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TOPIC HIGHLIGHT

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Hepatitis B: Epidemiology and prevention in developing countries

Elisabetta Franco, Barbara Bagnato, Maria Giulia Marino, Cristina Meleleo, Laura Serino, Laura Zaratti

Elisabetta Franco, **Laura Zaratti,** Department of Public Health, University Tor Vergata, via Montpellier 1, 00133 Rome, Italy
Barbara Bagnato, **Maria Giulia Marino,** PhD Program for Methodologies in Preventive Medicine and Therapy, **University** Tor Vergata, via Montpellier 1, 00133 Rome, Italy
Cristina Meleleo, Laura Serino, Specialization School for Hygiene and Preventive Medicine, University Tor Vergata, via Montpellier 1, 00133 Rome, Italy
Author contributions: **Franco E coordinated the work; Bagnato** B, Marino MG, Meleleo C, Serino L and Zaratti L performed the literature search and evaluation; **all authors collaborated in writ**ing the paper.
Correspondence to: Elisabetta Franco, MD, Professor of Hygiene, Department of Public Health, University Tor Vergata, via Montpellier 1, 00133 **Rome, Italy.** franco@med.uniroma2.it
Telephone: +39-06-72596122 Fax: +39-06-2025285
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Abstract

Hepatitis B virus (HBV) infection is a serious global public health problem. The infection may be transmitted through sexual intercourse, parenteral contact or from an infected mother to the baby at birth and, if contracted early in life, may lead to chronic liver disease, including cirrhosis and hepatocellular carcinoma. On the basis of the HBV carrier rate, the world can be divided in 3 regions of high, medium and low endemicity. The major concern is about high endemicity countries, where the most common route of infection remains vertical transmission from mother to child. Screening of all pregnant women and passive immunization with human hepatitis B immunoglobulin are not affordable for many developing countries. **The infection rate can** be reduced by modifying behavior, improving individual education, testing all blood donations, assuring asepsis in clinical practice and screening all pregnant women. However, **availability of a safe and efficacious vaccine** and adoption of appropriate immunization strategies are the most effective means to prevent HBV infection and its consequences. The unsolved problem for poorest countries, where the number of people currently infected is high, is the cost of the vaccine. A future challenge is to overcome the social and economic hurdles of maintaining and improving a prevention policy worldwide to reduce the global burden of the disease.

Key words: Hepatitis B; Developing countries; Endemicity; Seroprevalence; Vaccine

Peer reviewers: Frank Tacke, Professor, Department of Medicine III, University Hospital Aachen, Pauwelsstr 30, Aachen 52074, Germany; **Pierluigi Toniutto, Professor, Medical Liver** Transplant Unit, Internal Medicine, University of Udine, Piazzale SM della Misericordia 1, 33100 **Udine, Italy**

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INTRODUCTION

Viral hepatitis type B is a common, serious disease caused by the hepatitis B virus (HBV), a partially double-stranded DNA virus of the Hepadnaviridae family. Four major serotypes (adw, ayw, adr and ayr) and nine minor subtypes have been serologically identified at the hepatitis B surface antigen (HBsAg) level. The complete sequencing of DNA from HBV isolates worldwide has led to the identification of eight genotypes (from A to H) and a number of subgenotypes, showing different ethno/geographic distributions. HBV genotypes have also been associated with different clinical outcomes and response to interferon therapy. HBV is one of the main causes of hepatic

decompensation, cirrhosis and hepatocellular carcinoma (HCC). Acute disease usually occurs when the immune response is well preserved, while patients with an immunodeficiency are more likely to develop a chronic disease, then becoming a source for new infections. The likelihood that an HBV infection become chronic depends upon the age at which a person is infected, infants and young children being the most likely to develop chronic infection[1,2].

HBV is carried in blood and other body fluids, including saliva, tears, semen and vaginal secretions. Depending on the epidemiological pattern within a geographic area, the main ways of transmission are sexual intercourse, parenteral contact or infection of the baby at birth from an infected mother. Globally, about one third of the population has been infected with HBV; six percent are chronic carriers and over 600 000 people die each year from acute disease or chronic sequelae secondary to HBV infection. On the basis of the HBV carrier rate, the world can be divided in to high, medium and low endemicity regions. The major concern is about high endemicity countries, especially in Asia and Africa, where the most common routes of infection remain vertical transmission from mother to child and horizontal transmission between children[1].

