CUBA UNEXPLAINED EVENTS INVESTIGATION – FINAL REPORT

Havana, Cuba, August 2016 to March 2019

This report summarizes findings from the CDC investigation to date regarding a symptom cluster among U.S. Government staff and family members stationed in Havana, Cuba.

This analysis is based on data available to the CDC. The findings and interpretations may change if new information becomes available.

Centers for Disease Control and Prevention
12/3/2019
CUBA UNEXPLAINED EVENTS INVESTIGATION — FINAL REPORT

Havana, Cuba, August 2016 to March 2019

EXECUTIVE SUMMARY

Setting: In late 2016, U.S. Government (USG) employees and their families stationed in Havana, Cuba, began reporting multiple and varying non-specific symptoms, following an unusual auditory or sensory event. Following initial complaints by USG employees, the U.S. Department of State (DoS) requested USG employees and eligible family members (EFMs) report any unusual auditory or sensory events followed by onset of symptoms to the in-country medical team.

Primary Objectives: In December 2017, DoS requested CDC conduct an epidemiologic investigation. CDC aimed to 1) systematically analyze all medical records from available sources, 2) establish an epidemiologic case definition for the investigation, and 3) describe the pattern and timing of symptoms relative to time in Cuba.

Case Definition: A review of abstracted records identified onset of symptoms while in Cuba or within two weeks of returning from Cuba. A presumptive case was defined as biphasic onset of symptoms while in Cuba or within two weeks of returning from Cuba, unexplained by past medical history or alternative diagnosis. The initial phase of symptoms included at least one of the following symptoms:

- Head pressure
- Disorientation
- Nausea
- Headache
- Vestibular disturbances
- Auditory symptoms
- Vision changes

The secondary phase had a distinct separate onset from the initial phase and included at least one of the following symptoms:

- Vestibular disturbances
- Cognitive deficits

A possible case was defined as onset of symptoms while in Cuba or within two weeks of returning from Cuba with a biphasic onset of symptoms that did not include vestibular disturbances or cognitive deficits in the secondary phase. A possible case was also defined as a pattern of vestibular disturbances or cognitive deficits with unknown onset and at least one of the following symptoms without alternative explanation:
- Head pressure
- Disorientation
- Auditory symptoms
- Vision changes

Persons who experienced symptoms that did not meet either presumptive or possible case definition were classified as not likely cases.

**Salient Findings:**

**Epidemiological Investigation:** CDC abstracted existing medical records for 95 persons evaluated by the DoS, University of Miami (UM), University of Pennsylvania (Penn), and National Institutes of Health (NIH) to collect specific information to develop a case definition. Of the 95 persons whose medical records CDC evaluated, 15 had illness that met the criteria for a presumptive case definition. CDC classified 31 others as possible cases and the remaining 49 as not likely to be a case. Non-systematic data collection and the lack of a control population limited the statistical analyses possible.

**Pattern of symptoms:** The most commonly reported initial symptoms were auditory symptoms (n=13), headache (n=12), and nausea (n=10). Vestibular disturbances and cognitive deficits were the most commonly reported symptoms among all persons (n=42). Overall, 19 persons had enough information to identify a biphasic onset, of whom 79% (n=15) reported a subsequent onset of vestibular disturbance(s) or cognitive deficit(s).

**Conclusions and Follow-up:** This is the first attempt to use information from multiple medical centers to create a case definition that could be critical for conducting a future prospective case-control study and for identifying risk or mitigating factors for this condition. As of December 2018, among the 15 presumptive cases, 9 (60%) persons reported improvement and none reported worsening in their clinical course.

