# The Changing Epidemiology of Hepatitis B in the United States

## Need for Alternative Vaccination Strategies

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To determine trends in the incidence and epidemiology of acute hepatitis B in the United States we conducted intensive surveillance for viral hepatitis in four sentinel counties from October 1, 1981, to September 30, 1988. The overall incidence of hepatitis B remained relatively constant throughout the study period (average, 13.2 cases per 100 000 population), but disease transmission patterns changed significantly. The proportions of hepatitis B cases accounted for by homosexual activity and health care employment decreased 62% and 75%, respectively; the proportions of cases accounted for by parenteral drug use and heterosexual exposure increased 80% and 38%, respectively. The percentage of patients for whom no risk factor was identified (30% to 40%) did not change over time. These patients tended to belong to minority populations, and their socioeconomic level was low. The decline in the number of hepatitis B cases among homosexual men probably results from the modification of high-risk sexual behavior; the decline among health care workers is due mostly to hepatitis B immunization. The current strategy for prevention of hepatitis B, which targets high-risk groups for immunization, has failed to have a significant impact on the incidence of disease.

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HEPATITIS B VIRUS (HBV) is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma worldwide.[1] The most serious consequences of HBV infection are primarily the result of chronic HBV infection, which occurs in 6% to 10% of infected adults, approximately 25% of infected children aged 1 to 5 years, and 70% to 90% of infected infants.[1-3] Transmission of HBV in the United States and other developed countries primarily is through parenteral or sexual exposure, and commonly recognized risk factors include male homosexual activity, illicit parenteral drug use, occupational exposure to blood, sexual or household exposure to an HBV-infected contact, and heterosexual activity with multiple partners.[4-6]

The Centers for Disease Control, Atlanta, Ga, began conducting nationwide surveillance for hepatitis B (serum hepatitis) in 1966, and until 1985 the incidence of reported disease increased. Underreporting and incomplete serological testing and epidemiologic evaluation of all reported cases, however, made it difficult to accurately assess changes in the incidence of disease and risk factors associated with HBV transmission. To more accurately define the incidence and epidemiology of all types of viral hepatitis, a program of intensive surveillance for acute viral hepatitis was begun in several "sentinel counties" in September 1979[7]; since October 1981, it has been focused on four counties.[5,8]

## METHODS

Eligibility criteria for selection as a sentinel county included a reported incidence of acute hepatitis of at least 20 cases per 100 000 population, a total of at least 100 cases of hepatitis (all types) reported per year, and testing rates for hepatitis B surface antigen (HBsAg) of at least 80%. In 1981 the four counties selected were Jefferson County (Birmingham), Alabama; Denver County (Denver), Colorado; Pinellas County (St Petersburg), Florida; and Pierce County (Tacoma), Washington. These counties have populations of 500 000 to 800 000. The annual study periods were defined by fiscal year (October to September); from October 1, 1981 (fiscal year 1982), through September 30, 1988 (fiscal year 1988), all patients with acute viral hepatitis reported to the four county health departments were eligible for the study.

### Case Definition

The criteria for inclusion in the study were a physician's diagnosis of acute viral hepatitis, including a discrete date of onset of clinical symptoms or signs, serum aminotransferase activity greater than 2.5 times the upper limit of normal, and exclusion of other causes of liver injury. All patients were tested for total and immunoglobulin M (IgM) antibody to hepatitis A virus (anti-HAV), HBsAg, and antibody to HBsAg. From 1982 through 1983, patients also were tested for antibody to hepatitis B core antigen (anti-HBc); those who were positive for anti-HBc but negative for HBsAg were tested for IgM anti-HBc. From 1984 through 1988, all patients were tested for IgM anti-HBc. Cases were classified as to the type of viral hepatitis by the following serological criteria: hepatitis A, positive for IgM anti-HAV; hepatitis B, positive for HBsAg or IgM anti-HBc if tested; and non-A, non-B hepatitis, negative for IgM anti-HAV and HBsAg or IgM anti-HBc if tested.

