Gulf War Illness Research: Case Definitions and Health Measures

Lea Steele, Ph.D.
Director, Veterans Health Research Program
Institute of Biomedical Studies
Baylor University
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Gulf War Illness Research: If You Don’t Measure it, You Can’t Study It

Background

- After 23 years, urgent need for Gulf War veterans’ studies that succeed; i.e., pose priority research questions optimally, and answer them in a clear and replicable way
- Improved research requires improved and consistent methods for evaluating the health of Gulf War veterans
- This includes the need for an evidence-based, widely accepted case definition for Gulf War Illness
- Also need “optimized” and consistent health measures and methods:
  - Improve validity and reliability of research findings
  - Improve comparability across studies
Gulf War Illness Research: *Health Measures and Outcomes*

**Not a New Idea**

## Gulf War Illness Research: *Health Measures and Outcomes*

### Overview

- Case Definitions for Gulf War Illness
- Symptom Assessment in Gulf War Veterans
- Other Health Measures of Importance

### Overview:

*Defining Gulf War Illness in 1990-91 Gulf War Veterans*
Post War Illness in 1990-1991 Gulf War Veterans

**Gulf War Syndrome, Undiagnosed Illness, Gulf War Veterans’ Illnesses, Chronic Multisymptom Illness, Gulf War Illness**

- All refer to the same thing: well-documented pattern of symptoms found at significantly elevated rates in all population studies of 1990-91 Gulf War veterans
- Not explained by standard lab tests or by well-established medical or psych diagnoses
- Widespread problem in 1991 GW veterans, little improvement with time

Problem: Still no generally accepted case definition for GWI

- Gulf War illness currently defined on basis of veterans’ symptoms
- After 23 years, hundreds of millions of dollars of research: studies still use different case definitions, sometimes no case definition
- Research results difficult to interpret, impossible to integrate
- Has slowed progress for addressing this problem
“My symptoms began in the Gulf with severe abdominal cramping and severe diarrhea. I also had terrible headaches and bouts of dizziness and tingling. Once I returned to the base in Germany, the headaches persisted, and I experienced the cramps and diarrhea on a cyclic basis.

I also went through periods of night sweats. And there were periods where I would sleep a lot because I was so fatigued. My joints were stiff, and my knees would swell after I ran. It was harder for me to do things without feeling short of breath. These symptoms became worse as time passed....

Ever since my return from the Gulf, I’ve been plagued by multiple rashes and lesions on my face, neck, arms and back. They come and go.”

SSgt BJ, Desert Storm veteran, U.S. Army

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### Studies Identify Consistent Symptom Domains

#### Table 2. Symptom Domains Affecting Gulf War Veterans at Excess Rates

<table>
<thead>
<tr>
<th>Gulf War Veterans Studied</th>
<th>Method Used to Identify Domains</th>
<th>Symptom Domains Described</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Neuro/ Cognition/Mood</td>
</tr>
<tr>
<td>U.S. Veterans, All Branches</td>
<td></td>
<td>+ + + + + +</td>
</tr>
<tr>
<td>10,423 veterans in national survey$^{702}$</td>
<td>Factor analysis</td>
<td>+ + + + +</td>
</tr>
<tr>
<td>1,546 Kansas veterans$^{447}$</td>
<td>Correlation analyses</td>
<td>+ + + + +</td>
</tr>
<tr>
<td>1,161 veterans from 7 states$^{409}$</td>
<td>Factor analysis</td>
<td>+ + + + +</td>
</tr>
<tr>
<td>867 veterans in Washington, Oregon$^{190}$</td>
<td>Factor analysis</td>
<td>+ + + ± ±</td>
</tr>
<tr>
<td>1,886 Iowa veterans$^{203}$</td>
<td>Factor analysis</td>
<td>± + ±</td>
</tr>
<tr>
<td>Other Countries</td>
<td></td>
<td>+ + + + + ±</td>
</tr>
<tr>
<td>9,588 U.K. veterans$^{205}$</td>
<td>Factor analysis</td>
<td>+ + + + +</td>
</tr>
<tr>
<td>3,454 U.K. veterans$^{591,125}$</td>
<td>Factor analysis</td>
<td>+ na + + +</td>
</tr>
<tr>
<td>1,322 Australian veterans$^{195}$</td>
<td>Factor analysis</td>
<td>+ + ± + ±</td>
</tr>
</tbody>
</table>
Gulf War Illness: Studies Identify Concurrent Symptoms in Multiple Domains

