Comprehensive control (or elimination) of hepatitis B virus transmission in the United States

F B Hollinger

Abstract

In the United States, the reported rate of hepatitis B has declined by over 50% since 1987, probably as a result of vaccination programmes, behavioural changes, refinements in blood screening procedures, and the availability of virus inactivated blood components. The majority of new hepatitis B infections occur in 20-39 year olds, and perinatal transmission is uncommon except in certain at risk groups. Initial efforts to control hepatitis B in the US were targeted at high risk groups, including health care personnel. Then, in 1988, the Centers for Disease Control and Prevention (CDC) recommended screening of all pregnant females for hepatitis B surface antigen and full immunisation of infants born to those testing positive. A recommendation for universal immunisation of infants was endorsed in 1991. Compliance has been slow but progressive. The CDC also has recommended 'catch up' immunisation of adolescents and high risk children and adults. Demonstration projects suggest that these can be successful, given the provision of free or low cost vaccine and appropriate support. Hepatitis B vaccination has been shown to be cost effective and should be integrated into the routine childhood immunisation schedule. Responses to hepatitis B vaccine have largely been shown to be durable, although at least one booster dose after five to 10 years seems prudent, especially if a low dose, yeast derived vaccine has been used.

(*Gut* 1996; 38 (suppl 2): S24-S30)

Keywords: hepatitis B virus, vaccine, United States, epidemiology, guidelines.

Epidemiology

In the United States in 1993, 43 012 cases of viral hepatitis were reported to the National Morbidity and Mortality Reporting System of the Centers for Disease Control and Prevention (CDC), yielding a rate of about 17 cases per 100 000 population, of which 31% were characterised as hepatitis B (Fig 1).¹ Approximately 63% of the hepatitis B cases were reported in persons 20 to 39 years of age, and the highest rates were seen among young adults 25 to 29 years of age. Since 1987, the reported rate of hepatitis B has declined by over 50%, presumably as a direct result of universal immunisation of neonates, vaccination of occupationally exposed groups, behavioural or

lifestyle changes of high risk groups, refinements in the screening of blood donors, and the use of virus inactivated products in patients with bleeding disorders (Fig 2).² (Also, Margolis and the CDC, personal communication.)

Data from the 1988-1992 National Health and Nutrition Examination Survey III (NHANES III), in which over 14 000 sera were assayed, were found to be similar to the NHANES II data from specimens collected between 1976 and 1980. This second survey³ found a low prevalence of hepatitis B virus (HBV) infection among children under 16 years of age. This supports the hypothesis that perinatal or childhood transmission of HBV is a minor contributor of HBV prevalence in this part of the world, except in special at risk groups. In that study, the overall weighted estimate of HBV infection (based on reactivity for antibodies to hepatitis B core antigen (anti-HBc)) was 4.8% (3.2% in white participants and 13.7% in black participants) and infection was age dependent. By 65 to 74 years of age, about 7% of white subjects had HBV seromarkers compared with 40% of black participants. Hepatitis B surface antigen (HBsAg) was detected in 0.3% of the subjects, with sera from 0.2% of white subjects and 0.9% of black subjects being positive. In addition, the rate of active HBV infection was about four times greater in male than in female participants. Thus black subjects, both male and female, had higher rates of active infection than white subjects. HBV prevalence was highest in the South and lowest in the Midwest. It was also higher in communities with more than 250 000 inhabitants, and among people with a positive serology for syphilis. In addition, Asian-Pacific Islanders, and Alaska natives were significantly more prone to be infected with HBV than other race/ethnicity groups. Finally, the overall prevalence of HBsAg among subsets of pregnant Asian-Americans was 8.3% (range 1.9% to 11.4%), of whom 34.9% were also positive for hepatitis B e antigen (HBeAg) (range 10.0% to 47.5%).⁴

Between 1982 and 1988, the overall incidence of hepatitis B remained comparatively constant, although disease and transmission patterns underwent a dramatic change. For example, in a study conducted by the CDC in four sentinel counties in the US, the proportion of acute hepatitis cases associated with homosexual activity decreased from 20% to 7%, presumably due to modifications of high risk behaviour occurring in this cohort in an attempt to prevent infection with human immunodeficiency virus (HIV).⁵ Conversely, the proportion of cases increased from 15% to approximately 27% in groups associated with

Baylor College of Medicine, Houston, Texas, USA
F Blaine Hollinger

Correspondence to:
Dr F Blaine Hollinger,
Baylor College of Medicine,
Division of Molecular
Virology, One Baylor Plaza,
Texas Medical Center,
Houston, Texas 77030-
3498, USA.

