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Editorial

Hepatitis B-infected pregnant women & their newborns: Implement knowledge in your community

"Recently a promising young pediatrician in a Sub-Saharan African country died in his early thirties after presenting with weight loss, jaundice, and increasing RUQ pain. One month later, his brother, a mathematician and few years older, died with similar symptoms. Both had typical presentations of hepatitis B virus (HBV) related liver disease acquired at birth and after a rather symptom free interval of some 3 decades complicated by the development of hepatocellular carcinoma at a by now incurable stage. The disease predominates in young males and may typically present in the 3-4th decade of life. We dedicate this editorial to our colleague and his brother and hope for renewed awareness and motivation to prevent HBV-related deaths".

The World Health Organization (WHO) designated World Hepatitis Day (July 28) to focus on the battle against viral hepatitis that includes hepatitis B, frequently transmitted from mother to child [mother-to-child transmission (MTCT)] around birth and during the first years of life. July 28 is the birthday of Dr Baruch Blumberg, the late Nobel laureate, who along with his colleagues in 1967 discovered the Hepatitis B virus (Australia Antigen), and in 1969 introduced the first plasma-derived hepatitis vaccine. This year also marks the 41st anniversary of a 1981 landmark article by Beasley *et al*[1], who identified hepatitis B as a key player in the development of hepatocellular carcinoma. In the same year, his group published a randomized clinical trial that showed how hepatitis B immunoglobulin (HBIG) could dramatically reduce HBV transmission in newborns[2]. Brechot *et al*[3] demonstrated integration in the host-genome (the human hepatocyte's DNA) that enhances the development of liver cell cancer (HCC.) This unique feature makes HBV different from the other hepatitis viruses that are RNA viruses. The ability to integrate contributes to the HCC risk of patients with chronic active hepatitis B with and without cirrhosis, unlike hepatitis C, where HCC only develops if the patient has full-blown cirrhosis. Risk may be confounded by alcohol, obesity and other factors.

The identification of the HBV virus was followed by vaccine development, initially plasma derived from infected patients, but now effectively and safely synthesized[4]. Although new vaccines are under development with the potential for fewer shots and higher potency, many effective vaccines are available worldwide. In the 1970s, a worldwide effort to vaccinate newborns, and initially for six diseases was led and supported by the WHO, aligning with many other organizations and charitable partnerships. In the 1980s, once the impact of HBV immunization on disease and HCC prevention had become clear, HBV vaccination was added to the Expanded Program for immunization (EPI) in 1992[5] and rapidly implemented in many countries[6]. This was a major event: Vaccination to prevent chronic liver disease and hepatocellular carcinoma became a reality! Many countries later introduced catch-up programmes to benefit people who missed the HBV vaccinations during early childhood[7,8].

Meanwhile, effective therapy for chronic hepatitis B became also available (interferon, nucleos(t)ide analogues). More potent agents with greatly diminished resistance issues made chronic hepatitis B control a reality and mitigated chronic liver disease and HCC. Unfortunately, whereas HBV viral control can be achieved, eradication is, as yet, not feasible. This situation is mainly due to the inability to reach and eradicate the intranuclear coiled DNA in the infected hepatocyte[9]. Both hepatitis B and human

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immunodeficiency virus (HIV) can be suppressed by antiviral therapy, whereas with hepatitis C, global viral eradication is now the rule and a 2030 target by the WHO[10]. HBV therapy goals include suppression of the virus with reduced inflammatory activity, and the associated development of cirrhosis and hepatocellular carcinoma. In some instances, scar formation may even reverse. This situation reflects a paradigm shift concerning the reversibility of cirrhosis. Antivirals can also reduce and/or eliminate the source of infection and, therefore, the spread of the disease. Finally, among immunosuppressed patients, hepatitis flares of inactive HBV disease can be prevented or controlled by therapeutic agents[11].

