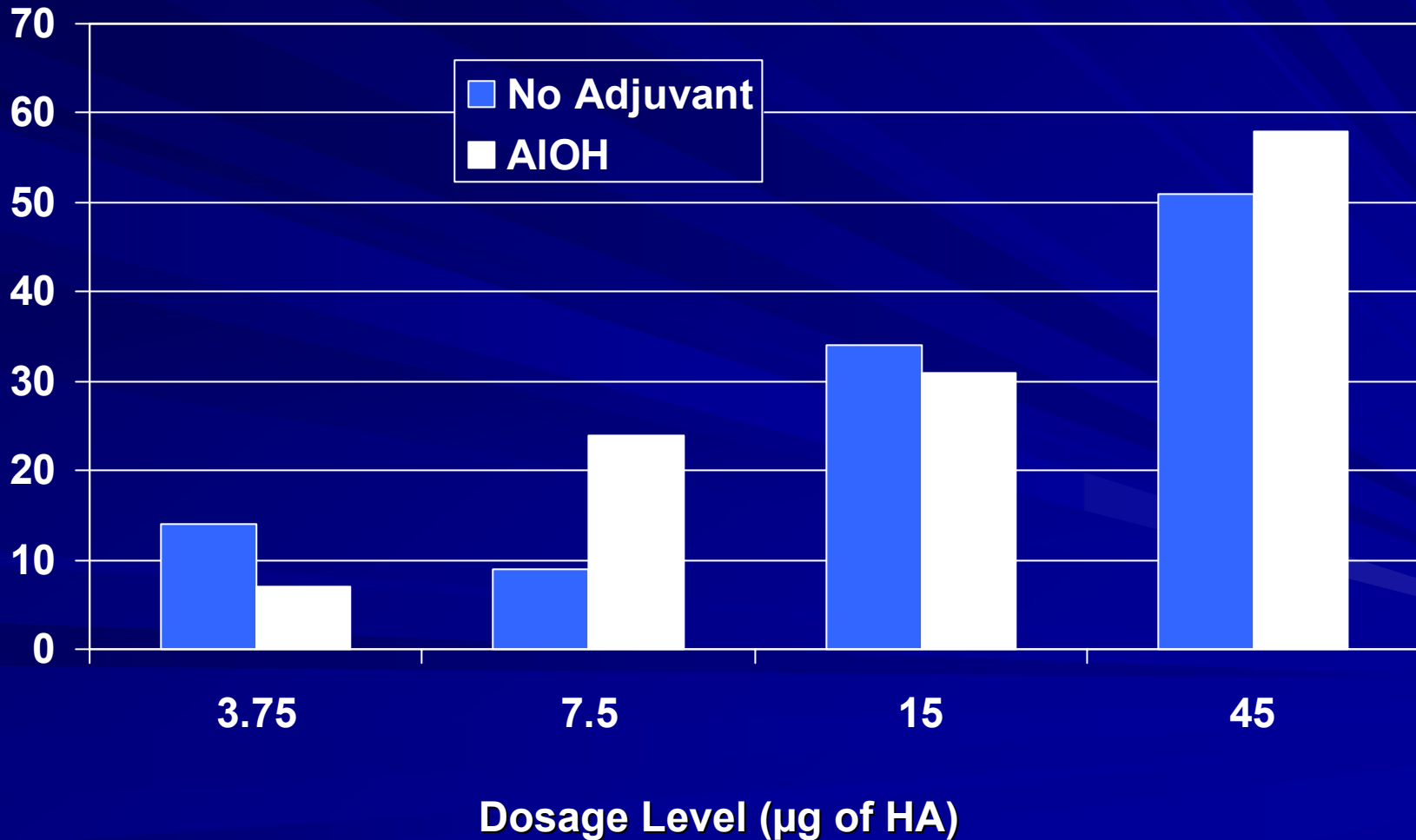
7.5 with adjuvant significantly greater than 7.5 without adjuvant

