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REVIEW

Hepatitis B vaccine development and implementation

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ABSTRACT

Vaccination against hepatitis B is the most effective strategy to control HBV infection. The first licensed hepatitis B vaccine was developed by the purification of hepatitis B surface antigen (HBsAg) from plasma of asymptomatic HBsAg carriers. Then, the recombinant DNA technology enabled the development of recombinant hepatitis B vaccine. A series of three doses vaccine can elicit long-term protection more than 30 y. Concurrent use of hepatitis B immunoglobulin and hepatitis B vaccine has substantially reduced the mother-to-child transmission of HBV, nearly zero infection in children of carrier mother with negative hepatitis B e antigen (HBeAg) and 5–10% infection in children of HBeAg-positive mothers. By the end of 2018, 189 countries adopted universal hepatitis B vaccination program, which has dramatically reduced the global prevalence of HBsAg in children <5 y of age, from 4.7% in the prevaccine era to 1.3% in 2015. However, the implementation of universal hepatitis B vaccination in some regions is suboptimal and timely birth dose vaccine is not routinely administered in more than half of newborn infants. Optimal worldwide universal hepatitis B vaccination requires more efforts to overcome the social and economic challenges.

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Introduction

Chronic hepatitis B virus (HBV) infection is a serious health problem. Although antiviral agents against HBV have been widely applied to treat chronic hepatitis B, the drugs cannot completely eliminate the virus in the host. Vaccination against hepatitis B is the most important strategy to control HBV infection. The unexpected discovery of "the Australia antigen" in 1964,[1] which was designated as "hepatitis associated antigen" in 1969 and was formally changed to hepatitis B surface antigen (HBsAg) in 1972 after visualization of Dane particles (HBV virions) with electron microscope in 1970,[2] opened the way to develop hepatitis B vaccine.

Development of hepatitis B vaccine

Plasma hepatitis B vaccine

HBV cannot efficiently replicate in cell cultures, indicating that it is impossible to develop hepatitis B vaccine based on in vitro culture system. Dr Krugman and his colleagues conducted the pioneering work on developing hepatitis B vaccine. They showed that boiling destroyed the infectivity of HBV carriers' plasma,[3] active immunization of individuals with the boiled plasma induced antibodies against HBsAg (anti-HBs) and the immunized subjects were partially protected against HBV challenge,[4] and hepatitis B immunoglobulin (HBIG) showed effective in preventing HBV infection in human.[5] These studies demonstrated the possibility of viral antigens naturally produced in HBV carriers in developing hepatitis B vaccine.

Electron microscopy found that the 22-nm spherical particles (HBsAg) in the circulation of HBV carriers are much excess over the 42-nm HBV virions,[2] and the concentration of circulation HBsAg is as high as 200 μg/mL.[6] Meanwhile, chimpanzees were found to be susceptible to human HBV infection,[7] which provided an animal model to evaluate the efficacy and safety of hepatitis B vaccine. Given the high concentrations of circulation HBsAg, HBsAg purified from the plasma of asymptomatic carriers had been extensively studied to develop the hepatitis B vaccine.

The purification of plasma HBsAg usually included isopycnic banding and rate zonal separation by ultracentrifugation, chemical purification procedures, and the treatment of purified HBsAg with formalin to eliminate the potential HBV contamination.[8,9] The chimpanzees immunized with the purified HBsAg were protected against HBV challenge.[10] As the candidate vaccine was derived from the plasma of HBV carriers, who were likely co-infected with other pathogens such as HIV, the preparation of plasma-derived hepatitis B vaccine consisted of a series of steps that can exclude and destruct all known animal viruses tested then, including ultracentrifugation, digesting the partially purified HBsAg with pepsin at pH 2, unfolding the HBsAg in 8 M urea solution followed by renaturation, gel filtration, treating the purified HBsAg in formalin.[11] Extensive studies confirmed the safety and high efficacy of hepatitis B vaccine in preventing acute hepatitis B,

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asymptomatic infection, and chronic HBV carrier,[12-14] leading to the first licensed vaccine in USA in November 1981,[15] and in France in 1982.[16] The licensed plasma hepatitis B vaccine became commercially available in 1982. Although HBV is classified into various serotypes, all isolates of HBV share the *a* antigenic determinant and hepatitis B vaccine is subtype cross-protective.[17]

Recombinant hepatitis B vaccine

While the plasma hepatitis B vaccine is safe and effective, the relatively high cost of the vaccine limited its widespread use. The theoretical safety concerns associated with the plasma from HBV carriers who may be co-infected with HIV and other pathogens also impeded the use of this vaccine. Additionally, the HBV-infected human plasma source is restricted, particularly when the prevalence of HBsAg has decreased after the vaccination against HBV. These factors led to search for alternative hepatitis B vaccines.

The successful cloning of HBV S gene in bacteria showed the possibility of using recombinant HBsAg as hepatitis B vaccine.[18,19] Since the HBsAg synthesized in bacteria is not able to properly assemble as particles similar to those in natural infection in human, the expression of the S gene was tried in eukaryotic systems. The HBsAg synthesized in the yeast Saccharomyces cerevisiae is able to assemble into particles similar to the 22-nm particles produced in human.[20] The hepatitis B vaccine composed of HBsAg purified from the recombinant yeast cells potently induced anti-HBs response in mice, monkeys, and chimpanzees, and the vaccinated chimpanzees were completely protected against intravenous challenge of homologous or heterologous human HBV.[21] Extensive clinical trials in human demonstrated that the recombinant yeast hepatitis B vaccine was safe and had comparable quantity, quality, specificity of anti-HBs response, and similar protective efficacy as human plasma vaccine did.[22–27] In 1986, the recombinant HB vaccine was approved by the USA Food and Drug Administration. Since then, the recombinant hepatitis B vaccine has gradually replaced the plasma hepatitis B vaccine. In the mainland China, production of plasma hepatitis B vaccine was discontinued in 2000. Since 2001, all hepatitis B vaccines used in China have been composed of recombinant HBsAg.[28] Currently, plasma hepatitis B vaccine is no longer used worldwide and all hepatitis B vaccines contain recombinant HBsAg.

Newly licensed hepatitis B vaccine

A new hepatitis B vaccine, named HEPLISAV-B®, was licensed for adults ≥18 y old in 2018, and the new vaccine requires just two doses at 1 month interval,[29] instead of three doses during a 6-month period. The HEPLISAV-B, which had been named HBsAg-1018 ISS before it was approved, contains recombinant HBsAg combined with a novel, Toll-like receptor 9 agonist adjuvant, an oligodeoxynucleotide that contains immunostimulatory CpG motifs, which can stimulate B cells and plasmacytoid dendritic cells by binding to Toll-like receptor 9.[30]

In clinical trials in adults at age 40–70 y, the anti-HBs seroprotection (anti-HBs ≥10 mIU/mL) rate in subjects vaccinated with HBsAg-1018 ISS was 96.6% at 4 weeks following the second injection, higher than 24.0% in subjects vaccinated with the conventional hepatitis B vaccine, and at 4 weeks after the third vaccination, the seroprotection rate had also significant difference in subjects injected with HBsAg-1018 ISS and conventional vaccine (100% vs. 73.1%), demonstrating that HBsAg-1018 ISS is superior to the conventional vaccine.[31] A further clinical trial in adults at age 40–70 y demonstrated that the seroprotection rate in subjected injected with two doses of HBsAg-1018 ISS at an interval of 4 weeks was significantly higher than that in subjects who received three doses of conventional hepatitis B vaccine at week 28 following the first vaccination (94.8% vs. 72.8%), demonstrating that HBsAg-1018 with two doses is superior to conventional hepatitis B vaccine with three doses,[32] which was further proved in healthy adults at age 18–70 y.[33] Other studies in patients with chronic kidney disease or with chronic kidney disease and type 2 diabetes mellitus showed that three doses (20 μg HBsAg) of HBsAg-1018 at week 0, 4, and 24, respectively, had higher seroprotection rate than four double doses (40 μg HBsAg) of conventional hepatitis B vaccine at week 0, 4, 8, and 24, respectively,[34,35] while the safety of the new vaccine is comparable to that of the conventional hepatitis B vaccine.[36]

The newly licensed hepatitis B vaccine can elicit higher anti-HBs response more rapidly, which can provide earlier protection. The two-dose schedule at 1 month interval can increase the adherence of full vaccination. While the new vaccine does not have additional side effects in clinical trials, the long-term safety data remain further observation.

Therapeutic hepatitis B vaccine

It is known that the clearance of HBV in host requires both the innate and adaptive humoral and cellular immune responses. The elimination of virions in hepatocytes is mainly dependent upon the T-cell responses. Thus, great efforts have been taken to develop therapeutic hepatitis B vaccine using different genes of HBV, including P, C, S and/or pre-S gene, with various techniques, based on protein, protein-antibody complex, peptide, or DNA, to stimulate the humoral and/or cellular immune responses.[37-40] However, although the therapeutic vaccines elicited specific humoral and/or cellular immune responses in human or experimental animals and showed promising therapeutic effects in some experimental animals,[37,38] the clinical efficacy of the therapeutic vaccines is limited.[40-42] Thus, far more breakthrough studies are required to develop effective therapeutic vaccines against hepatitis B in human.

