# Human Herpesvirus 6 Positivity on the FilmArray Meningitis/ Encephalitis Panel Needs Clinical Interpretation.

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## Published In/Presented At

Slenker, A. K., Royer, T. L., & Villalobos, T. (2019). Human Herpesvirus 6 Positivity on the FilmArray Meningitis/Encephalitis Panel Needs Clinical Interpretation. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*, *69*(1), 192–194. https://doi.org/10.1093/cid/ciz058

incidence eventually falls faster among the unvaccinated than among vaccinees, bringing these 2 incidence rates closer together. Thus, later in the influenza season, vaccine effectiveness (VE) can artifactually seem to wane (unless susceptibility is measured and adjusted for).

For this kind of bias to arise, the groups compared must have differential depletion of their susceptible individuals. In our vaccinee-only study, the groups compared were persons vaccinated earlier in the year vs those vaccinated later in the year. Before influenza begins to circulate, there is no depletion of susceptibles. After influenza begins to circulate—and if there really is no waning of VE—the rate of depletion of susceptibles among the vaccinees will be the same regardless of when they were vaccinated. In this no-waning scenario, there is no potential for bias related to depletion of susceptibles.

(If VE really does wane, then the early vaccinees would be less protected than the later vaccinees and would get more depleted of their susceptibles. In this case, the amount of waning would be underestimated rather than exaggerated.)

However, bias in the direction of exaggerating waning is potentially introduced by the inclusion of persons who are vaccinated after the influenza season is under way and have less time to be depleted. To address this concern, we restricted our analysis to the 90% of our study population that was vaccinated before 1 December (before the influenza season ever started in Northern California during the 2010–2016 study period), and our estimate of waning changed very little. (Our estimate of the increased odds of influenza with every 28 days since vaccination went from 1.16 to 1.18.)

### Notes

***Financial support.*** This work was supported by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (grant number 1R01AI107721-01).

***Potential conflicts of interest.*** All authors: No reported conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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**Clinical Infectious Diseases® 2019;69(1):191–2**

DOI: 10.1093/cid/ciy1085

## Human Herpesvirus 6 Positivity on the FilmArray Meningitis/Encephalitis Panel Needs Clinical Interpretation

To the Editor—We read with interest the article by Green et al [1] regarding the clinical significance of human herpesvirus 6 (HHV-6) positivity on the FilmArray meningitis/encephalitis (ME) panel. We have had a similar experience and would like to add our own institution's findings to this interesting topic.

Our institution, Lehigh Valley Health Network (LVHN), is made up of 7 hospitals serving the suburban and rural areas surrounding Allentown, Pennsylvania. The ME panel was introduced 23 February 2016 to 3 of these hospitals, including our large 800-bed tertiary care center and children's hospital. Notably, LVHN performs kidney and pancreas solid organ transplants only. As previously described, this panel is a multiplex cerebrospinal fluid nucleic acid test that detects 14 different targets with excellent sensitivity and specificity and a rapid turnaround time [1, 2].

We reviewed all of the cases of HHV-6 positive ME panel results from 23 February 2016 to 24 September 2018. Each patient's electronic medical record was reviewed for the following information: demographics, comorbidities, test results, radiology results, treatments, and 30-day mortality. Three providers reviewed the cases and then formulated a consensus to determine potential causality: an infectious disease specialist (A. K. S.), a transplant infectious disease specialist (T. L. R.), and a pediatric infectious disease specialist (T. V.). The authors assigned either (1) primary infection, including congenital infection, or the following regarding HHV-6 encephalitis: (2) unlikely, (3) possible, or (4) probable HHV-6 encephalitis [3–7]. This study was approved by the institutional review board at LVHN.

A total of 1516 ME panels were performed during the study period. Nineteen patients (1.3%) were identified with a positive HHV-6 result. HHV-6 was the fourth most common organism identified after enterovirus (60), herpes simplex virus type 2 (24), and varicella zoster virus (20), after excluding duplicate testing. Nine patients (47%) were ≤18 years of age and 10 (53%) were >18 years of age. Eight (88%) of the pediatric cases were thought to represent primary HHV-6 infection, resulting in a rapid discontinuation of antibiotics. Upon review, none of the adult cases was thought to represent HHV-6 encephalitis and the patients were discharged with a myriad of alternative diagnoses (Table 1). Interestingly, 3 of the adult patients were inappropriately treated with ganciclovir and in 1 patient this test result caused a delay in diagnosis of steroid-responsive encephalitis.