Vaccination is the most effective measure to reduce the global incidence of hepatitis B. Compared to other healthcare interventions, vaccination is an economically advantageous option, both in terms of cost-effectiveness and benefit-cost ratios. In 1991, the World Health Organization (WHO) recommended that all countries introduce a policy of universal hepatitis B vaccination to prevent and control HBV infection and its long term sequelae on a global scale. By the end of 2008, hepatitis B vaccine for infants was introduced nationwide in 177 countries. To date, global hepatitis B vaccine coverage is estimated at 69%[2,3].

GLOBAL PREVALENCE AND EPIDEMIOLOGY OF HEPATITIS B: FOCUS ON DEVELOPING COUNTRIES

HBV infection occurs all over the world. The WHO has estimated that there are more than 2 billion HBV infected people and about 378 million chronic carriers worldwide. There are approximately 620 000 HBV related deaths each year. In addition, approximately 4.5 million new HBV infections occur worldwide each year, of which a quarter progresses to liver disease. In high endemic areas, like central Asian republics, Southeast Asia, Sub-Saharan Africa and the Amazon basin, the HBV carrier rate is over 8%. In low endemic regions, like the United States, Northern Europe, Australia and parts of South America, HBsAg prevalence is less than 2%. The Middle East, some Eastern European countries and the Mediterranean basin are considered areas of intermediate endemicity with a carrier rate between 2% and 8%[1].

In many countries, after the introduction of mass immunization campaigns, the prevalence of HBV notably changed, resulting in a decrease of the HBsAg carrier rate and HCC incidence[2]. It was estimated that liver cancer represents approximately 4% of all new cancer cases diagnosed worldwide and that more than 50% of liver cancers were attributable to HBV. The highest age-adjusted incidence rate (> 20 per 100 000) was reported from Southeast Asian and Sub-Saharan African countries that are endemic for HBV infection. Up to 90% of infants infected during the first year of life and 30%-50% of children infected between one to four years of age develop chronic infections and about 25% of adults who become chronically infected during childhood die from HBV-related liver cancer or cirrhosis[4].

HBV continues to be the major HCC risk factor worldwide, although its importance will continue to decrease during the next decades due to the widespread use of the HBV vaccine in newborns[5-13].

In the last few years, more and more data have been produced in developing countries and areas with high/intermediate endemicity where the most common route of infection is still vertical transmission from mother to child and horizontal transmission between children, particularly siblings[2,14-20].

Globally, perinatal HBV transmission accounts for an estimated 21% of HBV-related deaths, while regionally it ranges from 13% in the Eastern Mediterranean region to 26% in the Western Pacific region. Recent studies in Africa confirm the relatively high HBsAg seroprevalence in pregnant women, irrespective of age, parity, gestational age, residence, history of blood transfusion, dental manipulation, tattooing and circumcision[14]. The maternal-neonatal transmission was studied in Libya where HBsAg positivity was 1.5% and transmission 60.9% and in Ghana with a HBsAg prevalence of 16% but a materno-fetal transmission only in 8.4% of neonates[15,19].

In high endemic areas, other important modes of HBV transmission concern some high-risk groups such as health care workers (HCWs)[21-25], but also sexual contacts[26] and intravenous drug use[27-32]. The predominant ways of infection in areas of low endemicity play a role. Parenteral or percutaneous routes of HBV transmission, such as needle stick injury and mucus membrane splash in healthcare setting, as well as tattooing, piercing, sharing razors or toothbrushes, are also important in spreading the virus[33-35]. Surgery and dental care may be a source of infection; transfusion-related infections have currently become very rare in developed countries thanks to the improved serology and advances in molecular blood screening but can be an important source of infection in the poorest countries[36-45].

