Exploring the optimal vaccination strategy against hepatitis B virus in childhood (Review)

ANNA KRAMVIS[1], IOANNIS N. MAMMAS[2-4] and DEMETRIOS A. SPANDIDOS[4]

[1]Hepatitis Virus Diversity Research Unit, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of The Witwatersrand, Johannesburg 2193, South Africa; [2]Paediatric Clinic, Aliveri, 34500 Island of Euboea; [3]First Department of Paediatrics, University of Athens School of Medicine, 11527 Athens; [4]Department of Clinical Virology, Medical School, University of Crete, 71003 Heraklion, Greece

Received February 16, 2023; Accepted May 29, 2023

DOI: 10.3892/br.2023.1631

Abstract. Vaccination against hepatitis B virus (HBV) remains the most effective strategy against HBV infection in humans. The present review summarized the optimal vaccination strategies against HBV in childhood. The following points are discussed: i) When and how the first HBV vaccines were developed; ii) the dosages, schedules and injection routes that are used for HBV vaccination; iii) the contraindications for HBV vaccination in the general paediatric population; iv) the challenges with the use of multivalent vaccines; v) the long-term immunogenicity and duration of protection against HBV; vi) the use of selective HBV vaccination and the hepatitis B immune globulin strategy in HBV-exposed infants; and vii) the effectiveness of the current HBV vaccination schemes. The present review is based on a Paediatric Virology Study Group (PVSG) webinar performed in the context of the 8th Workshop on Paediatric Virology.

Contents

Correspondence to: Professor Anna Kramvis, Hepatitis Virus Diversity Research Unit, Department of Internal Medicine, School of Clinical Medicine, Faculty of Health Sciences, University of the Witwatersrand, 7 York Road, Parktown, Johannesburg 2193, South Africa
E-mail: Anna.Kramvis@wits.ac.za

Key words: hepatitis B, hepatitis B virus, vaccination, research limited settings, prevention, paediatric virology

1. Historical insights on HBV vaccines

The discovery of hepatitis B virus (HBV) and the development of the HBV vaccine involved serendipity and luck. In his book entitled 'Hepatitis B: The hunt for a killer virus' (1), Professor Baruch S. Blumberg (1925-2011), winner of the 1976 Nobel Prize, states that: 'The most significant outcome of our research has, probably been the invention and the introduction of the HBV vaccine'. Professor Blumberg was awarded the Nobel Prize for 'discoveries concerning new mechanisms for the origin and dissemination of infectious diseases', and, specifically, for the discovery of HBV. The vaccine was invented in 1969, 2 years after the recognition of HBV, as one of the causative agents of hepatitis. The HBV vaccine is the first vaccine against two viruses, HBV and hepatitis D virus (HDV; satellite virus of HBV), chronic disease, sexually transmitted disease and cancer. Professor Blumberg's initial research focussed on gene distribution and disease susceptibility in different ethnic groups. In the serum of a patient with transfused haemophilia, he and his co-workers, discovered an antibody, which reacted with a protein in the serum of an Australian patient (2). Thus, it was named 'Australia' antigen (Au), which was associated with hepatitis and found to be identical to serum hepatitis antigen (SHAg) (3), now known as HBsAg.

As early as 1908, a virus was implicated as being the causative agent of liver disease. In the late 1940s and early 1950s, two different forms of virus were proposed to cause infective hepatitis (virus A: foecal-oral route of transmission) and serum hepatitis (virus B: blood-borne), respectively (4-6). The whole virus, named HBV, was only isolated and visualized following transmission and electron microscopy studies in 1970 (7). In addition to viral particles, the plasma of infected individuals also carries subviral, non-infectious particles, composed of HBsAg, at a ratio of 1:1,000, respectively (8).

The infectious particles can be separated from non-infectious particles using ultracentrifugation and the subviral particles enriched by enzymatic treatment and column separation, to eliminate viable virus. This was fundamentally the process used for the production of the first HBV vaccine by Professor Blumberg and his team. The first crude demonstration of active immunization and 59% protection was

performed by the New York paediatrician, Dr Saul Krugman, who inoculated children with a boiled, inactivated preparation of a 1:10 dilution of infectious serum in distilled water and then challenged them with infectious serum (9). In 1975, Merck was licensed to develop the vaccine, after the safety of the vaccine was demonstrated in chimpanzees (10-12) and consequently the first placebo-controlled, randomized, double-blind clinical trial demonstrated its efficacy in reducing the incidence of HBV infection (13).

The large-scale roll-out of these first-generation HBV vaccines began in 1984. Taiwan, where HBV was endemic, was the first country to introduce the nation-wide vaccination of all neonates in July, 1984 (14). In the first 15-month period, 78% of ~450,000 pregnant women were screened and 18% were HBsAg-positive, with half of them considered to be highly infectious. The schedule for the vaccination of infants born HBsAg-positive was 5 μg of plasma-derived vaccine at 1, 5 and 9 weeks, with a booster dose at 1 year (15). Negligible adverse side effects were experienced (15). In sub-Saharan Africa (SSA), which is also a geographical region where HBV is endemic, the first large-scale trial of HBV vaccination was performed in Gambia (16,17). The Gambia Hepatitis Intervention Study (GHIS) was established in 1986 to evaluate the protective effectiveness of infant HBV immunization in the prevention of chronic liver disease, particularly, hepatocellular carcinoma (HCC) and cirrhosis later in adult life. In both regions, the vaccination strategy, with plasma-derived HBsAg, led to the desired outcomes, namely in the reduction of the incidence and chronic carriage of HBV, with a concomitant decrease in the number of HCC cases, both in childhood and later in adulthood (8,14). Other countries, which adopted and implemented universal HBV vaccination early on, included Bulgaria (1989), Malaysia (1990), Italy, Spain, USA (1991) and Israel (1992) (18). On the other hand, several high-income countries, including Japan, Denmark, Finland, Norway, Sweden and the UK did not routinely vaccinate children until more recently (19). Sweden introduced infant vaccination in 2003; Japan, Norway and UK in 2019, whereas Denmark and Finland do not yet vaccinate children. Instead, the latter countries target immigrant groups from areas of a high HBV endemicity and adolescents with high-risk factors for HBV infection. In addition, they practice selective vaccination plus the administration of hepatitis B immune globulin (HBIG) to neonates born to HBsAg-/hepatitis B e antigen (HBeAg)-positive mothers following the screening of pregnant women (20).