For 75% of the cases identified, serological testing was performed at the Centers for Disease Control. Tests for HBsAg, anti-HBc, and antibody to HBsAg were performed using commercially available radioimmunoassays and

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for IgM anti-HAV and IgM anti-HBc using commercially available enzyme immunoassays (Abbott Laboratories, North Chicago, Ill). For 25% of the cases identified, serological testing was performed by local laboratories in each county using commercially available tests; for these cases, no serum samples were available for testing at the Centers for Disease Control.

### Epidemiologic Investigation

Each patient with hepatitis B was interviewed by a nurse to identify known and potential risk factors for acquiring hepatitis. A detailed description of the questionnaire has been published elsewhere.[5] Patients with a history within the preceding 6 months of one or more of the following risk factors were assigned exclusively to one risk group in the following hierarchy: blood transfusion, parenteral drug use, male homosexual activity, health care employment with frequent blood contact, hemodialysis, sexual or household contact with a hepatitis B patient or HBV carrier, residency in an institution for the developmentally disabled, and multiple (>1 in the preceding 6 months) heterosexual partners. If patients had none of these risk factors, attempts were made to obtain serum specimens from their household and sexual contacts to identify previously unrecognized HBV carriers or persons with acute subclinical infection. Serum specimens were obtained from the contacts of 57% of the patients; 19% had a contact who was positive for HBsAg or IgM anti-HBc, so these patients were assigned to the sexual or household contact group. Patients who had none of these risk factors were classified as having no known source for infection.

### Statistical Analysis

Incidence rates for hepatitis B were calculated using 1980 US Census data and yearly intercensal population estimates. The frequencies and distributions of demographic characteristics and risk factors associated with acquiring hepatitis were examined for each year and then compared. To show trends, the frequencies of some factors were averaged over several years; these trends were evaluated using the Mantel-Haenszel $\chi^2$ test for trend. Differences in proportions were compared using the two-tailed $\chi^2$ test or Fisher's Exact Test. For all tests, a $P$ value less than .05 was considered significant.

## RESULTS

During the 7 years of the study, 2273 patients with acute hepatitis B were reported, of whom 1917 (84%) consented to be interviewed. The overall incidence of hepatitis B remained relatively constant throughout the study period, although there were notable variations between counties (Table 1). In all but one county (Pierce), hepatitis B accounted for a constant proportion of the viral hepatitis reported (average, 47%; range, 34% to 62%). In these counties, hepatitis A accounted for an average of 28% of cases, and non-A, non-B hepatitis accounted for an average of 25% of cases. In Pierce County, hepatitis B accounted for an average of 40% of the viral hepatitis reported (range, 33% to 50%) until 1987, when an epidemic of hepatitis A became evident. The large number of hepatitis A cases reduced the proportion of the total cases attributable to hepatitis B to 18% in 1987 and 1988; however, the incidence of hepatitis B actually increased during this interval.

Table 1.—Reported Cases of Acute Hepatitis B in Four Sentinel Counties

| | No. of Cases (Rate per 100 000) | | | | |
|---|---|---|---|---|---|
| Year | Total | Jefferson | Denver | Pinellas | Pierce |
| 1982 | **331** (13.5) | 118 (17.6) | 73 (14.4) | 97 (12.8) | 43 (8.5) |
| 1983 | **286** (11.6) | 99 (14.8) | 80 (15.5) | 71 (9.2) | 36 (7.0) |
| 1984 | **326** (13.3) | 93 (13.8) | 109 (21.4) | 85 (10.6) | 39 (7.5) |
| 1985 | **343** (13.9) | 93 (13.8) | 98 (19.1) | 94 (11.7) | 58 (11.0) |
| 1986 | **303** (12.7) | 51 (7.5) | 80 (15.8) | 73 (9.0) | 99 (18.6) |
| 1987 | **350** (14.6) | 58 (8.4) | 96 (19.0) | 78 (9.4) | 118 (21.4) |
| 1988 | **334** (13.0) | 71 (10.5) | 62 (12.3) | 67 (8.0) | 134 (24.4) |

