Asian Pacific association for the study of liver (APASL) guidelines: hepatitis B virus in pregnancy

Manoj Kumar1 · Zaigham Abbas2 · Milad Azami3 · Maria Belopolskaya4 · A. K. Dokmeci5 · Hasmik Ghazinyan6 · Jidong Jia7 · Ankur Jindal1 · Han Chu Lee8 · Wei Lei9 · Seng Gee Lim10 · Chun-Jen Liu11 · Qiang Li12 · Mamun Al Mahtab13 · David H. Muljono14 · Madunil Anuk Niriella15 · Masao Omata16,17 · Diana A. Payawal18 · Shiv K. Sarin1 · Olivier Ségéral19 · Tawesak Tanwandee20 · Nirupma Trehanpati21 · Kumar Visvanathan22 · Jin Mo Yang23 · Man-Fung Yuen24 · Yingjie Zheng25 · Y. H. Zhou26

Received: 11 August 2021 / Accepted: 6 December 2021 / Published online: 3 February 2022
© Asian Pacific Association for the Study of the Liver 2022

Abstract
Hepatitis B virus (HBV) infection still remains a major public health issue in the Asia–Pacific region. Most of the burden of HBV-related disease results from infections acquired in infancy through perinatal or early childhood exposure to HBV in Asia–Pacific. Hepatitis B during pregnancy presents unique management issues for both the mother and fetus. These APASL guidelines provide a comprehensive review and recommendations based on available evidence in the literature, for the management of females with HBV infection through every stage of pregnancy and postpartum. These also address the concerns, management challenges, and required follow-up of children born to hepatitis B-positive mothers.

Keywords Hepatitis B · Acute Hepatitis B · Chronic Hepatitis B · Pregnancy

Introduction

Despite the availability of effective preventive measures including vaccination, hepatitis B virus (HBV) infection is still today a major public health issue worldwide, especially in the Asia–Pacific region. Chronic HBV infection may progress to hepatic decompensation, hepatocellular carcinoma, and cirrhosis.

Hepatitis B during pregnancy presents unique management issues for both the mother and the fetus.

Mother-to-child transmission (MTCT) is responsible for a majority of prevalent cases of chronic HBV infection in the Asia–Pacific region. Because HBV infection in infancy or early childhood often leads to chronic infection, it is important to take appropriate measures to prevent MTCT.

These guidelines are intended to be used by health-care providers, and suggest the preferred approaches to the management of females with HBV infection throughout the pregnancy and the postpartum period, and of children born to infected mothers. This document provides general guidelines only and will be applicable to the management of most of the patients, but should not replace clinical judgment for unique patients. In addition, despite increasing knowledge and research, some areas of uncertainty still exist and, therefore, appropriate choices should be made based on the evolving evidence, and the current literature as it evolves.

The experts from the members of the APASL guidelines’ development sub-committee were given specific areas for reviewing and writing consensus statements according to the level of evidence and strength of recommendation as per the current literature (Table 1) [1]. Then, the manuscript was circulated to all the members of the group for suggestions and endorsement.

Epidemiology of hepatitis B virus infection in pregnant females in Asia–Pacific

Review of literature

The burden of HBV infection in the general population including pregnant females is particularly high in

* Manoj Kumar
manojkumaradm@gmail.com; mksharma@ilbs.in
* Shiv K. Sarin
shivsarain@gmail.com; sksarain@ilbs.in

Extended author information available on the last page of the article
the Asia–Pacific region, although it varies widely among countries. The common routes of transmission of HBV are perinatal transmission; and horizontal transmission (during childhood through close contacts, unsafe injection practices, and transfusion of blood products) [2].

In the Asia–Pacific, most of the burden of HBV-related diseases results from infections acquired in infancy through perinatal or early childhood exposure to HBV. Infection acquired at an early age commonly becomes chronic: the rates of development of chronicity for infants infected in the first year of life, for children infected between 1 and 5 years of age, and peoples infected as adults are 80–90%, 30–50%, and <5%, respectively [3].

The World Health Organization (WHO) Global Health Sector Strategy on Viral Hepatitis 2016–2021 had defined targets for elimination of viral hepatitis as a major global public health threat by 2030 [4]. All WHO regions are working toward the 2030 global hepatitis B elimination target of a 90% reduction in new cases of chronic HBV infection (equivalent to <0.1% HBsAg prevalence among children aged 5 years). Other global targets for 2030 include 90% coverage of hepatitis B vaccine birth dose (within 24 h) (HepB birth dose vaccination) and other interventions to prevent MTCT of HBV, and 90% coverage of all doses of HBV vaccine (HepB3) [4].

For the purpose of reviewing the epidemiology in the Asia–Pacific region, the countries of the region were grouped as follows (according to geography): North Asia (Russia); Central Asia (Afghanistan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan); Western Asia (Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iran, Iraq, Israel, Palestine, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, Yemen); East Asia (China Mainland, Mongolia, North Korea, South Korea, Japan, Taiwan); Southeast Asia (Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, Vietnam); South Asia (Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka); and Pacific Countries (Australia, New Zealand, and Pacific Island Countries and Territories). Pacific Island Countries and Territories include Samoa, Bougainville, Cook Islands, Federated States of Micronesia, Fiji, French Polynesia, Guam, Kiribati, Nauru, New Caledonia, Papua New Guinea, Samoa, Solomon Islands, Tokelau Islands, Tonga, Tuvalu, Vanuatu, and Wallis and Futuna Islands.

North Asia (Russia)

In Russia, all pregnant females are tested for HBsAg in the first and in the third trimesters of pregnancy. Nevertheless, the data on the prevalence of chronic HBV infection in this population group are accessible only in some regions, since there is no general registration of this data. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 0.6% (95% CI 0.54–0.67%) and 0.03% (0.03–0.04%), respectively [5] (Table 2). In 2019, Russia achieved HepB3 coverage of 97% [6] (Table 2).

The available studies show that the prevalence of chronic HBV infection in pregnant females varies significantly depending on the region of Russia and the year the study was conducted. For example, HBsAg prevalence among pregnant female in Russia was reported as 0.7% in 2014 and 0.5% in 2015 [7]. Note that these data include all forms of hepatitis B, i.e., acute hepatitis B, as well as chronic HBV infection. The HBsAg detection rate in pregnant females also varies significantly across regions of Russia. In northern and central regions, the prevalence of HBsAg in pregnant females varies between 0.3 and 0.5%, while in south-eastern and eastern parts of the country, it reaches 1.4–1.5% [8–10].

Central Asia (Afghanistan, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan)

There are little data on HBV infection in pregnant females from Central Asian countries. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 5.9% (95% CI 4.63–7.17%) and 1.66% (1.16–2.2%) in Afghanistan. 2.26% (1.85–2.57%) and 0.22% (0.17–0.28%) in Kazakhstan. 2.55% (2.13–2.99%) and 0.64% (0.50–0.81%) in Kyrgyzstan, 2.52% (2.11–2.89%) and 0.29% (0.22–0.37%) in Tajikistan, 2.65% (2.23–3.02%) and 0.38% (0.28–0.46%) in Turkmenistan, and 4.34% (3.85–4.9%) and 0.42% (0.29–0.52%) in Uzbekistan, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 66%/37% in Afghanistan, 97%/93% in Kazakhstan, 95%/96% in Kyrgyzstan, 97%/99% in Tajikistan, 99%/99% in Turkmenistan, and 96%/99% in Uzbekistan, respectively [6].

While a low HBsAg prevalence in pregnant females has been reported from Afghanistan (1.14% in 2010) [11] and Kazakhstan (1.2% in 2016) [12], a much higher prevalence of 10.1% (in 2015) is reported from Tajikistan (however, the reliability of these data is questionable due to a small size of the considered group) [13]. There are no data regarding HBsAg positivity among pregnant females in Uzbekistan, Kyrgyzstan, and Turkmenistan.

Western Asia (Armenia, Azerbaijan, Bahrain, Cyprus, Georgia, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Oman, Qatar, Saudi Arabia, Syria, Turkey, United Arab Emirates, and Yemen)

There are little data on HBV infection in pregnant females from Western Asian countries. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 2.09% (95% CI 1.72–2.37%) and
0.16% (0.11–0.21%) in Armenia, 3.22% (2.79–3.63%) and 0.56% (0.41–0.72%) in Azerbaijan, 2.64% (2.25–3.03%) and 0.12% (0.09–0.16%) in Bahrain, 0.7% (0.67–0.72%) and 0.02% (0.01–0.02%) in Cyprus, 1.48% (1.46–1.5%) and 0.24% (0.21–0.28%) in Georgia, 1.53% (1.34–1.71%) and 0.09% (0.07–0.11%) in Iran, 1.98% (1.62–2.31%) and 0.43% (0.31–0.56%) in Iraq, 0.53% (0.43–0.62%) and 0.04% (0.02–0.05%) in Israel, 3.37% (3.26–3.48%) and 0.53% (0.50–0.56%) in Jordan, 1.17% (0.97–1.41%) and 0.07% (0.05–0.09%) in Kuwait, 2.82% (2.43–3.24%) and 0.58% (0.43–0.76%) in Lebanon, 2.5% (2.11–2.9%) and 0.09% (0.07–0.11%) in Oman, 1.4% (1.25–1.55%) and 0.10% (0.07–0.13%) in Qatar, 2.72% (2.31–3.14%) and 0.15% (0.12–0.19%) in Saudi Arabia, 3.08% (2.99–3.17%) and 0.82% (0.67–0.96%) in Syria, 2.43% (2.31–2.56%) and 0.17% (0.14–0.20%) in Turkey, 1.82% (1.51–2.11%) and 0.12% (0.09–0.17%) in United Arab Emirates, and 5.46% (4.93–6.0%) and 1.63% (1.28–2.01%) in Yemen respectively [5].

In Azerbaijan, 1.5% HBsAg positivity was found in 2010 in pregnant females [16].

In Iran, HBsAg prevalence in pregnant females range from 1.3% in 2014 to 0.18% in 2016 [16–26] (Table 2). In a recent meta-analysis published in 2018, the pooled prevalence of HBsAg among pregnant females was 1.35% (95% CI 1.22–1.48%) in Iran [27].

In Iraq, a case–control study done in Baghdad on 40 pregnant females visiting private-sector hospital in 2010–2011 showed HBsAg to be 5% [28]. However, another study done in primary health centers on 6975 pregnant females in 2016–2017 found HBsAg prevalence to be 0.13% [29].

Reported HBsAg prevalence in pregnant females in Israel, in a review in 1999, was ranging from 0.6 to 4% with rates varying among ethnic groups [30]. In a study published in 2010, on 186 619 deliveries from 1988 to 2007, at a University medical center, found HBsAg prevalence of 0.3% [31]. Another study on all singleton deliveries between the years 1991–2014 at a University Medical Center in Israel found 0.2% HBsAg prevalence in pregnant females [32].

Reported prevalence among pregnant females in Jordan ranges from 4.3 in 2002 to 5% in 2020 [33, 34].

A study done in 2012–2013 in 4062 pregnant females in the Hawalli Province in Kuwait found 0.3% HBsAg positivity [35].

In a recent study in Turkey on 11,015 refugee Syrian pregnant patients, HBsAg prevalence was found to be 1.1% between 2012 and 2018 [40].
Table 2  WHO targets indicators in the different countries in Asia–Pacific

| Country       | HepB3 coverage* | HepB-BD coverage* | Prevalence national | HBsAg prevalence for children < 5 years | HBsAg prevalence for pregnant females (recent data) |
|---------------|-----------------|-------------------|---------------------|-----------------------------------------|-------------------------------------------------|
| North Asia    |                 |                   |                     |                                         |                                                 |
| Russia        | 97% in 2019 [6] | NA                | 0.6% in 2019 (modeled) [5] | 0.03% in 2019 (modeled) [5] | 0.7% in 2014 [7]; 0.5% in 2015 [7] |
| Central Asia  |                 |                   |                     |                                         |                                                 |
| Afghanistan   | 66% in 2019 [6] | 37% in 2019 [6]   | 5.9% in 2019 (modeled) [5] | 1.66% in 2019 (modeled) [5] | 1.14% in 2010 [11] |
| Kazakhstan    | 97% in 2019 [6] | 93% in 2019 [6]   | 2.26% in 2019 (modeled) [5] | 0.22% in 2019 (modeled) [5] | 1.2% in 2016 [12] |
| Kyrgyzstan    | 95% in 2019 [6] | 96% in 2019 [6]   | 2.55% in 2019 (modeled) [5] | 0.64% in 2019 (modeled) [5] | NA                                               |
| Tajikistan    | 97% in 2019 [6] | 99% in 2019 [6]   | 2.52% in 2019 (modeled) [5] | 0.29% in 2019 (modeled) [5] | 10.1% in 2015 [13] |
| Turkmenistan  | 99% in 2019 [6] | 99% in 2019 [6]   | 2.65% in 2019 (modeled) [5] | 0.38% in 2019 (modeled) [5] | NA                                               |
| Uzbekistan    | 96% in 2019 [6] | 99% in 2019 [6]   | 4.34% in 2019 (modeled) [5] | 0.42% in 2019 (modeled) [5] | NA                                               |
| Western Asia  |                 |                   |                     |                                         |                                                 |
| Armenia       | 92% in 2019 [6] | 96% in 2019 [6]   | 2.09% in 2019 (modeled) [5] | 0.16% in 2019 (modeled) [5] | 0.2% in 1998, 0.5% in 1999 [14] |
| Azerbaijan    | 94% in 2019 [6] | 98% in 2019 [6]   | 3.22% in 2019 (modeled) [5] | 0.56% in 2019 (modeled) [5] | 1.5% in 2010 [15] |
| Bahrain       | 99% in 2019 [6] | 98% in 2019 [6]   | 2.64% in 2019 (modeled) [5] | 0.12% in 2019 (modeled) [5] | NA                                               |
| Cyprus        | 94% in 2019 [6] | NA                | 0.7% in 2019 (modeled) [5] | 0.02% in 2019 (modeled) [5] | NA                                               |
| Georgia       | 94% in 2019 [6] | 94% in 2019 [6]   | 1.84% in 2019 (modeled) [5] | 0.24% in 2019 (modeled) [5] | NA                                               |
| Iran          | 99% in 2019 [6] | 95% in 2019 [6]   | 1.53% in 2019 (modeled) [5] | 0.09% in 2019 (modeled) [5] | 1.3% in 2004 [17], 0.7% in 2011 [18], 1.2% in 2012 [19], 0.8% in 2014 [20], 1.2% in 2014 [21], 0.4% in 2014 [22], 1.6% in 2015 [23], 0.59% in 2015 [24], 1.56% in 2015 [25], 0.18% in 2016 [26] |
| Iraq          | 84% in 2019 [6] | 41% in 2019 [6]   | 1.98% in 2019 (modeled) [5] | 0.43% in 2019 (modeled) [5] | 5% in 2011 [28], 0.13% in 2017 [29] |
| Israel        | 96% in 2019 [6] | 95% in 2019 [6]   | 0.53% in 2019 (modeled) [5] | 0.04% in 2019 (modeled) [5] | 0.3% in 2007 [31], 0.2% in 2014 [32] |
| Jordan        | 89% in 2019 [6] | NA                | 3.37% in 2019 (modeled) [5] | 0.53% in 2019 (modeled) [5] | 4.3% in 2002 [33], 5% in 2020 [34] |
| Kuwait        | 91% in 2019 [6] | 93% in 2019 [6]   | 1.17% in 2019 (modeled) [5] | 0.07% in 2019 (modeled) [5] | 0.3% in 2012–2013 [35] |
| Oman          | 99% in 2019 [6] | 99% in 2019 [6]   | 2.5% in 2019 (modeled) [5] | 0.09% in 2019 (modeled) [5] | 7.1% in 2006 [36] |
| Qatar         | 98% in 2019 [6] | 97% in 2019 [6]   | 1.4% in 2019 (modeled) [5] | 0.1% in 2019 (modeled) [5] | 1% in 2006 [36] |
| Saudi Arabia  | 97% in 2019 [6] | 96% in 2019 [6]   | 2.72% in 2019 (modeled) [5] | 0.15% in 2019 (modeled) [5] | 2.44 in 2005 [37], 1.6% in 2008 [38], 4.1% in 2012 [39] |
| Syria         | 54% in 2019 [6] | NA                | 3.08% in 2019 (modeled) [5] | 0.82% in 2019 (modeled) [5] | 1.1% in 2018 [40] |
| Turkey        | 99% in 2019 [6] | 99% in 2019 [6]   | 2.43% in 2019 (modeled) [5] | 0.17% in 2019 (modeled) [5] | 1.6% in 2010 [41], 1.47% in 2011 [42], 3.3% in 2011 [43], 2.9% in 2011 [44], 5.7% in 2013 [45], 4% in 2015 [46], 1.2% in 2014 [47], 0.9% in 2016 [48], 1.5% in 2016 [49], 1.8% in 2018 [40] |
| United Arab    |                 |                   |                     |                                         |                                                 |
| United        | 98 in 2019 [6]  | 91% in 2019 [6]   | 1.82% in 2019 (modeled) [5] | 0.12% in 2019 (modeled) [5] | 1.5% in 2006 [36] |
| Emirates      |                 |                   |                     |                                         |                                                 |
| Yemen         | 73% in 2019 [6] | NA                | 5.46% in 2019 (modeled) [5] | 1.63% in 2019 (modeled) [5] | 10.8% in 2011 [50] |
| Region                   | HepB3 coverage* | HepB-BD coverage* | Prevalence national | HBsAg prevalence for children < 5 years | HBsAg prevalence for pregnant females (recent data) |
|--------------------------|-----------------|-------------------|---------------------|----------------------------------------|--------------------------------------------------|
| **East Asia**            |                 |                   |                     |                                        |                                                  |
| China Mainland           | 99% in 2019 [6] | 97% in 2019 [6]   | 5% in 2019 [51]     | 0.30% in 2019 (modeled) [5]            | 3.4% in 2010 in Haimen City [57], 5.49% in 2011 in Shenyang [58], 6.7% in 2012 (10 centers) [59], 3.2% in 2014 in 4 provinces [60], 7.07% in 2015 in Shaanxi province [61], 3.1% 2016 in Shenyang [62] |
| Mongolia                 | 98% in 2019 [6] | 98% in 2019 [6]   | 4.28% in 2019 (modeled) [5] | 0.29% in 2019 (modeled) [5]            | NA                                               |
| South Korea (Republic of Korea) | 98% in 2019 [6] | 92% in 2019 [6]   | 2.95% in 2019 (modeled) [5] | 0.10% in 2014 [64]                      | 3.32% in 2012 [67]                               |
| North Korea (Democratic People’s Republic of Korea) | 97% in 2019 [6] | 98% in 2019 [6]   | 10.47% in 2019 (modeled) [5] | 0.61% in 2019 (modeled) [5]            | NA                                               |
| Japan                    | 99% in 2019 [6] | 99% in 2019 [6]   | 3.04% in 2019 (modeled) [5] | 0.20% in 2019 (modeled) [5]            | 0.5% in 2011 [68]                                |
| Taiwan                   | 97.8% in 2016 [70] | NA                | 7.85% in 2019 (modeled) [5] | 0.16% in 2019 (modeled) [5]            | 5.9% in 2016 [71]                                |
| **South-East Asia**      |                 |                   |                     |                                        |                                                  |
| Brunei                   | 99% in 2019 [6] | NA                | 2.11% in 2019 (modeled) [5] | 0.1% in 2011 [64]                       | 3.2% in 1990 [74], 1.02% in 2011 [75]            |
| Cambodia                 | 92% in 2019 [6] | 88% in 2019 [6]   | 6.55% in 2019 (modeled) [5] | 0.56% in 2017 [72]                      | 4.39% in 2017 [72]                              |
| Indonesia                | 85% in 2019 [6] | 84% in 2019 [6]   | 3.62 in 2019 (modeled) [5] | 0.62 in 2019 (modeled) [5]              | 2.2% in 2014 in Jakarta [76], 2.76% in 2015 in 12 provinces [77], 6.1% in 2019 in Bandung [78] |
| Lao PDR                  | 68% in 2019 [6] | 55% in 2019 [6]   | 8.66% in 2019 (modeled) [5] | 1.7% in 2012 [64]                       | 4.4% in 2011 [79], 2.9% in 2012 [80], 8.2% in 2013 [81], 5.44% in 2008–14 [82] |
| Malaysia                 | 97% in 2019 [6] | 99% in 2019 [6]   | 1.26% in 2019 (modeled) [5] | 0.09% in 2019 (modeled) [5]             | 1.35% in 2008 [83]                               |
| Myanmar                  | 90% in 2019 [6] | 17% in 2019 [6]   | 2.39% in 2019 (modeled) [5] | 0.61% in 2019 (modeled) [5]             | 6.2% in 2016 [84]                                |
| Philippines              | 65% in 2019 [6] | 50% in 2019 [6]   | 8.24% in 2019 (modeled) [5] | 0.8% in 2018 [73]                       | 9.6% in 2014 [85], 1.43% in 2018 [86]             |
| Singapore                | 96% in 2019 [6] | 91% in 2019 [6]   | 2.69% in 2019 (modeled) [5] | 0.3% in 2010 [64]                       | NA                                               |
| Thailand                 | 97% in 2019 [6] | 99% in 2019 [6]   | 4.75% in 2019 (modeled) [5] | 0.36% in 2019 (modeled) [5]             | 6.2% in 2016 at Thai-Myanmar border [84], 1.4% in 2018 [87] |
| Timor-Leste              | 83% in 2019 [6] | 70% in 2019 [6]   | 4.13% in 2019 (modeled) [5] | 1.35% in 2019 (modeled) [5]             | 2.8% in 2014 [88]                                |
| Vietnam                  | 89% in 2019 [6] | 79% in 2019 [6]   | 6.6% in 2019 (modeled) [5] | 2.2% in 2012 [64]                       | 12.6% in 2009 – 2012 in Khan Hoa Province [89], 9.45% in 2012 in 5 regions [90], 7.8% in 2012 – 2014 in Thai Nguyen province [91] |
| **South Asia**           |                 |                   |                     |                                        |                                                  |
| Bangladesh               | 98% in 2019 [6] | NA                | 2.16% in 2019 (modeled) [5] | 0.13% in 2019 (modeled) [5]             | 0.4% in 2011 in rural areas [94]                 |
| Bhutan                   | 97% in 2019 [6] | 86% in 2019 [6]   | 2.62% in 2019 (modeled) [5] | 0.16% in 2019 (modeled) [5]             | NA                                               |
Table 2 (continued)

| Country          | HepB3 coverage* | HepB-BD coverage* | Prevalence national | HBsAg prevalence for children < 5 years | HBsAg prevalence for pregnant females (recent data) |
|------------------|-----------------|-------------------|---------------------|----------------------------------------|------------------------------------------------------|
| India            | 91% in 2019 [6] | 56% in 2019 [6]   | 2.93% in 2019 (modeled) [5] | 0.52% in 2019 (modeled) [5] | 0.25% in 2006 in South India [97], 1.1% in 2008 in North India [98] |
| Maldives         | 99% in 2019 [6] | 99% in 2019 [6]   | 2.86% in 2019 (modeled) [5] | 0.48% in 2019 (modeled) [5] | NA                                             |
| Nepal            | 93% in 2019 [6] | NA                | 1.12% in 2019 (modeled) [5] | 0.15% in 2019 (modeled) [5] | 0.32% in 2019 [100]                               |
| Pakistan         | 75% in 2019 [6] | NA                | 2.3% in 2019 (modeled) [5] | 0.54% in 2019 (modeled) [5] | > 12% in Bahawalpur, Hyderabad and Rahim Yar Khan regions in 2006–2007 [103–105], 0.34% in 2006 in Karachi [106], 1.37% in Swat in 2008 [107], 1.16% (0.96—1.37) in Peshawar district of Pakistan (in 2013–2014) [108], 2.78% in Rawalpindi in 2016–2017 [109] |
| Sri Lanka        | 99% in 2019 [6] | NA                | 1.5% in 2019 (modeled) [5] | 0.07% in 2019 (modeled) [5] | NA                                             |
| Pacific countries|                |                   |                     |                                        |                                                   |
| Australia        | 95% in 2019 [6] | NA                | 2.14 in 2019 (modeled) [5] | 0.07 in 2019 (modeled) [5] | 0.8% in South Wales in 2000 [114], 2% in 2 teaching hospitals in Sydney in 2003–2006 [115], 0.5% in Victoria between 2009 and 2017 [116] |
| New Zealand      | 92% in 2019 [6] | NA                | 0.9% in 2019 (modeled) [5] | 0.07 in 2019 (modeled) [5] | Decreasing trends from 1997 to 2009 [118]         |
| American Samoan  | NA              | NA                | 5.38% in 2019 (modeled) [5] | 0.2% in 2011 [64] | NA                                             |
| Cook Islands     | 98% in 2019 [6] | 99% in 2019 [6]   | 3.27% in 2019 (modeled) [5] | 0% in 2021 [64] | NA                                             |
| Federated States of Micronesia | 84% in 2019 [6] | 70% in 2019 [6] | 3.56% in 2019 (modeled) [5] | 0.30% in 2016 [64] | NA                                             |
| Fiji            | 99% in 2019 [6] | 99% in 2019 [6]   | 3.63% in 2019 (modeled) [5] | 0.47% in 2019 (modeled) [5] | 6.6% in 1998 [123], 2% in 2011 [124]             |
| French Polynesia | NA              | NA                | NA                   | 0% in 2014 [64] | NA                                             |
| Guam             | NA              | NA                | 5.03% in 2019 (modeled) [5] | 0% in 2015 [64] | 2% in 2014 [125]                                 |
| Kiribati         | 94% in 2019 [6] | 99% in 2019 [6]   | 7.47% in 2019 (modeled) [5] | 3.3% in 2014 [64] | 15.1% in 1998 [123], 9.2% in 2002–2003 [126]    |
| Marshall Islands | 82% in 2019 [6] | 98% in 2019 [6]   | 4.17% in 2019 (modeled) [5] | 1.2% in 2016 [64] | 8% in 2003–2003 and 10% in 2007 [127]            |
| Nauru            | 96% in 2019 [6] | 88% in 2019 [6]   | 4.76% in 2019 (modeled) [5] | 0.53% in 2019 (modeled) [5] | NA                                             |
| New Caledonia    | 96% in 2017 [6] | 96% in 2017 [6]   | 6.8% in 2000 [121] | 1.3% in 8–11 year old in 2001 [122] | 1.7–2.9 in 1996–1999 [128]                   |
| Niue             | 99% in 2019 [6] | 99% in 2019 [6]   | 3.6% in 2019 (modeled) [5] | 0% in 2015 [64] | NA                                             |
| Papua New Guinea | 35% in 2019 [6] | 25% in 2019 [6]   | 6.2% in 2019 (modeled) [5] | 2.3% in 2013 [64], 3.29% in 2014–2019 [120] | NA                                             |
| Pitcairn         | NA              | NA                | NA                   | NA                                      | NA                                             |
| Samoa            | 58% in 2019 [6] | 65% in 2019 [6]   | 5.24% in 2019 (modeled) [5] | 0.10% in 2014 [64] | NA                                             |
| Solomon Islands  | 94% in 2019 [6] | 66% in 2019 [6]   | 6.33% in 2019 (modeled) [5] | 3.1% in 2016 [64] | 13.7% in 2008 [129], 13.8% in 2015 [130]       |
In Turkey, HBsAg prevalence in pregnant females ranges from 1.6% in 2010 to 1.8% in 2018 [40–49] (Table 2). In a recent meta-analysis in 2018, the pooled prevalence of HBsAg in Turkey was 2.84% (95% CI 2.68–3.01%) [27].