Early on, a number of disadvantages of using patient-derived HBsAg for vaccine production were identified (8). Firstly, in the context of acquired immune deficiency syndrome (AIDS), whose infectious agent had not yet been identified, the safety of plasma-derived HBsAg was not guaranteed, particularly when considering that HBV was most often isolated from patients with AIDS. Secondly, the anticipated decrease in the prevalence of chronic hepatitis B, following widespread vaccination, would eventually lead to the supply of HBsAg from patient sera being limited.

Following the cloning of the HBV genome in 1978 by three groups independently (21-23), the road was opened for the production of HBsAg, HBcAg and HBV DNA, in large amounts *in vitro* using gene technology. Although glycosylated HBsAg can be expressed in mammalian cells, the process is costly and the yield is relatively low (8). The expression of HBsAg in yeast cells (*Saccharomyces cerevisiae*) provided sufficient HBsAg, which was glycosylated (24,25) and shown to be immunogenic both in chimpanzees (12) and in infants of HBsAg/HBeAg-positive mothers in Thailand (26). By 1986, the recombinant yeast vaccines became the accepted vaccines and in 1992, the World Health Organization (WHO) recommended global universal childhood HBV vaccination (27), considering that vaccination is an economically attractive option, both in terms of cost-effectiveness and benefit-cost ratios (28).

In the 1990s, third-generation vaccines were developed, following the transfection of mammalian cells with plasmids coding for pre-S/S proteins. These cells expressed and secreted the LHBsAg (large), MHBsAg (middle) and HBsAg (small) (29), either individually or in combination. Such a glycosylated preS1/preS2/S-containing vaccine, is licensed in Israel for the universal vaccination of infants and in some countries in East Asia. Together with new adjuvants developed, these vaccines have proved to be immunogenic in non-responders to the earlier vaccines (28). However, the yeast derived vaccines continue to be the HBV vaccine of choice.

By the year 2000, over a billion doses of vaccines had been administered globally (1). By December, 2021 (21 years later), globally, 190 countries had introduced the HBV vaccine with three doses (HepB3) for infants, with an 80% global coverage and different WHO regions demonstrating different coverages over the years. In addition, 111 WHO member states introduced the hepatitis B birth dose (HepB-BD), given within the first 24 h of life. Global coverage is 42%; 78% in the WHO Western Pacific Region, although considerably lower, at 17%, in the WHO African Region (30). The global coverage of both HepB3 and HepB-BD are below the targets set by the WHO for 2020. The targets set by the WHO for 2030 are ≥90% coverage for both HepB3 and HepB-BD (31). Mathematical modelling has predicted that with 90% vaccination coverage with the inclusion of HepB-BD would prevent 84% of global deaths associated with HBV, as opposed to a 68% reduction with HepB3 only (32). A more recent model has demonstrated that scaling up infant vaccination from 80 to 90% globally would avert 4.3 million deaths between 2015 and 2030, whereas a further 18.7 million new cases would be prevented by the administration of HepB-BD compared to HepB3 (33). This will require commitment from both policy makers and agencies involved in the implementation of successful HBV vaccination.

2. Dosages, schedules and injection routes

The age of infection is a determining factor for the development of chronic hepatitis B infection. In total, 90% of neonates born to HBeAg-positive mothers and 20-60% of children <5 years of age will become chronic carriers of HBV, as opposed to only 5% of adults, who are infected (34,35). Globally, HBV infection is acquired at birth or early childhood. Thus, it is crucial to implement the vaccination of infants as early as possible, ideally at birth, in order to: i) Prevent the perinatal mother-to-child transmission (PMCT) of HBV from HBsAg-positive mothers; ii) prevent the horizontal

