laxatives, wheat bran and intestinal antibiotics, the deoxycholate pool is contracted and CSI falls (4, 5). Thus maneuvers that alter colonic transit affect the DCA pool size and CSI. The observation that women of childbearing age also have prolonged transit times and greater tendency toward constipation is intriguing in light of the observations that this population group is at high risk for cholesterol gallstones (6).

An increased percentage of DCA in the bile acid pool has been observed in several studies examining gallstone subjects (5). The mechanism whereby DCA increases CSI is not entirely certain, although studies indicate that excretion of this bile acid causes a greater increase in cholesterol output than does an increase in chenodeoxycholic acid (CDCA). This difference is explained by the fact that DCA is more hydrophobic; this quality may cause a greater solubilization of bile canalicular cholesterol. An additional mechanism whereby DCA would increase CSI is that an increase in DCA pool size is generally paralleled by a decrease in the CDCA pool (5). Because CDCA has the strongest inhibitory effect on cholesterol output, a change in the ratio of DCA to CDCA may have significant effects on CSI. In addition to these mechanisms, there appears to be a direct correlation between the rate of biliary excretion of DCA and arachidonic acid content of human biliary lecithin (1). Increases in this lipid fraction might enhance prostaglandin synthesis by the gallbladder mucosa. Increased prostaglandin levels would increase mucus secretion by the gallbladder epithelium, thereby providing a more favorable framework for cholesterol nucleation (1). Thus colonic factors that increase DCA pool size may enhance cholesterol gallstone formation by several mechanisms.

Should we now add prolonged WGTT to the well-known risk factors for cholesterol gallstones (i.e., obesity, female sex, weight-reduction diets, hypertriglyceridemia and estrogens)? Certainly at this point it is difficult to do so. Krevsky et al. (7), using colonic transit scintigraphy, noted a lack of correlation between the number of bowel movements and the movement of feces through the colon. They suggest that studies counting the number of bowel movements or quantitating markers may not accurately reflect colonic transit. Improved methodologies that allow investigation to correlate colonic transit time with biliary bile acid and lipid composition would help answer this question.

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## HEPATITIS B VACCINE: SHOULD WE GIVE IT A SHOT?

*Bloom BS, Hillman AL, Fendrick AM, Schwartz JS.* A reappraisal of hepatitis B virus vaccination strategies using cost-effectiveness analysis. Ann Intern Med 1993; 118:298-306.
*Schaffner W, Gardner P, Gross PA.* Hepatitis B immunization strategies: expanding the target. Ann Intern Med 1993;118:308-309.

### ABSTRACT

***Objective:*** **To determine clinical and economic consequences of alternative vaccination strategies for preventing hepatitis B virus infection (HBV).**

***Methods:*** **Decision analysis was used to evaluate costs, outcomes, and cost-effectiveness of three HBV management strategies ("no vaccination," "universal vaccination," and "screen and vaccinate") in four populations (newborns, 10-year-old adolescents, a high-risk adult population, and the general adult U.S. population). Information on HBV incidence and prevalence, clinical course, and management of acute illness and chronic sequelae was obtained from the literature and a panel of experts. Actual payments (costs) were obtained from Blue Cross/Blue Shield and local pharmacies. Incremental cost-effectiveness was calculated from the perspective of the payer of medical care and subjected to sensitivity analysis.**

***Results:*** **Vaccination (with or without screening) prevents more disease at somewhat increased cost than no vaccination for the neonatal, adolescent, and adult populations. Vaccination (with or without screening) is a dominant strategy in adult high-risk populations (lower cost and greater benefit than no vaccination). Optimal cost-effectiveness, with nonmonetary benefits not discounted, results if all pregnant women are screened for active HBV infection, and HBV vaccine and hepatitis B immune globulin are administered to babies born to mothers with positive screening tests. Then HBV vaccine is administered to all children at age 10 and again 10 years later (incremental cost-per-year-of-life-saved relative to the "no vaccination" strategy is $375). A strategy of universal newborn vaccination alone leads to an incremental cost-per-year-of-life saved of $3332. If adolescents are vaccinated at age 10, incremental cost-per-year-of-life saved is $13,938; for the general adult population, the incremental cost-per-year-of-life saved of universal vaccination is $54,524. Discounting benefits will increase cost-per-year-of-life saved 7 to 12 times for all strategies.**

***Conclusions:*** **HBV vaccine is most cost-effective**

**when a strategy of screening newborns is combined with routine administration to 10-year-old children. The means to achieve substantial improvements in the health of the public in a cost-effective fashion are now available and should be pursued aggressively.**