We support the authors' conclusions that this diagnosis should only be

**Table 1. Case Series of Patients With Human Herpesvirus 6 Positivity**

| Age | Sex | Comorbidities | Presentation | CSF WBC, cells/mL | ID Consultation | MRI Consistent | Antiviral | HHV-6 Diagnosis | Diagnosis |
|---|---|---|---|---|---|---|---|---|---|
| 2 wk | F | None | Fever, shortness of breath | 21 | Yes | NP | No | Primary infection | RSV bronchiolitis, HHV-6 infection |
| 81 y | F | Hypothyroidism, HTN | Falls | 3 | No | NP | No | Unlikely | Ambulatory dysfunction |
| 9 mo | F | None | Fever, vomiting | 12 | No | NP | No | Primary infection | HHV-6 infection |
| 80 y | F | Crohn disease | Seizure | 51 | Yes | No | No | Unlikely | PRES |
| 26 y | F | Sjogren syndrome | Fever, leg ulcer, headache | 1 | Yes | No | No | Unlikely | Headache |
| 63 y | F | Hodgkin lymphoma in remission, splenectomy | Pain and weakness in legs | 38 | Yes | No | No | Unlikely | Varicella zoster radiculitis |
| 1 y | F | None | Seizure | 0 | Yes | No | No | Primary infection | HHV-6 infection |
| 56 y | F | DM, morbid obesity | Progressive lower extremity weakness | 0 | No | No | No | Unlikely | Guillain-Barré syndrome |
| 1 y | F | Chronic lung disease | Seizure | 0 | No | No | No | Primary infection | HHV-6 infection |
| 18 y | F | AML in remission | Headache | 2 | No | No | No | Unlikely | Dental abscess |
| 2 y | F | None | Fever, tremors | 0 | No | No | No | Primary infection | HHV-6 infection |
| 60 y | M | ITP | Confusion, "driving erratically" | 26 | Yes | No | Ganciclovir | Unlikely | Catastrophic antiphospholipid syndrome |
| 3 wk | M | None | Fever | 22 | Yes | No | No | Primary infection | HHV-6 infection |
| 1 wk | M | None | Vomiting, hypothermia | 21 | Yes | NP | No | Primary infection | Congenital vs postnatal HHV-6 infection |
| 2 y | M | None | Fever, shaking | 0 | No | NP | No | Primary infection | HHV-6 infection |
| 39 y | M | DM type 1, drug abuse | Fever, left-sided weakness | 179 | Yes | No | Ganciclovir | Unlikely | Drug-induced toxic/anoxic encephalopathy |
| 29 y | F | Obesity | Headache, cranial nerve palsy | 194 | Yes | No | Ganciclovir | Unlikely | Steroid-responsive encephalitis |
| 56 y | F | Seizures, hypothyroidism | Seizures, encephalopathy | 18 | No | No | No | Unlikely | Serotonin syndrome |
| 40 y | F | Fibromyalgia, Roux-en-Y gastric bypass | Headache | 9 | Yes | NP | No | Unlikely | Headache |

Abbreviations: AML, acute myelogenous leukemia; CSF, cerebrospinal fluid; DM, diabetes mellitus; HHV-6, human herpesvirus type 6; HTN, hypertension; ID, infectious disease; ITP, idiopathic thrombocytopenic purpura; MRI, magnetic resonance imaging; NP, not performed; PRES, posterior reversible encephalopathy syndrome; RSV, respiratory syncytial virus; WBC, white blood cell.

entertained in the right clinical situation, that is, in patients with immunosuppression and consistent imaging findings and laboratory results. We support the use of a result comment to guide providers on the interpretation of a positive HHV-6 result.

## Note

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**Clinical Infectious Diseases® 2019;69(1):192–4**



DOI: 10.1093/cid/ciz058