IMPACT OF HEPATITIS B IMMUNIZATION, EUROPE AND WORLDWIDE
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Abstract

Background. An estimated 2 billion people have serological evidence of infection with HBV. Despite the availability of a safe and effective vaccine since 1992, the introduction of hepatitis B vaccine in national immunization programmes did not pick up as expected. However, in the last few years the pace of introduction of this vaccine has increased due mainly to the advent of GAVI and support from the Vaccine Fund for the poorest 74 countries of the world. By May 2002, 154 countries now have routine infant immunization with hepatitis B vaccine. This paper reviews available published data on impact of hepatitis B vaccination.

Method. Published papers on impact of hepatitis B vaccination were searched using PubMed and Medline online search facilities. Papers on hepatitis B immunization programmes, impact of the vaccine on disease as well as papers on safety and efficacy of the vaccine were reviewed. Published papers that demonstrate the impact of hepatitis B vaccination are included in this paper. Other relevant document and reports were also reviewed.

Results. Where hepatitis B vaccine has been introduced in infant immunization programmes, HBsAg carrier rate in the vaccinated groups has decreased as much as 74% in less than 10 years (Italy), 96% in 7 years (Saudi Arabia, 93% in 15 years (Taiwan), 79% in 10 years (Thailand), 77% in five years (South Africa) and almost 100% in Alaska. A decline of more than 49% in the incidence of acute cases were reported from Italy and, an 80% decrease in Bulgaria. Taiwan demonstrated a 50% in the incidence of hepatocellular carcinoma in children 6 to 14 years of age. There is also evidence to show that adolescent and high risk immunization strategy could possibly miss a substantial proportion of early childhood infections with HBV. Some of the challenges that face further expansion of use of hepatitis B vaccine are high cost and low coverage and weak health infrastructure in many developing countries.

Conclusion. The currently available hepatitis B vaccines are safe and highly effective and that their use has had remarkable impact on reducing the burden of diseases caused by HBV. International support will be needed to further increase access to this vaccine for children living in developing world.

(i) Introduction

Hepatitis B, a viral infection of the liver, is a major global public health problem. It is estimated that about 30% of the world’s population, i.e. about 2 billion people, have serological evidence of infection with hepatitis B virus (HBV) and approximately 350 million of them are chronically infected with HBV. These chronically infected persons are at high risk of death from cirrhosis of the liver and liver cancer, diseases which kill almost a million persons annually worldwide.

(ii) Progress in the introduction of hepatitis B vaccine into national
An inactivated plasma-derived hepatitis B vaccine was licensed in November 1981 and became available for general use by 1982\textsuperscript{2}. In 1982 it was demonstrated that the surface antigen of HBV can be synthesized in yeast\textsuperscript{3}. Consequently, by 1986 a DNA recombinant hepatitis B vaccine was also available for general use. Both of these vaccines were proven to be safe and efficacious\textsuperscript{4,5,6,7,8} and more than one billion people have been immunized in the world since the beginning of implementation globally.

Despite availability progress in the introduction of these vaccines in infant immunization programmes globally was limited during the 1980s. This was partly due to the high cost of the vaccines and partly due to lack of clarity on how best to control hepatitis B on a population basis. For almost a decade, use of these vaccines was largely confined to protecting individuals at risk. In 1991 there were only 20 countries routinely using hepatitis B vaccine\textsuperscript{9} in infant programmes. In 1990, Ghendon\textsuperscript{10} outlined a potential WHO strategy for global elimination of new cases of hepatitis B. However, it was the Youndé Meeting\textsuperscript{a} of October 1991 that provided the impetus to move more urgently towards the elimination of hepatitis B. Immediately following the Youndé meeting, the Fourteenth Meeting of the Global Advisory Group of the Expanded Programme on Immunization, took place in Antalya, Turkey\textsuperscript{11}, and recommended the integration of hepatitis B vaccine into national immunization systems in all countries with a hepatitis B carrier prevalence (HBsAg) of 8\% or greater by 1995 and in all countries by 1997. This was the first time that targets were set and epidemiological parameters defined for the control and eventual elimination of hepatitis B. Following the endorsement of the recommendations of the Global Advisory Group by the World Health Assembly in May 1992\textsuperscript{12}, the number of countries with hepatitis B vaccine in their national immunization systems rose from 20 countries in 1991 to 80 in 1997, 90 in 1998\textsuperscript{11,9}, 114 in 1999 and 129 in 2000\textsuperscript{13}. By the end of 2000, 32\% of the global birth cohort had received a 3\textsuperscript{rd} dose of hepatitis B vaccine, based on reports from countries to WHO.