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The findings and interpretations of this analysis are the product of data available to CDC and could change if new information becomes available.
SETTING

In late December 2016, a United States Government (USG) employee serving in Havana, Cuba, first presented to their in-country embassy medical unit reporting multiple non-specific symptoms. Reported symptoms included vestibular disturbances, vision changes, cognitive deficits, auditory symptoms, sleep impairment, and headaches. During early February 2017, a second person reported an unexplained onset of similar symptoms. Following the second report, the Department of State (DoS) requested USG employees and eligible family members (EFMs) report any unusual auditory or sensory events followed by onset of symptoms to the in-country medical team. Additional USG employees reported similar unexplained symptoms, some pre-dating the onset of the original report. In response, DoS Bureau of Medical Services conducted initial clinical assessments of USG employees and EFMs reporting symptoms in-country. Clinicians from the University of Miami (UM) were invited to initially examine affected persons in Havana, and they continued to assess and treat self-identified affected persons who were medically evacuated to Miami, FL. The University of Pennsylvania (Penn) evaluated and treated additional self-identified affected persons. In June 2018, the National Institutes of Health (NIH) began systematically evaluating self-identified persons who might have previously sought care at UM, Penn, or both.¹

OBJECTIVES

On December 29, 2017, the DoS Bureau of Medical Services formally requested assistance from the U.S. Centers for Disease Control and Prevention (CDC) to investigate this unexplained phenomenon. DoS requested the following assistance from CDC: 1) lead a scientific inquiry for establishing an epidemiological case definition for the investigation; 2) identify risks and mitigating factors; 3) review medical treatment and testing conducted by the DoS Bureau of Medical Services, UM, and Penn; 4) characterize the illness; and 5) develop and disseminate appropriate communications regarding the unexplained phenomenon. After initial review of the available data, CDC developed three objectives 1) systematically analyze all medical records from available sources, 2) establish an epidemiological case definition for the investigation, and 3) describe the pattern and timing of symptoms relative to time in Cuba.

SALIENT FINDINGS (BY OBJECTIVE)

Review of Data from Available Sources

The DoS developed the Havana Acquired Brain Injury Tool (HABIT) to screen USG employees and EFMs already stationed in Havana, Cuba who self-reported symptoms and persons deploying to Havana, Cuba. As of March 6, 2019, DoS provided CDC with information for 68 persons visiting or stationed in Cuba. Information included pre-deployment HABIT results and medical evacuation assessments (including HABIT results) performed by DoS staff of persons reporting symptoms; 15 persons had only pre-deployment information. Not all persons who self-reported symptoms underwent evaluation with the HABIT. Persons who reported symptoms could seek care as necessary at UM, Penn, or both. In late 2018, NIH began offering persons who self-reported symptoms enrollment in a clinical research study that would systematically record information regarding their medical status.

The CDC team reviewed medical records for 95 persons who underwent evaluation, care, or treatment at one or more of four locations: DoS, Penn, UM, or NIH. A total of 158 records were available from 95 persons for review. Figure 1 details the number of persons from each data source.
The CDC team abstracted and reviewed information from the medical records and summarized findings on history of illness, relevant past medical history, clinical course, and objective diagnostic testing and assessments. (For a complete review of methods proceed to page 14.) Of note, CDC did not conduct any evaluations and relied on what was documented in medical records provided by DoS, Penn, UM, and NIH.

Overall, 62% (n=59) of evaluated persons had at least one symptom documented with no information regarding timing of onset, 53% (n=31) of whom had no description of onset — only a list of symptoms at clinical evaluation. Additionally, 33% (n=31) of evaluated persons had no abnormal objective findings recorded on physical examination, diagnostic testing, or clinical assessments. Dates of arrival to or departure from Cuba were missing for 47% (n=45) and 51% (n=48) of persons, respectively. Also missing were key demographics such as date of birth for 34% (n=33) and sex for 40% (n=38).

