Presentation 4 – Lea Steele

Vaccines

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IOM Conclusions

- IOM report 2002: AVA effective & acceptably safe
- Cochrane Collaboration: Safe & Effective; No need for additional study unless new vaccine

Vaccines: Information Considered by RAC

- Exposures: information on vaccines received
  - Studies, reports of vaccine safety/efficacy
  - Information on vaccine components
- Animal Studies
- Epidemiologic studies evaluating associations between vaccines and health outcomes in Gulf War veterans

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Information Considered by the Committee Prior to 2004 RAC Report

- Overview of epidemiologic findings re: vaccines
- Overview of components of anthrax vaccines
- U.K. and U.S. AVA contain different "ingredients", were administered differently; primary similarity is the active antigen
- Clinical studies of "next generation" anthrax vaccines include arms in which AVA is administered to study subjects
- RAC 2004 Recs:
  - *Include evaluation of chronic symptoms similar to GWI in AVA trials*
  - *Conduct retrospective studies of long-term effects of AVA related to military's mandatory AVIP*

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Types of Vaccines Received, Information on Safety/Efficacy

Vaccines

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Research Advisory Committee On Gulf War Veterans' Illnesses

Vaccines Administered to U.S. Military Personnel 1990-1991

IMMUNIZING AGENT	ARMY	NAVY	AIR FORCE	MARINE CORPS	COAST GUARD
Adenovirus (types 4 and 7)	B	B	B	B	H
Cholera	F	F	F	F	F
Hepatitis B	B,G,H	B,G,H	B,G,H	B,G,H	G,H
Influenza	A,B,R	A,B,R	A,B,R	A,B,R	B,G,H
Measles	B,G	B,G	B,G	B,G	B,G
Meningococcal (A,C,Y,W-135)	B,H	B,H	B,H	B,H	B,H
Mumps	G,H	G,H	G,H	G,H	G
Plague	C,D,E,G	D,G	E	A,G	E
Polio	A,R	A,R	A,R	A,R	A
Rabies	D,G,H	D,G,H	D,G,H	D,G,H	H
Rubella	B,G	B,G	B,G	B,G	B
Smallpox	B,H	B,H	B,H	B,H	B,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	B,E

F: All active duty personnel

B: Recruits

C: Navy divers

D: Special Operating Forces components

E: When deploying or travelling to high risk areas

F: Only when routine by host country directive

G: High risk occupational groups

H: As directed by applicable Surgeon General

R: Reserve components

X: Reserve personnel active 30 days during the season

Vaccines received in association with Gulf War Service

- Most personnel received multiple vaccines prior to deployment
  - Number varied
  - Specific types varied by branch, prior vaccine history
- Some shots given in theater
  - Most prominently gamma globulin, anthrax, botulinum toxoid vaccines
- Greatest attention/concern raised re: possible adverse effects of anthrax vaccine, multiple vaccinations

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20 Studies to Evaluate Adverse Events After Anthrax Immunization

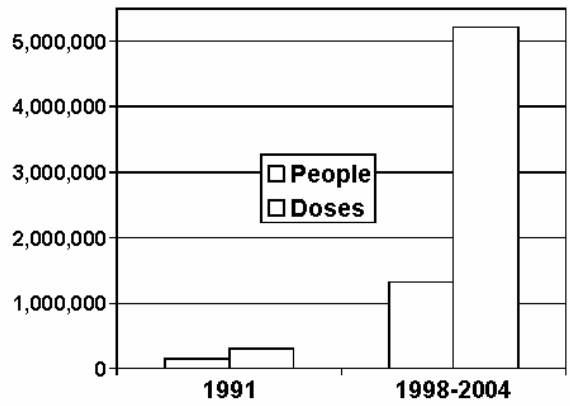
7 Apr 05

COL John D. Grabenstein, RPh, PhD, U.S. Army

Department of Veterans Affairs
Research Advisory Committee
on Gulf War Veterans' Illnesses

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Anthrax Vaccinees and Vaccinations



Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Anthrax Vaccine Safety Surveillance

- Mar 98 to Oct 04, > 5.2 million doses of anthrax vaccine to > 1.3 million people.
- Soreness, redness, itching, swelling at injection site:
  - Less than 2.5 cm: 30% of men, 60% of women.
  - More than 12 cm: 1% to 2%, both genders
  - Inject over deltoid **(not triceps)**
- Lump at injection site common, lasts a few weeks, goes away.
- Systemic symptoms—muscle or joint aches, headaches, rashes, chills, low-grade fever, nausea.
  - 5% to 35%, like other vaccines

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Anthrax Vaccine Safety Litany

	Vaccinees
Brachman Study, *Am J Public Health* 1962	379
CDC Observational Study, *Fed Reg* 1985	6,986
Ft Detrick Multi-Vaccine Studies, *BJHH* '58, *Ann Intern Med* 1965, 1974	99
Ft Detrick Long-Term Health Study, Vaccine 2004	142
Fort Bragg Booster Study (after Persian Gulf War), *Vaccine* 2002	495
USAMRIID Reduced-Dose / Route-Change Study, *Vaccine* 2002	173
Fort Detrick Special Immunization Program, *Vaccine* 2001	1,583
Canadian Forces Safety Evaluation, *Military Medicine* 2004	403
TAMC-601 Survey, *MMWR* 2000; 49:341-5, *J Occup Environ Med* 2003	601
US Forces Korea Records, *MMWR* 2000; 49:341-5, *Vaccine* 2003	2,824
VAERS review by AVEC, *Pharmacoepidemiol & Drug Safety* 2002, 2004	1,623
ROTC Cadets, Ft Lewis, *Med Surveil Mon Rep* 2001	73
USAF Air Combat Command Study, *Military Medicine* 2002	4,045
Fort Stewart Pregnancy Study, *JAMA* 2002	4,092
Army Disability Discharge Claims Database, *J Occup Envir Med* 2004	154,456
USAF Visual Acuity Study	958
Aviator Flight Physical Examinations	3,356
DMSS Hospitalization Cohort Study, *Vaccine* 2002	757,540 py
NHRC Hospitalization Cohort Study, *Vaccine* 2002	120,870 py
Male Fertility Study (sperm parameters), Fertility & Sterility 2005	254
Mycoplasma Study, *Emerging Infectious Diseases* 2002	(laboratory)

