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Review Article

Implementing Strategies for Hepatitis B Vaccination

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ABSTRACT. This study reviewed the effects of hepatitis B virus (HBV) vaccination programs on disease control and the need, if any, to introduce additional strategies taking into account the various risk factors of transmission. We performed a search conducted on vaccine administration, hepatitis B risk factors and the impact of HBV vaccination on prevention of disease, using the electronic database MEDLINE (1987 to 2008), EMBASE, OVID, Google (for Local websites and medical journals), Websites of Iranian universities and Iran medex in English and Persian language. We recommend in addition, to routinely practice the Extended Program of Immunization (EPI) schedules for infants as well as implementing HBV vaccination in selected adolescents at risk for HBV infection. Routine screening and immunization is mandatory in the following people: pregnant women and adults at risk for HBV infection including health-care workers, police, fire fighters, barbers, people with certain risk behaviors such as inmates of correctional facilities, injection-drug users and persons at risk for sexual transmission, as well as patients exposed to blood and blood products and those on chronic hemodialysis. Vaccine providers in areas with high rates of chronic HBV infection should assess infection screening by performing serologic tests in susceptible subjects to identify persons who require counseling and management. Also, additional studies are needed to determine the effectiveness of currently employed immunization strategies.

Introduction

Chronic hepatitis B virus (HBV) infection is the most common cause of cirrhosis and liver cancer worldwide. Approximately 45% of the world's population lives in regions where chronic HBV infection is endemic, including most of Asia and the Pacific Islands, Africa, and the Middle East,[1] resulting in the massive global burden associated with the infection.[2] Medical treatment of hepatitis B is expensive and sometimes futile due to drug resistance. Liver transplantation has limitations. In a study of 480 patients listed for liver transplantation (LT), cause of cirrhosis were cryptogenic in 143 (29.9%) and hepatitis B in 127 (26.5%).[3] Only

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about one-fifth of patients listed for LT in Iran received one, and a large proportion died before transplantation could be performed. In a study, risk factors for development of hepatocellular carcinoma (HCC) were assessed in 71 patients with HCC at a hospital in Ahwaz, Southern Iran from 1999 to 2004. In 30 patients (42%), liver cirrhosis was documented while 37 (52.1%) had hepatitis B.[4] Occult hepatitis B is relatively frequent among patients with chronic liver disease in Iran. It may be associated with more advanced liver pathology and more aggressive clinical course. Occult HBV infection causes strong suppression of viral gene expression.[5,6]

More than 20 years have elapsed since vaccination against HBV was introduced, first with a plasma-derived vaccine and later a recombinant DNA-derived vaccine. During this period, important changes have occurred in several aspects of this disease; the acute and chronic infection rates, the mortality of fulminant hepatitis B in infants and the incidence of HCC have all been effectively reduced by approximately 25%. Vaccination during childhood has produced adequate protection for up to 20 years later. Finally, it has been proven that the HBV vaccine is one of the safest vaccines available in the world.[7] Safe and effective vaccines against HBV infection have been available since 1982. The implementation of mass immunization programs, which were recommended by the World Health Organization in 1991, has dramatically decreased the incidence of HBV infection among infants, children, and adolescents in many countries.[8] The cost of management of complications of HBV infection, such as liver transplantation, as well as the low price of the vaccine argues for universal infant hepatitis B immunization.[9] Inclusion of vaccination against the HBV in the national infant immunization programs could prevent more than 80% of HBV-related death.[10] A model is used to calculate the age-specific risk of acquiring HBV infection, acute hepatitis B (illness and death), and progression to chronic HBV infection. HBV-related deaths among chronically infected persons were determined from HBV-related cirrhosis and HCC mortality curves, adjusted for background mortality. For the year 2000, the model estimated that 620,000 persons died worldwide from HBV-related causes: 580,000 (94%) from chronic infection-related cirrhosis and HCC and 40,000 (6%) from acute hepatitis B. In the surviving birth cohort for the year 2000, the model estimated that without vaccination, 64.8 million would become HBV-infected and 1.4 million would die from HBV-related disease. Routine infant hepatitis B vaccination, with 90% coverage and the first dose administered at birth would prevent 84% of global HBV-related deaths.[10]

To determine new strategies for complete coverage of HBV vaccination, every country needs to concern factors of infection transmission in its own region. We herewith review nationwide variations in vaccination programs, certain habits and occupations, and other routes that make the subjects susceptible to infection exposure. Also, we review the policy recommended for HBV immunization in Iran and other regional countries.