Administration of hepatitis B vaccine

Dosage, schedule, and injection route of hepatitis B vaccine

Initially, the HBsAg quantity of plasma hepatitis B vaccine was 20 or 40 μg per dose. A full course of vaccination requires three injections at 0, 1, and 6 months, respectively, named the

three-dose schedule. Because of its high cost and restrictive supply, the immunogenicity and protective efficacy of reduced dosage of hepatitis B vaccine had been studied, which appeared to be also effective.[43,44] However, as HBsAg synthesized in yeast shares the characters of natural HBsAg in human plasma except for glycosylation and the supply of recombinant HBsAg is unlimited, reduced dose of hepatitis B vaccine was no longer considered to a wise idea.[45]

Currently, a dose of hepatitis B vaccine contains 5–40 μg of recombinant HBsAg adsorbed on aluminum hydroxide or aluminum phosphate adjuvant, which is flexibly applicable in different subpopulations (Table 1). Usually, the dose for the infants, children and adolescents is half of the dose used for adults.[46] The vaccination course is still the three-dose schedule. In mainland China, the recommended dosage for infants born to HBsAg-negative and HBsAg-positive mothers was 5 and 10 μg, respectively.[28] Since 2011, the dosage has been switched to 10 μg for all infants, regardless of the maternal HBsAg status.

Hepatitis B vaccine should be intramuscularly injected on the anterolateral site of the thigh (for infants and children aged <2 y) or into the deltoid muscle (for older children and adults). It is not recommended to inject the vaccine into the buttock because this route appears to elicit decreased anti-HBs levels, probably associated with obesity,[47] and may potentially impair the sciatic nerve. When the gluteal muscle has to be used, it should avoid the central region of buttock, but use the upper outer quadrant. In the case of post-exposure prophylaxis, HBIG (passive immunoprophylaxis), and hepatitis B vaccine should be administered at different sites.

Indications and contraindications

Hepatitis B vaccine is recommended for all infants (universal vaccination) and children who did not receive hepatitis B vaccine during infancy (catch-up vaccination). For adults, it is generally recommended for those who are at increased risk for infection, including all medical, dental, laboratory, and other health care staff of hospitals, intimate contacts, or family members of HBV carriers, at-risk patients (chronic kidney diseases with hemodialysis, thalassemia, diabetes mellitus, co-infection of hepatitis C virus or HIV), and special groups such as homosexual males, commercial sexual workers, users of illicit drugs, and other high-risk groups.[48] In theory, anyone who is susceptible to HBV (negative for HBsAg, anti-HBs, and anti-HBc) may receive the vaccination except for those who have a contradiction.

A known history of anaphylaxis or serious adverse events after first injection of hepatitis B vaccine is a contraindication for further vaccination. It should also be cautious to vaccinate in individuals with history of allergic to yeast. Additionally, hepatitis B vaccination should be delayed in an individual with an acute or febrile disease. Hepatitis B vaccine does not have additional side effects in pregnant women and can be used during any trimester of pregnancy.

Table 1. Selected recombinant hepatitis B vaccine internationally or locally applied.

Vaccine name	Company, Country	HBsAg (μg)/volume (mL)	Other vaccine	Applicable subject
Engerix-B	GlaxoSmithKline, USA	10/0.5	None	From birth to age 19 y
		20/1.0	None	Adults (≥20 y)
		40/2.0	None	Immunocompromised individuals
Recombivax HB	Merck & Co, USA	5/0.5	None	From birth to age 19 y
		10/1.0	None	Adults (≥20 y)
		40/1.0	None	Immunocompromised individuals
Hepavax-Gene	Berna, Korea	10/0.5	None	Infants and children
		20/1.0	None	Adults
Euvax-B	Lucky Goldstar Chemical, Korea	10/0.5	None	Infants and children
		20/1.0	None	Adults
Revac-B	Bharat Biotech, India	10/0.5	None	≤10 y old children
		20/1.0	None	>10 y old children and adults
Heberbiovac-HB	Heber Biotec, Cuba	10/0.5	None	≤10 y old children
		10/1.0	None	>10 y old children and adults
HBvaxPro	MSD Pharma, Singapore	5/0.5	None	Pediatric/adolescent
		10/1.0	None	Adults
		40/1.0	None	Predialysis/dialysis patients
Hanxin	Hiss Bio, China	10/0.5	None	All ages
		20/1.0	None	All ages
Tiantan	Tiantan, China	10/0.5	None	<16 y
		20/1.0	None	≥16 y
Kangtai	Kangtai, China	10/0.5	None	<16 y
		20/1.0	None	≥16 y
Twinrix	GlaxoSmithKline, USA	20/1.0	Hepatitis A	1–15 y old
		20/1.0	Hepatitis A	Adult and adolescent ≥16 y
Pediarix	GlaxoSmithKline, USA	10/0.5	DTP/IPV	6 weeks to 6 y old
EasySix	Panacea Biotec, India	10/0.5	DTP-Hib/IPV	6 weeks to 6 y old
Pentavac SD-R	Human Biologicals, India	10/0.5	DTPa-/Hib	6 weeks to 6 y old
Quinvaxem	Crucell, Netherlands	10/0.5	DTPa-/Hib	age 6 weeks to 24 months
Hexaxim	Sanofi Pasteur, France	10/0.5	DTPa-IPV/Hib	age 6 weeks to 24 months

DTPa-/Hib: diphtheria, tetanus, pertussis, and Haemophilus influenzae type b
IPV: inactivated polio vaccine.

Combination with other vaccines

Of 189 countries incorporated hepatitis B vaccine in Expanded Program on Immunization, 109 have introduced birth dose of hepatitis B vaccine in newborn infants within 24 h after birth, with an overall global coverage 42%,[49] and other countries have not taken the policy of offering birth dose in newborn infants. These countries offer the first dose of hepatitis B vaccine together with four or five other vaccines conjugated into one vial, which includes each vaccine against diphtheria, tetanus, pertussis, Haemophilus influenzae type B, and hepatitis B (pentavalent, DTaP5-HBV-Hib), and polio (hexavalent, DTaP5-HBV-IPV-Hib). The vaccination schedule somewhat varies in different regions, scheduled at the age of 2, 4, and 6 months (the standard schedule in Latin America and Asia), at the age of 2, 3, and 4 months (the accelerated schedule in Europe), or at the age of 6, 10, and 14 weeks (expanded program of immunization schedule in South Africa and India).[50] Generally, the anti-HBs seroconversion rate and the persistence of the immunity in the vaccinees appear to be comparable to those vaccinated with hepatitis B vaccine alone.[50–52] However, the multivalent vaccine is not administered until 6 weeks or 2 months of age, leaving the infants susceptible to HBV during the very early life period. This is particularly for infants born to HBsAg-positive mothers or in families with other members with HBV infection. To overcome this problem, some countries adopt a combination of HBIG and hepatitis B vaccine in infants born to HBsAg-positive mothers at birth, and another dose of hepatitis B vaccine at 1 month of age if necessary, followed by three doses of pentavalent or hexavalent vaccine containing hepatitis B vaccine at scheduled time points.[53,54]

Immunogenicity, protection duration, and safety of hepatitis B vaccine

Immunogenicity of primary hepatitis B vaccination

A full course of primary hepatitis B vaccination requires three doses, usually at 0, 1, and 6 months schedules. An early study showed that, among 1.5–16 y old children vaccinated with plasma vaccine (16 μg HBsAg) prepared by the National Institute of Allergy and Infectious Diseases, USA, anti-HBs seroconversion reached 59% two weeks following the first dose and reached 100% one month after the second dose.[55] Most of infants who are vaccinated with 5 or 10 μg recombinant HBsAg produce undetectable anti-HBs or anti-HBs <10 mIU/mL after the first injection; the seroconversion rate (anti-HBs ≥10 mIU/mL) 1 month after the first dose was only 3% in infants vaccinated with 5 μg HBsAg,[56] or 7–9% in infants vaccinated with 10 μg HBsAg.[57,58] The anti-HBs seroconversion rate reaches 80–100% after the second injection.[56,57,59] Anti-HBs response is significantly enhanced after the third injection, with an overall 97–100% anti-HBs ≥10 mIU/mL,[56,58,60] and over 80% with anti-HBs ≥100 mIU/mL and over 40% with anti-HBs ≥1000 mIU/mL 1–5 months following the third dose.[60] Among the remaining infants who are assumed anti-HBs negative (<10 mIU/mL), there are still anti-HBs (6–8 mIU/mL) in the circulation.[60] Therefore, the recombinant hepatitis B vaccine is highly immunogenic.