## COMMENTS

HBV is the world's most common blood-borne viral infection, responsible for substantial morbidity and mortality. It is estimated that each year 4,000 to 5,000 persons in the United States die of HBV-related liver diseases, which include HCC. Despite the availability of an efficacious HBV vaccine for the past decade, the incidence of HBV infection has increased by 37%. Various vaccination strategies have been available for different risk groups defined by occupation, medical conditions and lifestyle, but compliance has been poor. Although one can understand the reasons underlying the poor vaccination rate among those persons in high-risk groups without routine access to preventive medical care, it is difficult to understand the poor vaccination rate for high-risk health-care professionals, of whom fewer than 50% complete a full series. A further problem complicating the control of HBV infection is that 30% of patients with acute HBV have no acknowledged risk factors. For these reasons groups such as the American Academy of Pediatrics, the Centers for Disease Control and Prevention and the American Academy of Family Practice now recommend universal vaccination of all infants. Unfortunately, this recommendation has met with skepticism amongst many primary-care providers who must administer yet another set of routine baby shots. The reasons for this reluctance include the facts that many pediatricians have not seen a case of HBV infection in their practice and that most pediatricians do not see the effects of HBV in children because most childhood infections are asymptomatic. Furthermore, some pediatricians feel that it is unlikely that many of the children they see in their private practices will eventually fall into a group at high risk for HBV infection as adults. Despite these rationalizations approximately five times as many deaths per year are attributed to HBV than to *Haemophilus influenzae* type B, and yet *H. influenzae* type B immunizations have received recent widespread acceptance by primary care physicians. Thus this excellent study yields important new information on both the cost-effectiveness and the improvement in public health expected with several different HBV vaccination strategies.

This paper expands on the previous efforts of Mulley et al., who examined the cost-effectiveness of the HBV vaccine more than 10 years ago. However, as the authors point out, in the past 10 years the incidence of HBV infection has increased and the cost of the recombinant vaccine has greatly decreased. Given these facts it is not surprising that the HBV vaccination program under study is more cost-effective than the suggested programs of 10 years ago. The study under comment was based on 30 years of follow-up, with an initial three-shot series and booster vaccinations every 10 years. Also included were the latest data on the efficacy and cost ($225 for adults and $160 for children) of the new recombinant vaccine. Although the study took into account patient compliance for all three shots in the initial vaccination series and boosters, these investigators chose to ignore the program costs necessary to ensure a high level of vaccine compliance. As many communities are discovering, it can not only be very difficult but also very expensive to improve on the dismal vaccination rates in some areas of the country where childhood immunization rates are less than 50%. These costs may have particular relevance to HBV vaccination programs; a disproportionate number of these unimmunized children are likely to be at high risk of HBV infection as adults. The decision-making tree in this paper also took into account many of the variables in HBV infection, through review of the literature or on the advice of an expert panel. These included the sensitivity and specificity of HBsAg screening; the incidence of acute infection in high-risk groups and the general adult population, adolescents, and newborns; the types of acute infection, from subclinical to fulminant; and the chronic sequelae of fulminant and nonfulminant acute infection. The authors then examined the costs of medical management of acute HBV infection and its sequelae. The treatment of chronic HBV infection included the use of interferon and liver transplantation. The study examined only direct medical costs. Indirect medical costs such as travel expenses to receive medical care and other indirect nonmedical costs such as time off work were not included in the analysis. Other authors have estimated nonmedical costs to be 10 times the direct medical costs. Costs were presented in two formats: either undiscounted or discounted at 5% per year.

The authors examined several vaccination strategies, including a "mixed strategy" of screening all pregnant women and vaccinating neonates born to infected mothers and vaccinating all adolescents at age 10 or as they become sexually active. The currently recommended strategy of vaccinating all newborns and five other strategies were also examined. These included vaccinating all adolescents, screening and vaccinating HBsAg-negative adults in the general population or high-risk adults or simply vaccinating all adults or all high-risk adults. All the vaccination strategies were compared with a no-vaccination strategy. The mixed strategy of screening and then vaccinating high-risk newborns and vaccinating all adolescents was the most cost-effective ($375 per year of life saved). The recommended strategy of vaccinating all newborns was approximately 10 times more expensive (about $3,200). Although neither of these strategies save a health care system money, they are both cost-effective compared with other medical treatments such *Pneumococcus* vaccination for adults older than 65 yr ($6,000) or kidney transplant ($7,500). The authors therefore suggest that the a mixed strategy be adopted. As is pointed out in the accompanying editorial it is, however, a formidable task to reach all 10-yr-olds for an expensive vaccine that requires three painful injections. Most pediatricians and

