Decrease in Enteroviral Meningitis - An Unexpected Benefit of COVID-19 Mitigation?

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Abstract

Enteroviral meningitis is seasonal, typically exhibiting a rise in prevalence in late summer/early fall. Based on clinical microbiology laboratory testing data of cerebrospinal fluid, the expected August/September/October peak in enteroviral meningitis did not occur in 2020, possibly related to COVID-19 mitigation strategies.

Introduction

Strategies in place to prevent spread of COVID-19 present a unique opportunity to assess potential effects of these interventions on other infectious diseases. For example, studies from China, Taiwan, Japan, South Korea, Singapore, Brazil, Australia, Chile, South Africa and the United States describe decreased influenza activity during the COVID-19 pandemic (8-14). We previously reported using high-volume clinical microbiology laboratory data to visualize seasonality of infectious agents, including *Legionella* species (1), *Bordetella pertussis* (2), and coronaviruses 229E, HKU1, NL63 and OC43 (3). Enteroviral meningitis is seasonal, with polymerase chain reaction (PCR) testing of cerebrospinal fluid (CSF) for enterovirus typically revealing a rise in positivity in August, September and October, and a nadir in the early part of the year. In 2020, however, we noted based on laboratory test positivity rates, that the expected late summer/early fall peak of enterovirus did not occur.

Methods and Results

We reviewed nine years of testing data for enteroviral meningitis at Mayo Clinic and Mayo Clinic Laboratories (Rochester, MN), comparing 2020 to the eight prior years. Testing was performed on CSF using either a laboratory-developed real-time PCR assay for enterovirus or the BioFire FilmArray Meningitis/Encephalitis (ME) panel; test utilization strategies were in place to prevent simultaneous ordering of both tests.

From January 2012 to November 2020, a total of 38,278 enterovirus real-time PCR tests (mean, 358 per month; range 101 to 687 per month) were performed, of which 3,129 (8.2%) were positive (Figure 1A). Compared to the years 2012-2019, in 2020, there was no summer/early fall peak in enteroviral CSF positivity, with positivity rates in August/September/October of 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019 and 2020 being 9.9/12.5/7.6, 16.2/17.3/17.2/, 13.7/16.4/11.4, 27.2/25.8/21.8, 15.8/11.0/10.6, 15.9/16.4/15.8, 8.1/11.9/10.0, 11.9/11.4/8.4, and 0.8/1.6/0.8%, respectively. Separately, we reviewed CSF positivity for enterovirus detected by the ME panel from

December of 2018 (when this test was first implemented in our laboratory) to November 2020; over this time period, 3,914 tests (mean, 163 per month; range 60 to 243 per month) were performed, of which 62 (1.6%) were positive for enterovirus. Whereas there was a marked peak in positivity (7.4%) in September of 2019, the positivity rate in September of 2020 was 0% (Figure 1B).

For comparison, results of testing for the other microorganisms on the ME panel are shown in the Supplemental Figure. Positivity rates for the bacterial and fungal targets, alongside human parechovirus, herpes simplex virus 1 and cytomegalovirus are generally low for this assay; there were no positive results for *Haemophilus influenza*e or *Neisseria meningitidis* in August, September or October 2020. There was no obvious change in the percent positivity for human herpes virus 6, varicella zoster virus or herpes simplex virus 2 in 2020. Also for comparison (data not shown), stool testing using the BioFire FilmArray Gastrointestinal (GI) panel over the past five years showed typical summer peaks in positivity for *Salmonella* species in all years, including 2020. Together, this suggests that the observed findings with enterovirus are unlikely to be related to a decrease in healthcare visits or testing patterns.

Discussion

We are not aware of a specific study examining enteroviral meningitis during the COVID-19 pandemic, although Chiu et al. and Lee et al. noted decreases in the incidence of enterovirus infection overall (not specifically meningitis) as well as all-cause pneumonia in Taiwan during the COVID-19 pandemic (6, 7). Dean et al. observed a reduction in pediatric emergency department visits for critical pediatric illness during the COVID-19 pandemic, postulating this to be related to decreased critical illnesses due to fewer non- COVID-19 infectious diseases and traumatic injuries (and not to patients avoiding healthcare) (4). Angoulvant et al. reported a decrease in the common cold, bronchiolitis, and acute otitis media, with no change in urinary tract infections, in children in France during the COVID-19 pandemic (5). Taken together with our findings, this suggests that respiratory infectious