The immunogenicity of hepatitis B vaccine in adults is somewhat lower than that in infants and children. After vaccinated with three serial doses of 20 μg HBsAg, the average seroprotection rate is more than 90% in adults, relatively higher in younger and lower in older, and drops to 60–70% in adults over age 60 y.[61] The immunogenicity of hepatitis B vaccine in high-risk subpopulations is considerably varied, ranging from >90% seroprotection rate in healthcare workers and young homosexual men to as low as 20–60% in patients with immunocompromised conditions, such as chronic renal disease or dialysis, type 2 diabetes mellitus, transplant recipients, chronic liver disease, inflammatory bowel disease, infection of HIV, and various cancers.[61] Therefore, higher vaccine dosage of HBsAg is required in the immunocompromised individuals, and sometimes it requires repeating another three serial doses of hepatitis B vaccine.[61] In addition, the newly licensed hepatitis B vaccine appears to induce higher anti-HBs response in immunocompromised patients.[34,35]

Long-term protection after primary hepatitis B vaccination

Studies demonstrated that the primary hepatitis B vaccination can provide long-term protection, more than 30 y in vaccinated children and adults.[62] Although it is still a concern whether the long-term protection in vaccinees who received reduced quantity of HBsAg (2.5 μg dosage, Recombivax-HB, Merck) or in individuals with high-risk of HBV exposure, such as healthcare workers, the immunity to HBV is appropriately maintained.[63,64] A booster dose in vaccinees who previously received primary hepatitis B vaccination during infancy appears not required, because the vaccinees with anti-HBs <10 mIU/mL or undetectable have brisk anamnestic immune response to HBsAg and authentic breakthrough infection of wild-type HBV with severe outcomes (acute hepatitis B or chronic carrier) in successfully vaccinated individuals is extremely rare.[65] Nevertheless, ongoing surveillance of vaccinees is required to clarify whether primary hepatitis B vaccination can confer longer or even lifelong protection.

Side effects

Numerous studies and widespread practical applications have demonstrated that hepatitis B vaccines are very safe.[66,67] Local reactions to hepatitis B vaccine, generally mild and transient, are the most reported side effects in children and adults. Anaphylaxis is the only serious adverse event that may occur following hepatitis B vaccination, with an estimated incidence of 1 case in 600,000 vaccine doses.[68]

Hepatitis B vaccination in newborn infants is not associated with febrile episodes, sepsis, neurologic events, or neonatal death.[69,70] To date, there is no evidence to ascertain the association of hepatitis B vaccine with other reported serious adverse events, including arthritis, Guillain-Barré syndrome, transverse myelitis, sudden infant death syndrome, and other chronic diseases such as multiple sclerosis, optic neuritis, chronic fatigue syndrome, and autoimmune disorders. No evidence of an association between hepatitis B vaccine and central demyelination was found.[71]

Reports of serious adverse events after hepatitis B vaccination are exceedingly rare. A case of serious adverse event after receipt of hepatitis B vaccine cannot be ascertained to a true causal association or a coincidental relationship. Therefore, it should be cautious to get a concrete conclusion based on the case reports. The release of inconclusive results by news media has negative impact for the implementation of universal hepatitis B vaccination.[72,73] Nevertheless, potential health risks associated with the vaccines should be continuously monitored.

Implementation of universal hepatitis B vaccination

Selective vs. universal hepatitis B vaccination

There are two hepatitis B vaccination strategies, universal vaccination in all infants and selective vaccination with concurrent use of hepatitis B vaccine and HBIG in HBV-exposed individuals such as infants born to HBsAg-positive mothers. When hepatitis B vaccine was initially licensed, most countries adopted selective vaccination because of the cost and restrictive supply of the vaccine. However, selective vaccination program targeting neonates with HBV exposure does not protect against horizontal transmission. Universal vaccination is the only practical strategy to achieve global eradication of hepatitis B.

Universal hepatitis B vaccination

Since the recombinant DNA technology can produce unlimited supplies of hepatitis B vaccine, it becomes feasible to prepare sufficient hepatitis B vaccine for the worldwide use. The World Health Organization (WHO) recommended in 1991 that all countries implement universal hepatitis B vaccination by 1997 to prevent and control on a global scale HBV infection.[74] This recommendation promoted all countries to incorporate hepatitis B vaccine into their national immunization program. However, worldwide implementation of universal vaccination is not an easy task. By 2000, only 116 of 215 countries adopted this policy, representing 31% of the global birth cohort.[75] In hepatitis B endemic regions, where economics is usually less developed, lack of funds is the main reason, whereas in the low-endemic regions, universal infant vaccination appears to be less importance, leading to reluctant to adopt this policy. Japan and UK did not take the universal vaccination policy until 2016 and 2017, respectively.[76-78]

The role of global alliance for vaccines and immunization in implementation of universal hepatitis B vaccination

Global Alliance for Vaccines and Immunization (GAVI), created in early 2000, initially supported by the Bill and Melinda Gates Foundation and currently supported by multiple partners, has played an important role in promoting implementation of universal hepatitis B vaccination in low and middle income countries. Following the first awards of vaccinating four million children against hepatitis B in 21 recipient countries in 2000,[79] universal infant hepatitis B vaccination program has been intensified in developing countries, including China and India, the two largest birth cohorts in the world. During 2011–2020, GAVI supported hepatitis B vaccination in children in 73 countries.[80] This resulted in a dramatic increase in vaccine coverage in infants from 1% in 1990 to 84% in 2015.[81] By the end of 2018, 189 countries adopted universal hepatitis B vaccination policy. Global coverage with three doses of hepatitis B vaccine is estimated at 84%, with the highest in the Western Pacific (maintained 90–91% during 2014–2018). In addition, 109 countries introduced birth dose to newborn infants within the first 24 h of life, and the global coverage is 42%.[49]

Prevention of mother-to-child transmission of HBV by hepatitis B vaccination

Infants born to HBV-infected mothers are at a risk for HBV infection. The main risk for perinatal infection is maternal high viral load (HBV DNA $>10^6$ IU/mL) or maternal positive for hepatitis B e antigen (HBeAg); HBeAg is well correlated with high viral load and is a marker of high viral load, since 80–90% HBeAg-positive mothers have HBV DNA $>10^6$ IU/mL.[82-84] Without prophylaxis measures, 70–90% of infants born to HBV carrier mothers with positive HBeAg are chronically infected, while 10–30% of infants born to carrier mothers with negative HBeAg are likely to become chronic infection. Therefore, prevention of mother-to-child transmission is critical in the control of chronic HBV infection.

Before the availability of hepatitis B vaccine, HBIG had been prepared and demonstrated to be effective in preventing perinatal HBV infection. Further studies showed that concurrent use of HBIG and hepatitis B vaccine in infants born to HBeAg-positive mothers has better protective efficacy than the use of either HBIG or hepatitis B vaccine alone. Thus, administration of HBIG and/or hepatitis B vaccine in infants of HBsAg-positive mothers has been recommended to prevent mother-to-child transmission of HBV.[85] Table 2 shows that the efficacy of concurrent use of HBIG and hepatitis B vaccine in newborn infants within 12 or 24 h after birth; the transmission has reduced from 10–30% to nearly 0% in children of HBeAg-negative carrier mothers, and from 70–90% to 4–12% in children of HBeAg-positive mothers. More recently, studies showed that more rapid (within 1 h after birth) use of HBIG and the vaccine in infants of HBeAg-positive mothers further reduced the transmission rate to 1.3–2.0%.[97,98]

Since HBIG is not easily available in some regions, the protection efficacy of hepatitis B vaccine alone was also investigated in infants born to HBV-infected mothers. An early study showed that, use of plasma hepatitis B vaccine alone, chronic HBV infection in infants born to mothers with positive HBsAg and HBeAg was 21%, remarkably lower than 73% of infants who were not vaccinated at all.[43] In Vietnamese newborn infants, with administration of recombinant hepatitis B vaccine alone, none of 102 infants born to HBV-infected mothers with negative HBeAg was infected, while 14.6% (12/82) infants born to mothers with positive HBsAg and HBeAg was infected.[99] Other studies also showed that hepatitis B vaccine alone in infants of HBeAg-negative carrier mothers appeared to be similarly effective, compared to the combination of HBIG and hepatitis B vaccine in preventing mother-to

Table 2. Mother-to-child transmission of HBV in children of HBV-infected mothers after neonatal immunoprophylaxis.

Region	Child birth year	No of HBsAg+ children/no of children (%)		No of HBsAg+ children/total no of children (%)
		Maternal HBeAg(−)	Maternal HBeAg(+)	
Singapore[86]	1980s	0/670 (0)	41/345 (11.88)	41/1015 (4.0)
Taiwan[87]	1996–2008	4/1773 (0.23)[a]	54/583 (9.26)	58/2356 (2.5)
Taiwan[88]	2007–2013	0/364 (0)	19/162 (11.7)[b]	19/526 (3.6)
China, south[89]	2006–2010	0/887 (0)	21/473 (4.4)	21/1360 (1.5)
China, northwest[90]	2008–2012	0/751 (0)	39/435 (8.97)	39/1186 (3.3)
China, northeast[91]	2012–2015	0/565 (0)	16/306 (5.2)	16/871 (1.8)
China, central and east[92]	2010–2012	0/758 (0)	20/419 (4.8)	20/1177 (1.7)
China, east[93]	2012–2015	0/126 (0)	6/164 (3.7)	6/290 (2.1)
Hong Kong[94]	2014–2016	0/486 (0)	7/155 (4.5)	7/641 (1.1)
USA[95]	1997–2010	1/2317 (0.04)	21/624 (3.37)	22/2941 (0.7)
USA[96]	2007–2013	0/772 (0)	12/362 (3.3)	12/1134 (1.1)

[a]Three of the four HBV-infected children were not administered HBIG after birth.
[b]Atleast 10 of the 19 HBV-infected children were injected with hepatitis B vaccine within 2–20 d after birth, but not within 24 h after birth (Wen WH, Chang MH, Zhao LL, et al. J Hepatol. 2013;59:24–30.).