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Disability Discharge Evaluations

- Sulsky SI, **et al. Disability among U.S. Army personnel vaccinated against anthrax. *Journal Occupational & Environmental Med* 2004;46:1065-1075.**
- Subjects: **U.S. Army personnel receiving ≥ 1 dose of anthrax vaccine adsorbed (AVA) between Mar 98 and Feb 02 vis-à-vis disability evaluation.**
- Methods: **29,332 disability evaluations among 716,833 active-duty Soldiers (154,456 vaccinated) over 4.25 years. Cox proportional-hazard models for risk of disability evaluation.**
- Results: **Adjusted hazard ratio (HR) 0.96 (95% CI: 0.92, 0.99). Unadjusted rates: 140 per 100,000 person-months if unvaccinated, 68 per 100,000 person-months if anthrax-vaccinated.**
- **Separate adjusted HRs for men, women, permanent and temporary disability, musculoskeletal and neurological conditions similar, 0.90 to 1.04. Latency assumptions did not affect results.**
- Conclusion: **Anthrax vaccination does not increase risk of disability evaluation, nor granting of disability finding.**

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Squalene as an Adjuvant

Squalene is an oil. Produced in human liver, required for life.

Squalene naturally present in blood at 250 parts per billion (ppb). Fingerprint oils. Food. Supplements (olive oil).

Squalene alone may induce antibodies, but it is not an adjuvant (help antigens) by itself.

Squalene needs to be in the form of an emulsion (like mayonnaise) to be an adjuvant.

To be an adjuvant, squalene needs to be present at 1% to 5% 10,000,000 parts per billion (1%) to 50,000,000 parts per billion (5%)

***FluAd* (Italian influenza vaccine), given to > 10 million people, contains MF59 adjuvant, which includes 1.95% squalene, 19,500,000 parts per billion**

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Squalene and Squalene Tests

A. SRI tests 17 lots of anthrax vaccine, all negative. Test capable of detecting as little as 140 ppb. Spanggord et al, 2002

B. FDA tests 3 vaccines: diphtheria, tetanus, anthrax. Finds squalene in each at 10 to 83 ppb. Tells Congress: "trace, naturally occurring, safe"

C. SRI improves test. Tests 33 lots: no squalene in 32 lots. Squalene in one lot at 1 to 9 parts per billion, or 1 to 9 parts per 1,000,000,000. Manuscript in progress.

Summary: Squalene not added as adjuvant to any US-licensed vaccine. Trace quantities may be present, concentration less than naturally present in human blood

Slide adapted from: Grabenstein JD. 20 Studies to Evaluate Adverse Events After Anthrax Immunization. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

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USAMRIID

Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing

Research Advisory Committee on Gulf War Illness Meeting
U.S. Department of Veterans Affairs
Lafayette Building
811 Vermont Street, NW Rm 819
Washington, D.C.

Phillip R. Pittman, MD, MPH
COL, MC, USA
Chief, Division of Medicine
USAMRIID
Fort Detrick, MD

7 April 2005

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Hyper Immunization

- **Studies have been done to assess the long-term medical risk of repeated injections with multiple antigens at Fort Detrick for many years.**
- **In the 1950s Fort Detrick had a group of workers who had received repeated injections with multiple antigens of bacterial, rickettsial and viral origins.**

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

What are the Fort Detrick Vaccine Safety Studies

- **1958 - Peeler RN, Cluff LE, Trever RW. Hyper-immunization of man. *Bulletin of the Johns Hopkins Hospital* 1958;103:183-98.**
- **1965 - Peeler RN, Kadull PJ, Cluff LE. Intensive immunization of man: Evaluation of possible adverse consequences. *Annals of Internal Medicine* 1965;63:44-57.**
- **1974 - White CS III, Adler WH, McGann VG. Repeated immunization: Possible adverse effects: Reevaluation of human subjects at 25 years. *Annals of Internal Medicine* 1974;81:594-600.**

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Study 3 : 25-year follow-up 1971: Conclusion

- **"These data and the accompanying evaluation of an intensively immunized population provide evidence that no obvious adverse effects result from repeated immunization."**
- **There are some laboratory mean values that are different but the means often were within the normal range and do not support a clinical illness.**
- **There were no disease or clinical symptom complex found related to multiple immunization in either studies over a 25 year period.**

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Available online at www.sciencedirect.com
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Vaccine 23 (2004) 525–536
Vaccine
www.elsevier.com/locate/vaccine

Long-term health effects of repeated exposure to multiple vaccines☆

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Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Long-term health effects?

- **The health of 155 former workers in a US military research program who had received multiple vaccines and 265 matched community controls was assessed.**
- **The vast majority of the study group were recruited and enrolled during a biannual alumni meeting in 1996 at Fort Detrick, MD.**
- **Controls were recruited from among age, race, gender matched community controls within Frederick county.**

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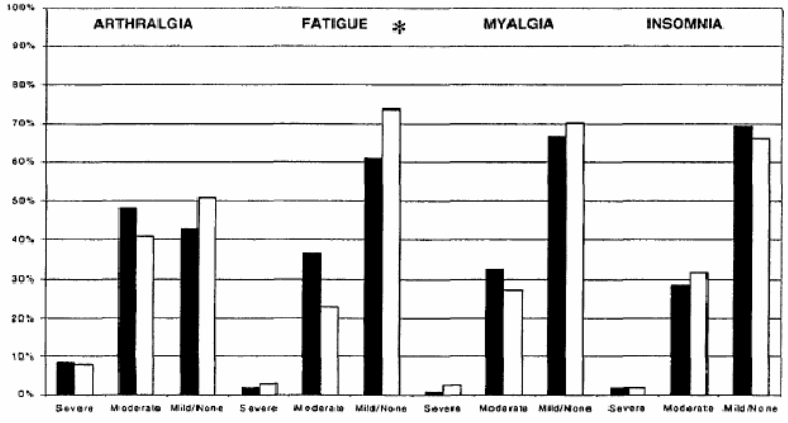