The medical team from UM began assessing persons in May 2017. Medical records received from UM contain descriptions of disease onset but did not consistently document all reported symptoms or abnormalities found during the physical exam, imaging, or other diagnostic screenings and assessments. For the six persons with only an UM chart, three contained no in-depth information on diagnostic testing or health assessments and the remaining four were missing information regarding symptom onset.
The Penn medical team began evaluating persons in August 2017 with an average of 203 days between assessment and perceived exposure. The main symptoms reported were vestibular deficits, oculomotor deficits, headaches, anxiety, sleep impairment, tinnitus, ear pain, or cognitive deficits after arriving in Havana, Cuba. While the Penn process for initial intake evolved over time, the team consistently captured presence or absence of symptoms and referred persons with symptoms for further testing and evaluation. Data were not standardized or consistent for all evaluated medical records as the primary documentation objective was for individual clinical evaluation and not a planned, prospective epidemiology study. However, all persons evaluated by Penn had at least one objective finding on the physical exam, diagnostic testing, or clinical assessment. Only 21% (n=11) of persons evaluated at Penn had a recorded onset date for all reported symptoms and 75% (n=71) of persons overall (evaluated anywhere) had at least one symptom identified upon clinical evaluation without a recorded onset date.

The seven medical records received from NIH were thorough, but on average persons seen at NIH arrived 618 days after initial symptom onset.

DoS records contained mainly information from the HABIT, a tool used for screening, and did not include information about timing of symptom onset. Several persons seen only at DoS had no documented symptoms while in Cuba or shortly after leaving Cuba, because if the HABIT identified symptoms, persons were referred for follow up at Miami or Penn.

**Commonly Reported Symptoms:** The 95 persons whose symptoms were reviewed for inclusion or exclusion as a case (Figure 1) reported multiple and varying symptoms including head pressure, disorientation, nausea, headache, vestibular disturbances (dizziness, vertigo, falling over easily), balance issues, difficulty walking, auditory symptoms (tinnitus, ear pain, ear pressure, sudden hearing loss), vision changes (decreased or blurry vision, double vision, eye pain, other vision change), and cognitive deficits (cognitive dysfunction, memory problems, difficulty finding words, difficulty reading, difficulty with basic math). When records contained onset dates, the most commonly reported initial symptoms were auditory symptoms, headache, and nausea. The most common symptoms of subsequent onset were vestibular disturbances and cognitive deficits (Table 1).

**Table 1. Reported qualifying symptom onset for all persons evaluated (n = 95)**

<table>
<thead>
<tr>
<th>Symptom reported</th>
<th>Persons with initial onset</th>
<th>Persons with subsequent onset</th>
<th>Total persons reporting symptom (including unknown onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorientation</td>
<td>5</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Head Pressure</td>
<td>5</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>Headache</td>
<td>12</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>5</td>
<td>20</td>
</tr>
<tr>
<td>Auditory symptoms*</td>
<td>13</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Cognitive deficits*</td>
<td>4</td>
<td>16</td>
<td>37</td>
</tr>
</tbody>
</table>
Case Definition
Based on the information abstracted from DoS, UM, Penn, and NIH records, and impressions gathered from the treating physicians CDC developed and applied the following stratified case definitions to all 95 evaluated persons.

Presumptive: Biphasic symptom onset with initial symptom onset while in Cuba or within two weeks of returning from Cuba including
- An initial phase that included at least one of the following symptoms with no alternative explanation
  - Head pressure
  - Disorientation
  - Nausea
  - Headache
  - Vestibular disturbances
  - Auditory symptoms
  - Vision changes
- AND, a secondary phase of symptoms that included at least one of the following symptoms with no alternative explanation
  - Vestibular disturbances
  - Cognitive deficits

Possible:
A possible case was defined as onset of symptoms listed in Table 1 while in Cuba or within two weeks of returning from Cuba with a biphasic onset of symptoms that did not include vestibular disturbances or cognitive deficits in the secondary phase. A possible case was also defined as a pattern of vestibular disturbances or cognitive deficits with unknown onset pattern and at least one of the following symptoms with no alternative explanation:
- Head pressure
- Disorientation
- Auditory symptoms
- Vision changes

Figure 2 depicts the process for applying the case definition to the 95 person’s medical records reviewed and abstracted by the CDC team. Overall, the process classified 15 presumptive, 31 possible, and 49 not likely cases.