-child transmission.[100,101] These results indicate that, in resource limited regions where HBIG is not available or prenatal HBsAg screening is not routinely performed, universal hepatitis B vaccination in newborn infants can also effectively prevent mother-to-child transmission in infants born to HBsAg-positive mothers, which emphasizes the importance of birth dose vaccine in infants in preventing perinatal HBV infection. However, in regions where HBIG is available, HBIG should still be administered in infants of HBeAg-negative carrier mothers in addition to the vaccine. HBIG is safe and has minimal side effects and the only concern is the cost. Infants born to HBeAg-negative carrier mothers are exposed to HBV during birth process; infants who were administered the vaccine alone showed to be more likely to have infection than those who were administered both HBIG and the vaccine in studies with much larger number of participants.[87,102] Thus, use of both HBIG and the vaccine should be the first choice of immunoprophylaxis in infants born to HBeAg-negative carrier mothers.[103] Since 2011, China has taken a policy to administer charge-free HBIG and hepatitis B vaccine in all infants born to HBsAg-positive mothers, regardless of maternal HBeAg status.

Challenges in the implementation of universal hepatitis B vaccination

Although recombinant hepatitis B vaccine can be produced unrestrictedly, globally universal vaccination requires sufficient qualified staff, nationally complete immunization program, safe injection equipment, adequate transportation, storage of the vaccine, and others. Based on the WHO reports, the HBsAg prevalence in African region and in some countries, such as Philippine, is relatively high,[81,104] indicating that the universal hepatitis B vaccination has not been taken well. In India, the vaccination coverage is enormously varied in different districts, and 45% of the children at age 1–5 y had not been vaccinated against hepatitis B during 2015–2016.[53]

Traditionally, hepatitis B vaccine should be transported and stored at 2–8°C, so-called cold chains, which is financially costing and has negative influence on the universal vaccination in countries where cold chains are not always available. However, studies demonstrated that hepatitis B vaccine is heat stable. The reactogenicity and immunogenicity of recombinant DNA hepatitis B vaccines stored at 37°C for 1 week, or 1 month, or at 45°C for 1 week, were comparable to those of the vaccine stored at 4°C.[105,106] When stored at 37°C for 7 months or 12 months, or at 45°C for 3 months, the potency of the vaccine is still adequate.[107,108] In the practical application, stored at ambient temperatures for 1 month or 3 months, the immunogenicity of the vaccine is same as that of the vaccine stored in cold chain.[109-111] These results clearly show that hepatitis B vaccine can be stored at ambient temperatures, however, all vaccine manufacturers recommend that the hepatitis B vaccines be stored at 2–8°C. Thus, transportation and storage of hepatitis B vaccine at ambient temperatures may be practically meaningful to raise the birth dose coverage in resource limited or remote regions.

Another factor that affected the universal implementation of hepatitis B vaccine is news release of unconfirmed adverse events, or scandals, attributed to the vaccine. This occurred in France in 1990s and in mainland China in 2014.[72,73] The scandals may destruct the confidence of physicians and publics on the safety of hepatitis B vaccine, leading to the decline of the vaccination in some infants. Rapid response with scientific evidence by both the health authority and academic society to the scandals and extensive communications with the media and public are required to minimize the negative impact and reestablish public trust on the safety of hepatitis B vaccine.[73]

Impact of universal hepatitis B vaccination on HBV infection

Decline of incidence of acute hepatitis B

In the regions where universal hepatitis B vaccination has been adopted, the incidence of acute hepatitis B has significantly reduced. In Alaska of USA, where hepatitis B was endemic, the universal hepatitis B vaccination program, including prevention of perinatal HBV infection, routine infant vaccination, and catch-up vaccination of older children and adults, eliminated the new HBV infections.[112] In Hong Kong, where

universal hepatitis B vaccination was started from 1988, the reported number of acute hepatitis B decreased steadily from 250 cases in 1988 to 41 cases in 2014.[113] In mainland China, the data from the enhanced sentinel surveillance in 200 counties showed that the annually reported incidence of acute hepatitis B dropped from 6.7/100,000 during 2009–2012 to 3.1/100,000 during 2013–2016.[114] In addition, the prevalence of anti-HBc (a marker of resolved acute infection in the absence of HBsAg), has been decreased from 31.5–41.9% before universal vaccination to 2.0–3.0% after universal vaccination in mainland China.[115]

Decline of HBsAg prevalence

Table 3 shows the representative results of declined prevalence of HBsAg in populations born after the implementation of universal hepatitis B vaccination. Based on the WHO estimation, the global prevalence of chronic HBV infection in children <5 y of age was reduced from 4.7% in the prevaccine era to 1.3% in 2015, varied in different regions, 0.2% in Region of the Americas, 0.4% in European Region, 0.7% in South-East Asia Region, 0.9% in Western Pacific Region, 1.6% in Eastern Mediterranean Region, and 3.0% in African Region.[81] The greatest achievement appears to be the substantial decline of HBsAg prevalence in the Western Pacific Region, where birth-dose hepatitis B vaccine has been routinely administered, from 8.3% in prevaccine era to 0.93% during 2002–2015.[104] After universal hepatitis B vaccination, it appeared that almost no chronic HBV infection occurs in children born to HBsAg-negative mothers.[121,122]

In addition, HBsAg prevalence in general young adults has also significantly declined in countries or regions where the universal hepatitis B vaccination program was adopt from the later of 1980s to early of 1990s. The prevalence of HBsAg in young adults aged 18–29 y in Taiwan in 2014 was 0.7% (9/1246),[117] far lower than over 10% in prevaccine era. In Singapore, the HBsAg prevalence was 1.1% among young adults aged 18–29 y in 2010, around half of the prevalence in 1998 and 2004.[123] In Hong Kong, HBsAg prevalence in pregnant women born before 1983 (prevaccine era), during 1983–1988 (selective vaccination in infants born to HBsAg-carriers) and after 1988 (universal vaccination) was 8.8%, 7.0%, and 3.1%, respectively.[124] These investigations demonstrated that universal hepatitis B vaccination in infancy has long-term impact on the prevalence of HBsAg in young adults. The universal hepatitis B vaccination in China has changed the prevalence of HBsAg from ~10% in prevaccine era to below 4.8% in general population in 2018.[125] It can be anticipated that the chronic HBV infection rate in countries where universal hepatitis B vaccination has been adopted will also be significantly reduced in the near future.

Decline of incidence of HCC and other liver diseases in children

As the etiology of HBV infection in the pathogenesis of hepatocellular carcinoma (HCC) has been well established, it is expectable that universal hepatitis B vaccination can also reduce the incidence of HCC in vaccinees. The study from Taiwan showed that the incidence ratio in children aged 6–14 y dropped from 4.5 per 100,000 before the universal vaccination to 1.9 in children 6–12 y after start of the vaccination program.[126] Long-term follow-up studies added more evidence of preventing the occurrence of HCC in vaccinees,[127,128] or even eliminating HCC in Alaska Native people of USA after universal hepatitis B vaccination.[129] Additionally, the implementation of universal hepatitis B vaccination has also decreased the incidence of fulminant hepatitis B and chronic liver diseases associated mortality in vaccinees.[129,130]

Table 3. Prevalence of HBsAg and anti-HBs in children and young adults after universal vaccination in selected regions.

Region	Initiation of Universal vaccination	Study period	Age (Y)	No	HBsAg+ (%)	Anti-HBs+ (%)
Alaska, USA[116,a]	April 1983	12/1993–1/1994	2–5	121	0 (0)	30/120 (25.0)
			6–10	150	0 (0)	56/146 (38.4)
			11–15	118	9 (7.6)	68/87 (78.2)
			16–20	60	11 (18.3)	28/30 (93.3)
			21–25	62	13 (21.0)	17/21 (81.0)
			26–30	92	20 (21.7)	19/20 (95.0)
Taiwan[117]	1986	1/1/2014–12/31/2014	<1–29	3299	17 (0.52)	1564 (47.4)
Singapore[118]	1987	8/2008–7/2010	1–6	400	0 (0)	255 (63.8)
			7–12	400	1 (0.30)	131 (32.8)
			13–17	400	3 (0.75)	94 (23.5)
China[119]	2002	9/2006–10/2006	1–<5	13276	(1.0)	(71.2)
			5–<10	11909	(1.4)	(55.5)
			10–<15	11844	(3.2)	(57.5)
China[120,b]	2002	10/2014–12/2014	>0.6–3	1270	2 (0.16)	1210 (95.3)
			4–6	822	3 (0.36)	733 (89.2)
			7–9	752	1 (0.13)	662 (88.0)
			10–12	598	6 (1.00)	504 (84.3)
China[115]	2002	10/2014–12/2014	1–4	12681	(0.3)	(71.6)
			5–14	9738	(0.9)	(52.9)
			15–29	9294	(4.4)	(56.9)

[a]The positive rate of anti-HBs was calculated with fully vaccinated subgroup as denominator.
[b]This study defined anti-HBs ≥2 mIU/mL as having immunity to hepatitis B.

Future directions

The currently available hepatitis B vaccine is safe and highly effective in the prophylaxis of HBV infection, yet the implementation of universal vaccination and timely birth dose is suboptimal. Although the hepatitis B vaccine appears to be thermostable and the vaccine stored at ambient temperature appears to have equivalent efficacy as the hepatitis B vaccine stored in cold chain, more evidence on the efficacy of hepatitis B vaccine transported and stored in ambient environments will be greatly valuable to improve the implementation of universal hepatitis B vaccination and timely birth dose in resource-limited regions and remote areas. Development of two-dose vaccine applicable in infants with comparable efficacy will be more convenient to implement universal hepatitis B vaccination.