Methods

We performed a search conducted on vaccine administration, hepatitis B risk factors and the impact of HBV vaccination on prevention of disease, using the electronic database MEDLINE (1987 to 2008), EMBASE, OVID, Google (for Local websites and medical journals), Websites of Iranian universities and Iran medex in English and Persian language.

Implementation Strategies for Hepatitis B Vaccination in Persons with Risk Factors

Maternal and inter-familial spread of HBV infection

A follow-up study was performed in 103 infants born to HBsAg and HBeAg positive mothers in Iran;[11] all infants received hepatitis B immune globulin (HBIG) and HBV vaccine; HBsAg was positive in three infants (3.6%) born to HBeAg negative mothers, significantly lower than the incidence of HBsAg positivity (33.3%) among infants born to HBeAg positive mothers. Seventeen infants (18.3%) were

poor responders and 34 (36.6%) were non-responders to vaccination. In this study, children who were poor or non-responders to HBV vaccination in these groups were relatively high and additional doses of the vaccine were required for satisfactory immunization. Vaccination alone did not induce immunity against hepatitis B in children whose mothers were HBsAg positive. Routine screening of pregnant women is necessary for determining whether neonates need hepatitis B immunoglobulin after birth.[12]

HBV seromarkers, including HBsAg and antibodies to HBsAg and core antigen (anti-HBc), were studied in 18,779 subjects from neonates to adults below 30 years of age in 2004. The birth cohort effect was evaluated by comparing the results of the same birth cohorts at different ages among this survey and the previous surveys in 1984, 1989, 1994, and 1999. The seropositive rates for HBsAg, anti-HBs, and anti-HBc were 1.2%, 50.5%, and 3.7%, respectively, in those born after the vaccination program (< 20 years of age) in 2004. A positive maternal HBsAg status was found in 89% of the HBsAg seropositive subjects born after the vaccination program. The absence of an increase in HBsAg seropositive subjects at different ages in the same birth cohorts born after the vaccination program implied no increased risk of persistent HBV infection with aging. Universal HBV vaccination provides long-term protection up to 20 years, and a universal booster is not indicated before adulthood. Maternal transmission is the primary reason for vaccine failure and is the challenge that needs to be addressed in future vaccination programs. This may include an appropriate hepatitis B immunoglobulin administration strategy for high-risk infants and involve efforts to minimize noncompliance.[13]

From 2003 to 2005, 60 cases of susceptible wives of infected husbands and 32 cases of susceptible husbands of infected wives in Babol, North of Iran, received recombinant hepatitis B (HB) vaccine at the time of marriage followed with the second and third doses at one and six months. Post-vaccination tests for HBsAg, anti-HBs and anti-hepatitis B core (HBc) were assessed two months after the last dose. The HBs antibody levels of 10 mIU/mL were considered to be protective. Those with anti-HBs levels of < 10 mIU/L received the second series of HBV vaccination. This study shows that administration of hepatitis B vaccine at the time of marriage prevents the transmission of hepatitis B virus in susceptible spouses.[14]

A total of 172 family members of 67 carriers of hepatitis B were tested for hepatitis B markers; 716 first-time blood donors from the Tuzla region of Bosnia and Herzegovina were used as controls. The prevalence of HBsAg was higher ($P< 0.001$) among family members of index cases (12.2%) than among controls (3.6%) with relative risk of 3.3 (95% confidence intervals = 1.9-5.8; $P < 0.05$). Rate of exposure among family members was 37.8% (65/172). Thus, in the area studied, both horizontal and vertical transmission exists, but maternal route is predominant. Female sex, HBeAg-positivity of index carrier and presence of HBsAg-positive mother in the family increased the risk for HBsAg-positivity and exposure among family members. Vaccination rate of family members of index cases is alarmingly low.[15]