In 2011, the prevalence of HBsAg among pregnant in Yemen was 10.8% [50].

**East Asia (China Mainland, Mongolia, North Korea, South Korea, Japan, and Taiwan)**

The HBsAg national prevalence and children under 5-year-old prevalence were estimated to be 5% (in 2018) [51], and 0.30% (0.20–0.50%) (in 2019) in China Mainland, respectively [5]. In 2019, China Mainland achieved HepB3 coverage of 99%, and HepB-birth dose coverage of 97% [6]. In China Mainland, the prevalence of HBsAg in child-bearing-aged females has been extensively investigated in several large cross-sectional studies including several millions of females as part of the Triple Elimination of MTCT of HIV, HBV, and Syphilis [51]. Currently, in this age group (20–49 years old), the overall prevalence of HBsAg is around 5.5% (4.9–11.8%) [52–56].

Specifically, the HBsAg prevalence in pregnant females (mostly aged 26–28 years, varying from 16 to 47 years) has also been widely reported as 4.5% (3.0–7.0%), with around 37% (26–67%) of them being also positive for HBeAg [57–62].

The modeled HBsAg national and children under 5-year-old prevalence in 2019 were estimated to be 4.28% (95% CI 3.88–4.7%) and 0.29% (0.20–0.36%) in Mongolia, respectively [5]. In 2019, Mongolia achieved HepB3 coverage of 98%, and HepB-birth dose coverage of 98% [6]. In Mongolia, the prevalence of HBsAg is 9.4% in child-bearing-aged females [63].

The modeled HBsAg national and children under 5-year-old prevalence in 2019 were estimated to be 2.95% (95% CI 2.81–3.1%) in 2019 [5], and 0.10% in 2014 [64] in South Korea (Republic of Korea), respectively. In 2019, South Korea (Republic of Korea) achieved HepB3 coverage of 98%, and HepB-birth dose coverage of 92% [6]. In South Korea (Republic of Korea), the prevalence of HBsAg in child-bearing-aged females (20–49 years) is 1.7–3.7% in recent years [65, 66]. In pregnant females, the HBsAg prevalence is 3.32% in 2012 [67].

The modeled HBsAg national and children under 5-year-old prevalence were estimated to be 2.95% (95% CI 2.81–3.1%) in 2019 [5], and 0.10% in 2014 [64] in South Korea (Republic of Korea), respectively. In 2019, South Korea (Republic of Korea) achieved HepB3 coverage of 98%, and HepB-birth dose coverage of 92% [6]. In South Korea (Republic of Korea), the prevalence of HBsAg in child-bearing-aged females (20–49 years) is 1.7–3.7% in recent years [65, 66]. In pregnant females, the HBsAg prevalence is 3.32% in 2012 [67].

The modeled HBsAg national and children under 5-year-old prevalence in 2019 were estimated to be 10.47% (95% CI 9.11–12.29%) and 0.61% (0.47–0.78%) in North Korea (Democratic People’s Republic of Korea) [5]. In 2019, North Korea (Democratic People’s Republic of Korea) achieved HepB3 coverage of 97%, and HepB-birth dose coverage of 98% [6]. There are no recent data on HBsAg prevalence in pregnant females in North Korea.
In 2019, the modeled HBsAg national prevalence and children under 5-year-old prevalence were estimated to be 3.04% (95% CI 2.67–3.37%) [5] and 0.20% (0.0–0.40%) in Japan, respectively [64]. In Japan, mother-to-child transmission is the major route of establishing chronicity of HBV, but it is less common than in other Asian countries. In 2019, Japan achieved HepB3 coverage of 99%, and HepB-birth dose coverage of 99% [6]. From June, 1985, all pregnant females were screened for the presence of serum HBsAg, and from January, 1986, the Government started financing programs for prevention of vertical transmission of HBV infection. This program involves HBsAg testing of all pregnant female and inoculation of anti-HBsAg human immunoglobulin (HBIG) and HBV vaccines to all infants born to HBsAg-positive mothers, which has led to extremely low prevalence of HBsAg in general population as well as pregnant female in Japan. In a recent study on pregnant female who gave birth at all delivery hospitals/clinics in Hiroshima prefecture between April 2010 and March 2011, it was found that overall HBsAg-positive rate was 0.51% (95% CI 0.40–0.63%), and an extremely low prevalence (0.10%; 95% CI 0.00–0.25%) was observed among pregnant female born after 1986. Perinatal HBV transmission is estimated to be almost completely inhibited in the next generation [68].

Taiwan is a success story of tackling hepatitis B virus infection. The modeled HBsAg national and children under-5-year-old prevalence in 2019 were estimated to be 7.85% (95% CI 7.5–9.19%) and 0.16% (0.13–0.18%) in Taiwan, respectively [5]. From epidemiology studies in Taiwan, the rate of HBsAg carriage was high in the general population (15–20%) before 1970; and more than 70% of hepatocellular carcinoma (HCC) was associated with chronic HBV infection [69]. To tackle this serious health problem, the Taiwan government launched a mass vaccination program against hepatitis B in July 1984, and the program was very successful in the prevention of new HBV infection in the young generations [69]. Statistics from the Ministry of Health and Welfare, Taiwan, revealed that the 2016 newborn HBV vaccination rate was as high as 97.8% [70]. To investigate the evolution of HBV infection status in pregnant mothers, Su et al. conducted a 32-year cross-sectional study using the data from the National Immunization Information System in Taiwan [71]. Maternal HBsAg and HBeAg data was collected from a screening program. The authors then used an age-period-cohort model to analyze 940 180 pregnant females collected in years 1996, 2001, 2006, 2011, and 2016, respectively. They found that the annual rate of HBsAg seropositivity decreased from 13.4% during 1984–1985 (before the era of nationwide vaccination) to 5.9% in 2016 (3 decades after vaccination program). The annual rate of HBeAg seropositivity decreased from 6.4% during 1984–1985 to 1.0% in 2016. Pregnant females born after July 1986 (the HBV vaccination cohort) had the lowest risk (relative risk = 0.27) of HBsAg positivity compared with those born before June 1984. After controlling the birth cohort effect, the rate of HBsAg carriage in pregnant female has been significantly decreased through the universal infant HBV immunization program. These findings suggested that the majority of perinatal HBV infection on the next generation will be prevented in Taiwan [71]. To further lower the risk of vertical transmission, new strategies in combination with the vaccination program have already been implemented in the post-immunization era in Taiwan, including the administration of birth dose HBIG and HBV vaccine to all newborns of chronic HBV-infected mothers and the administration of oral nucleos(t)ide analogue during the third trimester of pregnant females with high serum viral load.

Southeast Asia (Brunei Darussalam, Cambodia, Indonesia, Lao PDR, Malaysia, Myanmar, Philippines, Singapore, Thailand, Timor-Leste, and Vietnam)

The HBsAg national prevalence and children under-5-year-old prevalence were 2.11% (95% CI 1.82–2.41%) in 2019 (modeled) [5] and 0.10% in 2011 [64] in Brunei Darussalam, 6.55% (5.5–7.56%) in 2019 (modeled) and 0.56% in 2017 [72] in Cambodia, 3.62% (3.17–4.05%) in 2019 (modeled) and 0.62% (0.49–0.76%) [5] in Indonesia, 8.66% (7.32–10%) in 2019 (modeled) [5] and 1.7% (0.8–2.6%) in 2012 [64] in Lao PDR, 1.26% (1.14–1.38%) and 0.09% (0.07–0.12%) in 2019 (modeled) [5] in Malaysia, 2.39% (1.99–2.71%) and 0.61% (0.46–0.82%) in 2019 (modeled) [5] in Myanmar, 8.24% (7.2–9.36%) in 2019 (modeled) [5] and 0.70% in 2018 [73] in Philippines, 2.69% (2.52–2.86%) in 2019 (modeled) [5] and 0.30% in 2010 [64] in Singapore, 4.75% (4.43–5.09%) and 0.36% (0.28–0.45%) in 2019 (modeled) [5] in Thailand, 4.13% (3.34–4.93%) and 1.35% (1.01–1.80%) in 2019 (modeled) [5] in Leste, and 6.6% (6.3–6.92%) in 2019 (modeled) [5] and 2.20% (1.5–3.10%) in 2011 [64] in Vietnam, respectively (Table 2).

In 2019, HepB3/HepB-birth dose coverage was 92%/88% in Cambodia, 85%/84% in Indonesia, 68%/55% in Lao PDR, 97%/99% in Malaysia, 90%/17% in Myanmar, 65%/50% in Philippines, 96%/91% in Singapore, 97%/99% in Thailand, 83%/70% in Timor-Leste, and 89%/79% Vietnam, respectively [6]. In 2019, HepB3 coverage was 99% in Brunei Darussalam [6].

As reported in Table 2, HBsAg prevalence among pregnant females is >2% for all the countries in Southeast Asia (intermediate level) with data available and >7–8% for some of them (high level). However, many of these data were reported 10 years ago and recent national seroprevalence surveys are missing.

One old study in 1990 found 3.2% HBsAg positivity in pregnant females of Brunei Darussalam [74]. Another study done in a tertiary care hospital (in 2011) in Brunei found
HBsAg positivity was 1.4% [87].

One survey conducted among children (5–7 years old) born during 2010–2012 and their mothers in Cambodia found overall HBsAg positivity of 4.39% (95% CI 3.53–5.45%) among mothers and 0.56% (95% CI 0.32–0.98%) among children. HBsAg positivity was higher among children without hepatitis B vaccination [4.62% (95% CI 1.31–14.97%)], and among children with an HBsAg-positive mother [10.11% (95% CI 5.41–18.11%)]. Although hepatitis B vaccination birth dose (HepB-BD) was received by 78.4% of the children, only 54.4% received the birth dose timely [72].

In Indonesia, HBsAg prevalence of 2.2% was found among pregnant females in Jakarta (in 2014) [76]. HBsAg prevalence among 69,891 pregnant females across 12 provinces in Indonesia was 2.76% in 2015, with the lowest found in West Sumatra Province (1.6%) and the highest in West Papua Province (8.0%) [77]. A study conducted from July 2018 to April 2019 in 27 midwifery clinics and one private obstetric clinic in Bandung (Indonesia) found HBsAg positivity of 6.1% among the pregnant females [78].

In Lao PDR, in studies on children and mother pairs, HBsAg prevalence was found to be 4.4% (95% CI 3.0–5.7%) in 2011 [79] and 2.9% (95% CI 1.7–4.2%) in mothers in 2012 [80]. Another study has found HBsAg prevalence of 8.2% in 2013 [81]. In a recent retrospective study from Lao PDR, performed in a Hospital Laboratory on pregnant females from 2008 to 2014, showed overall HBsAg positivity of 5.44% (95 CI 5.1–5.8%), with the annual prevalence ranging from 4.6 to 6.2%. A slight but steady and significant decrease in prevalence over the 7 years of the study could be documented [82].

In a cross-sectional study of antenatal mothers who attended government health clinics in Ipoh (Malaysia) between July 2008 and October 2008 found HBsAg prevalence of 1.35% [83].

Among females tested (2012–2016) in antenatal clinics on the Thai-Myanmar border (immigrants and refugees from Myanmar), overall confirmed HBsAg prevalence was 6.2% [84].

In a study among pregnant subjects attending prenatal clinic at the Philippine General Hospital from January to July 2014, HBsAg positivity was found to be 9.6% [85], whereas another study found HBsAg prevalence of 1.43% in pregnant females admitted to a tertiary hospital in Philippines (from 2014 to 2018) [86].

In a recent hospital-based study from Thailand, on pregnant females attending antenatal clinics (2015–2018), HBsAg prevalence was 1.4% [87].

In a study on females delivering at private clinic (2013–2014) in Timor-Leste HBsAg prevalence was 2.8% [88].

In studies from Vietnam, HBsAg prevalence was 12.6% (95% CI 11.1–14.0%) in Khan Hoa Province, central Vietnam in 2009–2012 [89], 9.45% in 2012 in 5 regions [90], and 7.8% in 2012–2014 in Thai Nguyen province [91].

In these countries with high-prevalence populations, infant vaccination against HBV is crucial. Most of the countries in South-East Asia have achieved >90% HepB3 coverage (excepting a few countries like Indonesia, Lao PDR, Philippines, Timor-Leste, and Vietnam) and >50% of HepB-birth dose coverage (except Myanmar) as recommended by WHO for 2020. Currently >90% HepB-birth dose coverage has been achieved by some of the countries (Malaysia, Singapore, and Thailand) (Table 2). However, as reported in Table 2, HBsAg prevalence for children 5 years old remains >1% in a few countries (Lao PDR, Timor-Leste, and Vietnam) (WHO 2020 target) and >0.1% in most of the countries (WHO 2030 target).

South Asia (Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, and Sri Lanka)

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.16% (95% CI 1.97–2.35%) and 0.13% (0.10–0.16%) in Bangladesh, respectively [5]. In 2019, HepB3 dose coverage was 98% in Bangladesh [6]. In one old study (1992), HBsAg was positive in 3.6% in 500 pregnant mothers [92]. In another study on 1800 pregnant females who delivered from October 1995 to January 1996 at Dhaka Medical College Hospital, 63 of 1800 or 3.5% of the mothers were found to be HBsAg positive. Of the 63 HBsAg-positive mothers, 19 (30.2%) were found to be HBeAg positive. Only two of the HBsAg-positive mothers had established acute infection [93]. More recent studies have found decreasing trend. In a study (2011), HBsAg was positive in 0.4% of pregnant females in rural Bangladesh. This study was done years after incorporating hepatitis B vaccination schedule in the Expanded Program on Immunization (EPI) to vaccinate the children in rural Bangladesh; the prevalence is gradually declining [94].

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.62% (95% CI 2.53–2.73%) and 0.16% (0.13–0.17%) in Bhutan, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 97%/86% in Bhutan [6]. Data on HBsAg prevalence in pregnant females are lacking from Bhutan.

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.93% (95% CI 2.57–3.29%) and 0.52% (0.42–0.63%) in India, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 91%/56% in India [6]. Many studies from the Indian subcontinent have
looked specifically at the prevalence of HBsAg positivity in pregnant females. However, only very few studies were sufficiently large, with adequate number of females screened, to reach a meaningful conclusion. In one old study, HBsAg positivity in pregnant female was 3.7% in 1987 [95] and 1% in 1999 in North India [96]. More recent studies have found lower HBsAg prevalence in pregnant females: 0.25% in 2006 in South India [97] and 1.1% (2004–2008) in North India [98]. In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.86% (95% CI 2.37–3.39%) and 0.48% (0.34–0.64%) in Maldives, respectively [5]. In 2019, HepB3/HepB-birth dose coverage was 99%/99% in Maldives, respectively [6].

Nepal belongs to low endemic zone according to Hepatitis B surface antigen (HBsAg) seroprevalence, as the overall prevalence of hepatitis B in Nepal is estimated at 0.9% [99]. In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 1.12% (95% CI 1.02–1.23%) and 0.15% (0.11–0.18%) in Nepal, respectively [5]. In 2019, HepB3 coverage was 93% in Nepal [6]. In a nested prospective case study (2019), Shedain et al. found prevalence values of HBV 0.32% in 16,400 of pregnant females who attended a tertiary-level hospital over a period of 1 year. The infection was clustered in the indigenous ethnicities, nearly threefold higher infection compared to other than indigenous ethnicities. According to some authors, increased alcohol consuming pattern; seen in those indigenous communities, which can lead to increase the sexual risk behavior and unsafe sexual relationship that may be responsible for this high prevalence in those communities [100].

The overall prevalence of HBsAg was 2.5% in a prevalence survey carried out in 2010 to obtain national estimates on hepatitis B and C infections in Pakistan [101]. In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.3% (95% CI 2.04–2.61%) and 0.54% (0.43–0.68%) in Pakistan, respectively [5]. In 2019, HepB3 coverage was 75% in Pakistan [6]. Most of the studies from Pakistan on the prevalence of hepatitis B in pregnancy are hospital-based. One meta-analysis (2011) of nine studies showed the HBV prevalence of 5.872% ± 4.984% in pregnant females in Pakistan [102]. This extensive heterogeneity is due to the difference in the prevalence of hepatitis B in different regions of Pakistan and different periods. A very high frequency of ≥12% HBV infection in pregnant females has been reported in Bahawalpur, Hyderabad, and Rahim Yar Khan regions in 2006–2007 [103–105]. Other studies have found lower prevalence. Among pregnant females prevalence of HBsAg was found to be 0.34% in 2006 in Karachi [106], 1.37% in Swat in 2008 [107], 1.16% (95% CI 0.96–1.37%) in Peshawar district of Pakistan (in 2013–2014) [108], and 2.78% in Rawalpindi in 2016–2017 [109]. Moreover, HBsAg was generally reported with low frequency in private-sector patients and high in public-sector patients.

In Sri Lanka, the prevalence of HBsAg is generally low. In 2019, the modeled HBsAg national prevalence and under-5-year-old prevalence were 1.5% (95% CI 1.34–1.66%) and 0.07% (0.06–0.10%) in Sri Lanka, respectively [5]. In 2019, HepB3 coverage was 99% in Sri Lanka [6]. In Sri Lanka, although no specific studies on prevalence of HBV infections among pregnant mothers are available, it is reasonable to presume the prevalence is likely to be much lower than in the neighboring countries.

### Pacific Countries (Australia, New Zealand, and Pacific Island Countries and Territories)

Australia, New Zealand (NZ), and Pacific Island Countries and Territories (PICT) fall within the World Health Organization (WHO) Western Pacific Region which has a high prevalence of HBV and related morbidity [110]. The PICT consist of three regions incorporating many countries: Melanesia (comprising Fiji, New Caledonia, Papua New Guinea, the Solomon Islands, and Vanuatu); Micronesia (comprising the Federal States of Micronesia, Guam, Kiribati, Marshall Islands, Nauru, Palau); and Polynesia (comprising Samoa, American Samoa, Tonga, Cook Islands, Tuvalu, Tokelau, Niue, Wallis and Futuna, French Polynesia and the Pitcairn Islands).

New Zealand and Australia introduced universal HBV vaccination of infants in 1988 and 2000, respectively. By the year 2000, both NZ and Australia had introduced catch-up vaccination programs for adolescents and other high-risk groups [111]. In both the countries, birth dose HBV vaccination within 24 h of birth, along with hepatitis B immune globulin (HBIG), is given to infants born to HBsAg-positive mothers. Overall health outcomes are poorer and burden of communicable and noncommunicable diseases greater among indigenous peoples (Aboriginal and Torres Strait Islander people in Australia and Māori in New Zealand) as compared with non-Indigenous peoples. Immigration from other Asia–Pacific countries with high HBV prevalence is also common in Australia and NZ [110].

In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 2.14% (95% CI 1.94–2.34%) and 0.07% (0.06–0.09%) in Australia, respectively [5]. In 2019, HepB3 dose coverage was 95% in Australia [6]. In Australia, the majority of chronic HBV infections occur in migrants from endemic areas and their children, and also HBV prevalence is higher in Indigenous peoples (Aboriginal and Torres Strait Islander people) [112]. In Australia, 0.4–1.3% of pregnant females are chronically infected with HBV keeping with the low prevalence in general population [113]. HBsAg prevalence in pregnant females was 0.8% in South Wales in 2000 [114], 2% in 2 teaching hospitals in Sydney (2003–2006) [115], and 0.5% in Victoria among mothers of all singleton births between 2009 and 2017 [116].
In 2019, the modeled HBsAg national prevalence and children under-5-year-old prevalence were 0.9% (95% CI 0.78–1.01%) and 0.07% (0.05–0.08%) in New Zealand, respectively [5]. In NZ, Māori, Pacific, and Asian New Zealanders have higher HBV prevalence than European New Zealanders [117]. In 2019, HepB3 dose coverage was 92% in New Zealand [6]. A clear downwards trend was found in antenatal hepatitis B prevalence rates from 1997 to 2009 in one study, and is likely to be as a result of the introduction of the hepatitis B vaccine onto the universal schedule throughout New Zealand in 1988 [118].

The Pacific Islands and Territories (PICT) are very diverse socio-culturally, economically, geographically, and demographically [119].

The majority of PICTs are low-income and middle-income countries. Pacific Island Countries and Territories have moderate–high HBsAg prevalence (Table 2). The HBsAg national prevalence and children under-5-year-old prevalence were 5.38% (95% CI 4.45–6.28%) in 2019 (modeled) [5] and 0.20% in 2011 [64] in American Samoa, 3.27% (2.69–3.74%) in 2019 (modeled) [5] and 0% in 2012 [64] in Cook Islands, 3.56% (3.11–4.03%) in 2019 (modeled) [5] and 0.30% (0.10–0.50%) in 2016 [64] in Federated States of Micronesia, 3.63% (3.15–4.1%) in 2019 (modeled) [5] and 0.47% (0.34–0.58%) in 2019 (modeled) [5] in Fiji, 5.03% (4.31–5.86%) in 2019 (modeled) [5] and 0% in 2015 [64] in Guam, 7.47% (6.13–8.88%) in 2019 (modeled) [5] and 3.30% (2.4–4.6%) in 2014 [64] in Kiribati, 4.17% (3.52–4.86%) in 2019 (modeled) [5] and 1.20% (0.60–1.90%) in 2016 [64] in Marshall Islands, 4.76% (3.87–5.7%) in 2019 (modeled) [5] and 0.53% (0.36–0.69%) in 2019 (modeled) [5] in Nauru, 3.61% (2.92–4.23%) in 2019 (modeled) [5] and 0% in 2015 [64] in Niue, 6.2% (5.82–6.47%) in 2019 (modeled) [5] and 3.29% in 2014–2019 [120] in Papua New Guinea, 5.24% (4.25–6.3%) (modeled in 2019) [5] and 0.10% in 2014 [64] in Samoa, 6.33% (4.87–7.42%) (modeled in 2019) [5] and 3.1% (2.0–4.9%) in 2016 [64] in Solomon Islands, 6.37% (5.21–7.67%) in 2019 (modeled) [5] and 2.97% (1.99–4.12%) in 2019 (modeled) [5] in Tokelau Islands, 3.95% (3.23–4.59%) in 2019 (modeled) [5] and 0.41% (0.24–0.55%) in 2019 (modeled) [5] in Tonga, 5.76% (4.79–6.68%) in 2019 (modeled) [5] and 1.48% (1.03–2.0%) in 2019, (modeled) [5] in Tuvalu, and 5.16% (4.21–6.18%) in 2019 (modeled) [5] and 1.45% (0.96–1.95%) in 2019 (modeled) [5] in Vanuatu respectively. One study found HBsAg prevalence of 6.6% in young military recruits in 2000 in New Caledonia [121]. HBsAg prevalence was 1.3% in children 8–11 years in 2001 in New Caledonia [122].