Disclosure of potential conflicts of interest

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References

1. Blumberg BS, Alter HJ, Visnich S. A "new" antigen in leukemia sera. JAMA. 1965;191(7):541–46. doi:10.1001/jama.1965.03080070025007.
2. Dane DS, Cameron CH, Briggs M. Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. Lancet. 1970;1(7649):695–98. doi:10.1016/s0140-6736(70)90926-8.
3. Krugman S, Giles JP, Hammond J. Hepatitis virus: effect of heat on the infectivity and antigenicity of the MS-1 and MS-2 strains. J Infect Dis. 1970;122(5):432–36. doi:10.1093/infdis/122.5.432.
4. Krugman S, Giles JP, Hammond J. Viral hepatitis, type B (MS-2 strain). Studies on active immunization. JAMA. 1971;217 (1):41–45. doi:10.1001/jama.1971.03190010023005.
5. Krugman S, Giles JP, Hammond J. Viral hepatitis, type B (MS-2 strain) prevention with specific hepatitis B immune serum globulin. JAMA. 1971;218(11):1665–70. doi:10.1001/jama.1971.03190240019005.
6. Hollinger FB, Liang JK. Hepatitis B virus. In: Knipe D, Howley P, Griffin D editors. Fields virology. 4th. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2971–3036.
7. Maynard JE, Berquist KR, Krushak DH, Purcell RH. Experimental infection of chimpanzees with the virus of hepatitis B. Nature. 1972;237(5357):514–15. doi:10.1038/237514a0.
8. Gerin JL, Holland PV, Purcell RH. Australia antigen: large-scale purification from human serum and biochemical studies of its proteins. J Virol. 1971;7(5): 569–76. doi:10.1128/JVI.7.5.569-576.1971.
9. Hilleman MR, Buynak EB, Roehm RR, Tytell AA, Bertland AU, Lampson GP. Purified and inactivated human hepatitis B vaccine: progress report. Am J Med Sci. 1975;270(2):401–04. doi:10.1097/00000441-197509000-00025.
10. Buynak EB, Roehm RR, Tytell AA, Bertland AU 2nd, Lampson GP, Hilleman MR. Development and chimpanzee testing of a vaccine against human hepatitis B. Proc Soc Exp Biol Med. 1976;151(4):694–700. doi:10.3181/00379727-151-39288.
11. Hilleman MR, McAleer WJ, Buynak EB, McLean AA. The preparation and safety of hepatitis B vaccine. J Infect. 1983;7(Suppl 1):3–8. doi:10.1016/s0163-4453(83)96465-4.
12. Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszko WR, William DC, Sadovsky R, Morrison JM, Kellner A. Hepatitis B vaccine: demonstration of efficacy in a controlled clinical trial in a high-risk population in the United States. N Engl J Med. 1980;303(15):833–41. doi:10.1056/NEJM198010093031501.
13. Stevens CE, Szmuness W, Goodman AI, Weseley SA, Fotino M. Hepatitis B vaccine: immune responses in haemodialysis patients. Lancet. 1980;2(8206):1211–13. doi:10.1016/s0140-6736(80)92477-0.
14. Maupas P, Chiron JP, Barin F, Coursaget P, Goudeau A, Perrin J, Denis F, Mar ID. Efficacy of hepatitis B vaccine in prevention of early HBsAg carrier state in children. Controlled trial in an endemic area (Senegal). Lancet. 1981;1(8215):289–92. doi:10.1016/s0140-6736(81)91908-5.
15. Krugman S. The newly licensed hepatitis B vaccine. Characteristics and indications for use. JAMA. 1982;247(14):2012–15. doi:10.1001/jama.1982.03320390074052.
16. Goudeau A, Dubois F, Barin F, Dubois MC, Coursaget P. Hepatitis B vaccine: clinical trials in high-risk settings in France. (September 1975–September 1982). Dev Biol Stand. 1983;54: 267–84.
17. Szmuness W, Stevens CE, Harley EJ, Zang EA, Alter HJ, Taylor PE, DeVera A, Chen GT, Kellner A. Hepatitis B vaccine in medical staff of hemodialysis units: efficacy and subtype cross-protection. N Engl J Med. 1982;307(24):1481–86. doi:10.1056/NEJM198212093072403.
18. Burrell CJ, Mackay P, Greenaway PJ, Hofschneider PH, Murray K. Expression in Escherichia coli of hepatitis B virus DNA sequences cloned in plasmid pBR322. Nature. 1979;279(5708):43–47. doi:10.1038/279043a0.
19. Valenzuela P, Gray P, Quiroga M, Zaldivar J, Goodman HM, Rutter WJ. Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen. Nature. 1979;280(5725):815–19. doi:10.1038/280815a0.
20. Valenzuela P, Medina A, Rutter WJ, Ammerer G, Hall BD. Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature. 1982;298(5872):347–50. doi:10.1038/298347a0.
21. McAleer WJ, Buynak EB, Maigetter RZ, Wampler DE, Miller WJ, Hilleman MR. Human hepatitis B vaccine from recombinant yeast. Nature. 1984;307(5947):178–80. doi:10.1038/307178a0.
22. Scolnick EM, McLean AA, West DJ, McAleer WJ, Miller WJ, Buynak EB. Clinical evaluation in healthy adults of a hepatitis B vaccine made by recombinant DNA. JAMA. 1984;251 (21):2812–15. doi:10.1001/jama.1984.03340450028021.
23. Jilg W, Lorbeer B, Schmidt M, Wilske B, Zoulek G, Deinhardt F. Clinical evaluation of a recombinant hepatitis B vaccine. Lancet. 1984;2(8413):1174–75. doi:10.1016/s0140-6736(84)92740-5.
24. Davidson M, Krugman S. Immunogenicity of recombinant yeast hepatitis B vaccine. Lancet. 1985;1(8420):108–09. doi:10.1016/s0140-6736(85)92000-8.
25. Brown SE, Stanley C, Howard CR, Zuckerman AJ, Steward MW. Antibody responses to recombinant and plasma derived hepatitis B vaccines. Br Med J. 1986;292(6514):159–61. doi:10.1136/bmj.292.6514.159.
26. Yeoh EK, Chang WK, Ip P, Chan KH, Chan E, Fung C. Efficacy and safety of recombinant hepatitis B vaccine in infants born to HBsAg-positive mothers. J Infect. 1986;13(SupplA):15–18. doi:10.1016/s0163-4453(86)92608-3.
27. Stevens CE, Taylor PE, Tong MJ, Toy PT, Vyas GN, Nair PV, Weissman JY, Krugman S. Yeast-recombinant hepatitis B vaccine. Efficacy with hepatitis B immune globulin in prevention of perinatal hepatitis B virus transmission. JAMA. 1987;257 (19):2612–16. doi:10.1001/jama.257.19.2612.
28. Zhou YH, Wu C, Zhuang H. Vaccination against hepatitis B: the Chinese experience. Chin Med J. 2009;122(1):98–102. doi:10.3760/cma.j.issn.0366-6999.2009.01.018.
29. No authors listed. A two-dose hepatitis B vaccine for adults (Heplisav-B). JAMA. 2018;319(8): 822–23. doi:10.1001/jama.2018.1097.

