

# Gulf War Illness in the 1991 Gulf War and Gulf Era Veteran Population: An Application of the Centers for Disease Control and Prevention and Kansas Case Definitions to Historical Data

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## Introduction

In the initial years following the 1990–1991 Gulf War, reports of a complex array of medically unexplained symptoms began to emerge among US Gulf War veterans.<sup>1,2</sup> This cluster of symptoms, which included fatigue, pain, gastrointestinal symptoms, respiratory symptoms, dermatological symptoms, neurological symptoms and cognitive symptoms,<sup>3–9</sup> collectively became known as Gulf War illness (GWI). Twenty-six years later, GWI remains the most pressing health issue of Gulf War veterans. Although several war-related exposures have been associated with GWI,<sup>10–14</sup> no single exposure has been confirmed as the causative agent and no one single treatment has been identified.<sup>15</sup> There is no objective diagnostic test for GWI and the International Classification of Diseases Manual 10th edition has no diagnostic code for GWI. Although some unexplained illnesses and symptoms consistent with GWI are recognised as compensatable disabilities by the US Department of Veterans Affairs (VA), there is not a single validated and accepted case definition.<sup>16</sup> The lack of a single agreed-upon case definition has been challenging for both researchers and clinicians.

In 2013, VA charged the Institute of Medicine (IOM) with establishing a consensus case definition for GWI. IOM's final report acknowledged that the gaps in the literature made it unfeasible to develop a proper case definition,<sup>16</sup> but recommended that VA use its own data to fill those gaps and in the meantime employ the two most widely used case definitions for GWI: the Kansas<sup>11</sup> and the Centers for Disease Control and Prevention (CDC) case definitions.<sup>3</sup> In

this paper, we will apply modified Kansas and CDC case definitions for GWI to survey data collected in 1995 on a population-based sample of 20,917 Gulf War and Gulf Era veterans.

The specific aim of this paper is to identify veterans in the largest population-based longitudinal cohort of Gulf War and Gulf Era veterans who met the criteria for GWI by the Kansas and CDC definitions in the first 5 years following the 1990–1991 Gulf War, before the development of age-related chronic medical conditions. This contributes to the scientific literature by providing population-based estimates of GWI following the war, using the two IOM-recommended case definitions; the studies that produced the Kansas and CDC case definitions were not population based and were limited in size. Additionally, it identifies a cohort of representative veterans that the VA has been following since 1995 who were likely cases of GWI (before a name or case definition even existed). This subgroup can serve as a recruitment resource for VA's ongoing genomics research to identify a biomarker and genetic signals for GWI.

## Methodology

The data for this study come from the National Health Survey of Persian Gulf War Era Veterans (NHS), a population-based survey of 15,000 Gulf War (deployed) and 15,000 Gulf Era (non-deployed) veterans fielded in 1995. The 15,000 Gulf War veterans were sampled from all 693,826 US troops identified by the Department of Defense's Defense Manpower Data Center (DMDC) as having been

deployed (i.e. arrived) to the Gulf War between 1 August 1990 and 1 March 1991 (the end of the ground war). The 15,000 Gulf War Era veterans were sampled from 800,690 persons (half of all those who were in the military between September 1990 and May 1991) identified by DMDC as having served during that same time but had not deployed to the Gulf War. Both the Gulf War and Gulf Era samples had representation from each of the four branches of service (Air Force, Army, Marine Corps, Navy); women, National Guard and Reservists were over-sampled using a stratified design. Individuals sampled for the study were mailed a 16-page health questionnaire with a return-addressed postage-paid envelope. Veterans who did not return the mail survey were contacted and offered a computer-assisted telephone interview (CATI). Data collection took place between 1995 and 1997. A detailed narrative of the study design and methods has been described elsewhere.<sup>4</sup>

### Symptom measurement for case definitions of GWI

The 1995 NHS survey included a lengthy list of symptoms, health questions, and queries about onset and duration used in this analysis to identify veterans who satisfied the criteria for GWI. Symptoms and duration were obtained by the question, 'In the past year, have you had persistent or recurring problems with...?' Onset was assessed by the question, 'Did you first experience this before [2 August 1990], during [2 August 1990 – 30 June 1991] or after [1 July 1991] the Persian Gulf War?' For those respondents with missing symptom data, the majority were missing responses on a very few number of symptoms. If veterans could be identified as cases or non-cases based on the available data, that was done. If case status might change based on missing data, GWI status was set to missing. For example, if a veteran endorsed three of the symptoms required to be considered a case by the Kansas criteria, but had a missing value for other symptoms that are part of the Kansas definition, that veteran was coded as a case. However, if a veteran endorsed two of the symptoms required for the Kansas criteria, and had missing data on the rest of the symptoms that are required under the Kansas criteria, the veteran's GWI status was considered missing, as the veteran's case status could change based on the true value of the missing data.