In 1985, the epidemiology of hepatitis B virus in a healthy Middle Eastern population was studied. Residents of three remote villages and urban areas of Jordan were assessed for seroprevalence of HBsAg and HBV infection. There was evidence of familial clustering of HBV in two of the villages, with HBV carriers and infected children particularly aggregating around HBsAg-positive siblings. There was also a trend toward an association of HBsAg-positive children with HBsAg-positive mothers. HBV carrier prevalence correlated with family size, and HBV infection in the household increased proportionately with the number of carriers in the family. Hepatitis B e antigen (HBeAg) was detected most frequently in children and antibody to HBeAg, in adults. Postnatal early childhood transmission through contact among children of poorer and larger families probably accounts for the high endemicity of HBV in this region.[16]

Cross-infection control in health-care workers

Health-care workers (HCWs), especially physicians and dentists, can transmit serious viral

infections to patients during invasive procedures.[17] The risk of getting infected with various infectious agents is higher than in the general population, and they may play a role in transmitting infectious agents to others.[18]

Alavian in a study of coverage of HBV vaccination of 334 dentists in 2004 concluded the following: history of HBV vaccination in 94.9% of dentists, but complete vaccination was administered in 74.8% of dentists. Only 47.9% of them reported that they had been checked for HBV antibodies after vaccination. Some dentists did not follow cross-infection control methods in their practice, and it seems useful to encourage HCWs to check their immunity status.[19]

Disposal of dental waste was investigated at 37 randomly selected clinics in Ramallah and AI-Bireh cities: they included 31 private practice centers and six public/NGO clinics. Dentists were interviewed regarding their disposal of different forms of dental waste. Disinfectants and x-ray processing solution were thrown in the drain. For sharp objects, 13.5% of dentists used puncture-resistant containers (only in the public/NGO clinics), 45.9% discarded needles directly in the garbage after being recapped and 40.5% placed the used needles and blades in closed plastic bottles before throwing in the general garbage. Blood-soaked dressings and amalgam waste were also thrown in the garbage. While 10.75% of dentists were vaccinated against hepatitis B, 47% of the staff at private clinics was not.[20]

Traveling, immigration and refugees as vehicles of HBV infection

An analysis of 404 questionnaires was made in the United States: they included 203 questions on malaria and 201 on vaccine-preventable diseases. Few were vaccinated for their journey including 13% for hepatitis B. This airport survey emphasized the efforts needed to improve the level of awareness among travelers regarding the risk of disease acquisition overseas and the importance of pre-travel education, immunization, and malaria chemoprophylaxis.[21] European studies indicate that up to 67% of travelers traveling abroad participate in activities that put them at risk of exposure to hepatitis B. The results have implications for the individual traveler, as well as to the broader community. Infected travelers can be an important source of hepatitis B into their own home communities.[22] Hepatitis B transmission through the skin may occur through the use of contaminated medical, dental, or other instruments; all pilgrims should consider hepatitis B vaccination. One of the rites of Hajj is for men to have their head shaved. Although the Saudi authorities provide licensed barbers who use a new blade for each pilgrim, other barbers may not conform to such standards. Shaving with a previously used blade could carry a risk of hepatitis B and other blood borne infections, and so communal use of a razor or blade to shave each other should be avoided. Pilgrims should consider taking with them a disposable razor for this purpose. This will also help to protect against hepatitis C virus infection.[23] A study mentioned that US-born children of Hmong refugees apparently acquire HBV infection through both horizontal and perinatal transmission, and emphasize the importance of routinely integrating hepatitis B vaccine doses into the childhood vaccination schedule for all infants whose parents are from areas where HBV infection is highly endemic. In addition, the findings support the need for pediatricians to consider vaccinating older children (up to age 7 years) whose parents are from HBV-endemic areas.[24] Multiple strategies were used to increase hepatitis B vaccination rates among Asian-American and Pacific Islander children, including developing a task force consisting of members from public and private organizations. Specific strategies included: developing and distributing culturally specific hepatitis B educational materials, supporting a household cluster survey to assess hepatitis B vaccination coverage rates, conducting hepatitis B immunization and blood testing clinics at local Chinese language schools, and conducting outreach through media sources. The author stated that collaborations require persistence, patience, flexibility, and creativity to achieve community and public health goals.[25]