Table 2.—Incidence of Hepatitis B, by Race and Sex, in Four Sentinel Counties

| | Average Incidence (Range) per 100 000 Population | | |
|---|---|---|---|
| | All Years | 1982-1985 | 1986-1988 |
| Race | | | |
| W | 10.8 | 11.1 (9.7-12.0) | 10.5 (9.8-11.0) |
| B | 18.1 | 19.4 (18.4-22.5) | 16.4 (14.6-17.5) |
| Hispanic | 20.4 | 16.1 (12.7-22.8) | 26.0 (17.8-39.0)* |
| Other | 16.9 | 9.3 (9.2-9.4) | 27.0 (18.1-42.5)* |
| Sex | | | |
| M | 16.9 | 17.5 (15.2-19.4) | 16.2 (15.2-16.9) |
| F | 9.2 | 8.5 (7.9-9.1) | 9.8 (9.0-11.0) |

*$P<.05$, 1986 through 1988 vs 1982 through 1985.

Sixty percent of patients with hepatitis B were reported from primary medical care providers such as physicians, hospitals (inpatient and outpatient services), and clinics. Forty percent were reported or identified from other sources such as laboratories, contacts seeking postexposure prophylaxis, and the patients themselves. Although the hospitalization rates for patients reported with hepatitis B declined from 31% in 1982 to 12% in 1988 ($P<.001$), the clinical characteristics of the patients were similar in all years. An average of 86% of the patients were jaundiced; the mean bilirubin level was 7.7 mg/dL (132 μmol/L) (SD = 5.9 mg/dL [101 μmol/L]; range, 0.2 to 41.9 mg/dL [3 to 716 μmol/L]). Serum aminotransferase levels were 3 to 5 times the upper limit of normal in 5% of patients, 6 to 20 times the upper limit of normal in 22% of patients, and greater than 20 times the upper limit of normal in 73% of patients. Eleven patients with acute hepatitis B died, for an overall case-fatality rate of 0.5%.

The age and racial/ethnic distributions of the patients reported with hepatitis B were constant during the study period. Fewer than 1% were younger than 15 years, 63% were 15 to 29 years old, 26% were 30 to 44 years old, and 11% were 45 years or older; 68% were white, 20% were black, 8% were Hispanic, and the remaining 4% were Asian or Native American. The racial/ethnic distribution of the county populations was 78% white, 14% black, 6% Hispanic, and 2% other, comparable with the distribution of these groups in the United States.[9] Compared with the average incidence of hepatitis B in whites, however, the disease rates in the other racial/ethnic groups were almost twofold higher (Table 2). In addition, although the incidence in whites remained stable over the study period, the incidence in blacks decreased 15% (not significant) and the incidence in Hispanics and other racial/ethnic groups increased 61% ($P<.05$) and 190% ($P<.001$), respectively.

In the initial years of the study, the incidence of hepatitis B in males

Table 3.—Risk Factors for Acquiring Hepatitis B in Four Sentinel Counties

| Risk Factor | No. (%) of Cases | | | | | | |
|---|---|---|---|---|---|---|---|
| | 1982 (N=326) | 1983 (N=230) | 1984 (N=256) | 1985 (N=283) | 1986 (N=250) | 1987 (N=296) | 1988 (N=277) |
| Homosexual activity | 65 (19.9) | 46 (20.0) | 62 (24.2) | 56 (19.8) | 23 (9.2) | 26 (8.8) | 20 (7.2)* |
| Parenteral drug use | 50 (15.3) | 31 (13.5) | 36 (14.1) | 45 (15.9) | 66 (26.4) | 85 (28.7) | 75 (27.1)* |
| Heterosexual activity† | 48 (14.7) | 47 (20.4) | 51 (19.9) | 54 (19.1) | 66 (26.4) | 65 (22.0) | 72 (26.0)* |
| Health care employment | 10 (3.1) | 14 (6.1) | 11 (4.3) | 7 (2.5) | 3 (1.2) | 6 (2.0) | 3 (1.1)‡ |
| Blood transfusion | 13 (4.0) | 4 (1.7) | 3 (1.2) | 8 (2.8) | 7 (2.8) | 1 (0.3) | 1 (0.4)‡ |
| Household contact | 1 (0.3) | 6 (2.6) | 6 (2.3) | 7 (2.5) | 7 (2.8) | 5 (1.7) | 3 (1.1) |
| Hemodialysis | 1 (0.3) | 2 (0.9) | 1 (0.4) | 1 (0.4) | 0 | 2 (0.7) | 0 |
| Resident of institution for developmentally disabled | 1 (0.3) | 4 (1.7) | 0 | 0 | 1 (0.4) | 4 (1.4) | 0 |
| No known source | 137 (42.0) | 76 (33.0) | 86 (33.6) | 105 (37.1) | 77 (30.8) | 102 (34.5) | 103 (37.2) |