The 15 presumptive cases had recorded information about onset and reported symptoms that allowed for identification of a biphasic onset that included secondary onset of either cognitive deficit(s) or vestibular disturbance(s).
Among the 31 possible cases
- 4 persons reported a biphasic onset of symptoms listed in Table 1 but no cognitive deficit or vestibular disturbance
- 27 persons reported cognitive deficit(s) or vestibular disturbance(s) but lacked enough information to identify a biphasic onset of symptoms

Of the 49 not likely cases
- 22 persons did not meet the case definition because they lacked a recorded qualifying symptom with onset while in Cuba or within two weeks of returning from Cuba
- 8 persons had a medical history or plausible alternative explanation for all of their reported symptoms
- 15 persons only reported one symptom that was not explained by their medical history or another more plausible diagnosis or did not have a biphasic clinical course
- 4 persons had no reported time frame for onset and did not report cognitive deficit or vestibular disturbance as a symptom
Figure 2. Case Classification Process:

95 Persons’ Records Reviewed

73 Reported Symptoms* While in Cuba or Within Two Weeks of Leaving

22 Did Not Meet This Criterion

65 Reported Symptoms* With No Alternative Explanation

8 More Did Not Meet This Criterion

50 Reported ≥2 Symptoms* With No Alternative Explanation

15 More Did Not Meet This Criterion

19 Biphasic Onset

31 Undetermined Onset

15 Biphasic with Subsequent Cognitive Deficits or Vestibular Disturbances

15 Presumptive Cases

4 Biphasic but No Cognitive Deficits or Vestibular Disturbances

4 More Did Not Meet This Criterion

27 Cognitive Deficits or Vestibular Disturbances

31 Possible Cases

49 Not Likely Cases

* For these analyses, “symptoms” include headache, head pressure, disorientation, nausea, vestibular disturbances, auditory symptoms, vision changes, or cognitive deficits.
Persons with symptomatology classified as presumptive cases were most likely to report an initial onset of nausea or auditory symptoms than other symptoms (Table 2).

**Table 2. Documented qualifying symptom onset** for presumptive cases (n=15)**

<table>
<thead>
<tr>
<th>Symptom Documented</th>
<th>Initial onset</th>
<th>Subsequent onset</th>
<th>Total reporting each symptom (includes unknown onset)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorientation</td>
<td>5</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Head Pressure</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Nausea</td>
<td>8</td>
<td>4</td>
<td>12</td>
</tr>
<tr>
<td>Auditory symptoms*</td>
<td>8</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Cognitive deficits*</td>
<td>3</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Vestibular disturbances*</td>
<td>6</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Vision changes*</td>
<td>1</td>
<td>6</td>
<td>11</td>
</tr>
</tbody>
</table>

*Includes multiple symptoms, some persons reported different onsets for each symptom
**Not all symptoms had a known onset, but persons were classified as having presumptive cases if they had at least two qualifying symptoms with onset dates.

Describe the pattern and timing of symptoms relative to time in Cuba

**Descriptive Epidemiology:** Due to a high proportion of missing demographic data in the medical records received by CDC, reliable statistical tests for significant differences between demographic groups could not be performed (Table 3). However, it appears that in general, presumptive, possible, and not likely cases were in persons of similar gender and duty type (Temporary Duty [TDY] versus Permanent Change of Station [PCS]) to persons considered to be possible or not likely cases (Table 3). The exclusion of persons with plausible explanations for any symptom could be responsible for the apparent age difference between persons classified as presumptive and possible cases as the prevalence of medical comorbidities that could explain otherwise qualifying symptoms increases with age. Persons with symptomatology classified as presumptive cases in general were in Havana, Cuba for a shorter duration of time and reported a greater overall number of symptoms compared to persons with symptomatology classified as possible and not likely cases (Table 3). Ten of the 15 persons with symptomatology classified as presumptive cases (67%) reported at least one unexplained auditory or sensory event.
Table 3. Demographic characteristics by case status

