

# *Occurrence of ALS among Gulf War Veterans: Using the Epidemiology as a Guide to Intervention*

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## *Financial Support and Contributors*

This presentation is based on studies supported through grants or in-kind contributions from the following sources:

- Department of Defense and Department of Veterans Affairs through grants from the VA Cooperative Studies Program, CSP 500 (original study) and CSP 500a (surveillance study)
- HSR&D Program, Durham VA Medical Center
  - Drs. Allen, Coffman, Grambow and Oddone, and Ms. Linquist;
  - Dr. Miranda and her research staff
- Lexington VA Medical Center
  - Dr. Edward Kasarskis
- National Institutes of Health and University of Cincinnati
  - Drs. Ronnie D. Horner and Jun Ying

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## *Presentation Objectives*

- **Review Current Understanding of the Epidemiology of ALS among Gulf War Veterans**
- **Present Current Thoughts on the Emerging Evidence Relevant to the Etiology of the Outbreak (and hence Mechanism and Intervention)**

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## *I. Overview*

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## ***Clinical Description of ALS***

- A neuro-degenerative disease involving the death of motor neurons
- Invariably terminal with death typically occurring within 2-5 years post-onset
- Incidence increases with age, especially after 55 years of age
- Etiology is uncertain, although 10% of cases have a familial history

## ***Unique Aspects of the ALS Cluster among 1991 Gulf War Veterans***

- Relatively Young Men Affected (i.e., approximately 50% of cases under 25 years of age at onset)
- Individuals Fit for Combat (i.e., Healthy Warfighter Effect – Expected Rate below that of the General Population)
- Family History of ALS in ~10% of Cases (3 of 40 cases in original cohort)
- One of Largest Contemporary Clusters of Cases

## ***Intervention Through Epidemiology***

- **Current Cluster Represents an Unusual Occurrence**
- **Epidemiologist Study High-risk or Unusual Outbreaks to Discover Etiology**
- **Etiologic Knowledge may Suggest the Mechanism by which the Agent Exerts Its Effect**
- **Mechanism May Point to Therapies**

## ***II. Brief Review of the Epidemiology of the 1991 Gulf War Outbreak***

## *Reports on Occurrence of ALS among 1991 Gulf War Military Personnel*

Study	Case Ascertainment Time Period	Number of ALS Cases:		Risk Ratio (95% CI)
		Deployed	Non-deployed	
Smith, 2000	1991 - 1997	6	12	1.66 (0.62, 4.44)
Horner, 2003	1990 - 2000	40	67	1.92 (1.29, 2.84)
Coffman, 2005	1990 - 2000	42*	76*	1.77 (1.21, ---)
Horner, 2008 Update	1991 - 2001	48	76	1.90 (1.34, 2.69)
Barth, 2009	1991 - 2004	23	38**	0.96 (0.56, 1.62)

\* Best estimate from capture-recapture analysis

\*\* Based on 50% sample of non-deployed

## *Why So Few ALS Deaths among Deployed in Barth et al. ?*

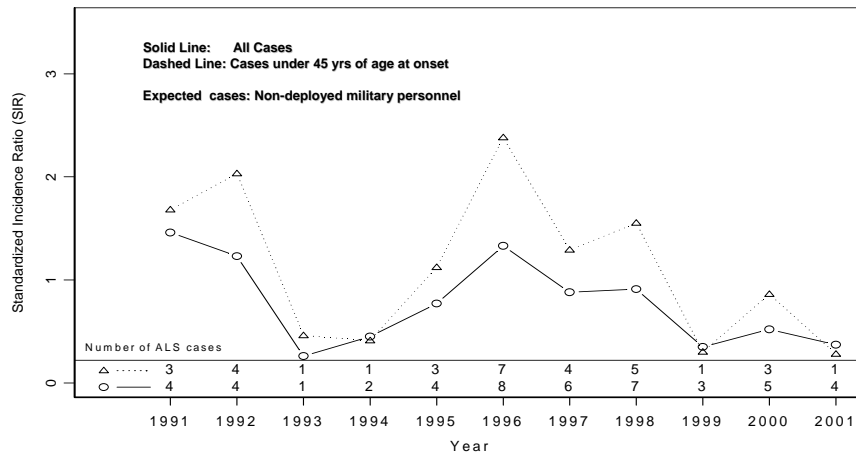
### ■ Definition of Study Population?