Injection drug users, prisoners, certain high risk behaviors predisposing for HBV exposure

Injecting drug users sharing blood-contaminated equipment are at risk of blood-borne virus infections. In a revaccination study,[26] the determinants of response to booster hepatitis B virus (HBV) vaccination in anti-HBs-seronegative adolescents who had received primary HB vaccination 15-18 years before, was explored. After controlling for pre-booster anti-HBs levels; cigarette smoking, betel-quid chewing, alcohol drinking, and indigenous ethnicity were significantly associated with elevated risks of non-response to booster HBV vaccination. A booster dose of HBV vaccine may be insufficient to induce immunological response in healthy adolescents who had undetectable pre-booster anti-HBs titers or who were of Malay-Polynesian ethnicity. Responses to booster vaccination are probably modified by recent cigarette smoking and/or betel-quid chewing.[27] In England and Wales, where less than 1% of the populations are likely to be injecting drug users (IDUs), approximately 38% of laboratory reports of HBV, and 95% of HCV reports are attributed to injecting drug use. There was only limited evidence of background HBV infection due to factors other than injecting. The models highlight the need to increase interventions that target new initiatives to reduce the transmission of blood-borne viruses.[28] The phenomenon of illicit drug use in Spain during the last 30 years has markedly increased due to the extremely serious consequences of heroin use (mainly injecting). We propose to maintain and to strengthen harm reduction programs including: methadone maintenance treatment (MMT), syringe exchange, save-use and injection rooms, hepatitis A and B vaccination, specific strategies targeted to reduce overdose mortality and cocaine related problems, and to re-evaluate the effectiveness of preventive and supply control strategies.[29] In a total of 102 self-reported drug users recruited between 1996 and 1997 in south-east England, the mean age at onset of illicit drug use for the entire sample was 15.33 years (SD 3.36); 3.7% (1/27), 20.4% (18/88), and 55.8% (48/86) had antibodies to HIV-1, HBc and HCV, respectively; 1.1% (1/88) tested positive for HBsAg, indicative of a carrier state. The poor uptake of hepatitis B vaccination among drug users, their poor response to HIV antibody test and poor health service utilization suggest the need for an urgent appraisal of service providers and a review of prevention and treatment strategies.[30]

In a study in Kermanshah of Iran,[31] 48 HIV-positive patients who did not have a history of HBV infection received the conventional three-dose HBV vaccine, and anti-HBs level was measured two months after the last dose. Only 14 (29.1%) of the 48 vaccinated HIV-infected patients had positive anti-HBs titers. The HIV-infected patients have a lower response rate to the conventional three-dose HBV vaccine. Higher and more booster doses in early immunologic stages of HIV infection are recommended in such patients.

In a study of 55% of potential participants (391/712) among female prisoners in Victoria who were offered hepatitis B immunization, 84% completed the three-dose series. Results led to the revision of key prison hepatitis B immunization policies and practices to ensure uniformity across Victorian prisons.[32] The advantages of modeling for hepatitis B vaccination programs in prison are stressed and an active case-finding approach is advocated. A higher reference level for inferring adequate immunization is also recommended, with booster injections for inmates who do not meet the higher reference after a primary course of vaccination.[33] In a study of hepatitis B vaccination trends in six STD clinics in the United States, the median rate of hepatitis B vaccination was 28 per 100 client visits. The median rate of vaccine series completion was 30%. This study shows that STD clinics can implement hepatitis B vaccination and reach large numbers of high-risk adults.[34] In October 1997, the Advisory Committee on Immunization Practices (ACIP) expanded its hepatitis B vaccination recommendations to include all unvaccinated children aged 0-18 years and made hepatitis B vaccine available through the Vaccines for Children program (VFC) for persons aged 0-18 years who are eligible for VFC. ACIP priorities for hepatitis B vaccination among children remain un-

changed and include all infants; children in populations at high-risk for HBV infection (e.g., Alaska Natives, Pacific Islanders, and children who reside in households of first-generation immigrants from countries where HBV infection is moderately or highly endemic); previously unvaccinated children aged 11-12 years; and older adolescents and adults in defined risk groups.[35]