<table>
<thead>
<tr>
<th></th>
<th>Presumptive (n = 15)</th>
<th>Possible (n = 31)</th>
<th>Not Likely (n = 49)</th>
<th>Overall (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median:</td>
<td>38</td>
<td>46</td>
<td>37</td>
<td>39</td>
</tr>
<tr>
<td>Range:</td>
<td>24–65</td>
<td>27–60</td>
<td>8–56</td>
<td>8–65</td>
</tr>
<tr>
<td><strong>Gender (% male)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing n (%)</td>
<td>0 (0%)</td>
<td>10 (33%)</td>
<td>28 (57%)</td>
<td>38 (40%)</td>
</tr>
<tr>
<td><strong>Time in Country (months)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median:</td>
<td>3</td>
<td>15</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Range:</td>
<td>0–26</td>
<td>0–26</td>
<td>0–28</td>
<td>0–28</td>
</tr>
<tr>
<td><strong>TDY vs PCS (% PCS)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing n (%)</td>
<td>4 (36%)</td>
<td>16 (52%)</td>
<td>32 (65%)</td>
<td>52 (55%)</td>
</tr>
<tr>
<td><strong>Number of Documented Symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median:</td>
<td>6</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Range:</td>
<td>2–8</td>
<td>2–8</td>
<td>1–4</td>
<td>0–8</td>
</tr>
</tbody>
</table>

TDY (Temporary Duty), PCS (Permanent Change of Station)

For 55% of the persons evaluated, some symptoms lacked a corresponding onset date. For those who did have documented onset date, onset ranged from May 2016 to May 2018 (Figure 3).

Clinical examination, imaging, and testing results among presumptive cases: Clinically relevant examinations, diagnostic imaging, and specialist assessments conducted by health care providers for the 15 persons with symptomatology classified as presumptive cases were reviewed. Despite the variability in the examinations and testing performed by clinicians from various medical specialties at several medical
centers, most patients have a complete neurological exam, magnetic resonance imaging (MRI), and neurocognitive testing completed. Table 4 describes the findings from examinations, imaging studies, and other assessments conducted among those whose symptomatology met the presumptive case definition criteria.
LIMITATIONS

Medical records reviewed for 95 persons varied in completeness with some medical records having in-depth evaluation notes and results while other sources had a relative paucity of relevant data. Furthermore, lack of common data fields across sources, missing variables, and incomplete data limited the CDC team's ability to classify cases. Finally, in most instances, clinicians did not evaluate affected persons until many months after symptom onset and after media exposure of the events, which could have biased the information collected and recorded, and thus clinical care decisions.

In traditional epidemiologic case finding, sensitivity, specificity, and predictive value depend on the prevalence of disease. In the absence of a definitive test for the condition under investigation, the team elected to prioritize specificity rather than sensitivity. Prioritizing specificity over sensitivity likely excluded persons who may have had similar exposure and outcome conditions resulting in misclassification of cases and non-cases. In general, sensitivity and specificity will depend on the prevalence of mimicking or masking conditions. Often, a more sensitive definition will be less specific and vice-versa. The choice of
where to draw the line between sensitivity and specificity depends on the cost of a false positive versus a false negative in a specific application.

The existing data available from medical records did not allow for thorough examination of risk and mitigating factors because information about potential risk and mitigating factors was limited. In addition, this study does not have a suitable comparison population to assess risk and mitigation factors.

The findings in this report are subject to additional limitations. Clinicians populated information in medical records in the course of clinical care rather than systematically collecting data for an epidemiologic investigation. Many initial patient encounters occurred months after the reports of unexplained illness began and therefore persons might not accurately remember their symptoms and experiences from the past. Moreover, the widespread media coverage of these unexplained events might have influenced symptoms and experiences reported to health care providers. Additionally, information was subject to clinician judgement and varied in the extent of inquiry and recording. The inconsistency in recorded information is not unusual given multiple medical centers and clinicians with various specialties were assessing a variety of persons with various clinical presentations over an extended period. However, this inconsistency hindered CDC’s ability to discriminate patterns in the data. The findings and interpretations of this analysis are the product on data available to CDC and could change if new information becomes available.

