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**Reply**

To the Editor—Maric and Cheng [1] make important points about the epidemiology of adenocarcinoma of the esophagus by comparing rates among US blacks and whites and among males and females. Essentially all diseases have multifactorial causes; the challenge is to identify those characteristics that are associated with the highest risk of disease development. Over the past 25 years, adenocarcinoma of the esophagus has been rapidly increasing among persons in developing countries [2]. When disease rates change rapidly, environmental factors usually play the critical role. The fact that the increase in esophageal adenocarcinomas is disproportionate in different ethnic groups and among men, compared with that among women, implies differential exposure to the offending factor(s). As Maric and Cheng indicate, differences in body mass index are clearly one part of the puzzle.

The rates for many diseases differ substantially for men and women. Despite nearly similar rates of exposure to *Helicobacter pylori*, duodenal ulcer rates are 2-4-fold higher among men than among women, a differential that cannot be entirely explained by known risk factors such as smoking. For noncardia gastric cancer, another disease associated with *H. pylori*, rates among men also are substantially greater than those among women [3]. However, analysis of incidence data indicates that rates among both men and women rise appreciably with age; the age at which the big increase begins in women is shifted ~10 years later than that for men, and the slopes of the 2 curves after the 10-year shift are nearly identical [4]. Thus, the differential in disease rates can be largely explained by a protective factor that women have for ~10 years longer than men. A similar phenomenon has been observed for atherosclerotic heart disease (ASHD), and most evidence suggests that female hormones are involved in the protective effect. ASHD rates increase substantially among women after menopause, in essence paralleling trends among men. The rise in esophageal adenocarcinomas is relatively recent, and the numbers are not yet large; however, in the future, analysis of age-specific rates by sex may be useful.

Regardless of these considerations, it now has become clear that gastroesophageal reflux disease (GERD) is the most important risk factor for the development of esophageal adenocarcinoma [5] and that GERD is becoming more prevalent [6]. It is critically important to identify the triggers for this phenomenon; my hypothesis is that the lack of *cag* H. *pylori* strains (which I term “acagia”) is a major risk factor for development of Barrett’s esophagus and subsequent adenocarcinoma.

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**Reemergence of Invasive *Haemophilus influenzae* Type b Disease in Alaska: Is It Because of Vaccination with Polyribosylribitol Phosphate Outer Membrane Protein Complex (PRP-OMPC) or Failure to Vaccinate with PRP-OMPC?**

To the Editor—We read with interest the article by Galil et al. [1] on the reemergence of invasive *Haemophilus influenzae* type b (Hib) disease in a well-vaccinated population in remote Alaska. The authors describe a dramatic decline in cases of invasive Hib disease among Alaska Natives following near-exclusive vaccination with the Hib conjugate vaccine polyribosylribitol phosphate outer membrane protein complex...
Pharyngeal colonization with Hib, its role in disease transmission, and the effect of vaccination on colonization remain poorly understood. Barbour [2] found Hib carriage in 8% of children 4 years after vaccination with Hib conjugate vaccine, compared with 5% in unvaccinated children. Among Hib carriers, an inverse relationship between Hib colony count and anti-PRP concentration was found: all vaccinated Hib carriers had very low Hib colony counts. In another study, Barbour et al. [3] noted that both the mechanism and the duration of conjugate vaccine inhibition of Hib colonization are uncertain. Hall et al. [4] studied Hib carriage in Alaska Natives in 1982–1983 and found a colonization level of 6.8% despite historically very high rates of invasive Hib disease. They concluded that “mechanisms for increased exposure which would not be reflected in high carriage rates may exist for these young children.” [4, p. 1190]. Furthermore, the Galil study found no differences in the prevalence of colonization between villages with and without recent cases of invasive Hib disease that would explain the outbreak cases.

A potential misinterpretation of the study would be that the elimination of Hib carriage is primarily dependent on the choice of Hib vaccine. As Galil et al. [1] suggest, other factors may have contributed to continuing Hib carriage in this population of Alaska Natives.

Never-vaccinated children, older than the population studied by Galil et al., are recognized as a source of nasopharyngeal Hib carriage [5]. Although 97% of the population surveyed had received ≥3 doses of a Hib conjugate vaccine, no vaccine coverage information was available for children in the remaining 46 villages. Given that a convenience sample was used, it is likely that the villages chosen for the carriage survey also were more receptive to vaccination campaigns.

If age-appropriate Hib vaccination coverage were variable or if older never-vaccinated children were found to carry Hib, sources of Hib transmission could persist. In an environment of incomplete coverage, it would be impossible to definitively assess the impact of Hib vaccination on Hib carriage, because pockets of unvaccinated children could serve as reservoirs for reintroducing the organism. These populations may have served as the source of Hib transmission to young infants susceptible by virtue of vaccination with DTP-HbOC, the “unmasking effect” described by the authors.