### Kansas definition of GWI

We analysed the survey data using modified Kansas and CDC case definitions, due to the limitations of the

retrospective dataset. In order to be considered a case by the Kansas definition in this analysis, the veteran must have reported symptoms (by endorsing yes) in three of the following six domains: fatigue (excessive fatigue not due to exercise, problems getting to sleep or staying asleep, awoken feeling tired or worn out after a full night of sleep), pain (generalised muscle aching or cramps, joint aching or pain, back pain or spasms), neurological/mood/cognition (headaches, feeling dizzy/lightheaded/faint, blurred vision, numbness or tingling in extremities, tremors or shaking, sensitivity to certain smells or chemicals, difficulty concentrating, difficulty remembering words when speaking, feeling down or depressed, feeling irritable or having angry outbursts, feeling moody, feeling anxious), gastrointestinal (diarrhoea, nausea/upset stomach, stomach or abdominal pain and cramping), respiratory (difficulty breathing or shortness of breath, problems with coughing, wheezing in chest) and skin (skin rashes). Data on symptom severity were not available. The symptoms must have been present in the past 12 months, and the veteran must have first experienced the symptom during or after the Gulf War.

The Kansas case definition excludes individuals with certain physical and psychiatric conditions from screening positive for GWI.<sup>11</sup> Veterans who endorsed that they had ever been told by a doctor that they had any of the following conditions were classified as non-cases by the Kansas definition, even if they met the symptom criteria: cancer, diabetes, heart disease (coronary heart disease or tachycardia), liver disease (hepatitis or cirrhosis) and stroke. Additionally, veterans who endorsed an overnight hospital stay in the past year due to a mental illness were also excluded from case consideration. Veterans who indicated that they had had an overnight hospital stay in the past year but did not indicate the reason for hospitalisation were excluded from analyses. If exclusion criteria were missing, then the veteran's status was considered missing for Kansas GWI. Veterans who were excluded from case consideration due to either endorsing an exclusion criteria or missing information on symptoms were not excluded from the denominator of the prevalence calculation. This is consistent with the methods employed by Steele.<sup>11</sup>

### CDC definition of GWI

To be considered a GWI case by the CDC definition in this analysis, the veteran must have two symptoms from three of the following domains: fatigue (excessive fatigue not due to exertion, fatigue lasting more than 24 hours after exertion), mood and cognition (feeling

depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, problems getting to sleep or staying asleep, trouble finding words) and musculoskeletal (joint pain, muscle pain). The symptoms must have been present in the past 12 months, and first been experienced during or after the Gulf War. The same rules for missing data were applied for the CDC definition as applied to the Kansas definition. However, consistent with the original measure, no exclusion criteria for comorbidities were applied.<sup>3</sup>

### Statistical analysis

Bivariable and multivariable analyses were performed using SAS version 9.4.<sup>17</sup> Frequencies and prevalence were calculated and reported. Logistic regression was used to produce unadjusted odds ratios (OR) comparing the odds of meeting the criteria for the two different GWI case definitions in deployed compared to non-deployed. Multivariable logistic regression was used to produce adjusted odds ratios comparing the odds of meeting the criteria for the two different GWI case definitions in deployed compared to non-deployed controlling for sex, race, age, service branch and unit component.