Strategy of schedule HBV vaccination

Asia and Africa have previously been classified as areas of high endemicity for HBV, but in some countries highly effective vaccination programs have shifted this pattern toward intermediate or low endemicity. In the Middle East, Bahrain, Iran, Kuwait are areas of low endemicity. Cyprus, Iraq and the United Arab Emirates have intermediate endemicity, and Egypt, Jordan, Oman, Palestine, Yemen and Saudi Arabia have high endemicity.[36] There are 23 areas in Eastern Mediterranean region. Hepatitis B vaccine is used in 15 areas. All these countries use three primary doses of vaccine in infancy. The immunization time varies from birth (12 areas) to nine months of age. In Cyprus, hepatitis B vaccine is used in a four-dose schedule, including a booster dose given to five to six-year-old children.[37]

South Africa implemented a vaccination program against HBV into the EPI in 1995. This study assessed the impact of universal childhood HBV vaccination program in reducing HBsAg carriage in the first five years (1995-1999) since its implementation, in 598 babies recruited from the Northern Province, South Africa. The overall sero-protection rate was 86.8% in vaccinated babies, while 13.2% had anti-HBs levels < 10 mIU/mL. However, 0.9% (5/582) babies, tested positive for anti-HBc, all of whom had anti-HBs titres > 10 mIU/ml and were negative for HBV DNA. Anti-HBc positivity was probably maternal in origin, or may represent sub-clinical averted HBV infections.[38]

Approximately 60% of the populations have a history of HBV infection, and 9.8% of persons in China are chronically infected with HBV and at risk for premature death from liver disease. Each year, an estimated 263,000 persons in China die from HBV-related liver cancer or cirrhosis, accounting for 37 to 50% of HBV-related deaths worldwide. Because most HBV infections occur during infancy or early childhood, when HBV infection is most likely to become chronic, vaccination of infants beginning at birth is the key strategy for preventing chronic HBV infection. China has established a goal to reduce chronic HBV infection among children aged < 5 years to < 1% by 2010. Achieving this goal will require continued commitment to increasing vaccination coverage in impoverished regions and ensuring that infants born at home are vaccinated within 24 hours of birth.[39]

The prevalence of HBV infection in a study in Cyprus showed that the carrier rate of HBs Ag in the blood donor and army recruit samples ranged between 0.77% and 1.01% and the prevalence of past infection between 11.1% and 13.6%. Among high-risk groups, the highest carrier rate was found in family contacts of HBsAg carriers (18.27%), in mentally retarded children (6.12%) and in institutionalized adult patients (5.40%). A national vaccination program has to be implemented for containing its spread.[40]

In a study of 221 children in Istanbul, the complete vaccination rate among the study population was 84.5% while 3.2% of all children were totally non-vaccinated. Reasons for non-vaccination were: being in the village and could not reach the health care center; having no knowledge about vaccination; the father of the child did not allow vaccination; intercurrent illness of child during vaccination time and missed opportunities like not to shave off a vial for only one child. Paternal and maternal levels of education and immigration time of both parents to Istanbul were found to influence whether children were completely vaccinated or non-vaccinated.[41] Hepatitis B virus infection is endemic in the Kingdom of Saudi Arabia (KSA). The Jizan region in the South-Western area of the country was noted for a high prevalence of HBsAg carrier rate. In a study carried out between 1995 and 1998, the low prevalence of HBsAg in children, provides evidence for the effectiveness and efficacy of the integration of hepatitis B vaccination into the extended pro-

gram of immunization in KSA. The significant decline of HBV markers among unvaccinated Saudi adults indicated an indirect effect of other factors (for example health education and socio-economic progress) on the prevalence and transmission of HBV in Jizan. In areas of high endemicity, the epidemiological characteristics of HBV are modified significantly by the combination of HBV vaccination and other complimentary control strategies.[42] Saudi Arabia has included universal administration of HBV vaccine to all infants since 1990, and from 1990 to 1995 this vaccine was also routinely administered to children at school entry. The prevalence of HBsAg among children before this program was reported to be 6.7%. The prevalence varied by region, ranging from 0.03% to 0.72% with a mean prevalence of 0.15%. There was a clear decline in incidence among children.[43]