*$P<.001$, $\chi^2$ test for trend.
†Includes sexual contact with a hepatitis B patient, with a hepatitis B virus carrier, or with multiple partners.
‡$P<.01$, $\chi^2$ test for trend.

was twofold higher than that in females (Table 2). From 1986 through 1988, the incidence in males decreased 7% and the incidence in females increased 15%, although neither was statistically significant.

The disease transmission patterns of hepatitis B changed significantly over the study period (Table 3). From 1982 through 1985, three major risk factors accounted for more than half of the disease transmission: male homosexual activity was reported by an average of 21% of patients; parenteral drug use by an average of 15%; and heterosexual exposure (sexual contact with a hepatitis B patient, with an HBV carrier, or with multiple partners) by an average of 18%. Of the patients with heterosexual exposure, 9% acquired disease from partners with acute hepatitis B, 32% from partners with acute subclinical or chronic infection detected through serological testing of contacts, and 59% presumably from multiple partners (most of whom could not be located for HBV serological testing). Other recognized sources for infection included health care employment with frequent blood contact, reported by an average of 4% of patients; blood transfusions, an average of 3%; household contact with a known hepatitis B patient or an HBV carrier, an average of 2%; hemodialysis, an average of 0.5%; and residency in an institution for the developmentally disabled, an average of 0.5%. No source of infection was identified for an average of 37% of patients; for half of these patients, however, no serum specimens were obtained from contacts.

From 1986 through 1988, although the overall incidence of disease remained stable, the proportion of patients who reported parenteral drug use increased significantly, to an average of 27% ($P<.001$) (Table 3), and replaced homosexual activity as the most common risk factor for hepatitis B. The proportion of patients whose risk factor for hepatitis B was heterosexual exposure (as defined above) also increased significantly—to 25% ($P<.001$; 23% had partners with acute hepatitis B, 13% had partners with acute subclinical or chronic infection, and 64% had multiple partners). In contrast, the proportion of patients who reported male homosexual activity declined to an average of 8% ($P<.001$), that of patients who reported health care employment with frequent blood contact declined to an average of 1% ($P<.01$), and that of patients who reported blood transfusions also declined to an average of 1% ($P<.01$). No significant changes occurred in the percentage of patients who reported other risk factors or no identifiable source for infection. Except for the increase in parenteral drug use, the trends described were similar for all counties. The increase in parenteral drug use was most striking in Pierce County and accounted for the county's sharp increase in disease incidence.

All the trends in risk factors observed for the group as a whole were observed in each racial/ethnic group. Blacks, however, were more likely to have no identifiable source for infection than