30. Krieg AM. CpG motifs in bacterial DNA and their immune effects. Annu Rev Immunol. 2002;20: 709–60. doi:10.1146/annurev.immunol.20.100301.064842.
31. Sablan BP, Kim DJ, Barzaga NG, Chow WC, Cho M, Ahn SH, Hwang SG, Lee JH, Namini H, Heyward WL. Demonstration of safety and enhanced seroprotection against hepatitis B with investigational HBsAg-1018 ISS vaccine compared to a licensed hepatitis B vaccine. Vaccine. 2012;30(16):2689–96. doi:10.1016/j.vaccine.2012.02.001.
32. Heyward WL, Kyle M, Blumenau J, Davis M, Reisinger K, Kabongo ML, Bennett S, Janssen RS, Namini H, Martin JT. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared to a licensed hepatitis B vaccine in healthy adults 40–70 years of age. Vaccine. 2013;31(46):5300–05. doi:10.1016/j.vaccine.2013.05.068.
33. Janssen JM, Jackson S, Heyward WL, Janssen RS. Immunogenicity of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in subpopulations of healthy adults 18–70 years of age. Vaccine. 2015;33(31):3614–18. doi:10.1016/j.vaccine.2015.05.070.
34. Janssen RS, Mangoo-Karim R, Pergola PE, Girndt M, Namini H, Rahman S, Bennett SR, Heyward WL, Martin JT. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease. Vaccine. 2013;31(46):5306–13. doi:10.1016/j.vaccine.2013.05.067.
35. Janssen JM, Heyward WL, Martin JT, Janssen RS. Immunogenicity and safety of an investigational hepatitis B vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) compared with a licensed hepatitis B vaccine in patients with chronic kidney disease and type 2 diabetes mellitus. Vaccine. 2015;33(7):833–37. doi:10.1016/j.vaccine.2014.12.060.
36. Hyer R, McGuire DK, Xing B, Jackson S, Janssen R. Safety of a two-dose investigational hepatitis B vaccine, HBsAg-1018, using a toll-like receptor 9 agonist adjuvant in adults. Vaccine. 2018;36(19):2604–11. doi:10.1016/j.vaccine.2018.03.067.
37. Martin P, Dubois C, Jacquier E, Dion S, Mancini-Bourgine M, Godon O, Kratzer R, Lelu-Santolaria K, Evlachev A, Meritet JF, et al. TG1050, an immunotherapeutic to treat chronic hepatitis B, induces robust T cells and exerts an antiviral effect in HBV-persistent mice. Gut. 2015;64(12): 1961–71. doi:10.1136/gutjnl-2014-308041.
38. Whitacre DC, Peters CJ, Sureau C, Nio K, Li F, Su L, Jones JE, Isogawa M, Sallberg M, Frelin L, et al. Designing a therapeutic hepatitis B vaccine to circumvent immune tolerance. Hum Vaccin Immunother. 2019. Epub ahead of print. doi:10.1080/21645515.2019.1689745.
39. Gehring AJ, Protzer U. Targeting innate and adaptive immune responses to cure chronic HBV infection. Gastroenterol. 2019;156(2):325–37. doi:10.1053/j.gastro.2018.10.032.
40. Fanning GC, Zoulim F, Hou J, Bertoletti A. Therapeutic strategies for hepatitis B virus infection: towards a cure. Nat Rev Drug Discov. 2019;18(11):827–44. doi:10.1038/s41573-019-0037-0.
41. Mancini-Bourgine M, Fontaine H, Scott-Algara D, Pol S, Bréchot C, Michel ML. Induction or expansion of T-cell responses by a hepatitis B DNA vaccine administered to chronic HBV carriers. Hepatology. 2004;40(4):874–82. doi:10.1002/hep.20408.
42. Michel ML, Deng Q, Mancini-Bourgine M. Therapeutic vaccines and immune-based therapies for the treatment of chronic hepatitis B: perspectives and challenges. J Hepatol. 2011;54(6):1286–96. doi:10.1016/j.jhep.2010.12.031.
43. Wong VC, Ip HM, Reesink HW, Lelie PN, Reerink-Brongers EE, Yeung CY, Ma HK. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis-B vaccine and hepatitis-B immunoglobulin. double-blind randomised placebo-controlled study. Lancet. 1984;1(8383):921–26. doi:10.1016/s0140-6736(84)92388-2.
44. Moyes CD, Milne A, Dimitrakakis M, Goldwater PN, Pearce N. Very-low-dose hepatitis B vaccine in newborn infants: an economic option for control in endemic areas. Lancet. 1987;1(8523):29–31. doi:10.1016/s0140-6736(87)90712-4.
45. Kane M. Reduced doses of hepatitis B vaccines: is it a good idea? Bull World Health Organ. 1995;73:529–30.
46. Poland GA, Jacobson RM. Clinical practice: prevention of hepatitis B with the hepatitis B vaccine. N Engl J Med. 2004;351(27):2832–38. doi:10.1056/NEJMcp041507.
47. Liu F, Guo Z, Dong C. Influences of obesity on the immunogenicity of hepatitis B vaccine. Hum Vaccin Immunother. 2017;13(5):1014–17. doi:10.1080/21645515.2016.1274475.
48. Abara WE, Qaseem A, Schillie S, McMahon BJ, Harris AM. High value care task force of the American college of physicians and the centers for disease control and prevention. Hepatitis B vaccination, screening, and linkage to care: best practice advice from the American college of physicians and the centers for disease control and prevention. Ann Intern Med. 2017;167(11):794–804. doi:10.7326/M17-1106.
49. WHO. Immunization coverage. Fact sheet. Updated 2019 Jul 15. http://www.who.int/mediacentre/factsheets/fs378/en/.
50. Syed YY. DTaP-IPV-HepB-Hib vaccine (Hexyon®): an updated review of its use in primary and booster vaccination. Paediatr Drugs. 2019;21(5):397–408. doi:10.1007/s40272-019-00353-7.
51. Vesikari T, Xu J, Johnson DR, Hall J, Marček T, Goveia MG, Acosta CJ, Lee AW. Hepatitis B and pertussis antibodies in 4- to 5-year-old children previously vaccinated with different hexavalent vaccines. Hum Vaccin Immunother. 2019; 1–8. Epub ahead of print. doi:10.1080/21645515.2019.1673119.
52. Kosalaraksa P, Chokephaibulkit K, Benjaponpitak S, Pancharoen C, Chuenkitmongkol S, B'Chir S, Da Costa X, Vidor E. Persistence of hepatitis B immune memory until 9–10 years of age following hepatitis B vaccination at birth and DTaP-IPV-HB-PRP~T vaccination at 2, 4 and 6 months. Hum Vaccin Immunother. 2018;14(5):1257–65. doi:10.1080/21645515.2018.1426418.
53. Khan J, Shil A, Mohanty SK. Hepatitis B vaccination coverage across India: exploring the spatial heterogeneity and contextual determinants. BMC Public Health. 2019;19(1):1263. doi:10.1186/s12889-019-7534-2.
54. Insulander M, Lindh G, Stenkvist J, Samuelson A, Fischler B. Long-term follow-up of a vaccination program for infants born to HBsAg-positive mothers in Stockholm county, Sweden. Vaccine. 2020;38(4):790–93. doi:10.1016/j.vaccine.2019.10.100.
55. Zahradnik JM, Heiberg D, Hollinger FB. Hepatitis B vaccine: immune responses in children from families with an HBsAg carrier. Vaccine. 1985;3(5):407–13. doi:10.1016/0264-410x(85)90132-x.
56. Hu Y, Wu Q, Xu B, Zhou Z, Wang Z, Zhou YH. Influence of maternal antibody against hepatitis B surface antigen on active immune response to hepatitis B vaccine in infants. Vaccine. 2008;26(48):6064–67. doi:10.1016/j.vaccine.2008.09.014.
57. Giammanco G, Li Volti S, Mauro L, Bilancia GG, Salemi I, Barone P, Musumeci S. Immune response to simultaneous administration of a recombinant DNA hepatitis B vaccine and multiple compulsory vaccines in infancy. Vaccine. 1991;9(10):747–50. doi:10.1016/0264-410x(91)90291-d.
58. Belloni C, Orsolini P, Martinetti M, Chirico G, Cerbo RM, Comolli G, Maccarini U, Barlassina C, Togni C, Polatti F, et al. Control of hepatitis B: evaluation of two different vaccinal schedules in newborns from HBsAg negative mothers. New Microbiol. 1993;16(3): 237–44.
59. Perrin J, Coursaget P, Ntareme F, Chiron JP. Hepatitis B immunization of newborns according to a two dose protocol. Vaccine. 1986;4(4):241–44. doi:10.1016/0264-410x(86)90137-4.
60. Huang H, Ning M, Liu J, Chen J, Feng J, Dai Y, Hu Y, Zhou YH. Comparison of antibody response to hepatitis B vaccination in infants with positive or negative maternal hepatitis B e antigen (HBeAg) in cord blood: implication for the role of HBeAg as an immunotolerogen. Hum Vaccin Immunother. 2019;15(9):2183–86. doi:10.1080/21645515.2019.1575712.