To evaluate the effectiveness of HBV vaccination among household contacts of HBV carriers in Tulkarm district, Palestine, quantitative anti-HBs in 161 household contacts was measured after vaccination. A seroprotective anti-HBs response was elicited in all vaccinated subjects.[44] In a study in Pakistan, of 3533 children screened for HBsAg, the infection rate was 3.3%. HBsAg was more prevalent in subjects who received therapeutic injections (69.2%) and vaccination in the government healthcare facilities (70.7%).[45]

Some developing countries fail to achieve desirable vaccination coverage; Afghanistan is one such country. A study analyzed reports of infant immunization from 331 districts across seven regions of Afghanistan between 2000 and 2003. Geographic information system (GIS) analysis was used to visualize the distribution of immunization coverage in districts and to identify geographic inequalities in the process of improvement of infant immunization coverage. The results of multivariate logistic regression analysis indicated a significant negative association between lack of security in the region and achievement of 80% coverage of immunization regardless of available resources for immunization, while resource availability showed no relation to immunization coverage.[46] In the aftermath of the war in Iraq, widespread looting and intentional damage to government facilities resulted in the interruption of public services and utilities. Basic communications were disrupted nationally. Public health headquarters, clinics, and laboratories were damaged, records were ruined, and equipment was stolen, and many health-care workers reportedly feared either to commute to their worksites or to remain after dark.[47]

The Primary Health Care (PHC) network of Iran consists of a rural and an urban branch. Iran's Primary Health Care system consists of a rural branch operated by mobile male and female teams, and an urban branch still in the process of changing from cure-oriented care to emphasis on health education, nutrition, and maternal-child health services. Complete immunization coverage by age one year was better in rural areas (44.1%), than in urban areas (28.2%) and Teheran (34.9%). The reason for better coverage in rural areas is that village workers actively search out, visit, and immunize children, while in urban areas physicians provide dominant care, but do not insist on immunization.[48]

Since universal vaccination of infants, prevalence of hepatitis B has a decreasing trend in Iran. Recent strategies of health ministry for vaccination of the young people will reduce the mode of transmission of HBV.[49] Universal vaccination of all neonates against HBV has been implemented in the Islamic Republic of Iran since 1993. To evaluate the efficacy of the program, two large sero-epidemiologic surveys were conducted before and after mass vaccination on a representative sample of 1/1000 of the population. The overall seropositivity rate showed no significant decline between 1991 and 1999 but in the age group 2-14 years the rates reduced significantly (1.3% versus 0.8%, $P < 0.05$). Interestingly, we observed a significantly higher decline in HBV carrier rate in rural (1.5% versus 0.6%) than urban areas (1.1% versus 0.9%). Universal vaccination significantly decreased the carrier rate among young children in this country.[50]

Vaccination and controlling antibody response to vaccine is the mainstay of hepatitis B pre-

vention. The immunogenicity of a recombinant hepatitis B vaccine in neonates of two cities of Iran; Urmia and Kerman was evaluated.[51] A higher seroprotection rate and significantly increased serum anti-HBs antibody titer were induced in vaccinated neonates from Urmia compared to Kerman. These findings suggest contribution of ethnic and environmental factors in the antibody response to recombinant HBV vaccine. The immunity derived from the HBV vaccine was assessed by measuring the antibody in 3752 children who were vaccinated in a routine vaccination program in three cities of Iran (Isfahan, Khoramabad, Shahrekord). Overall, 723 children (19.3%) had antibodies levels < 10 MIU/mL and 1096 (29.2%) had antibodies levels ≥ 100 MIU/mL.[52]

To determine persisting antibody levels in healthy children aged 6-9 years vaccinated at birth, blood samples were collected from 374 vaccinated children attending Shiraz Primary School, Iran from 2002 to 2003. The anti-HBs titer was detected in 17% of the eight-year-old children, 7.7% of the seven-year-old children and 46.6% of the six-year-old children. The decrease was greatest in the nine-year-old children; more than half (54.3%) had a titer of less than 10 IU/ml, indicating a decrease in antibody levels with increasing age/time. Antibody titer declined with time. In comparison with other countries, the antibody titer in Iranian children was much lower.[53]