### Results

Table 1 provides the demographic characteristics of the study population. Overall, 20,917 veterans responded to the survey (response rate=70%); of those, 11,441 were Gulf War veterans and 9,476 were Gulf Era veterans. Table 2 provides information on the frequency and proportion of veterans who had missing symptom data or exclusion criteria for the Kansas case definition only. For the Kansas case definition analysis, 2,588 veterans had exclusion criteria (1,809 deployed (15.8%) and 779 non-deployed (8.2%)) and 1,396 had ambiguous case status due to missing items (855 deployed (7.5%) and 541 non-deployed (5.7%)). The chi-square test comparing the proportion of missing and excluded data in deployed to non-deployed was significant ( $p<0.001$ ). For the CDC case definition analysis, 1,053 veterans had ambiguous case status due to missing items 590 (5.2%) in deployed and 463 (4.9%) in non-deployed; these proportions did not significantly differ ( $p=0.37$ ).

Table 3 provides the frequency, prevalence and unadjusted odds of meeting the criteria for GWI by the Kansas definition by military and demographic characteristics. Overall, about 41% of Gulf War veterans and 17% of Gulf Era veterans met the Kansas criteria for GWI. Certain subgroups of Gulf War veterans were more likely to meet the Kansas criteria

**Table 1: Demographic and military characteristics of Gulf War and Gulf Era veterans participating in the 1995 National Health Survey of Persian Gulf War Veterans and Their Families**

Characteristic	Gulf War (N=11,441)		Gulf Era (N=9,476)	
	N	%	N	%
<b>Sex</b>				
Male	9,310	81.4	7,399	78.1
Female	2,131	18.6	2,077	21.9
<b>Race</b>				
White	8,434	73.7	7,114	75.1
Black	2,177	19.0	1,654	17.5
Hispanic	492	4.3	372	3.9
Other	315	2.8	319	3.4
Unknown	23	0.2	17	0.2
<b>Age in 1995*</b>				
21–24	635	5.6	640	6.8
25–34	6,163	53.9	4,324	45.7
35–44	2,822	24.7	2,686	28.4
45–54	1,525	13.3	1,484	15.7
55+	284	2.5	332	3.5
<b>Branch</b>				
Air Force	1,425	12.5	1,266	13.4
Army	7,237	63.3	6,010	63.4
Marine Corps	1,279	11.2	1,020	10.8
Navy	1,500	13.1	1,180	12.5
<b>Unit component</b>				
Active duty	4,262	37.3	3,812	40.2
National Guard	3,241	28.3	2,515	26.5
Reserves	3,938	34.4	3,149	33.2

\*Age data missing for 22 respondents

for GWI, including females (43.9%), those aged 21–24 years at the time of data collection (49.6%), those in the Army (43.8%) and those in the Reserves (41.8%). Similar findings were also observed among Gulf Era veterans. The following subgroups were significantly more likely to meet the Kansas criteria for GWI among Gulf Era veterans: females (21.8%), those aged 21–24 years at the time of data collection (20.9%) and those in the Army (18.0%). However, in non-deployed participants, membership in the National Guard and Reserves was found to be a protective factor

Table 2: Frequency of missing symptom data and exclusion criteria among respondents

	Kansas				CDC			
	Deployed (N=11,441)		Non-deployed (N=9,476)		Deployed (N=11,441)		Non-deployed (N=9,476)	
	N	%	N	%	N	%	N	%
Cases	8,777	76.7	8,156	86.1	10,851	94.8	9,013	95.1
Missing symptom data	855	7.5	541	5.7	590	5.2	463	4.9
Exclusions	1,809	15.8	779	8.2	N/A		N/A	

Table 3: Frequency, prevalence, unadjusted odds ratios and 95% confidence interval of meeting the Kansas criteria for Gulf War illness in 1995 among Gulf War and Gulf Era veterans participating in the National Health Survey of Persian Gulf War Veterans and Their Families