HBV vaccination for infants and children started between 1995 and 1997 in all PICT, including birth dose delivery in most countries. Younger age at first pregnancy in PICT increases risk of mother-to-child transmission, as a greater proportion of young mothers are HBV envelope antigen (HBeAg) positive with high viral load. In 2019, HepB3/ HepB-birth dose coverage was 98%/99% in Cook Islands, 84%/70% in Federated States of Micronesia, 99%/99% in Fiji, 94%/99% in Kiribati, 82%/98% in Marshall Islands 96%/99% in Nauru, 99%/99% in Niue 35%/25% in Papua New Guinea, 58%/65% in Samoa, 94%/66% in Solomon Islands, 99%/99% in Tonga, 92%/98% in Tuvalu, and 90%/82% in Vanuatu, respectively [6].

One of the largest and most complete HBsAg prevalence studies in PICT was by Wilson et al. who reported HBsAg prevalence based on serological surveys conducted in 1998 (across Fiji, Vanuatu, Tonga, and Kiribati as part of a vaccination efficacy study (published 2000, after HBV vaccination introduction). The survey found HBsAg prevalence among pregnant females of 6.6% in Fiji, 15.1% in Kiribati, 18.6% in Tonga, and 12.3% in Vanuatu [123].

HBsAg prevalence of 2% was found in antenatal females in 2011 in Nausori, Fiji [124].

HBsAg prevalence was 2% in 2014 in Guam among pregnant females [125].

A study conducted in 2002 and 2003 found HBsAg prevalence of 9.2% (CI 4–15%) in 269 pregnant females in Tarawa, Kiribati [126].

HBsAg prevalence in Marshallese pregnant females was 8% in 2003–2003 and 10% in 2007 [127].

Studies conducted in the East-Coast provincial hospital (New Caledonia) (from 1996 to 1999) found HBsAg prevalence ranging from 1.7 to 4.9% in pregnant females [128].

In Solomon Islands, among pregnant females, studies have found HBsAg prevalence of 13.7% in 2008 (antenatal cohort in Honiara, Gizo, and Munda) [129], and 13.8% in 2015 among pregnant females attending antenatal clinic in Honiara [130].

**Areas of future research**

Countries need to generate accurate and large-scale data on prevalence of HBsAg in pregnant females, and their virological characteristics.

**Immunopathogenesis of hepatitis B virus infection (acute and chronic) in pregnancy**

**Review of literature**

**Immunopathogenesis of acute HBV infection in pregnancy**

There is scarcity of reports on acute hepatitis B infection in pregnancy; however, it seems that the clinical course does not differ from pregnant females to non-pregnant females [131]. The usual disease course would likely be uneventful. Under a very rare circumstance, fulminating hepatitis occurs.
Natural history of HBV infection is determined by complex interactions between virus and the host immune response [132]. In pregnancy, maternal immunity is totally altered to tolerate semi-foreign body of fetus, and also pregnancy is associated with increased adrenal corticosteroids and other hormones that play a significant role in altering host immunity and viral replication.

There are greater chances of acute liver failure in pregnancy due to acute HBV infection, but at the same time, others have reported none of the detrimental effect of pregnancy on clinical recovery in acute HBV infection [133].

Due to weak T-cell response, HBsAg loss and seroconversion may be delayed in the pregnant females with acute hepatitis B than non-pregnant [131]. T cells are markedly reduced during early pregnancy up to the 20th week of gestation to reduce the level of immunity. Increased hormone levels during pregnancy, including progesterone, estrogen, and human chorionic gonadotropin, have been shown to have a clear suppressive effect on cell-mediated immunity. HBV-specific CD8 T cells play a pivotal role in clearing the acute HBV infection; however, it is observed that HBV-specific T-cell responses are weaker or absent in pregnant females than non-pregnant females or adult males [134].

Immunopathogenesis of chronic HBV infection in mothers during pregnancy and postpartum period

The immunological changes during pregnancy and the postpartum period affect the natural history of chronic HBV infection. Biochemical hepatic flares and higher rates of HBeAg loss (and HBsAg clearance) have been reported in the early postpartum period due to immune reconstitution [135]. Most flares are self-limited and do not require therapy, but some can be severe, resulting in liver failure [136]. HBeAg-positive mothers have higher incidence of ALT flares as compared to the HBeAg-negative mothers. HBeAg titers <1:650 among HBeAg-positive mothers have been shown to be associated with HBeAg clearance in the postpartum period [137]. Immunological changes (like regulatory T-cell expansion and an increase in Th1 cytokines, IFN-γ, and IL-12) occurring during pregnancy to prevent fetus rejection are reversed after delivery [138].

There are also some differences in immune responses among HBeAg-positive mothers (higher frequency of CD19 + B cells, lower frequency of CD3 + CD4 + T cells, and peripheral NK-cell inhibition) as compared to HBeAg-negative mothers [139].

Reactivation of chronic HBV infection has also been reported during pregnancy [140]. Cortisol levels peak at around delivery, and a sudden decrease in levels during postpartum period has effects similar to steroid withdrawal, causing HBV reactivation. Defective HBV-specific T-cell responses also occur in the peripartum period [141].

Immunopathogenetic mechanisms involved in MTCT

HBV MTCT can potentially occur prenatal or intra-uterine, natal or at the time of birth, and postpartum. Most HBV infections occur perinatally (at birth or soon after) in unvaccinated infants, but historically reports have suggested that approximately 3% to 8% of infections may occur through the intra-uterine route [142]. However, the findings that, after administration of HBG and hepatitis B vaccine in newborn infants, MTCT of HBV occurs only in 2–3% of infants born to HBsAg-positive mothers (<0.1% of infants of HBeAg-negative mothers and 5–10% of infants of HBeAg-positive mothers) clearly indicate that historically estimated intra-uterine transmission appears to be overstated. It is believed that intra-uterine transmission of HBV is the most significant contributor to MTCT and immunoprophylaxis failure [see below].

The presence of HBeAg and other viral proteins (like HBx) can affect the risk of MTCT. Maternal HBeAg seropositivity is a significant risk factor for MTCT. In chronic HBV infection, HBeAg has an immunomodulatory role, and early in utero exposure to HBeAg may promote chronicity instead of viral clearance [143].

Studies in mouse models have shown that conditioning of hepatic macrophages by maternal HBeAg generates anti-inflammatory macrophages, which lead to HBV persistence. However, in the absence of HBeAg preconditioning, macrophages acquire a proinflammatory phenotype, leading to HBV clearance by activated CD8 + T cells [144].

In pregnant females with viral loads of > 3 log10 copies/mL, functional hepatitis B X protein (HBx) produced in HBV-infected placenta cells could activate phosphoinositide 3-kinase in placenta, which signals inhibition of apoptosis in placental cells, allowing for HBV persistence in trophoblasts [145].

High viral load is a known significant risk factor for MTCT [see below]. Placental infection occurs progressively through different cellular layers from maternal to the fetal side, with the depth of placental tissue infection in direct proportion to maternal viral load [146].

Occult HBV infection (OBI) is characterized by serum HBsAg negativity with or without serum antibodies (anticore and/or anti-HBs), and HBV DNA in serum or liver or extra-hepatic reservoirs (peripheral blood mononuclear cells or lymphoid system). OBI may occur in infants born to HBsAg-positive mothers despite the receipt of immunoprophylaxis. Most studies show very low or no OBI in vaccinated children born to HBsAg-positive mothers [147]. Further studies are needed to assess the vertical transmission of OBI and its clinical implications.
In one Japanese study, genotype C was associated with increased perinatal transmission rates as compared to genotype B. However, the increased MTCT risk may be due to higher viral loads and HBeAg positivity in mothers with HBV genotype C infection [148]. Other studies did not find an association between MTCT risk and the HBV genotype [149].

Naturally occurring HBV variants are selected under host pressure. One study found that in HBeAg-negative pregnant females having precore mutant G1896A and HBV DNA levels of 4–5 log10 copies/mL, HBV transplacental transmission did not occur (no HBV DNA was found in the analyzed placenta), and no passive-active immunoprophylaxis failure was seen in the infants at 1 year of age [150]. Another retrospective study from China Mainland suggested that dual basal core promoter mutants have a protective role in MTCT, as these were found in mothers who did not transmit HBV to their neonates; but this association may also be related to lower maternal viral loads in pregnant females with dual basal core promoter mutants [151].

Impaired dendritic cell function and decreased levels of follicular T cells (CD4+ C-X-C chemokine receptor type 5+), plasma B cells (CD19+ CD38+) within PBMCs, and low serum IL-21 were found in mothers in association with MTCT, versus mothers who did not transmit HBV to their infants. Also, newborns showed transcriptomic imprints of their mothers, suggesting that mothers’ immune signatures could be a potential marker for MTCT [152, 153].

**Hepatitis B vaccine-specific responses in infants born to mothers who were HBsAg positive and role in immune response to HBV vaccine**

One Taiwanese study found that only 16% of the peoples who had received the HBV vaccine as infants had anti-HBs at 15 years of age [154]. The factors associated with blunted immune response in infants born to HBsAg-positive and HBeAg-positive mothers include transplacental passage of HBsAg and transient HBsAg positivity in the infants [155].

Increasing the vaccine dose from 10 to 20 μg improved the immunogenicity among the infants born to HBeAg-positive and HBsAg-positive mothers [156]. Also, HBV vaccine alone is as effective as the combination of HBIG plus vaccine, in preventing HBV infection in infants born to HBeAg-negative mothers [157].

Lower amounts of the T helper 1 cytokine IL-2 secretion in an in vitro stimulation assay has been found to be associated with vaccine failure among infants receiving the complete immunoprophylaxis [158]. In utero encounter to HBV antigens is suggested by the HBV-specific T-cell responses in uninfected vaccinated infants born to HBeAg-negative chronic HBV-infected mothers; although this exposure does not impair the neonatal B-cell and T-cell responses to the HBV vaccine [159]. HBV-specific T-cell responses can be seen in children for up to 10 years after their primary infant vaccination, despite having negative or low anti-HBs levels [160].

**Trained immunity in infants born to mothers who were HBsAg positive and role in immunoprophylaxis failure**

Exhaustion of HBV-specific CD8+ T-cell responses is one of the mechanisms for HBV persistence. Diminished expression of CD3+ T-cell receptor zeta chain is associated with functionally defective CD8+ T cells (producing less interferon-γ) and reduced expression of the cytotoxicity marker CD107a in HBsAg-positive newborns versus HBsAg-negative and healthy newborns [161]. HBsAg-positive pregnant females have also shown immature transitional B cells and decreased plasma B cells continuously from third trimester till delivery. Also, higher pre-vaccination levels of immature transitional B cells were found in HBsAg-positive newborns compared with HBsAg-negative infants born to HBsAg-positive mothers. The frequency of immature transitional B cells declined at 12 months after vaccination in HBsAg-positive newborns, whereas no changes were observed in HBsAg-negative and uninfected healthy newborns [162]. Although, these novel observations added a new perspective in understanding the key mechanisms of HBV chronicity in newborns, yet it is unknown when this phenomenon starts during pregnancy; therefore, it may be worthwhile to analyze the kinetics of TCR zeta expression and regulatory T cells throughout pregnancy.

Serum cytokine profiling from neonates born to HBsAg-positive mothers revealed a cytokine signature compatible with a Th1-like response (high levels of IL-12 p40 and low levels of Th2 cytokines IL-4, IL-5, IL-13, and IL-10) and a decrease in proinflammatory cytokine profile (IL-1β and IL-6). Also, cord blood mononuclear cells from neonates who were HBsAg positive showed a stronger response compared to healthy controls to an unrelated bacterial challenge. Despite increased levels of IL-12p40 and IFN-α2 in HBV-induced trained immunity, HBV-specific T-cell response was lacking which indicates that trained immunity may induce monocytes in cord blood to fight against other pathogens, but does not help in HBV clearance [163]. It is presumed that placental DCs and neutrophils secrete IL-12p40, and thus play a direct role in the modulation of maternal or neonatal infections. Maternal HBeAg “trains” Kupffer cells in utero, thus playing a role in HBV persistence [144].

**Areas of future research**

Further studies are necessary in serially collected samples from mothers and infants to clearly understand the dynamics
of the host immune response in association with HBV flares and MTCT.

Although combined maternal HBeAg positivity and high viral loads is an established risk factor for MTCT, HBV genotype, PC/BCP mutations, and risk of immunoprophylaxis failure is not well understood and may be an area of future studies.

Further studies are needed to assess the vertical transmission of OBI despite appropriate immunoprophylaxis and its clinical implications.

How hepatitis B virus infection (acute and chronic) impacts the health of pregnant females and outcome of pregnancy

Review of literature

Many epidemiologic studies have reported possible impact of maternal HBV infection on the perinatal and pregnancy-related outcomes. However, results from studies have been contradictory and the possible role of maternal HBV infection in the pathogenesis of pregnancy-related outcomes remained unresolved. A study suggested that higher HBV viral load may be associated with poorer pregnancy-related outcomes [164].

A prospective cohort study from China Mainland suggested that maternal chronic HBV infection was associated with an increased risk of miscarriage [165].

A few studies from China also demonstrated significant associations between maternal chronic HBV infection and low birth weight or small-for-gestational age [166, 167]. However, studies from the U.S. reported no significant association between maternal chronic HBV infection and small-for-gestational age [168, 169].

For gestational diabetes mellitus, a meta-analysis revealed that maternal chronic HBV infection had a 47% increased risk of gestational diabetes mellitus (adjusted odds ratio: 1.47) compared with those without HBV infection [170]. This association might stem from low-grade systemic inflammatory response from HBV infection [171].

For pregnancy-induced hypertension, previous case-control and cohort studies have demonstrated inconclusive results [172, 173]. A recent meta-analysis suggested that maternal chronic HBV infection was associated with 23% decreased risk of pre-eclampsia [174]. However, most of included studies were case-control studies and possible mechanism has not been postulated for this association.

Impact of maternal chronic HBV infection on preterm birth is also inconclusive. A meta-analysis demonstrated no association between maternal chronic HBV infection and preterm labor [175]. However, another recent meta-analysis suggested a significant association between maternal chronic HBV infection and premature birth [176]. Of note, abnormal liver function test and concomitant fatty liver were stronger risk factors for preterm birth than maternal chronic HBV infection in previous study [177]. It is possible that liver inflammation per se plays an important role of preterm birth regardless of maternal chronic HBV infection.

Cohort studies from China Mainland demonstrated that maternal chronic HBV infection was associated with an increased risk of intrahepatic cholestasis of pregnancy [178, 179].

A study from U.S. found that patients with chronic HBV infection were less likely to perform cesarean delivery. However, studies from Asia showed that patients with HBV infection had an increased rate of cesarean delivery. This result might stem from on maternal request or obstetrician’s recommendation based on the belief that cesarean delivery reduces mother-to-child transmission [180].

No associations were found between chronic HBV infection and adverse perinatal outcomes, including gestational diabetes mellitus, pre-eclampsia, placenta previa, premature separation of placenta, premature rupture of membranes, preterm birth, and low birth weight in females undergoing assisted reproductive technology [181].

Recommendations

Hepatitis B viral infection in the mother does impact the perinatal and pregnancy-related outcomes both in the mother and the newborn. The maternal effects include miscarriage, gestational diabetes mellitus, pregnancy-induced hypertension, preterm birth, intrahepatic cholestasis of pregnancy, and cesarean delivery. However, the data from available studies are not strong enough to associate these complications to mere HBV infection (B2).

Areas of future research

Whether serum HBV viral load is associated with increased risk of perinatal outcomes in maternal HBV infection should be further investigated.

Impact of pregnancy on hepatitis B virus infection severity and outcomes (acute and chronic) and management of liver disease (general management and use of antivirals) in pregnant females with hepatitis B virus infection

Review of literature

Although the management for patients with acute and chronic HBV infection during pregnancy is similar to that
of non-pregnant patients, several issues may be considered because of the presence of the fetus in pregnant patients. These will be addressed under different scenarios described below.

There is scarcity of reports on acute hepatitis B infection in pregnancy; however, it seems that the clinical course is not differ from non-pregnant state [131], and hence, the management would mainly be supportive. The usual disease course would likely be uneventful. Under a very rare circumstance, when fulminating hepatitis occurs, the management decision would be made with the considerations of the chance of spontaneous liver function recovery in the mother and the degree of fetus maturity. As such, liver transplantation and early fetal delivery may be contemplated accordingly.

Obstetricians sometimes would manage chronic HBV-infected patients with pregnancy for pregnancy-related liver problems and hepatitis B virus-related problems, both of which, in particular, the latter would involve the management by hepatologists. The most common liver problem in pregnancy is HBV flares. Incidence of HBV flare and hepatic decompensation has been studied in a large retrospective study recruiting 310 chronic HBV-infected patients with pregnancy (19 received nucleos(t)ide analogs (NA) before pregnancy; 16 received NA during the first or second trimesters; 5 during the third trimester) [182]. ALT flares [defined by ≥ 2 × upper limit of normal (ULN)] occurred in 14% during pregnancy and 16% within 6 months of delivery. ALT flares ≥ 5 × ULN or ≥ 10 × ULN occur in ≤ 5% during pregnancy or postpartum period. Overall, 12% of patients with ALT flares developed jaundice and 2% [2 patients (1 with pre-existing cirrhosis)] developed hepatic decompensation. According to another study with 158 pregnant females, ALT flares developed in 3.4% during pregnancy and 4.3% after delivery [136]. No flares were severe and no liver decompensation was observed. As mentioned above, ALT flares can also occur during the postpartum period. According to one study (n = 317), postpartum ALT flares > 2 × ULN and > 5 X ULN occurred in 9.8% and 1.9% in CHB mothers [183]. Another study with 126 patients reported 25% chance of postpartum ALT flares which usually resolved spontaneously [184]. Acute-on-Chronic liver failure (ACLF) due to HBV reactivation had been reported in a case series of 5 patients (all were non-cirrhotic) and all recovered with antiviral treatment [185]. Rarely happened condition is patients requiring liver transplantation for fulminating hepatic failure due to HBV reactivation [140, 186]. In summary, mild ALT flares during and shortly after delivery are not uncommon, whereas hepatic decompensation is rare.

Although NA treatment would theoretically reduce the chance of ALT flares due to HBV reactivation, whether it should be given routinely would depend on the different scenarios.

**Patients who are already on long-term NA therapy before conception**

In the patients who are already on long-term NA therapy before conception, the question would be whether the treatment should be stopped once pregnancy is planned or confirmed. There are two major considerations in this context: (1) whether NA would increase the risk of fetus anomalies if it is continued throughout the pregnancy and (2) whether discontinuation of NA therapy would jeopardize the liver condition of the mothers and if in case becoming severe, adversely affects the fetus. To date, on one hand, there are no prospective control studies to compare the mother and fetus outcome between those continue and those discontinue NA therapy. On the other hand, there is absence of evidence on the hypothetical chance of teratogenic effects of the HBV treatment continuation that we could learn from the experience from HIV pregnancy registry. According to the Antiretroviral Pregnancy Registry, of the 11 867 females on anti-retroviral therapies for HIV and/ or HBV infection, the rate of birth defects was 2.7% which is very similar to the rate (2.72%) in the general population [187]. Among the NAs, tenofovir disoproxil fumarate (TDF), lamivudine (LAM), and telbivudine (LdT) have been assessed as providing good maternal and infant safety [188, 189].

Among the currently available NAs, LdT and TDF are classified as category B drugs (no risk in animal studies, but unknown in humans), whereas LAM, adefovir (ADV), and entecavir (ETV) are classified as category C drugs (teratogenic in animals, but unknown in humans) by the US FDA. Category B NAs (LdT and TDF) may be considered for mothers needing antiviral treatment during the first through third trimester of pregnancy.

As LAM and LdT have low genetic barriers that may lead to the emergence of drug-resistant strains of HBV [190], TDF should be the first choice for pregnant females. If the pregnant female has impaired renal functions or osteoporosis, LdT or LAM can be used [191, 192]. ETV and ADV should be avoided in females with pregnancy intention, because these drugs have potential serious adverse effects or teratogenesis [191]. If these drugs have been taken before pregnancy, it should be changed to TDF [192].

The newly approved tenofovir alafenamide (TAF) has been recommended for CHB treatment in many parts of the world owing to its better renal and bone safety profile compared to TDF. However, there are limited data on the use of TAF in pregnancy, while it is not recommended during breastfeeding [193].

Concerning the effect on the liver if treatment is stopped, it is well known that around 40–50% of non-pregnant chronic HBV-infected individuals would have ALT flares after NA cessation [194], with majority of the events happening within the first-year treatment cessation. In the context of
chronic HBV-infected patients with pregnancy, according to a study, 8 (6 of those had fivefold increase in ALT levels) out of 12 patients would experience ALT flares after stopping NA treatment during pregnancy [195]. According to another study, ALT flares occurred in 31% of patients who stopped NA during the first trimester (16% of patients who stopped NA before pregnancy) [196]. Cases of acute exacerbation of HBV with liver failure that eventually required urgent liver transplantation have been reported [140, 186].

There are two factors in pregnancy which would enhance the chance of ALT flares postpartum after treatment cessation. First, pregnant females are relatively younger and, therefore, more immune active. They are expected to have a higher chance of HBV reactivation upon treatment cessation. Second, it is known that pregnancy induces immune suppressive state in the mothers to reduce fetal rejection. Together with the increased cortisol, estrogen, and progesterone levels, it creates a potential favorable condition for the HBV to replicate. One study had demonstrated an increase in HBV DNA levels and a decrease in ALT levels during pregnancy, while these profiles reversed after pregnancy [197]. However, another study found that HBV DNA levels during pregnancy were highly variable with some patients having a rise in third trimester or postpartum period, while majority of patients having static HBV DNA levels throughout the pregnancy [198]. Further to these findings, a recent study had shown that pregnant CHB patients had a shift toward Th1 response over Th2 during peripartum period with the host immunologically attempting to clear the virus [199], although it usually fails. At the same time, cortisol levels would decrease immediately after delivery enhancing a steroid withdrawal effect [137].

These combined factors would increase the chance of HBV reactivation, especially during the later course of pregnancy and early course after delivery. Taken all the above findings and considerations together, it is recommended that NA would better to be continued throughout the pregnancy and early postpartum to avoid uncontrolled HBV reactivation. This recommendation would be much stronger in patients with advanced fibrosis/cirrhosis. It is because severe flares, maternal mortality, and fetal death occur in 15%, 1.8%, and 5.2%, respectively, after treatment cessation according to a retrospective study of 400 pregnant females with HBV-related cirrhosis [200].

If a woman was planning pregnancy or a pregnant chronic HBV-infected mother was taking the NA of FDA-defined pregnancy category C drugs, it is recommended to switch to a FDA-defined pregnancy category B drugs.

### Treatment naïve chronic HBV-infected patients who become pregnant

The second scenario applies in treatment naïve chronic HBV-infected patients who become pregnant. As mentioned above, HBV reactivation can occur as a result of alteration of immune regulation during and after pregnancy (postpartum). Immune reconstitution during early postpartum period is associated with ALT flares and hence increased HBeAg and HBsAg loss. According to one study, HBV DNA flares (defined by > 2 log IU/mL) and ALT flares (defined by 5 X ULN or 3 X the baseline values) occur in 9% and 6% of patients during pregnancy and 4% and 10% within 3 months of delivery, respectively [201]. Fifty percent of these ALT flares were observed during the second trimester or earlier. According to another study examining 146 pregnant chronic HBV-infected patients not receiving antiviral treatment, the median ALT levels significantly increase from 17 U/L at baseline to 29 U/L at postpartum period [202]. In addition, 7 “immunotolerant” patients developed postpartum ALT flares with the median ALT level of 75 U/L [202]. ACLF due to HBV reactivation has been reported in chronic HBV-infected patients with pregnancy [140]. This is likely due to the natural decline of cortisol levels (usually peaked at term and delivery) during postpartum period mimicking the steroid withdrawal effect. Close monitoring of the HBV DNA and ALT flare profiles during pregnancy and postpartum period for those who are not on NA throughout the pregnancy is recommended. This monitoring should be extended till 6 months post-delivery. If the severe ALT flares are evidenced, prompt initiation of NA treatment should be implemented.

