

## Most effective preventive measure, key to reducing perinatal hepatitis-B virus, a global health strategy: Systematic review

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**ABSTRACT:** Background: over 240 million of people are chronic hepatitis B carriers globally, acquired basically through vertical transmission. The infection is proportionally represented in all continent across the global.

Purpose: The aim of this study is to systematically review articles to identify the most effective preventive measure to curb perinatal transmission of hepatitis B.

Methods: A systematic search was done in PubMed and Science Direct for review and research articles with keywords used in this review. The research was restricted to January 2016 to December 2019 for open access review and research articles. I also searched for bibliographies for original research and studies

Principal Results: Perinatal transmission hepatitis B is the main cause of chronic hepatitis B. Interventions like routine vaccination Hepatitis B virus (HBV) vaccine, combination of HBV vaccine and Hepatitis B Immunoglobulin, Antiviral therapy, and route of delivery (cesarean section and vaginal) has significantly influence in transmission of Hepatitis B to newborns. The combined interventions enumerated in World Health Organization (WHO) Health Strategy for curbing viral hepatitis is the ideal way to eliminate the disease by 2030

Major Conclusion: Identified preventive measure for curbing the spread of mother-to child transmission of Hepatitis B, singly not efficacious enough to eliminate the infection. Challenges identified in each implementation is solved with combination of two or more strategies put together. This is in agreement with WHO global health strategy 2030, for preventing viral hepatitis. More so, there is the need to identify the most effective preventive measure using meta-analysis.

**KEYWORDS:** Perinatal transmission, Hepatitis B, Global Health Strategy, Mother-to-Child-Transmission, Preventive Measure.

### 1 INTRODUCTION

Globally, it is projected that, Hepatitis B virus (HBV) is found in 257 million individuals, which killed 887,000 people in 2015 and others live with complications and major risk factor deaths from liver cirrhosis and hepatocellular carcinoma (HCC),<sup>[1-8]</sup> making it critical public health concern and major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma. <sup>[6, 7, 9-11]</sup> The infection is grouped into four phases, *namely immune tolerance phase, immune activation phase, low or non-viral replication phase and reactivation phase.*<sup>[12]</sup> More so, over 240 million individuals are chronic hepatitis B carriers, acquired basically through vertical transmission. <sup>[12-18]</sup> This occurs in the process of giving birth or immediately after delivery. The Hepatitis B surface antigen (HBsAg) is found in the following, body fluid, cord blood, breast milk, amniotic fluid, vaginal fluid and infant gastric content. <sup>[19]</sup>

In regions where the prevalence rate of Hepatitis B more than 7%, chronic form of the disease is acquire, mainly through mother to child transmission. <sup>[12, 20, 21]</sup> Hepatitis B infected pregnant women also infected their babies during delivery. Infected babies become chronic carriers. Studies have elucidated that, the possibility for an infection to become chronic depends largely on the age of the person.<sup>[1]</sup> Infected children under 6years are likely to develop chronic hepatitis due to vertical transmission from their mothers.<sup>[1]</sup> About 80 – 90% of babies develop chronic infection within the first year of life, of which 30-50% of them get chronic infection before age 6, unless they are vaccinated at birth.<sup>[1, 4, 12]</sup> Majority of chronic hepatitis is common among developing countries with the highest occurrence in western Pacific and African sub region, with prevalent rate of 6.2% and 6.1% respectively.<sup>[6]</sup> The projection Hepatitis B virus among the general public in Europe, South-East Asia, and Eastern-Mediterranean is 1.6%, 2.0% and 3.3% respectively.<sup>[1, 6]</sup> A systematic review done by JJ Otta, shows that, there was an increase

in chronic HBV infection among children 0 – 14 years in Southern Sub Sahara Africa and Eastern Sub Sahara Africa, with prevalence rate of 9% and 7% respectively.<sup>[2]</sup>

However, there are strategies recommended by WHO to curb this worrying condition. Perinatal transmission has been reduced by 10-15% by implementing active-passive immune-prophylaxis strategy, administering antepartum antiviral drugs to chronic infected patient with increased viral loads within the third trimester of pregnancy, given hepatitis B vaccine to babies immediately after delivery.<sup>[13, 19, 22]</sup> Combine administration of Hepatitis B immunoglobulin (HBIG) within 24hours after delivery with 3 dose vaccination scheduled of Hepatitis B viral vaccine (HBV).<sup>[1, 19]</sup>