Figure 1: Acute viral hepatitis in the United States in 1993 based on cases reported to the CDC National Morbidity and Mortality reporting system.¹ (n=43 012).

parenteral drug abuse and in heterosexuals who had sexual contact with a hepatitis B patient, with an HBV carrier, or with multiple partners. Hepatitis B in health care workers fell to 1% from a range of 3% to 6%, perhaps as a direct result of immunisation programmes. In approximately one third of the cases, no known source of exposure was identified. Most of these persons belonged to minority populations and their socioeconomic level was low. Upon closer inspection, many of these cases were reclassified into the active heterosexual category, although covert parenteral exposure also remained a possibility.

Vaccination strategy and progress toward control of hepatitis B

While seroprevalence data and the clinical ascertainment of cases delineated groups at risk for contracting hepatitis B, additional data were needed to develop and defend a national vaccination strategy. Information derived from pre-vaccine clinical data clearly shows that immunisation against HBV can be justified by morbidity and mortality data and thus merits

*Provisional data

Figure 2: Estimated incidence of acute hepatitis B in the United States from 1978 to 1995 in association with various events. DOL=Department of Labor; OSHA=Occupational Safety and Health Administration. (Courtesy of H Margolis and the CDC.)

TABLE I Outcome of hepatitis B virus infection compared with selected preventable diseases of children (adapted from reference 7)

Disease	Cases per 100 000	Deaths
Hepatitis B		
Acute	54.00	320
Cirrhosis/HCC		5500
Haemophilus influenza b		
Invasive disease	5.40	531
Meningitis	3.60	354
Poliomyelitis	35.00	1500
Measles	240.00	380
Congenital rubella	0.04	-

inclusion in the routine paediatric immunisation schedule (Table I).^{6,7} Analysis of age group specific acquisition of acute and chronic HBV infections showed that the development of a carrier state with its attendant sequelae is more likely to occur after HBV infection of infants and children than after infection of healthy adults (Fig 3).⁷⁻⁹ Although only 8% of all HBV infections in the US occur in infants and young children, these infections account for 36% of the chronic disease that is ultimately observed (Fig 4). In contrast, overt clinical disease and mortality from acute fulminant hepatitis is more likely to occur in healthy adults, not in children.

IMMUNISATION OF HIGH RISK GROUPS

Based on prevalence of HBV in specific risk groups, initial efforts to control hepatitis B in the US were directed toward groups at high risk of contracting the infection. These groups were believed to comprise some 25 million susceptible persons, of whom only about 7% had received the vaccine by 1988, six years after the vaccine was launched in the US. It was widely acknowledged that if all members of these groups could be identified and vaccinated, the incidence of hepatitis B would rapidly decrease. However, except for health care personnel, for whom governmental regulations mandated immunisation of those likely to be exposed to bloodborne pathogens, recognition and recruitment of people within these target groups have been unrewarding. Indeed, most new infections were occurring in persons who had not acknowledged that they were at increased risk.

IMMUNISATION OF INFANTS

An inability to identify a substantial portion of HBsAg positive pregnant women based on a selective screening strategy ultimately led to a 1988 recommendation by the Advisory Committee on Immunization Practices (ACIP) of the US Public Health Service that all pregnant females be screened for HBsAg and that infants born to HBsAg positive mothers receive hepatitis B immune globulin (HBIG) at birth, followed by a course of hepatitis B vaccine.¹⁰ This represented the first phase in the CDC's programme to control or eliminate HBV infection in the US (Table II). In November 1991, the ACIP recommended universal immunisation of infants.¹¹ This phase 2 plan was endorsed in 1992 by the American Academy of Pediatrics (AAP) and the American Academy

Figure 3: Relation between age and outcome after acute HBV infection.⁸

of Family Physicians (AAFP). Recently, four states have passed laws requiring hepatitis B immunisation for entry into kindergarten or elementary school while an additional 14 states have legislation either pending or in various stages of completion. Also in 1991, the Occupational Safety and Health Administration's (OSHA) Bloodborne Pathogens standard (29 1CFR 1910) was issued that required employers to offer hepatitis B vaccinations free of charge to all persons at substantial risk of directly contacting body fluids.