internists will likely welcome the opportunity to practice more preventive medicine with adolescents who will need to make more routine office visits for their vaccinations, as is the current practice with preschool children. Nevertheless, physicians and public policy makers, including local school boards, must be convinced of the benefits of universal HBV vaccination for any vaccination strategy to be effective. New school-immunization policies that would require proof of vaccination on entry to junior high or middle schools would help immeasurably. Many school districts have already adopted a policy requiring booster injection of the mumps/measles/rubella (MMR) vaccine to prevent measles outbreaks similar to the ones seen recently in many communities. These same districts could also require HBV vaccination. Revaccination of children after another 10-yr cycle, at 20 yr of age, is much more problematic, although it is hoped that the duration of the protection against HBV infection lasts longer than 10 yr.

An important feature of decision-making analysis involves testing of the many variables that inevitably involve uncertainties associated with trying to predict future events. Therefore the authors examined best-case *and* worst-case scenarios. A worst-case scenario for the vaccine program included low rate of vaccine efficacy and low incidence of costly sequelae to HBV infection, whereas in the best-case scenario the vaccine was presumed to be very effective and the incidence of costly sequelae of HBV infection also very high. The differences in cost per year of life saved between the best-case and worst-case scenarios varied only twofold, still suggesting that HBV vaccine programs would be cost-effective compared with other medical treatments. As expected, the cost of implementing a vaccine program was also sensitive to the cost of the vaccine. It was estimated in a best-case scenario that the cost of a single dose of HBV vaccine (including administration) would have to be about $10 to $15 for the vaccine program to break even with a no-vaccination policy.

In summary, we agree with the authors of the article and the accompanying editorial that a universal vaccination program should be implemented. For any program to be effective, however, it will require the full support of the medical community and an educated public. Moreover, because the benefits of this program will not be seen for many years it is necessary to vigorously continue with efforts to vaccinate persons in high-risk groups, especially sexually active adults.

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## IS MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN THE MISSING LINK IN ABETALIPOPROTEINEMIA?

*Wetterau JR, Aggerbeck LP, Bouma ME, Eisenberg C, Munck A, Hermier M, Schmitz J, Gay G, Rader DJ, Gregg RE.* Absence of microsomal triglyceride transfer protein in individuals with abetalipoproteinemia. Science 1992;258:999-1001.

### COMMENTATOR'S ABSTRACT

**In the study reported by Wetterau et al., a recently characterized heterodimeric protein called microsomal triglyceride transfer protein was undetectable on immunoblotting of samples from intestinal biopsies of human subjects with the genetic disorder abetalipoproteinemia. With only one fourth to one fifth the soluble proteins of homogenized intestinal biopsy specimens of normal human subjects and patients with different fat-absorption defects, the 88-kD subunit of microsomal triglyceride transfer protein was clearly detectable. Protein disulfide isomerase, the 55-kD subunit of microsomal triglyceride transfer protein, was present in tissue of all subjects tested, including those with abetalipoproteinemia. Consistent results were obtained with an *in vitro* assay that measures triglyceride transfer between phospholipid membranes: triglyceride transfer continued at constant rates for more than 1 hr in samples from biopsies in normal human subjects, whereas no measurable triglyceride transfer was detected in the same material from abetalipoproteinemia patients. The apparent absence of the 88-kD subunit of microsomal triglyceride transfer protein most likely explains this debilitating disorder. This new observation coincides with the recent articulation of a novel hypothesis about the subcellular mechanisms by which enterocytes and hepatocytes assemble triglyceride-rich particles containing the large hydrophobic protein apolipoprotein B in two steps. In the first step, a small (~200 Å), apolipoprotein B–rich microemulsion particle containing small amounts of triglycerides and cholesteryl esters in its core is formed and released into the lumen of the rough endoplasmic reticulum. The second step requires the synthesis of larger triglyceride-rich particles lacking apolipoprotein B in the smooth endoplasmic reticulum. Fusion of these two particles is postulated to yield nascent very low density lipoproteins or chylomicrons that can be secreted by hepatocytes and enterocytes, respectively. In classic abetalipoproteinemia patients, no apolipoprotein B is found in blood plasma, and chylomicrons, very low density lipoproteins and low-density lipoproteins are absent. The two-step model of triglyceride-rich particle formation predicts that, in the absence of microsomal**