Studies have shown that, caesarean section as route of delivering babies has a significant influence reducing the cause of chronic hepatitis B infection but criticize by others too. It has been proven by some studies that, these strategies by WHO has substantial impact on preventing mother to child transmission of chronic hepatitis B.<sup>[19]</sup> The yeast-recombinant vaccine is more efficacious than plasma-derived vaccines, as proven by analyses of US trials of HBIG and HBV vaccine in high-risk infants. Scientists in South-eastern Asia (specifically in Taiwan) have recorded intense decrease in new cases of HBV-related conditions among infants, proven that vaccine can prevent HCC, following the universal childhood immunization implemented in the mid-1980s.<sup>[23]</sup>

About 50 million new cases are been diagnosis globally each year, through prenatal transmission, notwithstanding the vaccination program and other preventive measures practice worldwide.<sup>[6, 20]</sup> Some scientist are of the view that, these are not entire efficient, for instance, inoculation of HBV vaccines with the HBIG given within first day of life, to babies whose mothers are HBsAg-positive, was not efficacious. The study which was conducted in China with 214 infants, unequivocally state that, those babies who were infected through intrauterine transmission, were not protected by immunoglobulin and the vaccination.<sup>[19, 24]</sup> New cases of the infections is reduced through vaccination United State of America (USA) and elsewhere, however, about 250 million of people with chronic hepatitis B do not have protection from the vaccines given.<sup>[25]</sup> Vaccination is also ineffective if the viral load in the mother's blood or body fluid is very high.<sup>[26]</sup> Granting the fact that, authorities in this study area recommend that, prophylaxis should be administered to pregnant women within 6 – 9 months, who are suspected to transmit HBV to their newborns. The argument remains, about the appropriate antiviral drug, the ideal viral load that needed treatment, when to start and end the treatment during and after delivery respectively.<sup>[27]</sup> This review seeks to bring to bear the most effective method of preventing chronic hepatitis B by use systematic review of other review articles in relation to the WHO 2030 global health strategies to eliminating viral Hepatitis.<sup>[28]</sup>

### 1.1 MODE OF MOTHER TO CHILD TRANSMISSION AND EFFECTS

HBV spreads, when uninfected person get into contact with the body fluid and mucosal exposure of infected blood. Body fluids such saliva, menstrual, vaginal, seminal fluids and content of placenta, it can also spread through skin contact.<sup>[1, 26, 29]</sup> More so, the disease is transmitted among unimmunized individuals who have sex with multiple partners or commercial workers. The use and reuse of contaminated sharp objects like syringes, razors, tooth brush and activities like some medical surgical and dental procedures can spread the infection.<sup>[1, 9, 30, 31]</sup>

The virus is still infectious outside the body of an infected individual for one week with an incubation period of 1 to 6 months,<sup>[1]</sup> which attach the liver and causes both acute and chronic form of the disease.<sup>[1]</sup> Before age 5 years, hepatitis B positive mother are likely to infect their babies which develop into chronic infection. This is perinatal transmission is common in areas where there is high prevalence of hepatitis B infection.<sup>[1]</sup>

The mechanism of mother to child transmission can be categorized into 3 possible routes, according to Panpan Yi and colleagues.<sup>[16, 32]</sup> Namely, transplacental transmission of HBV in utero (intrauterine) natal transmission during delivery (intrapartum) and postnatal transmission during care or through breast milk (postpartum).<sup>[16]</sup> Intrauterine transmission occurs in instances where there is placenta damage by contraction of muscle of the womb, like in threatened abortion, amniocentesis, infections like toxoplasma, and genetic transmission, sperm cell and oocytes. Intrapartum transmission on the other hand, is seen in the act of delivery, when the newborn gets into contact with the mother's body fluids or blood and can also occur threatened preterm labor, where contraction of uterus may cause laceration of the placenta. The third route which is postpartum transmission, is realized when the newborn suckles the breast milk or get into contact with the body fluid of the infected mother.<sup>[16, 32]</sup>

Daniel Candotti et al, used the plasma samples of some pregnant women Ghana, and paired umbilical cord blood, for testing HBV surface antigen and deoxyribonucleic acid (DNA). Mother to child transmission was identified among 17 out of 204 (8.3%) paired HBV carrier women.<sup>[32]</sup> Africa, plasma samples, obtained at delivery from 1368 pregnant Ghanaian women and paired umbilical cord blood or newborn whole blood samples, were tested for HBV surface antigen (HBsAg) and DNA. A 16% prevalence of HBV chronic carriers, defined as detectable HBsAg and/or HBV DNA, was found, 80% contained less than 1 $\times$ 10<sup>4</sup>

IU ml<sup>-1</sup> HBV DNA and 99% were infected with genotype E strains. HBV maternofetal transmission was documented in 17 out of 204 (8.3 %) paired HBV carrier women–cord blood/newborn samples.

