pathogenicity of various bacterial species carried in the upper respiratory tract, a phenomenon we referred to as “copathogenesis.” The mechanism(s) by which such potentiation may have occurred are unknown. We speculated that the 1918 virus may have had increased tropism for or have been unusually cytopathic for tracheobronchial cells, facilitating access of bacteria to the peripheral bronchopulmonary tree and leading to massive diffuse bacterial bronchopneumonia that was poorly responsive to therapies of the time.

Dr. Kilbourne joins us in noting the remarkable measles epidemics in US Army training camps during the winter of 1917–1918, less than a year before the influenza pandemic. The measles epidemics were the result of an unfortunate “natural experiment” in which young men from remote rural areas, many of whom had escaped measles virus infection in childhood, were brought together in crowded barracks during the winter/spring season of measles circulation. Although in years prior to 1918 measles had generally been a less deadly disease than influenza would prove to be a year later, the case fatality rate for measles was, paradoxically, much higher. Deaths in these cases resulted largely from streptococcal or pneumococcal bronchopneumonias pathologically indistinguishable from those caused by pandemic influenza several months later [3]. Thus, copathogenic properties of the 1918 influenza virus may have been generic and not specific to the 1918 virus or to influenza viruses in general.

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**Evidence against Helicobacter pylori Being Related to Childhood Asthma**

To the Editor—Chen and Blaser recently reported an inverse relationship between *Helicobacter pylori* seropositivity and asthma in children, and they suggest that early exposure to *H. pylori* may cause immunological changes that protect against the development of asthma—a proposition in keeping with the “hygiene hypothesis” [1]. Northeastern Peninsular Malaysia is unique in the developing world because of its extraordinarily low prevalence rate of *H. pylori* infection [2]. The prevalence rates among adults are in the order of 4%–5%, and this is reflected in the very low incidence of *H. pylori*–related diseases, such as gastric cancer and peptic ulcer disease [2–4]. In contrast, other infectious diseases such as enteric infection and typhoid are still common in the area. If lack of exposure to *H. pylori* is an important determinant of childhood asthma in children, the prevalence rates of childhood asthma in northeastern Peninsular Malaysia might be expected to be high. The available data, however, do not support this expectation.

In 2001, a survey among schoolchildren in the district of Kota Bharu in northeastern Peninsular Malaysia revealed that the prevalence of wheezing at any time in the preceding 12 months was 5.4% among children 6–7 years old and 5.7% among children 13–14 years old [5]. Wheezing in the previous 12 months was an index of asthma that allowed direct comparison with prevalence figures reported in the International Study of Asthma and Allergies in Childhood (ISAAC), a survey that involved 56 countries [6]. The observed prevalence rates for this index of asthma in northeastern Peninsular Malaysia [5] were quite low when compared with the ranked order of prevalence rates reported by country in the ISAAC study [6], indicating that, as far as asthma was concerned, northeastern Peninsular Malaysia is not a high-prevalence area. Interestingly, the overall prevalence of wheezing in the previous 12 months for the country of Malaysia, as reported in the ISAAC study [6], was 6.2% among children 6–7 years old and 9.1% among children 13–14 years old. These figures are higher than those for northeastern Peninsular Malaysia [5], despite the fact that the overall *H. pylori* infection rates in northeastern Peninsular Malaysia are almost certainly lower than the national average. This does not necessarily negate the hygiene hypothesis, but it speaks against a unique role for *H. pylori* infection in childhood as a protective factor against asthma. The prevalence of *H. pylori* infection is inversely related to household hygiene, such that the presence of *H. pylori* could act as a marker or surrogate for antigens associated with the protective effect postulated by the hygiene hypothesis and not be directly involved.

Chen and Blaser [1] concede that their study cannot separate *H. pylori* infection as etiologically important or as a marker for other variables. We propose that the data from northeastern Peninsular Malaysia, where hygiene is poor but *H. pylori* is absent, serves to test the hypothesis about whether *H. pylori* itself is protective against childhood asthma. Overall, the results are consistent with the notion that *H. pylori* infection is not protective against asthma in childhood. The presence of populations in which there is a naturally low prevalence of *H. pylori* infection allows investigators to examine hypotheses that make predictions about the effects of the decreasing prevalence of *H. pylori* infection worldwide. In Malaysia, the dire consequences, such as ad-
enocarcinoma of the esophagus, that researchers have predicted will occur in association with the loss of *H. pylori* infection, are not seen [7].

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Reply to Raj et al.

To the Editor—we thank Raj et al. for the interesting points they raise. However, we do not believe that they are directly relevant to the observations we report [1].

The proportion of a disease that is attributable to an exposure, namely population attributable risk, is a function of the prevalence of the exposure and the strength of the disease-exposure association. It does not depend on the prevalence of the disease. Using the estimates of the prevalence of *Helicobacter pylori* infection (9.8%) and the odds ratio for asthma associated with *H. pylori* positivity (0.49), we estimated that 48.6% of asthma could be attributable to not carrying *H. pylori* among children <13 years old represented in data from the National Health and Nutrition Examination Survey 1999–2000. Data that describe groups of individuals, rather than the individuals themselves, are called "ecological" [2], and it is well recognized that ecological data may not pertain to data for the specific individuals in those groups or to the comparison of individuals across the groups [2, 3]. The ecological observation that the prevalence of *H. pylori* infection and the prevalence of asthma are low in north-eastern Peninsular Malaysia does not indicate the proportion of the asthma risk that can be explained by *H. pylori* infection, nor does it test the hypothesis of a causal relationship between *H. pylori* infection and asthma risk, because the prevalence of asthma among *H. pylori*–positive individuals was not compared with that among *H. pylori*–negative individuals in the population, and we do not know the strength of the association between *H. pylori* status and asthma risk. In addition to the strength of the association, a set of criteria proposed by Hill can be used to help assess a potential cause and effect relationship. We have discussed Hill’s criteria regarding the relationship between *H. pylori* and asthma risk elsewhere [4].

*H. pylori* strains differ in antigenicity [5], and the use of heterologous strains in the serologic assays used [6], as in the study in Peninsular Malaysia [7], could explain their remarkably low prevalence rates. The populations surveyed in Peninsular Malaysia are an anomaly compared with similar groups in developing countries [8]. Because *H. pylori* has been present in humans at least since before the last migration out of Africa (~58,000 years ago), and humans migrated to all corners of the world [9], one possible explanation for the findings of Raj et al. is that there was one or more ancient bottleneck in the transmission of *H. pylori*, so that a local population group evolved in its absence. Over the millennia, there would have been continued selection for human and microbial phenotypes to maximize host fitness in the absence of *H. pylori* [10]. Another possibility is the presence of local inhibitors of *H. pylori* in drinking water or diet that have long reduced transmission, prevalence, or microbial load. Neither of these situations is at all analogous to the rapid decline in the prevalence of *H. pylori* infection seen in the United States [11] and other developed countries [11].

The strength of the association between *H. pylori* infection and asthma risk may vary by population, depending on the prevalence of other risk factors for asthma that may modify the effect of *H. pylori* infection in the population. Research is needed to identify the potential factors that may modify the association between *H. pylori* infection and asthma risk to explain population differences. It is possible that the risk of asthma associated with *H. pylori* infection is lower in Peninsular Malaysia, compared to that in the United States. However, we would not be able to know this without a well-conducted, population-based study in Peninsular Malaysia that directly evaluates the *H. pylori* status of individuals in relation to their asthma risk.

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