Currently, 8 different GWI case definitions, 4 other methods to classify “Cases”

Examples (from very broad to very narrow)

- **Oregon GWUI**: 1 “unexplained” symptom required (prev: unknown)
- **CDC CMI**: 1 symptom required in 2 of 3 symptom domains (prev: ~ 50% of GW veterans)
- **Kansas GWI**: Moderately severe symptoms required in 3 of 6 symptom domains (prev: ~ 34% of GW veterans)
- **Haley**: 3 syndromes—complex algorithm to determine symptom scores (combined prev: ~ 14% of GW veterans)
- **Kang/VA**: 4 neurological symptoms (prev: ~2% of GW veterans)
What Makes a Good GWI Case Definition?

“True Gulf War Illness” Target Condition

What Makes a Good GWI Case Definition?

Gulf War Illness Case Definition
What Makes a Good Case Definition? 3 Scenarios

1. Ideal Case Definition
2. Case Definition Lacks Specificity
3. Case Definition Lacks Sensitivity

In real terms, what are the effects of using inadequate case definitions for GWI?

Poor Specificity: Controls routinely identified as GWI “Cases”

Poor Sensitivity: GWI Cases routinely identified as “Controls”

- Undermines any study designed to identify effective treatments, or determine biological differences between GWI and “healthy” controls.

- At best, will “muddle” any study results. At worst, can yield results that are completely erroneous.
What Makes a Good Case Definition?

1. Depends on purpose
   (e.g. research use, clinical use, other)
2. Should “optimally” distinguish individuals with the condition from those who don’t have it

VA Gulf War Research Strategic Plan: Case Definition Process

- VA Gulf War Research Strategic Plan: 2013 - 2017
- Major undertaking: initiated in April 2011
- Led by Dr. Max Buja: 10 working groups, >45 participants (included members of 3 different VA research advisory panels and VA researchers, administrators)

5.3: Establish an Evidence-Based Case Definition of Chronic Multisymptom Illness in Gulf War Veterans
VA Gulf War Research Strategic Plan:

5.3: Establish an Evidence-Based Case Definition of Chronic Multisymptom Illness in Gulf War Veterans

Outline of the Process

1. **Review of the literature pertaining to GWI case definition**

2. **Comprehensive analytic effort, using extensive amount of available data**
   - Analytic assessment of existing case definitions—strengths and weaknesses in relation to priorities of interest
   - Assessment of different algorithms, strategies for optimizing case def

3. **Expert Consensus Process:** Final case definition developed by consensus panel of experts in GWI research, relevant expertise in methods for developing symptom-based case definitions

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**Major considerations in optimizing research case definition**

- Specificity
- Sensitivity
- Reliability
- Portability for use in different settings, different study types
- Strategy for considering other medical/psych conditions to be exclusionary for CMI (vs. comorbid)
- Subgroup identification
- Use in clinical practice, and special considerations
2013: VA Contracts with IOM to Develop Case Definition for CMI

VA Charge to IOM Committee

An ad hoc committee will develop a case definition for chronic multisymptom illness (CMI) as it pertains to the 1990–1991 Gulf War Veteran population. The committee will comprehensively review, evaluate, and summarize the available scientific and medical literature regarding symptoms for CMI among the 1991 Gulf War Veterans.

In addition to reviewing and summarizing the available scientific and medical literature regarding symptoms and case definitions for CMI among Gulf War Veterans, the committee will evaluate the terminology currently used in referring to CMI in Gulf War Veterans and recommend appropriate usage.