- Deployment: 8/1/90 – 3/31/91 vs. 8/2/90 – 07/31/91
- Result: N=621,902 vs. N=696,118 ( $\Delta=74,216$ )
- Non-deployed: 50% sample so equivalent to other studies

### ■ Definition of Case?

- Motor Neuron Disease (335.2) or ALS (335.20)

## *Epidemic Curve for Deployed Military Personnel (vs. Non-deployed Military)*

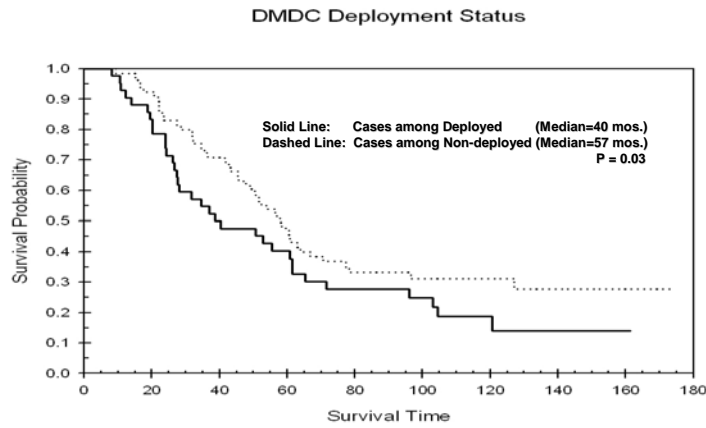


Horner et al. *Neuroepidemiology* 2008; 31: 28-32

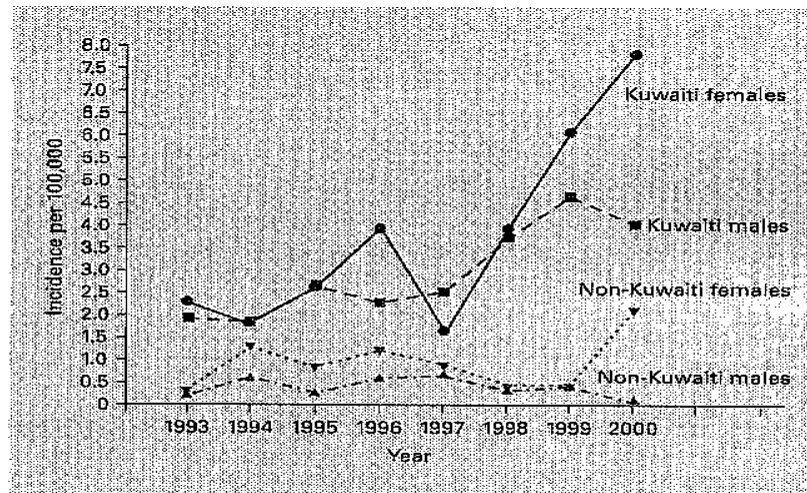
## *Descriptive Epidemiologic Studies*

- **No Persian Gulf Variant of ALS is Apparent (Dr. Kasarskis)**
  - Shorter survival for Deployed versus Non-deployed Cases
- **No Known Data on ALS as Endemic or Epidemic in Native Middle East Populations**
  - Dramatic increase in MS in Kuwaiti Population during decade after 1991 War (Alshubaili et al, *Eur Neurol* 2005; 53: 125-131)

## *Survival of ALS Cases by Deployment Status: A Distinguishing Characteristic*



Survival curves adjusted for age and type: bulbar vs. non-bulbar. Kasarskis et al. ALS, 2008; 16: 1-7



**Fig. 1.** Incidence of MS in Kuwait according to sex and nationality, 1993–2000.

Source: Alshubaili et al, Eur Neurol 2005; 53: 125-131

### ***III. Update on the Inquiry into the Etiology of the Outbreak***

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#### ***Quest for Clues to the Etiology***

- **Military Service as a General Risk for ALS  
(Dr. Weiskopf)**
- **Sartwell's Model to Assess Likelihood of  
Common Source or Common Time Point of  
Exposure**
  - Shape of Cumulative Distribution of Case Onset
- **GIS Analysis of Spatial "Hot Spots" in the  
Theater of War (Dr. Miranda)**
  - Common Points of Exposure in Geographical  
Space (and Time)