### Portal hypertension in chronic HBV-infected females with established cirrhosis

Another issue is management of portal hypertension in chronic HBV-infected females with established cirrhosis. These patients usually have a relatively lower chance of conception because of two reasons. First, they are relatively older. Second, patients with liver cirrhosis would have hypothalamic–pituitary dysfunction and disturbed sex hormone metabolism [203], both of which would adversely affect fertility. Because of this, the incidence of cirrhosis in pregnant females is found to be very low with approximately 1 in 5950 pregnancies [204]. Nonetheless, in chronic HBV-infected pregnant patients with cirrhosis, portal hypertension may be exaggerated during pregnancy due to the normal physiological changes associated with pregnancy. These include increase in blood volume, increase in heart rate, and decrease in systemic vascular resistance. It has been shown that MELD score is predictive for significant liver-related complications during pregnancy [205]. In particular,
MELD > 10 is highly sensitive and specific for predicting liver decompensation during pregnancy [205].

For patients with compensated cirrhosis and with a plan for pregnancy, screening for varices is required before pregnancy and preventive measure for acute variceal bleeding, e.g., endoscopic ligation is required. Acute variceal bleeding with catastrophic outcomes can occur during pregnancy in 18–32% of these patients [206] with the mortality rate of up to 50% [207]. It usually occurs during the second trimester or during delivery. It is more related to the gravid uterus and to repeated Valsalva maneuvers [208]. It is recommended to perform endoscopy surveillance with endoscopic ligation for medium- and large-sized varices during the second trimester in patients even with the absence of varix in the first screening before pregnancy. This procedure is safe and effective in preventing acute variceal bleeding. If bleeding risk is assessed to be high (in patients with large varices), non-selective beta blocker may be considered [209]. Close fetal monitoring is necessary for the possibility of fetal bradycardia and intra-uterine growth retardation. Nevertheless, overall, propranolol therapy appears to be quite safe for pregnancy. The use of vasopressin (may also be applicable to octreotide) is, however, contraindicated because of the decrease in placental perfusion and increased risk of placental abruption [210]. Several successful cases with the use of transjugular intrahepatic portosystemic shunt (TIPS) have been reported [211]. Worsening of ascites with compromised respiratory function has also been reported in these patients [212].

Patients with stable chronic HBV disease undergoing prophylactic treatment to prevent mother-to-child transmission

The final scenario is patients with stable chronic HBV disease undergoing prophylactic treatment to prevent mother-to-child transmission based on the high HBV DNA levels (> 200,000 IU/mL) [see below].

Recommendations

Acute hepatitis B infection in patients with pregnancy usually requires specialized supportive treatment (weak recommendation, moderate-quality evidence); and if severe and progressive, urgent liver transplantation may be needed. Early termination of pregnancy and early fetal delivery are rarely required (B2).

For females already on NA treatment before pregnancy with established advanced fibrosis/cirrhosis, continuation of the NA treatment throughout the pregnancy is highly recommended (B1).

For females already on NA treatment before pregnancy with less-advanced fibrosis, continuation of NA treatment during pregnancy should be considered (C1).

During pregnancy, switching from FDA classified pregnancy category class C to class B should be considered. TDF is recommended as the first choice antiviral for pregnant females (B1).

For chronic HBV-infected females who were not eligible for antiviral treatment, and are thus treatment-naïve at the time of pregnancy, HBV DNA and ALT levels monitoring are mandatory throughout the pregnancy, and up to 6 months after pregnancy, treatment is indicated with significant flares (B1).

Pregnant females with chronic HBV infection and established cirrhosis and with a plan for pregnancy should undergo a surveillance endoscopy to screen to varices; prophylactic variceal management is recommended before pregnancy (C1).

For pregnant females with cirrhosis, it is recommended to perform endoscopy surveillance with endoscopic ligation for medium- and large-sized varices during the second trimester in patients even with the absence of varix in the screening before pregnancy (C1).

Areas of future research

Whether or not to continue NAs in females already on NA treatment before pregnancy and with less-advanced fibrosis requires further studies.

Whether to start NA in pregnant females who before getting pregnant were not eligible for anti-HBV therapy needs further studies.

More data on TAF safety in pregnancy are needed.

Mother-to-child transmission (MTCT) of hepatitis B virus [mechanisms and associated factors]

Review of literature

Mother-To-Child Transmission (MTCT) of HBV refers to the entry and replication of maternally derived HBV in offspring to produce novel virions. MTCT of HBV is a major cause of chronic HBV infection. Before the availability of hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine, MTCT of HBV occurred in 70–90% of the children born to HBsAg- and HBeAg-positive mothers and 10–40% of those born to HBeAg-negative mothers. With the administration of HBIG and hepatitis B vaccine, MTCT rates in children of HBeAg-positive and HBeAg-negative chronic HBV-infected mothers have been reduced to 4–10% and <0.1%, respectively [213, 214]. MTCT of HBV is considered to occur
during ante-partum (in utero), intra-partum (during labor and delivery), or postpartum (after birth) period.

**HBV in utero transmission**

In utero transmission of HBV refers to the replication of HBV in fetal hepatocytes before birth. Although it is considered that HBV DNA may integrate in ova and granular cells and HBV may infect embryos [215], the findings that the neonatal immunoprophylaxis protected against MTCT of HBV in almost all infants born to HBeAg-negative mothers [213, 214], or born to HBeAg-positive mothers who received oral antivirals during the third trimester of pregnancy [216, 217] indicate the unlikelihood of HBV in utero transmission through infection of embryos.

The presence of HBsAg and/or HBV DNA in umbilical or peripheral blood samples collected shortly after birth was presumably considered to be a consequence of in utero transmission [218, 219]; this was also assumed to be the main reason for MTCT of HBV after passive–active immunoprophylaxis (i.e., immunoprophylaxis failure) [220]. However, longitudinal observations showed that most of infants with positive HBsAg and/or HBV DNA at birth were not HBsAg positive in the follow-up [221, 222]. Thus, the presence of HBsAg or HBV DNA at birth just indicates exposure to, but not infection with HBV [222].

As a general rule, the prerequisite for in utero transmission of a microbial pathogen is that it can cross placentas. However, HBV is not cytopathogenic and there is no evidence for placental damage caused by HBV. Theoretically, placental barrier may prevent the entry of HBV into fetus. The findings that acute hepatitis B occurring in the first or second trimester of pregnancy rarely caused HBV infection in infants indicate that the virus does not easily cross the placenta [223]. The lack of anti-HBc IgM in newborn infants of HBV-infected mothers also suggests little in utero transmission [224].

To date, there are no practicably available ways to define HBV in utero transmission. As aforementioned, the presence of HBsAg and/or HBV DNA in umbilical cord blood or infants shortly after birth cannot be used to define in utero transmission [221, 222]. It is generally accepted that persistence of positive HBsAg from birth to several months of age can define in utero transmission [225]; however, the measurement of HBV markers was performed at intervals of one or more months and the dynamic changes of HBsAg or HBV DNA levels during these intervals were unknown. Because the maternal HBsAg in infants may remain for more than 1 month [226] and seroconversion of HBsAg may be detected 4–5 weeks after inoculation of HBV in experimentally infected chimpanzees [227], it is possible that, if newborn infants are infected during intra-partum period, they may actively produce viral markers before the disappearance of maternally derived HBsAg and/or HBV, leading to the persistence of HBsAg in circulation. Thus, the reported persistence of HBsAg and/or HBV DNA at intervals of 1 month or more does not necessarily mean true in utero transmission, and the possibility of transmission occurred during intra-partum period cannot be excluded.

In summary, MTCT of HBV by in utero transmission, if really occurs, should be very rare. More convincing evidence is required to demonstrate HBV in utero transmission.

**HBV intra-partum transmission**

HBV intra-partum transmission refers to the entry of maternal HBV in newborn infants during labor and/or delivery and, subsequently, the replication of HBV in infants. The vast majority of MTCT of HBV occurs during the intra-partum period. Maternal blood can cross placenta during labor [228]. After starting the first stage of labor, the repetitive and strong contractions of the uterus may cause maternal–fetal microtransfusion or transplacental leakage, leading to the entry of maternal HBsAg and HBV into expectant infants, which may explain the presence of HBsAg and/or HBV DNA in > 30% of infants at birth [221, 222]. During the second stage of labor, an infant directly comes in contact with maternal HBV-containing body fluids, during which maternal HBV may enter into newborn infants through obvious or imperceivable lesions of skin and/or mucosa. Thus, all infants born to HBsAg-positive mothers, regardless of HBeAg state or HBV DNA level, inevitably undergo exposure to maternal HBV.

In addition, before the availability of immunoprophylaxis, MTCT of HBV occurred in 70–100% of infants born to mothers who had acute hepatitis B near delivery [229], but rarely occurred in infants born to mothers with acute hepatitis B occurred during the first or second trimester of pregnancy [223]. The reason is likely that the mothers with acute hepatitis B around delivery might have high viral load at delivery, which is a main risk factor for MTCT of HBV, whereas the mothers with acute hepatitis B at the first or second trimester might have resolved the infection or might have low viral level at delivery.

**HBV postpartum transmission**

In the era of no immunoprophylaxis against hepatitis B, postnatal transmission of HBV from HBsAg-positive mothers to their offsprings occasionally occurred because of the close contacts. With the universal vaccination against hepatitis B in all infants and administration of HBIG in infants of HBsAg-positive mothers as well, postnatal transmission of HBV rarely occurs. Theoretically, HBV may be transmitted through breastfeeding, because HBV can be detected in breast milk and nipple cracks may occur during
breastfeeding. However, studies showed that breastfeeding does not have additional risk for infection in infants [see below].

**Risk factors for MTCT of HBV**

*Maternal HBV DNA level and HBeAg state:* Maternal high HBV DNA level (viral load) is a main risk factor for MTCT and immunoprophylaxis failure. Studies showed that maternal HBV DNA levels that may cause immunoprophylaxis failure are somewhat varied, ranging from >2 × 10^5 IU/ml or >2 × 10^6 IU/ml measured with commercial reagents made in China Mainland [221, 222], >10^7 IU/ml tested with Abbott Real-Time HBV DNA assay [230], to >2 × 10^7 IU/ml (10^8 copies/ml) detected with Roche reagents [214]. A meta-analysis was done by WHO to assess the risk of perinatal infection according to the maternal HBV viral load (measured by log10 IU/ml) among infants who received a timely birth dose and HBIG. Studies with a small sample size (<10 subjects) were excluded. When timely birth dose and HBIG were used, there was no breakthrough infection reported when the maternal HBV DNA viral load was below 5.3 log10 IU/ml (200,000 IU/mL) [231]. Therefore, it is generally accepted to use HBV DNA ≥ 2 × 10^5 IU/ml as a threshold for risk of MTCT after the immunoprophylaxis [192, 231, 232].

HBeAg-positive individuals have higher HBV DNA levels.

In Asia, the median HBV DNA levels in HBeAg-negative chronic HBV-infected pregnant females are approx 3–4 log10 IU/ml, and the proportion of >10^6 IU/ml is only 0.5–1.8%, while the HBV DNA levels in HBeAg-positive pregnant females are >7 log10 IU/ml and the proportion of >10^6 IU/ml or >10^8 copies/ml is over 80% [98, 233]. Immunoprophylaxis failure occurs in <0.1% of children born to HBeAg-negative mothers, but in 4–10% of children born to HBeAg-positive mothers [213, 214]. Thus, the presence of HBeAg in pregnant females indicates the risk of MTCT even after immunoprophylaxis. Meta-analysis by WHO to assess the performance (sensitivity and specificity) of HBeAg tests in pregnant female with HBV infection in identifying female with high HBV DNA levels (≥5.3–6.2 log10 IU/mL), found good sensitivity [88.2% (95% CI 83.9–91.5)] and specificity [92.6% (95% CI 90–94.5)] of HBeAg for diagnosis of HBV viremia ≥5.3–6.2 log10 IU/mL [231]. For predicting the risk of mother-to-child transmission, HBeAg had high sensitivity [99.1% (95% CI 61.8–100)], but low specificity [55.7% (95% CI 34.0–75.5)]. When restricted to children receiving birth dose vaccine plus HBIG, HBeAg had a sensitivity of 98.8% (95% CI 52.0–100) and specificity of 49.2% (95% CI 25.1–73.7). Thus, compared to HBV DNA, HBeAg has high sensitivity but lower specificity for predicting the risk of mother-to-child transmission. HBV DNA quantification is the best method to determine eligibility for tenofovir prophylaxis in pregnant females to prevent MTCT. However, HBeAg can be used as an alternative test in settings with limited access to HBV DNA quantification [231].

*Time of immunoprophylaxis in newborn infants:* Newborn infants of HBsAg-positive mothers are exposed to maternal HBV during labor and delivery; those who are born to mothers with high viral loads are exposed to more amounts of maternal viruses. Theoretically, if the maternal viruses can be completely neutralized by the immunoprophylaxis as well as the neonatal innate immunity before they enter into hepatocytes, MTCT will not occur at all. Studies showed that delayed or missed use of HBIG and/or hepatitis B vaccine may increase the likelihood of MTCT [234, 235].

Recent studies showed that, after early (within 1 h after birth) administration of HBIG and hepatitis B vaccine, MTCT of HBV in infants born to HBeAg-positive mothers was reduced to 1.2–2.4% [236], much lower than reported rate of 4–10% in infants who received recommended immunoprophylaxis within 12 or 24 h after birth[213, 214]. Thus, timely administration of the immunoprophylaxis in newborns is critical for preventing MTCT of HBV.

*Other risk factors for MTCT of HBV:* Recently, it has been proposed that quantification of HBsAg may predict MTCT of HBV [237, 238]; however, this is controversial [239].

Investigations on the association between HBV genotypes or mutations in the ‘a’ determinant of S gene and MTCT remain inconclusive [240].

In addition, studies on the issue of whether cesarean section may reduce MTCT of HBV showed conflicting results [see below].

**Recommendations**

MTCT of HBV mainly occurs during labor and delivery. The rate and timing of intra-uterine transmission is not well known and requires further studies (B2).

Known risk factors for MTCT are high maternal HBV DNA level or positive HBeAg status, and suboptimal use of HBIG and/or hepatitis B vaccine after birth. (A1).

**Areas of future research**

More studies on searching convincing evidence of in utero transmission are needed.

Whether quantification of HBsAg may predict MTCT of HBV needs to be studied.

The effect of cesarean section in preventing MTCT in females with high viral load or positive HBeAg if they do not receive antivirals during the trimester of pregnancy.
Prevention of mother-to-child transmission

Review of literature

Mother-to-child transmission (MTCT) of HBV is the leading mode of transmission in endemic populations [231]. The infected children of HBV-infected mothers become a reservoir of infection for subsequent horizontal infection in the community, and the HBV infected females in turn continue maternal-to-infant transmission to their descendants. The prevention of MTCT is the most effective mean of interrupting this vicious cycle, reducing the prevalence of HBV infection in successive generations [241].

Immunoprophylaxis and prevention of MTCT

Without any intervention, MTCT of HBV is 70–90% if mother is HBsAg-positive and HBeAg-positive; and 10–30% if mother is HBsAg-positive only [241]. Timely hepatitis B vaccination birth dose (HepB birth dose) alone is 70–95% effective in preventing MTCT [241–243]. Timely HepB birth dose plus the completion of hepatitis B vaccine series is > 95% effective in preventing MTCT [242].

Thus, all infants should receive the first dose of hepatitis B vaccine as soon as possible (preferably within 24 h) after birth, followed by completion of the vaccination series. In the case of preterm babies, the birth dose should be given even if the baby weight is <2 kg, but should be followed by a further three vaccine doses starting at 6 weeks of age [244]. This is because the hepatitis B vaccine has reduced immunogenicity in preterms with <2 kg weight [245].

Many studies including Cochrane systematic reviews indicate that combination of Hepatitis B vaccine with HBIG is more efficient in reducing MTCT prevalence than vaccine or HBIG alone [246, 247].

One systematic review found that 200 IU HBIG had equivalent effectiveness to 100 IU HBIG in infants born to HBsAg-positive mothers for preventing HBV infection [relative risk: 1.08, (0.64–1.82)] and HBeAg-positive mothers [relative risk: 0.84 (0.39–1.77)] [248].

Although a combination of HBV vaccine plus HBIG is the optimum strategy to prevent HBV infection in babies of HBsAg-positive mothers, utility of addition of HBIG to vaccine in babies of HBeAg-negative mothers is unclear. One recent meta-analysis concluded that HBV vaccine alone is equally effective to vaccine plus HBIG for neonates of HBeAg-negative chronic HBV-infected mothers in preventing MTCT of HBV infection [249]. In full-term neonates born to HBeAg-negative chronic HBV infected mothers, prevention against MTCT of HBV infection achieved by timely HBV vaccination may not be significantly improved by additional HBIG use [231]. Moreover, due to cost, supply, and safety issues, HBIG use may not be feasible in many regions. It has been shown that HBV vaccine without HBIG has a protective efficacy of 70–95% in HBeAg-positive chronic HBV-infected mothers also [250]. These findings support the use of hepatitis B vaccine alone in settings where use of HBIG is not feasible. Very recently, it was reported that a free-immunoglobulin alternative strategy using HBeAg RDT/ALT algorithm to assess eligibility for TDF prophylaxis associated with an early vaccination in delivery room could reduce HBV MTCT to 1.48% [95% CI 0.40–3.74] for TDF-eligible pregnant female, 0% [95% CI 0–1.41] for those treated more than 1 month, and to 1.06% [95% CI 0.39–2.30] for not TDF-eligible female [251].

Antiviral therapy for the prevention of MTCT

Antivirals can be useful in HBsAg-positive pregnant females as an additional measure to prevent MTCT of HBV. A WHO-commissioned systematic review and meta-analysis (included 129 studies) found that antivirals had protective effect in preventing MTCT [TDF 300 mg: odds ratio (OR) 0.16, 95% CI 0.10–0.26; lamivudine 100 mg: OR 0.17, 95% CI 0.13–0.22; and telbivudine 600 mg: OR 0.10, 95% CI 0.08–0.13]. TDF has a high barrier to drug resistance, and should be the first choice.. All studies in the meta-analysis included HBIG in both trial arms (except six studies, in which the use of HBIG was not reported) [231]. Another systematic review and meta-analysis on 7463 studies also concluded that peripartum antiviral prophylaxis is highly effective, specifically TDF, for the prevention of HBV MTCT [252].

Also there was no adverse effects of maternal TDF prophylaxis on infant bone mineral density at 1 year of age [231].

The maternal HBV DNA levels above which maternal NAs treatment should be started for preventing MTCT is ≥200,000 IU/mL or ≥5.3 log10 IU/mL. HBV DNA quantification is the best method to determine eligibility for TDF prophylaxis in HBsAg-positive mothers for prevention of MTCT. However, HBeAg can be used as an alternative test in settings with limited access to HBV DNA quantification [231].

HBeAg RDTs could also represent an option to identify females at risk of transmission [253]. The overall sensitivity of identifying high viremia with RDTs is lower as compared to the laboratory enzyme immunoassay techniques [254]. Nevertheless, their possible use in decentralized areas is a major advantage for many countries in the region where it is not possible to have access to enzymatic techniques or viral load quantification outside the capital city.

In many countries, HBeAg-negative chronic HBV infections are common. HBeAg-negative chronic HBV infection is characterized by the lack of serum HBeAg, persistent or fluctuating moderate to high levels of serum HBV DNA.
HBV DNA level was not found in many studies [239]. However, the correlation of HBsAg level with maternal HBsAg level has been associated with higher risk of MTCT of HBV [237], as high maternal HBsAg level has been associated with higher risk of HBV immunoprophylaxis failure in some studies [238]. However, the correlation of HBsAg level with maternal HBV DNA level was not found in many studies [239]. Further prospective studies are needed before introduction of HBsAg quantification as a reliable test in pregnant females for eligibility of maternal NAs prophylaxis to prevent MTCT of HBV [215].

Varying schedules have been suggested to start and stop peripartum antiviral prophylaxis, ranging from starting at 24–28 to 28–32 weeks of gestation, and from stopping at delivery to 12 weeks postpartum [192, 231]. The WHO meta-analysis found that effectiveness of TDF prophylaxis for preventing MTCT was similar irrespective of the timing of start of TDF: TDF prophylaxis starting at < 28 weeks for preventing MTCT was similar irrespective of the timing of start of TDF: TDF prophylaxis starting at < 28 weeks (OR 0.10, 95% CI 0.04–0.25), 28 weeks (OR 0.24, 95% CI 0.13–0.44), or > 28 weeks (OR 0.09, 95% CI 0.02–0.32) [231]. Some studies suggest that earlier start of NAs, i.e., in the second trimester, might be more efficacious than in the third trimester as this might lead to greater viral load reduction in females treated earlier [252]. A Bayesian network meta-analysis and system review showed that the risk of MTCT decreased significantly in pregnant females accepting intervention before 28 weeks of gestation, as compared to those initiating after 28 weeks [relative risk: 0.019, (0.00034–0.19)] [256]. In the recent PROHM study, HBV transmission rate was 6.52% [1.37–17.9] for those treated less than 1 month as compared to 0% [95% CI 0–1.41] for those treated more than 1 month [251].

There has been some concern that NA (used for MTCT prevention only) withdrawal at or after delivery might increase the risk of peripartum flares [197]. The WHO meta-analysis found that 8% of the mothers receiving TDF during pregnancy experienced a flare after discontinuation, compared with 6% of mothers who did not receive TDF at a matched time-point. This suggests that discontinuation of TDF prophylaxis might not increase the risk of flare [risk difference: 0.00 (95% CI 0.04–0.04)] [231]. Most flares are mild and self-limiting; only a few require antiviral therapy [184, 257]. Another meta-analysis found similar rate of hepatitis flare among mothers discontinuing antiviral treatment immediately after delivery, 4 weeks postpartum, and 12 weeks postpartum [258]. Thus, HBsAg-positive pregnant females receiving antivirals for MTCT prevention can discontinue antiviral treatment immediately after delivery or continue up to 12 weeks postpartum. HBV DNA could rebound after antiviral discontinuation: close monitoring should be done and antiviral treatment can be considered if meeting treatment indications for therapy [259].

One study found that 6 weeks postpartum is the peak period of hepatitis flares, and 96.0% of the hepatitis flares occurred within 24 weeks postpartum. Therefore, follow-up to at least 24 weeks postpartum after discontinuation of antivirals (used for MTCT only) should be done [260]. One study on chronic hepatitis B virus-infected females who received telbivudine beginning at week 24 or 28 of gestation and followed up to 52 weeks postpartum found that, compared with female having a normal ALT level throughout pregnancy, those with elevated ALT had a significantly higher rate of ALT flare after telbivudine withdrawal (25.0% vs 11.9%; p = 0.039). And females with elevated ALT during pregnancy who continued antiviral treatment to 52 weeks postpartum had a significantly higher HBeAg seroconversion and decline in HBsAg levels [261]. Thus, pregnant females with ALT flares during pregnancy should undergo monitoring and continue long-term antiviral treatment after delivery, and stopping rules as per guidelines for other chronic HBV-infected patients should be followed. Females with evidence of advanced liver fibrosis/cirrhosis should also continue long-term antiviral treatment after delivery, and stopping rules as per guidelines for other chronic HBV-infected patients should be followed [259].

Recent studies have found that children with and without fetal exposure to TDF during late pregnancy to prevent maternal transmission of HBV had comparable long-term growth, renal function, and bone development, assessed by serum bone metabolism markers and DXA scans, up to 6–7 years of age [262].

### Recommendations

All newborns should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 h. The birth dose should be followed by three doses to complete the primary series (A1).

HBIG prophylaxis, in conjunction with HBV vaccination, may be of additional benefit for newborn infants whose mothers are HBsAg positive and also HBeAg positive. In full-term neonates born to mothers who are HBsAg positive but HBeAg negative, protection against perinatally acquired infection achieved by immediate vaccination against HBV (given within 24 h) may not be significantly improved by the addition of HBIG (B1).
Pregnant females testing HBsAg positive with an HBV DNA ≥ 5.3 log10 IU/mL (≥ 200,000 IU/mL) should receive antiviral prophylaxis for prevention of mother-to-child transmission of HBV. This is in addition to appropriate immunoprophylaxis (B1).

In settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV (B2).

Tenofovir disoproxil fumarate (TDF) is recommended for pregnant females with HBV requiring antiviral prophylaxis for prevention of mother-to-child transmission of HBV (B1).

The antiviral should be initiated at 24–28 weeks of gestation for preventing MTCT. For pregnant females with high viremia who are visiting the hospital after 28 weeks of gestation, antiviral intervention should be initiated immediately. The pregnant mothers should be made aware of the intra-uterine risk of HBV transmission, even with low HBV DNA levels, and can be given a choice of starting antiviral therapy from the first trimester of pregnancy (C2).