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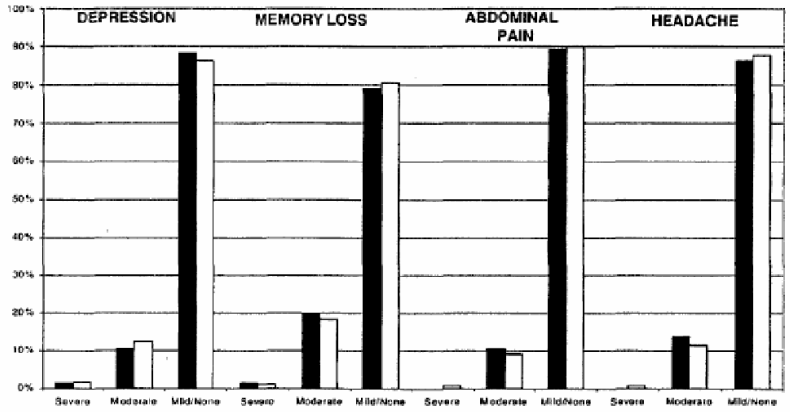

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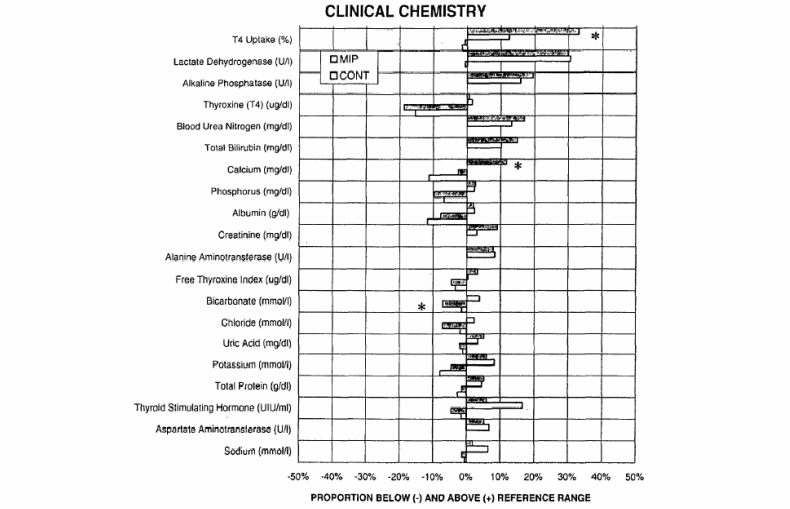

Fig. 2. Comparison of abnormal serum chemistry values for MIP (dark-colored bars) and control (light-colored bars) subjects. The proportions of each group with values above and below the laboratory reference range for each test are displayed as positive and negative, respectively. Asterisk denotes test for which a statistically significant difference between MIP and control subjects was seen (one-tailed *P*-value adjusted for multiple comparisons).

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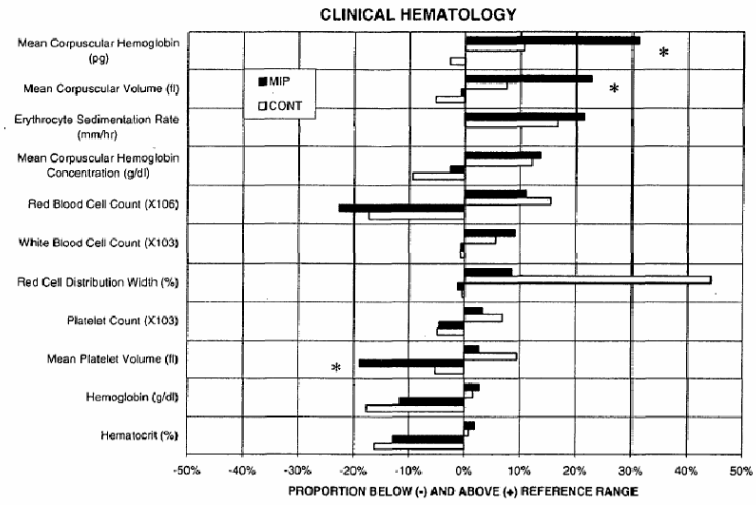

Fig. 3. Comparison of abnormal clinical hematology values for MIP (dark-colored bars) and control (light-colored bars) subjects. The proportions of each group with values above and below the laboratory reference range for each test are displayed as positive and negative, respectively. Asterisk denotes test for which a statistically significant difference between MIP and control subjects was seen (one-tailed P-value adjusted for multiple comparisons).

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Journal of Immunological Methods 286 (2004) 47–67

JIM
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Research Paper

Detection of antibodies to squalene III. Naturally occurring antibodies to squalene in humans and mice☆

Gary R. Matyas[a,*], Mangala Rao[a], Phillip R. Pittman[b], Robert Burge[c], Iris E. Robbins[a,1], Nabila M. Wassef[a,2], Brandie Thivierge[a], Carl R. Alving[a]