A study by Yongjun and colleagues, where mice were used to determine mechanism of mother to child transmission of Hepatitis B infection, found out that, HBV-specific cytotoxic T lymphocyte response of HBV-negative mice born to a HBV-positive mother, was impaired. This led to identification of HBV in these mice when HBV DNA was introduced into their system. This confirms the study conducted by Le Ye Lee and friends, that, the umbilical cord HBV DNA increased with maternal HBV DNA has an association with maternal HBeAG positivity.<sup>[29]</sup> It was also realized that, the presence or absence of virus depends on the existence or nonappearance of maternal HBeAG shows how hepatic macrophages of offspring mice were polarized by HBeAG.<sup>[5]</sup> The transmission mechanism of viral Hepatitis B gives us a clear understanding, of the effective intervention to implement in order to prevent this deadly infection.<sup>[16]</sup>

## **2 PREVENTIVE MEASURES**

Elimination of Viral Hepatitis B infection needs a number of plans such as appropriate treatment given to chronic HBV patient, bridging the transmission route and vaccinating individuals at risk, a strategic pillar recommended by WHO to prevent Viral Hepatitis infection.<sup>[1, 33]</sup> A detail package of measures to eliminate perinatal transmission of HBV has been created, which includes the administration of antiviral drugs and on viral hepatitis testing for pregnant women, mothers and infants.<sup>[1, 14, 15]</sup> It is recommended by WHO that, all babies should be given HBV vaccine, immediately after delivery or latest 24 hours after delivery. Studies have elucidated that, the low incidence of chronic HBV infection among children less than age 5 years, is sequel of this approach proposed by WHO to member countries.<sup>[1, 9, 33]</sup> For instance, it was estimated in 2015 that, there was a reduction prevalence rate from 1.3% compared to pre-vaccination period of 4.7% among under 5 years children.<sup>[1]</sup>

### **2.1 HEPATITIS B VIRUS VACCINE**

This strategy has been implemented by member countries in order to immunize by vaccinating children at birth and 3 doses before age 5 year for protection which will last for at least 20 years.<sup>[1, 30, 33-35]</sup> Hepatitis B vaccination is critical plan for elimination of mother to child transmission of the infection in epidemic.<sup>[14, 15]</sup> A retrospective survey review by Alison and colleagues in Haimen, China, depict that, out 183 fully vaccinated babies born of HBsAg positive mothers, had a serological test done of which 175 test were available. The result indicated that, 171 (80.1%) babies were negative.<sup>[11]</sup> After 20 years of implementing this idea,<sup>[36]</sup> prevalence rate in Taiwan reduced drastically from 9.8% to 0.5% among children less than 15 years.<sup>[37]</sup> Similarly, there was a reduction prevalence of 83% among children younger than 15 years in China.<sup>[21]</sup> However the potency of the vaccine should be maintained especially within 2 to 8 degrees Celsius or 40 degrees Celsius when using the controlled Temperature Chain strategy recommended by WHO.<sup>[38]</sup>

Inoculation of hepatitis B virus vaccine to infants of highly infected HBeAg-positive mothers (16.8%) are likely to be infected, which leads to chronic form of the infection, regardless of proper immunization compared to babies born to HBeAg Negative mothers (1.6%).<sup>[21]</sup> High maternal viral load of > 7log<sub>10</sub> copies/ml, about 10% of infants born to HBeAg-positive HBsAg mother acquire chronic hepatitis B regardless of the doses of vaccination received. A higher viral load (> 9log<sub>10</sub> copies/ml) will result in 30% of vaccinated infants to develop form of the infection.<sup>[33]</sup> A study in China, also recommend booster of vaccine to given to children at high risk of developing the infection, when their anti-HB has disappeared.<sup>[39]</sup> Genotype C mothers with high viral loads are more likely to give birth to babies who will be infected despite been immunized.<sup>[35]</sup> Genotype C is also identified as an independent factor for chronic hepatitis B in Shanghai, China.<sup>[40]</sup> It is therefore, documented by Paganelli et al, that, vaccination are therefore changing the HBV genotype distribution. This might defeat the WHO 2030 global strategy to eradicate HBV infection unless other preventive measures and policies are put in place.<sup>[21, 33]</sup> In agreement, Cochrane review done in 2006, recorded that, hepatitis B vaccine alone is not potent as compared to combination of HBIG with Hepatitis B vaccine, preventing the transmission of the virus.<sup>[41]</sup> Compliance rate for hepatitis B vaccination is one of the challenges identified by Jeanne S. Sheffield and colleagues. Compliance is high among children but less than 50% among adults, especial sex workers.<sup>[42]</sup>