The introduction of hepatitis B vaccine into developing countries received a further boost with the formation of the Global Alliance on Vaccines and Immunization (GAVI). GAVI is an international coalition of immunization partners.\textsuperscript{b} GAVI has targeted the 74 countries with per capita GNP less than US $ 1000 for assistance. Globally it is estimated that nearly 37 million children of the 132 million born every year are not receiving basic immunization. The great majority of unreached children, or 28 million, live in developing countries, and of those, 25 million are in the poorest countries\textsuperscript{15}. The strategic objectives of GAVI are ‘to improve access to sustainable immunization services, expand the use of existing cost-effective vaccines, accelerate the development and introduction of new vaccines, and make immunization coverage an integral part of the design and assessment of health systems and international development efforts.’\textsuperscript{14} Hepatitis B is one of the vaccines included in GAVI support to these 74 countries. To date 38 countries have received approval for support for the introduction of hepatitis B vaccines and the rest are in the process of applying for support from the Vaccine Fund. As of June 2002 154 countries have hepatitis B vaccination in their infant immunization programmes (Fig1).

![Fig 1. Global status of countries using HepB vaccine in their national immunization system, May 2002](image-url)
(iii) Impact of hepatitis B immunization

Primary indicators of a positive impact of hepatitis B vaccination may include (1) decline in acute cases of hepatitis B, (2) reduction in the proportion of deaths attributable to cirrhosis of the liver or hepatocellular carcinoma and, (3) falling seroprevalence of HBsAg in vaccinated population. Unlike the situation with other vaccine-preventable diseases, the efficacy of hepatitis B prevention programs is not based solely on surveillance of acute disease. In particular, because most infections in children are asymptomatic, acute disease surveillance will not reliably measure the initial impact of routine infant vaccination. However, trends in acute hepatitis B disease incidence can be used to evaluate the effectiveness of programs directed at adolescents and adults who are more likely to have symptomatic infections after HBV exposure. Because most of the HBV-associated morbidity and mortality is related to chronic infection, demonstrating a reduction in the prevalence of chronic infection in children is the major early indicator of program success. The serious adverse outcomes that are related to the acquisition of chronic HBV infection occur several decades after exposure; thus, much of the benefit of infant immunization on prevention of cirrhosis and liver cancer will not be realized for decades after a program is started.

(a) Impact data from Europe

In the WHO European Region, 35 of 51 reporting countries include hepatitis B vaccine in their national immunization programmes, and several other countries provide hepatitis B vaccine either to adolescent or high risk individuals or pursue a mix of both approaches. Italy was one of the few countries in Europe to introduce hepatitis B vaccination, initially based on a high risk approach, but expanded to cover both infant and adolescents in 1991. Between 1985 and 1996, the prevalence of chronic HBV infection rate has fallen from 3.4% to 0.9% \(^{16}\) with the greatest decline in the age group 15-24 years. Another study \(^{17}\) from Tuscany, Central Italy, between 1992 and 1996 there was a 49% decline in the reported cases of acute hepatitis B in the age group 15 to 24 year olds living in Tuscany with no cases occurring in vaccinated adolescents.
Prior to the introduction of the national program, a “Pilot Project of Universal Immunization” was started in 1983 in a hyper endemic area, Afragola, of southern Italy\textsuperscript{18}. Comparing the incidence of acute viral hepatitis five year before hepatitis B immunization was introduced with the incidence five years after introduction, annual incidence dropped from 63 per 100,000 to 3 per 100,000. The HBsAg carrier prevalence in the general population decreased from 13.4\% in 1978 to 3.7\% in 1997; in children and adolescent it dropped from 6.8\% to 0.7\%, in young people from 10.2\% to 1.1\% and, in adults from 15.8\% to 4.0\%, demonstrating the remarkable impact of mass immunization on the prevalence of hepatitis B.