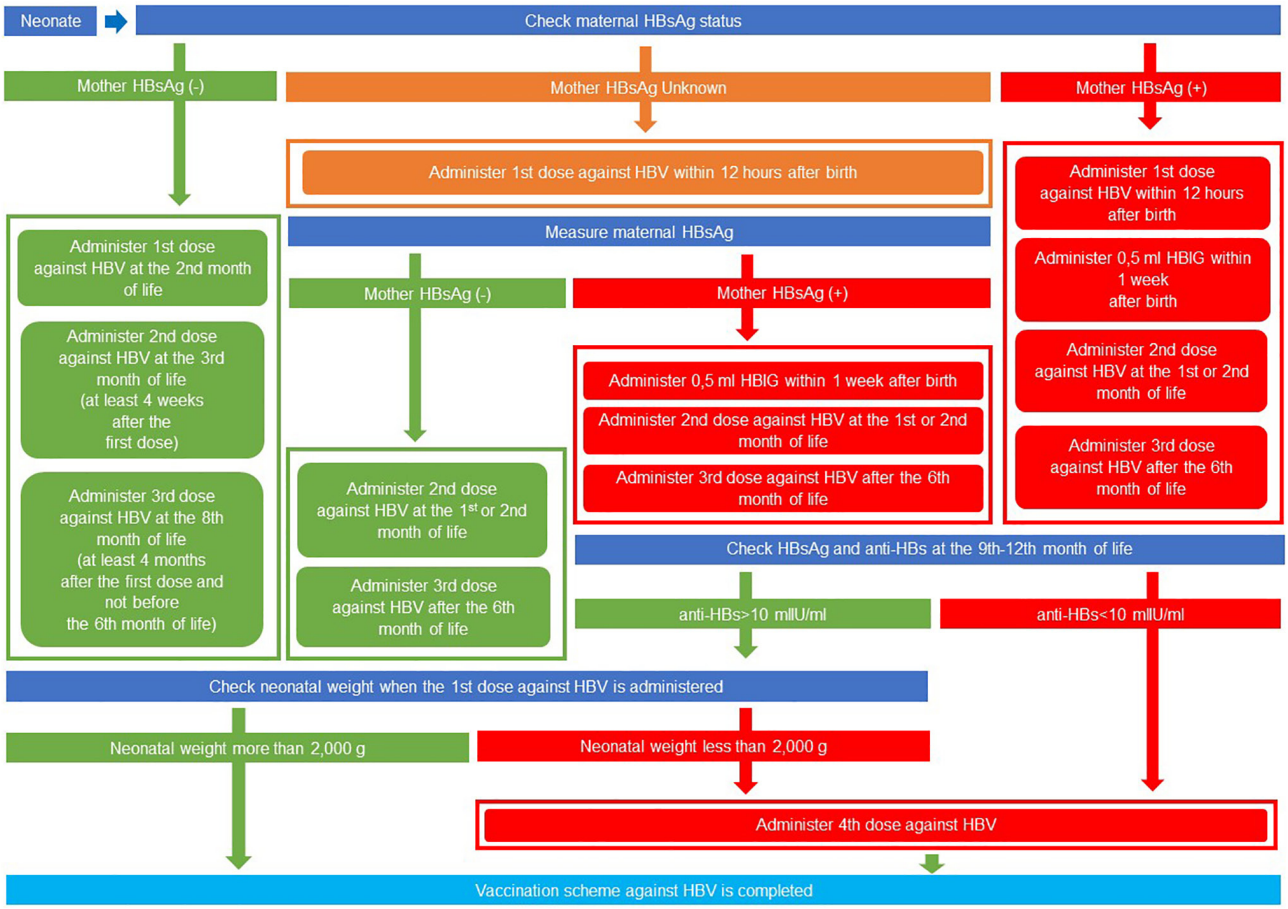

Figure 1. Algorithm of the vaccination scheme against HBV based on the 2023 Hellenic National Vaccination Programme. HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBIG, hepatitis B immune globulin; anti-HBs, antibodies against HBsAg.

transmission of HBV in early childhood; iii) confer long-term immunity against future exposures later on in life, thus leading to protection against acute hepatitis B in adolescents and adults, following either sexual or nosocomial transmission; iv) prevent HCC; and v) protect against HDV infection.

The vaccination schedules have varied over the course of the years and are dependent on local epidemiological criteria and national programmes. For optimal efficacy, the vaccine should be administered within 12 to 24 h after birth, as the levels of antibodies against HBsAg (anti-HBs) decline over time when the vaccine is administered >24 h (36). The most frequently recommended schedule is three doses of the vaccine administered at 0, 1 and 6 months to infants; however, there are a range of alternative schedules administered in different countries. The latest HBV vaccine WHO position paper states: 'The birth dose should be followed by 2 or 3 additional doses to complete the primary series. Both of the following options are considered appropriate: (i) a 3-dose schedule of HBV vaccine, with the first dose (monovalent) being given at birth and the second and third (monovalent or as part of a combined vaccine) given at the same time as the first and third doses of the *diphtheria-tetanus-pertussis* (DTP)-containing vaccine; or (ii) 4 doses, where a monovalent birth dose is followed by 3 (monovalent or combined vaccine) doses, usually given with other routine infant vaccines; the additional dose does not cause any harm. The interval between doses should be at least 4 weeks.' (37). The standard paediatric dose is 5 to 10 μg HBsAg, whereas the standard adult dose is 10 to 20 μg, with 40 μg administered to patients who are immunocompromised and in those undergoing dialysis. An accelerated schedule of three doses of the vaccine administered at 0, 1 and 2 months, followed by a booster dose administered at 12 months, is recommended for health care workers exposed to HBV or a susceptible sexual partner of a patient with acute hepatitis B in order to provide rapid protection (28). The algorithm of the vaccination scheme against HBV, based on the 2023 Hellenic National Vaccination Programme (https://www.moh.gov.gr), is presented in Fig. 1.

To achieve the optimal response, the vaccine is administered intramuscularly into the anterolateral thigh in neonates and infants <1 year of age, or into the deltoid region in children >1 year of age and in adults. Buttock administration and the intradermal route are not recommended (28). Administration into the gluteal muscle results in reduced immunogenicity and in the risk of sciatic nerve injury (37). The HBV vaccine (monovalent or combined) and other vaccines administered during the same visit should be administered at different injection sites (37).

Infants and children exhibit a 100% response to the vaccine, with anti-HB levels being >10 mIU/ml, the levels necessary for immunity. Furthermore, 95% of adults are protected following the administration of three doses. Thus, booster doses of the HBV vaccine are not required for immunocompetent individuals, whereas for immunocompromised patients regular

testing is required, with boosters administered if anti-HB titres decrease to <10 mIU/ml (18,38).

3. Contraindications for HBV vaccination

The safety of the HBV vaccines has been demonstrated by both clinical trials and post-approval follow-up. Between 1 to 7.5% of vaccinated children were shown to develop adverse events, a percentage lower than that observed in adults, with the frequency of adverse events decreasing with each additional injection [(39) and references cited therein]. The most commonly reported adverse events include pain and swelling at the injection site, and fever and mild systemic reactions, such as fever, irritability, poor appetite, diarrhoea and vomiting, generally lasting for 1 to 2 days (39,40). There is no evidence to associate an increase in the number of febrile episodes, sepsis evaluations, allergic or neurological reactions or medical procedures in neonates and infants (41). The frequency of severe vaccine reactions related to HBV vaccination is extremely low (42). Epidemiological studies have found no association between HBV vaccination and sudden infant death (SID) (43,44), diabetes mellitus (45) and demyelinating diseases (46), including Guillain-Barre syndrome (47). Although certain studies have suggested that HBV vaccination may be a risk factor for the development of multiple sclerosis (48), a previous systematic review and meta-analysis did not establish such a link (49). The WHO specifies only two contraindications to the HBV vaccination: An allergic reaction to any vaccine component and anaphylaxis to a previous dose (37). For pre-term neonates, a low birth weight (<2 kg) is not a contraindication to HBV vaccination. HBV vaccination is safe, although with possible reduced immunogenicity; therefore, pre-term babies should receive HepB-BD within 24 h, followed by three (and not two) subsequent doses. HBV vaccination is not contraindicated for pregnant and lactating women (37).