Concerns

Compliance with these recommendations has been slow but progressive. Initial reasons given by parents for not accepting immunisation for their infants was safety of the vaccine, a perceived lack of need for the product, and cost.¹² Concerns of paediatricians centred on the adoption of yet another immunisation schedule to their well baby clinics and the potential need for booster doses at an age when risk becomes an issue. Regardless, paediatricians were more than twice as likely to agree with the CDC recommendations and to immunise their patients than were family physicians, unless the parent specifically requested hepatitis B vaccination. However, family physicians would vaccinate an infant if high risk was perceived to be present. It is noteworthy that family physicians who were members of the AAFP, on the faculty of a medical school, a participant in a Health Management Organization (HMO)

programme, or who practised in a metropolitan area were more likely to support the CDC recommendations. Factors affecting their decision to recommend hepatitis B vaccine to infants were similar to those given by the parents, but also included concerns pertaining to the requirement for multiple injections (pincushion effect) at a single visit when the hepatitis B vaccine is incorporated into the routine childhood immunisation programme.

Compliance

In a recent nationwide survey of paediatricians and 133 maternity hospitals with greater than 100 births per year, 47% of full term nurseries routinely offered hepatitis B vaccine to all newborns.¹³ An additional 41% of the nurseries vaccinated subsets of infants who were perceived to be at high risk, who were unregistered, or at the request of the paediatricians. Among paediatricians surveyed, 85% indicated that they initiated hepatitis B vaccination by two months of age, with the vast majority performing this function prior to discharging the infant from the hospital. Among 144 neonatal intensive care units, 59% provided routine hepatitis B vaccine to their preterm infants. Immunisations were initiated just before discharge in 73% while 13% of the preterm infants were vaccinated at birth, a time which may result in suboptimal seroconversion. For example, Lau *et al*¹⁴ showed that the response rate to three doses of vaccine was only 70% in preterm infants weighing 1000–2000 g, yielding a geometric mean anti-HBs concentration of 61 mIU/ml, compared with 100% and 679 mIU/ml, in normal term infants (Fig 5). The disinclination of nurseries and neonatal intensive care units to vaccinate infants routinely often had more to do with the high cost of the vaccine and the lack of reimbursement than it did with other issues.

In a 1992 survey of 3982 infants, representing 0.1% of all hospital births in the US, only 36% received vaccine before discharge.¹⁵ It is noteworthy that infants born in hospitals that have established policies governing hepatitis B vaccination were six times more likely to be vaccinated than infants born in hospitals without such a policy. In San Francisco, which has a hepatitis B infant vaccination project in the newborn care units of all maternity hospitals, vaccination is provided free of charge to infants less than 1 year of age.¹⁵ As a result, hepatitis B immunisation is initiated in 82% of infants prior to their discharge. In Connecticut, hepatitis B vaccination was publicised by the Department of Public Health and Addiction

Figure 4: Age group specific acquisition of acute and chronic HBV infection in the United States based on 1989 estimates.^{8,9}

TABLE II Plan of action for the comprehensive control of hepatitis B virus transmission in the United States

Phase 1
Universal screening of pregnant women for HBsAg
Phase 2
Universal immunisation of infants
Phase 3
Catch up immunisation of adolescents and high risk children and adults

Figure 5: Response of preterm and full term infants to hepatitis B vaccine (Engerix-B) based on seroconversion rates and geometric mean concentrations (GMC).¹⁴