Pregnant females taking antivirals for preventing MTCT only can discontinue antiviral treatment immediately after delivery or continue up to 12 weeks postpartum (C2), and should be monitored closely for hepatitis flare and rebound of HBV DNA till at least 24 weeks (C2).

Pregnant females with ALT flares during pregnancy or evidence of advanced liver fibrosis or cirrhosis should continue long-term antiviral treatment after delivery, and stopping rules as per guidelines for CHB patients should be followed (C1).

Follow-up to at least 24 weeks postpartum after discontinuation of antivirals (used for MTCT only) should be done (C1).

**Areas of future research**

Use of HBsAg level and HBeAg testing as a cost-effective alternative to HBV DNA viral load measurement to determine eligibility for antiviral prophylaxis for MTCT of HBV needs to be studied.

When to stop antivirals after delivery in female and how to follow up such females remain to be studied.

Data regarding the maternal and infant safety of TAF in pregnant females with chronic hepatitis B and the efficacy to prevent MTCT of hepatitis B need to be generated.

Development of RDTs for HBeAg with higher diagnostic accuracy, and evaluation of the performance of HBeAg tests in the presence of co-infection with HIV, HCV, and HDV and in different genotypes are needed.

**Safety of invasive obstetric procedures in the pregnant females with hepatitis B virus infection in terms of mother-to-child transmission and optimum mode of delivery in HBsAg-positive mother**

**Review of literature**

Invasive procedures during pregnancy such as amniocentesis, chorionic villus sampling, fetal blood sampling, and minimally invasive or open fetal surgery can contribute to MTCT and immunoprophylaxis failure in the newborns. Thus, appropriate management during these invasive procedures is important to minimize the MTCT risk.

Studies have found that amniocentesis is an independent factor for the intra-uterine transmission of HBV [263, 264]. In one case–control study on infants who were born to HBsAg-positive mothers without antiviral exposure and completed appropriate immunization, it was found that there were no significant differences in the vertical transmission rates between the amniocentesis group and the control group if the maternal HBV DNA levels were < 6.99 log10 copies/ml. However, among mothers with HBV DNA levels ≥ 7 log10 copies/ml (≥ 2 × 10⁶ IU/ml), a significantly higher vertical transmission rate was seen in the amniocentesis group vs. the control group (50% vs. 4.5%, respectively, \( p = 0.006 \) [263]. In a recent large retrospective study, 143 HBsAg-positive females with amniocentesis were compared with 605 matched (based on maternal viral loads, antiviral therapy regimens, and delivery dates) non-amniocentesis cases. Pregnant females with serum HBV DNA ≥ 7.0 log10 copies/ml were offered antiviral therapy. MTCT rate was significantly higher in the females undergoing amniocentesis as compared to those not undergoing amniocentesis (2.80% vs. 0.50%; RR, 5.64, 95% CI 1.28–24.93). In the amniocentesis group, maternal HBV DNA ≥ 7.0 log10 IU/ml and HBeAg positivity were associated with higher MTCT rates; and antiviral therapy reduced MTCT rate from 14.3 to 0% (\( p = 0.554 \)) when maternal HBV DNA was ≥ 7.0log10 IU/ml [265]. Thus, for HBsAg-positive mothers planned for invasive procedures such as amniocentesis, counseling should include the risk of MTCT of HBV if the serum HBV DNA is > 7.0 log10 IU/ml [266].

The risk and benefit of antiviral prophylaxis in the prevention of MTCT of HBV in highly viremic pregnant mothers, before or immediately after invasive procedures including amniocentesis, remain largely unknown. Available data were very limited in the literature. Besides, the starting and stopping points of maternal treatment for short-term NAs prophylaxis also remain unclarified.
Non-invasive alternatives should be explored in mothers who require prenatal invasive diagnostic procedures. Among females who need invasive testing, amniocentesis is preferable to chorionic villus sampling. Transplacental amniocentesis should be avoided. The risks and benefits of any invasive procedures should be explained to the patient and informed consent obtained [267].

The major route of perinatal HBV transmission is due to newborn’s contact with the HBsAg-positive mother’s blood or secretions during delivery. Despite administration of birth dose HBV vaccine plus HBIG, some transmission risk remains for mothers with high HBV DNA levels [See above]. The method of delivery that minimizes the likelihood of MTCT of HBV remains a controversial issue. Recent studies demonstrated a lower risk of HBV transmission with elective cesarean section compared with vaginal delivery. A recent meta-analysis [268] comparing the risk of MTCT of HBV between vaginal delivery versus cesarean section delivery concluded that the risk of HBV infection in cesarean births was significantly lower than that of vaginal delivery in mothers without antiviral prophylaxis during pregnancy. Fortunately at present, for pregnant mothers with high viral load detected during delivery, the risk of MTCT of HBV can be minimized through application of antiviral agent early during third trimester [see above]. Cesarean section should not be performed for the sole indication of reducing risk of vertical HBV transmission.

**Recommendations**

The risk of intra-uterine HBV transmission in pregnant mothers with high serum HBV DNA level (≥ 7 log10 IU/mL) and planned for invasive genetic testing procedures such as amniocentesis should be discussed with the pregnant mother and relatives; weighing of the benefits and harms is needed (C2).

Cesarean section should not be performed for the sole indication of reducing risk of vertical HBV transmission (C1).

**Areas of future research**

Further prospective studies on risk factors of HBV transmission in pregnant females undergoing invasive procedures like amniocentesis, and the effect of antiviral therapy on the HBV transmission in such mothers are needed.

**Assisted conception in chronic hepatitis B virus-infected females in terms of mother-to-child transmission**

**Review of literature**

Couples seeking help for assisted conception may be infected with chronic hepatitis B virus. They cannot be denied access to the assisted reproductive technology (ART). For many of them, access to such services may be restricted on ethical, geographical, and financial grounds. They may be avoiding unprotected intercourse using condoms to minimize the risk of infecting their partner. The direct threat to their health can be reduced or eliminated by a modification of practices, guidance, and procedures. Assisted procreation may be required for safe conception if the viral infection cannot be effectively treated or if the couple needs fertility treatments because of an infertility diagnosis (e.g., low sperm counts).

Several assisted reproduction procedures, such as in vitro fertilization (IVF) and intra-cytoplasmic sperm injection (ICSI), are available. Fertility clinics screen patients for blood-borne viral infections, including HBV to prevent vertical transmission and for laboratory safety. From the ethical point of view, there is no reason to advise against assisted reproduction treatment in HBsAg-positive individuals [269]. However, limited access to specialist clinics equipped to cater for these couples and restricted funding may impact negatively couples obtaining risk-reducing assisted reproduction treatment.

**Effect of female chronic HBV infection on pregnancy outcomes in assisted reproduction**

It has been shown that HBV exists in ovarian tissues (including oocyte and follicular fluid), and can pass the zona pellucida. Therefore, a potential risk of transmission to the embryo exists, which could explain the finding of MTCT despite immunoprophylaxis [270]. In one study, HBsAg was detected in the nuclei and cytoplasm of oocytes and embryos in 6 of 10 HBsAg-negative male/HBsAg-positive female couples (and in 13 of 20 oocytes and embryos) [271]. In another study, the rates of positivity in oocytes and embryos were higher in females with high serum levels of HBV DNA levels; and also in females with HBsAg-positive mothers [272].

Some studies have shown lower rates of fertilization, cleavage, high-quality embryos, and pregnancy in chronic HBV-infected infertile females as compared to non-infected females [273, 274]. Although lower ovarian reserve; and lower rates of fertilization and high-quality embryos have been found in females with HBV DNA levels ≥ 5 × 10^2 IU/mL [275], one systematic review showed that among
infertile females with chronic HBV infection undergoing assisted reproduction, there was slightly lower rates of fertilization, but similar rates of cleavage, high-quality embryos, implantation, pregnancy, and abortion, as compared to infertile females without chronic HBV infection [276].

Most studies suggest that the risk of maternal vertical HBV transmission during an IVF procedure is similar to that with spontaneous conception and pregnancy [277–279]. One study on 12 babies born to couples with HBV-positive oocytes and/or embryos found that the presence of HBsAg in oocytes and embryos might not result in the vertical transmission of HBV in the offspring of chronic HBV-infected mothers [279]. A study on 251 HBsAg-positive females (305 children, 176 born with assisted conception, and 129 born with natural conception; 7.5% of children were HBsAg positive at birth), found that HBsAg positivity rate among children at birth was similar in the assisted conception group and the natural conception group (6.3% vs. 9.3%) [280].

**Effect of chronic HBV on male fertility and pregnancy outcome**

Chronic HBV infection can adversely affect male fertility, specifically sperm count, and progressive motility. HBV exposure could lead to reactive oxygen species generation, lipid peroxidation, reduction of total antioxidant capacity, activation of caspases, and DNA fragmentation, resulting in increased apoptosis of sperm cells and loss of sperm membrane integrity and causing sperm dysfunctions [281]. Results of one study suggested that chronic HBV infection in male was associated with poor sperm quality. There were increased rates of astheno-zoospermia and oligo-zoospermia. The embryo transfer outcomes and clinical pregnancy rates in ICSI cycles were decreased, but do not affect the outcome of IVF [282]. One study reported that the percentage of normal sperm morphology in HBV-seropositive husbands was significantly lower than that of seronegative counterparts (5.0% versus 10.0%, p = 0.009). However, there was no adverse effect of chronic HBV infection on the assisted reproduction outcomes [278]. Another study addressing the effect of male chronic HBV infection on outcomes of IVF and embryo transfer treatment included the 215 couples undergoing their first oocyte donation cycles, 19 couples with seropositive husbands/seronegative wives had lower implantation rate, and lower clinical pregnancy rate, but the difference was not statistically significant [283].

HBV can integrate into sperm chromosomes, causing mutagenic effects, and there is the possibility of vertical transmission of HBV via the germ cells [284]. This finding supports the assumption that human sperm cells may act as vectors for the vertical transmission of HBV genes via the germline to progeny [285]. These findings make the sperm washing procedures to remove seminal plasma for reducing the vertical transmission risk debatable. However, the vaccination of female partners against hepatitis B may eliminate the risk of transmission to the mother as well as to the fetus [286].

**Microbial contamination of the IVF system**

In the embryology laboratory, microbial contamination of the IVF system deserves attention. Cross-contamination of samples is possible within liquid nitrogen storage tanks, since HBV can survive in liquid nitrogen [287]. It can be prevented using sterile techniques and supplementing culture media with screened sera or serum substitutes and antibiotics. Persons whose biological material is to be cryopreserved should be screened for HBV, HCV, and HIV, and separate containers should be used for infected and non-infected material. One study failed to detect viral sequencing from the spent culture media and liquid nitrogen samples of oocytes and embryos from hepatitis B infected females [288].

**Recommendations**

Assisted reproduction could be done following the same guidelines as in other pregnant females with chronic HBV infection (C2).

**Areas of future research**

Effect of maternal HBV DNA levels on rate of fertilization, rate of cleavage, quality of embryos, implantation, pregnancy, abortion, and rate of vertical transmission among infertile females with CHBV infection undergoing assisted reproduction requires further large-scale studies.

**Postpartum follow-up of children of chronic HBV-infected mothers**

**Review of literature**

Infants should be given appropriate immunoprophylaxis [see above]. Although a combination of active and passive immune prophylaxis is the optimum strategy to prevent HBV infection in babies of HBsAg-positive mothers, its utility in HBeAg-negative mothers is uncertain [see above].

Follow-up of infants born to HBsAg-positive mothers, including the post-vaccination serological testing, is important. Although routine post-vaccination testing is not necessary, it is important for babies born to HBsAg positive, and should be done at 9–18 months of age, 1–2 months after the last dose of HBV vaccine [289].

The post-vaccination serological testing should include HBsAg and anti-HBs titer tests. Passive immunization with
Hepatitis International (2022) 16:211–253

HBeAg titers correlated positively with the corresponding HBV DNA in breast milk (both colostral HBsAg and HBeAg titers correlated positively with the corresponding level in maternal blood) [296, 297], clinical studies have failed to demonstrate breastfeeding as a contributor to MTCT of HBV. In a meta-analysis of 10 prospective controlled trials (751 infants in the breastfeeding group and 873 infants in the non-breastfeeding group), there was no significant difference in MTCT of HBV (i.e., infant peripheral blood HBsAg or HBV DNA positivity at age 6–12 months), between the breastfeeding and the non-breastfeeding group [OR: 0.86 (95% CI 0.51–1.45), p = 0.56]. The rate of anti-HBs development was also similar between the two groups [OR: 0.98 (95% CI 0.69–1.40), p = 0.99]. Thus, breastfeeding (without cracked or bleeding nipples or lesions) does not contribute to MTCT of HBV after proper immunoprophylaxis in the infants [298]. The majority of studies were not randomized controlled; and did not study HBV markers in the breast milk or HBV DNA levels in newborns and the mothers. Also, correlation between the rate of MTCT and the duration of breastfeeding has not been studied.

Lactoferrin present in the human milk has antiviral activity against various viruses including HBV, HCV, and HIV [299, 300]. Milk stasis and breast engorgement (resulting from irregular or non-exclusive breastfeeding) have been shown to increase the epithelial permeability, more efficient para-cellular transfer of HIV, and increased HIV RNA in breast milk [301]. Whether the same applies to HBV is unknown. Thus, exclusive breastfeeding needs to be promoted especially in regions with low socio-economic standards, given the beneficial effects of exclusive breastfeeding on morbidity and mortality of the babies.

Another important consideration is the safety of antivirals taken by the breastfeeding mothers for the babies. Among HIV-positive mothers treated with lamivudine 300 mg/day, although the mean concentration of lamivudine in the breast milk was slightly higher (1.8 mg/mL) as compared to that in maternal serum (0.7 mg/mL), the mean concentration of lamivudine was very low in the infant’s serum (0.03 mg/mL), indicating minimal absorption of lamivudine in the infants [302]. Although transient and asymptomatic hematological toxicity has been observed in HAART-exposed infants (15.9% neutropenia at 1 month of age vs 3.7% in unexposed group), there were no differences in hematological and hepatic toxicity between breast-fed and formula-fed infants from 2 to 6 months postpartum [303].

Tenofovir disoproxil fumarate (TDF) is a prodrug of tenofovir. After being administered orally, TDF is quickly absorbed from the gut and is converted into tenofovir. As very low level of tenofovir is present in the breast milk and tenofovir also has poor absorption from the GIT, the concentration of tenofovir in infant’s blood is very low. Among HIV-infected mothers on long-term treatment including 300 mg oral TDF, very low median tenofovir blood concentrations in the infants have been found (24 ng/ml and 0 ng/ml at 6 and 12 months of age, respectively) [304]. In another study on HIV-positive mothers treated with 300 mg TDF,
none of the infants had a measurable tenofovir concentration in their blood [305].

Tenofovir concentrations in breast milk are also very low. In one study on HIV-infected mothers taking TDF 300 mg daily, median concentration of tenofovir in the breast milk was 5.0 ng/ml at 1 month and 2.5 ng/ml at 12 months postpartum [304]. Another study reported median maximum concentration of tenofovir in breast milk was 5.0 ng/ml at 1 month and 2.5 ng/ml at 12 months postpartum [305]. For comparison, the mothers taking TDF at a dose of 300 mg per day, the maternal plasma maximum tenofovir concentration during pregnancy ranged from 245 to 280 ng/ml [306]. Therefore, breast-fed infants experience much lower drug exposure from breast milk [307]. The daily tenofovir dose ingested from breast milk is estimated at 0.4–2.1 µg/kg/day, which represented 0.01–0.04% of the proposed pediatric therapeutic daily dose of 6 mg/kg/day [307]. These data from the HIV-infected mothers can be extrapolated to the HBV-infected mothers, as well. As there is negligible exposure to tenofovir of infants from breastfeeding (of mothers on TDF treatment), breastfeeding should be continued in females receiving TDF.

Tenofovir alafenamide fumarate (TAF), is a new oral prodrug of tenofovir. As compared to TDF, TAF delivers targeted increased intracellular levels of tenofovir, thus reducing the circulating tenofovir exposure. The enhanced safety profile of TAF makes it the ideal antiviral to use in pregnant and breastfeeding HBsAg-positive mothers.

Recommendations

Breastfeeding should be encouraged, as without cracked or bleeding nipples or lesions, breastfeeding does not contribute to MTCT of HBV after proper immunoprophylaxis in the infants (B1).

Breastfeeding should not be contraindicated in females receiving tenofovir for prophylaxis or treatment of HBV, and mothers on TDF treatment should be encouraged to breastfeed (B1).

Areas of future research

If irregular or non-exclusive breastfeeding contributes to increased infectivity of human milk in HBV-infected mothers, needs evaluation.

Anti-HBV effects of components of breast milk, and the mechanisms of no additional risk of MTCT caused by breastfeeding need to be studied.

To properly evaluate the role of breastfeeding in HBV MTCT, more randomized controlled trials with detailed breast milk HBV marker testing and HBV DNA levels in mother/child blood and duration of breastfeeding are needed.

Data on whether a woman on entecavir safely breastfeed are lacking.

Figure 1 shows the overall algorithm of maternal and infant management of pregnant females found to be HBsAg-positive first time during HBsAg screening during pregnancy or previously known chronic HBsAg-positive females who become pregnant (and are not on long-term antivirals). Figure 2 shows the overall algorithm of maternal and infant management of previously known chronic HBsAg-positive females who become pregnant and are already on long-term antivirals.

Public health aspects of HBV infection in pregnancy

Review of literature

Hepatitis B is still a major cause of morbidity and mortality due to liver diseases in the Asia-Pacific region. The burden of HBV infection remains disproportionately high in low- and middle-income countries, with most cases occurring from infection acquired soon after birth or during early childhood [308]. The World Health Assembly endorsed the Global Health Sector Strategy (GHSS) on viral hepatitis in May 2016, and proposed to eliminate viral hepatitis as a public health threat by 2030 [4]. Elimination is defined as a 90% reduction in incidence and a 65% reduction in mortality, compared with the 2015 baseline. The prevalence of HBsAg in children under 5 years of age is considered a surrogate indicator of the cumulative incidence of chronic HBV infections, and reduction in the prevalence of HBsAg in children under 5 years to <0.1% by 2030 is one of the global targets [4]. Other global targets for 2030 include 90% coverage of timely HepB birth dose vaccination and 90% coverage of HepB3 [4].

WHO had recommended to include the hepatitis B vaccine in the Expanded Programme on Immunization (EPI) in 1992 [309]. In 2017, the latest update of the WHO position paper recommended for the universal immunization of infants (with three or four doses of hepatitis B vaccine), and giving the first dose of hepatitis B vaccine within 24 h after birth [310]. The birth dose of hepatitis B vaccine should be given as early as possible. If the immunization service is not located in the same health facility (like private clinics, home delivery), it could delay the first vaccine injection, as reported in Cambodia [311]. Injection of the first dose of vaccine just after birth in delivery room could be an effective public health measure by avoiding missed opportunities. Universal immunization of infants with hepatitis B vaccine, including a timely birth dose, is the most effective intervention to prevent MTCT. Other interventions to reduce MTCT
of hepatitis B virus can be implemented using this as the base (Fig. 3) [231].

**HBsAg screening of pregnant females**

Universal HBsAg screening of pregnant females is being conducted in many regions and countries of the world, but is not done in resource-limited regions and countries [312]. Many countries have adopted routine screening of all pregnant females, regardless of the HBsAg seroprevalence in the general population [313]. Testing should be done as early as possible during pregnancy, so that appropriate measures can be undertaken for the management of the mother, and to reduce the risk of MTCT. If not done during pregnancy, screening can also be performed during labor or after delivery. Laboratory-based immunoassays are the preferred assays. In settings with limited access to laboratory testing and/or where access to rapid testing would facilitate linkage to care and treatment, rapid diagnostic tests (RDTs) can be used to improve access. According to WHO, in regions with $\geq 0.4\%$ of HBsAg prevalence, further virological evaluation and staging of liver disease can be started after a single positive serological assay HBsAg detection. In regions with $< 0.4\%$ HBsAg prevalence, confirmation of HBsAg positivity on the same immunoassay with a neutralization step or a second different RDT assay should be considered [313].

The offering HBV testing alongside existing HIV services should be considered for scaling up HBV testing for pregnant females and their partners [231].

Pregnant females found to be HBsAg positive during screening should be tested HBV DNA or HBeAg or both, along with assessment of the severity of the liver disease. High levels of HBV DNA ($\geq 200,000$ IU/mL) and/or HBeAg positivity are associated with high risk of MTCT of HBV, and these females are candidates for antiviral therapy for prevention of MTCT. In an important meta-analysis, Ott et al. examined the global prevalence of HBeAg status in female of child-bearing age in 2005, and found a global prevalence of 24–32% which had only marginally decreased since 1990 [314]. Consequently, we can surmise that almost 1/3 of females of child-bearing age carry a higher risk of MTCT despite infant immunization and HBIG. In resource-limited settings, the WHO recommends HBeAg status to be tested as a surrogate marker for those with high viral load [see above].
HBsAg screening of pregnant females should be accompanied by pre- and post-test counseling. Pre-test information should include: the benefits of early diagnosis of HBV infection for their own health, as well as to reduce the risk of MTCT; and importance of testing for other infections. Post-test information for HBsAg-positive females should include: use of antivirals for the mother if needed; measures to reduce the risk of MTCT of HBV infection; encouraging family and partner screening; encouraging to deliver in a health facility to ensure access to MTCT services; encouraging breastfeeding; and importance of HBsAg testing for the infant [313].

Linkage to care of the HBsAg-positive mother is also important, to prevent loss to follow up and missing the opportunity to assess liver disease in the mother and the need for antiviral treatment as appropriate. Unvaccinated HBsAg-negative pregnant females can be offered HBV vaccination. Follow-up of HBsAg-positive pregnant females should continue through the postpartum period and beyond as per the clinical situation [313].
A higher prevalence of HBV infection in the general population is found among pregnant females from marginalized or stigmatized groups (e.g., people who inject drugs, sex workers) or minority groups (migrants, indigenous populations). They also have poor access to health care. Integrated antenatal services for HBV, HIV, and syphilis provide an opportunity to reach out to marginalized and minority groups. Appropriate measures should be taken to ensure that these groups have access to health services without stigma and discrimination [231, 313].

Appropriate measures should be taken to maintain confidentiality and prevent stigma and discrimination against those females who are found to be HBsAg positive. Health-care worker training and rights-based frameworks are needed to achieve this [231].

Prevention of mother-to-child transmission of hepatitis B virus

All infants should receive appropriate immunoprophylaxis as early as possible after birth [see above] [231].

Antivirals as an additional measure to prevent MTCT in selected pregnant females should be used [see above]. Epidemiological and modeling studies have suggested that infant HBV vaccination alone would be insufficient to reach the 0.1% HBsAg prevalence goal in children by 2030 [231]. Worldwide, scaling up HBV vaccination to a 90% coverage of the three-dose hepatitis B vaccine, including timely birth dose, would prevent an additional 14 million new neonatal HBV infections over the next 10 years. Giving tenofovir prophylaxis to eligible pregnant females in addition to the HBV vaccination (including timely birth dose) would prevent an additional 2.9–3.0 million neonatal infections over the same period [231]. HBeAg can be used as an alternative test in settings where access to HBV DNA quantification is limited [See above] [231]. The challenges in providing tenofovir prophylaxis for MTCT prevention in eligible pregnant females include costs and availability of HBV DNA tests and tenofovir, lack of trained health-care workers, and lack of capacity and infrastructure [231].

Use of tenofovir prophylaxis to prevent MTCT in addition to HBV vaccination can reduce health inequities in low-income regions where HBIG is not feasible. The drug is available within HIV national programs.

However, interventions based on testing of pregnant females followed by tenofovir prophylaxis are costlier than hepatitis B vaccination of infants alone. Therefore, tenofovir prophylaxis in addition to HBV vaccination may not be feasible in low-income regions currently [231].

Scaling up timely birth dose is the most cost-effective option. Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among under 5 children through vaccination should focus on increasing their vaccination coverage, including timely birth dose. Improving HepB-birth dose coverage is a first step as it is still <90% in many countries of the Asia–Pacific (Table 2). Birth dose continues to be a challenge for countries with low rates of health facilities deliveries and lack of skilled birth attendants [315]. Community-based interventions can be enhanced by training village health volunteers and expanding HepB-BD in the community by giving birth dose in home in case of home deliveries, as reported from Myanmar. Vaccine out-of-the-cold chain is another option [316]. For countries with high rates of health facilities deliveries, providing the first dose of vaccine in delivery room should be considered.

In countries that have already scaled up the timely birth dose, adding antenatal HBsAg testing of pregnant females and tenofovir prophylaxis in eligible females is an additional measure to prevent MTCT which may be cost-effective in some regions [231]. All eligible pregnant and breastfeeding females living with HBV infection can safely use tenofovir [See above].