RAC-GWVI 2014 Recommendations re: GWI Case Definition

RAC endorsed the case definition process outlined by VA strategic plan, reiterated the importance of:

- **Review of literature** pertaining to GWI case definition
- **Evidence based**: In-depth statistical assessment of different case definition approaches, using large body of existing data
- **Consensus-driven**: Final case definition developed by consensus of GWI research experts, clinicians, GW veterans, VA, CDMRP

Recommended that VA use the term **Gulf War illness** for the symptomatic condition resulting from 1991 Gulf War service.
IOM 2014 CMI Case Definition Report

Recommendations to VA

1. VA use the CDC and Kansas case definitions because they capture the most commonly reported symptoms.

2. VA systematically assess existing data to identify additional features of chronic multisymptom illness (e.g. onset, duration, severity, exclusionary criteria) to produce a more robust case definition.

3. VA use the term Gulf War illness rather than chronic multisymptom illness.

- Also clarified that factor analysis should not be used to define GWI “cases”-

CDC and Kansas Case Definitions

**CDC CMI Case Definition** (prev: ~ 50% of GW veterans)
- Requires at least 1 symptom (≥ 6 months) in 2 of 3 symptom domains (fatigue, pain, cognitive/mood)
- No exclusionary criteria

**Kansas GWI Case Definition** (prev: ~33% of GW veterans)

*Inclusion criteria:*
- Multiple/moderately severe symptoms (≥ 6 months) in at least 3 of 6 symptom domains

*Exclusion criteria:*
- No serious medical/psych dx that account for symptoms or preclude accurate symptom reporting
Analytic Considerations: Developing Algorithm for Defining GWI

Example using data from Kansas Veterans

- 6 statistically-defined symptom domains sign. higher in GW vets:
  - Fatigue/sleep problems
  - Somatic pain symptoms
  - Neuro/cognitive/mood symptoms
  - Gastrointestinal symptoms
  - Respiratory symptoms
  - Skin symptoms

- Roughly same proportion (29-30%) of Gulf War and nondeployed veterans had some symptoms in 1 or 2 symptom domains

- Roughly same proportion reported dx with many medical conditions (e.g., diabetes, heart disease, cancers)

Gulf War Illness: Studies Identify Concurrent Symptoms in Multiple Domains

- PAIN SYMPTOMS
  - Joint Pain
  - Muscle Pain

- NEUROLOGIC SYMPTOMS
  - Memory Problems
  - Headaches
  - Dizziness
  - Mood Changes

- FATIGUE SYMPTOMS
  - Fatigue
  - Sleep Problems

- GASTROINTESTINAL SYMPTOMS
  - Diarrhea
  - Nausea

- RESPIRATORY SYMPTOMS
  - Persistent Cough
  - Wheezing

- SKIN PROBLEMS
  - Rashes
  - Other Problems
Burden of Symptoms in Kansas Gulf War and Nondeployed Era Veterans

- Nondeployed Veterans
- Gulf War Veterans

Prevalence of Exclusionary Conditions and Symptom Groups Among Kansas Gulf War-Era Veterans

- Nondeployed Veterans
- Gulf War veterans
**Raises Issues re: Specificity**

**Consideration of Exclusionary Criteria in Defining GWI**

- **Issue**: Can (or should) GW veterans with other diagnosed conditions also be considered GWI cases?

- **Can be tricky**: Pros and cons differ for different studies, in different situations (e.g., large/small, cohort/case-control, different study questions, etc.)

- **Evidence can inform this decision**: can evaluate impact of incorporating different strategies for using exclusionary criteria

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**Exclusionary Diagnoses (Kansas GWI case def)**

**Later sample of 646 KS and Missouri Gulf War Vets (2001)**

<table>
<thead>
<tr>
<th>Diagnosis/Condition dx by Physician</th>
<th>Number of Veterans</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic problems due to serious injury</td>
<td>27</td>
<td>4%</td>
</tr>
<tr>
<td>Heart disease</td>
<td>21</td>
<td>3%</td>
</tr>
<tr>
<td>Cancer</td>
<td>18</td>
<td>3%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>18</td>
<td>3%</td>
</tr>
<tr>
<td>Liver disease</td>
<td>12</td>
<td>2%</td>
</tr>
<tr>
<td>Dx schizophrenia</td>
<td>3</td>
<td>&lt; 1%</td>
</tr>
<tr>
<td>Excluded for any medical diagnoses</td>
<td>102</td>
<td>16%</td>
</tr>
<tr>
<td>Excluded for any psych diagnoses</td>
<td>12</td>
<td>2%</td>
</tr>
</tbody>
</table>
Impact of Using Different GWI Case Definitions on Research Results