Characteristic	Gulf War (N=11,441) n (%)	OR (95%CI)	Gulf Era (N=9,476) n (%)	OR (95%CI)
<b>Overall</b>	4,646 (40.7)		1,629 (17.2)	
<b>Sex</b>				
Male	3,710 (39.8)	**	1,176 (15.9)	**
Female	936 (43.9)	1.18 (1.01, 1.30)	453 (21.8)	1.48 (1.31, 1.67)
<b>Race</b>				
White	3,430 (40.7)	**	1,180 (16.6)	**
Black	888 (40.8)	1.01 (0.91, 1.10)	312 (16.6)	1.17 (1.02, 1.34)
Hispanic	195 (39.6)	0.96 (0.80, 1.15)	72 (19.4)	1.21 (0.93, 1.57)
Other	127 (40.3)	0.99 (0.78, 1.24)	63 (19.8)	1.24 (0.93, 1.64)
Unknown	6 (26.1)	0.52 (0.20, 1.31)	2 (11.8)	0.67 (0.15, 2.94)
<b>Age in 1995</b>				
21–24	315 (49.6)	3.12 (2.86, 4.28)	134 (20.9)	3.73 (2.36, 5.98)
25–34	578 (41.8)	2.28 (1.73, 3.01)	791 (18.3)	3.15 (2.03, 4.89)
35–44	1,113 (39.4)	2.07 (1.56, 2.75)	489 (18.2)	3.13 (2.01, 4.88)
45–54	567 (37.2)	1.88 (1.40, 2.52)	192 (12.9)	2.09 (1.32, 3.31)
55+	68 (23.9)	**	22 (6.6)	**
<b>Branch</b>				
Air Force	463 (32.5)	**	193 (15.2)	**
Army	3,171 (43.8)	1.62 (1.44, 1.83)	1,081 (18.0)	1.22 (1.03, 1.44)
Marine	538 (42.1)	1.51 (1.29, 1.77)	180 (17.7)	1.19 (0.95, 1.49)
Navy	474 (31.6)	0.96 (0.82, 1.12)	175 (14.8)	0.97 (0.78, 1.21)
<b>Unit component</b>				
Active duty	1,667 (39.1)	**	734 (19.3)	**
National Guard	1,331 (41.1)	1.09 (0.99, 1.91)	379 (15.1)	0.74 (0.65, 0.85)
Reserve	1,648 (41.8)	1.12 (1.03, 1.22)	516 (16.4)	0.82 (0.73, 0.93)

\*\*Reference category

**Table 4: Frequency, prevalence, unadjusted odds ratios and 95% confidence interval of meeting the US Centers for Disease Control and Prevention (CDC) definition for Gulf War illness in 1995 among Gulf War and Gulf Era veterans participating in the National Health Survey of Persian Gulf War Veterans and Their Families**

Characteristic	Gulf War (N=11,441) n (%)	OR (95%CI)	Gulf Era (N=9,476) n (%)	OR (95%CI)
<b>Overall</b>	<b>5,792 (50.6)</b>		<b>1,628 (17.2)</b>	
<b>Sex</b>				
Male	4,552 (48.9)	**	1,165 (15.8)	**
Female	1,240 (58.2)	1.46 (1.32, 1.60)	463 (22.3)	1.54 (1.36, 1.73)
<b>Race</b>				
White	4,116 (48.8)	**	1,192 (16.8)	**
Black	1,219 (56.0)	1.34 (1.21, 1.47)	312 (18.9)	1.16 (1.00, 1.33)
Hispanic	296 (60.2)	1.58 (1.32, 1.90)	69 (18.6)	1.13 (0.87, 1.48)
Other	151 (47.9)	0.97 (0.77, 1.21)	53 (16.6)	0.99 (0.73, 1.34)
Unknown	10 (43.5)	0.81 (0.35, 1.84)	2 (11.8)	0.66 (0.15, 2.90)
<b>Age in 1995</b>				
21–24	336 (52.9)	1.32 (1.00, 1.74)	125 (19.5)	1.77 (1.21, 2.60)
25–34	2,945 (47.8)	1.07 (0.84, 1.36)	715 (16.5)	1.45 (1.02, 2.03)
35–44	1,520 (53.9)	1.36 (1.07, 1.74)	505 (18.8)	1.69 (1.19, 2.38)
45–54	855 (56.1)	1.49 (1.16, 1.92)	241 (16.2)	1.41 (0.98, 2.02)
55+	131 (46.1)	**	40 (12.1)	**
<b>Branch</b>				
Air Force	523 (36.7)	**	190 (15.0)	**
Army	4,172 (57.7)	2.35 (2.09, 2.64)	1,091 (18.2)	1.26 (1.06, 1.49)
Marine	575 (45.0)	1.41 (1.21, 1.64)	163 (16.0)	1.08 (0.86, 1.35)
Navy	522 (34.8)	0.92 (0.79, 1.07)	184 (16.0)	1.05 (0.84, 1.30)
<b>Unit component</b>				
Active duty	1,890 (44.4)	**	701 (18.4)	**
National Guard	1,840 (56.8)	1.65 (1.50, 1.80)	414 (16.5)	0.87 (0.77, 1.00)
Reserve	2,062 (52.4)	1.38 (1.27, 1.51)	513 (16.3)	0.86 (0.76, 0.98)

\*\*Reference category

compared to active duty for meeting the Kansas case definition of GWI. The adjusted odds ratio of meeting the Kansas criteria for GWI comparing deployed to non-deployed participants, controlling for military and demographic characteristics, was 3.34 (95% CI: 3.12, 3.57).