CONCLUSION

This epidemiologic investigation by CDC systematically analyzed clinical data for persons seen at the DoS Bureau of Medical Services, UM, Penn, and NIH for whom CDC received records. The CDC developed the epidemiologic case definition from the existing medical records on 95 persons self-identified as having symptoms or evaluated by DoS prior to deployment. The primary steps of an epidemiologic investigation are to establish the existence of an outbreak and verify the diagnosis. However, one challenge with this investigation is the lack of a well-defined medical diagnosis and an uncertain source of exposure attributable to the physical symptoms experienced by USG employees and EFFMs. The CDC’s epidemiologic case definition focused on the pattern and timing of symptom onset relative to time in Cuba.

The evaluations conducted thus far have not identified a mechanism of injury, process of exposure, effective treatment, or mitigating factor for the unexplained cluster of symptoms experienced by those stationed in Havana, Cuba.

Despite initially considering a retrospective case-control study to assess risk and mitigating factors, CDC does not recommend this approach because information collected after large gaps of time is subject to several types of bias. Given that interviews with persons with and without symptoms would take place after more time elapsed from the onset of unexplained events and initial symptoms experienced, the data collected would be subject to increasing recall bias, rendering it less likely to be as accurate as information collected immediately after the event. A retrospective case-control study is also at risk for selection bias because persons who choose to participate in the case-control study might be meaningfully different from those who do not participate and could lead to a misleading conclusion. Another challenge with a retrospective case-control study includes the potential for misattribution of symptoms to unrelated adverse events. In summary, the above limitations of a retrospective case-control study in this situation, especially the time delay between onset of symptoms and data collection, could generate misleading or obscured findings.
Given the aforementioned limitations of a retrospective case-control study, CDC recommends a prospective case-control investigation should new cases arise. CDC is preparing for an investigation in conjunction with the DoS. This approach would reduce the likelihood of the biases and limitations listed previously in a future investigation. CDC is working with partners to disseminate findings from this investigation to the medical community and the public.

METHODS

CDC treated the request by DoS as a public health response and convened a CDC team of subject matter experts in epidemiology, neurology, toxicology, occupational health, infectious diseases, behavioral health, and radiation health.

The DoS developed a screening tool (HABIT) based on the initially reported symptoms. The screening tool collected current symptoms and used a neurocognitive assessment to assess immediate memory and concentration and the balanced error scoring system (BESS) or modified BESS (mBESS) to assess vestibular disturbance. UM or Penn received USG employees and EFMs requiring further evaluation for treatment.

Data Collection and Abstraction: CDC received data from four sources

- DoS screening evaluations of USG employees and EFMs from February 2017 through May 2018
- UM medical records for evaluations and testing performed at UM from May 2017 through July 2017
- Penn medical records for evaluations and testing performed at Penn or by collaborating therapists from August 2017 through August 2018
- NIH medical records for evaluations and testing performed at NIH from June through December 2018

CDC received access to the Penn and UM charts in August 2018 and began receiving unredacted DoS medical records for Cuba-related patients in November 2018.

The medical records from Penn were reviewed and abstracted between September and December 2018, and information available in the electronic medical record system (EPIC) on the date of review was included. Instead of access to an electronic medical record system, the other sources provided copies of medical records to CDC. Medical records from UM were reviewed and abstracted in October 2018. All available information in unredacted DoS medical records provided by November 2018 were included in the review. NIH began systematically evaluating patients in June 2018 and provided a copy of the medical records to CDC in December 2018. NIH records were reviewed and abstracted in January 2019.