PRP-OMPC is highly effective. In Israel, the efficacy and effectiveness of the vaccine were 98.7% and 94.9%, respectively, and cases of disease in infants <3 months old (prior to the age when one can expect a direct protective effect of vaccine) dropped sharply, consistent with vaccine-induced reduction in pharyngeal Hib carriage (herd immunity) [6]. Among the Navajo in the southwestern United States, a population similar in Hib disease incidence and risk factors to the Alaska Natives, PRP-OMPC had >95% efficacy against invasive disease in infants aged 2–18 months after 2 doses of vaccine [7].

Although the study by Barbour et al. [3] demonstrated persistent pharyngeal Hib carriage following vaccination with Hib conjugate vaccines, several studies have documented a reduction in Hib carriage levels following vaccination with Hib conjugate vaccines [8–10]. However, he effect of Hib conjugate vaccines on carriage may vary substantially among populations with high and low rates of invasive Hib disease incidence [11]. The study by Galil et al. was conducted in a population that experienced one of the highest reported incidence rates of invasive Hib disease in the prevaccine era [12]. The only other published study on the effect of any Hib conjugate vaccine on carriage in a population with a high incidence of invasive Hib disease found that pharyngeal carriage in a Navajo population vaccinated with PRP-OMPC decreased from 4.8% to 2.3% [13].

The report by Galil et al. [1] underscores the need for further investigation of the role of pharyngeal colonization in the transmission of invasive Hib disease as well as of the effect of Hib vaccination on carriage. We agree that early seroprotection, high levels of vaccine coverage, and continued disease surveillance are crucial to attaining the goal of invasive Hib disease eradication.

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Reply

To the Editor—We thank Dargan et al. [1] for their interest in our recent report of the reemergence of invasive *Haemophilus influenzae* type b (Hib) disease in rural Alaska Native infants. We appreciate their support for the key messages of our study, specifically the need for early protection in this population, high levels of vaccination coverage, continued surveillance for invasive Hib disease, and further investigation of the epidemiology of pharyngeal colonization, including the effect of Hib vaccination on carriage. The results of this study were instrumental in reestablishing polyribosylribitol phosphate *Neisseria meningitidis* outer membrane protein (PRP-OMP) vaccine as the Hib conjugate vaccine for the first dose of the Hib vaccination program in Alaska. The resumption of the use of PRP-OMP for the first dose has led to a return to lower rates of infant Hib disease in rural Alaska Natives, an indication of the unique immunologic features of this vaccine.

As Dargan et al. [1] note, our knowledge of the effect of Hib conjugate vaccination on colonization is incomplete, and the relationship between colonization and disease transmission remains unclear; however, we will clarify several points raised by their letter. The study of the effect of PRP-OMP vaccine on colonization in the Navajo population is not the only study of the effect of Hib vaccination on colonization in a high-incidence population [2]. Adegbola et al. [3], in a randomized, controlled trial of the impact of PRP–tetanus toxoid Hib conjugate vaccine on oropharyngeal carriage in The Gambia, found a 60% reduction in the prevalence of carriage (11.0% among unvaccinated children vs. 4.4% among fully vaccinated children). In addition, persistent Hib carriage has been documented in Australian Aboriginal children, despite routine vaccination with PRP-OMP vaccine; this population also experienced a high incidence of Hib disease and an epidemiologic pattern similar to that observed in rural Alaska Natives [4]. Dargan et al. note that the study by Barbour et al. [5] showed no difference in Hib colonization 4 years after immunization with *H. influenzae* oligosaccharide-CRM197 (HbOC) [5]. However, this study included just 60 infants who had received HbOC in an immunogenicity trial 4 years earlier and were living in a general population of unimmunized children, not a setting in which herd immunity would be expected. The more pertinent comparison is with studies of Hib colonization following widespread vaccination of the entire population. These studies convincingly document a substantial reduction in Hib colonization and provide the basis for understanding the herd immunity that occurs following widespread immunization [6–8].

Dargan et al. [1] accurately point out that the contribution of Hib colonization in older children and adults to transmission is poorly understood. The influence of vaccination coverage rates and the regimen and vaccine used is likewise unclear. We should clarify that infants in rural Alaska are routinely vaccinated during well-child visits and itinerant public health nurse visits, not through vaccination campaigns, as Dargan et al. suggest, and that immunization coverage levels in Alaska, including rural Alaska Native populations, are as high as, or higher than, the national average. In general, by 2 years of age >90% of Alaska Native children, including those in the villages in our study, have received ≥3 doses of Hib conjugate vaccines. Therefore, low vaccination coverage rates are not likely to explain our observations.

Further research into the factors that contribute to the elimination of Hib colonization in various populations is urgently needed. At this time, the role of factors such as carriage in older age groups, the intensity of colonization and transmission, the vaccination schedule, and the vaccine used in Alaska is not clearly elucidated. We agree that it would be a misinterpretation of the results of this study to suggest that we would not have observed continued colonization had another Hib conjugate vaccine been used. To address the remaining questions, we have initiated several other studies that we hope will clarify the relative importance of these various factors and lead to improved strategies for elimination of Hib disease in Alaska and elsewhere.