Viral hepatitis contributes significantly to the global burden of disease. An estimated two billion people have been exposed to HBV, and close to 300 million people worldwide are affected by chronic hepatitis B infection[12]. HBV affects disproportionate populations with chronic infections caused by hepatitis B and hepatitis C in regions such as South-East Asia, sub-Saharan Africa (SSA)[13,14]. An estimated 40 million people are infected with chronic HBV in India, and over 60 million people are infected in SSA. Two features are striking: Only a fraction (<1-2%) have received treatment among nearly all (>90%) who could benefit from treatment; most are not yet even diagnosed[15]. Most lack access to treatment for various reasons[15], and socioeconomic factors prevail in low-income countries. Though universal screening would be an option, this is not easily doable or necessarily a priority in all parts of the world. Practical recommendations have included limiting screening to countries where HBV is highly endemic, while other countries target specific at-risk groups. This includes prison populations (high risk but potentially also an effective treatment environment), men who have sex with men, unsafe needle practices (remarkably frequent) or beyond the professional use (illicit drugs), migrant populations that move from endemic areas to low prevalence countries, and healthcare professionals. Universal precautions are very important.

To reduce MTCT of infected mothers and effectively prevent the acquisition of HBV, passive and active vaccination have remained key, but recommended policies evolved over time. The current recommendations is universal vaccination of all new born infants within 24 hours after birth (HepB-BD) as a start of the regular vaccination schedule, and HBIG administration within 12 hours in case of HBV infected mothers[16]. The initial preventative strategy with plasma-derived HBIG was soon accompanied by a drop of HCC in children and eradication of has become undisputed as the way to prevent worsening disease and HCC[17].

Among risk groups with specific implications are pregnant women, known to be infected prior to pregnancy or identified during maternal screening at the initial antenatal visit. Perinatal and early life MTCT is a major factor for the newborn acquiring HBV infection. Universal screening of pregnant women for HBV (and HIV) has been advocated, followed by early vaccination if there are no signs of HBV (safe in pregnancy) and if infected with HBV, also passive immunization (HBIG) within 12 h after delivery. Although increasingly aggressive strategies were very successful compared to taking no action, in recent years, the failure rate has received more attention. Even if policies are implemented, there is an estimated failure rate of some eight per cent in mostly high income countries, and likely more depending circumstances in low-income countries, and many newborns still get infected in early infancy. This is unfortunate because the immature immune system in early life will fail to clear the virus in about 90 per cent of cases, which sharply contrasts with healthy adults who will clear the virus (develop full immunity) in >95 per cent of cases[18]. Major factors for failure include the lack of implementation of timely vaccination for various reasons such as incorrect interpretation of test results and inability to comply with recommended vaccination policies. Numerous other factors deserve consideration[19].

Unfortunately, less than a quarter (20.3%) of countries in Africa have initiated the HBV vaccine birth dose (HepB-BD) WHO recommendation[19]. Birth-dose vaccination has helped reduce the prevalence of chronic HBV infection but the limited implementation of the programme may defer elimination as a WHO target for 2030 by 10-20 years[20].

HBV-infected women who have a high viral load in pregnancy (and are often HBe-Ag positive) remain at risk for MTCT. Failure to eliminate HBV in early life, and when typically asymptomatic, the infected persons will become a source of infection with all its detrimental long-term disease consequences that will persist and spread in society. It can take decades before the tip of the iceberg shows up, not uncommonly as dramatically as in our young pediatrician and his

brother. The current view is that women who are found to be HBV infected through high maternal HBV DNA viral load (≥200,000 IU/mL) or are HBeAg positive, should begin in the second trimester of pregnancy and close monitoring of pregnancy through six months post birth[21,22]. The decrease in viral load is expected to reduce transmission risks by a further 70 per cent or more[23]. Cost-effectiveness analysis and further review of options were recently published for a specific country[24].

What are opportunities for clinical and research-oriented professionals to contribute to the success of World Hepatitis Day and, specifically, the health of pregnant women and newborns? What are research opportunities? The latter represents a broad spectrum, including the need for quality control studies to help us identify where to do better. Excellent vaccines are available. Antivirals are available. However: are we doing enough in our communities? Can we address challenges with minimally sophisticated and largely already available resources? Obtaining major new publishable information would be helpful career wise, but the primary focus may simply be how any programme efforts add to the improved health of our communities. This in itself could be a primary reward. Outlining how one accomplished the improvements and dealt with the hurdles unique to your situation could be helpful to others.

Some suggestions below are in line with the WHO suggestions/priorities related to eradicating viral hepatitis B. We limit ourselves to hepatitis B, although various aspects may also apply to HCV (Box)[16,25,26].

(*i*) Assess the awareness and attention that this problem gets in your own community/hospital/practice. Is there any indication that it is adequately addressed? What are the hurdles? Are there opportunities? Do we know when in our community HBV vaccination was implemented and therefore know when the age of "unlikely vaccinated" started?