### **2.2 COMBINATION OF HEPATITIS B IMMUNOGLOBULIN AND HEPATITIS B VIRUS VACCINE**

In order to bridge the gap identified in given HBV vaccine alone, WHO has recommended the addition of Hepatitis B immunoglobulins (HBIG) to babies of HBsAg-positive mothers within 24 hours. Combined administration of vaccination with Hepatitis B immunoglobulin (HBIG) is implemented as standard protocol for newborns whose mother are Hepatitis B positive.<sup>[21]</sup> A study compared HBIG and HBV vaccine in high risk babies in USA, it proven that, yeast-recombinant vaccine is efficacious than plasma-derived vaccine<sup>[23]</sup>, which is given routine as part of Expanded Immunization Program worldwide. It therefore recommended by Z. Shi et al that HBIG should be given to complement the routine HBV vaccine given to infant, due to its effectiveness and safeness to interrupt HBV intrauterine infections.<sup>[24]</sup> Combined administration of hepatitis B

immunoglobulin and vaccination within 12 hours after delivery, has decreased the rate of vertical transmission from >90% to <10%.<sup>[17]</sup> There is reduction in the risk of occurrence of hepatitis among infants born of HBeAg-negative mothers but not change in entire protection rate, when given HBIG.<sup>[14, 21]</sup> It was also affirmed by Alison et al, after review Haimen City CDC unpublished data that, 4 babies still tested HBsAg after been given Hepatitis B vaccine and HBIG within 24 hours after delivery. Their mothers were HBeAg, with a viral load between  $8 \times 10^6$  and  $5 \times 10^7$  [11]

### 2.3 ANTIVIRAL DRUGS THERAPY

Maternal serum HBsAg titer and mode of delivery, influence perinatal transmission of Hepatitis B. Elective cesarean section and vaginal delivery as mode of delivery 10.2% and 28% risk of mother to child transmission of the infection respectively. It has been suggested by studies that, antepartum antiviral treatment like, nucleoside analogs, telbivudine and tenofovir disoproxil fumarate, should be given to chronic hepatitis B patient with high viral load. During 6 -9 months of pregnancy, mothers with high viral load are given either lamivudine, telbivudine or tenofovir to reduce transmission rate.<sup>[13, 21, 33, 40, 43]</sup> It is also shown elsewhere that, nucleoside or nucleotide analogs, as the first line of treatment, is helpful and safe in decreasing the incidence of vertical transmission among pregnant women with high HBV DNA load,<sup>[3, 33]</sup> but it is ineffective against HBsAg seroclearance, hence a high risk of post-treatment virology failure.<sup>[44]</sup> Siemienut RA, et al Randomized Control Trial, state that, combination of Antiretroviral Therapy reduce the risk of mother to child transmission of infection, such Hepatitis B and HIV.<sup>[45]</sup>

Prevention of chronic hepatitis through management of perinatal transmission comes with a lot of challenges, such as, the failure of passive-active immunoprophylaxis in newborns, effect and necessity of periodical HBIG injection to mothers, safety of antiviral prophylaxis with nucleoside, benefit of different delivery ways and safety of breastfeeding are some concerns raised in these management.<sup>[16]</sup>

More so, there are numerous factors that leads to antiviral drug resistance. High viral load, resistant variants, slow response, prior therapy with nucleoside analogue leading cross resistance, high body mass index, patient immune status and compliance have been as factors which contribute to drug resistance.<sup>[35]</sup> Notwithstanding immunoprophylaxis against viral hepatitis in pregnancy, mother to child transmission is occur persist in at least 10% of infants born to mother with high viral load.<sup>[43]</sup> Aslam et al in a study documented that, HBV can resurface during pregnancy and postpartum period, when advanced chronic HBV positive pregnant mothers suspend the antiviral treatment. During pregnancy, the cell mediated immunity is suppressed, which prevent the denial of the semi-allogenic fetus. This contributes to rise in HBV replication and elevated level of aminotransferases during pregnancy and immediately after delivery.<sup>[43]</sup> It is recorded by two different studies conducted in USA that, in real clinical setting, HBeAg seroconversion rate is expressively low, especially in entecavir treated patient and 10% for nucleoside analogue.<sup>[3]</sup>