Table 4 provides the frequency, prevalence and unadjusted odds of Gulf War and Gulf Era veterans meeting the criteria for the CDC definition for GWI.

Overall, about 51% of Gulf War veterans and 17% of Gulf Era veterans met the criteria for GWI. Certain subgroups of Gulf War veterans were more likely to meet the CDC case definition including females (58.2%), those who identified as Hispanic (60.2%), those who identified as black (56.0%), those in the Army (57.7%), and those in the National Guard (56.8%) and Reserves (52.4%). Certain subgroups of Gulf Era veterans were significantly more likely to meet the CDC case definition including females



(22.3%), those in the Army (18.2%) and those on active duty (18.4%). The same protective effect was observed among those in the National Guard and Reserves in the Gulf Era. The adjusted odds ratio of meeting the criteria for the CDC case definition of GWI was 5.27 (95% CI: 4.93, 5.63).

### Discussion

This paper describes the methods used to apply modified Kansas and CDC case definitions of GWI to data collected in 1995 as part of the largest population-based longitudinal cohort study of Gulf War and Gulf Era veterans in the United States. Overall, 40.6% of Gulf War veterans met the criteria for GWI by the Kansas definition, and 50.6% met the criteria by the CDC definition. In the Gulf Era population, the prevalence of GWI by the Kansas definition and the CDC definition were the same: 17.2%. Regardless of deployment status or case definition, females were significantly more likely to meet the criteria for GWI. The adjusted odds ratios comparing the odds of meeting the Kansas criteria for GWI in Gulf War veterans compared to Gulf Era veterans was 3.34 (95% CI: 3.12, 3.57). The adjusted odds ratios comparing the odds of meeting the CDC criteria for GWI in Gulf War veterans compared to Gulf Era veterans was 5.27 (95% CI: 4.93, 5.63).

About 41% of the Gulf War veterans in our study met the case criteria by the Kansas case definition, which is higher than what was found by Steele (34%) in a study of Gulf War veterans in Kansas conducted in 1998.<sup>11</sup> Additionally, the prevalence was higher among Gulf Era veterans in the current study (17.2%) than in Steele's original study (8.3%). The discrepancies in GWI prevalence between Steele's and our findings may be explained by differences in study population, study administration and the use of a modified case definition. Steele and colleagues randomly selected a sample of veterans who were residents of Kansas at the time of the study, who had served in the military during the time of the Gulf War, and who were no longer on active duty (n=2,030). While a random sample from the entire population of veterans living in Kansas who served during the Gulf War would generate a representative sample of these veterans living in Kansas, it is possible that this does not represent the entire United States veteran population that served during the Gulf War. The proportion of female veterans in the current study is higher than reported in the Steele study (20% vs 13%), and females were significantly more likely to meet the criteria for GWI by the Kansas criteria in this study. This may partially explain why the current study found an overall higher prevalence of GWI. Additionally, the mode of data collection

may have influenced responses. The Steele study collected data via phone interview<sup>11</sup> while the data presented here were mostly collected by mail survey (70%). Participants may have felt more comfortable disclosing symptoms and conditions on a paper survey than over the phone.

In our study, 50.6% of Gulf War veterans met the criteria for GWI using the CDC case definition. This is higher than Fukuda et al. reported in the seminal paper that defined GWI by the CDC criteria (45%).<sup>3</sup> We suspect that differences in the study population account for these differences. The seminal paper by Fukuda et al. determined the case definition of a 'mystery illness' that CDC was asked to investigate by factor analysis.<sup>3</sup> The study consisted of the Air National Guard unit with the 'mystery illness' located in Pennsylvania, as well as three comparison groups (another Air National Guard unit in Pennsylvania that completed a different mission, and an Air National Guard unit and an active duty Air Force unit located in Florida); no other service branches were included. The total number of veterans studied was 3,723 and 86% were male. The current study relies on a population-based cohort sampled to include geographic representation as well as representation from all four branches of service. The current study also had a larger proportion of females (20%), and females were significantly more likely to meet the CDC criteria for GWI, which also may contribute to the increased prevalence estimates for the population overall as females had a higher prevalence of GWI than males.