4. Challenges with multivalent vaccines

Multivalent vaccines, introduced in the early 1990s, provided a notable advancement in immunizations. In multivalent formulations, the HBV vaccine is combined with the DTP, *Haemophilus influenzae* type B (Hib) and inactivated polio (IPV) vaccines. Multivalent vaccines include *Pediarix* [GlaxoSmithKline Biologicals (GSK)], used in the USA (50), with three hexavalent vaccines currently licensed in Europe: *Vaxelis* (Sanofi Pasteur and MSD), *Hexyon* (Sanofi Pasteur) and *Infanrix Hexa* (GSK) (51). The multivalent vaccines have different formulations and/or schedules (50,51) but can be used interchangeably if necessary. A vaccine containing recombinant HBsAg and inactivated hepatitis A virus *Twinrix* (GSK) is used for the vaccination of individuals aged ≥18 years. The obvious advantage of combined vaccines is the reduced number of injections required for paediatric immunization, with fewer doctor visits, less pain, increased safety with fewer syringes, less wastage and thus, reduced immunization programme costs. The use of multivalent vaccines leads to improved coverage and compliance rates and timeliness, as well as benefits in shipment and storage (51,52). However, the monovalent HBV vaccine must be used at birth, as multivalent vaccines containing HBV, DTP and Hib antigens have a reduced immunogenicity when administered before the age of 6 weeks. Monovalent vaccines include *Engerix-B* (GSK) and *Recombivax* HB (Merck & Co., Inc.). Compared to the monovalent HBV vaccine, slight increases in short-term adverse events (fever, redness, swelling, etc.) have been documented for the multivalent formulations. Another disadvantage of using multivalent vaccines is that production issues may arise due to the complexity of combined vaccines; this therefore requires contingence planning in the event of vaccine shortages.

Routine vaccination with pentavalent and hexavalent combinations, including DTP, Hib, HepB3 and IPV has been used in vaccination programmes for >15 years, with Europe taking the lead compared to other regions worldwide (51). In total, 20 of 33 European countries routinely used hexavalent vaccines in children (51). Multivalent vaccines have a good immunogenicity, safety and tolerability and can be administered with other paediatric vaccines, including pneumococcal conjugate vaccines, rotavirus, meningococcal conjugate, measles, mumps, rubella and varicella vaccines (51). Different schedules have been used with good antibody titres obtained, regardless of the posology used (51).

5. Long immunogenicity and long-term protection

The cut-off value, which measures the vaccine response, at 1 to 2 months after receiving a complete HepB3 scheme, is a concentration of anti-HB B >10 mIU/ml and considered to be protective. This was determined from a study that demonstrated that children who did not mount this level of antibodies could become infected with HBV (53). Response to the vaccine is considered a surrogate marker for clinical protection. Following vaccination, anti-HB levels decline over time at a rate dependent on the age of vaccination. Findings extrapolated from previous research (50) have shown that at 18 years post-vaccination, only 16% of individuals who had received HepB3 prior to the age of 1 year had anti-HB levels >10 mIU/ml (54-56) compared to 74%, who had been vaccinated when they were >1 year of age (57-63). However, even for previously vaccinated individuals, whose anti-HB levels decline to <10 mIU/ml, an anamnestic response can be elicited following a booster for up to 30 years following initial vaccination (62-64). Both the antibody and cellular response have been shown to persist (65).

Thus, an initial vaccine response can protect against hepatitis B, either acute or chronic, for as long as 30 years post-vaccination, regardless of whether anti-HB levels persist at levels ≥10 mIU/ml or not (64-66). Thus, immunocompetent individuals do not require boosters, provided they had received the complete vaccine series at the recommended schedules either as children or adults. However, there have been exceptions and HBV infection has been documented infrequently in vaccinated individuals. In a study on 3.7 million blood donors, nine HBV DNA-positive, HBsAg/anti-HBc-negative donors were identified (1 in 410,540 donations) and evaluated for vaccination status. In total, six of the nine HBV-DNA-positive donations were from vaccinated individuals, whose infections were subclinical and resolved (67). In addition, four of the nine

donors contracted the HBV infection from their sexual partners (67). In an Italian study, 362 of 11,311 (3.2%) cases with acute hepatitis B were vaccinated (68). The possible reasons cited for the breakthrough HBV infections in vaccinated individuals include incomplete vaccination (68); infection with vaccine-escape S mutant strains of HBV (68); and infection with genotypes expressing serological subtype different to the vaccine strain, belonging to subgenotype A2, which expresses *adw*2 (67). Thus, individuals, who are at high risk of HBV infection or immunocompromised, should be monitored and given a booster, especially if the anti-HBs levels decline below 10 mIU/ml.

6. Selective HBV vaccination

Neonates, born to HBsAg-/HBeAg-positive mothers, are at a high risk of being infected perinatally i.e., PMCT. Thus, it is critical to offer additional temporary protection until the neonates respond to the HepB-BD. The immediate administration of HBIG can provide such protection. As previously demonstrated, the HBsAg-carrier rate was high, at 92%, when neonates were administered the placebo, whereas it decreased to 26% in those who received three HBIG doses at birth, and at 3 and 6 months, and 54% among infants who received a single dose of HBIG at birth only (69). HBIG should be administered in conjunction with HepB-BD and not instead of the birth dose. Importantly, the co-administration of HBIG does not suppress the anti-HB response (37). As previously demonstrated, compared to the administration of the vaccine alone, the additional administration of HBIG enhanced the protection of neonates born to HBsAg-positive mothers (70). However, the improvement in protection is not significant in full-term neonates born to HBsAg-positive/HBeAg-negative mothers (71). Infants who have received post-exposure prophylaxis may be safely breastfed beginning immediately after birth (50).

Despite the administration of HepB-BD and/or HBIG, a low frequency of PMTC can occur in neonates born to HBsAg-positive/HBeAg-positive mothers with high viral loads (71). Thus, the prevention of PMTC requires an incremental approach (72) as follows: i) At least three doses of the HBV vaccine, including a timely birth dose within 24 h; ii) HBsAg testing and linkage-to-care of mothers with follow-up of infants; iii) the administration of HBIG for children born to HBsAg-positive mothers; and iv) finally, antiviral treatment (high viral load).