diseases other than COVID-19 may be being affected by strategies to reduce the spread of COVID-19. Enteroviral meningitis is a central nervous system infection, with transmission of the associated virus typically occurring person-to-person; it seems to have been impacted by COVID-19 control strategies. This is also supported by there being no obvious change human herpes virus 6, varicella zoster virus or herpes simplex virus 2 positivity rates in CSF in 2020, viruses which typically reactivate to cause central nervous system infection. While our observation regarding enteroviral meningitis is not surprising, we are unaware that it has been previously observed. It is possible there may be a delay in peak of positivity of enteroviral meningitis, and that cases may rise in the months to come; given that we are now beyond the typical seasonal peak however, this seems unlikely. It is possible that the findings reported are unique to us; it would be interesting to examine PCR positivity rates for enterovirus in other regions. Enteroviral meningitis is not a universally reportable disease in the United States, and therefore, use of laboratory data to recognize changing epidemiology can be helpful. The epidemiologic changes observed in enteroviral meningitis may relate to physical distancing, masking, hand hygiene, school closures, teleworking, and/or reductions in travel associate with COVID-19. Our findings do not prove causality, and the changing epidemiology of enteroviral meningitis could relate to other factors than COVID-19 control strategies. Overall, however, it seems plausible that the two are connected, providing a unique opportunity to observe how the epidemiology of various infectious diseases can be impacted by precautionary efforts implemented on a global scale.

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References

1. Rucinski SL, Murphy MP, Kies KD, Cunningham SA, Schuetz AN, Patel R. 2018. Eight years of clinical *Legionell*a PCR testing illustrates a seasonal pattern. J Infect Dis 218:669-670.
2. Bhatti MM, Rucinski SL, Schwab JJ, Cole NC, Gebrehiwot SA, Patel R. 2017. Eight-year review of *Bordetella pertussis* testing reveals seasonal pattern in the United States. J Pediatric Infect Dis Soc 6:91-93.
3. Rucinski SL, Binnicker MJ, Thomas AS, Patel R. 2020. Seasonality of coronavirus 229E, HKU1, NL63, and OC43 from 2014 to 2020. Mayo Clin Proc 95:1701-1703.
4. Dean P, Zhang Y, Frey M, Shah A, Edmunds K, Boyd S, Schwartz H, Frey T, Stalets E, Schaffzin J, Vukovic AA, Reeves S, Masur T, Kerrey B. 2020. The impact of public health interventions on critical illness in the pediatric emergency department during the SARS-CoV-2 pandemic. J Am Coll Emerg Physicians Open doi:10.1002/emp2.12220.
5. Angoulvant F, Ouldali N, Yang DD, Filser M, Gajdos V, Rybak A, Guedj R, Soussan-Banini V, Basmaci R, Lefevre-Utile A, Brun-Ney D, Beaujouan L, Skurnik D. 2020. COVID-19 pandemic: Impact caused by school closure and national lockdown on pediatric visits and admissions for viral and non-viral infections, a time series analysis. Clin Infect Dis doi:10.1093/cid/ciaa710.
6. Chiu NC, Chi H, Tai YL, Peng CC, Tseng CY, Chen CC, Tan BF, Lin CY. 2020. Impact of wearing masks, hand hygiene, and social distancing on influenza, enterovirus, and all-cause pneumonia during the coronavirus pandemic: Retrospective national epidemiological surveillance study. J Med Internet Res 22:e21257.
7. Lee HH, Lin SH. 2020. Effects of COVID-19 prevention measures on other common infections, Taiwan. Emerg Infect Dis 26:2509-2511.

8. Olsen SJ, Azziz-Baumgartner E, Budd AP, Brammer L, Sullivan S, Pineda RF, Cohen C, Fry AM. 2020. Decreased influenza activity during the COVID-19 pandemic - United States, Australia, Chile, and South Africa, 2020. MMWR Morb Mortal Wkly Rep 69:1305-1309.

9. Liu M, Deng L, Wang D, Jiang T. 2020. Influenza activity during the outbreak of coronavirus disease 2019 in mainland China. Biosaf Health doi:10.1016/j.bsheal.2020.08.005.

10. Sakamoto H, Ishikane M, Ueda P. 2020. Seasonal Influenza Activity During the SARS-CoV-2 Outbreak in Japan. JAMA 323:1969-1971.

11. Lee H, Lee H, Song KH, Kim ES, Park JS, Jung J, Ahn S, Jeong EK, Park H, Kim HB. 2020. Impact of Public Health Interventions on Seasonal Influenza Activity During the SARS-CoV-2 Outbreak in Korea. Clin Infect Dis doi:10.1093/cid/ciaa672.

12. de Souza Luna LK, Perosa DAH, Conte DD, Carvalho JMA, Alves VRG, Cruz JS, Bellei N. 2020. Different patterns of Influenza A and B detected during early stages of COVID-19 in a university hospital in Sao Paulo, Brazil. J Infect 81:e104-e105.