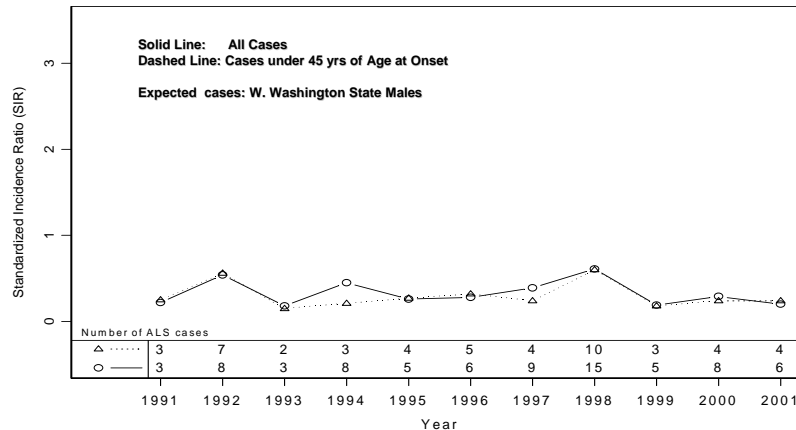
## ***Why Military Service Does Not Explain the 1991 Gulf War Outbreak***

- **Weiskopf Study: Higher risk of ALS among those with any military service.**
  - ❑ Overall risk: 1.53 (95% CL = 1.12, 2.09); Highest risk: Army and Navy, but not Air Force
  - ❑ Increasing risk with increasing number of wars during military service; no association with years of service
  - ❑ Population was older individuals: Mean age was 64.7 yrs for “Never Served” versus 62.8 years for “Served”
  - ❑ Horner Study: Approx. 50% under 25 yrs of age; 98% under 55 yrs of age

## ***Military Service and ALS Risk: Evidence from a Civilian Population***

- **W. Washington State Study: Additional Evidence?**
  - ❑ Half of the men had served in the military
  - ❑ Observed rate: 2.12 per 100,000 per year
  - ❑ Anecdotal report: 2-fold greater risk among men who had served in military
  - ❑ If 2-fold risk with military service, observed rate is an average; “civilian” rate enhanced by 50%
  - ❑ Comparison of enhanced civilian rate to military rate should “drive” risk ratio toward the null

## “Epidemic Curve” for Non-Deployed Military Personnel vs. W. Washington State Men

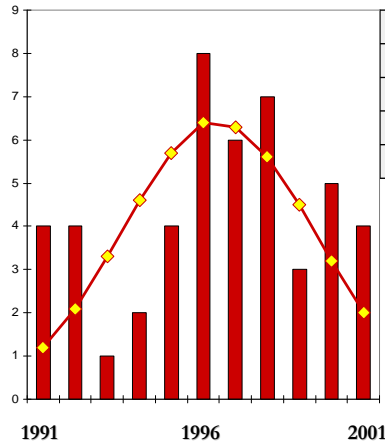


Horner et al. *Neuroepidemiology* 2008; 31: 28-32

## Assumptions of Sartwell’s Model

- **Multiplicative (growth) Process in Pathogenesis of Agent or Toxic By-products**
  - ❑ Threshold at which Symptoms Appear
  - ❑ Incubation Period = Time from Symptom Onset – Time of Exposure
- **Inherent Individual Variation in Incubation Period**
- **Functional Form of Onset Distribution Independent of Incubation Period Length and Agent Dosage**
- **A Lognormal Distribution Infers:**
  - ❑ Common Source of Exposure
  - ❑ Common Time of Exposure

## *Distribution of Time of Onset Among All Deployed ALS Cases*

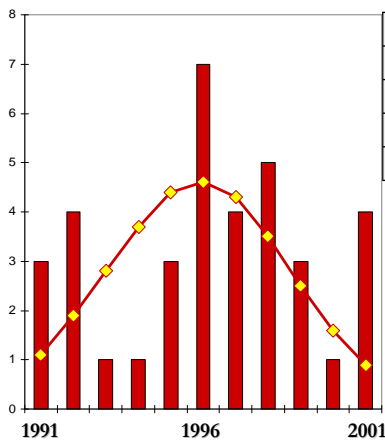


Goodness-of-Fit Tests for Lognormal Distribution				
Test	Statistic		p Value	
Kolmogorov-Smirnov	D	0.15782142	Pr > D	0.042
Cramer-von Mises	W-Sq	0.10629498	Pr > W-Sq	0.091
Anderson-Darling	A-Sq	0.67369320	Pr > A-Sq	0.075