PERCENT WITH \geq 4-FOLD RISE IN SERUM HAI ANTIBODY LEVEL 1 MONTH AFTER DOSE 2

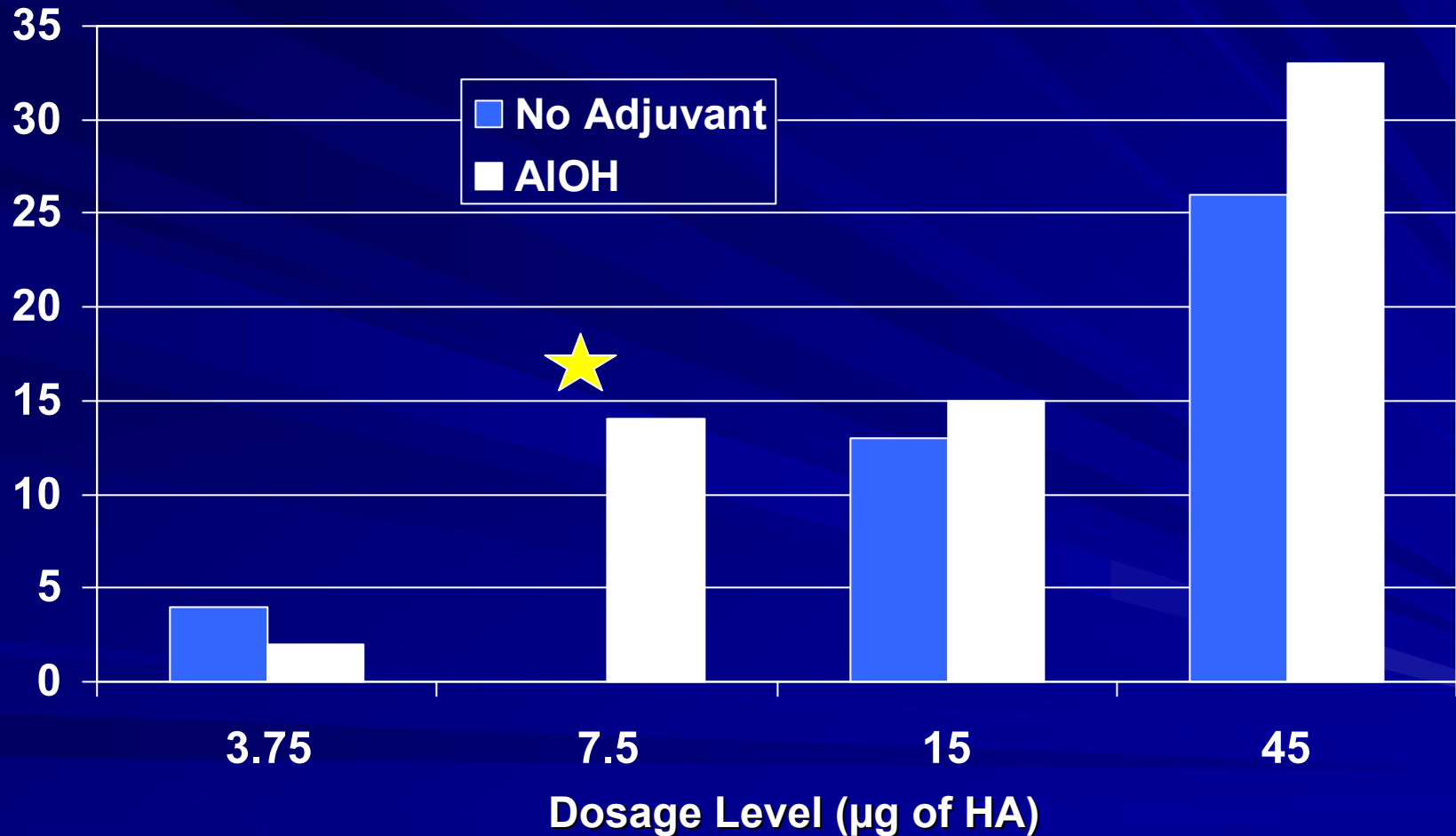


★ 7.5 with adjuvant significantly greater than 7.5 without adjuvant

PERCENT WITH \geq 4-FOLD RISE IN SERUM NEUT ANTIBODY LEVEL 1 MONTH AFTER DOSE 2

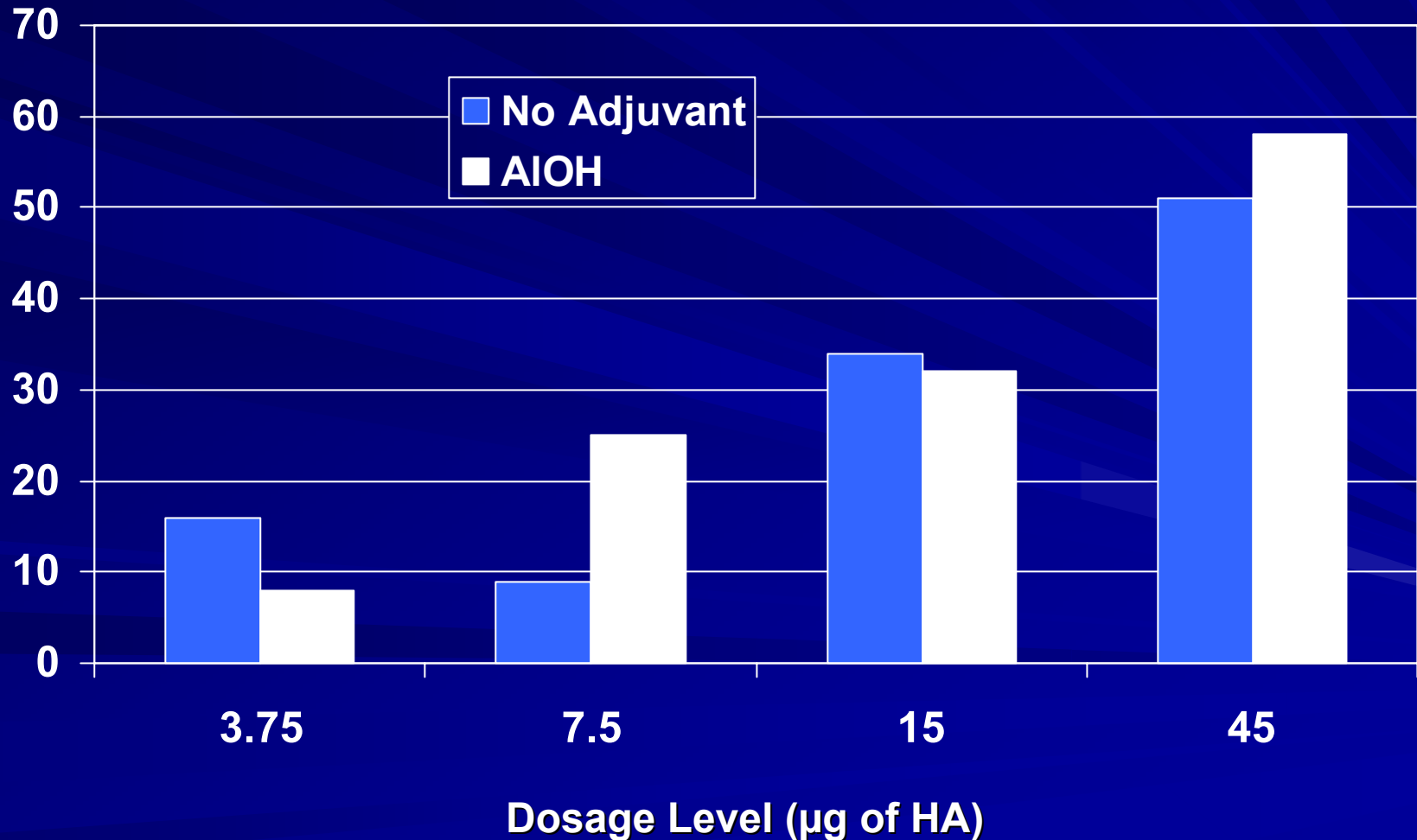


PERCENT WITH SERUM HAI ANTIBODY LEVEL ≥ 40 1 MONTH AFTER DOSE 2



★ 7.5 with adjuvant significantly greater than 7.5 without adjuvant

PERCENT WITH SERUM NEUT ANTIBODY LEVEL ≥ 40 1 MONTH AFTER DOSE 2



SERUM HAI ANTIBODY RESPONSES AFTER DOSE 2

HA (mcg)	GMT	≥ 4-fold Rise	≥40 Post
3.75	5.7 (4.9,6.5)	4 (0,12)	4 (0,12)
3.75+	5.4 (4.8,5.9)	2 (0,9)	2 (0,9)
7.5	5.3 (4.9,5.8)	0 (0,6)	0 (0,6)
7.5+	7.7 (6.0,9.9)	14 (6,25)	14 (6,25)
15	8.5 (6.3,11.4)	13 (5,24)	13 (5,24)
15+	8.1 (6.3,10.6)	14 (6,25)	15 (7,27)
45	12 (9.3,15.4)	25 (17,34)	26 (18,35)
45+	14.8 (11.2,19.6)	33 (24,42)	33 (24,42)

SUMMARY

- Aluminum hydroxide-adjuvanted inactivated subvirion influenza A/H5N1 vaccine was well tolerated in dosages up to 45µg.
- Dose-response relationships for serum antibody responses were observed for both formulations.

SUMMARY/CONCLUSION

- A significant effect of aluminum hydroxide adjuvant was observed only at the 7.5 μ g dosage level; however, response to non-adjuvanted vaccine was unexpectedly low.
- Overall, a significant beneficial effect of aluminum hydroxide adjuvant was not observed.

THANKS

- **Staff and subjects at participating VTEUs**
- **Roland Levandowski MD, Shy Shorer MD, Kathy Muth RN MS, Jean Hu-Primmer MS and DMID**
- **EMMES and PPD**
- **Safety Monitoring Committee**
 - Karen Kotloff, MD
 - Michael Keefer, MD
 - Richard Frothingham, MD
 - Mark Udden, MD

EXTRA SLIDES

SAFETY

Serious Adverse Events (05-0127)

•5 SAEs were reported as of January 2007; all occurred >2 months after the second dose, and all were considered to be unrelated to vaccination

- Appendicitis**
- Tenosynovitis**
- Gastroenteritis requiring hospitalization**
- Breast cancer**
- Gallstone pancreatitis**