Following the introduction of immunization with hepatitis B in 1991 in Bulgaria, by 1992 a coverage level of 71.3\% was reached and a dramatic decline in the reported annual incidence of acute hepatitis B in infants was seen, from 22 to 30 per 100,000 in the early 1980s to 5.6 per 100,000\textsuperscript{19}.

(b) Impact data from the rest of the world

In July 1984 Taiwan introduced, one of the earliest countries of the world to do so, infant immunization with hepatitis B. Within ten years of introduction of the vaccine, the HBsAg prevalence declined from 9.3\% to 1.3\%\textsuperscript{21} in children younger than 12 years. (Fig 3)

![Fig 3. HBsAg prevalence rate (%) in <12 yrs old, Taiwan, 1984 to 1994](image)

The incidence of hepatocellular carcinoma in children aged 6 to 14 years declined from 0.7 per 100,000 between 1981 and 1986, to 0.57 per 100,000 between 1986 and 1990, and to 0.36 per 100,000 between 1990 and 1996\textsuperscript{22}. The HBsAg prevalence among persons younger than 15 years of age have declined from 9.8\% in 1984 to 0.7\% in 1999\textsuperscript{23}, thereby reducing a hyper endemic country to that of low endemic status within 15 years of the introduction of hepatitis B immunization programme.

Since hepatitis B vaccination began in the United States in 1982, the prevalence of chronic HBV infection has been reduced substantially among populations whose infection rates previously were high. For example, in 1994, the prevalence of chronic HBV infection among Alaska Natives aged <10 years (i.e. children born after routine vaccination began) was zero, compared with 16\% among Alaska Natives aged 11-30 years\textsuperscript{24}.

The positive impact of mass hepatitis B vaccination, wherever studies were conducted, is demonstrated...
beyond doubt. In Thailand, in less than ten years after vaccination the overall HBsAg prevalence has declined from 3.4% to 0.7% among the 1 to 18 year-olds examined\textsuperscript{25}. In the Gambian Hepatitis Intervention Study\textsuperscript{26}, it was shown the protective efficacy of the vaccine in preventing chronic infection in the first three years of life is estimated to be 95%, and the risk of becoming chronically infected is highest in those infected early in life. Despite a relatively high prevalence of HBV infection in the general population and women of child-bearing age, integrating infant immunization within the current EPI schedule of 6, 10 and 14 weeks has a significant impact on reducing the prevalence of chronic infection, as shown by the South Africa experience where the carrier rate declined from 12.8% in three year-olds to 3.0% within five years of initiation of the vaccination programme. Similarly, in Saudi Arabia, following the introduction of the vaccine, the overall HBsAg prevalence dropped from 6.7% in 1989 to 0.3% in 1997\textsuperscript{20} in children aged 1 to 12 years.

The effectiveness of routine infant hepatitis B immunization in significantly reducing or eliminating the prevalence of chronic HBV infection has been demonstrated in a variety of countries and settings. In general, studies conducted in high HBV-endemic areas have demonstrated declines in the prevalence of chronic HBV among children to <2% after introduction of the vaccine (Table 1). The greatest impact has been achieved in countries that have achieved high vaccine coverage among infants, and where a birth dose of vaccine was administered to infants. In Alaska, where high vaccine coverage among infants has been achieved, and all infants receive a birth dose of vaccine, HBV transmission among children has been eliminated (Harpaz). Many long-term hepatitis B immunization programs have demonstrated a greater than expected benefit in terms of disease reduction when compared with levels of vaccination coverage. A possible reason for this finding is that the pool of individuals that is highly infectious to others is greatly reduced by preventing chronic infections in children. Not only are new infections in children more likely to become chronic, but chronically infected children are likely to be HBeAg positive and highly infectious to others. Thus, by preventing infections in children, the number of HBeAg-positive persons declines rapidly over time because of the inherent clearance of HBeAg in older persons.

### Table 1. Studies evaluating the effectiveness of routine infant hepatitis B immunization in reducing the prevalence of chronic HBV infection in children.

