The disease we recognize today as hepatitis A had been proven many decades ago to be transmitted by the fecal-oral route and had been classified loosely as “infectious,” in contrast to “serum,” hepatitis before the viral agent, hepatitis A virus (HAV), was visualized in 1973 [1]. Within half a decade, HAV had been cultivated in vitro, and a prototype vaccine was developed [2, 3]. During the early 1990s, large-scale clinical trials proved the efficacy and safety of hepatitis A vaccines [4, 5], and, by 1995, the first hepatitis A vaccine was licensed. Initially, the vaccine was targeted at groups at high risk for infection [6], which reduced the annual incidence of reported new cases from ~12/100,000 population (ranging cyclically between ~9/100,000 and 14/100,000) before vaccination to as low as ~7/100,000 population by 1999. Implementation of this vaccination policy initiated a progressive, decade-long reduction in the annual incidence of new cases that was accelerated after 1999, when childhood hepatitis A vaccination was recommended in communities with historically high rates of acute hepatitis A [7] (with the annual incidence falling to 2.7/100,000 population not only in vaccinated children but also in cohorts of older children and adults, such that herd immunity was achieved). Still, during the early part of this decade, foodborne outbreaks of hepatitis A, some affecting hundreds of victims, continued to make headline news and to claim lives [8]. Ultimately, in 2006, to generalize the benefit of hepatitis A vaccine and to reduce further the frequency of vaccine-preventable illness and death, the US Public Health Service recommended universal childhood hepatitis A vaccination [9].

In a 1998 report, Vento et al. [10] described a series of cases of fulminant acute hepatitis A in persons with chronic hepatitis C, leading to the conclusion that acute hepatitis A superimposed on chronic hepatitis C in particular and on chronic liver disease (CLD) in general was likely to exacerbate the severity of acute hepatitis A, which otherwise was self-limited and generally mild to moderate [11]. Although Vento’s experience was not confirmed by others [12, 13] and although patients with CLD are generally not at increased risk of acute hepatitis A, the Advisory Committee on Immunization Practices of the US Public Health Service included patients with CLD as candidates for hepatitis A vaccination in its original 1996 recommendations issued for vaccination of high-risk groups [6].

Even before the introduction of hepatitis A vaccine, rates of HAV infection, but not of disease severity, had begun to fall. In developing countries, exposure to hepatitis A is almost universal during early childhood, when HAV infection is associated with an asymptomatic or mildly symptomatic illness. In the United States and other developed countries in the pre-vaccination era, improvements in environmental hygiene during the last half of the twentieth century resulted in a decline in the frequency of hepatitis A [14], in the exposure of children to HAV, and in the prevalence of immunity to hepatitis A. This secular trend resulted in the emergence of succeeding generations that have remained susceptible to HAV infection into adulthood. When hepatitis A occurs in adults, the illness tends to be clinically more severe [15] (often being associated with jaundice and indications for hospitalization) and results more frequently in fulminant hepatitis. Paradoxically, as the prevalence of hepatitis A fell and susceptibility to HAV infection increased among adults, clinically severe acute cases of hepatitis A tended to become more common—that is, the natural history of acute hepatitis A worsened! Potentially, vaccination that prevents acute hepatitis A should blunt this trend and reduce severe and fatal instances of acute hepatitis A.

In this issue of the Journal, Vogt et al. [16] report that, indeed, on the basis of an analysis of death certificates that included hepatitis A as the underlying cause of death, mortality resulting from acute hepatitis A declined by 32% between the prevaccine period of 1990–1995 and the post–vaccination recommendation period of 2000–2004. These declines paral-
eled the reduction in reported hepatitis A incidence rates that occurred after the introduction of hepatitis A vaccine. Lending strength to the observation is the more profound 45% reduction in hepatitis A mortality in the 17 predominantly Southwestern and Western states with historically high rates of hepatitis A that had implemented the 1999 recommendation that all children be vaccinated, compared with the 23% decline in states that were not included in the 1999 vaccine recommendation. Just as impressive as the trend in hepatitis A mortality was the large proportion of hepatitis A deaths for which underlying CLD was listed on the death certificate as a contributing cause of death—45% of the 511 deaths recorded between 1999 and 2004. In addition, hepatitis A deaths occurred a median of a decade and a half earlier among those with CLD than among those without underlying CLD (55 vs. 69 years), suggesting that acute hepatitis A resulted in a more premature demise among those with underlying CLD.