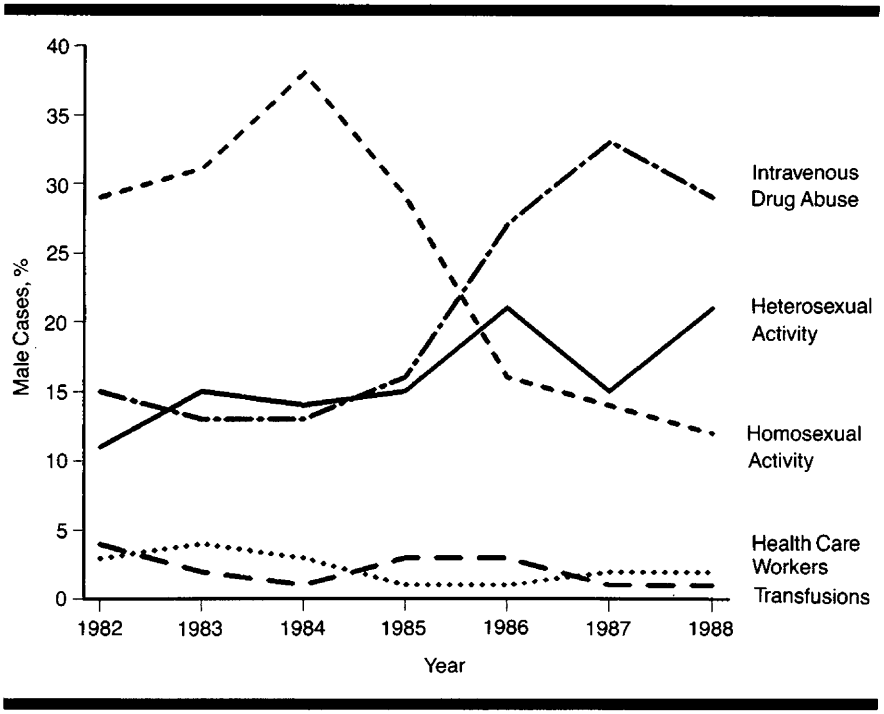


Fig 1.—Selected risk factors for acquiring hepatitis B in males in four sentinel counties from 1982 through 1988. Heterosexual activity indicates sexual contact with a hepatitis B patient, with a hepatitis B virus carrier, or with multiple partners; health care workers are those who had frequent contact with blood.

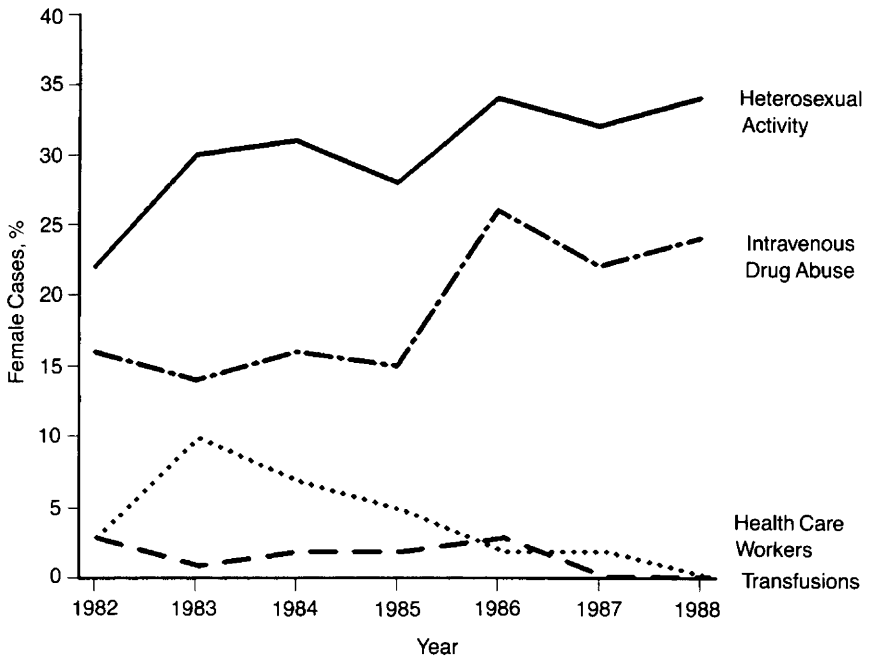


Fig 2.—Selected risk factors for acquiring hepatitis B in females in four sentinel counties from 1982 through 1988. Heterosexual activity indicates sexual contact with a hepatitis B patient, with a hepatitis B virus carrier, or with multiple partners; health care workers are those who had frequent contact with blood.

were whites or persons in other racial/ethnic groups (41% vs 33%, $P<.01$).