The prevalence of the infection in HCWs, a high risk group for acquiring infection with blood born pathogens due to occupational contact with infected body fluids, depends upon HBV prevalence in the general population. In India, an intermediate endemic zone where the estimated prevalence rate of HBV in the healthy general

population is around 4.7%, a recent study showed a 5% HBsAg positivity in HCWs, but a highest seropositivity of around 40% among laboratory technicians[23]. In Taiwan, among HCWs who were exposed to high risk patients, nearly 16% had HBV[24]. In north-west Turkey between 2002 and 2003, the occupational hazard of exposure to HBV was evaluated among 595 nurses. In total, 18.7% had been exposed to HBV infection and 2.7% were HBsAg positive. This result was in accordance with findings of several other studies, showing the level of prevalence for exposure to HBV among nurses to be between 16%-20%. In this study, 28% of nurses working in high risk departments were not vaccinated. Education plays a role in exposure to infection, with a decreasing trend from nurses that had received a normal high-school or equivalent education and those who had been educated to university standard[23].

Transfusion-related infections are an important source of HBV transmission, especially in the poorest countries. In countries with advanced medical, diagnostic and laboratory services, a large proportion of blood is used in sophisticated treatments requiring a high level of transfusion support, including chemotherapy, open heart surgery, organ transplantation and the management of hematological disorders such as leukemia, thalassemia and hemophilia. The pattern of blood usage is very different in countries where diagnostic and treatment options are more limited, with a much greater proportion of transfusions being given to women with obstetric emergencies and children suffering from severe anemia, often resulting from malaria and malnutrition. Data from WHO shows that, of the estimated 80 million units of blood donated annually worldwide, only 38% is collected in the developing world where 82% of the world's population live[44]. In 2007, 162 countries provided data to WHO on 85.4 million blood donations. The data comes from countries that account for a total of 5.9 billion people, representing 92% of the global population. About one fourth of the countries are not able to screen all blood donations for one or more of the transfusion-transmissible infections, including HIV, hepatitis B, hepatitis C and syphilis; only 48% of blood donations in developing countries are screened following basic quality assurance procedures; only 25% of the hospitals performing transfusions in developing countries and 33% of the hospitals in transitional countries have a transfusion committee to monitor transfusion practices, compared to 88% of the hospitals in developed countries[37].

In Sub-Saharan Africa, the risk of transfusion-transmitted infections is thought to be substantial because of the high prevalence of these infections, the frequent use of paid or replacement donors and incomplete screening coverage[41]. In most Latin American and Asian countries, blood and blood products are now regularly screened for HBsAg; for example, in Brazil where the screening of blood became mandatory in 1993, the prevalence of HBsAg decreased significantly from 0.36% in 1998 to 0.14% in 2005 due to the better control of blood donors and the decreasing infection rate in the general population[36].

In the majority of the Latin American countries where endemicity is intermediate/low, sexual intercourse is thought to be the most common route by which HBV infection is transmitted. In Brazil, a study from Victoria showed a HBV prevalence of 3.8% in HIV patients, while in other settings the prevalence rates ranged from 5.7% to 24.3%. While chronic HBV infection in the setting of HIV/AIDS is not considered an opportunistic infection, it is a common co-existing infection seen in HIV-infected individuals because of the shared modes of transmission[26].

Drug use is another important route of transmission of HBV. In Latin America, in low endemicity areas, injectable drug-related and sexual transmission of hepatitis viruses are a significant problem among young, HIV-infected and heterosexual individuals, even if the use of parenteral drugs is not common in these regions[27].

PREVENTION OF HEPATITIS B INFECTION

Prevention of HBV infection is a public health priority, especially for those groups at major risk of becoming chronic carriers.

Infection rate can be reduced through a modification of behavior and improving individual education. Testing of all blood donations and assuring asepsis in clinical practice reduce the risk of contracting HBV. Moreover, screening of all pregnant women helps to avoid mother to child transmission at birth. Administration of human hepatitis B immunoglobulin contributes to preventing neonatal infection and can be used after exposure to HBV as prophylaxis. Vaccination is the most effective means of preventing hepatitis B, cirrhosis and hepatocellular carcinoma worldwide[46-51].