As reported in Table 2, the majority of countries in Asia–pacific have the capacity to provide HBsAg testing in ANC, but there are not yet effective national screening programs in routine for many of them. For positive HBsAg pregnant females, availability of HBV DNA and/or HBeAg testing is a concern for many countries. In these countries, ANC and deliveries are mainly conducted by midwives at the decentralized level (primary health centers, district hospitals) with no access to HBV DNA viral load measurement and immuno-enzymatic tests. The use of HBeAg rapid diagnosis tests as reported in Cambodia [255] or the use of HBV DNA point of care [317] could improve detection of pregnant females eligible for antivirals for MTCT prevention. Access to immunoglobulin is also limited in many countries of Asia–Pacific (Table 3).

Programmatic considerations

Strong government leadership, commitment, and multi-sectoral collaboration with a wide range of stakeholders are needed at all levels. Also, EMTCT of HBV activities must be integrated with the national/regional response to viral hepatitis. Normative guidance (including policies, guidelines, and implementation protocols) is needed for standardized implementation of services.

Civil society involvement in the planning, development, and implementation of the EMTCT programs should be encouraged.

Services delivery of HBV interventions for pregnant females should be guided by the principles of universal health coverage, so that a pregnant woman’s ability to pay does not determine her access to available services. Efforts should be made to include HBV EMTCT services in national health insurance schemes to minimize out-of-pocket expenses.
Table 3  Current status of interventions to eliminate mother-to-child transmission (MTCT) of hepatitis B virus as public health policy in the different countries of Asia–Pacific

| Country                      | Antenatal testing for HBsAg | Antenatal testing for HBeAg | HBV DNA if positive HBsAg | Antiviral prophylaxis for MTCT prevention (if yes, eligibility) | HBIG for exposed infants | Post-vaccination anti-HBs testing |
|------------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------------------------------------------|--------------------------|-----------------------------------|
| North Asia                   |                             |                             |                           |                                                                 |                          |                                   |
| Russia                       | Yes                         | Yes, partially              | Limited, Out of pocket    | Yes, if HBV DNA > 10^6 IU/ml                                    | Yes, partially           | No                                |
| Central Asia                 |                             |                             |                           |                                                                 |                          |                                   |
| Afghanistan                  | No                          | NA                          | NA                        | NA                                                              | NA                       | NA                                |
| Kazakhstan                   | Yes                         | No                          | Yes                       | NA                                                              | NA                       | No                                |
| Kyrgyzstan                   | Yes, partially              | No                          | Yes, partially            | Yes, if HBV DNA > 10^7 IU/ml                                    | NA                       | No                                |
| Tajikistan                   | Yes, partially              | No                          | No                        | No                                                              | No                       | No                                |
| Turkmenistan                 | Yes, partially              | No                          | No                        | No                                                              | No                       | No                                |
| Uzbekistan                   | Yes, partially              | No                          | No                        | No                                                              | No                       | No                                |
| Western Asia                 |                             |                             |                           |                                                                 |                          |                                   |
| Armenia                      | Yes                         | Yes, partially              | Out of pocket             | Out of pocket                                                   | Limited, out of pocket   | No                                |
| Azerbaijan                   | Yes                         | No                          | No                        | No                                                              | No                       | No                                |
| Bahrain                      | Yes                         | No                          | No                        | Out of pocket                                                    | No                       | No                                |
| Cyprus                       | Yes                         | No                          | No                        | Out of pocket                                                    | No                       | No                                |
| Georgia                      | Yes, partially              | Yes, partially              | Out of pocket             | Out of pocket                                                    | No                       | No                                |
| Iran                         | Yes, if high risk behavior  | Yes, partially              | Limited, out of pocket    | Out of pocket                                                    | Yes                      | No                                |
| Iraq                         | NA                          | NA                          | NA                        | NA                                                              | NA                       | NA                                |
| Israel                       | Yes                         | Yes, partially              | Out of pocket             | Out of pocket                                                    | Yes                      | No                                |
| Jordan                       | Yes                         | No                          | Out of pocket             | Out of pocket                                                    | No                       | No                                |
| Kuwait                       | Yes, partially              | Yes, partially              | Out of pocket             | Out of pocket                                                    | Yes                      | No                                |
| Oman                         | Yes, partially              | Yes, partially              | Out of pocket             | Out of pocket                                                    | Yes                      | No                                |
| Qatar                        | Yes                         | Yes, partially              | Out of pocket             | Out of pocket                                                    | Yes                      | No                                |
| Saudi Arabia                 | Yes, partially              | Yes, partially              | Out of pocket             | Out of pocket                                                    | Yes                      | No                                |
| Syria                        | NA                          | NA                          | NA                        | NA                                                              | NA                       | NA                                |
| Turkey                       | Yes                         | Yes, partially              | No                        | HBV DNA > 200,000 IU/mL or HBeAg +                               | Yes                      | Yes                               |
| United Arab Emirates         | Yes                         | Yes, partially              | Out of pocket             | Out of pocket                                                    | Yes                      | No                                |
| Yemen                        | NA                          | NA                          | NA                        | NA                                                              | NA                       | NA                                |
| East Asia                    |                             |                             |                           |                                                                 |                          |                                   |
| China Mainland               | Yes                         | Yes, partially              | No                        | HBV DNA > 200,000 IU/mL                                         | Yes                      | 7–9 months, pilot only            |
| Mongolia                     | Yes                         | Yes                         | Yes                       | HBeAg(+) with HBV DNA > 200,000 IU/mL                            | Yes, infants of HBeAg(+) mothers only | Yes, 2 months after completion of vaccination |
| South Korea (Republic of Korea) | Yes                      | Yes                         | Yes                       | HBV DNA > 200,000 IU/mL                                         | Yes                      | Yes                               |
| North Korea (Democratic People’s Republic of Korea) | NA          | NA                          | NA                        | NA                                                              | NA                       | NA                                |
| Japan                        | Yes                         | Yes                         | Not official policy       | Not official policy                                              | Yes                      | Yes                               |

© Springer
### Table 3 (continued)

| Country          | Antenatal testing for HBsAg | Antenatal testing for HBeAg | HBV DNA if positive HBsAg | Antiviral prophylaxis for MTCT prevention (if yes, eligibility) | HBIG for exposed infants | Post-vaccination anti-HBs testing |
|------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------------------------------------------|--------------------------|----------------------------------|
| Taiwan           | Yes                         | Yes                         | Yes                       | HBV DNA > 200,000 IU/mL                                         | Yes                      | Yes                              |
| South-East Asia  |                             |                             |                           |                                                                 |                          |                                  |
| Brunei           | Yes                         | Yes                         | Yes                       | HBV DNA > 10^6 IU/ml hepatology clinics                          | Yes                      | Yes, 9–12 months                 |
| Cambodia         | Not in routine              | Yes (RDT)                   | No                        | HBeAg algorithm in a research study                              | Limited. Out of pocket   | No                               |
| Indonesia        | Not in routine              | No                          | No                        | No                                                               | Limited. Out of pocket   | No                               |
| Lao PDR          | Yes                         | No                          | No                        | No                                                               | Limited. Out of pocket   | No                               |
| Malaysia         | Yes                         | Yes                         | Yes                       | HBV DNA > 200,000 IU/mL or HBeAg +                              | Yes                      | Yes, 9 months                    |
| Myanmar          | Not in routine              | No                          | No                        | No                                                               | Limited. Out of pocket   | No                               |
| Philippines      | Yes                         | No                          | No                        | No                                                               | Limited. Out of pocket   | No                               |
| Singapore        | Yes                         | Yes                         | Yes                       | HBV DNA > 200,000 IU/mL                                         | Yes                      | Yes, 3 months after completion of vaccination |
| Thailand         | Yes                         | Yes                         | Yes                       | HBeAg + or HBV DNA > 200,000 IU/mL                               | Yes but out of pocket    | Yes                              |
| Timor-Leste      |                             |                             |                           |                                                                 |                          |                                  |
| Vietnam          | Yes                         | Yes                         | Yes                       | HBV DNA > 200,000 IU/mL                                         | Yes                      | No                               |
| South Asia       |                             |                             |                           |                                                                 |                          |                                  |
| Bangladesh       | Yes                         | Yes                         | Yes                       | Yes                                                               | Yes                      | No                               |
| Bhutan           | NA                          | NA                          | NA                        | Yes                                                               | NA                       | NA                               |
| India            | Not as public health policy | Not as public health policy | Not as public health policy | Not as public health policy                                     | Yes, but out of pocket   | No                               |
| Maldives         | NA                          | NA                          | NA                        | NA                                                               | NA                       | NA                               |
| Nepal            | Yes                         | Yes                         | Yes                       | Yes                                                               | Yes                      | No                               |
| Pakistan         | Yes                         | No                          | No                        | No                                                               | Yes                      | No                               |
| Sri Lanka        | Not as public health policy | Not as public health policy | Not as public health policy | Not as public health policy                                     | Not as public health policy | No                               |
| Pacific Countries|                             |                             |                           |                                                                 |                          |                                  |
| Australia        | Yes                         | Yes                         | Yes                       | HBV DNA > 200,000 IU/mL                                         | Yes                      | Yes, 3–12 months after completing primary series |
| New Zealand      | Yes                         | Yes                         | Yes                       | HBV DNA > 200,000 IU/mL                                         | Yes                      | Yes, 3–12 months after completing primary series |
| American Samoan  | Yes                         | No                          | No                        | No                                                               | Yes                      | No                               |
| Cook Islands     | Yes                         | No                          | No                        | No                                                               | Yes                      | No                               |
| Federated States of Micronesia | Yes | No | No | No | Yes | No |
| Fiji             | Yes                         | No                          | No                        | No                                                               | Yes                      | No                               |
Stigma and discrimination may be experienced by people and families affected by hepatitis B. Confidentiality of test results must be ensured. Steps should be taken to prevent stigma and discrimination against HBsAg-positive pregnant females and other family members, in health-care settings and in the communities [231].

Training and capacity building of health workforce are needed to ensure availability of trained staff in providing EMTCT interventions. Training and capacity-building strategies related to EMTCT of HBV may include the development of algorithms for HBsAg screening of all pregnant females and appropriate measures to prevent MTCT (including timely administration of the HepB birth dose to all infants); training on assessment of liver diseases in the pregnant females and antivirals use for treatment of pregnant female or prevention of MTCT; training on follow-up of exposed infants, including post-vaccination serological testing; and follow-up of females with HBV infection after delivery.

**Recommendations**

All pregnant females should be screened for HBsAg as early as possible in the pregnancy. Screening should be performed in each pregnancy, regardless of previous HBV vaccination or previous negative HBsAg test results (C1).

HBsAg screening of pregnant females should include pre- and post-test counseling and linkage to further care as appropriate (C1).

Scaling up timely birth dose is the most cost-effective option for preventing MTCT. Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among under 5 children through vaccination should focus on increasing their vaccination coverage, including timely birth dose (A1).

Countries that have already scaled up the timely birth dose, adding antenatal HBsAg testing of pregnant females and tenofovir prophylaxis in eligible females as an additional opportunity to prevent MTCT may be cost-effective in some regions (B1).

**Areas of future research**

Studies to evaluate the efficacy of TDF in preventing MTCT of HBV among females whose infants did not receive HBIG or a timely birth dose are needed.

Different service delivery models for providing integrated HBV, HIV, and syphilis services to pregnant females need to be studied.

Evaluation of service delivery models and measures to provide equitable health services access without stigma and discrimination (especially to vulnerable, marginalized or minority groups) are required.
Conclusions

The purpose of these guidelines is to provide scientific and specific guidance for the management of chronic HBV-infected pregnant females and newborn from pregnancy planning to postpartum period. There are unavoidable limitations to the process of development of guidelines that mainly reflect the low quality of the existing clinical studies and the small number of good quality randomized controlled trials in pregnant females with chronic HBV infection.

There is a need for higher quality data and many potential areas of future research as highlighted after each section in these guidelines. Further scientific research in future will address many of the areas of uncertainty that currently exist. It is hoped that these guidelines will be used as guidance only and clinical judgment will be used by the practitioners in making clinical decisions for the benefit of their patients.

Author contributions All the authors wrote their respective parts of the manuscript and then reviewed the final manuscript and recommendations.

Funding No funding was taken from any pharmaceutical company.

Declarations

Conflict of interest Manoj Kumar, Zaigham Abbas, Milad Azami, Maria Belopol’skaya, A. K. Dokmeci, Hasmik Ghazinyan, Jidong Jia, Ankur Jindal, Han Chu Lee, Wei Lei, Seng Gei Lim, Chun-Jen Liu, Yingjie Zheng, Y. H. Zhou declare that they have no conflict of interest.

Ethical approval Not applicable.

Informed consent Not applicable.

Data availability All data, materials, and software applications support the published claims and comply with field standards.

