Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplemental EEE Case Reports

**Patient 1.**

A 9-year-old male (247134; Table 1) with suspected meningitis, presented with rhinorrhea, cough, fever, headache and vomiting, with 3 widespread tonic-clonic seizure episodes progressing to status epilepticus. During the next 12 hours he exhibited decreased alertness, decreased mental status, hemiparesis and a positive Babinski response on the left side. Brain MRI revealed T2 ($T_2$-weighted images) and FLAIR (Fluid attenuated inversion recovery) hyperintensity of multiple lesions (Fig. S2A-C). After 5 days, he was alert, oriented, but with left hemiparesis. One month later, he exhibited no sequelae.

**Patient 2**

A 2-year-old male (247135, Table 1) presented with fever, cough, vomiting, and seizures with impaired alertness. After 48 hours, he developed focal status epilepticus, with further deterioration of consciousness, and was ventilated. Brain MRI showed T2 and FLAIR hyperintensity of multiple lesions (Fig. S2E, F). At discharge he exhibited right hemiparesis and psychomotor retardation, which continued for at least 18 months.

**Patient 3**

A one-year-old female (247550, Table 1) presented with fever, vomiting, drowsiness and decreased alertness with focal seizures, progressing to generalized status epilepticus, and
required ventilation. Computational tomography (CT) showed diffuse brain edema with left frontal hypodensity (Fig. S2D). Two months later her electroencephalogram showed multifocal epileptic activity and she had residual sequelae including spastic quadriparesis, psychomotor retardation, and recurrent seizures; she remained in a vegetative state for at least 18 months.

**Patient 4**

A one-year-old male (247551, Table 1) presented with fever, vomiting, diarrhea and asthenia. He developed status epilepticus and required ventilation. Brain MRI showed lesions on T2, and FLAIR, with increased signal intensity at the cortical/subcortical level in the left parietal and temporal lobes bilaterally (Fig. S2G, H). After 5 months he was readmitted for seizures and fever, and continued to suffer psychomotor retardation and seizures 18 months after discharge.

**Patient 5**

A thirteen-year-old male (247419, Table 1) presented with fever, headache, vomiting and somnolence. Imaging was not performed. Serology revealed IgM seroconversion for EEEV between 1-2 days after onset, but surprisingly, VEEV was isolated from those same sera. He later (day 40) displayed IgM seroconversion to VEEV as well, and recovered fully prior to discharge.
Figure S1. Flowchart of outbreak specimen processing from patients from Darien and East Panama provinces (May 29 – September 15, 2010).

190 patients

- 59 patients did not meet case definition
- 99 patients met case definition for suspected case
- 19 patients met case definition for probable case
- 13 patients missing symptom information

Laboratory diagnosis
(Serological confirmation for sera>3 days from symptom onset; RT-PCR and/or viral isolation for samples ≤3 days from symptom onset)

<table>
<thead>
<tr>
<th>Confirmed positive:</th>
<th>1 EEEV 1 VEEV</th>
<th>5 EEEV 6 VEEV</th>
<th>7 EEEV 3 VEEV 1 EEEV &amp; VEEV</th>
<th>8 EEEV 6 VEEV</th>
<th>11 EEEV 11 VEEV 1 EEEV &amp; VEEV</th>
<th>TOTAL:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative (EEE and VEE):</td>
<td>53</td>
<td>85</td>
<td>7</td>
<td>4</td>
<td>149</td>
<td></td>
</tr>
<tr>
<td>Not tested:</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>9</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

1. Patients with symptoms such as fever alone, headache alone, respiratory or gastrointestinal symptoms
2. Suspected case: fever and headache (or irritability in <1 yo children)
3. Probable case: suspected case with altered mental status and/or seizures
4. Not tested due to poor specimen quality or inadequate specimen
Figure S2. Radiologic findings from Panamanian patients suffering from EEE. A-C, patient 247134. A. Axial T2-weighted images and FLAIR shows increased signal intensity at the fronto-temporal cortical/subcortical level; B. Axial T2-weighted images and FLAIR image with hyperintense at the basal ganglia, lenticular nucleus and right thalamus; C. Sagittal FLAIR shows increased signal intensity at the midbrain, basal ganglia and brain stem. D, patient 247550. Axial CT shows diffuse brain edema with left frontal hypodensity. E-F, patient 247135. E. Axial T2-weighted images and FLAIR shows bilateral frontal hyperintensity at the cortical/subcortical level, F. Coronal T2-weighted images and FLAIR with increased signal intensity in the thalamus, basal ganglia and bitemporal hyperintense, G-H, patient 247551. G. Axial T2-weighted images and FLAIR shows cortical/subcortical and left parietal hyperintense, H. Axial T2-weighted images and FLAIR shows bilaterally increased signal intensity at the temporal lobes at the cortical/subcortical.