The first vaccines, available between 1981 and 1982, were produced by harvesting the hepatitis B surface antigen from plasma of chronic HBsAg carriers and contained highly purified 22 nm HBsAg particles inactivated through a combination of urea, pepsin, formaldehyde and heat. These immunogenic plasma-derived vaccines have been used with success in several hundred million individuals and are still produced in Asia and used in a number of countries. Concern about the safety of these vaccines regarding transmission of blood-borne pathogens has proved to be unfounded. In the mid 1980s, recombinant DNA hepatitis B vaccines containing HBsAg expressed in HBV transfected yeasts (i.e. *Saccharomyces cerevisiae*), the so-called "second" generation hepatitis B vaccine, were commercialized. This new technology offered the potential of unlimited production, which allowed the hepatitis B vaccine to become one of the most widely used in the world. Several hundred million doses of hepatitis B vaccine have been administered worldwide with an excellent record of safety and efficacy. Similar results were obtained in India, where a new recombinant DNA HBV vaccine was produced[52,53].

Following a full course of vaccination (3 doses given at 0, 1 and 6 mo), seroprotection rates of antibodies against HBsAg (anti-HBs) are close to 100% in children

and almost 95% in healthy young adults. People who are elderly, obese, heavy smokers or immunocompromised, including those infected with HIV, may have suboptimal responses when vaccinated. Immunodeficient patients, such as those undergoing hemodialysis or immunosuppressant therapy, require higher doses of vaccine and more injections (i.e. at months 0, 1, 2 and 6) to achieve an adequate immune response. Rapid protection (i.e. for health care workers exposed to HBV or a susceptible sexual partner of an acute hepatitis B patient) can be achieved through the adoption of an accelerated schedule, including 3 doses of vaccine administered at 0, 1 and 2 mo, followed by a booster dose given at 12 mo. The site of injection and mode of administration are critical factors in achieving an optimal response. The vaccine should be given intramuscularly into the deltoid region in children (≥1 year of age) and adults or into the anterolateral thigh in newborns and infants (< 1 year of age). The intradermal route and buttock administration are not recommended. Hepatitis B vaccines are well tolerated. Side effects are generally mild, transient and confined to the site of injection (erythema, swelling, induration). Systemic reactions (fatigue, slight fever, headache, nausea, abdominal pain) are uncommon. However, in recent years, the safety of the hepatitis B vaccine has been questioned, but extensive studies concluded that there is no reason to change the current policies of vaccination. Hepatitis B vaccination is not contraindicated in pregnant or lactating women. The only absolute contraindications are known hypersensitivity to any component of the vaccine or a history of anaphylaxis to a previous dose.

Follow-up studies have shown that the vaccine-induced antibody persists over periods of at least 10-15 years and that the duration of anti-HBs is related to the antibody peak level achieved after primary vaccination. Follow-up of those vaccinated has shown that the antibody concentrations usually decline over time but clinically significant breakthrough infections are rare. Evidence indicates that successfully vaccinated individuals who have lost their antibodies over time usually show a rapid anamnestic response when boosted with an additional dose of vaccine or when exposed to the HBV. This means that the immunological memory for HBsAg can outlast the anti-HBs detection, providing long-term protection against acute disease and the development of an HBsAg carrier state. For immunocompromised patients, regular testing and booster administrations when anti-HBs antibody level falls below 10 mIU/mL are recommended instead.

Antibodies to the hepatitis B surface antigen are mainly targeted to bind the amino acid hydrophilic region, referred to as a determinant of HBsAg. This provides protection against infection with all HBV genotypes and is responsible for the broad immunity afforded by hepatitis B vaccination. The emergence of HBV S-gene mutants possibly able to escape the vaccine-induced response was suggested. However, at least at present, the overall impact of such mutants remains low and they do not pose a public health threat or a need to modify the established hepatitis B vaccination programs[1,2].

STRATEGIES FOR PREVENTION OF HEPATITIS B INFECTION SUITABLE FOR DEVELOPING COUNTRIES

In 1991, WHO recommended that all countries with a high hepatitis B disease burden should introduce the hepatitis B vaccine in their routine immunization programs by 1995 and all other countries by 1997. However, uptake of the vaccine was slow and the targets were not met. Even when the initial high price of the vaccine came down substantially, most low-income countries were unable to secure the funds needed to introduce the vaccine. Before the launch of GAVI (Global Alliance for Vaccines and Immunization) in 2000, less than 10% of the world's poorest countries were using hepatitis B vaccine in their routine immunization programs.