### 3 ROUTE OF DELIVERY

The influence of mode of delivery (cesarean section and vaginal deliveries) to, mother to child transmission of hepatitis B, has also been assess to ascertain a number of researchers. A study with meta-analysis conducted in China, revealed that, cesarean section has significant impact for reducing perinatal transmission of hepatitis B. Out of 5105 women who delivered through cesarean section, 223 of them transmitted the infection to their newborns, representing 4.37%. On the other hand, 447 women transmitted the infection to their babies, out of 4801 mothers who had vaginal delivery, representing 9.31%.<sup>[46]</sup> However, other authors are of the view that, cesarean section as mode of delivery, has no significant effect on mother to child transmission of viral hepatitis B.

By and large, greater population of susceptible or infected persons do not access to prevention services, not tested, do not use or adhere to regimen, and cannot access chronic care services.<sup>[14, 15]</sup> Several articles reviewed under preventive measures in this writing revealed that, although, the measures are somewhat effective, there some significant gaps identified in their implementation. About 9% -20% of babies born of HBeAg mothers are still infected with the infection.<sup>[16, 46]</sup>

### 4 WORLD HEALTH ORGANIZATION 2030 AGENDA ON PREVENTING VIRAL HEPATITIS B

As part of the efforts to attain universal health coverage under the sustainable development goal 3 (target 3.3), WHO has developed a strategy to prevent spread of viral Hepatitis especial Hepatitis B. Studies have shown that, hepatitis B is main of cause of chronic hepatitis B with over 240 million carriers globally.<sup>[13-15, 47, 48]</sup> Wide-ranging plan is needed to reduce the incidence of mother to child transmission of hepatitis B to zero, by preventing pregnant women with chronic hepatitis B virus infection, injecting hepatitis B vaccine to babies the first 24 hours after delivery, safe delivery practices, improving maternal and child health services, and development of new interventions to prevent trans based on antiviral treatment.<sup>[14, 15]</sup> This strategy seeks to achieve a lot of health target including 2030 agenda.<sup>[14, 15]</sup> It is estimate that, over 20 million deaths will occur within the 2015 and 2030, with the high level for over 40 years, if preventive measures are not expanded and scale-up to curb

this menaces.<sup>[14, 15]</sup> The worrying trend is that, less than 5% of individuals living with chronic hepatitis know the status.<sup>[14, 15]</sup> It therefore necessary to create awareness and make diagnostic service easily accessible to all.

#### **4.1 GLOBAL VISION**

The vision strategy is to have viral hepatitis transmission free world, with already infected people having easy access to safe, affordable and effective prevention, care and treatment service.<sup>[14]</sup>

#### **4.2 GOAL**

Reducing viral hepatitis to zero level of infection, as key public health threat by 2030. It is targeted that, 10 million infections will be reduced to 0.9 million infections by 2030, of which hepatitis B virus infections reduced by 95% and 90% prevalence rate reduction of among HBsAg children,<sup>[14, 23]</sup> by increasing vaccination coverage at birth by 90%.<sup>[49]</sup>