Services, who sent letters discussing the ACIP and AAP recommendations to all newborn care units and paediatricians in the state. After this intensive promotion, a survey of seven maternity hospitals in three cities showed that 69% of 529 infants received a dose of hepatitis B vaccine before discharge from the hospital (range 40% to 96%). Vaccine coverage was usually higher when it was provided free using public sector funds and when a policy existed to offer vaccine routinely. Finally, 1992 and 1993 National Health Interview Surveys of 4584 children less than 6 years of age showed that the proportion of children who received three doses of hepatitis B vaccine by 12 months of age increased steadily from less than 1% in 1989 to 31% in 1992.¹⁵ These data are encouraging and illustrate that proper promotion of the vaccine, coupled with a hospital based vaccination policy and free vaccine, can result in higher vaccine coverage.

'CATCH UP' IMMUNISATION

The final phase of the CDC programme on the elimination of HBV transmission in the US includes 'catch up' immunisation of adolescents and high risk children and adults (see Table II). In comparison with the programme for infants, this vaccination strategy is more difficult to achieve. However, catch up vaccination in these groups is important because 92% of the acute infections that are reported occur in adolescents and adults (see Fig 4).^{8,9} Correspondingly, 64% of the chronic infections that ultimately develop each year are derived from this population. As over 99% of children in the US remain in school until age 13, vaccine delivery programmes targeted at adolescents can significantly expand the benefits of the hepatitis B vaccine programme. Should the duration of immunity wane, this also is an appropriate age for booster inoculations to be given. Demonstration projects in San Francisco (California), Baton Rouge (Louisiana), and Oregon suggest that catch up programmes can be successful if certain considerations are satisfied.¹⁶ For instance, each of these programmes provided free vaccine to the participants, a powerful incentive to any programme. While a pre-existing on site clinic and nurse in the middle school were logistically

desirable, it was not essential for carrying out these programmes. Over 75% of the parents consented to having their child immunised and from 65% to 78% of the consented subjects completed three doses of vaccine. Factors that influenced the successful implementation of the vaccination programmes included presentations to students regarding the risk of HBV infection, early enlistment and support of school officials, flexibility in the vaccination programme, and minimal disruption of school activities. Positive peer pressure also induced a greater number of students to participate. Finally, a funding mechanism, such as the Congressionally approved Vaccines For Children (VFC) programme, is essential if the goal of the CDC's phase 3 programme is to be achieved.

The Alaska experience – a comprehensive control programme

The population based hepatitis B vaccination programme in Alaska has incorporated all phases of the CDC programme into its health care delivery system, including maternal HBsAg screening, universal immunisation of infants, and catch up vaccination of susceptible persons. The mass immunisation programme was started in 1983. Ten years later, in 1994, a seroprevalence study was conducted among residents of seven villages who were 2 to 30 years of age. (McMahon, personal communication.) Among 504 children who were born after the vaccination programme was introduced, 95% had received three doses of plasma derived hepatitis B vaccine, a rate that was similar to the coverage achieved for other childhood immunisations. Of 520 susceptible older children, adolescents, and adults, 76% were fully vaccinated. During 10 years of follow up, break through infections, defined as multiple serial specimens from subjects that were positive for anti-HBc, occurred in only 12 vaccinees born after the vaccine programme was started. This yielded a rate of 0.86 infections per 1000 person years of follow up. None of the 12 subjects were HBsAg positive or developed clinical symptoms of infection, but seven of nine showed a significant rise in their anti-HBs concentrations, indicating an anamnestic response. This risk of transmission can be compared with a 1983 historical control

Figure 6: Incidence of symptomatic hepatitis B observed in Alaska natives residing in southwest Alaska between 1981 and 1993. Points A and B represent the start and finish, respectively, of an immunisation demonstration project in 17 villages in 1981 to 1982. Mass immunisation began in all villages at point C in 1983. (Adapted from reference 17.)