In Africa, the resource-limited settings use of HBIG may not be feasible due to safety, supply and cost restraint issues (73). In addition, in the WHO Africa region, the coverage of HepB-BD is the lowest globally (74). In 1995, the HBV vaccine was introduced into the Expanded Programme on Immunisation (EPI) in South Africa. The HBsAg-based vaccine is administered as 6, 10 and 14 weeks after birth, with a booster at 18 months, all as part of a multivalent vaccine (75). Universal coverage is relatively low at 74% and individuals born prior to 1995 are excluded. Even though the South African National Guidelines recommend the HepB-BD, the introduction of catch-up vaccination and maternal HBV screening, these recommendations are yet to be implemented. These limitations allow PMCT to occur in infants born to HBsAg-positive mothers with high viral loads. Nevertheless, the introduction of HepB-B3 has resulted in decrease in the chronic carriage of HBV (76-78). Novel HBV prevention strategies that are being explored, include mRNA and viral vector-based vaccines by researchers in South Africa (79).

7. Effectiveness of HBV vaccination

The major impact that universal HBV vaccination has had on HBV-associated morbidity and mortality was demonstrated by the outcomes in Taiwan, which was the first country to introduce universal HBV vaccination in 1984. By 1986, universal infant coverage was achieved, with preschool children vaccinated by 1987, and older children and adults by 1990. Following the introduction of universal infant vaccination, the HBV carriage in infants, born to highly viraemic HBsAg-positive mothers, decreased from 90 to 15%, with a 10-fold decrease in incidence in these infants and children infected later by horizontal vaccination. This decrease in chronic HBV carriage translated to a marked decrease in the incidence of HCC in HBV vaccinees (80). The incidence of HCC was statistically significantly lower in vaccinated children compared to unvaccinated birth cohorts, with the relative risk of a vaccinee developing HCC being 0.31 ($P<0.001$), compared with an unvaccinated child (81). Despite the high coverage of infant immunization in Taiwan, a small number of children still developed HCC (82). The reasons for this include vaccine failure and neonates born to highly viraemic mothers not receiving HBIG. Furthermore, during the early days of HBV vaccination, the first dose was administered at 6 weeks, allowing for infection to occur in early life. This realization led to the introduction of HepB-BD. Similarly, universal neonate vaccination coupled with mass screening and the immunization of susceptible Alaska Natives has eliminated HCC and acute symptomatic HBV infection among Alaska Native children (83).

Unfortunately, the situation has not been as efficient in SSA and the implementation of the HBV vaccine programme has been suboptimal, even though the vaccine was introduced early in the 1980s in some countries (84,85). There are a number of reasons for this, including financial and human resource constraints, the high percentage of babies born in rural communities, poor delivery services, as well as hepatitis B being overshadowed by the 'block-busters' HIV/AIDS, malaria and tuberculosis (73). This has led to only a 71% coverage of HepB3 in the WHO Africa region compared to an 80% global coverage as of July 15, 2015, with different continents, WHO regions and countries exhibiting different levels of coverage (30). Moreover, until 2001, coverage was very low in the Africa region, with the coverage levels increasing thereafter, being higher or equal to those in South-East Asia between 2001 and 2011, thereafter plateauing at levels below those of South-East Asia; please refer to the administered and official HBV vaccination coverage (3rd dose, %) in the different WHO regions reported annually through the WHO/UNICEF Joint Reporting Form on Immunization (JRF) (86). Full protection requires that babies receive all three doses of the vaccine. In a number of countries in SSA, this is not the case, due to the

lack of access to health services in rural areas, the lack of funding from governments, and the education of both health care workers and the public in general. At 17%, HepB-BD coverage remains dismally low in SSA. A large number of births take place at home outside health facilities, and thus the administration of HepB-BD is not possible.

8. Conclusions and future perspectives

In order to eliminate HBV, a multiprong approach is required (73,87). The interventions necessary include: i) Prevention, involving the timely and universal HepB3 and HepB-BD vaccination of neonates and susceptible individuals, with full coverage and completion of the course; ii) the interruption of transmission by ensuring blood and injection safety, the prevention of PMCT and harm prevention; and iii) population-based testing and treatment. In addition to these interventions, it is critical that advocacy and education are improved. Governments and public health officials need to be encouraged to fund, implement and administer the vaccine schedules, including the HBV-BD. Moreover, both health care workers and the public need to be educated about the importance of timely vaccination and completion of all doses of the vaccination schedules. Pregnant women are a key target population, and they thus need to be further educated about the importance of prevention of HBV by vaccination of their neonates soon after birth.

However, there are several challenges faced in resource-limited settings in SSA (73), including the paucity of good data due to of lack of surveillance; limited access to laboratories and health services; the suboptimal interruption of HBV transmission routes, in particular, PMCT; no population-based testing and treatment; resource-limited settings in SSA are within the epicentre of the HIV pandemic; and inadequate public health responses.

Efficient vaccination against HBV, with universal coverage, including the Hep-BD and completion of the full course of vaccination is the first step to the elimination of HBV and the consequent clinical manifestations of the infection, including HCC. Although this may appear to be a challenge only in resource-limited settings, such as SSA, hepatitis B remains a global concern. Increasing migration from areas where HBV continues to be endemic to areas of low endemicity exposes an increasing number of individuals to the virus, and thus a concerted, global strategy is required.

Acknowledgements

The present study was published in the context of the 8th Workshop on Paediatric Virology organised virtually on October 20, 2022, by the Institute of Paediatric Virology (https://www.paediatricvirology.org) based on the island of Euboea (Greece), under the auspices of the World Academy of Sciences (WAS) and the support of the Department of Clinical Virology of the University of Crete School of Medicine and the First Department of Paediatrics of the University of Athens School of Medicine. The authors would like to thank Professor Maria Theodoridou, Professor Emerita of Paediatric Infectious Diseases at the University of Athens School of Medicine and President of the Hellenic Vaccination Committee for her valuable comments.

Funding

No funding was received.

Availability of data and materials

Not applicable.

Authors' contributions

AK contributed to the conception and design of the study, wrote the original draft, and edited and critically revised the manuscript. INM and DAS edited and critically revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

DAS is the Editor-in-Chief for the journal, but had no personal involvement in the reviewing process, or any influence in terms of adjudicating on the final decision, for this article. AK is a member of the Academic Board of the Institute of Paediatric Virology. INM and DAS are co-founders of the Institute of Paediatric Virology.