When hepatitis A deaths were stratified by age in 2-decade increments, the authors found that the contribution of underlying CLD was highest (63%) in those aged 40–59 years, who were born between 1940 and 1964. This subpopulation corresponds relatively closely with the baby-boom generation, the population cohort whose epidemic experimentation with injection drug use from the 1960s to the 1980s [17] left a legacy of chronic hepatitis C decades later and bestowed on them the dubious distinction of having the highest prevalence of chronic hepatitis [18, 19]. How important is the role of chronic hepatitis C in hepatitis A–related deaths? Although hepatitis C was the underlying cause of CLD in only 41% of those whose deaths were attributed to hepatitis A, hepatitis C was concentrated most heavily in the cohort of 40–59-year-olds; 67% of all hepatitis A deaths for which hepatitis C was a cofactor occurred in this age cohort. Therefore, in the population that had the highest concentration of all cases of chronic hepatitis C, hepatitis C was the most common underlying cause of CLD contributing to hepatitis A mortality.

Because fulminant hepatitis A is so uncommon [20], most of us who care for patients with chronic hepatitis C never see fulminant hepatitis A in our patients with hepatitis C, and conflicting data have been published on the severity of superimposed acute hepatitis A in patients with underlying chronic hepatitis [10, 12, 13]. Therefore and because of other factors that mitigate against successful adult-vaccination strategies, the recommendation that patients with chronic hepatitis C receive hepatitis A vaccine has not been followed faithfully [21]. The study by Vogt et al., however, relies on a sophisticated large-population analysis to identify a microepidemiologic trend in hepatitis A mortality that might not be recognized by even the most experienced hepatologist. Moreover, despite the reduction in hepatitis A incidence and mortality during the postvaccination era, Vogt et al. found that the proportion of hepatitis A deaths with underlying CLD actually increased from 44% in 1999 to 67% in 2004. This report should refocus our attention on the importance of targeting our patients with chronic hepatitis C—and other chronic liver disorders—for hepatitis A vaccination.

Are these observations valid? Potentially, the observed decline in the incidence of hepatitis A and of hepatitis A deaths could have resulted from the regular cyclical reduction in hepatitis A cases that has been recorded every 10–15 years [22]; the fact that declines in hepatitis A mortality occurred even in states for which universal childhood vaccination programs were not recommended leaves unresolved the potential contribution of natural variation to the observations reported. In addition, reliance on death-certificate diagnoses is only as good as the notorious imprecision of death-certificate entries and of the methodologies used to capture and interpret disease-code data. As with any good scientific observation, the apparent answer to one question leads to the generation of others. To support the observations in the report by Vogt et al., future investigators will have to monitor the annual incidence of hepatitis A and hepatitis A mortality after the 2006 recommendation for implementation of universal childhood vaccination; the distinctions observed through 2004 by Vogt et al. between the states targeted in the 1999 recommendation for childhood vaccination and those without childhood-vaccination recommendations should be eliminated after 2006. If the trend observed by Vogt et al. is truly vaccine related and not an artifactual consequence of natural cyclical variation in hepatitis A incidence, then future monitoring should document the blunting of these cyclical trends in hepatitis A. Finally, if underlying CLD does contribute substantially to hepatitis A mortality, then improved targeting of hepatitis A vaccine to those with CLD—perhaps most readily demonstrated in patients with chronic hepatitis C born between 1940 and 1964—should be reflected by a reduction in hepatitis A mortality.

Vaccines should prevent disease and disease consequences. For hepatitis A, the time from virus discovery to vaccine availability was 2 decades, and the time from vaccine availability to fulfillment of the vaccine’s promise may be even quicker—the vaccine dividend has been dramatic.

References