

Presentation 12 – Lea Steele

**Gulf War Illnesses and Vaccines:
Overview of Epi Findings, Remaining Issues**

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on Gulf War Veterans' Illnesses
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**Possible Association of Gulf War Illnesses with
Vaccines Received during the Gulf War**

- Review of Epi Findings and RAC Discussions to Date
- Remaining Issues re: Vaccines and GWI

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**Vaccines and Gulf War Illnesses:
Issues Discussed**

- Epi studies consistently show association of GWI with vaccines
- Greatest concerns have been raised about the anthrax vaccine
 - > High rate of acute reactions, little info re: long-term effects
 - > Problems associated with manufacturing process?
 - > Problems with individual components of the vaccine?
- GWI-type problems among nondeployed veterans, recipients of the anthrax vaccine?

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**Vaccines and Gulf War Illnesses:
Remaining Issues**

- Research re: squalene antibodies in Gulf War veterans, AVA recipients
- Additional research related to long-term followup of AVA recipients
- Problems with vaccines other than anthrax given during the Gulf War?
- Additional research related to receipt of multiple vaccines
- Considerations re: combinations of specific vaccines, vaccines with other exposures?
- Evidence related to chronic immune activation associated with receipt of vaccines, TH1-TH2 shift (Rook hypothesis)
- Other aspects of vaccine safety (e.g. scheduling, individual components)

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Vaccines and Gulf War Illnesses: Remaining Issues Squalene

- Anti-squalene antibodies in Gulf War veterans?
 - > Do veterans with Gulf War illnesses have an elevated level of antibodies to squalene?
 - > Is presence of these antibodies a marker for and/or a cause of GWI?
- Was squalene in vaccines used during the Gulf War?
 - > Used as an adjuvant to enhance vaccine immunogenicity?
 - > In vaccines for some other reason?
 - > Levels capable of causing chronic illness?

Vaccines and Gulf War Illnesses: Remaining Issues
 Squalene Antibodies in Ill Gulf War Veterans?

Asa, Cao, Garry (2000)

	ASA assay <u>positive</u>
Blinded sample	
PGW sick (n=38)	95 %
PGW, well (n=12)	0 %
Nondepl Gulf era (n=6)	100 %
Unblinded sample	
Gulf veterans (n=86)	69%
Blood bank donors (n=48)	5%

Vaccines and Gulf War Illnesses: Remaining Issues
 Squalene Antibodies in Post-Gulf AVA Recipients?

Asa, Wilson, Garry (2002)

	Symp?	ASA <u>positive</u>
Pilot: 6 AVIP with GWI-like symps	all (by def)	100%
Blinded sample		
19 healthy nonmilitary (age/sex matched)	0 (by def)	16%
25 AVIP vaccine recipients	52%	32%
- 17 got AVA from 5 lots	76%	47%
- 8 got AVA from other lots	0%	0%

Squalene: Additional Information

- No other identified studies have compared levels of anti-squalene antibodies in ill vs. healthy Gulf War veterans
- Squalene and related compounds are known to cause an autoimmune condition when injected into animals
- FDA testing identified extremely low levels of squalene in several lots of AVA, as well as diphtheria and tetanus vaccines
- Government reports indicate that squalene has never been used as an adjuvant in AVA

The Squalene Issue:
Boils down to a simple question

Are anti-squalene antibodies associated with Gulf War illnesses?

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The Squalene Issue: The primary question

Are anti-squalene antibodies associated with Gulf War illnesses?

- If NO, there is no issue
- If YES, secondary questions:

Do anti-squalene antibodies result from an immune response to squalene in AVA (as an adjuvant or for some other reason), which caused chronic illness?

OR

Are anti-squalene antibodies a marker for other pathological mechanisms underlying Gulf War illnesses (e.g., poorly understood immune abnormalities resulting from multiple vaccines, specific vaccines, or other causes)?

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The Squalene Issue: The primary question

Are anti-squalene antibodies associated with Gulf War illnesses?

- Asa/ Garry paper on GWI and squalene antibodies raises a straightforward question and testable hypothesis
- GAO report concurred, and recommended that a study be done to address this question
- If Asa findings are refuted, the issue can be put to rest
- If anti-squalene antibodies are found disproportionately in ill Gulf veterans, additional questions should be addressed

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Vaccines and Gulf War Illnesses: Remaining Issues

Other Potential Problems with AVA?

- Problems with manufacturing process, quality control?
- Problems with specific components of the vaccine?
 - > Earlier review by Dr. Melling
 - > PA common to both UK and US vaccines
 - > Higher level of PA associated with change in manufacturing process?
- 1990 AVA vs. current AVA?

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Vaccines and Gulf War Illnesses: Remaining Issues
Other Vaccines Received During the Gulf War

Identified problems with vaccines other than AVA?