References

1. Blumberg BS. Hepatitis B: The hunt for a killer vaccine. Princeton and Oxford: Princeton University Press, 2002.
2. Alter HJ and Blumberg BS: Further studies on a 'new' human isoprecipitin system (Australia antigen). Blood 27: 297-309, 1966.
3. Prince AM: Relation of Australia and SH antigens. Lancet 2: 462-463, 1968.
4. MacCallum FO: Early studies of viral hepatitis. Br Med Bull 28: 105-108, 1972.
5. MacCallum FO: Hepatitis. Am J Dis Child 123: 332-335, 1972.
6. MacCallum FO: 1971 International symposium on viral hepatitis. Historical perspectives. Can Med Assoc J 106(Spec Issue): (Suppl): S423-S426, 1972.
7. Dane DS, Cameron CH, and Briggs M: Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. Lancet 1: 695-698, 1970.
8. Gerlich WH: Medical virology of hepatitis B: How it began and where we are now. Virol J 10: 239, 2013.
9. Krugman S, Giles JP and Hammond J: Viral hepatitis, type B (MS-2 strain). Studies on active immunization. JAMA 217: 41-45, 1971.
10. Purcell RH and Gerin JL: Hepatitis B subunit vaccine: A preliminary report of safety and efficacy tests in chimpanzees. Am J Med Sci 270: 395-399, 1975.
11. Hilleman MR, Buynak EB, Roehm RR, Tytell AA, Bertland AU and Lampson GP: Purified and inactivated human hepatitis B vaccine: Progress report. Am J Med Sci 270: 401-404, 1975.
12. Buynak EB, Roehm RR, Tytell AA, Bertland AU II, Lampson GP and Hilleman MR: Development and chimpanzee testing of a vaccine against human hepatitis B. Proc Soc Exp Biol Med 151: 694-700, 1976.
13. Szmuness W, Stevens CE, Harley EJ, Zang EA, Oleszko WR, William DC, Sadovsky R, Morrison JM and 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 303: 833-841, 1980.