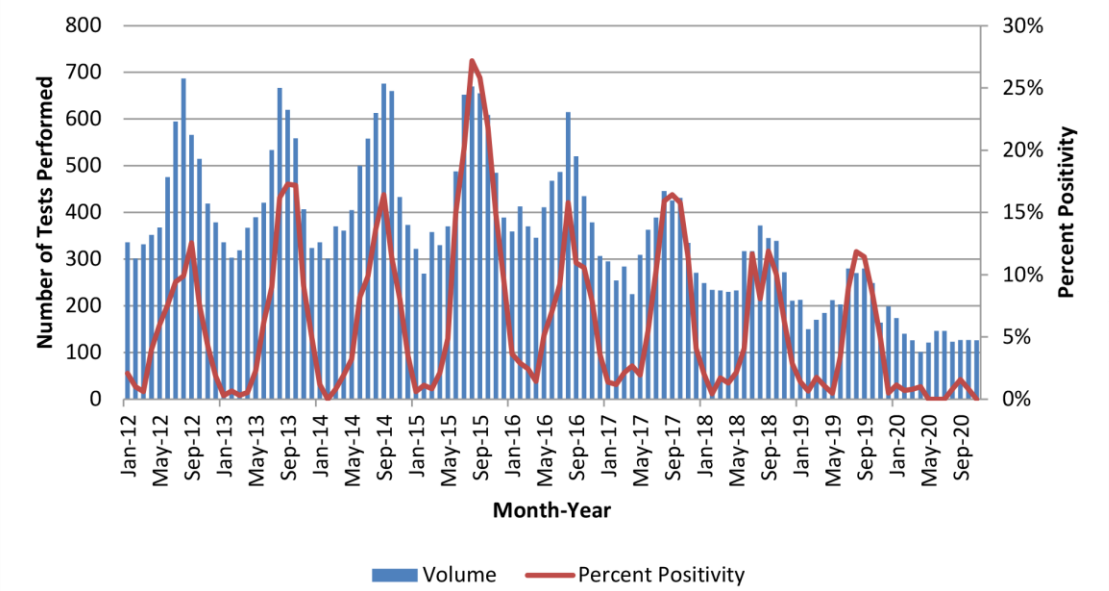
13. Kuo SC, Shih SM, Chien LH, Hsiung CA. 2020. Collateral benefit of COVID-19 control measures on influenza activity, Taiwan. Emerg Infect Dis 26:1928-1930.

14. Soo RJJ, Chiew CJ, Ma S, Pung R, Lee V. 2020. Decreased influenza incidence under COVID-19 control measures, Singapore. Emerg Infect Dis 26:1933-1935.

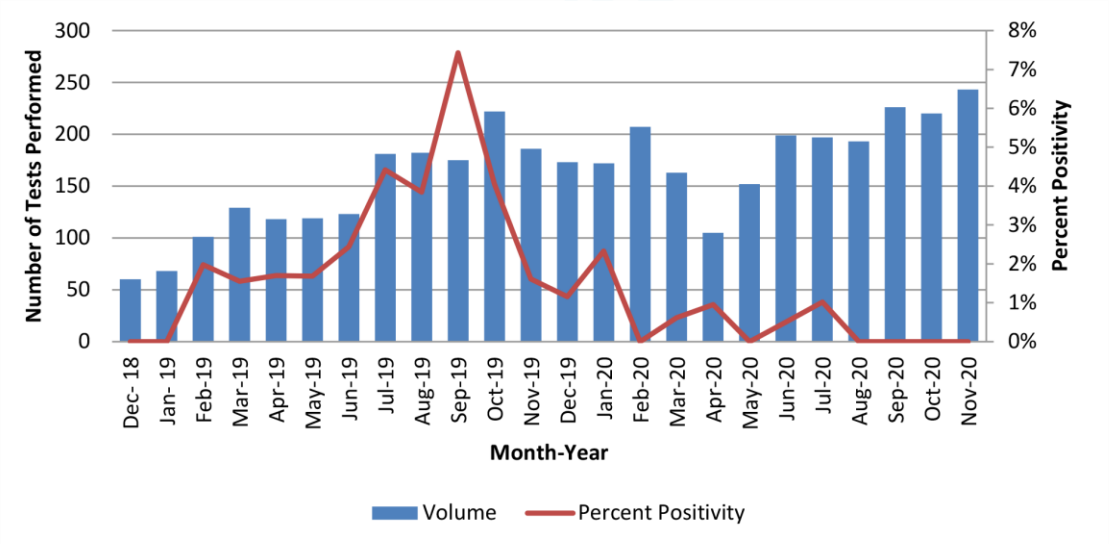
Figure 1. A. Cerebrospinal fluid enterovirus PCR performed from January 2012, through November 2020, showing the monthly total numbers of tests performed (blue bars) and percent positivity (red line). In every year except 2020, there has been a rise in positivity in the late summer/early fall, with a peak in August/September/October. **B.** Cerebrospinal fluid enterovirus PCR performed as part of the BioFire Meningitis/Encephalitis panel from December 2018 through November 2020, showing the monthly total numbers of tests performed (blue bars) and percent positivity (red line). There was a rise in positivity in the summer and fall, with a peak in September in 2019 but not 2020.

Figure 1

A.


Number of Tests Performed
Percent Positivity
Month-Year
Volume
Percent Positivity

B.


Number of Tests Performed
Percent Positivity
Month-Year
Volume
Percent Positivity