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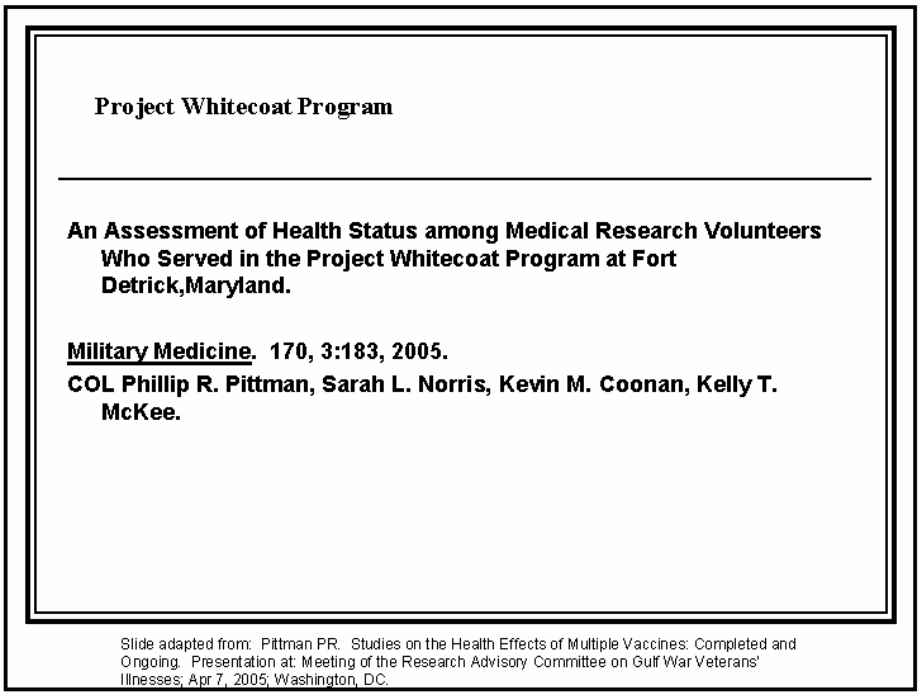
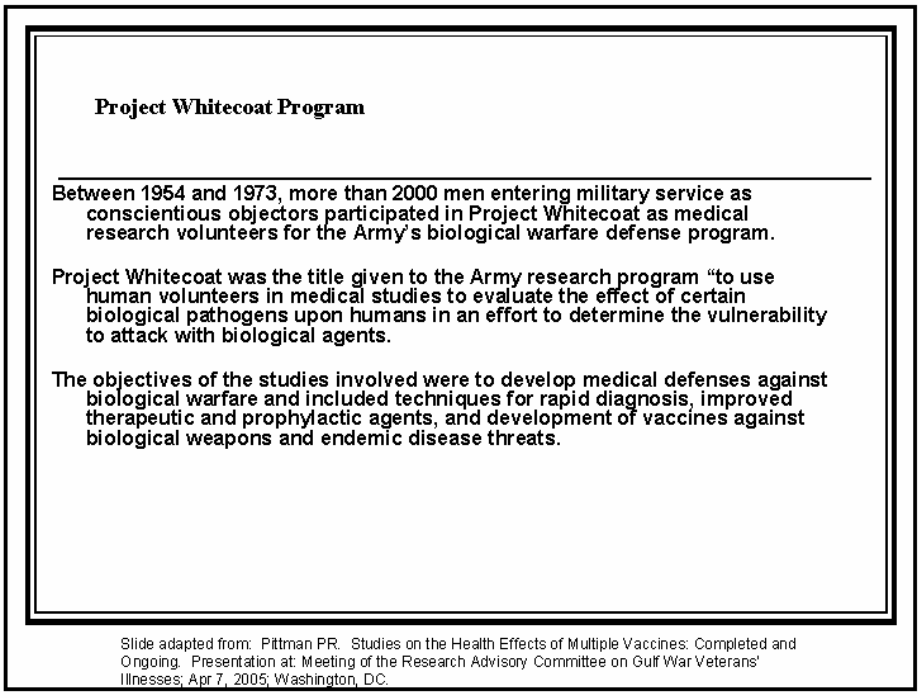

Project Whitecoat Program
An Assessment of Health Status among Medical Research Volunteers Who Served in the Project Whitecoat Program at Fort Detrick,Maryland.
Military Medicine. 170, 3:183, 2005.
COL Phillip R. Pittman, Sarah L. Norris, Kevin M. Coonan, Kelly T. McKee.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Project Whitecoat Program
Between 1954 and 1973, more than 2000 men entering military service as conscientious objectors participated in Project Whitecoat as medical research volunteers for the Army's biological warfare defense program.
Project Whitecoat was the title given to the Army research program "to use human volunteers in medical studies to evaluate the effect of certain biological pathogens upon humans in an effort to determine the vulnerability to attack with biological agents.
The objectives of the studies involved were to develop medical defenses against biological warfare and included techniques for rapid diagnosis, improved therapeutic and prophylactic agents, and development of vaccines against biological weapons and endemic disease threats.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Project Whitecoat Program

The group participated in more than 135 clinical research studies involving exposure to live agents, receipt of investigational vaccines, and studies of metabolic and psychological effects of environmental-and infection-induced stress.

This study was designed to assess the long-term effects on health of these men resulting from their involvement in this vital program.

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

EXPOSURES

- 358 volunteers "Exposed" (received study product) to:
  - Investigational vaccines: 197
  - Disease-causing agents: 211
  - Antibiotics/other therapeutic agents: 46
- 164 "Controls" (did not receive study product)

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

VACCINE EXPOSURES

- VEE: 73
- Tularemia: 45
- Yellow Fever: 31
- EEE: 29
- WEE: 28
- Plague: 13
- Q-fever: 11
- Rift Valley fever: 8
- Anthrax: 7
- Chikungunya: 6
- Adenovirus: 4

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

DISEASE AGENT EXPOSURES

- *Coxiella burnetii* (Q-fever): 58
- Sandfly fever: 30
- Staphylococcal enterotoxin B (SEB): 20
- *Francisella tularensis* (tularemia): 11
- Venezuelan equine encephalitis (VEE): 7
- *Pseudomonas* endotoxin: 2