References

1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490
2. Sarin SK, Kumar M, Eslam M, George J, Al Mahtab M, Akbar SMF, et al. Liver diseases in the Asia–Pacific region: a Lancet Gastroenterology and Hepatology Commission. Lancet Gastro- enterol Hepatol. 2020;8(2):167–228
3. World Health Organization. Operationalizing elimination of mother-to-child transmission of Hepatitis B virus in the Western Pacific Region. World Health Organization Regional Office for the Western Pacific, Manila, Licence: CC BY-NC-SA 3.0 IGO. 2021
4. World Health Organization. Global health sector strategy on viral hepatitis 2016–2021. World Health Organization, Geneva. 2016. (http://www.who.int/hepatitis/strategy2016-2021/gshs-hep/en/)
5. https://www.globalhep.org/country-data-dashboards
6. https://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragehepb3.html
7. Esaulenko V, Lyalina LV, Trifonov GF, Pokrovsky VI, Totolyan AA. Viral hepatitis in the Russian Federation. Analytical review. Issue 10/E. SPb: FBUN NIEM named after Pasteur, 2016. 152 (In Russian)
8. Ganina AA, Kyuregyan KK, Mikhailov ML. Detection rate of hepatitis among pregnant female screened for TORCH-infections medical alphabet No. 19/2016, Volume No. 3 Modern Laboratory. 41. https://www.elibrary.ru/item?id=29992553 (In Russian)
9. Belopol’skaya MA, Avrutin VY, Ostankova YV, Dmitrieva MI, Rukoiatkina EA, Dmitriev AV, Kalinina VO. Modern trends and problems of hepatitis B in pregnant womenin St-Petersburg: prevalence and genetic variants of virus. HIV Infect Immunosuppr 2017; 9(4). https://hiv.bmoc.spb.ru/journal/article/view/305/281. (In Russian)
10. Kovaleva TA. Chronic viral hepatitis B and C during pregnancy: clinical and epidemiological, psychosocial, pathogenetic aspects. 2017; 327. https://www.dissercat.com/content/khornicheskie-virusnye-gapatit-v-i-s-v-period-beremennosti-kliniko-epidemiologicheskie-psikh (In Russian)
11. Köse Ş, Göl S, Tatar B, Temur M, Göl B. HBV, HCV and HIV seroprevalence in pregnant women admitted to İzmir Aegean Obstetrics and Gynecology Training and Research Hospital: 2010–2011 İzmir Ege Doğum ve Kadin Hastahkleri Eğitim ve Araştırma Hastanesi’ne başvuran gebeliklere HBV, HCV ve HIV seroprevalansları: 2010–2011. Türk Hıj Den Biyol Derg 2017; 74(1): 21–28. Doi: https://doi.org/10.5505/TurkHijyen.2016.39259
12. Nersesov AV, Berkinbayev SF, Junusbekova GA, Jumabayeva AE, Novitskaya MS, Kyanash N. Prevalence of viral hepatitis among residents of South Kazakhstan region. Medicine (Almaty). 2016;171(9):30–33 (In Russian)
13. Azimova SM, Odnayev RI Chronic hepatitis “B” in pregnant women. Bull Acad Sci Repub Tajikistan. Department of Biological and Medical Sciences. 2015; 2:89–93 (In Russian)
14. https://aua.am/chsr/PDF/2000/HepatitB_FINAL.pdf
15. Agayev S, Geleishvili M, Rush T, Maes E. Evaluation of surveillance system for hepatitis B in pregnant women in Baku, Azerbaijan. 2009. https://www.terphinet.org/evaluation-of-surveillance-system-for-hepatitis-b-in-pregnant-women-in-baku-azerbaijan-may-2009-%E2%80%93
16. Khachatryan S, Vanyan A, Sahakyan G. Hepatitis B immunoprophylaxis in Armenia. Blood. 2015;20(20):53
17. Aminzadeh Z, Gachkar L, Sayyadi Anari AR. Frequency of HBsAg positive in pregnant womenRafsanjan in the year 2003. J Rafsanjan Univ Med Sci. 2004;3(2):126–133 (Persian)
18. Mohebbi SR, Sanati A, Cheraghipour K, Rostami Nejad M, Shalmani HM, Zali MR. Hepatitis C and hepatitis B virus infection: epidemiology and risk factors in a large cohort of pregnant women in Lorestan, West of Iran. Hepat Mon. 2011;11(9):736–739
19. Motamedifar M, Amini E, Talezadeh Shirazi P, Sarvari J. The prevalence of HBsAgandHBsAbamongpregnantwomenreferring to Zeinabiyeh Hospital, Shiraz Iran. Shiraz E Med J. 2012;13(4):187–196
20. Motazakker M, Shokat Nagadeh M, Khalili F, Shayeri B. Hepatitis B virus infection among pregnant women attending health care centers of Urmia. J Uilan Univ Med Sci. 2014;23(89):45–50 (Persian)
21. Shoghli A, Nabavi SM, Alavian SM, Kolifarhood G, Goya MM, Namazi R, et al. Hepatitis B surface antigen prevalence in pregnant women: a cross-sectional survey in Iran. Int J Prev Med. 2014;5(Suppl 3):S213–S218
22. Mobin AR, Mohammadian F, Mazloomzadeh S, Esmaeilzadeh A, SorourI Zanjani R, Savabi S, et al. Seroprevalence of Hepatitis B virus among pregnant women referred to healthcare centers of Zanjan. Zanjan Univ Med Sci J. 2014;22(93):96–104 (Persian)
23. Kavosi A, Vizvari P, Mohammadi G, Jouybari L, Sanagu A. Seroprevalence of positive HbsAg and its associated factors in pregnant women referred to health centers of Agh-Ghala city in 2010–2012. Iran J Obstet Gynecol Infertil. 2015;18(149):8–16 (Persian)
24. Kheiri L, Makvandi S. The prevalence of hepatitis B surface antigen (HBsAg) and its influencing factors in pregnant women referring to Healthcare Centers of Dehloran, Iran in 2011–2012. J Midwifery Reprod Health. 2015;3(3):424–429
25. Afzali H, Momen Heravi M, Moravveji SA, Poorrahnama M. Prevalence of hepatitis B surface antigen in pregnant women in Beheshiti Hospital of Kashan, Isfahan. Iran Red Crescent Med J. 2015;17(7):e20598
26. Bayani M, Bizat R, Bayani F, Siadati S. The effect of hepatitis B vaccination at birth on reducing the prevalence of hepatitis B surface antigen among rural pregnant women in Babol, Iran. J Babol Univ Med Sci. 2016;18(1):7–10
27. Malekifar P, Babanejad M, Izadi N, Alavian SM. The frequency of HBsAg in pregnant women from eastern Mediterranean and Middle Eastern countries: a systematic review and meta-analysis. Hepat Mon. 2018;18(9):e58830
28. Mahdi BM, Saour M, Abdulrazzaq HJ. Evaluation of hepatitis B virus infection in pregnant women. Int J Biomed Res. 2015;6(06):379–381
29. Ali SS, Salman BR. Seroprevalence of Hepatitis B surface antigen among pregnant women visiting primary health centers in Baghdad Al-jadida sector in Baghdad. J Fac Med Baghdad. 2018;60(1):43–46
30. Zamir C, Dagan R, Zamir D, et al. Evaluation of screening for hepatitis B surface antigen during pregnancy in a population with a high prevalence of hepatitis B surface antigen-positive/ hepatitis B e antigen-negative carriers. Pediatr Infect Dis J. 1999;18(Suppl 3):262–266
31. Safir A, Levy A, Sirkuler E, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier status as independent risk factor for adverse perinatal outcome. Liver Int. 2010;30:765–770
32. Abu Freha N, Wainstock T, Menachem TN, Sheiner E. Maternal hepatitis B virus or hepatitis C virus carrier status and long-term endocrine morbidity of the offspring-a population-based cohort study. J Clin Med. 2020;9(3):796
33. Batayneh N, Bdour S. Risk of perinatal transmission of hepatitis B virus in Jordan. Infect Dis Obstet Gynecol. 2002;10(3):127–132
34. Othman B, Al-Najjar MAA, Othman D, Al-Qudah R, Basheti I. Prevalence, knowledge of and attitude towards hepatitis B virus among pregnant females in Jordan. J Viral Hepat. 2020;27(11):1108–1118
35. Madi N, Al-Tawalih H, Abdul Khalid D, Al-Nakib W. A relatively high number of pregnant women in kuwait remain susceptible to rubella: a need for an alternative vaccination policy. Med Princ Pract. 2014;23:145–148
36. Al Awaideh S, Abu-Elyazeed R, Al Hosani H, Al Mullah A, Al Busaidey A, Al Amiry A, et al. Sero-epidemiology of hepatitis B infection in pregnant women in Oman, Qatar and the United Arab Emirates. J Infect. 2006;52:202–206
37. Khalil MK, Al-Mazrou YY, Al-Jeffri M, Al-Ghamdi YS, Mishkhas A, Bakhsh M, et al. Serosurvey of hepatitis B surface antigen in pregnant Saudi women. East Mediterr Health J. 2005;11(4):640–647
38. Alrowaily MA, Abolfotouh MA, Ferwanah MS. Hepatitis B virus seroprevalence among pregnant females in Saudi Arabia. Saudi J Gastroenterol. 2008;14(2):70–72
39. Bani I, Mahfouz MS, Gaffar EMA, Elhassan I, Yassin AO, Ageely HM. Prevalence and risk factors of hepatitis B virus among pregnant women in Jazan Region-Kingdom of Saudi Arabia. J Biol Agric Healthc. 2012;2(8):45–48
40. Yalçın Bahat P, Turan G, Yüksel Özgür B, Bağcı CK. Comparison of hepatitis B, hepatitis C, and HIV seropositivity of Syrian and Turkish pregnant women. Turk J Obstet Gynecol. 2019;16(2):95–99
41. Evirgen Ö, Aksakal M, Melek I, Önlém Y, Sabahattin O. Seropositivity of hepatitis B and hepatitis C in women who were admitted to Hatay Maternity and Children’s Hospital. Viral Hepat Derr. 2010;16(2):111–116
42. Yavuzcan A, Altunbas A, Altunbas S. An unexpected low Hepatitis B sero-prevalence in pregnant women from the rural South-eastern Turkey. Afr J Microbiol Res. 2011;5(23):3942–3945
43. Gönen I. The frequency of HBV and HCV in pregnant women in rural areas. Viral Hepat Derr. 2011;17(2):66–68
44. Deveci O. Investigation of intrauterine transmission of hepatitis B Virus to children from HBsAg-positive pregnant women. J Microbiol Infect Dis. 2011;1(1):14–16
45. Balık G, Ustüner I, Kagitci M, Ural UM, Tekin YB, Sentürk S. HBsAg, antiHBs and anti-HCV seroprevalence in pregnant women living in Rize region. Dicle Med J. 2013;40(2):254–257
46. Aynigolu A, Aynigolu Ö, Tarık A, Aydin M, Alunok ES. HBsAg, anti-HBs and anti-HCV seropositivity rates among pregnant women attending a University Hospital in Zonguldak. Viral Hepat J. 2015;21(1):31–34
47. Dogan K, Guraslan H, Ozel G, Aydan Z, Yasar L. Seroprevalence rates of Toxoplasma gondii, rubella, cytomegalovirus, syphilis, and hepatitis B, seroprevalence rate in the pregnant population in Istanbul. Turk Parazitol Derg. 2014;38(4):228–233 (Turkish)
48. Guckan R, Killinc C, Gozdemir E. HBBSAG, anti Hbs, anti -HCV and anti -HIV seroprevalence in pregnant women living. Asian Pac J Nurs. 2016;3(1):9–12
49. Furuncugoğlu Y, Bolukbas FF, Bolukbas C, Torun P, Ozturk R. Changes in the prevalence of HBV infection in pregnant women in Turkey between 1995 and 2015: a 20-year evaluation. Postgrad Med J. 2016;92(1091):510–513
50. Murad EA, Babiker SM, Gasim GI, Rayis DA, Adam I. Epide- miology of hepatitis B and hepatitis C virus infections in preg- nant women in Sana’a, Yemen. BMC Pregnancy Childbirth. 2013;13:127
51. Chen CT. Global prevalence of hepatitis B virus infection and prevention of mother-to-child transmission. Lancet Gastroenterol Hepatol. 2018;3(9):598–599
52. Zheng H, Cui FQ, Wang FZ, et al. The epidemiology of hepa-titis B virus infection in women of reproductive age in highly endemic areas in China. J Viral Hepat. 2018;25(1):88–96
53. Wang Y, Zhou H, Zhang L, et al. Prevalence of chronic hepatitis B and status of HBV care among rural women who planned to conceive in China. Sci Rep. 2017;7(1):12090
54. Liu J, Zhang S, Liu M, Wang Q, Shen H, Zhang Y. Distribution of ABO/Rh blood groups and their association with hepatitis B virus infection in 3.8 million Chinese adults: a population-based cross-sectional study. J Viral Hepat. 2018;25(4):401–411
55. Zhang L, Wang YY, Huang YJ, et al. Status of HBsAg seroprevalence in 15 million rural couples in China: a cross-sectional study. Sci Rep. 2017;7:42822
56. Xin X, Wang Y, Cheng J, et al. Seroepidemiological sur-vey of hepatitis B virus infection among 764,460 women of
childbearing age in rural China: a cross-sectional study. J Clin Virol. 2016;81:47–52
57. Evans AA, Cohen C, Huang P, et al. Prevention of perinatal hepatitis B transmission in Haimen City, China: results of a community public health initiative. Vaccine. 2015;33(26):3010–3015
58. Ding Y, Sheng Q, Ma L, Dou X. Chronic HBV infection among pregnant women and their infants in Shenyang, China. Virol J. 2013;10:17
59. Zhang L, Gui X, Wang B, et al. A study of immunoprophylaxis failure and risk factors of hepatitis B virus mother-to-infant transmission. Eur J Pediatr. 2017;176(3):416–423
60. Fang F, Zhang G, Zheng H, et al. Post-vaccination serological testing of infants born to hepatitis B surface antigen positive mothers in 4 provinces of China. Vaccine. 2017;35(33):4229–4235
61. Chen T, Wang J, Qiu H, et al. Different interventional criteria for chronic hepatitis B pregnant women with HBsAg(+) or HBeAg(−): epidemiological data from Shaanxi, China. Medicine (Baltimore). 2018;97(27):e11406
62. Sheng QI, Wang SJ, Wu YY, Dou XG, Ding Y. Hepatitis B virus serosurvey and awareness of mother-to-child transmission among pregnant women in Shenyang, China: an observational study. Medicine (Baltimore). 2018;97(22):10931
63. Dashtseren B, Bungert A, Bat-Ulzii P, Enkhbat M, Lkhagva-Ochir O, Jargalsaihan G, et al. Endemic prevalence of hepatitis B and C in Mongolia: a nationwide survey amongst Mongolian adults. J Viral Hepat. 2017;24(9):759–767
64. Woodring J, Pastore R, Brink A, Ishikawa N, Takashima Y, Cho EJ, Kim SE, Suk KT, et al. Current status and strategies for hepatitis B control in Korea. Clin Mol Hepatol. 2017;23(3):205–211
65. Hur YJ, Choe SA, Choe YJ, Paek J. Hepatitis B surface antigen and antibody positivity among women of childbearing age after three decades of universal vaccination in South Korea. Int J Infect Dis. 2020;104:551–555
66. Kim JH, Kim JS, Lee JJ, et al. Survey of perinatal hepatitis B virus transmission after Korean National Prevention Program in a tertiary hospital. Korean J Intern Med. 2014;29(3):307–314
67. Sugiyama A, Ohisa M, Nagashima S, Yamamoto C, Nishida Y, Tohme R.A. Progress toward hepatitis B control and elimination of mother-to-child transmission of hepatitis B virus—Western Pacific Region, 2005–2017. MMWR Morb Mortal Wkly Rep. 2019;68:195–200
68. Cho EJ, Kim SE, Suk KT, et al. Current status and strategies for hepatitis B control in Korea. Clin Mol Hepatol. 2017;23(3):205–211
69. Hur YJ, Choe SA, Choe YJ, Paek J. Hepatitis B surface antigen and antibody positivity among women of childbearing age after three decades of universal vaccination in South Korea. Int J Infect Dis. 2020;104:551–555
70. Kim JH, Kim JS, Lee JJ, et al. Survey of perinatal hepatitis B virus transmission after Korean National Prevention Program in a tertiary hospital. Korean J Intern Med. 2014;29(3):307–314
71. Sugiyama A, Ohisa M, Nagashima S, Yamamoto C, Chuo C, Fuji T, et al. Reduced prevalence of hepatitis B surface antigen positivity among pregnant women born after the national implementation of immunoprophylaxis for babies born to hepatitis B virus-carrier mothers in Japan. Hepatol Res. 2017;47(12):1329–1334
72. Chen DS. Fighting against viral hepatitis: lessons from Taiwan. Hepatology. 2011;54:381–392
73. CDC. Center for disease control, Taiwan 2015 national various immunization completion rate. 2017. http://www.cdc.gov.tw/professional/page.aspx?treeid=5b0231beb94edf&conetreeid=3D1DC342B28E123
74. Su WJ, Chen SF, Yang CH, Chuang PH, Chang HF, Chang MH. The impact of universal infant hepatitis B immunization on reducing the hepatitis B carrier rate in pregnant women. J Infect Dis. 2019;220:1118–1126
75. Ork V, Woodring J, Shafigul Hossain M, et al. Hepatitis B surface antigen seroprevalence among pre- and post-vaccine cohorts in Cambodia. 2017. Vaccine. 2019;37:5059–5066
76. Minta AA, Silva MWT, Shrestha A, et al. Hepatitis B surface antigen seroprevalence among children in the Philippines, 2018. Vaccine. 2021;39:1982–1989
77. Sebastian VJ, Bhattacharya S, Ray S, Daud JH. Prevalence of hepatitis-B surface antigen in the pregnant women of Brunei Darussalam. Southeast Asian J Trop Med Public Health. 1990;21:123–127
78. Htwe O, Coates PD, Krasu M, Tju H, Soe NN, Tan C, et al. Prevalence of hepatitis B and other infections among pregnant women seen in a referral centre in Brunei Darussalam. Brunei Med J. 2013;9(4):220–226
79. Gunardi H, Zaimi LF, Soedjatmiko AR, Muljono DH. Current prevalence of hepatitis B infection among parturient women in Jakarta, Indonesia. Acta Med Indones. 2014;46:3–9
80. Muljono HD. Epidemiology of Hepatitis B and C in Republic of Indonesia. Euroasian J Hepatogastroenterol. 2017;7(1):55–59
81. Girawan D, Judistiana RTD, Risam NA, Bestari MB, Nugraha ES, Ermaya YS, et al. The high prevalence of negative hepatitis B surface antibody (Anti-HBs) among pregnant women in bandung, Indonesia: a community-based study. Int J Hepatol. 2020;19(2020):3414869
82. Norizuki M, Kitamura T, Komada K, et al. Serologic testing of randomly selected children after hepatitis B vaccination: a cross-sectional population-based study in Lao People’s Democratic Republic. BMC Infect Dis. 2019;19:1–9
83. Xuevatongsa A, Komada K, Kitamura T, et al. Chronic hepatitis B prevalence among children and mothers: results from a nationwide, population-based survey in Lao People’s Democratic Republic. PLoS ONE. 2014;9:e88829
84. Black AP, Nonuathong P, Nanthavong N, Souvannaso C, Vili-vong K, Jutavijitum P, et al. Hepatitis B virus in the Lao People’s Democratic Republic: a cross sectional serosurvey in different cohorts. BMC Infect Dis. 2014;14:457
85. Choisy M, Kromalaphet S, Xaydalasouk K, Quest F, Lathaphasavang V, Buissou Y. Prevalence of hepatitis B virus infection among pregnant women attending antenatal clinics in Vientiane, Laos, 2008–2014. Hepat Res Treat. 2017;2017:1–5
86. Shamsuddin K, Marmuji LZ. Weighted analysis of prevalence and risk factors of hepatitis B infection among antenatal mothers in Ipoh. Singap Med J. 2010;51:800–805
87. Bierhoff M, Angkura-waranon C, Myat Min A, Gilder ME, Win Tun N, Keereevijit A, et al. Maternal hepatitis B infection burden, comorbidity and pregnancy outcome in a low-income population on the myanmar-thailand border: a retrospective cohort study. J Pregnancy. 2019;25(2019):8435019
88. Carpio GCA, Taguba AQ, Tan LCO, Ong JP, Daez MLO. Prevalence and risk factors of hepatitis B infection in pregnant women at the prenatal clinic of the university of the Philippines—Philippine General Hospital. Int Dig Dis Forum Hong Kong Electron Only Abstr. 2015;13(7):E83
89. Mendoza IT, Jose SM. The association of chronic hepatitis B infectivity with fetomaternal outcome: a retrospective cohort study in a tertiary hospital. PJOEG. 2020;44(2):16–24
90. Thamkantho M, Chatychinda C. Characteristics, prevalence, and HBeAg correlation of hepatitis B in pregnancy: a siriraj hospital experience. J Med Assoc Thailand. 2020;103:276–280
91. Hall C, Gibbons M, Murphy D, Nourse C. Prevalence of hepatitis B infection in women delivering at a community health centre in Dili, Timor-Leste and discussion of programmatic challenges. Trans R Soc Trop Med Hyg. 2015;109(4):280–282
92. Miyakawa M, Yoshida L-M, Nguyen H-AT, et al. Hepatitis B virus infection among pregnant mothers and children at the introduction of the universal vaccination program in Central Vietnam. Sci Rep. 2021;11:8676
93. Dunford L, Carr MJ, Dean J, Nguyen LT, Ta Thi TH, Nguyen BT, et al. A multicentre molecular analysis of hepatitis B and blood-borne virus coinfections in Viet Nam. PLoS ONE. 2012;7(6):e39027
94. Nguyen VTT, Trang HTQ, Ishikawa N, Anh Nguyen L, Anh LAK, Minh TB, et al. Feasibility, benefits, and cost-effectiveness of adding universal hepatitis B and syphilis testing to routine
antenal care services in Thai Nguyen province, Vietnam. Int J
AIDS. 2021;32(2):135–143
92. Akhter S, Talukder MQ, Bhuiyan N, Chowdhury TA, Islam MN,
Begum S. Hepatitis B virus infection in pregnant mothers and its
transmission to infants. Indian J Pediatr. 1992;59(4):411–415
93. Karim Rumi MA, Begum K, Sawkat Hassan M, Munir Hasan
SM, Golam Azam M, Nadim Hasan K, et al. Detection of hepato-
tis B surface antigen in pregnant women attending a public
hospital for delivery: Implication for vaccination strategy in
Bangladesh. Am J Trop Med Hyg. 1998;59(2):318–322
94. Shamsuzzaman M, Singhhasivanon P, Kaewkungwal J, Law
Nayak NC, Panda SK, Bhan MK, Guha DK, Zuckerman AJ.
95. Pande C, Sarin SK, Patra S, Bhutia K, Mishra SK, Pahuja S,
96. Abass F, Thomas RD, Rajkumar A, Gupta N, Puliyl JM. Con-
97. Naveira MCM, Badal K, Dhakal J, Mayer NA, Pokharel B,
98. Ali M, Idrees M, Ali L, Hussain A, Ur Rehman I, Saleem S,
99. Qureshi H, Bile KM, Jooma R, Alam SE, Afridi HUR. Preva-
100. Shedain PR, Baral G, Sharma KR, Dhakal J, Del Prado RF. Seroprevalence of hepatitis B and C in Nepal: a
101. Sandesh K, Varghese T, Harikumar R, Beena P, Sadsharan VP,
102. Bindu CS, et al. Prevalence of hepatitis B and C in the normal
population and high risk groups in north Kerala. Trop Gastroen-
terol. 2006;27(2):80–83
103. Pande C, Sarin SK, Patra S, Bhutia K, Mishra SK, Pahuja S, et al. Prevalence, risk factors and virological profile of chronic
hepatitis B virus infection in pregnant women in India. J Med Virol. 2011;83(6):962–967
104. Naveira MCM, Badal K, Dhakal J, Mayer NA, Pokharel B,
105. Ahmad A, Khichi QG, Rehman A. Hepatitis B markers Profes-
sional Med. J. 2007;1:307–311
106. Youssani S, Mumtaz F, Memon A, Memon MA, Sikandar R.
Antenatal screening for hepatitis B and C virus carrier state at a
university hospital. JLMUHS. 2006;5:24–27
107. Hakeem A, Khan MS, Abdullah M, Rehman A, Hashmi ML.
Prevalence of HbsAg AND anti HCV in pregnant ladies attend-
ing antenatal clinic at Sheikh Zayed Medical Complex, Rahim
Yar Khan, Esclapulo. 2006.2:6–8
108. Sheikh SM. Hepatitis B and C: value of universal antenatal
screening. J Coll Phys Surg Pak. 2009;19(3):179–182
109. Khattak ST, Ali Marwat M, Khattak IU, Khan TM, Naheed T.
Comparison of frequency of hepatitis B and hepatitis C in preg-
nant women in urban and rural area of district Swat. J Ayud Med Coll Abbottabad. 2009;21(2):12–15
110. Ahmad I. Prevalence of Hepatitis B and C Viral Infection
Among Pregnant Women in Peshawar, Pakistan. Hepat Mon.
2016;16(6):e36383
111. Jamil A, Hamid S, Aziz Q, Asim M. Prevalence of hepatitis B
among pregnant women. JIMDC. 2018;7(2):128–131
112. Howell J, Pedran A, Cowie BC, Doyle J, Getahun A, Ward J,
et al. Aiming for the elimination of viral hepatitis in Australia,
New Zealand, and the Pacific Islands and Territories: where are
we now and barriers to meeting World Health Organization tar-
gets by 2030. J Gastroenterol Hepatol. 2019;34(1):40–48
113. Howell J, Balderson G, Hellard M, et al. The increasing burden
of potentially preventable liver disease among adult liver transplant
recipients: a comparative analysis of liver transplant indication
by era in Australia and New Zealand. J Gastroenterol Hepatol.
2016;31:434–441
114. Graham S, Guy RJ, Cowie B, et al. Chronic hepatitis B preva-
lence among Aboriginal and Torres Strait Islander Australians
since universal vaccination: a systematic review and meta-anal-
ysis. BMC Infect Dis. 2013;13:403
115. Bergin H, Wood G, Walker SP, Hui L. Perinatal management of
hepatitis B virus: clinical implementation of updated Australa-
sian management guidelines. Obstet Med. 2018;11(1):23–27
116. O’Sullivan BG, Gidding H, Law MG, Kaldor JM, Gilbert GL,
Dore GJ. Estimates of chronic hepatitis b virus infection in Aus-
tralia in 2000. Aust N Z J Public Health. 2004;28:212–216
117. Guirgis M, Zekry A, Yan K, Bu YM, Lee A. Chronic hepatitis B
infection in an Australian antenatal population: seroprevalence
and opportunities for better outcomes. J Gastroenterol Hepatol.
2009;24(6):998–1001
118. Giles ML, Davey MA, Wallace EM. Chronic hepatitis B infec-
tion and the risk of gestational diabetes: a cross-sectional study.
BJOG. 2020;127(9):1147–1152
119. Robinson T, Bullen C, Humphreys W, Hornell J, Moyes C. The
New Zealand hepatitis B screening programme: screening covering
prevalence of chronic hepatitisB infection. N Z Med J. 2005;118:U1345
120. Addiddle M. Impact of universal hepatitis B vaccination on ante-
natal hepatitis B prevalence in the Midlands region of the North
Island New Zealand. N Z Med J. 2011;124(1332):40–44
121. WHO: Country cooperation strategy at a glance: Pacific Island
countries. 2011. http://wpro.who.int/en
122. Lee AU, Mair L, Kevin B, Gandi L, Tarumori O, Lee C, et al.
Prevalence of chronic hepatitis B in Oro Province, Papua New
Guinea. West Pac Surveill Resp J. 2020;11(4):6–9
123. Baudouceau O, Berlitz A, Buisson Y. Hepatites B, C et E en
Nouvelle-Calédonie. Etude séro-épidémiologique chez les
appelés du contingent. Hepatitis B, C, and E in New Caledonia
Seropidemiologic study in military recruits. Med Trop (Mars).
2000;60(2):167–170 (French)
124. Berlitz-Arthaud A, Perolat P, Buisson Y. 10 year assessment of
infant hepatitis B vaccination program, in the Loyalty Islands
(New Caledonia). Vaccine. 2003;21(21–22):2737–2742
125. Wilson N, Ruff TA, Rana BJ, Leydon J, Locarnini S. The effec-
tiveness of the infant hepatitis B immunisation program in Fiji,
Kiribati, Tonga and Vanuatu. Vaccine. 2000;18:3059–3066
126. Tuinakelo LR, Tayler-Smith K, Khogali M, Marks GB. Preva-
127. Fischer G, Wang S, Ahring S, Fowler K, Hainline S, Chinglong
M, et al. An investigation of perinatal hepatitis B virus infections

 Springer
Hepatology International (2022) 16:211–253
among a high risk population: the delivery hospital as a safety net. Pediatr Infect Dis J. 2009;28(7):593–597

128. Ménard D. Toxoplasmose, rubéole, tréponématoses, hépatite virale B et infection par le VIH chez les femmes suivies pour la grossesse de la population de la côte Est de Nouvelle-Caledonie [Toxoplasmosis, rubella, syphilis, hepatitis B and HIV infection in women being followed for pregnancy in a population on the east coast of New Caledonia]. Bull Soc Pathol Exot. 2001;94(5):403–405

129. https://www.aidstdatabank.org/sites/default/files/resource/sgs-antenatal-women-youth-solomon-islands-2008.pdf

130. Getahan A, Baekalia M, Panda N, Lee A, Pualhi E, Khan S, et al. Seroprevalence of hepatitis B surface antigen in pregnant women attending antenatal clinic in Honiara Solomon Islands, 2015. World J Hepatol. 2016;8(34):1521–1528

131. Han YT, Sun C, Liu CX, Xie SS, Xiao D, Liu L, et al. Clinical features and outcome of acute hepatitis B in pregnancy. BMC Infect Dis. 2014;14:368

132. Ratnam D, Visvanathan K. New concepts in the immunopathogenesis of Chronic hepatitis B: the importance of the innate immune response. Hepatol Int. 2008;2(1):12–18

133. Jonas MM. Hepatitis B and pregnancy: an underestimated issue. Liver. 2009;29(Suppl 1):133–139

134. Mohite BJ, Rath S, Bal V, Kamat SA, Marathe SN, Zuckerman AJ, et al. Mechanisms of liver cell damage in acute hepatitis B. J Med Virol. 1987;22(3):199–210

135. Chang CY, Aziz N, Poongkunran M, Javaid A, Trinh HN, Lau DT, et al. Serum aminotransferase flares in pregnant and postpartum women with current or prior treatment for chronic hepatitis B. J Clin Gastroenterol. 2018;52:255–261.106–110

136. Bzowej NH, Tran TT, Li R, Belle SH, Smith CI, Khalili M, et al. Total alanine aminotransferase (ALT) flares in pregnant North American women with chronic hepatitis B infection: results from a prospective observational study. Am J Gastroenterol. 2019;114:1283–1291

137. Lin HH, Wu WY, Kao JH, Chen DS. Hepatitis B post-partum e antigen clearance in hepatitis B carrier mothers: correlation with viral characteristics. J Gastroenterol Hepatol. 2006;21:605–609

138. La Rocca C, Carbone F, Longobardi S, Matarese G. The immunology of pregnancy: regulatory T cells control maternal immune tolerance toward the fetus. Immunol Lett. 2014;162:41–48

139. Li L, Wang L, Huang C, Diao L, Zhang Y, Zhang X, et al. Chronic hepatitis B infection alters peripheral immune response in women with reproductive failure. Am J Reprod Immunol. 2019;81:e13083

140. Singhal A, Kanagala R, Jallil S, Wright HL, Kohli V. Chronic HBV with pregnancy: reactivation flares causing fulminant hepatic failure. Ann Hepatol. 2011;10:233–236

141. Liaw YF. Hepatitis flares and hepatitis B e antigen serumconversion: implication in anti-hepatitis B virus therapy. J Gastroenterol Hepatol. 2003;18:246–252

142. Wong F, Pai R, Van Schalkwyk J, Yoshida EM. Hepatitis B in pregnancy: a concise review of neonatal vertical transmission. J Med Virol. 2002;67:20–26

143. Foaud H, Maklad S, Mahmoud F, El-Karaky H. Occult hepatitis B virus infection in children born to HBsAg-positive mothers after neonatal passive-active immunoprophylaxis. Infection. 2015;43(3):307–314

144. Xue DZ, Yan YP, Choi BC, Xu JQ, Men K, Zhang JX, et al. Risk factors and mechanism of transplacental transmission of hepatitis B virus: a case-control study. J Med Virol. 2002;67:20–26

145. Shrivastava S, TrehanPati N, Patra S, Kottillil S, Pande C, Trivedi SS, et al. Increased regulatory T cells and impaired functions of circulating CD8 T lymphocytes is associated with viral persistence in hepatitis B virus-positive newborns. J Hepatol. 2013;59:582–591

146. Shrivastava S, TrehanPati N, Kottillil S, Sarin SK. Decline in immature transitional B cells after hepatitis B vaccination in hepatitis B positive newborns. Pediatr Infect Dis J. 2013;32:792–794
200. Shaheen AA, Myers RP. The outcomes of pregnancy in patients with cirrhosis: a population-based study. Liver Int. 2010;30:275–283

201. Chang CY, Azir N, Poongkunran M, Javaid A, Trinh HN, Lau D, et al. Serum alanine aminotransferase and hepatitis B DNA flares in pregnant and postpartum women with chronic hepatitis B. Am J Gastroenterol. 2016;111:1410–1415

202. Samadi Kochaksaraei G, Castillo E, Osman M, Simmonds K, Scott AN, Oshiomogho JI, et al. Clinical course of 161 untreated and tenofovir-treated chronic hepatitis B pregnant patients in a low hepatitis B virus endemic region. J Viral Hepat. 2016;23:15–22

203. Burra P, De Martin E, Gitto S, Villa E. Influence of age and gender before and after liver transplantation. Liver Transpl. 2013;19:122–134

204. Aggarwal N, Sawhney H, Suril V, Vasistha K, Jha M, Dhiman RK. Pregnancy and cirrhosis of the liver. Aust N Z J Obstet Gynaecol. 1999;39:503–506

205. Westbrook RH, Yeoman AD, O’Grady JG, Harrison PM, Devlin J, Heneghan MA. Model for end-stage liver disease score predicts outcome in cirrhotic patients during pregnancy. Clin Gastroenterol Hepatol. 2011;9:694–699

206. Tan J, Surti B, Saab S. Pregnancy and cirrhosis. Liver Transpl. 2008;14:1081–1091

207. Cheng YS. Pregnancy in liver cirrhosis and/or portal hypertension. Am J Obstet Gynecol. 1977;128:812–822

208. Rasheed SM, Abdel Monem AM, Abd Ellah AH, Abdel Fattah MS. Prognosis and determinants of pregnancy outcome among patients with post-hepatitis liver cirrhosis. Int J Gynaecol Obstet. 2013;121:247–251

209. Hay JE. Liver disease in pregnancy. Hepatology. 2008;47:1067–1076

210. Allen AM, Hay JE. Review article: the management of cirrhosis in women. Aliment Pharmacol Ther. 2014;40:1146–1154

211. Pillai AK, Joseph AM, Reddick M, Toomay S, Kalva S. Intravascular US-guided transjugular intrahepatic portosystemic shunt creation in a second-trimester pregnancy to prophylactically decompress abdominal wall varices before cesarean section. J Vasc Interv Radiol. 2014;25:481–483

212. Lelef-Mailu FJ, Mariara CM. Pregnancy in a patient with portal hypertension secondary to liver cirrhosis. BMJ Case Rep. 2018;2018:bcr2017223076

213. Chen HL, Lin L, Hu FC, Lee JT, Lin WT, Yang YJ, et al. Effects of maternal screening and universal immunization to prevent mother-to-infant transmission of HBV. Gastroenterol. 2012;142(4):773–781

214. Cheung KW, Seto MTY, Kan ASY, Wong D, Kou KO, So PL, et al. Immunoprophylaxis failure of infants born to hepatitis B carrier mothers following routine vaccination. Clin Gastroenterol Hepatol. 2018;16(1):144–145

215. Cheung KW, Lao TT. Hepatitis B—vertical transmission and the prevention of mother-to-child transmission. Best Pract Res Clin Obstet Gynaecol. 2020;68:78–88

216. Zeng QL, Yu ZJ, Ji F, Li GM, Zhang GF, Xu JH, et al. Tenofovir alafenamide to prevent perinatal hepatitis B transmission: a multicenter, prospective, observational study. Clin Infect Dis. 2021. https://doi.org/10.1093/cid/ciaa1939

217. Jourdain G, Ngo-Giang-Huong N, Harrison L, Decker L, Khamduang W, Tierney C, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. N Engl J Med. 2018;378(10):911–923