Based on the DoS screening tool and reports published by UM, the team developed an abstraction tool to abstract relevant clinical information from the available data sources. To direct the secondary analysis of the available data, the CDC team started with an initial review of 52 available Penn medical records. The review systematically collected reported symptoms, completed clinical tests, prescribed therapies, and overall provider interpretation of progress. The team conducted a case series analysis to direct updates to the abstraction tool in October 2018.

The updated abstraction tool was used to systematically collect information from DoS and UM and update the information collected from Penn. The final abstraction tool included:
- Demographic information such as age, sex, governmental department, employer deployment type, and date of arrival and departure from Havana, Cuba
- Description of any documented auditory or sensory events
- History of the current illness, including documented symptoms and date and order of onset
- Relevant past medical history
- Clinical course of illness, including recommended therapies and their impact on documented symptoms
- Objective findings on physical examination, diagnostic testing, and clinical assessments
- Assessment of anxiety, stress, and sleep disturbance before and after initial onset of illness

Case Definition Development:

Information from DoS, UM, or Penn available to the CDC team were abstracted for each person. CDC used the abstracted data to create an epidemic curve of first symptom onset and frequency table of documented symptoms. CDC considered frequency of documented symptoms, team interpretation of the case series analysis, and clinical impressions from DoS, UM, and Penn to create a working case definition focused on three factors:

1. After discussions with the medical teams at DoS, UM, and Penn, the CDC team concluded that the symptom-inducing event or stimulus occurred while persons were in Cuba. The team only evaluated symptoms that occurred while in Cuba or within two weeks of leaving Cuba. This decision was to increase specificity and exclude symptoms most likely unrelated to the syndrome under investigation based on clinical knowledge of the hypothesized causes set forth by the medical teams.

2. Upon reviewing the records, reported symptoms appeared to evolve over time and often included the emergence of new symptoms while some presenting symptoms resolved. This suggested a biphasic (appearance of one set of symptom(s) followed by another set of symptom(s) days to weeks later) clinical course as opposed to a progressive, relapsing/remitting, or monophasic illness.

3. CDC individually evaluated each symptom based on the clinical interpretation of the medical teams. CDC excluded a symptom from analysis if it identified a pre-existing condition or more plausible alternative diagnosis. CDC implemented this criterion to reduce the likelihood of classifying persons without the condition under investigation as presumptive cases.

For this investigation of case characteristics and potential exposure factors, specificity was deemed more important than sensitivity to prevent dilution of case findings by including non-cases. Missing relevant data, such as accurate onset date, impacted the ability to correctly assign case status to some persons. As a result, CDC might have excluded persons who experienced the condition under investigation as cases in this analysis. CDC does not intend the epidemiologic case definition to influence clinical decisions regarding treatment or compensation.

Criteria for case inclusion

- Initial symptom onset occurring while in Cuba or within two weeks of returning from Cuba
- Presence of at least two symptoms including headache, head pressure, disorientation, nausea, vestibular disturbance(s), auditory symptoms, vision changes, and cognitive deficit(s). At least one symptom must be vestibular disturbance, auditory symptoms, vision changes, or cognitive deficit(s).
- The symptoms had to occur without a recorded alternative diagnosis (including pre-existing conditions or new diagnosis) or explanation based on available medical records
- A biphasic symptom onset that included the subsequent onset of vestibular disturbance or cognitive deficit

Not all persons evaluated reported an auditory or sensory event prior to their onset of symptoms, nor did reports of auditory or sensory events consistently correspond temporally with symptom onset. The case definition did not require a documented auditory or sensory event, which will allow for examining any possible correlation between auditory or sensory phenomena and the unexplained symptoms under investigation.

Data Analysis: The analysis included general summary statistics for age, gender, time in country, number of documented symptoms, and temporary versus permanent placement in country for all persons with data available to CDC. The number of persons reporting onset of initial symptom(s) by month of first documented symptom was also calculated. The analysis also included the proportion of persons reporting each symptom by case status (i.e., presumptive, possible, and not likely).

REFERENCES