Hepatitis B virus prevalence has decreased dramatically in Iranian population during the last decade, and now it is classified as having low endemicity for hepatitis B infection. Improvement of the people's knowledge about HBV risk factors, national vaccination program since 1993 for all neonates, and vaccination of high-risk groups could be the cause of this decrease. The HBV vaccination was started in infants in two provinces (Zanjan and Semnan) in 1989, and in 1993 the vaccination was included in the Expanded Program on Immunization (EPI) countrywide. After 13 years of implementation, the coverage has reached an appropriate level from 62% in 1993 to 94% in 2005. Evaluation of risk factors in HBV infected people is important for designing the strategies to control the disease. Intensifying HBV vaccination of high-risk groups, surveillance of hepatitis B infected subjects, and control on the health status of refugees will further decrease the frequency of the disease in Iran. In addition, the consideration of all possible routes of transmission in subjects without risk factors for infection is necessary.[54]

In a study of 5036 patients admitted to emergency Swiss university hospital, prevalence of anti-HBc was 6.7%. Factors independently associated with positive anti-HBc were intravenous drug abuse, foreign country of birth, non-white ethnicity and age ≥ 60 years. About 75% of all participants were not vaccinated against hepatitis B or did not know their vaccination status. Emergency rooms should be considered as targets for public health programs that encourage vaccination, patient education and screening of high-risk patients for liver disease.[55]

In a survey in France,[56] it has been mentioned that the main target for hepatitis B vaccination has never been reached, since less than 30% of infants were immunized in 2000. In France, exhaustive population surveys have revealed a vaccine coverage rate of over 21.7% and very low three-dose vaccine coverage among infants (19.8%), children (23.3%), and adolescents.[57]

A study was conducted to measure immunization coverage among pre-school children in four selected medically underserved areas and to determine predictors of coverage levels.[58] The survey was based on stratified cluster probability sample designs in which clusters of dwelling units were selected and all households in selected clusters were screened for the presence of children aged 12 to 35 months in Detroit, New York, San Diego, and rural Colorado. Immunization histories were obtained from parents and providers for these children. The overall response rate for eligible children ranged from 79.4 to 88.1%. Coverage levels for most individual vaccines were > 90% in all sites except Detroit.

Hawaii implemented routine infant hepatitis B vaccination in 1992 and required it for school entry in 1997. The incidence of symptomatic acute hepatitis B in Hawaian children and adolescents aged ≤ 19 years decreased

from 4.5 cases per 100,000 in 1990 to 0.0 during 2002-2004. Hepatitis B virus infection has nearly been eliminated in Hawaii children born after universal infant hepatitis B vaccination was implemented.[59]

There are still controversies about safety of extending vaccination to general population. Hepatitis B vaccination efficacy is high in infants, children and adolescents. It may be lower in adults and at risk populations.[60] Although still debated, the hypothesis of a putative role of hepatitis B vaccine in the pathogenesis of demyelinating disease should prompt to pursue experimental and epidemiological research to better understand the links between infectious environment and inflammatory chronic diseases.

In a study in Switzerland,[61] a birth cohort of 85,000 individuals was followed to assess various vaccination strategies. According to this study, systematic prenatal screening reduced the number of chronic infections by 11% and prevented six deaths per year. According to this study, universal vaccination against hepatitis B is more cost-effective than the current selective vaccination strategy of newborns.