218. Ghendon Y. Perinatal transmission of hepatitis B virus in high-incidence countries. J Virol Methods. 1987;17(1–2):69–79

219. Pan CQ, Duan ZP, Bhamidimarrri KR, Zou HB, Liang XF, Li J, et al. An algorithm for risk assessment and intervention of mother to child transmission of hepatitis B virus. Clin Gastroenterol Hepatol. 2012;10(5):452–459

220. Beasley RP, Hwang LY, Lee GC, Lan CC, Roan CH, Huang FY, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. Lancet. 1983;2(8359):1099–1102

221. Zhang L, Gui XE, Wang B, Fan JY, Cao Q, Mullane K, et al. Serological positive markers of hepatitis B virus in femoral venous blood or umbilical cord blood should not be evidence of in-utero infection among neonates. BMC Infect Dis. 2016;16(1):408

222. Liu J, Xu B, Chen T, Chen J, Feng J, Xu C, et al. Presence of hepatitis B virus markers in umbilical cord blood: exposure to or infection with the virus? Dig Liver Dis. 2019;51(6):864–869

223. Schweitzer IL. Vertical transmission of the hepatitis B surface antigen. Am J Med Sci. 1975;270(2):287–291

224. Goudreau A, Yvonnet B, Lesage G, Barin F, Denis F, Coursaget P, et al. Lack of anti-HBe IgM in neonates with HBsAg carrier mothers argues against transplacental transmission of hepatitis B virus infection. Lancet. 1983;2(8359):1103–1104

225. Lin HH, Lee TY, Chen DS, Sung JL, Ohito H, Etoh T, et al. Transplacental leakage of HBsAg-positive maternal blood as the most likely route in causing intrauterine infection with hepatitis B virus. J Pediatr. 1987;111(6 Pt 1):877–881

226. Tse K, Siu SL, Yap KT, Chan SM, Que TL, Lui WY, et al. Immuno-prophylaxis of babies born to hepatitis B carrier mothers. Hong Kong Med J. 2006;12(5):368–374

227. Shikata T, Karasawa T, Abe K. Two distinct types of hepatitis B in experimental hepatitis B virus infection. Am J Pathol. 1980;99(2):353–368

228. Masuzaki H, Miura K, Miura S, Yoshiura K, Mapendano CK, Nakayama D, et al. Labor increases maternal DNA contamination in cord blood. Clin Chem. 2004;50(9):1709–1711

229. Merrill DA, Dubois RS, Kohler PF. Neonatal onset of the hepatitis-associated-antigen carrier state. N Engl J Med. 1972;287(25):1280–1282

230. Lu Y, Zhu FC, Liu JX, Zhai XJ, Chang ZJ, Yan L, et al. The maternal viral threshold for antiviral prophylaxis of perinatal hepatitis B virus transmission in settings with limited resources: a large prospective cohort study in China. Vaccine. 2017;35(48 Pt B):6627–6633

231. Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy. World Health Organization. Geneva. 2020. Licence: CC BY-NC-SA 3.0 IGO

232. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67(4):1560–1599

233. Zhou YH. Issues meriting further study in preventing mother-to-infant transmission of hepatitis B by antiviral therapy during pregnancy. Matern Fetal Med. 2019;1(1):42–47

234. Hu Y, Zhang S, Luo C, Liu Q, Zhou YH. Gaps in the prevention of perinatal transmission of hepatitis B virus between recommendations and routine practices in a highly endemic region: a provincial population-based study in China. BMC Infect Dis. 2012;12:221

235. Wang F, Zheng H, Zhang G, Ding Z, Li F, Zhong G, et al. Effectiveness of prevention of mother-to-child transmission practice in three provinces of Southern China. Hum Vaccin Immunother. 2015;11(8):2061–2067

236. Huang H, Xu C, Liu L, Chen L, Zhu X, Chen J, et al. Increased protection of earlier use of immunoprophylaxis in preventing perinatal transmission of hepatitis B virus. Clin Infect Dis. 2020. https://doi.org/10.1093/cid/ciaa898

237. Sun KX, Li J, Zhu FC, Liu JX, Li RC, Zhai XJ, et al. A predictive value of quantitative HBsAg for serum HBV DNA
level among HBeAg-positive pregnant women. Vaccine. 2012;30(36):5335–5340

238. Wen WH, Huang CW, Chie WC, Yeung CY, Zhao LL, Lin WT, et al. Quantitative maternal hepatitis B surface antigen predicts maternally transmitted hepatitis B virus infection. Hepatology. 2016;64(5):1451–1461

239. Thilakanathan C, Wark G, Maley M, Davison S, Lawler J, Lee A, et al. Mother-to-child transmission of hepatitis B: examining viral cut-offs, maternal HBsAg serology and infant testing. Liver Int. 2018;38(7):1212–1219

240. Xiao Y, Sun K, Duan Z, Liu Z, Li Y, Yan L, et al. Quasispecies characteristic in “a” determinant region is a potential predictor for the risk of immunoprophylaxis failure of mother-to-child-transmission of sub-genotype C2 hepatitis B virus: a prospective nested case-control study. Gut. 2020;69(5):933–941

241. Epidemiology of vaccine preventable diseases. The pink book course textbook, 13th edition. Atlanta (GA): Centers for Disease Control and Prevention. 2015. (https://www.cdc.gov/vaccines/pubs/pinkbook/hepb.html)

242. Hepatitis B vaccines: WHO position paper—July 2017. Weekly epidemiological record. 2017; 92(27):369–92. http://www.who.int/immunization/policy_position_papers/hepatitis_b/en/

243. Beasley RP, Trepo C, Stevens CE, Szmuszz W. The e antigen and vertical transmission of hepatitis B surface antigen. Am J Epidemiol. 1977;105(2):94–98

244. Linder N, Vishne TH, Levin E, Handsher R, Fink-Kremer I, Waldman D, et al. Hepatitis B vaccination: long term follow-up of the immune response of preterm infants and comparison of two vaccination protocols. Infection. 2002;30:136–139

245. Saari TN, American Academy of Pediatrics-Committee on Infectious Diseases. Immunization of preterm and low birth weight infants. Pediatrics. 2003;112:193–198

246. Lee C, Gong Y, Brok J, Boxall EH, Glud C. Effect of hepatitis B immunisation in newborn infants of mothers positive for hepatitis B surface antigen: systematic review and meta-analysis. BMJ. 2006;332:328–336

247. Isaacs D, Kilham HA, Alexander S, Wood N, Buckmaster A, Royle J. Ethical issues in preventing mother-to-child transmission of hepatitis B by immunisation. Vaccine. 2011;29(37):6159–6162

248. Fu S, Yao NJ, Feng YL, Li J, Wu YC, Tian Z, et al. The efficacy of two different dosages hepatitis B immunoglobulin in interrupting mother-to-infant transmission of hepatitis B virus: a systematic review and meta-analysis. J Hepatol. 2019;70:E124

249. Machaira M, Papaevangelou V, Vouloumanou EK, Tansarli GS, Falagas ME. Hepatitis B vaccine alone or with hepatitis c vaccine in infants born to HBsAg-positive mothers: a systematic review and meta-analysis. J Antimicrob Chemother. 2015;70:396–404

250. Milone A, West DJ, Chinh DV, Moyes CD, Poerschke G. Field study evaluation of the efficacy and immunogenicity of recombinant hepatitis B vaccine without HBIG in newborn Vietnamese infants. J Med Virol. 2002;67:327–333

251. Segeral O, Dim B, Durier C, et al. Immunoglobulin-free alternative strategy to prevent HBV mother to child transmission in Cambodia: preliminary results of the ANRS 12345 TA PROHM study. EASL International Liver Congress, June 23–26, 2021. Abstract OS-865

252. Funk AL, Lu Y, Yoshida K, Zhao T, Boucheron P, van Holten J, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. Lancet Infect Dis. 2021;21(1):70–84

253. Ségéral O, N’Diaye DS, Prak S, Nouhin J, Chhum S, Khamduang W, et al. Usefulness of a serial algorithm of HBsAg and HBeAg rapid diagnosis tests to detect pregnant women at risk of HBV mother-to-child transmission in Cambodia, the ANRS 12328 pilot study. J Clin Virol. 2018;109:29–34

254. Seck A, Ndiaye F, Maylin S, Ndiaye B, Simon F, Funk AL, et al. Poor sensitivity of commercial rapid diagnostic tests for hepatitis B e antigen in Senegal, West Africa. Am J Trop Med Hyg. 2018;99(2):428–434

255. Segeral O, Dim B, Durier C, Prak S, Chhim K, Vong C, et al. Hepatitis B e antigen (HBeAg) rapid test and alanine aminotransferase level-based algorithm to identify pregnant women at risk of HBV mother-to-child transmission: the ANRS 12345 TA PROHM study. Clin Infect Dis. 2020;71(10):e587–e593

256. Wu Y, Liu J, Feng Y, Yu S, Ji F, Ge L, et al. Efficacy and safety of antiviral therapy for HBV in different trimesters of pregnancy: systematic review and network meta-analysis. Hepatol Int. 2020;14:180–189

257. Yi W, Pan CQ, Li MH, et al. The characteristics and predictors of postpartum hepatitis flares in women with chronic hepatitis B. Am J Gastroenterol. 2018;113(5):686–693

258. Zhao Y, Feng Y, Wu Y, Ji F, Chen T. Hepatic flare after antiviral treatment withdrawal in post-partum for pregnancy of chronic hepatitis B virus infection: a pairwise and Bayesian network meta-analysis. J Hepatol. 2019;70:E127

259. Sarin SK, Kumar M, Lau GK, Abbas Z, Chan HL, Chen CJ, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int. 2016;10(1):1–98

260. Wang XX, Lu JF, Wu YL, Ma LN, Jin Y, Cao ZH, et al. Clinical study on liver function, virology, serological changes and the safety of drug withdrawal in pregnant women who are chronic HBV carriers during pregnancy and postpartum. Zhonghua Gan Zhang Bing Za Zhi. 2019;27(4):261–266 (Chinese)

261. Liu J, Wang J, Jin D, Qi C, Yan T, Cao F, et al. Hepatic flare after telbivudine withdrawal and efficacy of postpartum antiviral therapy for pregnancies with chronic hepatitis B virus. J Gastroenterol Hepatol. 2017;32(1):177–183

262. Wen WH, Chen HL, Shih TT, Wu JF, Ni YH, Lee CN, et al. Long-term growth and bone development in children of HBV-infected mothers with and without fetal exposure to tenofovir disoproxil fumarate. J Hepatol. 2020;72(6):1082–1087

263. Yi W, et al. Risk of vertical transmission of hepatitis B after amniocentesis in HBs-antigen-positive mothers. J Hepatol. 2014;60:523–529

264. Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. J Viral Hepat. 2012;19:e18–e25

265. Han Z, Zhang Y, Bai X, Yin Y, Xu C, Hou H. Mother-to-child transmission of hepatitis B virus after amniocentesis: a retrospective matched cohort study. Prenat Diagn. 2019;39:431–440

266. Dionne-Odom J, et al. #38: hepatitis B in pregnancy screening, treatment, and prevention of vertical transmission. Am J Obstet Gynecol. 2016;214:6–14

267. Visvanathan K, Dusheiko G, Miles G, Wong ML, Phung N, Walker S, et al. Managing HBV in pregnancy. Prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, UK and New Zealand key opinion leaders. Gut. 2016;65(2):340–350

268. He R, Wen P, Xiong M, Fan Z, Li F, Luo D, et al. Cesarean section in reducing mother-to-child HBV transmission: a meta-analysis. J Matern Fetal Neonatal Med. 2020;20:1–9

269. Steyaert SR, Leroux-Roels GG, Dhont M. Infections in IVF: systematic review and guidelines. Hum Reprod Update. 2000;6:432–441

270. Mak JSM, Lao TT. Assisted reproduction in hepatitis carriers during pregnancy and vertical transmission of hepatitis B surface antigen. Am J Gastroenterol. 2012;99(2):428–434

271. Walker S, et al. Managing HBV in pregnancy. Prevention, prophylaxis, treatment and follow-up: position paper produced by Australian, UK and New Zealand key opinion leaders. Gut. 2016;65(2):340–350
B virus transmission during in vitro fertilization. Fertil Steril. 2011;95:1667–1671

272. Hu XL, Zhou XP, Qian YL, Wu GY, Ye YH, Zhu YM. The presence and expression of the hepatitis B virus in human oocytes and embryos. Hum Reprod. 2011;26:1860–1867

273. Lin J, Sha Y, Qiu P. Effects of hepatitis B virus infection in women with different ovarian reserve on outcomes of in vitro fertilization and embryo transfer. Reprod Contracept. 2017;37:106–111

274. Shi L, Liu S, Zhao W, Zhou H, Ren W, Shi J. Hepatitis B virus infection reduces fertilization ability during in vitro fertilization and embryo transfer. J Med Virol. 2014;86:1099–1104

275. Liu L, Liu Q, Wen Y. Ovarian reserve function in fertile women with HBV infection. J Reprod Med. 2016;25:27–31

276. Yao N, Ma Y, Wang J, Zhang X, Zhao Y, Chen Y, et al. Role of influence female chronic hepatitis B virus infection in assisted reproduction and infantile outcomes: a systematic review and meta-analysis. Hepatology. 2019;70:599A

277. Chen H, Ge H-S, Lv J-Q, Wu X-M, Xi H-T, Huang J-Y, et al. Chronic hepatitis B virus infection in women is not associated with IVF/ICSI outcomes. Arch Gynecol Obstet. 2014;289:213–217

278. Lee VCY, Ng EHY, Yeung WSB, Ho PC. Impact of positive hepatitis B surface antigen on the outcome of IVF treatment. Reprod Biomed Online. 2010;21:712–717

279. Jin L, Nie R, Li Y, Xiao N, Zhu L, Zhu G. Hepatitis B surface antigen in oocytes and embryos may not result in vertical transmission to offspring of hepatitis B virus carriers. Fertil Steril. 2016;105:1010–1013

280. Nie R, Wang M, Liao T, Qian K, Zhu G, Jin L. Assisted conception does not increase the risk for mother-to-child transmission of hepatitis B virus, compared with natural conception: a prospective cohort study. Fertil Steril. 2019;111:348–356

281. Kang X, Xie Q, Zhou X, Li F, Huang J, Liu D, et al. Effects of hepatitis B virus protein exposure on sperm membrane integrity and functions. PLoS ONE. 2012;7:e33471

282. Zhou X-P, Hu X-L, Zhu Y-M, Qu F, Sun S-J, Qian Y-L. Comparison of semen quality and outcome of assisted reproductive techniques in Chinese men with and without hepatitis B. Asian J Androl. 2011;13:465–469

283. Bu Z, Kong H, Li J, Wang F, Guo Y, Su Y, et al. Effect of male hepatitis B virus infection on outcomes of in vitro fertilization and embryo transfer treatment: insights from couples undergoing oocyte donation. Int J Clin Exp Med. 2014;7:1860–1866

284. Huang J-M, Huang T-H, Qi H-Y, Fang X-Z, Zhan H-T, Liu H-X, et al. Effects of hepatitis B virus infection on human sperm chromosomes. World J Gastroenterol. 2003;9:736–740

285. Ali BA, Huang T-H, Salem H-H, Xie Q-D. Expression of hepatitis B virus genes in early embryonic cells originated from hamster ova and human spermatozoa transfected with the complete viral genome. Asian J Androl. 2006;8:273–279

286. Qc C, Yu Z. Is hepatitis B virus transmitted via the male germ line? A seroepidemiological study in fetuses [Internet]. International journal of infectious diseases: IJD: official publication of the International Society for Infectious Diseases. Int J Infect Dis. 2013. Available from: https://pubmed.ncbi.nlm.nih.gov/23154176/

287. Practice Committee of the American Society for Reproductive Medicine. Recommendations for reducing the risk of viral transmission during fertility treatment with the use of autologous gametes: a committee opinion. Fertil Steril. 2020;114:1158–1164

288. Cobo A, Beller J, de los Santos MJ, Remohi J. Viral screening of spent culture media and liquid nitrogen samples of oocytes and embryos from hepatitis B, hepatitis C, and human immunodeficiency virus chronically infected women undergoing in vitro fertilization cycles. Fertil Steril. 2012;97:74–8.

289. World Health Organization. Hepatitis B vaccines WHO position paper. Weekly Epidemiol Rec. 2009;84:405–420

290. Mast EE, Margolis HS, Fiore AE, Brink EW, Goldstein ST, Wang SA, et al. A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP) part 1: immunization of infants, children, and adolescents. MMWR Recomm Rep. 2005;54:1–31

291. Tan KL, Goh KT, Oon CJ, Chan SH. Immunogenicity of recombinant yeast-derived hepatitis B vaccine in nonresponders to perinatal immunization. JAMA. 1994;271:859–861

292. Kramer MS, Aboud F, Mironova E, Vanliloch I, Platt RW, Matush L, et al. Breastfeeding and child cognitive development: new evidence from a large randomized trial. Arch Gen Psychiatry. 2008;65:578–584

293. Koletzko B, von Kries R, Closa R, Escribano J, Scaglioni S, Giovannini M, et al. Can infant feeding choices modulate later obesity risk? Am J Clin Nutr. 2009;89:1502S–1508S

294. Shantakumar S, Terry MB, Teitelbaum SL, Britton JA, Milikan RC, Moorman PG, et al. Reproductive factors and breast cancer risk among older women. Breast Cancer Res Treat. 2007;102:365–374

295. Petrova M, Kamburov V. Breastfeeding and chronic HBV infection: clinical and social implications. World J Gastroenterol. 2010;16(40):5042–5046

296. Lin HH, Hsu HY, Chang MH, Chen PJ, Chen DS. Hepatitis B virus in the colostra of HBeAg-positive carrier mothers. J Pediatr Gastroenterol Nutr. 1993;17:207–210

297. Yang D, Li Y, Song J. Significance of detection of HBV-DNA in maternal blood and CMV-DNA by polymerase chain reaction in screening mothers’ milk. Hunan Yikedaxue Xuebao. 1999;24:44–46

298. Shi Z, Yang Y, Wang H, Ma L, Schreiber A, Li X, et al. Breast-feeding of newborns by mothers carrying hepatitis B virus: a meta-analysis and systematic review. Arch Pediatr Adolesc Med. 2011;165(9):837–846

299. Egashira M, Takayanagi T, Moriuchi M, Moriuchi H. Does daily intake of bovine lactoferrin-containing products ameliorate rotavirus gastroenteritis? Acta Paediatr. 2007;96:1242–1244

300. Li S, Zhou H, Huang G, Liu N. Inhibition of HBV infection by bovine lactoferrin and iron-, zinc-saturated lactoferrin. Med Microbiol Immunol. 2009;198:19–25

301. Thea DM, Aldrovandi G, Kankasa C, Kasonde P, Decker WD, Semrau K, et al. Post-weaning breast milk HIV-1 viral load, blood prolactin levels and breast milk volume. AIDS. 2006;20:1539–1547

302. Shapiro RL, Holland DT, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. J Infect Dis. 2005;192:720–727

303. Bae WH, Wester C, Smeaton LM, Shapiro RL, Lockman S, Onyait K, et al. Reproductive factors and breast obesity risk? Am J Clin Nutr. 2009;89:1502S–1508S

304. Palombi L, Pirillo MF, Marchei E, Jere H, Sagno JB, Luhanga R, et al. Antiretroviral therapy among infants. AIDS. 2008;22:1633–1640

305. Palombi L, Pirillo MF, Marchei E, Jere H, Sagno JB, Luhanga R, et al. Antiretroviral therapy among infants. AIDS. 2008;22:1633–1640

306. Kobayashi S, Saito H, Takahashi H, Yamada A, Kurosawa K, Yamazaki S, et al. Concentrations of tenofovir, lamivudine and efavirenz in breast milk of women in Botswana receiving antiretroviral treatment. J Infect Dis. 2005;192:720–727

307. Shapiro RL, Holland DT, Capparelli E, et al. Antiretroviral concentrations in breast-feeding infants of women in Botswana receiving antiretroviral treatment. J Infect Dis. 2005;192:720–727

308. Obaid H, Alsina M, Charpentier F, et al. Breast milk pharmacokinetics of emtricitabine, tenofovir and lamivudine using dried blood and breast milk spots in nursing African mother-infant pairs. J Antimicrob Chemother. 2018;73:1013–1019
306. Best BM, Burchett S, Li H, Stek A, Hu C, Wang J, et al. Pharmacokinetics of tenofovir during pregnancy and postpartum. HIV Med. 2015;16:46–51
307. Hu X, Wang L, Xu F. Guides concerning tenofovir exposure via breastfeeding: a comparison of drug dosages by developmental stage. Int J Infect Dis. 2019;87:8–12
308. Ghazinyan HL. Hepatitis B and Pregnancy. Blood. 2015;2(20):46–47
309. Hepatitis B. Vaccines. Wkly Epidemiol Rec. 2009;84(40):405–419
310. Hepatitis B: vaccines: WHO position paper, July 2017. Wkly Epidemiol Rec. 2017;92(27):369–392
311. Ork V, Woodring J, Shafigul Hossain M, Wasley A, Nagashima S, Yamamoto C, et al. Hepatitis B surface antigen seroprevalence among pre- and post-vaccine cohorts in Cambodia, 2017. Vaccine. 2019;37(35):5059–5066
312. Thio CL, Guo N, Xie C, Nelson KE, Ehrhardt S. Global elimination of mother-to-child transmission of hepatitis B: revisiting the current strategy. Lancet Infect Dis. 2015;15(8):981–985
313. WHO guidelines on hepatitis B and C testing. World Health Organization, Geneva. 2017. Licence: CC BY-NC-SA 3.0 IGO
314. Ott JJ, Stevens GA, Wiersma ST. The risk of perinatal hepatitis B virus transmission: hepatitis B e antigen (HBeAg) prevalence estimates for all world regions. BMC Infect Dis. 2012;9(12):131
315. Allison RD, Patel MK, Tohme RA. Hepatitis B vaccine birth dose coverage correlates worldwide with rates of institutional deliveries and skilled attendance at birth. Vaccine. 2017;35:4094–4098
316. Petit D, Tevi-Benissan C, Woodring J, Hennessey K, Kahn A-L. Countries’ interest in a hepatitis B vaccine licensed for the controlled temperature chain; survey results from African and Western Pacific regions. Vaccine. 2017;35:6866–6871
317. Abravanel F, Lhomme S, Trémeaux P, et al. Performance of the Xpert HBV viral load assay versus the aptima quant assay for quantifying hepatitis B virus DNA. Diagn Microbiol Infect Dis. 2020;96:114946

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Manoj Kumar1 · Zaigham Abbas2 · Milad Azami3 · Maria Belopolskaya4 · A. K. Dokmeci5 · Hasmik Ghazinyan6 · Jidong Jia7 · Ankur Jindal1 · Han Chu Lee8 · Wei Lei9 · Seng Gee Lim10 · Chun-Jen Liu11 · Qiang Li12 · Mamun Al Mahtab13 · David H. Muljono14 · Madunil Anuk Niriella15 · Masao Omata16,17 · Diana A. Payawal18 · Shiv K. Sarin19 · Olivier Ségéral19 · Tawesak Tanwandee20 · Nirupma Trehanpati21 · Kumar Visvanathan22 · Jin Mo Yang23 · Man-Fung Yuen24 · Yingjie Zheng25 · Y. H. Zhou26

Zaigham Abbas
drzabbas@gmail.com
Milad Azami
milad98azami@gmail.com
Maria Belopolskaya
belopolskaya.maria@yahoo.com
A. K. Dokmeci
akdokmeci@hotmail.com
Hasmik Ghazinyan
ghazinian@gmail.com
Jidong Jia
jiamd@263.net
Ankur Jindal
ankur.jindal3@gmail.com
Han Chu Lee
hch@amc.seoul.kr
Wei Lei
weelai@163.com
Seng Gee Lim
mdclimsg@nus.edu.sg
Chun-Jen Liu
cjlui@ntu.edu.tw
Qiang Li
doctorliqiang@gmail.com; doctorliqiang@aliyun.com
Mamun Al Mahtab
shwapnil@agni.com

David H. Muljono
davidhm@eijkman.go.id
Madunil Anuk Niriella
maduniln@yahoo.co.uk
Masao Omata
aug8808@yahoo.co.jp
Diana A. Payawal
dianapayawal@yahoo.com
Olivier Ségéral
olivier_segeral@uhs.edu.kh
Tawesak Tanwandee
tawesak@gmail.com
Nirupma Trehanpati
trehanpati@gmail.com
Kumar Visvanathan
kv@unimelb.edu.au
Jin Mo Yang
jmyangdr@catholic.ac.kr
Man-Fung Yuen
mfyuen@hku.hk
Yingjie Zheng
yjzheng@shmu.edu.cn
Y. H. Zhou
zgr03summer@126.com