Unpublished data



## *Distribution of Time of Onset Among Deployed ALS Cases <45 yrs at Onset*



Goodness-of-Fit Tests for Lognormal Distribution				
Test	Statistic		p Value	
Kolmogorov-Smirnov	D	0.12657200	Pr > D	0.053
Cramer-von Mises	W-Sq	0.10629859	Pr > W-Sq	0.092
Anderson-Darling	A-Sq	0.78108665	Pr > A-Sq	0.041

Unpublished data



## ***Spatial GIS Findings on Potential Etiologic Agents***

- **Elevated Risk Associated with Khamisiyah:  
OR = 1.7 (95% CL = 0.7, 3.7)**
- **Exposure to Oil Well Fire Smoke not Modeled**
- **Current Effort is a Spatio-temporal GIS Analysis**
  - **Determine if Exposures Match in Time as well as Space**
  - **Model the Oil Well Fire Smoke Exposure**

## ***Other Potential Causes of Outbreak***

- **Adjuvants in Anthrax Vaccine: Aluminum Hydroxide and Squalene** (Shaw, Petrik. J Inorg Biochem 2009; 103: 1555-1562; Petrik et al. Neuromolecular Med 2007; 9: 83-100)
- **Exposure to Cyanobacteria which Produce Neurotoxic BMAA** (Cox et al. Amyotrophic Lat Sclerosis 2009, Suppl 2: 109-117)
- **Neurotoxicity via Heavy Metals in Desert Soil** (Based on Conversations with Capt. Mark Lyles, DMD, PhD)
- **Head Trauma** (Schmidt et al. J Neurol Sci 2010; 291: 22-29)

## **Adjuvants in Anthrax Vaccine and Motor Neuron Death**

- **Murine Model: Adjuvants Injected at Doses Equivalent to Those Received by US Military**
- **Progressive Decrease in Strength (~50% of strength of controls) via “hang time” Test**
- **Cognitive Deficits: 4.3 errors per trial vs. 0.2 errors in Water Maze**
- **35% Loss of Motor Neuron and 350% Increase in Astrocytes in Spinal Cord**

Petrik et al. *Neuromolecular Med* 2007; 9: 83-100



## ***Gulf-specific Environmental Exposures***

- **Exposure to Cyanobacteria which Produce Neurotoxic BMAA (Cox et al. Amyotrophic Lat Sclerosis 2009, Suppl 2: 109-117)**
  - Cyanobacteria produce beta methylamino-L-alanine
  - “Mats” and “Crusts” wide-spread in Deserts of Qatar and yield BMAA in Dust
- **High Concentrations of Heavy Metals in Desert Soil of Kuwait and Iraq (Per Conversations with Capt. Mark Lyles, DMD, PhD)**



## **Lead, Head Trauma and ALS in Military Veterans**

- **Lead and ALS** (Fang et al. Am J Epidemiol 2010; 171: 1126-1133)
  - Blood Lead Levels Higher in 184 Cases vs. 194 Controls with Doubling of Blood Lead: Risk of ALS 1.9 (95% CI=1.3-2.7)
  
- **Head Trauma and APOE-4** (Schmidt et al. J Neurol Sci 2010; 291: 22-29)
  - In 241 Cases and 597 Controls: ALS Odds=2.33 (95% CI=1.18-4.61) if Injury within Prior 15 yrs
  - Strongest Risk in APOE-4 Carriers

## ***Further Thoughts on the Etiology***

- **Dose-Response or Threshold Effect?**
  - Multiple Exposures to One Agent
  - Exposures to Multiple Agents
  - Rapid Time to Toxic Dose
  
- **Agent or Mechanism: Which is Most Salient?**
  - Human Body has Limited Arsenal to Deal with Exposures
  - E.g., 8-10 liver enzymes to metabolize most drugs

## *Thoughts on the Mechanism*

- **Could the Pathology of Neurodegenerative Conditions Reflect a Common Mechanism to Protect Neurons:**
  - Detoxification of Neuro-toxicants
  - Anti-Oxidative Stress
  - Anti-Inflammation
  - Anti-Apoptosis
- **Is there Genetically Mediated Variation in Neuro-protective Response to Neuro-toxicants?**

## *IV. Concluding Thoughts*

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## ***Evidence and Next Steps***

- **2-fold Higher Risk of ALS among 1991 Gulf War Veterans**
- **Elevated Risk Probably Not Explained by Methodological Biases**
- **Etiology Remains Uncertain; Exposures Immediately Prior to or During Deployment May Be Involved**
- **Perhaps It Will be More Useful to Focus on Mechanism vs. Specific Etiologic Agent(s)**