With support from GAVI through its financing arm, The Vaccine Fund, by December 2003, over 42 million children in low-income countries had been immunized with hepatitis B vaccine; as a result, over 500 000 premature deaths from hepatitis B have been prevented among children born in 2001-2003[54].

The most recent available data show global hepatitis B vaccine coverage at 69% with the following regional distribution: 67% in the African region; 76% in the European region; 81% in the Eastern Mediterranean region; 88% in the Americas; and 89% in the Western Pacific. Coverage in the South-East Asia region increased from 29% to 41% from 2007 to 2008. The immunization coverage with the 3rd dose of Hepatitis B vaccines in infants, in 2009, for country is: ≥ 90% (108 countries or 56%, most of them in low endemic areas); 80%-89% (31 countries or 16%); 50%-79% (31 countries or 16%); < 50% (7 countries or 4%); Hepatitis B not on schedule (16 countries or 8%)[55].

In 2005, the World Health Assembly approved and the United Nations Children's Fund (UNICEF) Executive Board endorsed the Global Immunization Vision and Strategy (GIVS). The primary objective of GIVS was to reduce vaccine-preventable disease mortality and morbidity by two-thirds by 2015 compared to 2000.

A mathematical model was developed to estimate the cost required to reach this goal in 117 low- and lower-middle-income countries and the study conclusions were that, in the 72 poorest countries, up to 40% of the overall resource needs were unmet[56].

WHO recommends that all countries introduce the hepatitis B vaccine into routine national infant immunization programs. Furthermore, in countries where a high proportion of infections with HBV are acquired perinatally (specifically in countries where the prevalence of chronic HBV infection in the general population is ≥ 8%), WHO recommends the first dose of hepatitis B vaccine be given as soon as possible after birth (< 24 h) to prevent perinatal HBV transmission.

In 2006, birth-dose coverage varied widely by region,

from 3% to 71%. Birth-dose coverage for states with ≥ 8% prevalence of chronic HBV infection was 36% (range by region, 1%-92%), and for countries with < 8% prevalence, it was 20%. Among the 81 states with immunization schedules that include a birth dose of hepatitis B vaccine, 22 (27%) did not report coverage data on the birth dose. It is likely that the reporting of the coverage of newborns with hepatitis B vaccine through the reporting form could be improved[57].

When introducing the hepatitis B vaccine into infant immunization programs, national policy-makers must decide when to begin the vaccine series: (1) at birth for all infants; (2) at birth but targeted only at newborns of HBV-infected women; or (3) at the same time in the immunization schedule as other vaccines are administered for all infants (for example, at 6 wk when other vaccines in the Expanded Program on Immunization are initiated), which is too late to prevent perinatal HBV infection. Administering a birth dose of hepatitis B vaccine only to newborns of HBV-infected women is usually not feasible in developing countries where the endemicity is high; this strategy is prone to error and misses post-exposure prophylaxis of infants, even in countries where testing and identifying infected women during pregnancy are well established. Additionally, it fails to provide early pre-exposure protection to babies born to uninfected women who may live with infected household contacts. Administering hepatitis B vaccine to infants within 24 h after birth is logistically challenging for several reasons. Firstly, many infants, especially in remote or poor areas, are born at home without the services of skilled attendants and therefore no trained providers are present to administer immunizations. Secondly, infant vaccines are usually given by specialized providers in well-baby clinics or other outpatient health settings, or during outreach immunization sessions in the community, but care of mothers during delivery and of infants immediately after birth is often provided by maternal health workers; so administering a birth dose of hepatitis B vaccine requires the coordination of these two types of workers. Thirdly, in many parts of the world, vaccines are delivered from central stores to peripheral clinics at monthly or at even longer intervals; these are primarily intended for use during periodic immunization sessions. Thus, the hepatitis B vaccine needed for the birth dose may not be available every day for administration to newborns.