- Issue: What are effects of using broader/narrower GWI case definitions on research findings?
- Can evaluate analytically in multiple ways
- Risk Factor Example: Use of CDC, Kansas case defs generally identify same direction of association, but different magnitude

Use of Different Case Definitions to Assess Risk Factors for Gulf War Illness in 304 Kansas and Missouri GW Veterans

<table>
<thead>
<tr>
<th>Exposure/Risk Factor</th>
<th>OR: CDC Case Def</th>
<th>OR: KS Case Def</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticide-treated uniforms</td>
<td>1.88</td>
<td>3.72*</td>
</tr>
<tr>
<td>Skin pesticides</td>
<td>2.30*</td>
<td>2.89*</td>
</tr>
<tr>
<td>Used PB pills</td>
<td>1.99*</td>
<td>3.21*</td>
</tr>
<tr>
<td>Participated in ground combat</td>
<td>1.43</td>
<td>1.42</td>
</tr>
<tr>
<td>Heard chemical alarms</td>
<td>1.09</td>
<td>1.31</td>
</tr>
<tr>
<td>Living area fogged with pesticides</td>
<td>1.03</td>
<td>1.33</td>
</tr>
</tbody>
</table>

*p< 0.05
Current Efforts Focused on Case Definition:

Office of Congressionally Directed Medical Research Programs (CDMRP) GWIRP

- Major priorities of CDMRP’s GWI Research Program include improvement of GWI case definition; funded 2 large projects, now underway:
  - Fort Devens cohort: longitudinal evaluation of symptom data to improve GWI case definition, based on current symptom profile
  - Baylor project (with Westat): National study of Gulf War and era veterans to characterize current symptoms, optimize case definition

- FY2014 preannouncement: Invites proposals to develop consensus case definition for GWI

Additional Health Measures of Importance

Symptom Assessment in Gulf War Veterans

- Symptoms, by definition, are self-reported
- Symptom assessment for research studies differs from clinical evaluation of symptoms; key is to be systematic
- What symptoms? How to query them? What characteristics of symptoms (e.g. onset, duration, severity, frequency?)
- Accurate case ascertainment and health assessment depend on the strength of the symptom inventory used.
Additional Health Measures of Importance

Symptom Assessment in Gulf War Veterans

- In the 1990s, symptom questionnaires developed by multiple groups to provide a systematic inventory of symptoms reported by veterans (e.g. VA Registry, DOD Registry, King’s College studies, NHRC/Seabees studies, CDC, VA National Study, Kansas study).

- Some of the best symptom inventories came from the CDC (Fukuda/Air Force study, Iowa study). These provided clear, systematic questions about symptom occurrence, onset, duration, and severity.

- Some approaches were not successful, e.g., asking about different symptoms in different ways, “open-ended” symptom queries, with no information on current symptoms or severity.

Example of currently used symptom inventory: Kansas symptom questionnaire

- Kansas study (1998-1999): Questionnaire “synthesized” symptom questions from large studies through 1998: CDC (Air Guard and Iowa), UK (King’s College), NHRC (Seabees), VA National Survey. It reviewed other studies, both registry questionnaires.

- Objective was to provide data on the broad spectrum of symptoms known to affect Gulf War veterans, and to provide data comparable to other large population-based studies.

- Queried symptoms' presence/absence, time of onset, duration, severity.
Symptom Assessment in Gulf War Veterans

Example: Kansas symptom questionnaire

Provides case status for both:
- Kansas GWI
- CDC (Fukuda) CMI

with 2 additional symptoms:
- “Presumed CFS”

Versions for either:
- CATI interview
- Paper/pencil survey

Please answer these questions as completely as possible.
If you are not sure of the answer to any question, please give your best estimate.
If you have no idea of the correct answer, indicate by writing “DON’T KNOW” in the blank.
If you prefer not to answer any question, indicate by writing “NO ANSWER” in the blank.