61. Van Den Ende C, Marano C, Van Ahee A, Bunge EM, De Moerlooze L. The immunogenicity and safety of GSK's recombinant hepatitis B vaccine in adults: a systematic review of 30 years of experience. Expert Rev Vaccines. 2017;16(8):811–32. doi:10.1080/14760584.2017.1338568.
62. Bruce MG, Bruden D, Hurlburt D, Zanis C, Thompson G, Rea L, Toomey M, Townshend-Bulson L, Rudolph K, Bulkow L, et al. Antibody levels and protection after hepatitis B vaccine: results of a 30-year follow-up study and response to a booster dose. J Infect Dis. 2016;214(1): 16–22. doi:10.1093/infdis/jiv748.
63. Osiowy C. From infancy and beyond … ensuring a lifetime of hepatitis B virus (HBV) vaccine-induced immunity. Hum Vaccin Immunother. 2018;14(8):2093–97. doi:10.1080/21645515.2018.1462428.
64. Bini C, Grazzini M, Chellini M, Mucci N, Arcangeli G, Tiscione E, Bonanni P. Is hepatitis B vaccination performed at infant and adolescent age able to provide long-term immunological memory? An observational study on healthcare students and workers in Florence, Italy. Hum Vaccin Immunother. 2018;14(2):450–55. doi:10.1080/21645515.2017.1398297.
65. Zhao H, Zhou YH. Revaccination against hepatitis B in late teenagers who received vaccination during infancy: yes or no? Hum Vaccin Immunother. 2018;14(2):456–63. doi:10.1080/21645515.2017.1397243.
66. Haber P, Moro PL, Ng C, Lewis PW, Hibbs B, Schillie SF, Nelson NP, Li R, Stewart B, Cano MV. Safety of currently licensed hepatitis B surface antigen vaccines in the United States, Vaccine Adverse Event Reporting System (VAERS), 2005–2015. Vaccine. 2018;36(4):559–64. doi:10.1016/j.vaccine.2017.11.079.
67. Moro PL, Zheteyeva Y, Barash F, Lewis P, Cano M. Assessing the safety of hepatitis B vaccination during pregnancy in the Vaccine Adverse Event Reporting System (VAERS), 1990–2016. Vaccine. 2018;36(1):50–54. doi:10.1016/j.vaccine.2017.11.039.
68. Centers for Disease Control and Prevention. Update: vaccine side effects, adverse reactions and precautions. Recommendations of the advisory committee on immunization practices. MMWR. 1996;45(RR–12): 1–35.
69. Lewis E, Shinefield HR, Woodruff BA, Black SB, Destefano F, Chen RT, Ensor R. Vaccine safety datalink workgroup. Safety of neonatal hepatitis B vaccine administration. Pediatr Infect Dis J. 2001;20(11):1049–54. doi:10.1097/00006454-200111000-00009.
70. Eriksen EM, Perlman JA, Miller A, Marcy SM, Lee H, Vadheim C, Zangwill KM, Chen RT, DeStefano F, Lewis E, et al. Lack of association between hepatitis B birth immunization and neonatal death: a population-based study from the vaccine safety datalink project. Pediatr Infect Dis J. 2004;23(7): 656–62. doi:10.1097/01.inf.0000130953.08946.d0.
71. Mouchet J, Salvo F, Raschi E, Poluzzi E, Antonazzo IC, De Ponti F, Bégaud B. Hepatitis B vaccination and the putative risk of central demyelinating diseases -a systematic review and meta-analysis. Vaccine. 2018;36(12):1548–55. doi:10.1016/j.vaccine.2018.02.036.
72. Stahl JP, Denis F, Gaudelus J, Cohen R, Lepetit H, Martinot A. Hepatitis B vaccination and adolescents: a lost generation. Med Mal Infect. 2016;46(1):1–3. doi:10.1016/j.medmal.2015.11.002.
73. Yue C, Sun X, Wei N, Yu W, Cui F, Wang H, Li L, Zhang L, Shi G, An Z. Quick assessment of the influence of the hepatitis B vaccine event on children's vaccination. Hum Vaccin Immunother. 2016;12(10):2611–15. doi:10.1080/21645515.2016.1187351.
74. Li X, Dumolard L, Patel M, Gacic-Dobo M, Hennessey K. Implementation of hepatitis B birth dose vaccination–worldwide, 2016. Wkly Epidemiol Rec. 2018;93(7): 61–72.
75. Alter MJ. Epidemiology and prevention of hepatitis B. Semin Liver Dis. 2003;23(1):39–46. doi:10.1055/s-2003-37583.
76. Ujiie M, Sasaki K, Yoshikawa N, Enami T, Shobayashi T. Introduction of a hepatitis B vaccine into the national routine immunisation programme of Japan. Lancet Infect Dis. 2016;16(12):1325. doi:10.1016/S1473-3099(16)30463-7.
77. Torjesen I. UK adds hepatitis B to infant vaccination schedule. BMJ. 2017;358: j3357. doi:10.1136/bmj.j3357.
78. Mandal S. Introduction of universal infant hepatitis B immunisation in the UK- paving the way to elimination. Hum Vaccin Immunother. 2019;15(2):440–43. doi:10.1080/21645515.2018.1528837.
79. Maurice J. First countries to be recipients of GAVI funds. Bull World Health Organ. 2000;78:1477–78.
80. Lee LA, Franzel L, Atwell J, Datta SD, Friberg IK, Goldie SJ, Reef SE, Schwalbe N, Simons E, Strebel PM, et al. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. Vaccine. 2013;31(Suppl 2): B61–72. doi:10.1016/j.vaccine.2012.11.035.
81. WHO. Global Hepatitis Report. 2017. https://www.who.int/hepatitis/publications/global-hepatitis-report2017-executive-summary/en/.
82. Sun KX, Li J, Zhu FC, Liu JX, Li RC, Zhai XJ, Li YP, Chang ZJ, Nie JJ, Zhuang H. A predictive value of quantitative HBsAg for serum HBV DNA level among HBeAg-positive pregnant women. Vaccine. 2012;30(36):5335–40. doi:10.1016/j.vaccine.2012.06.036.
83. Wen WH, Chang MH, Zhao LL, Ni YH, Hsu HY, Wu JF, Chen PJ, Chen DS, Chen HL. Mother-to-infant transmission of hepatitis B virus infection: significance of maternal viral load and strategies for intervention. J Hepatol. 2013;59(1):24–30. doi:10.1016/j.jhep.2013.02.015.
84. Liu J, Bi Y, Xu C, Liu L, Xu B, Chen T, Chen J, Pan M, Hu Y, Zhou YH. Kinetic changes of viremia and viral antigens of hepatitis B virus during and after pregnancy. Medicine. 2015;94(45): e2001. doi:10.1097/MD.0000000000002001.
85. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, Moyer LA, Bell BP, Alter MJ. Advisory Committee on Immunization Practices (ACIP). A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54:1–31.
86. Oon CJ, Lim GK, Ye Z, Goh KT, Tan KL, Yo SL, Hopes E, Harrison TJ, Zuckerman AJ. Molecular epidemiology of hepatitis B virus vaccine variants in Singapore. Vaccine. 1995;13(8):699–702. doi:10.1016/0264-410x(94)00080-7.
87. Chen HL, Lin LH, Hu FC, Lee JT, Lin WT, Yang YJ, Huang FC, Wu SF, Chen SC, Wen WH, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterology. 2012;142(4): 773–81.e2. doi:10.1053/j.gastro.2011.12.035.
88. Wen WH, Huang CW, Chie WC, Yeung CY, Zhao LL, Lin WT, Wu JF, Ni YH, Hsu HY, Chang MH, et al. Quantitative maternal hepatitis B surface antigen predicts maternally transmitted hepatitis B virus infection. Hepatology. 2016;64(5): 1451–61. doi:10.1002/hep.28589.
89. Yin Y, Wu L, Zhang J, Zhou J, Zhang P, Hou H. Identification of risk factors associated with immunoprophylaxis failure to prevent the vertical transmission of hepatitis B virus. J Infect. 2013;66(5):447–52. doi:10.1016/j.jinf.2012.12.008.
90. Zhang L, Gui X, Fan J, Wang B, Ji H, Yisilafu R, Li F, Zhou Y, Tong Y, Kong X, et al. Breast feeding and immunoprophylaxis efficacy of mother-to-child transmission of hepatitis B virus. J Matern Fetal Neonatal Med. 2014;27(2): 182–86. doi:10.3109/14767058.2013.806901.
91. Wang C, Wang C, Jia ZF, Wu X, Wen SM, Kong F, Hu KQ, Li J, Jiang J, Niu JQ. Protective effect of an improved immunization practice of mother-to-infant transmission of hepatitis B virus and risk factors associated with immunoprophylaxis failure. Medicine. 2016;95(34):e4390. doi:10.1097/MD.0000000000004390.
92. Lu Y, Zhu FC, Liu JX, Zhai XJ, Chang ZJ, Yan L, Wei KP, Zhang X, Zhuang H, Li J. The maternal viral threshold for antiviral prophylaxis of perinatal hepatitis B virus transmission in settings with limited resources: a large prospective cohort study in China. Vaccine. 2017;35(48Pt B):6627–33. doi:10.1016/j.vaccine.2017.10.032.
93. Liu J, Xu B, Chen T, Chen J, Feng J, Xu C, Liu L, Hu Y, Zhou YH. Presence of hepatitis B virus markers in umbilical cord blood: exposure to or infection with the virus? Dig Liver Dis. 2019;51(6):864–69. doi:10.1016/j.dld.2018.11.003.