TABLE III Cost effectiveness of selected medical interventions (1992, US Dollars)

Intervention	Cost per year of life saved (\$)
Routine infant hepatitis vaccination	1852
Antepartum administration of anti-Rh immune globulin	2339
Smoking cessation – nicotine gum	7450
Neonatal intensive care (1000–1400 g infants)	7987
Coronary artery bypass surgery (left main disease)	10 595
Pneumococcal vaccination (>65 years of age)	11 456

TABLE IV Public and private sector childhood vaccine costs (United States, 1993)

Vaccine	Cost per series (\$)	
	Public sector*	Private sector†
Diphtheria-tetanus-pertussis (5 doses)	7.13	50.69
Oral polio (4 doses)	7.47	21.51
Measles-mumps-rubella (2 doses)	21.78	41.70
Haemophilus b conjugate (4 doses)	21.46	60.52
Hepatitis B (3 doses)		
Infant of HBsAg negative mother	20.55	32.10
Infant of HBsAg positive mother‡	60.68	86.75

*CDC contract price. †Manufacturer's list price. ‡Includes cost of HBIG.

group of age matched subjects in which 37% were anti-HBc positive and 15% were HBsAg positive.

In a second study, 90% of the susceptible population residing in southwest Alaska (9840 residents) were immunised, and all infants were offered the vaccine at birth.¹⁷ (Also, McMahon, personal communication.) Between 1981 and 1993, the annual incidence of acute symptomatic hepatitis B declined from 215 cases per 100 000 to 7–14 cases per 100 000, with most of the decline occurring within the first two years of the programme (Fig 6). These studies illustrate that successful elimination of HBV transmission in a highly endemic region is feasible.

Issues and concerns

COST EFFECTIVENESS

Although the safety of the HBsAg vaccines has been adequately demonstrated, a number of concerns about the vaccine programme in the US remain. A major deterrent to a successful conclusion is the absence of third party reimbursement, though several investigators have examined the economic attractiveness of the hepatitis B vaccination strategies. These studies conclude that universal vaccination of infants, combined with catch up programmes, are cost effective.^{18 19} Prevention of hepatitis B through a broad based vaccine programme – and the morbidity and mortality associated with it – is less expensive than treating the

TABLE V Longterm protection from HBV infection among responders to plasma derived hepatitis B vaccine

Group ^{ref}	Number	Follow up (y)	Anti-HBc+ve (%)	HBsAg+ve (%)
Homosexual men				
Hadler <i>et al</i> ²¹	634	9	11	0.3
Stevens <i>et al</i> ⁴	127	10	4.7	0
Alaska natives				
Wainwright <i>et al</i> ^{22 23}	130	9	0.5	0
High risk infants				
Hwang <i>et al</i> ²⁴	654	5	7.0	0.5
Stevens <i>et al</i> ⁴	104	5	6.7	0

Modified from Margolis,⁸ with permission.

disorder once it develops, and should be funded through legislative action. Cost per year of life saved compares favourably with other medical intervention programmes that are being promoted in the US (Table III). (Margolis and the CDC, personal communication.) Similarly, public and private sector vaccine costs for hepatitis B, as of 1993, are comparable with other paediatric vaccines (Table IV). (Margolis and the CDC, personal communication.) Finally, taking into account work loss costs, direct medical costs (discounted at 5%), and programme costs (discounted at 5%), a significant net benefit has been computed for both the at risk perinatal and universal infant vaccination programmes.²⁰ Although the net benefit seems to be minimal for the adolescent programme, its importance in accelerating the benefits of hepatitis B prophylaxis cannot be overemphasised.

DURATION OF IMMUNITY

The issue concerning duration of immunity must be continually updated, preferably by evaluating persons who reside in low endemicity regions of a country, where natural boosting will not confound the analysis. Most of our data are derived from the use of plasma derived vaccine. Whether these results can be applied to the recombinant derived products will not be confirmed until completion of longterm follow up studies, which are currently in progress. Table V reviews the longterm protection that has been observed in persons who developed an adequate anti-HBs response after vaccination.^{4 8 21–24} These results are encouraging as hepatitis B infection among immunocompetent adults who have been vaccinated has not been observed. However, durability of immunity using the recombinant vaccines – especially in those situations where lower doses have been approved for use in infants – must be carefully monitored. For example, among infants vaccinated in Alaska, about 70% of those receiving the plasma derived vaccine had anti-HBs values greater than 10 mIU/ml when evaluated two to four years later, whereas the response rate was only 15% to 32% for those infants who received the Merck and Co, Inc recombinant vaccine (Fig 7). (McMahon *et al*, personal communication.) The lowest frequency occurred in those infants who received the least immunogen (2.5 µg per dose). Based on age at first injection, anti-HBs values greater than 10 mIU/ml were less common 10 years after vaccination in children who had been immunised in infancy or early childhood than in older children (53% and 73%, respectively, versus 85%). As most infants are currently being given lower doses of HBsAg, a large population of vaccine recipients will lack measurable levels of anti-HBs when they enter school. If cell mediated immunity (memory) remains intact, exposure to HBV should provide enough time for protection considering the relatively long incubation period associated with this disease. Nevertheless, we should remember that longterm efficacy

