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EDITORIAL COMMENTARY

Is Parotitis One More Complication of Influenza? The Ongoing Challenge of Determining Causal Associations

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(See the Major Article by Rolfes et al on pages 485–92 and the Major Article by Elbadawi et al on pages 493–501.)

> *In what circumstances can we pass from this observed* association *to a verdict of* causation*? Upon what basis should we propose to do so?*
>
> Sir Austin Bradford Hill [1]

Influenza is a protean disease. The epidemiology in humans and animals, clinical manifestations, and efficacy of vaccine seem to change constantly. For clinicians, the range of clinical manifestations of influenza is particularly vexing. Influenza infection can range from asymptomatic infection to otitis media, tracheobronchitis, the familiar influenzalike illness with abrupt onset of fever, cough, and myalgia, to hemorrhagic pneumonia, with or without bacterial infection, sepsis, and, all too often, death [2]. Influenza causes misery, disease, and death by exacerbating underlying conditions such as asthma, chronic obstructive pulmonary disease, and cardiovascular disease. Recent studies confirm a strong association of influenza with acute myocardial infarctions [3]. Less common manifestations include bronchiolitis, croup, toxic shock syndrome, myositis, myocarditis, pericarditis, encephalitis, transverse myelitis, and other neurologic complications [4]. It is not always clear whether syndromes associated with influenza reflect damage due to viral replication in the target tissue, secondary damage due to the inflammatory response, antibody-antigen mediated disease, or bacterial infection due to disruption of mucosal and immunologic defenses.

It can be challenging to determine whether the temporal association between a viral illness and rare complications indicates that the virus is causally associated with the syndrome. In this issue of *Clinical Infectious Diseases,* 2 related articles explore the association of sporadic nonmumps parotitis with influenza and other viral infections [5, 6]. The investigations were triggered by reports in December 2014 and January 2015 of an unusual number of cases of parotitis in patients without evidence of mumps. Most had confirmed influenza infection. The possible association of influenza with parotitis had been previously reported in a small number of patients [7, 8]. The Centers for Disease Control and Prevention (CDC) notified state and local health departments of the possible cluster of influenza-associated parotitis in January, prompting a variety of case finding efforts of varying intensity. As increased reports came in, the CDC launched 2 studies and invited health departments to participate.

The first study, described by Elbadawi and colleagues [5] sought to define viruses associated with nonmumps parotitis. Patients with acute parotitis during the winter season (1 October 2014 to 31 May 2015) but without serologic or virologic evidence of mumps or contact with a known mumps case were eligible. They were included if they had a viral infection detected by local testing or had a buccal swab specimen available for testing at the CDC. A total of 325 cases of nonmumps parotitis were reported; 294 had viral testing with polymerase chain reaction at the CDC for mumps virus, influenza, adenovirus, human parainfluenza virus (HPIV) 1–4 and a number of herpesviruses, including herpes simplex virus (HSV) 1 and 2, cytomegalovirus, Epstein-Barr virus (EBV), and human herpesvirus (HHV) 6A and 6B. The variability of case finding efforts makes it difficult to make any reasonable estimates of the true incidence or seasonality of nonmumps parotitis. Strikingly, influenza A(H3N2) was detected in 156 (53%) of 294 buccal swab specimens from patients with parotitis. Because these specimens are not optimal for detecting influenza RNA, this may be an underestimate. HHV6B was detected in 42 (14%), EBV in 32 (13%), HPIV2 in 8 (3%) and HSV1 in 4 (1.4%), and a few patients had adenovirus (1%), HPIV3 (0.7%), or HSV2 (0.3%). The authors report that 52% of patients with influenza and parotitis reported influenzalike illness, and in 63%, these symptoms preceded the onset of parotitis, in contrast to patients in whom HHV6B or EBV was detected (32% and 27%, respectively).

In the second study, reported by Rolfes et al [6], 50 case patients with influenza and parotitis were matched to 124 control patients with laboratory-confirmed influenza but without parotitis. Controls were matched by age group, state of

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residence, date of specimen collection, and hospitalization status. Case patients were strikingly less likely than controls to have received an antiviral medication (27% vs 64%; odds ratio, 0.2; 95% confidence interval, .1–.4) and more likely to have received an antibiotic (65% vs 22%; 9.9; 4.1–23.9). Sequencing by next generation sequencing revealed that 95% of viruses from case patients and all viruses from control belonged to clade 3C.2a, the most common circulating drifted strain that season. No unusual changes in other genes were detected in the virus sequences from parotitis case patients that might suggest a change in tissue tropism.

We are left to ask whether these reports and others prove that influenza—or for that matter EBV, HHV6B, or respiratory viruses other than influenza—can cause parotitis. The frequency with which respiratory viruses can be detected with polymerase chain reaction, particularly in small children [9] means that we must be cautious when associating viral detection with a new syndrome. The pioneering epidemiologist Austin Bradford Hill observed that epidemiologic studies can only demonstrate association. They cannot by themselves prove causation, but causation can be inferred by thoughtful consideration of a number of criteria [1]. These criteria, known to generations of students as the *Bradford Hill criteria* include strength of association, consistency, specificity, temporality, biologic gradient (or dose response), plausibility, coherence, experimental data, and analogy. Molecular epidemiology, advances in statistics and data science, and greater understanding of biology have changed how we understand and apply the Bradford Hill criteria [10], yet they remain useful.

The presence of influenza virus in the oral secretions of 53% of patients with parotitis suggests strength of association, although there is no appropriate control group. Influenza is shed for a median of 3–7 days in normal hosts [11], and prolonged shedding is rare, making coincidental detection less likely. In contrast, EBV and HHV6B are herpesviruses that cause life-long infection and are frequently detected in the saliva of asymptomatic persons [12], including astronauts on the international space station [13]. Other reports of influenza A(H3N2) detection among patients with parotitis during the same season in Canada [14], England [15], and Scotland [16] provide evidence of consistency. The presence of influenzalike illness before parotitis is consistent with a temporal relation. The apparent protective effect of antivirals might imply that inhibition of viral replication decreases the occurrence of parotitis, consistent with a dose response. It is biologically plausible that influenza virus could cause parotitis, perhaps by replication in salivary epithelium or by bacterial superinfection of the parotid, as seen in postinfluenza bacterial sinusitis and pneumonia. However, there is no suggestion of suppurative parotitis in the reports.

In the absence of experimental data or the demonstration that influenza virus replicates in salivary glands, it will be hard to prove to a high degree of scientific certainty that influenza causes parotitis. There are potential weaknesses in both of the current studies [5, 6], including case finding strategies leading to an increased prevalence of influenza cases in the sample, selection bias, the use of buccal swab specimens alone, and the limited ability to completely exclude mumps or bacterial infection. However, the contributions of Elbadawi, Rolfes, and colleagues strongly suggest that parotitis can be added to the long list of syndromes caused by influenza.

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