Symptom Assessment in Gulf War Veterans
Example: Kansas symptom questionnaire

<table>
<thead>
<tr>
<th>Symptom</th>
<th>NO</th>
<th>YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feeling unwell after physical exercise or exertion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Problems getting to sleep or staying asleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not feeling rested after you sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in your joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stiffness in your joints</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain in your muscles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body pain, where you hurt all over</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feeling dizzy, lightheaded, or faint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eyes very sensitive to light</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blurred or double vision</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Numbness or tingling in your extremities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tremors or shaking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low tolerance for heat or cold</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Having physical or mental symptoms after breathing in certain smokes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please indicate if you have had a persistent problem with each of the following symptoms over the past six months. If you have had this problem, please rate it as mild, moderate, or severe and indicate if it first became a problem before you deployed to the Gulf, or during/after your deployment.

If YES

<table>
<thead>
<tr>
<th>How would you rate this problem?</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before deployment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>During deployment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After deployment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When did you first have this problem?

<table>
<thead>
<tr>
<th>Date of first symptom occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before deployment</td>
</tr>
<tr>
<td>During deployment</td>
</tr>
<tr>
<td>After deployment</td>
</tr>
</tbody>
</table>
Health Studies of Gulf War Veterans

Other Prominent Issues re: Health Measures

- High Priority: Identification of objective measures with sufficient sensitivity/specificity to use for diagnostic purposes

- Objective biomarkers will also provide important tools for identifying biological subgroups, changes in health over time, and effects of treatment interventions

- Can also document health status of Gulf War veterans using standardized assessment tools, for example:
  - Functional status, quality of life: (SF36, SF36V, SF12)
  - Neuropsychological functioning: (multiple domains, tests)
  - Pain assessments (e.g. McGill, VAS)
  - Fatigue assessments (e.g. Chalder)
  - Sleep assessments (e.g. Pittsburg sleep inventory)
  - Gastrointestinal instruments (e.g. Rome criteria for IBS, etc)
  - Autonomic testing, autonomic symptom inventories (e.g. Mayo)
  - Other: respiratory testing, exercise capacity

- These tests can be used to quantify status of overall health or particular health domain, for comparative purposes:
  - e.g. comparison to general population
  - Comparisons between GWI cases and controls (i.e., “sick” vs. “healthy” veterans)
  - Clinical trials: Comparisons between treated/untreated (e.g., active vs. placebo)
Health Studies of Gulf War Veterans

Other Prominent Issues re: Health Measures

• No standardized instruments currently identified as “best” for studies of Gulf War veterans

• Choice of instrument will depend on study question, purpose:
  ▶ e.g., if study focused on pain issues, would use pain instrument and/or VAS

Important Question:
How Best to Measure Treatment Response/Outcomes?

Optimal treatment outcome measure would be change in biomarker: pre-vs. post-treatment

• Cases currently identified by symptoms, so important to assess pre- vs. post-changes in symptom burden (presence/absence of symptoms, symptom severity)

• Also desirable to assess changes in wellbeing, function

• Should assess changes in any specific health domain targeted by treatment intervention (e.g. pain inventory, visual analog scale; frequency and severity of diarrheal episodes, quality of sleep)

• Important NOT to focus exclusively on targeted domain—want to find out if treatment benefits symptoms more generally, overall health and functional status (e.g., Amin et al CPAP study)
Health Measures in Gulf War Veterans:

Summary

- Accelerated progress in Gulf War health research requires the use of better, more consistent methods and measures.
- Until diagnostic biomarkers are available, advances in GWI research will be greatly facilitated by establishing an evidence-based, widely accepted case definition for Gulf War Illness.
- Important to assess symptoms systematically.
- Use of standardized instruments to assess functional status, symptom domains of interest for particular study question.
- Overall, GW research effort would benefit from testing and validation of particular instruments and measures for purposes of studying GWI.