When males and females were analyzed separately, the distribution and relative importance of the various risk factors differed distinctly. For males, the decline in importance of homosexual activity and the increase in importance of parenteral drug use can be seen clearly (Fig 1). For females, heterosexual exposure was the most common risk factor reported in all years, although parenteral drug use, which increased over time, was also an important risk factor (Fig 2). The decline in health care employment as a risk factor for hepatitis B is most prominent among females. In 1988 no cases with a history of health care employment were reported among females, and only three cases were reported among males. Females were more likely to have no identifiable source for infection than were males (40% vs 33%, $P<.01$).

Only 14 of the patients with hepatitis B were younger than 15 years: 1 had a history of blood transfusion, 6 lived in a household with an HBV carrier, 1 lived in an institution for the developmentally disabled, and the remaining 6 had no identifiable source for infection. Males and females aged 15 to 44 years accounted for the majority (89%) of cases of hepatitis B, and their patterns of disease transmission were similar to those shown in Figs 1 and 2. In persons aged 45 years or older of either sex, heterosexual exposure was the major risk factor for hepatitis B in all years, accounting for an average of 23% of cases. Parenteral drug use was uncommon in this group (one case in 7 years), but homosexual activity (11%), health care employment (8%), and transfusions (14%) accounted for substantial numbers of cases from 1982 through 1985. Declining numbers of cases were reported in these three risk groups after this time; in 1988 no cases of hepatitis B in persons aged 45 years or older were attributable to homosexual activity or health care employment, and only one case was attributable to blood transfusion. Persons in the oldest and the youngest age groups were more likely to have no identifiable source for infection than were persons aged 15 to 44 years (55% vs 34%, $P<.01$).

Of patients who had no identifiable source for infection, 15% had been unemployed for at least 6 months or lived in a household where the head of the household was unemployed, a possible measure of low socioeconomic level. This measure of low socioeconomic level was associated with 22% of the females who had no identifiable source for infection, compared with 7% of the males ($P<.001$); with 19% of blacks and 25% of other nonwhite racial/ethnic groups, compared with 10% of whites ($P=.04$); and with persons younger than 15 years or older than 44 years, compared with persons 15 to 44 years of age (20% vs 12%, not significant). The prevalence of serological markers that indicate previous (but not recent) HBV infection among the household and sexual contacts of the patients with no identifiable source for infection was 19%.

## COMMENT

The sentinel counties are typical of many areas in the United States with respect to the average incidence of hepatitis B, the variations in incidence observed in different geographic areas, and the distribution of racial/ethnic groups.[9,10] More important, the recent changes in transmission patterns of hepatitis B in the sentinel counties have been observed nationwide, and the variations in these patterns are typical of the variations seen in different parts of the country.[10]

The 62% decrease in the proportion of hepatitis B cases accounted for by homosexual men is most likely a result of a modification of high-risk sexual behavior to lessen the risk of human immunodeficiency virus infection.[11,12] Acquisition of human immunodeficiency virus infection is declining in certain cohorts of homosexual men,[13] and the incidence of other sexually transmitted diseases among this group seems to be declining as well.[14,15] In contrast, the proportion of cases of hepatitis B due to heterosexual exposure increased 38%, paralleling the recent increases in cases of primary and secondary syphilis, which also have occurred primarily in heterosexuals.[15] Although sexual activity always has been one of the leading risk factors for transmission of HBV, this study shows that heterosexual activity has now replaced homosexual activity in importance.