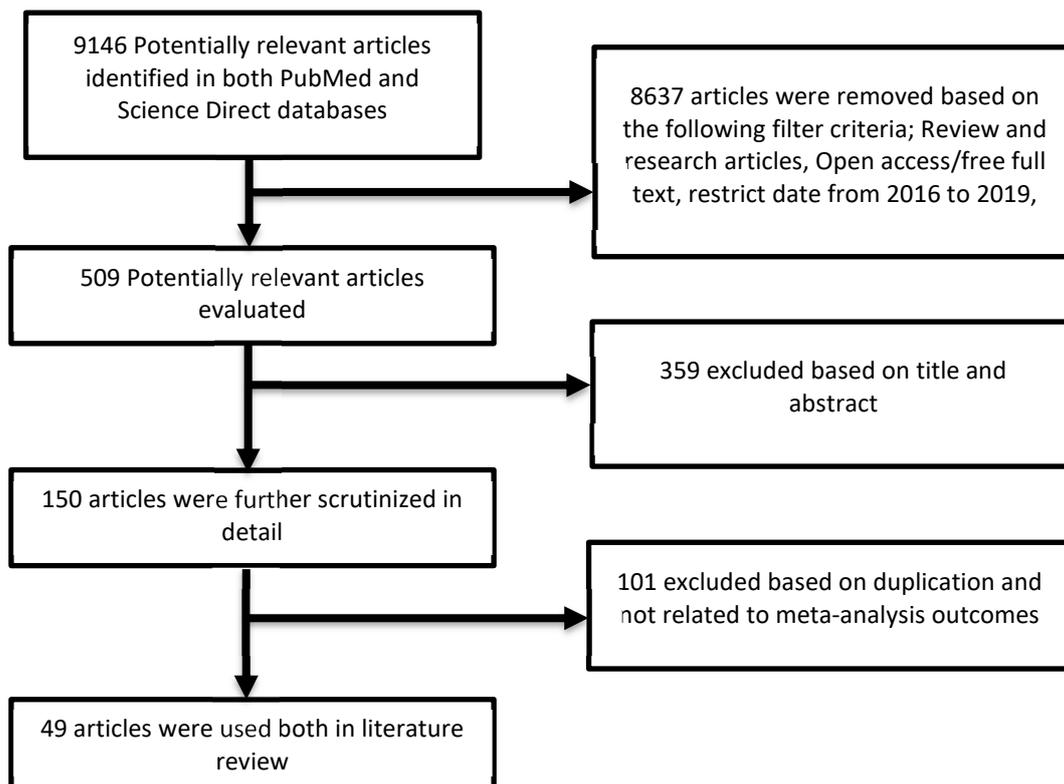
### **5 STRATEGIC DIRECTION**

To achieve the goals set, five strategic directions were fixed to guide critical actions by member countries. These strategies are; *information for focused action (know your epidemic and response)*, *interventions for impact (covering the range of services needed)*, *delivering for equity (covering the populations in need of services)*, *financing for sustainability (covering the financial costs of services)*, *Innovation for acceleration (looking towards the future)*.<sup>[14]</sup>

As part of the specific goals set by WHO to expand provision of vaccine given within 24hours after delivery, from 39% in 2015 to 50% in 2020 and 90% by 2030. This service is delivered together with “hepatitis B testing” of pregnant women and “development of new approaches to strengthen antiviral therapy.”<sup>[23]</sup> These plans suggest that, prevention of viral hepatitis needs diverse measures and if not most effective one, to eliminate this deadly infection before 2030.

### **6 METHOD**

A systematic search was in done in PubMed and ScienceDirect for review and research articles with following key words; “Mother- to Child Transmission” AND “Hepatitis B”, “vertical transmission” AND “Hepatitis B”, “Perinatal transmission” AND “Hepatitis B”, “Maternal-fetal transmission” AND “Hepatitis B”, “Transmission mechanism” AND Hepatitis B”, “Mother to child transmission” AND “Hepatitis B” AND “Meta-Analysis”. The research was restricted to January 2012 to April 2019 for open access review (free full text) and research articles.



*Algorithm for systematic review of articles*

## 7 CONCLUSION

The fact has been established by numerous studies that, perinatal transmission hepatitis B is the main cause of chronic hepatitis B. However, there are interventions recommended by WHO and proven by number of studies to be effective. Interventions like routine vaccination HBV vaccine, combination of HBV vaccine and HBIG, Antiviral therapy, and some even document that, route of delivery has significantly influence in transmission of Hepatitis B to newborns. These and other interventions suggested by various studies have challenges which hinder the goal of eliminating viral hepatitis from the globe. It is therefore, recorded in the health strategy to combine preventive measures to fight the spread of this deadly infection by 2030.

## RECOMMENDATION

There is the need to fully implement the WHO Health strategy 2030, for preventing viral Hepatitis in all countries. It is comprehensive and recommend implementation of different plans at a go, to ensure effective elimination of viral hepatitis by 2030. Secondly, detail meta-analysis review should be done, using preventive measure the outcome of the analysis. This will help us determine the most effective intervention to prevent mother to child transmission of hepatitis B.

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## CONFLICT OF INTEREST

The author has no interest in any of the issues raised or in relation with any of the institutions mentioned in this article.

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