<table>
<thead>
<tr>
<th>Study site (reference)</th>
<th>No. tested*</th>
<th>Follow-up (years)</th>
<th>Vaccine coverage</th>
<th>% Chronic infection Before</th>
<th>After</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska (Harpaz)</td>
<td>268</td>
<td>1-10</td>
<td>96%</td>
<td>16</td>
<td>0.0</td>
</tr>
<tr>
<td>Rural China\textsuperscript{36}</td>
<td>10399</td>
<td>1-9</td>
<td>NA</td>
<td>14.6</td>
<td>1.6</td>
</tr>
<tr>
<td>FSM\textsuperscript{†}</td>
<td>364</td>
<td>3-4</td>
<td>82%</td>
<td>NA\textsuperscript{‡}</td>
<td>1.1</td>
</tr>
<tr>
<td>FSM\textsuperscript{†} (Mahoney)</td>
<td>544</td>
<td>2</td>
<td>37%</td>
<td>12</td>
<td>2.9</td>
</tr>
<tr>
<td>Gambia\textsuperscript{38}</td>
<td>675</td>
<td>9</td>
<td>100%</td>
<td>10</td>
<td>0.6</td>
</tr>
<tr>
<td>Indonesia\textsuperscript{39}</td>
<td>2519</td>
<td>4</td>
<td>&gt;90%</td>
<td>6.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Saipan\textsuperscript{40}</td>
<td>200</td>
<td>3-4</td>
<td>94%</td>
<td>9</td>
<td>0.5</td>
</tr>
<tr>
<td>Samoa\textsuperscript{41}</td>
<td>435</td>
<td>7-8</td>
<td>87%</td>
<td>7</td>
<td>0.5</td>
</tr>
<tr>
<td>Saudi Arabia\textsuperscript{20}</td>
<td>4791</td>
<td>1-8</td>
<td>85%</td>
<td>6.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Shanghai, China</td>
<td>3193</td>
<td>1-9</td>
<td>NA</td>
<td>8.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Taiwan\textsuperscript{21}</td>
<td>424</td>
<td>7-10</td>
<td>73%</td>
<td>10</td>
<td>1.1</td>
</tr>
<tr>
<td>Taiwan\textsuperscript{42}</td>
<td>1337</td>
<td>7</td>
<td>89.7</td>
<td>9.7</td>
<td>0.7</td>
</tr>
<tr>
<td>Taiwan\textsuperscript{43}</td>
<td>1500</td>
<td>6</td>
<td>92.4</td>
<td>10.5</td>
<td>1.7</td>
</tr>
<tr>
<td>Thailand\textsuperscript{44}</td>
<td>3373</td>
<td>0-5</td>
<td>90.4</td>
<td>5.4</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Number of subjects tested in follow-up serosurveys after implementation of programme.
†Federated States of Micronesia.
‡Not available.

iv) Challenges to the expanding of hepatitis B vaccine use
(a) Poor immunization delivery infrastructure and low coverage

In many developing countries the infrastructure for immunization is weak. Following the declaration of the achievement of Universal Child Immunization in the early 1990s, there has not been much support for strengthening routine immunization systems in developing countries and, at the same time, most of these countries lacked the national resources to maintain systems built in the ‘70s and ‘80s. Therefore, in many countries access to basic immunization services has become weak. In many of these countries the cold chain system is rapidly ageing, if not non-functional in many places; lack of trained human resources for immunization and lack of financial resources for routine operational activities such as surveillance and supervision are impediments to expanding access. Therefore, it is not surprising that in many countries the reported coverage even for routine immunization is less than optimal (Fig 4).


Since hepatitis B vaccine is a relatively new entrant within the national immunization programmes of many countries, from the data reported to WHO, hepatitis B vaccination coverage is even lower (Fig 5.). Many countries, particularly developed ones, do not report coverage to the WHO.