The aim of the European Sero-Epidemiology Network two was to coordinate and standardize the serological surveillance of vaccine-preventable diseases in Europe. By combining these standardized and qualitative results for the markers mentioned earlier, it was possible to achieve comparable estimates of the proportion of the population susceptible to HBV, vaccinated against HBV, with a past HBV infection, and with a current infection or chronic carrier state. Standardization is a very important tool that allows for international serological comparisons to assess the current vaccination policies and the progress of HBV control in Europe.[62] A priority for the African region is the upgrading of the management skills of the health workers involved in EPI. A major constraint in the region is the need for a good "cold chain" to ensure that vaccines are stored and transported within the safe temperature range.[63] Vaccination rates are low in clinical practice, and public health and educational programs are needed to overcome barriers to facilitate timely implementation of these recommendations. The use of a combined vaccination, possibly using an accelerated administration schedule, provides convenience and may increase compliance.[64] Efforts are needed to improve methods to identify areas with low immunization coverage so that resources can be directed to places where interventions are needed.[65]

Middle school vaccine mandates are the only state policy associated with improved hepatitis B vaccine coverage.[65] Among Asian-American and Pacific Islander (AAPI) children in the United States, household HBV transmission remains relatively high. More progress can be made if more health departments in the largest cities conduct high school hepatitis B interventions, and implement effective tracking/reminder/recall procedures to ensure receive hepatitis B vaccination.[66]

The recommended infant HBV schedule [59] depends on the mother's HBsAg status and the birth weight: infants born to HBsAg-negative mothers should receive the first dose at 0 to 2 months, the second dose at 1 to 4 months, and the third dose at 6 to 18. Infants born to HBs Ag-positive mothers should receive post-exposure prophylaxis of both hepatitis B immune globulin (HBIG) and HBV within 12 hours of birth, regardless of gestational age. They should ideally receive their second and third doses of vaccine. If the mother is chronically infected with hepatitis B, the infant should be tested for both HBsAg and hepatitis B surface antibody (anti HBs) at 9 to 15 months of age to detect infection or to prove successful vaccination, respectively. Infants born to mothers with unknown HBsAg status should be given HBV within 12 hours of birth. Maternal blood should be drawn at the time of delivery to determine HBsAg status. If the test result is positive, HBIG should be given as soon as possible, but no later than one week of age. Because seroconversion rates are lower in premature infants weighing less than two kg and even lower for those below one kg, the optimum timing for HBV vaccine in prematures is in debate. The initial dose of the vaccine should not be counted towards the HBV series completion if the infant weighs less than two kg. For premature

infants with an HBsAg-negative mother, HBV is best delayed for one month or until the infant weighs two kg or until hospital discharge, if less than one month of age but growing well.

Hepatitis B vaccination strategies may vary from country to country depending on HBV endemicity, predominant modes of infection, age of infection, and health care resources. In areas with high endemicity like Korea, transmission of virus from carrier mothers to infants during the perinatal period, and from other horizontal sources to infants and children, account for most cases of HBV infection. Theoretically therefore, routine infant immunization supplemented with prenatal screening of pregnant women for HBsAg or HBeAg and mass immunization of children is the appropriate strategy for control of hepatitis B in these countries. To prevent primary liver cancer associated with HBV infection, however, immunization of adults at high-risk would also be prudent. Mandatory vaccination of all neonates is recommended in highly endemic areas, together with hepatitis B immune globulin in babies born to HBsAg carrier mothers.[67]

The contribution of each mode of transmission to morbidity and mortality must be known in order to develop the optimal vaccination program. Those countries that vaccinate only children will produce an impact in early life, but it will not be until those vaccinated children reach adolescence or early adult life that any impact on sexual transmission will be seen. The long-term objective of a hepatitis B vaccination program is to prevent virus transmission in all age-groups, with the ultimate aim of eliminating the infection, even in long-term, of eradicating the virus. Ministry of Health and Medical Education in Iran held the mass campaign of immunization against hepatitis B for those born from 1989 to March 2007. During this campaign, 1,320,000 people were vaccinated and about 90% coverage was reached. Evaluation of risk factors in HBV infected people is important for designing the strategies to control the disease.[68]

The results of a study support the economic attractiveness of universal hepatitis B vaccination of school-age children and adolescents. In geographic regions with a high burden of HBV infection, vaccination may be economically attractive at incidence rates as low as 2 to 3 hepatitis B reported cases per 100,000 per year.[69]

In conclusion, education, prevention, and health care maintenance are major routes of controlling hepatitis B infection. Education of the general population, screening and medical management of high-risk groups by targeted prevention programs for preventive practices is mandatory.

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