14. Gerlich WH: Prophylactic vaccination against hepatitis B: Achievements, challenges and perspectives. Med Microbiol Immunol 204: 39-55, 2015.
15. Chen DS, Hsu NH, Sung JL, Hsu TC, Hsu ST, Kuo YT, Lo KJ and Shih YT: A mass vaccination program in Taiwan against hepatitis B virus infection in infants of hepatitis B surface antigen-carrier mothers. JAMA 257: 2597-2603, 1987.
16. Whittle HC, Inskip H, Hall AJ, Mendy M, Downes R and Hoare S: Vaccination against hepatitis B and protection against chronic viral carriage in The Gambia. Lancet 337: 747-750, 1991.
17. The Gambia Hepatitis Intervention Study The Gambia Hepatitis Study Group: Cancer Res 47: 5782-5787, 1987.
18. Shepard CW, Simard EP, Finelli L, Fiore AE and Bell BP: Hepatitis B virus infection: Epidemiology and vaccination. Epidemiol Rev 28: 112-125, 2006.
19. Kane MA: Status of hepatitis B immunization programmes in 1998. Vaccine 16 (Suppl): S104-S108, 1998.
20. Komatsu H: Hepatitis B virus: Where do we stand and what is the next step for eradication? World J Gastroenterol 20: 8998-9016, 2014.
21. Pasek M, Goto T, Gilbert W, Zink B, Schaller H, MacKay P, Leadbetter G and Murray K: Hepatitis B virus genes and their expression in E. coli. Nature 282: 575-579, 1979.
22. Valenzuela P, Gray P, Quiroga M, Zaldivar J, Goodman HM and Rutter WJ: Nucleotide sequence of the gene coding for the major protein of hepatitis B virus surface antigen. Nature 280: 815-819, 1979.
23. Charnay P, Pourcel C, Louise A, Fritsch A and Tiollais P: Cloning in Escherichia coli and physical structure of hepatitis B virion DNA. Proc Natl Acad Sci USA 76: 2222-2226, 1979.
24. Valenzuela P, Medina A, Rutter WJ, Ammerer G and Hall BD: Synthesis and assembly of hepatitis B virus surface antigen particles in yeast. Nature 298: 347-350, 1982.
25. Harford N, Cabezon T, Crabeel M, Simoen E, Rutgers A and De Wilde M: Expression of hepatitis B surface antigen in yeast. Dev Biol Stand 54: 125-130, 1983.
26. Poovorawan Y, Sanpavat S, Pongpunlert W, Chumdermpadetsuk S, Sentrakul P and Safary A: Protective efficacy of a recombinant DNA hepatitis B vaccine in neonates of HBe antigen-positive mothers. JAMA 261: 3278-3281, 1989.
27. McGregor A, WHO: World Health Assembly. Lancet 339: 1287, 1992.
28. Zanetti AR, Van Damme P, and Shouval D: The global impact of vaccination against hepatitis B: A historical overview. Vaccine 26: 6266-6273, 2008.
29. Gerlich WH, Glebe D, Kramvis A and Magnius LO: Peculiarities in the designations of hepatitis B virus genes, their products, and their antigenic specificities: A potential source of misunderstandings. Virus Genes 56: 109-119, 2020.
30. World Health Organization (WHO): Immunization Coverage. WHO, Geneva, 2023. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage. Accessed Oct 10, 2022.
31. World Health Organization (WHO): Interim guidance for country validation of viral hepatitis elimination. WHO, Geneva, 2021. Accessed Oct 10, 2022.
32. Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE and Margolis HS: A mathematical model to estimate global hepatitis B disease burden and vaccination impact. Int J Epidemiol 34: 1329-1339, 2005.
33. Nayagam S, Thursz M, Sicuri E, Conteh L, Wiktor S, Low-Beer D and Hallett TB: Requirements for global elimination of hepatitis B: a modelling study. Lancet Infect Dis 16: 1399-1408, 2016.
34. Hoofnagle JH, Doo E, Liang TJ, Fleischer R and Lok AS: Management of hepatitis B: Summary of a clinical research workshop. Hepatology 45: 1056-1075, 2007.
35. McMahon BJ: The natural history of chronic hepatitis B virus infection. Semin Liver Dis 24 (Suppl 1): S17-S21, 2004.
36. Marion SA, Tomm Pastore M, Pi DW and Mathias RG: Long-term follow-up of hepatitis B vaccine in infants of carrier mothers. Am J Epidemiol 140: 734-746, 1994.
37. Hepatitis B vaccines: WHO position paper - July 2017. Wkly Epidemiol Rec 92: 369-392, 2017 (In English, French).
38. Are booster immunisations needed for lifelong hepatitis B immunity? European Consensus Group on Hepatitis B Immunity. Lancet 355: 561-565, 2000.
39. Niu MT, Rhodes P, Salive M, Lively T, Davis DM, Black S, Shinefield H, Chen RT and Ellenberg SS: Comparative safety of two recombinant hepatitis B vaccines in children: Data from the Vaccine Adverse Event Reporting System (VAERS) and Vaccine Safety Datalink (VSD). J Clin Epidemiol 51: 503-510, 1998.
40. McMahon BJ, Helminiak C, Wainwright RB, Bulkow L, Trimble BA and Wainwright K: Frequency of adverse reactions to hepatitis B vaccine in 43,618 persons. Am J Med 92: 254-256, 1992.
41. Lewis E, Shinefield HR, Woodruff BA, Black SB, Destefano F, Chen RT and Ensor R; Vaccine Safety Datalink Workgroup: Safety of neonatal hepatitis B vaccine administration. Pediatr Infect Dis J 20: 1049-1054, 2001.
42. Liu Y, Zhang M, Yang M and Chen Q: Adverse Events of Vaccination against Hepatitis B Virus in Post-Marketing Surveillance from 2005 to 2017 in Guangdong Province, China. Vaccines (Basel) 10: 1087, 2022.
43. Niu MT, Salive ME and Ellenberg SS: Neonatal deaths after hepatitis B vaccine: The vaccine adverse event reporting system, 1991-1998. Arch Pediatr Adolesc Med 153: 1279-1282, 1999.
44. 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 23: 656-662, 2004.
45. DeStefano F, Mullooly JP, Okoro CA, Chen RT, Marcy SM, Ward JI, Vadheim CM, Black SB, Shinefield HR, Davis RL, *et al*: Childhood vaccinations, vaccination timing, and risk of type 1 diabetes mellitus. Pediatrics 108: E112, 2001.
46. DeStefano F, Verstraeten T, Jackson LA, Okoro CA, Benson P, Black SB, Shinefield HR, Mullooly JP, Likosky W, Chen RT, *et al*: Vaccinations and risk of central nervous system demyelinating diseases in adults. Arch Neurol 60: 504-509, 2003.
47. Duclos P: Safety of immunisation and adverse events following vaccination against hepatitis B. Expert Opin Drug Saf 2: 225-231, 2003.
48. Hernan MA, Jick SS, Olek MJ and Jick H: Recombinant hepatitis B vaccine and the risk of multiple sclerosis: A prospective study. Neurology 63: 838-842, 2004.
49. Sestili C, Grazina I and La Torre G: HBV vaccine and risk of developing multiple sclerosis: A systematic review and meta-analysis. Hum Vaccin Immunother 17: 2273-2278, 2021.
50. Schillie S, Vellozzi C, Reingold A, Harris A, Haber P, Ward JW and Nelson NP: Prevention of Hepatitis B Virus Infection in the United States: Recommendations of the Advisory Committee on Immunization Practices. MMWR Recomm Rep 67: 1-31, 2018.
51. Obando-Pacheco P, Rivero-Calle I, Gómez-Rial J, Rodríguez-Tenreiro Sánchez C and Martinón-Torres F: New perspectives for hexavalent vaccines. Vaccine 36: 5485-5494, 2018.
52. Maman K, Zöllner Y, Greco D, Duru G, Sendyona S and Remy V: The value of childhood combination vaccines: From beliefs to evidence. Hum Vaccin Immunother 11: 2132-2141, 2015.
53. Jack AD, Hall AJ, Maine N, Mendy M and Whittle HC: What level of hepatitis B antibody is protective? J Infect Dis 179: 489-492, 1999.
54. Dentinger CM, McMahon BJ, Butler JC, Dunaway CE, Zanis CL, Bulkow LR, Bruden DL, Nainan OV, Khristova ML, Hennessy TW and Parkinson AJ: Persistence of antibody to hepatitis B and protection from disease among Alaska natives immunized at birth. Pediatr Infect Dis J 24: 786-792, 2005.
55. Hammitt LL, Hennessy TW, Fiore AE, Zanis C, Hummel KB, Dunaway E, Bulkow L and McMahon BJ: Hepatitis B immunity in children vaccinated with recombinant hepatitis B vaccine beginning at birth: A follow-up study at 15 years. Vaccine 25: 6958-6964, 2007.
56. Samandari T, Fiore AE, Negus S, Williams JL, Kuhnert W, McMahon BJ and Bell BP: Differences in response to a hepatitis B vaccine booster dose among Alaskan children and adolescents vaccinated during infancy. Pediatrics 120: e373-e381, 2007.
57. McMahon BJ, Dentinger CM, Bruden D, Zanis C, Peters H, Hurlburt D, Bulkow L, Fiore AE, Bell BP and Hennessy TW: Antibody levels and protection after hepatitis B vaccine: Results of a 22-year follow-up study and response to a booster dose. J Infect Dis 200: 1390-1396, 2009.
58. Funderburke PL and Spencer L: Hepatitis B immunity in high risk health care workers. Seven years post vaccination. AAOHN J 48: 325-330, 2000.
59. McMahon BJ, Bruden DL, Petersen KM, Bulkow LR, Parkinson AJ, Nainan O, Khristova M, Zanis C, Peters H and Margolis HS: Antibody levels and protection after hepatitis B vaccination: Results of a 15-year follow-up. Ann Intern Med 142: 333-341, 2005.