Fig 5. Reported Global HepB3 vaccine, 1989-2000

(Source: WHO vaccine-preventable diseases: monitoring system, 2001 global summary)

Therefore, it is necessary to support countries with weak immunization systems to strengthen their programmes if acceptable coverage for vaccination is to be achieved. Further, it is essential that countries strengthen their monitoring systems to demonstrate progress as well as identify areas of weaknesses where
(b) Financial sustainability

Even though a safe and effective hepatitis B vaccine became available since 1982, cost was a major deterrent to countries. However, in the last few years the cost has fallen largely due to economies of scale as well as competition from Asian manufacturers. Despite this, the current quoted price for UNICEF procurement of hepatitis B vaccine is US $0.61 per dose in a single dose vial and US $ 0.25 to 0.43 per dose for a ten-dose vial\textsuperscript{28}. This is still relatively a higher price compared to the less than one dollar for the traditional six routine EPI antigens. Therefore, financial sustainability will continue to be a major challenge for most countries where limited resources must be scattered across competing public health demands.

(c) Missed opportunity

Many countries still pursue either adolescent programmes or high risk targeted strategies for delivering hepatitis B vaccine. While this is consistent with the World Health Assembly resolution of 1992 where it was recommended that countries with carrier prevalence less than 2\% may consider immunization of adolescents as an addition or alternate strategy to infant immunization. Studies indicate that a substantial proportion of potential target groups are likely to be missed by employing high risk strategies\textsuperscript{29}. In at least 30\% of patients with hepatitis B there is no identifiable risk and the current strategy to target occupational risk groups reaches no more than 5\% of those who account for the total disease burden. A third factor is that fewer than 25\% heterosexual exposure can identify a known infected contact, thereby bring forth the importance of recognizing the role of heterosexual activity in the transmission of HBV. Recent analysis of widely available data\textsuperscript{30} also indicates that an adolescent programme is likely to miss a substantial proportion of infection that is acquired during infancy and early childhood even in a country of low endemicity for hepatitis B transmission. These findings strengthen the recommendation that routine universal childhood immunization is the most effective way to reduce the burden of diseases due to HBV infection and there is a potential for substantial missed opportunities for in countries that pursue either adolescent or high risk immunization strategies only.

(d) Concerns about safety of hepatitis B vaccine

While poor countries are still grappling with issues of cost and weak infrastructure, in developed countries there are concerns raised about safety of hepatitis B vaccination that is directly impacting use of the vaccine. Despite robust scientific evidence that hepatitis B vaccine neither causes nor triggers demyelinating diseases including multiple sclerosis (MS)\textsuperscript{31,32,33,34,35}, the debate still continues, fuelled by extensive media coverage on it, resulting in some countries even halting vaccination programmes.

Although concerns have been expressed over the past 20 years that certain chronic illnesses might be caused by hepatitis B vaccine, no evidence exists that any of these diseases is caused by the vaccine. The vaccine continues to be considered safe by WHO, the US Food and Drug Administration, and other national professional vaccination advisory groups. To maintain high hepatitis B vaccine coverage, public health professionals must ensure that safety of hepatitis B vaccine is monitored appropriately through credible scientific studies that assure the public that vaccines are safe.

(v) Conclusion and recommendations

HBV infections contribute to a significant global burden of diseases. Safe and effective vaccines against the disease are available and their use is rapidly expanding, particularly with GAVI and support for the 74
poorest countries of the world. From available data the positive impact of the vaccine in reducing the disease burden due to HBV infection is evident. There are also still many challenges to achieve the goal of universal childhood immunization with hepatitis B. Therefore, to continue to promote access to hepatitis B vaccines worldwide, the following are recommended.

◆ Universal infant immunization is the most effective way to reduce the global burden of diseases due to HBV infection
◆ Development partners, agencies and the global community must support poorer countries to strengthen their health care delivery systems and in particular, national immunization programmes, so that vaccines are delivered safely and high coverage is attained and sustained.
◆ Efforts are needed to support countries to ensure sustained funding for immunization programmes.

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α The Youndé International Conference on Control of Hepatitis B in the Developing World, October 7-9, 1991, was convened by the World Health Organization, The International Task Force on Hepatitis B Immunization, Ministry of Health, Republic of Cameroon, and the University of Youndé.

β GAVI is an international coalition of partners which includes international organizations (WHO, UNICEF, World Bank), philanthropic institutions (Bill & Melinda Gates Children’s Vaccine Programme, Rockefeller Foundation), the private sector (International Federation of Pharmaceutical Manufacturers Association, IFPMA), research and public health institutions. GAVI was officially launched in January 2000 in Davos, Switzerland at the World Economic Forum.