Figure 7: Per cent subjects anti-HBs value ≥ 10 mIU/ml observed at different time intervals based on three types of vaccine given to infants. PDV=plasma derived vaccine; RDV=recombinant derived vaccine; RDV, low=low dose form of recombinant derived vaccine (2.5 μ g). (From McMahon et al, personal communication.)

with the recombinant vaccines in low risk populations has not been validated, a fact that often is ignored when discussing longterm protection. Thus, we must remain vigilant. However, a booster dose on entry into kindergarten or middle school seems to be a reasonable compromise until this information has been assembled.

Guidelines

All infants should receive hepatitis B vaccine, which should be integrated into the routine childhood vaccination schedule. This programme has been shown to be cost effective. Screening of all pregnant women for HBsAg, and the administration of HBIG and vaccine to infants of HBsAg positive mothers (including those who are also anti-HBe positive), is extremely important if chronic liver disease and hepatocellular carcinoma (HCC) are to be prevented. Household members and sexual contacts of HBsAg positive persons need to be screened and vaccinated if susceptible. Prevacination serological testing is not indicated unless the person is a member of a group that has been shown to have a high rate of infection, such as Alaska natives, Asians, injection drug abusers, immigrants from endemic areas, and family members of carriers. The vaccine should not be given in the buttocks, in the same extremity with diphtheria-tetanus-pertussis vaccine, intradermally, or in the same syringe with other vaccines. Finally, periodic antibody testing is not needed, although determination of response is recommended for persons who are at high risk of contracting HBV. Whether booster doses of vaccine should be given remains controversial. However, for the moment, it is comforting to know that few, if any, relevant clinical infections have occurred among vaccine responders who have been followed up for up to 10 years (see Table V), even if they have lost detectable antibody. Unfortunately, limited data, especially with the recombinant vaccines, and the role of natural boosters in an endemic environment, cloud the issue. In the interim, at least one booster dose five to 10 years after completing the basic

immunisation series seems prudent, especially if the low dose, yeast derived vaccine has been given.

This work was supported in part by the Eugene B Casey Foundation.