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Whitecoat Project

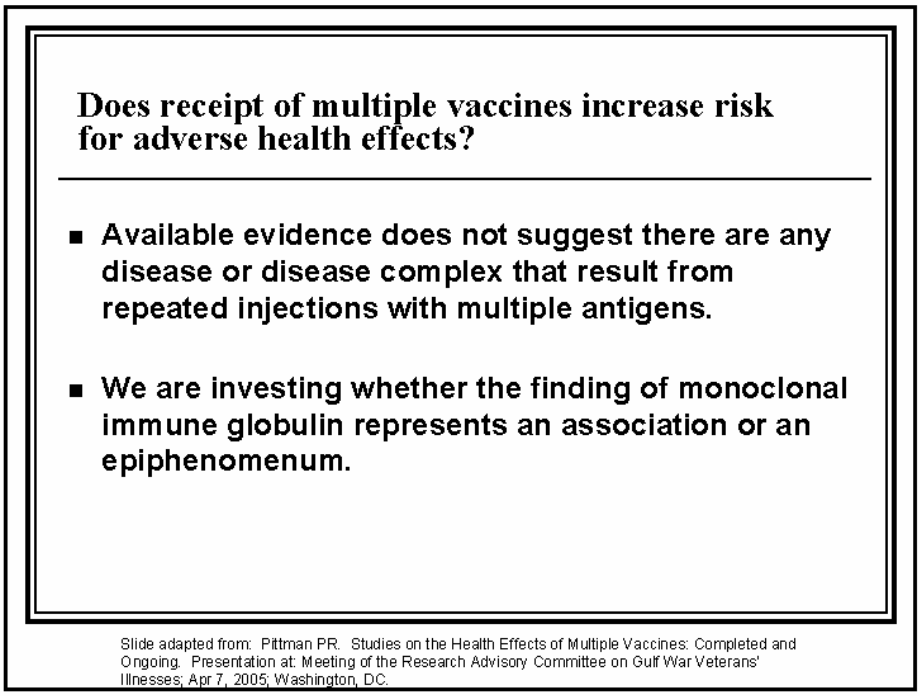
- Asthma reported more frequently among tularemia vaccine recipients than controls (13.3% vs 2.4%, p=0.049)
- Asthma reported more frequently in group exposed to non-agents than controls (13.0% vs 2.4%, p=0.050)
- No definite association

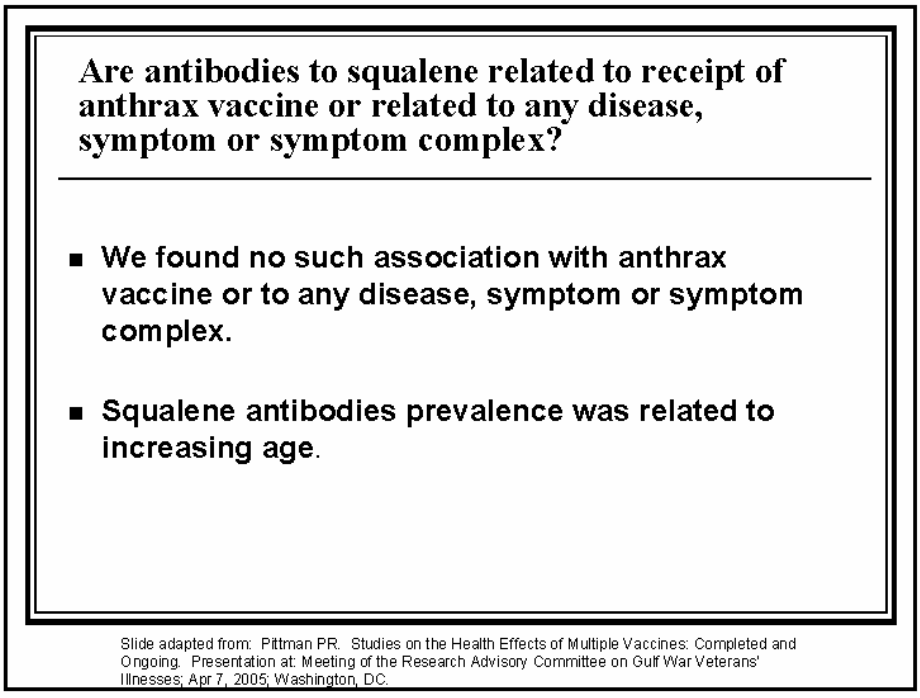
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

CONCLUSIONS (CONT)

- No significant differences between "exposed" and "unexposed" subjects with regard to self-reported diseases or medical conditions
- No differences between individuals participating in one and those participating in two or more studies with regard to any outcome measured (general health, exercise level, children, symptoms, or medical conditions)

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Does receipt of multiple vaccines increase risk for adverse health effects?
Available evidence does not suggest there are any disease or disease complex that result from repeated injections with multiple antigens.
We are investing whether the finding of monoclonal immune globulin represents an association or an epiphenomenum.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.


Are antibodies to squalene related to receipt of anthrax vaccine or related to any disease, symptom or symptom complex?
We found no such association with anthrax vaccine or to any disease, symptom or symptom complex.
Squalene antibodies prevalence was related to increasing age.
Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

CONCLUSION

- Vaccines, including multiple vaccine antigen injections, appear to have a safe long-term health outcome.

Slide adapted from: Pittman PR. Studies on the Health Effects of Multiple Vaccines: Completed and Ongoing. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Animal Studies: Effects of Vaccines

Vaccines

★☆★ RAC-GWVI

Assessment of a role of stress-activated kinases in the pathogenesis of Gulf War Syndrome

Ya Fang Liu M.D. & Ph.D.
Department of Pharmacology
Boston University School of Medicine

Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

Stress-activated kinases

They are a group of enzymes or kinases that are activated in response to stressful stimuli such as UV light, γ–irradiation, inflammatory cytokines, certain chemicals, toxins.

Activation of these kinases indicates that cells or neurons are undergoing cellular stress.

Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

Pathological role of stress-activated kinases

Over-activation of stress-activated kinases can induce dysfunction of central nervous and immune systems.

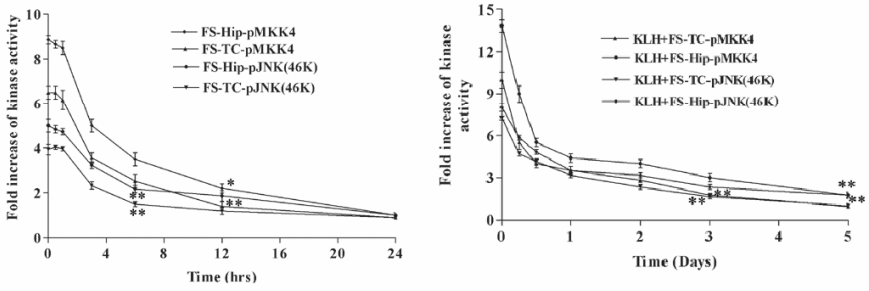
Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

Hypothesis

Stress, vaccination, and exposure to one or more chemicals may synergistically act on stress-activated kinases. Over-activation of these stress-activated kinases may lead to dysfunction in the central nervous and immune systems, contributing the majority of symptoms observed in patients with GWS

Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.