Of equal concern is the 80% increase both in the proportion and in the absolute numbers of hepatitis B patients who have a history of parenteral drug use, indicating no modification of, or impact of educational programs on, this high-risk behavior during the period of the study. Similar increases nationwide have been seen in cases of hepatitis A, hepatitis B, and non-A, non-B hepatitis, suggesting that hepatitis associated with parenteral drug use is a widespread problem.[16,17]

The changes observed in hepatitis B associated with health care employment and transfusions are also important. The significant decline in the numbers of health care workers (75%) reported with hepatitis B is probably a direct result of immunization with hepatitis B vaccine and of wider implementation of universal blood precautions. Since licensure of hepatitis B vaccine in 1982,

approximately 2.5 million persons have been vaccinated; 80% of these are health care workers (M. Sanyour, MBA, Merck Sharp & Dohme, oral communication, October 2, 1989). The decline in transfusion-associated hepatitis B may be related to changes in the donor population that result from the exclusion of persons at high risk for human immunodeficiency virus infection, the exclusion of human immunodeficiency virus antibody–positive donors, and, after 1986, the exclusion of donors positive for anti-HBc, a surrogate strategy implemented to reduce the incidence of transfusion-associated non-A, non-B hepatitis.[18]

For 30% to 40% of patients with hepatitis B, no risk factor that accounted for transmission could be identified. Some of these patients may have been infected by an unidentified HBsAg-positive contact, since serum specimens were obtained from the household and sexual contacts of only half of these patients. A recent case-control study done in the sentinel counties showed that unemployment, a possible surrogate measure of low socioeconomic level, was associated significantly with hepatitis B patients who had no source for infection.[5] In the current study, among the household and sexual contacts of the hepatitis B patients with no identifiable source for infection, the prevalence of HBV markers was 19%, higher than the 4% to 7% reported for the general population.[19,20] Higher endemic rates of HBV infection have been associated with low socioeconomic level.[21]

The incidence of hepatitis B in nonwhite racial/ethnic groups was almost twice that in whites; in Hispanics and other groups, the incidence increased twofold to threefold over the study period. A serological survey of a probability sample of the US population (National Health and Nutrition Examination Survey) reported that from 1976 to 1980 the prevalence of HBV infection among blacks was five times higher than among whites.[20] In the current study, blacks, Hispanics, and other groups who had no source for HBV infection were more likely than whites to be unemployed. Although not a risk factor itself, low socioeconomic level may indicate lifestyles, behaviors, or habits that result in greater risk for HBV infection.

The current strategy for prevention of hepatitis B in the United States is to immunize the groups at high risk of infection[6]; however, the incidence of reported hepatitis B in the United States has increased steadily over the past decade and continued to increase through 1985 despite the introduction of hepatitis B vaccine in 1982.[10] The apparent lack of impact of hepatitis B vaccine on disease incidence and its limited impact on transmission patterns is attributable to several factors. One of the most important is that at least 30% of patients with hepatitis B cannot be associated with an identifiable risk factor, placing them out of reach of an immunization strategy that targets only high-risk groups. These patients tend to belong to minority populations and to have characteristics associated with low socioeconomic level. To be effective, education and prevention programs need to be designed specifically for these groups, as has been suggested for programs aimed at preventing human immunodeficiency virus infection.[21] A second factor is that the majority of persons who receive vaccine as a result of the current strategy have been persons who acquire HBV infection through occupational exposure, a group that accounted for no more than 5% of cases even before vaccine was introduced. A third factor contributing to the apparent lack of effect of hepatitis B vaccine has been the inability to reach certain high-risk populations and deliver vaccine before infection occurs. Among patients with heterosexual exposure, the current study found that fewer than 25% could identify a known infected contact. In these patients, postexposure prophylaxis may have prevented infection.[22] In the remaining patients, however, infection resulted from exposure to a contact with subclinical infection or to multiple partners. Targeting these persons for vaccination would be virtually impossible without vaccinating all heterosexuals.

For the current hepatitis B immunization strategy to have a significant impact on disease incidence, the role of heterosexual activity in the transmission of HBV must be recognized by both those at risk and their health care providers. We must question, however, the feasibility of immunizing a significant proportion of persons who have multiple heterosexual partners or who are parenteral drug users before these populations become infected with HBV. The ideal immunization strategy to accomplish such a goal is universal immunization of infants or adolescents or both. This strategy would lead to disease prevention by providing immunity from infection before persons engage in risk-taking behavior and could preclude infections in persons who have no known risk factors.

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