60. Spradling PR, Williams RE, Xing J, Soyemi K and Towers J: Serologic testing for protection against hepatitis B virus infection among students at a health sciences university in the United States. Infect Control Hosp Epidemiol 33: 732-736, 2012.
61. Stevens CE, Toy PT, Taylor PE, Lee T and Yip HY: Prospects for control of hepatitis B virus infection: Implications of childhood vaccination and long-term protection. Pediatrics 90 (1 Pt 2): 170-173, 1992.
62. Watson B, West DJ, Chilkatowsky A, Piercy S and Ioli VA: Persistence of immunologic memory for 13 years in recipients of a recombinant hepatitis B vaccine. Vaccine 19: 3164-3168, 2001.
63. Williams JL, Christensen CJ, McMahon BJ, Bulkow LR, Cagle HH, Mayers JS, Zanis CL, Parkinson AJ and Margolis HS: Evaluation of the response to a booster dose of hepatitis B vaccine in previously immunized healthcare workers. Vaccine 19: 4081-4085, 2001.
64. 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 214: 16-22, 2016.
65. Simons BC, Spradling PR, Bruden DJ, Zanis C, Case S, Choromanski TL, Apodaca M, Brogdon HD, Dwyer G, Snowball M, *et al*: A Longitudinal Hepatitis B vaccine cohort demonstrates long-lasting hepatitis B Virus (HBV) cellular immunity despite loss of antibody against HBV surface antigen. J Infect Dis 214: 273-280, 2016.
66. Leuridan E and Van Damme P: Hepatitis B and the need for a booster dose. Clin Infect Dis 53: 68-75, 2011.
67. Stramer SL, Wend U, Candotti D, Foster GA, Hollinger FB, Dodd RY, Allain JP and Gerlich W: Nucleic acid testing to detect HBV infection in blood donors. N Engl J Med, 364: 236-247, 2011.
68. Tosti ME, Alfonsi V, Lacorte E, Mele A, Galli C, Zanetti AR and Romanò L; SEIEVA Collaborating Group: Acute Hepatitis B After the Implementation of Universal Vaccination in Italy: Results from 22 years of surveillance (1993-2014). Clin Infect Dis 62: 1412-1418, 2016.
69. Beasley RP, Hwang LY, Stevens CE, Lin CC, Hsieh FJ, Wang KY, Sun TS and Szmuness W: Efficacy of hepatitis B immune globulin for prevention of perinatal transmission of the hepatitis B virus carrier state: Final report of a randomized double-blind, placebo-controlled trial. Hepatology 3: 135-141, 1983.
70. Lee C, Gong Y, Brok J, Boxall EH and Gluud C: Hepatitis B immunisation for newborn infants of hepatitis B surface antigen-positive mothers. Cochrane Database Syst Rev (2): CD004790, 2006.
71. World Health Organization (WHO): Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection. WHO, Geneva, 2015. https://apps.who.int/iris/handle/10665/154590. Accessed Oct 10, 2022.
72. Viral Hepatitis Prevention Board (VHPB): Prevention and control of hepatitis B with combined vaccines and timely birth dose vaccination: Hanoi, Vietnam. VHPB, Belgium, 2018. https://www.vhbp.org/node/229. Accessed Oct 10, 2022.
73. Kramvis A: Challenges for hepatitis B virus cure in resource-limited settings in sub-Saharan Africa. Curr Opin HIV AIDS 15: 185-192, 2020.
74. World Health Organization (WHO): Immunization coverage. WHO, Geneva, 2022. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage. Accessed Oct 10, 2022.
75. Spearman CW, Sonderup MW, Botha JF, van der Merwe SW, Song E, Kassianides C, Newton KA and Hairwadzi HN; Division of Hepatology, Department of Medicine, University of Cape Town, South Africa: South African guideline for the management of chronic hepatitis B: 2013. S Afr Med J 103 (5 Pt 2): 337-349, 2013.
76. Amponsah-Dacosta E, Lebelo RL, Rakgole JN, Burnett RJ, Selabe SG and Mphahlele MJ: Evidence for a change in the epidemiology of hepatitis B virus infection after nearly two decades of universal hepatitis B vaccination in South Africa. J Med Virol 86: 918-924, 2014.
77. Tsebe KV, Burnett RJ, Hlungwani NP, Sibara MM, Venter PA and Mphahlele MJ: The first five years of universal hepatitis B vaccination in South Africa: Evidence for elimination of HBsAg carriage in under 5-year-olds. Vaccine 19: 3919-3926, 2001.
78. Burnett RJ, Kramvis A, Dochez C and Meheus A: An update after 16 years of hepatitis B vaccination in South Africa. Vaccine 30 (Suppl 3): C45-C51, 2012.
79. Maepa MB, Ely A, Kramvis A, Bloom K, Naidoo K, Simani OE, Maponga TG and Arbuthnot P: Hepatitis B Virus Research in South Africa. Viruses 14: 1939, 2022.
80. Chang MH: Decreasing incidence of hepatocellular carcinoma among children following universal hepatitis B immunization. Liver Int 23: 309-314, 2003.
81. Chang MH, You SL, Chen CJ, Liu CJ, Lee CM, Lin SM, Chu HC, Wu TC, Yang SS, Kuo HS, *et al*: Decreased incidence of hepatocellular carcinoma in hepatitis B vaccinees: A 20-year follow-up study. J Natl Cancer Inst 101: 1348-1355, 2009.
82. Chang MH, Chen TH, Hsu HM, Wu TC, Kong MS, Liang DC, Ni YH, Chen CJ and Chen DS; Taiwan Childhood HCC Study Group: Prevention of hepatocellular carcinoma by universal vaccination against hepatitis B virus: The effect and problems. Clin Cancer Res 11: 7953-7957, 2005.
83. McMahon BJ, Bulkow LR, Singleton RJ, Williams J, Snowball M, Homan C and 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 54: 801-807, 2011.
84. Prozesky OW, Szmuness W, Stevens CE, Kew MC, Harley EJ, Hoyland JA, Scholtz JE, Mitchell AD, Shabangu A, Kunene E, *et al*: Baseline epidemiological studies for a hepatitis B vaccine trial in Kangwane. S Afr Med J 64: 891-893, 1983.
85. Prozesky OW, Stevens CE, Szmuness W, Rolka H, Harley EJ, Kew MC, Scholtz JE and Mitchell AD: Immune response to hepatitis B vaccine in newborns. J Infect 7 (Suppl 1): S53-S55, 1983.
86. World Health Organization (WHO): Maternal, Newborn, Child and Adolescent Health and Ageing: Data Portal. WHO, Geneva, 2022. https://platform.who.int/data/maternal-newborn-child-adolescent-ageing. Accessed Oct 10, 2022.
87. World Health Organization (WHO): Global Hepatitis Report 2017. WHO, Geneva, 2017. https://www.who.int/publications/i/item/9789241565455. Accessed Oct 10, 2022.