KLH significantly prolongs activation of MKK4 in the brain



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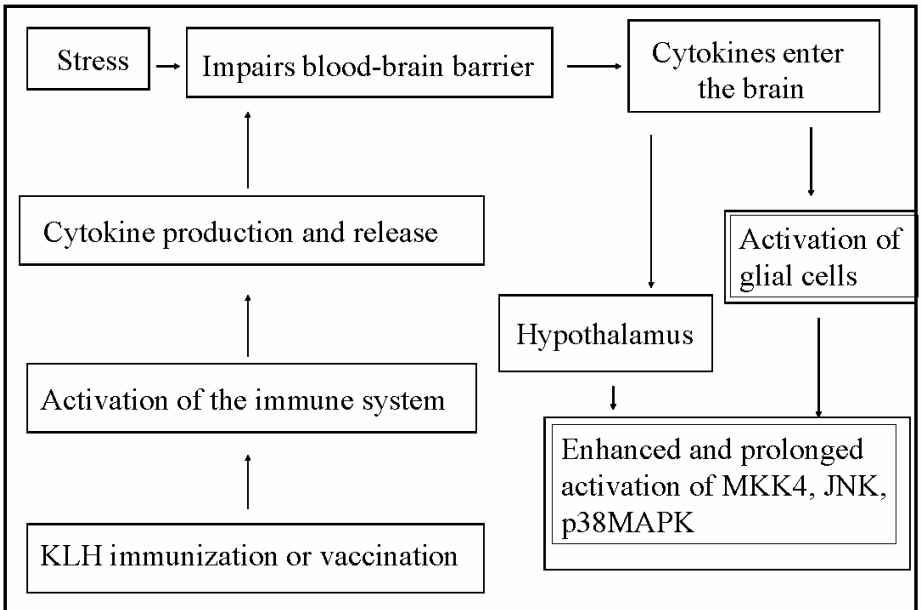

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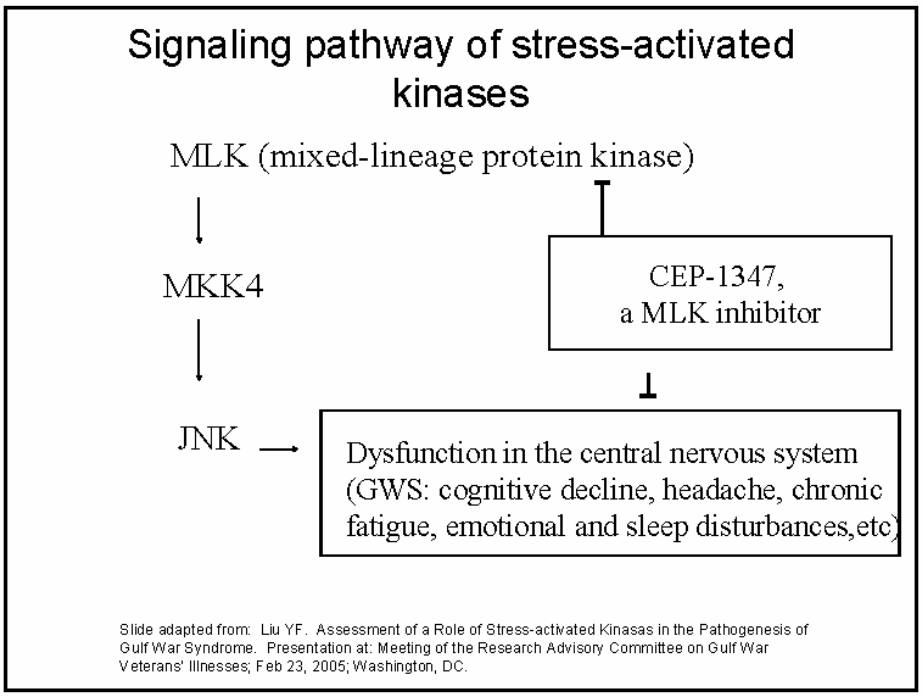
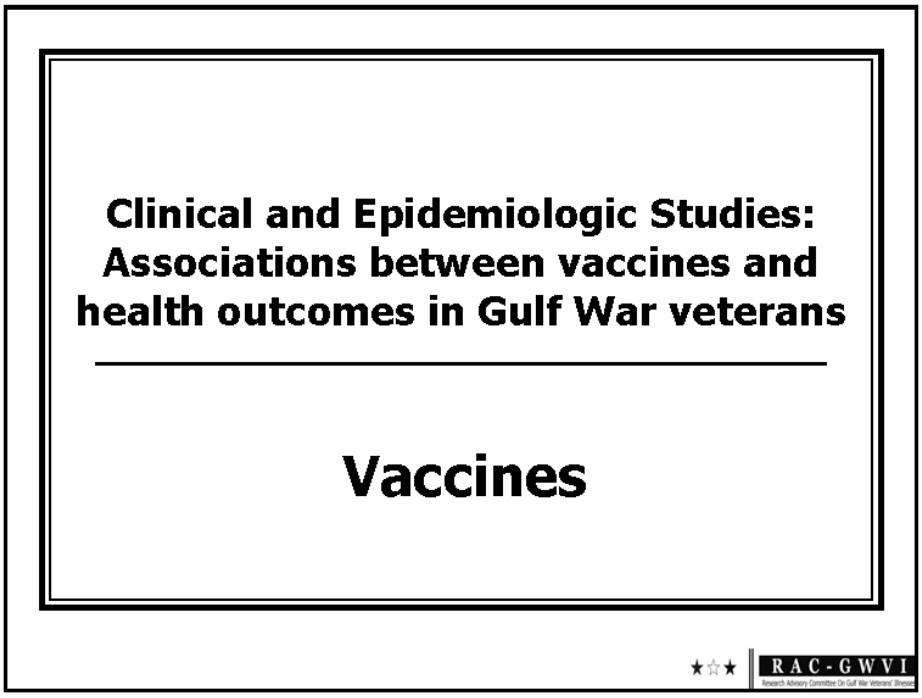

Signaling pathway of stress-activated kinases
MLK (mixed-lineage protein kinase)
MKK4
JNK
CEP-1347, a MLK inhibitor
Dysfunction in the central nervous system (GWS: cognitive decline, headache, chronic fatigue, emotional and sleep disturbances,etc)
Slide adapted from: Liu YF. Assessment of a Role of Stress-activated Kinasas in the Pathogenesis of Gulf War Syndrome. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Feb 23, 2005; Washington, DC.


