decide). We know, however, that a person infected with Zika virus might not have easily observable symptoms. Even if persons accept the possibility of sexual transmission, they might not engage in safe sex practices with asymptomatic infected partners.

If persons understand Zika virus through a mental model informed by dengue or chikungunya, public health officials should address potential confusion, especially in light of differences (e.g., sexual transmission) that might be misunderstood or ignored. Even when not confusing the illnesses, participants clearly conceptualized Zika in comparison with relatively more familiar illnesses. In this way, they operated in similar fashion as consumers encountering novel products do (9,10). Public health messaging might leverage this tendency. If it is easiest to understand a new outbreak in comparison to a previous one, using analogy or direct comparison might be effective but will also require careful emphasis on what is new.

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References

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Cerebrospinal Fluid Immunoglobulins as Potential Biomarkers of Chikungunya Encephalitis

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Chikungunya virus causes fever and severe polyarthritis or arthralgia and is associated with neurologic manifestations that are sometimes challenging to diagnose. We demonstrate intrathecal synthesis of chikungunya antibodies in a patient with a history of acute infection complicated by encephalitis. The specificity of the intracerebral immune response supports early chikungunya-associated encephalitis diagnosis.

Chikungunya virus (CHIKV) is an alphavirus transmitted by infected Aedes mosquitoes (Ae. aegypti and Ae. albopictus) (1). Global expansion epidemics have been
The disease is characterized by acute fever, maculopapular rash, headache, and disabling rheumatism (1,2). Neurologic complications may occur, including encephalopathy, encephalitis, myelitis, and Guillain-Barré syndrome (3–5). Differentiating CHIKV infection from other arbovirus infections is difficult because of co-occurring conditions and similar manifestations (3). Detection of viral RNA and specific antibodies in cerebrospinal fluid (CSF) suggests neurotropic evidence of CHIKV (2,3), but whether these antibodies are synthesized locally or derived from blood has not been demonstrated (6,7). We detected intrathecal synthesis of CHIKV IgG by specific antibody index in a case of encephalitis (6).

In January 2016, a 69-year-old woman had sudden fever (38°C), intense generalized arthritis, prostration, and cognitive alterations characterized by forgetting and exchanging words. She used analgesics without relief. After 1 week, a maculopapular rash with intense pruritus appeared on her upper limbs. A few days later, her rash and fever abated, but other symptoms continued. She was referred for consultation 3 months after symptom onset. Physical examination revealed bilateral finger and knee arthritis (online Technical Appendix Figure, https://wwwnc.cdc.gov/EID/article/24/5/17-1763-Techapp1.pdf). Neurologic examination showed slow thinking, inattention, and mild confusion. She had a history of dengue and Zika virus infections. Results of a routine blood analysis were unremarkable.

We performed several antibody tests: anti-CHIKV ELISA (IgM and IgG; EUROIMMUN, Luebeck, Germany); Panbio Dengue IgG Indirect ELISA and Dengue IgM Capture ELISA (Panbio, Brisbane, Queensland, Australia); and immunochromatographic assay (GenBody Zika IgG/IgM; Biotech Business, Chungnam, South Korea). Results for specific IgG and IgM are shown in the Table. CSF analysis demonstrated leukocytes 1 cell/mm³ protein 29 mg/dL; glucose 40 mg/dL; blood–CSF barrier function based on albumin quotient 6 × 10⁻⁵; IgG index 0.43 (reference <0.7); and intrathecal IgG fraction (IgG₆₆) of total IgG found in CSF, <0% (6,7). In addition, we quantitatively determined the synthesis of specific antibodies by antibody index (AI) (6). We used an ELISA test for DENV IgG and ELISA for CHIKV IgG in paired CSF and serum. We calculated AI as the ratio between the specific IgG and total IgG quotient, considering that there was no intrathecal synthesis of total IgG (IgG₆₆ <0%). The sample dilutions for dengue were 1:8 for CSF and 1:4,000 for serum. Sample dilutions for CHIKV were 1:2 for CSF and 1:101 for serum (6,8). AI was 1.14 for dengue and 7.24 for CHIKV, with AI reference range <1.5 (online Technical Appendix).

Brain magnetic resonance imaging showed foci with hyperintense signal in the T2-weighted sequences and fluid attenuation inversion recovery bilaterally in subcortical frontoparietal areas. The patient showed substantial progressive improvement of cognitive alterations and arthralgia after starting antiinflammatory treatment; she took nimesulide for 2 months, followed by prednisolone (20 mg/d) with progressive reduction for another 2 months.

Our results demonstrate the quantitation of intrathecally synthesized CHIKV IgG. We diagnosed CHIKV-associated encephalitis on the basis of fever and altered mental status for >24 hours and positive CHIKV IgM antibodies in serum (9). CSF analysis results were unremarkable except for elevated CHIKV AI, the only evidence of brain inflammation. Brain imaging showed unspecific lesions; viral encephalitis may occur without pleocytosis or specific parenchymal abnormalities (9).

The identification of specific etiologies of viral encephalitis may be difficult in arbovirus- endemic areas (3). Co-infections with Zika virus, CHIKV, and DENV are frequent (1,3), and neurologic manifestations may also be similar (4,5). Although this case-patient also had a history of DENV and Zika infection with specific IgG in serum and CSF, we did not detect intrathecal synthesis of DENV antibodies (6–8) as did Puccioni-Sohler et al. in a previous study (8). Our findings show that the quantitation of antibodies synthesized in the brain may be useful in the differential diagnosis of neurologic diseases caused by arboviruses. The detection of specific intrathecal synthesis of antibodies is a known tool for the diagnosis of infections including herpes simplex virus, varicella zoster virus, measles, rubella, neuroborreliosis, and human T-cell leukemia virus type 1 (6–8).