94. Cheung KW, Seto MTY, Kan ASY, Wong D, Kou KO, So PL, Lau WL, Jalal K, Chee YY, Wong RMS, et al. Immunoprophylaxis failure of infants born to hepatitis B carrier mothers following routine vaccination. Clin Gastroenterol Hepatol. 2018;16(1): 144–45. doi:10.1016/j.cgh.2017.07.013.
95. Kubo A, Shlager L, Marks AR, Lakritz D, Beaumont C, Gabellini K, Corley DA. Prevention of vertical transmission of hepatitis B: an observational study. Ann Intern Med. 2014;160 (12):828–35. doi:10.7326/M13-2529.
96. Schillie S, Walker T, Veselsky S, Crowley S, Dusek C, Lazaroff J, Morris SA, Onye K, Ko S, Fenlon N, et al. Outcomes of infants born to women infected with hepatitis B. Pediatrics. 2015;135(5): e1141–7. doi:10.1542/peds.2014-3213.
97. Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, Salvadori N, Cressey TR, Sirirungsi W, Achalapong J, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med. 2018;378(10): 911–23. doi:10.1056/NEJMoa1708131.
98. Hu Y, Xu C, Xu B, Hu L, Liu Q, Chen J, Liu J, Liu L, Yang J, Chen T, et al. Safety and efficacy of telbivudine in late pregnancy to prevent mother-to-child transmission of hepatitis B virus: a multicenter prospective cohort study. J Viral Hepat. 2018;25 (4): 429–37. doi:10.1111/jvh.12834.
99. Milne A, West DJ, Chinh DV, Moyes CD, Poerschke G. Field evaluation of the efficacy and immunogenicity of recombinant hepatitis B vaccine without HBIG in newborn Vietnamese infants. J Med Virol. 2002;67(3):327–33. doi:10.1002/jmv.10071.
100. Yang YJ, Liu CC, Chen TJ, Lee MF, Chen SH, Shih HH, Chang MH. Role of hepatitis B immunoglobulin in infants born to hepatitis B e antigen-negative carrier mothers in Taiwan. Pediatr Infect Dis J. 2003;22(7):584–88. doi:10.1097/01.inf.0000073123.93220.a8.
101. Lu Y, Liang XF, Wang FZ, Yan L, Li RC, Li YP, Zhu FC, Zhai XJ, Li J, Zhuang H. Hepatitis B vaccine alone may be enough for preventing hepatitis B virus transmission in neonates of HBsAg (+)/HBeAg(-) mothers. Vaccine. 2017;35(1):40–45. doi:10.1016/j.vaccine.2016.11.061.
102. Wang F, Zheng H, Zhang G, Ding Z, Li F, Zhong G, Chen Y, Jia Y, Miao N, Wu Z, et al. Effectiveness of prevention of mother-to-child transmission practice in three provinces of Southern China. Hum Vaccin Immunother. 2015;11(8): 2061–67. doi:10.1080/21645515.2015.1023972.
103. Xu B, Liu L, Yang J. Combined prophylaxis is still better than vaccine only in children of HBV-infected mothers with negative HBeAg. Gastroenterology. 2012;143(1):e42–3. doi:10.1053/j.gastro.2012.04.044.
104. Wiesen E, Diorditsa S, Li X. Progress towards hepatitis B prevention through vaccination in the Western Pacific, 1990–2014. Vaccine. 2016;34(25):2855–62. doi:10.1016/j.vaccine.2016.03.060.
105. Just M, Berger R. Immunogenicity of a heat-treated recombinant DNA hepatitis B vaccine. Vaccine. 1988;6(5):399–400. doi:10.1016/0264-410x(88)90137-5.
106. Van Damme P1, Cramm M, Safary A, Vandepapelière P, Meheus A. Heat stability of a recombinant DNA hepatitis B vaccine. Vaccine. 1992;10(6):366–67. doi:10.1016/0264-410x(92)90064-q.
107. Stephenne J. Development and production aspects of a recombinant yeast-derived hepatitis B vaccine. Vaccine. 1990;8 (Suppl):S69–73. doi:10.1016/0264-410x(90)90221-7.
108. Braun LJ, Jezek J, Peterson S, Tyagi A, Perkins S, Sylvester D, Guy M, Lal M, Priddy S, Plzak H, et al. Characterization of a thermostable hepatitis B vaccine formulation. Vaccine. 2009;27 (34): 4609–14. doi:10.1016/j.vaccine.2009.05.069.
109. Otto BF, Suarnawa IM, Stewart T, Nelson C, Ruff TA, Widjaya A, Maynard JE. At-birth immunisation against hepatitis B using a novel pre-filled immunisation device stored outside the cold chain. Vaccine. 1999;18(5–6):498–502. doi:10.1016/s0264-410x(99)00242-x.
110. Hipgrave DB, Maynard JE, Biggs BA. Improving birth dose coverage of hepatitis B vaccine. Bull World Health Organ. 2006;84 (1):65–71. doi:10.2471/blt.04.017426.
111. Breakwell L, Anga J, Dadari I, Sadr-Azodi N, Ogaoga D, Patel M. Evaluation of storing hepatitis B vaccine outside the cold chain in the Solomon Islands: identifying opportunities and barriers to implementation. Vaccine. 2017;35(21):2770–74. doi:10.1016/j.vaccine.2017.04.011.
112. Harpaz R, McMahon BJ, Margolis HS, Shapiro CN, Havron D, Carpenter G, Bulkow LR, Wainwright RB. Elimination of new chronic hepatitis B virus infections: results of the Alaska immunization program. J Infect Dis. 2000;181(2):413–18. doi:10.1086/315259.
113. Lin AW, Wong KH. Surveillance and response of hepatitis B virus in Hong Kong special administrative region, 1988–2014. Western Pac Surveill Response J. 2016;7(1):24–28. doi:10.5365/WPSAR.2015.6.3.003.
114. Miao N, Zheng H, Sun X, Shen L, Wang F, Cui F, Yin Z, Zhang G, Wang F. Enhanced sentinel surveillance for hepatitis B infection in 200 counties in China, 2013–2016. PLoS One. 2019;14(4): e0215580. doi:10.1371/journal.pone.0215580.
115. Cui F, Shen L, Li L, Wang H, Wang F, Bi S, Liu J, Zhang G, Wang F, Zheng H, et al. Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy, China. Emerg Infect Dis. 2017;23(5): 765–72. doi:10.3201/eid2305.161477.
116. Peach D, McMahon BJ, Bulkow L, Funk E, Harpaz R, Margolis HS. Impact of recurrent epidemics of hepatitis a virus infection on population immunity levels: Bristol Bay, Alaska. J Infect Dis. 2002;186(8):1081–85. doi:10.1086/343815.
117. Ni YH, Chang MH, Jan CF, Hsu HY, Chen HL, Wu JF, Chen DS. Continuing decrease in hepatitis B virus infection 30 years after initiation of infant vaccination program in Taiwan. Clin Gastroenterol Hepatol. 2016;14(9):1324–30. doi:10.1016/j.cgh.2016.04.030.
118. Ang LW, Tey SH, Cutter J, James L, Goh KT. Seroprevalence of hepatitis B virus infection among children and adolescents in Singapore, 2008–2010. J Med Virol. 2013;85(4):583–88. doi:10.1002/jmv.23496.
119. Liang X, Bi S, Yang W, Wang L, Cui G, Cui F, Zhang Y, Liu J, Gong X, Chen Y, et al. Epidemiological serosurvey of hepatitis B in China–declining HBV prevalence due to hepatitis B vaccination. Vaccine. 2009;27(47): 6550–57. doi:10.1016/j.vaccine.2009.08.048.
120. Lin X, Yang J, Lu H, Zhou Y, Zhou G, Wu H, Xu C, Wu Q, Liu J, Chen S, et al. Minimization of hepatitis B infection among children in Jiangsu, China, 12 years after integration of hepatitis B vaccine into the expanded program on immunization. Vaccine. 2016;34(51): 6458–63. doi:10.1016/j.vaccine.2016.11.022.
121. Hu Y, Zhang S, Luo C, Liu Q, Zhou YH. Gaps in the prevention of perinatal transmission of hepatitis B virus between recommendations and routine practices in a highly endemic region: a provincial population-based study in China. BMC Infect Dis. 2012;12: 221. doi:10.1186/1471-2334-12-221.
122. Patel MK, Le Calvez E, Wannemuehler K, Ségalin JM. Hepatitis B vaccination coverage and prevalence of hepatitis B surface antigen among children in French Polynesia, 2014. Am J Trop Med Hyg. 2016;94(6):1370–75. doi:10.4269/ajtmh.15-0903.
123. Ang LW, Cutter J, James L, Goh KT. Seroepidemiology of hepatitis B virus infection among adults in Singapore: a 12-year review. Vaccine. 2013;32(1):103–10. doi:10.1016/j.vaccine.2013.10.057.
124. Lao TT, Sahota DS, Chan PKS. Three decades of neonatal vaccination has greatly reduced antenatal prevalence of hepatitis B virus infection among gravidae covered by the program. J Infect. 2018;76(6):543–49. doi:10.1016/j.jinf.2018.04.003.
125. Xu C, Chen T. Global prevalence of hepatitis B virus infection and prevention of mother-to-child transmission. Lancet Gastroenterol Hepatol. 2018;3(9):598–99. doi:10.1016/S2468-1253(18)30198-5.
126. Chang MH, Shau WY, Chen CJ, Wu TC, Kong MS, Liang DC, Hsu HM, Chen HL, Hsu HY, Chen DS. Hepatitis B vaccination and hepatocellular carcinoma rates in boys and girls. JAMA. 2000;284(23):3040–42. doi:10.1001/jama.284.23.3040.
127. Chien YC, Jan CF, Chiang CJ, Kuo HS, You SL, Chen CJ. Incomplete hepatitis B immunization, maternal carrier status, and increased risk of liver diseases: a 20-year cohort study of 3.8 million vaccinees. Hepatology. 2014;60(1):125–32. doi:10.1002/hep.27048.

128. Chang MH, You SL, Chen CJ, Liu CJ, Lai MW, Wu TC, Wu SF, Lee CM, Yang SS, Chu HC, et al. Long-term effects of hepatitis B immunization of infants in preventing liver cancer. Gastroenterology. 2016;151(3): 472–80. doi:10.1053/j.gastro.2016.05.048.
129. McMahon BJ, Bulkow LR, Singleton RJ, Williams J, Snowball M, Homan C, Parkinson AJ. Elimination of hepatocellular carcinoma and acute hepatitis B in children 25 years after a hepatitis B newborn and catch-up immunization program. Hepatology. 2011;54(3):801–07. doi:10.1002/hep.24442.
130. Ramírez-Soto MC, Ortega-Cáceres G, Cabezas C. Trends in mortality burden of hepatocellular carcinoma, cirrhosis, and fulminant hepatitis before and after roll-out of the first pilot vaccination program against hepatitis B in Peru: an analysis of death certificate data. Vaccine. 2017;35(31):3808–12. doi:10.1016/j.vaccine.2017.05.086.