Ecological and individual data both indicate that influenza inhibits rhinovirus infection

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We read the article "Virus–virus interactions impact the population dynamics of influenza and the common cold" by Nickbakhsh et al. (1) with great interest. The authors analyzed a large Scottish dataset consisting of virology results from patients with acute respiratory illnesses and used mathematical models to identify a negative interaction between influenza and rhinovirus (RV) infection. Furthermore, they performed epidemiologic simulations demonstrating that influenza-mediated induction of a refractory period could account for the significant reduction in RV illness prevalence. In fact, we demonstrated that influenza can induce a refractory period using individual-level data obtained from a cohort of children that we prospectively followed in the fall of 2009 (2).

We prospectively followed 161 school-age children (age 4 to 12 y) for 8 consecutive weeks in September and October of 2009 in Wisconsin, obtaining nasal specimens on a weekly basis for viral analysis by multiplex PCR. In our community-based study, RV infections were most prevalent in early to mid-September, and less frequent in October. The H1N1 pandemic began in the early fall and did not peak until late October of 2009, and the H1N1 vaccine was not available until the final week of October after our final sample was obtained. To determine whether infection with a given virus increased or decreased susceptibility to another virus 1 wk later, we used generalized linear mixed-effect models with a random effect for subject. In our study, RV infection did not reduce the risk of H1N1 infection the following week (odds ratio [OR], 0.68; 95% confidence interval [CI], 0.37 to 1.2; $P = 0.21$). In contrast, H1N1 infection significantly reduced the risk of RV infection the following week (OR, 0.19; 95% CI, 0.07 to 0.54; $P = 0.02$), suggesting that RV does not prevent H1N1 infection but H1N1 infection can reduce the risk of subsequent infection with RV. This suggests that the negative interaction between RV and H1N1 is unidirectional.

The methods of the two studies are quite different and yet yield complementary results. The study by Nickbakhsh et al. included a large urban population and spanned multiple years but was limited in not including longitudinal results from individual patients to determine whether infection with one virus reduced risk of infection with a second virus. Our study, while smaller in size and conducted over a single season, included serial sampling of the same individual during an unusual season when both RV and influenza infections were quite common. In addition, the surveillance study design included samples from both sick and well children. The combined results provide evidence that infection with influenza induces a refractory period for RV infections that could influence the seasonal epidemiology of RV infections and illnesses, which are especially important in children and adults with chronic respiratory diseases such as chronic obstructive pulmonary disease and asthma (3).

1 S. Nickbakhsh *et al.*, Virus–virus interactions impact the population dynamics of influenza and the common cold. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 27142–27150 (2019).
2 K. M. Kloepfer *et al.*, Increased H1N1 infection rate in children with asthma. *Am. J. Respir. Crit. Care Med.* **185**, 1275–1279 (2012).
3 M. C. Altman *et al.*, Evolving concepts in how viruses impact asthma. *J. Allergy Clin. Immunol.*, 10.1016/j.jaci.2019.12.904 (2020).

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