Clinical and Epidemiologic Studies: Associations between vaccines and health outcomes in Gulf War veterans
Vaccines
RAC-GWVI

ANTHRAX VACCINATION AND SELF-REPORTED SYMPTOMS, FUNCTIONAL STATUS AND MEDICAL CONDITIONS IN THE NATIONAL HEALTH SURVEY OF GULF WAR ERA VETERANS AND THEIR FAMILIES

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Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

COMPARISION GROUPS

N= 4601 self-report, received anthrax vaccination (40.2%)

N= 3861 self-report, unknown if received anthrax vaccination (33.7%)

N= 2979 self-report, did not receive anthrax vaccination (26.0%)

N= 352 anthrax vaccination record on file with DoD

N= 11,441 all Gulf veterans

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TABLE 4. Prevalence and adjusted odds ratios of selected self-reported severe symptoms among 11,441 Gulf War veterans according to self-report of anthrax vaccination; also for 352 Gulf War veterans for whom anthrax vaccination is documented in DoD records.

Symptoms	Self-Reported Anthrax Vaccination: Yes (N=4601)	Unknown (N=3861)	No (N=2979)	Documented DoD (N=352)	Adjusted Odds Ratio (95%CI) †: Anthrax Vaccination Yes‡	Unknown‡	DoD*
Joint aches or pain	21.8	16.8	9.7	16.5	2.05 (1.76-2.39)	1.76 (1.51-2.06)	1.50(1.08-2.10)
Runny nose	21.7	17.8	12.9	20.5	1.53 (1.33-1.76)	1.43 (1.24-1.64)	1.32(0.98-1.81)
Headaches	21.4	17.7	11.3	16.8	1.69 (1.46-1.95)	1.53 (1.32-1.77)	1.18(0.85-1.64)
Back pain/spasms	20.4	18.5	12.4	13.1	1.54 (1.34-1.78)	1.51 (1.31-1.74)	0.98(0.69-1.40)
Anxious, irritable or upset	19.2	15.1	8.2	15.0	2.02 (1.72-2.38)	1.75 (1.49-2.06)	1.46(1.03-2.07)
Excessive fatigue	18.8	13.4	7.1	14.3	2.19 (1.85-2.60)	1.83 (1.54-2.18)	1.62(1.14-2.31)
Sleep difficulty	18.3	13.8	7.6	15.1	2.04 (1.72-2.40)	1.71 (1.44-2.02)	1.57(1.11-2.21)
Awaken tired or worn out	17.8	13.8	7.8	14.0	1.86 (1.57-2.19)	1.62 (1.38-1.92)	1.33(0.93-1.91)
Been depressed or blue	15.4	11.8	6.7	12.1	1.94 (1.62-2.31)	1.65 (1.38-1.97)	1.43(0.99-2.06)
Reflux, heartburn, indigestion	14.8	11.9	6.7	12.0	1.93 (1.62-2.31)	1.72 (1.44-2.06)	1.65(1.13-2.43)

†CI: Confidence Interval

‡Adjusted odds ratios (95%CI) were derived from logistic models. Reference category was self-report "No." Adjustment was made for number of vaccines received other than anthrax (0,1,...5); gender (male vs. female); age in 1991 (<30 vs. ≥30 yrs.); race (white vs. other); marital status (single vs. ever married); rank (officer or warrant vs. enlisted); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves); current alcohol use (within past 12 months); and current cigarette use (within past 12 months).

*Adjusted odds ratios (95% CI) for documented vaccination by DoD records relative to self-report "No" were derived through stratified Cochran-Mantel-Haenszel (15) analysis. Adjustment was made for variables that were correlated with both exposure (anthrax vaccine) and outcome (severe symptom). These confounding factors included number of vaccines received other than anthrax, (≤ 2 vs ≥ 3); gender (male vs female); branch of service (non-ground troops vs. ground troops); unit component (active duty vs. National Guard or Reserves).

Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

TABLE 6. Prevalence of severe symptoms among 352 Gulf War veterans for whom anthrax vaccination records exist in DoD stratified by self-reported response to question on anthrax vaccination.

Symptoms	Documented DoD N=352: Yes N=260	Unknown N=58	No N=34
Joint aches pain	17.7	12.1	15.2
Runny nose	22.8	10.3	20.6
Headaches	18.1	17.5	5.9
Back pain/spasms	14.2	12.1	5.9
Anxious, irritable or upset	18.0	8.6	2.9
Excessive fatigue	17.4	6.9	2.9
Sleep difficulty	17.8	8.6	5.9
Awaken tired or worn out	17.1	6.9	2.9
Been depressed or blue	14.2	6.9	5.9
Reflux, heartburn, indigestion	12.0	10.5	14.7

Significance probability for Wilcoxon signed ranks test, $p < .01$ (2-tailed). (17)

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CONCLUSIONS

- This survey data along with the DoD list of Gulf War veterans who received anthrax vaccine provide an opportunity to evaluate the long-term health consequences of anthrax vaccination.
- Those who reported exposure to anthrax vaccination do express more adverse health outcomes than those who reported no anthrax vaccination.
- The possibility of a reporting bias in exposure history should be carefully considered when one evaluates the health consequences of anthrax vaccination based on self reported vaccination data.