Interventions that could improve birth-dose coverage include: increasing the number of infants born in facilities or attended by skilled health staff; improving coordination between immunization staff and maternal health staff; integrating delivery of the birth dose of hepatitis B vaccine into part of essential newborn care; improving the reach of the cold chain; exploring options for delivering the vaccine to infants born and residing in areas beyond the cold chain; and conducting health promotion and training to improve awareness among providers and parents of the importance of administering hepatitis B vaccine within 1 d after birth[2, 14-20].

Immunizing newborns with the hepatitis B vaccine should be the highest priority in highly endemic areas where the contribution of perinatal transmission to the overall disease burden is greatest. Nevertheless, even in countries with < 8% prevalence of chronic HBV infection, vaccinating newborns may be an important control strategy. Disease modeling suggests that the implementation of a birth dose of hepatitis B vaccine in WHO regions with a relatively low prevalence of chronic HBV infection, such as the Americas or Europe, will result in an additional 10%-20% reduction in HBV mortality in those regions compared with a hepatitis B vaccination schedule without a birth dose[57,58].

Post-exposure prophylaxis was thoroughly studied in infants born to HBeAg-positive HBsAg carrier mothers. The efficacy of protecting from chronic HBsAg carriage with passive-active immunoprophylaxis in these infants is more than 90%. In the case of hepatitis B immune globulin (HBIG) being skipped, active immunization is still effective, but the effectiveness of protecting from chronic HBV infection decreases slightly to more than 83%. The other means to increase the effectiveness of immunization against perinatal mother-to-infant HBV infection is to give HBIG to newborns of all HBsAg carrier mothers, as is done in the United States and in most European countries, but the costs rises considerably.

Although immunizing with universal vaccination is the only way to control HBV infection, recent advances in the specific treatment have enabled suppression of the chronic viral infection. Because humans are the only reservoir of the virus, if HBV could be eradicated or strongly and effectively suppressed in human carriers, the spread of HBV would be prevented.

Chronic hepatitis B can be treated by α-interferon (IFN- α; regular or pegylated) or nucleoside analogs. In properly chosen patients with chronic hepatitis B, 30%-40% will have a sustained virological response 6-12 mo after IFN-α treatment. More importantly, 30%-70% of the initial virological responders will clear serum HBsAg on follow up. The wide range of HBsAg clearance may be due to different durations of follow up, different treatment regimens, different distributions of HBV genotypes and different ethnic background of the patients. Seronegativity of HBsAg has very important implications: it signifies a better prognosis for patients and a much lower infectivity of the previous HBsAg carrier. The oral nucleoside analogs are effective and very well-tolerated. At present, these treatments are indicated for HBV carriers with disease activities; nevertheless, there may be exceptions: because high maternal viral load of HBV is the most critical factor in perinatal HBV transmission, even after on-schedule immunoprophylaxis, lowering the maternal viral load by antiviral therapy may reduce the perinatal HBV infection[59].

CONCLUSION

In spite of the decrease of the burden related to HBV

infection due to the adoption of mass immunization campaigns all over the world, the number of people still currently infected, especially in developing countries, will represent a public health concern in the foreseeable future. Improving prevention policy worldwide is mandatory in order to reduce the global burden of the disease.

A substantial number of WHO member states in areas with low or intermediate hepatitis B endemicity have implemented vaccination of newborns with the hepatitis B vaccine. Consideration should be given to implementing routine vaccination of newborns against HBV infection globally to prevent mortality and morbidity due to infection acquired perinatally.

Unfortunately, screening of all pregnant women and the use of human hepatitis B immunoglobulin as passive immunization is not affordable for many developing countries, so child vaccination remains the only means to prevent HBV spreading.

With its relatively modest costs and high benefits, HBV immunization continues to be one of the best values for public health investment today.

Moreover, enforced testing for HBsAg of blood donations in those countries where it is not a universal requirement yet could be an important measure to prevent infections in clinical settings, as well as maintaining asepsis in invasive techniques and vaccination for high risk groups.

A future challenge is to overcome the social and economic hurdles to maintain and improve prevention policy worldwide to reduce the global burden of the disease.

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