- > Hasn't been looked at in detail, among U.S. personnel with complete shot records
- > No long-term follow up data for most vaccines; some known to be associated with rare cases of chronic neurological complications

IMMUNIZING AGENT	ARMY	NAVY	AIR FORCE	MARINE CORPS	COAST GUARD
Adeno virus (Types 4 and 7)	B	B	B	B	H
Cholera	F	F	F	F	F
Hepatitis B	E,O,H	E,O,H	E,O,H	E,O,H	O,H
Influenza	A,B,H	A,B,R	A,B,R	A,B,R	E,O,H
Meadeloc	E,O	E,O	E,O	E,O	E,O
Meningococcal (A,C,Y,W135)	E,H	B,H	E,H	E,H	E,H
Mumps	O,H	O,H	O,H	O,H	O
Plague	C,D,E,O	D,O	E	A,O	E
Polio	A,R	A,R	A,R	A,R	A
Rabies	D,O,H	D,O,H	D,O,H	D,O,H	H
Rubella	E,O	E,O	E,O	E,O	B
Smallpox	E,H	E,H	E,H	E,H	E,H
Tetanus/diphtheria	A,B,R	A,B,R	A,B,R	A,B,R	A,B
Typhoid	C,E,H	H	C,E,H	H	E
Yellow fever	C,D,E	A,R	C,E	A,R	E,E

A: All active duty personnel
B: Routine
C: Anti-bias
D: Special Operating Forces component
E: W/extended stay or housing in high risk areas
F: Only when required by host country's endemicity
G: High risk occupational groups
H: As directed by applicable Surgeon General
R: Reserve component
X: Reserve personnel active 30 days during AU season

Association of Individual Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Boyd, 2003 (975 Gulf vets in Registry)	High vs. low # of symptoms	Botulinum	OR = 1.78*
		Anthrax	OR = 1.72*
		Meningococcus	OR = 1.57*
		Others	NS
Canadian MOD (3,113 Gulf vets)	Chronic fatigue Cogn dysf	"nonroutine" (anthrax, plague)	OR = 1.92* OR = 1.28*
Gray, 2002 (3,881 POW vets)	GWI case def	Meningococcus	OR = 3.64* (unadj); 1.30* (adj)
		Botulinum	OR = 4.92* (unadj); 1.29 (adj)
		Anthrax	OR = 3.72* (unadj); 1.01 (adj)
		Plague	OR = 3.23* (unadj); 0.94 (adj)
Wolfe, 2002 (1,200 Gulf vets)	CMI	Typhoid	OR = 2.34* (unadj); 0.93 (adj)
		Anthrax	OR = 1.5* (adj)
Urwin, 1999 (2,755 Gulf vets)	CMI	Anthrax	OR = 1.5*
		Plague	OR = 1.3*
		Tetanus	OR = 1.3*
		Any biological Other	OR = 1.5* NS

* Indicates statistical significance, p < 0.05

Vaccines and Gulf War Illnesses: Remaining Issues
Multiple Vaccines

- Problems with Receipt of Multiple Vaccines Simultaneously?
 - > Epi studies of Gulf-era veterans suggest association of GWI with # of vaccines received
 - > Little detail re: combinations of specific vaccines
 - > Some studies of effects of multiple vaccines in other populations

Association of Multiple Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Cherry, 2001 (8210 Gulf vets)	Symptom severity score	0	ALL* 2.0 -26.4
		1-3	2.8 -2.7
		4-6	3.5 9.2
		7-9	4.2 23.6
		10+	4.5* 34.4
Hotopf (823 Gulf vets w/shot records)	CMI	Postdeployment	
		0/1	OR = 1.0
		2	OR = 2.2*
		3	OR = 2.4*
		4	OR = 2.2*
5+	OR = 5.0*		
Australian study (1,428 Australian vets, used shot records)	# of symptoms	0	Ratio of means = 1.0
		1-4	RM = 0.9
		5-9	RM = 1.0
		10+	RM = 1.3*

* Indicates statistical significance, p < 0.05

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- Vaccines and Gulf War Illnesses**
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- Epi studies suggest associations
 - > ORs not particularly large for individual vaccines, but little attempt to look at exposure subgroups
 - > Role of multiple vaccines and combinations of individual vaccines requires additional study
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- Vaccines and Gulf War Illnesses:
 Recent Research Informs Remaining Questions**
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- Additional research related to long-term followup of AVA recipients
 - Research re: squalene antibodies in vaccine recipients
 - Additional research related to receipt of multiple vaccines
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- Vaccines and Gulf War Illnesses:
 Speakers**
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- Dr. John Grabenstein
 - Dr. Phillip Pittman
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