CHIKV has attracted increasing attention because of its spatial spread and the high number of epidemics. Chikungunya has been associated with debilitating arthropathy for months or years after the initial infection, along with severe neurologic complications such as encephalitis (4,5,10). The detection of the etiologic agent of a central nervous system disease may be difficult, considering that PCR results for CHIKV are positive only during the first days of infection (1). In addition, the presence of specific antibodies in CSF may be derived from blood (6,7). The detection of intrathecal synthesis of CHIKV IgG may be useful as a specific laboratory brain marker for diagnosis of encephalitis and other neurologic complications associated with CHIKV infection. This result provides evidence of viral neurotropism and can be useful for supporting public health.

Table. Results of the detection of IgM and IgG against chikungunya virus, dengue virus, and Zika virus, Brazil, 2016

<table>
<thead>
<tr>
<th>Target virus</th>
<th>Sample type</th>
<th>Serum IgM</th>
<th>Serum IgG</th>
<th>Cerebrospinal fluid IgM</th>
<th>Cerebrospinal fluid IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chikungunya</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
<td>Reactive</td>
</tr>
<tr>
<td>Dengue</td>
<td>Not reactive</td>
<td>Not reactive</td>
<td>Not reactive</td>
<td>Not reactive</td>
<td>Reactive</td>
</tr>
<tr>
<td>Zika</td>
<td>Not reactive</td>
<td>Reactive</td>
<td>Not reactive</td>
<td>Reactive</td>
<td></td>
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</tbody>
</table>
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Author contributions: M.P.-S. drafted the study concept and acquired and interpreted data; L.C.F., M.J.C.-C., and M.C.F.S. acquired data and conducted laboratory analyses; M.P.-S., M.G.Z., and M.C.F.S. revised the manuscript; and R.S.K. conducted neuropsychological tests included as supplementary data.

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Chronic Genotype 3 Hepatitis E in Pregnant Woman Receiving Infliximab and Azathioprine

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Acute hepatitis E virus infection during pregnancy has a high fatality rate in developing countries. Little data are available on chronic infection in pregnant women. We report a case of chronic hepatitis E during treatment with infliximab and azathioprine, without adverse event during pregnancy and with spontaneous resolution after delivery.

Hepatitis E virus (HEV) genotype 1 causes a high number of deaths of pregnant women in developing countries (1). The few reported cases of HEV during pregnancy in industrialized countries (2–5) mainly relate to acute genotype 3 infection. We report the course of autochthonous
Cerebrospinal Fluid Immunoglobulins as Potential Biomarkers of Chikungunya Encephalitis

Technical Appendix

We quantitatively determined the synthesis of specific antibodies in a patient with chikungunya disease by antibody index (AI) as described by Reiber and Felgenhauer (6). The antibody index discriminates the pathologic fraction of specific brain-derived CSF immunoglobulin, considering the transfer of blood proteins into CSF. It is based on the analysis of specific antibodies in paired serum and CSF by ELISA technique, and the blood–CSF barrier function (Q_{alb}). We used the Panbio Dengue Indirect IgG ELISA kit (Panbio, Brisbane, Australia) and the Anti-Chikungunya virus (IgG) ELISA kit (EUROIMMUN, Luebeck, Germany). We calculated the antibody index (AI = Q_{spec}/Q_{IgG}) with the ratio between the specific IgG and total IgG, considering that there was no intrathecal synthesis of total IgG (IgG_{IF} < 0%). We established a reference curve of 0.05–2.0 absorbance units on the basis of serial dilution of the manufacturer’s positive control. We defined the maximum value of absorbance as 100 arbitrary concentration units. The sample dilutions for dengue virus were 1:8 for CSF and 1:4000 for serum; for CHIKV, 1:2 for CSF and 1:101 for serum (6–8).

For IgG IF> 0%: AI = Q_{specific} / Q_{Limit (IgG)}
For IgG IF < 0%: AI = Q_{specific} / Q_{IgG}

Q_{specific} = CSF OD x dilution / Serum OD x dilution
Q_{IgG} = CSF total IgG / Serum total IgG
Q_{Limit (IgG)} = 0.93 x (Q_{alb}^2 + 6 x 10^{-6})^{1/2} – 1.7 x 10^{-3}

IgG_{IF} = IgG_{IF} = [Q_{IgG} – Q_{Limit (IgG)}] / Q_{IgG} x 100
Evolution

After 2 months, the patient returned for follow-up; we detected no evidence of neurocognitive disorder from the results of a battery of neuropsychological tests. The assessment tools included a mini mental state examination, Beck depression inventory, Wechsler Memory Scale (logical memory I/II, visual reproduction, arithmetic, digit span (forward and backward), cube, vocabulary, digit symbol), auditory verbal learning, Rey-Osterrieth Complex figure, trail making test A/B, verbal semantic and phonetic fluency, Stroop Victoria test, and grooved pegboard (dominant and nondominant hands).

Technical Appendix Figure. Arthritis associated with chikungunya virus infection. Swelling and hyperemia in ankle (A) and fingers (B) of a 69-year-old woman with post-chikungunya tenosinovitis 90 days after acute infection with chikungunya virus, Rio de Janeiro, Brazil.