- Centers for Disease Control and Prevention. Final 1993 reports of specified notifiable diseases. *MMWR* 1994; 43: 597-603.
- Centers for Disease Control. Hepatitis Surveillance Report No 55, 1994.
- McQuillan GM, Townsend TR, Fields HA, Carroll M, Leahy M, Polk BF. Seroepidemiology of hepatitis B virus infection in the United States, 1976 to 1980. *Am J Med* 1989; 87 (suppl 13A): 5-10S.
- Stevens CE, Toy PT, Tong MJ, et al. Perinatal hepatitis B virus transmission in the United States: prevention by passive-active immunization. *JAMA* 1985; 253: 1740-5.
- Alter MJ, Hadler SC, Margolis HS, et al. The changing epidemiology of hepatitis B in the United States: need for alternative vaccination strategies. *JAMA* 1990; 263: 1218-22.
- Hollinger FB and the North American Regional Study Group. Controlling hepatitis B virus transmission in North America. *Vaccine* 1990; 8 (suppl): S122-8.
- West DJ, Margolis HS. Prevention of hepatitis B virus infection in the United States: a pediatric perspective. *Pediatr Infect Dis J* 1992; 11: 866-74.
- Margolis HS. Prevention of acute and chronic liver disease through immunization: hepatitis B and beyond. *J Inf Dis* 1993; 168: 9-14.
- Hollinger FB. Hepatitis B virus. In: Fields BN, Knipe DM, Howley PM, et al, eds. *Fields Virology* 3rd ed. Philadelphia: Lippincott-Raven 1996: 2739-807.
- Advisory Committee on Immunization Practices (ACIP). Prevention of perinatal transmission of hepatitis B virus: prenatal screening of all pregnant women for hepatitis B surface antigen. *MMWR* 1988; 37: 341-6.
- Centers for Disease Control. Hepatitis B virus: a comprehensive strategy for eliminating transmission in the United States through universal childhood vaccination. Recommendations of the Immunization Practices Advisory Committee (ACIP). *MMWR* 1991; 40 (RR-13): 1-25.
- Freed GL, Bordley WC, Clark SJ, Konrad TR. Universal hepatitis B immunization of infants: reactions of pediatricians and family physicians over time. *Pediatrics* 1994; 93: 747-51.
- Kim SC, Sinai LN, Casey R, Pinto-Martin JA. Universal hepatitis B immunization. *Pediatrics* 1995; 95: 764-6.
- Lau Y-L, Tam AYC, Ng KW, et al. Clinical and laboratory observations. Response of preterm infants to hepatitis B vaccine. *J Pediatr* 1992; 121: 962-5.
- Woodruff BA, Stevenson J, Yusuf H, et al. Progress toward integrating hepatitis B vaccine into routine infant immunization schedules in the United States, 1991-1994 (in press).
- Centers for Disease Control. Hepatitis B vaccination of adolescents - California, Louisiana, and Oregon, 1992-1994. *MMWR* 1994; 43: 605-8.
- McMahon BJ, Wainwright RB. Protective efficacy of hepatitis B vaccines in infants, children, and adults. In: Ellis RW, ed. *Hepatitis B vaccines in clinical practice*. New York: Marcel Dekker, 1993: 243-61.
- 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.
- Krahn M, Detsky AS. Should Canada and the United States universally vaccinate infants against hepatitis B? A cost-effectiveness analysis. *Med Decision Making* 1993; 13: 4-20.
- Margolis HS, Coleman PJ, Brown RE, Mast EE, Sheingold SH, Arevalo JA. Prevention of hepatitis B virus transmission by immunization: an economic analysis of current recommendations. *JAMA* 1995; 274: 1201-8.
- Hadler SC, Francis DP, Maynard JE, et al. Long-term immunogenicity and efficacy of hepatitis B vaccine in homosexual men. *N Engl J Med* 1986; 315: 209-14.
- Wainwright RB, McMahon BJ, Bulkow LR, et al. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population. *JAMA* 1989; 261: 2362-6.
- Wainwright RB, McMahon BJ, Bulkow LR, Parkinson AJ, Harpster AP, Hadler SC. Duration of immunogenicity and efficacy of hepatitis B vaccine in a Yupik Eskimo population - preliminary results of an 8 year study. In: Hollinger FB, Lemon SM, Margolis HS, eds. *Viral hepatitis and liver disease*. Baltimore: Williams & Wilkins, 1991: 762-6.
- Hwang LY, Lee CY, Beasley RP. Five year follow-up of HBV vaccination with plasma-derived vaccine in neonates: evaluation of immunogenicity and efficacy against perinatal transmission. In: Hollinger FB, Lemon SM, Margolis HS, eds. *Viral hepatitis and liver disease*. Baltimore: Williams & Wilkins, 1991: 759-61.

Discussion

Zuckerman: In one of your graphs, you showed that the incidence of hepatitis B was still

increasing, even while the vaccine was being used, but then it started to decline. Surely, education had a lot to do with this. That is, changes in behaviour presumably occurred as a result of education following the emergence of HIV.

Hollinger: I think changes in life style and behavioural patterns as a result of the HIV

epidemic probably had a lot to do with it. Nevertheless, the vaccine also seemed to be playing a part, because there was a drop in the rate of hepatitis B among health care workers. Then again, there also were considerable changes instituted by hospitals and laboratories in terms of wearing gloves and recapping needles.