While the prevalence estimates of GWI by the Kansas and CDC case definitions are higher in this study than what was found in the Fukuda and Steele studies, the excess prevalence of GWI in the Gulf War veteran group is consistent with what other studies have reported. Previous cohort studies have reported an excess prevalence of 25–32% of GWI in deployed Gulf War veterans compared to Gulf Era veterans.<sup>8,9,18</sup> In the current study the excess prevalence observed in the Gulf War veterans by the Kansas definition is 23.5%, and 33.4% by the CDC case definition. It is interesting that in the non-deployed group (Gulf Era veterans) the prevalence of GWI was 17.2% for both case definitions. This may suggest that there is an underlying prevalence of symptom-based conditions (often referred to as chronic multisymptom illness) in the veteran population.

A paper by Blanchard et al. reported on an in-depth clinical exam protocol in a subset of this cohort (1,061 Gulf War veterans and 1,128 Gulf Era veterans).<sup>19</sup> Participants in the Blanchard et al. study were involved in 2 days of data collection by

survey procedures, medical history and physical examination. Blanchard applied the CDC criteria for classification of using duration, category and clustering of symptoms to define cases. The Blanchard study provided important findings regarding associations between GWI and other syndromes (chronic fatigue syndrome, fibromyalgia, metabolic syndrome and arthralgia), supporting that the deployed veterans with GWI had statistically significant higher prevalence of chronic fatigue syndrome.<sup>19</sup> The study also provided evidence of an association between GWI and pre-deployment psychiatric conditions, specifically anxiety disorders and depression not related to post-traumatic stress disorder.<sup>19</sup> The present study has relied on self-reported survey data from the same cohort that formed the sampling frame for Blanchard's 2001 study, but the data used for the present study were collected in 1995 and 1996. The current study has extended these important findings by using symptom self-report on the entire cohort of respondents and has further expanded the inquiry through application of the Kansas definition of GWI.

One of the major strengths of this study is that the data come from the largest population-based study of Gulf War and Gulf Era veterans in the United States to date. While there are numerous studies that have reported the prevalence of GWI among Gulf War veterans, none have been this large or nationally representative. The response rate for this study was 70%, and while nonresponse analysis indicated that non-respondents (in both Gulf War and Gulf Era groups) were more likely to be unmarried, younger, non-white and enlisted rank at the time of the Gulf War, we don't believe response bias is responsible for our findings.<sup>4</sup>

The current study analysed data from almost 21,000 Gulf War and Gulf Era veterans, sampled from all over the United States and stratified to ensure representation of women, service branch (proportional to the deployed population), and National Guard and Reserves. Additionally, the time between the end of the Gulf War and when the data collection for this study took place was less

than 5 years, so the chance of recall bias regarding symptom onset is diminished. Currently, one of the challenges with identifying Gulf War veterans with GWI is that as this group of veterans ages, the development of other medical conditions can mask, exacerbate or mimic the symptoms of GWI, making it difficult to distinguish. However, because these data were collected within 5 years of the end of the war, before the typical onset of comorbid chronic medical conditions, the identified cases are likely to be true cases of GWI that developed during or immediately following the war.

The analyses presented here have taken a unique approach to examining historical symptom data to understand the applicability of case definitions that evolved over time through study of the Gulf War veteran population. This new view has presented a previously unrealised opportunity to assess what may represent the best estimation of the affected population: those who experienced the early onset of symptoms following the precipitating event. The data collection that occurred in 1995 was the baseline assessment of a longitudinal study that is still in follow-up, with the most recent data collection in 2012.<sup>20</sup> The veterans identified with GWI in this longitudinal study provide an invaluable resource, as they represent those with likely true GWI and are the most ideal veterans to enrol in the types of studies that are of most importance at this stage, including treatment studies and epigenetic studies. As such, the current study results will be a valuable resource for future studies examining GWI.

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