Those not directly involved in the care of these patients can, by just asking and drawing attention to the problem, create an opening. The COVID-19 pandemic has taught us about the vital role of community leaders in and outside the medical profession that could help. Those more directly involved in obstetrical care and public health programmes (care providers at all levels involved in obstetrical care: nurses, midwives, physicians including primary care, infectious disease, hepatology and public health team members) may identify major opportunities. Has this been made a joint venture and responsibility? Are all patients screened for HBV, vaccinated if needed and identified as needing prompt passive/active vaccination around birth? Is there proper screening implemented for those who will have a home delivery? Who in your place/community may already have tools to document the screening and efficacy of programmes? It may take cases like our young paediatrician and his brother to motivate and renew plans that may have been neglected. How can your programme be improved, and what hurdles exist? It has been noted that, in theory, all patients in their obstetrics practices should have HBV status documented. However, in the real world and in the communities, they attended to, it was the true exception rather than the rule to find this information in the records. This aspect needs to be taken care of.

Among specific priorities in community research could be a focus on how to identify women with a high viral load that would be candidates for antiviral therapy. This may sometimes be for the treatment of their disease, but for most, it will certainly initially be to prevent perinatal transmission. Unfortunately, current HBV-DNA testing (viral load) is often too costly and beyond reach in many places worldwide. Could cheaper, locally available markers be used or compared (such as titres of HBsAg)? A recent meta-analysis suggested that HBeAg could be a viable candidate[27]. Could mobile equipment like an elastography device (Fibroscan R) help in the assessment of disease severity, in point-of-care testing to identify high-risk patients that need therapy for HBV beyond prophylaxis? If the viral load is very high, should we follow the week 28 initiation of antivirals or consider it even earlier if very high viral loads? Have we created better platforms for medical communication during COVID-19 that may also help other initiatives?

(*ii*) Societal disparities, magnified since COVID-19, and equitable access to care, including screening, are a major challenge. Vaccination programmes have come to a standstill, putting many at risk and requiring major catch-up. Among the many topics that need to be addressed is that while screening for HBV is one intervention, more action must be taken if it has implications. Perinatal care is a major opportunity. A point-of-care emphasis that tries not only to identify patients infected with the HBV but also provides a further diagnostic and treatment pathway to assess if long-term treatment is indicated and a further follow up is essential.

Box. Spectrum of opportunities for healthcare workers and others to prevent mother-to-child transmission of hepatitis B

Preventing hepatitis B MTCT
1. What is the awareness of the problem in your community? Can you identify someone with similar symptoms to our vignette? Challenges? Is the issue adequately addressed? Ask and explore! When was HBV vaccination implemented?
2. What can you do?
(a) In your non-professional role/community member?
(*i*) Community initiatives (school, social, youth, sport or religious organization?)
(*ii*) Political/administrative activities?
(*iii*) Educational opportunities, need for catch-up vaccinations
(b) In your professional role as healthcare worker (clerical role, nurse, physician, midwife and obstetrician): Identify your team members include leaders in community
(*i*) Perinatal care: Was your patient vaccinated?
(*ii*) Collaborative efforts of all parties, streamline, role clarification
(*iii*) Not limited to facilities/in-patients but also implementation if delivery at home
(c) Early perinatal check for HBsAg
(*i*) If positive test for HBeAg, HBV-DNA if possible
(*ii*) Vaccinate mother as needed (safe and good opportunity in second-trimester pregnancy)
(*iii*) Implement HBV antivirals as needed
(*iv*) Newborn should receive
• HBIG (0.5 ml) IM within 12 h of birth
• All newborns' hepatitis B vaccine birth dose within 12-24 h after birth

Source: Refs 16,25,26. MTCT, mother-to-child transmission; IM, intramuscularly; HBIG, hepatitis B immunoglobulin; HBV, hepatitis B virus

Screening for the early detection of HCC has had an impact in high-income countries. If done in low-income countries without a pathway to treatment, goals and potential benefits need to be defined. An important consideration is the level of access to digital platforms and the literacy of patients. Have specific tools been developed to reach and target specific populations?

The many complexities of implementing vaccination were recently well summarized in a review[18]. As academics and practicing healthcare providers, we may also need to increase our openness and understanding of those who oppose vaccinations for various reasons.

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