Slide adapted from: Mahan CM. Anthrax Vaccination and Self-reported Symptoms, Functional Status and Medical Conditions in the National Health Survey of Gulf War Era Veterans and Their Families. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Oct 28, 2003; Washington, DC.

Vaccines and Gulf War Illnesses:

Squalene Antibodies in Ill Gulf War Veterans?

Asa, Cao, Garry (2000)

	ASA assay positive
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%

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Squalene Antibodies in Post-Gulf AVA Recipients?

Asa, Wilson, Garry (2002)

	Symps?	ASA positive
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%

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Additional information on Anthrax Vaccine

- Anthrax vaccine is among the most reactogenic vaccines in the VAERS
- Adverse effects related to number of doses
- Receipt of anthrax vaccine consistently related to chronic ill health in epidemiologic studies of Gulf War veterans
- Adverse effects generally found to be higher in female than male AVA recipients
- Pertussis (UK adjuvant for AVA) used experimentally to generate autoimmune disease in animals

Slide adapted from: Golomb BA. Vaccinations and Illness in Persian Gulf Veterans. Presentation at: Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses; Apr 7, 2005; Washington, DC.

Epidemiologic Studies: Association of Individual Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Boyd, 2003 (973 Gulf vets in Registry)	High vs. low # of symptoms	Botulinum Anthrax Meningococcus Others	OR = 1.78* OR = 1.72* OR = 1.57 NS
Canadian MOD (3,113 Gulf vets)	Chronic fatigue Cogn dysf	"nonroutine" (anthrax, plague)	OR = 1.92* OR = 1.28*
Gray, 2002 (3.831 PGW vets)	GWI case def	Meningococcus Botulinum Anthrax Plague Typhoid	OR = 3.64* (unadj); 1.30*(adj) OR = 4.92* (unadj); 1.28 (adj) OR = 3.72* (unadj); 1.01 (adj) OR = 3.23* (unadj); 0.94 (adj) OR = 2.34* (unadj); 0.93 (adj)
Wolfe, 2002 (1290 Gulf vets)	CMI	Anthrax	OR = 1.5* (adj)
Unwin, 1999 (2,735 Gulf vets)	CMI	Anthrax Plague Tetanus Any biological Other	OR = 1.5* OR = 1.3* OR = 1.3* OR = 1.5* NS

* Indicates statistical significance, p<0.05

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Association of Multiple Vaccines with Health of Gulf Veterans

Study	Outcome	Vaccine	Findings
Cherry, 2001 (8,210 Gulf vets)	Symptom severity score		All* / Periph*
		0	2.0 / -26.4
		1-3	2.8 / -2.7
		4-6	3.5 / 8.2
		7-9	4.2 / 23.6
		10+	4.5* / 34.4
Hotopf (923 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 (1,426 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:
Information Considered by RAC in 2004-2005

- Vaccine exposure/adverse effects
- Clinical/Epidemiologic studies

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Vaccines: Summary of Information Considered

Vaccine Exposures/Adverse Effects

- Multiple vaccines given to GW veterans; most concern raised about AVA, effects of multiple vaccines
- Changes in AVA manufacturing process around the time of the Gulf War, concerns about quality control/contamination in early 1990s. Current AVA may not be comparable to 1990 AVA
- AVA has now been given to >1 million U.S. military; multiple studies suggest minimal long-term concerns re: VAERS claims, hospitalization, disability claims

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Vaccines: Summary of Information Considered

Vaccine Exposures/Adverse Effects

- USAMRID studies indicate that intensive receipt of multiple vaccinations, in general, not associated with chronic health problems; limitations in generalizability of these findings
- No systematic evaluation of chronic symptom complexes similar to those seen in Gulf war veterans with respect to:
  - *AVA; specifically 1990-1991 AVA*
  - *Multiple vaccinations associated with 1990-1991 Gulf War*

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Vaccines: Summary of Information Considered

Clinical and Epidemiologic Studies

- Epidemiologic studies consistently identify sign. associations between individual vaccines and chronic ill health in Gulf War veterans
  - *Anthrax: ORs ~ 1.3 – 3.7*
  - *Botulinum toxoid: ORs ~1.8 – 4.9*
  - *Meningococcus: ORs ~1.6 – 3.6*
- Epidemiologic studies also support associations between increased number of vaccines and chronic ill health in Gulf War veterans
- Important to consider reporting bias in studies relying on self-reported receipt of vaccines

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Vaccines: Summary of Information Considered

Clinical and Epidemiologic Studies: Squalene

- Asa et al report association between chronic symptoms and presence of antibodies to squalene in ill Gulf War veterans and recipients of AVA in AFIP
- USAMRID studies suggest squalene antibodies naturally occur in the general population, increase with age
- Additional ongoing Army study is assessing presence/absence of squalene antibodies in ill/healthy Gulf War veterans

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Unanswered Questions re: Vaccines and the Health of Gulf War Veterans

- Anthrax or other Gulf War-era vaccines associated with long-term symptom complexes similar to those reported by Gulf War veterans?
- Adverse effects of Gulf War-era vaccines in nondeployed military personnel?
- Little information on GW veterans' health in relation to specific vaccine combinations
- No evaluation of vaccine-related risk in Gulf War subgroups (e.g. by branch, unit, lot)
- Possible interaction of vaccines with other Gulf War exposures?

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Vaccines and Gulf War Illnesses: Unanswered Questions Related to Squalene

- Anti-squalene antibodies in Gulf War veterans?
  - Do veterans with Gulf War illnesses have an elevated level of antibodies to squalene (whether or not in relation to AVA)?
  - If so, is their presence 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 (e.g., contaminant)?
  - Levels capable of causing chronic illness?

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Discussion of Recommendations

Animal/Toxicological Research:
- *Neuro, immune effects of combinations of vaccines; vaccines in combination with other exposures?*

Epidemiologic Studies: studies should focus on 1991 vaccines
- Blinded case/control evaluation of squalene antibodies in ill/healthy Gulf veterans using ASA and Army assays
- Identify Gulf veteran subgroups known to have received AVA, compare health parameters to group that didn't
- Epi evaluations of other individual and combinations of Gulf War-era vaccines among veterans who have shot records

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