ECDC SUPPLEMENTARY MATERIAL

Pathogen data sheet: HBV

Data sheet to support the development of the ECDC technical guidelines on the prevention of donor-derived transmission of Hepatitis B Virus (HBV) through Substances of Human Origin

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Abbreviations

ALT	Alanine transaminase
Ag	Antigen
cccDNA	Covalently closed circular DNA
CHB	Chronic hepatitis B
CI	Confidence interval
CLIA	Chemiluminescence immunoassay
CMIA	Chemiluminescence microparticle immunoassay
COVID-19	Coronavirus disease 2019
DNA	Deoxyribonucleic acid
ECDC	European Centre for Disease Prevention and Control
EC	European Commission
ECLIA	Electrochemiluminescence immunoassay
EDQM	European Directorate for the Quality of Medicines & Healthcare
EEA	European Economic Area
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
EU	European Union
FDA	United States Food and Drug Administration
FT	First-time donors
HBcAg	HBV core antigen
HBeAg	Hepatitis B e antigen
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDV	Hepatitis Delta virus
HIV	Human immunodeficiency virus
ID	Individual donation
IU	International units
IRR	Incidence rate ratio
iWP	Infectious window period
JPAC	Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
LOD	Limit of detection
MP	Minipool
MSM	Men who have sex with men
NA	Not applicable
NAT	Nucleic acid test
NC	Not calculated
ND	No data reported
NR	Not reported
OBI	Occult HBV infection
PCR	Polymerase chain reaction
PWID	People who inject drugs
RP	Repeat donors
RR	Residual risk
SoHO	Substances of human origin (excluding solid organs)[1]
STI	Sexually transmitted infection
TESSy	The European Surveillance System
UV	Ultraviolet
WHO	World Health Organization
WP	Window period

[1] As per the Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC.

Foreword

This document is intended to support the discussions of the ad hoc scientific expert panel convened for the development of ECDC technical guidelines on the prevention of donor-derived transmission of communicable diseases through substances of human origin (SoHO) (ECDC/AD/2023/20), specifically for the hepatitis B virus. These technical guidelines are prepared in the context of Regulation (EU) 2024/1938 of the European Parliament and of the Council of 13 June 2024 on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC. Solid organs are excluded from the definition of SoHOs in the scope of the Regulation as well as from the scope of this document.

Last major update: 6 September 2024

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1 Description of the pathogen

Classification and relevant features

The classification and cell tropism of the hepatitis B virus (HBV) are described in Table 1.

Table 1. Hepatitis B virus classification

Feature	Value
Realm	*Riboviria*
Family	*Hepadnaviridae*
Genus	*Orthohepadnavirus*
Characteristics	Partially double-stranded deoxyribonucleic acid (DNA) virus
Cell tropism	– Hepatocytes – Peripheral blood mononuclear cells – CD34+ hematopoietic stem cells[a]
Receptors on host cell	Hepatocytes: – Heparan sulphate proteoglycan (binding factor only) – Sodium taurocholate cotransporting polypeptide Peripheral blood mononuclear cells: unknown.

[a] *in vitro evidence only.*
Source: [1-3].

2 Description of the disease

Modes of transmission

HBV is transmitted through exposure to infected bodily fluids, including blood, semen, and vaginal fluids [4]. HBV can be transmitted through:

- Vertical transmission (also called mother-to-child transmission) during pregnancy or delivery.
- Exposure to contaminated syringes or medical equipment in a healthcare setting.
- Exposure to contaminated syringes in the context of intravenous drug use.
- Needle-stick injuries or other injuries occurring outside a healthcare setting (e.g. bites, tattoos, piercings).
- Unprotected sexual contact with a partner with an infection.
- Transfusion of infectious blood or blood components and plasma-derived medicinal products.
- Transplantation of different tissue types or organs from a donor with an infection.

Documented transmission categories from newly diagnosed hepatitis B cases in the EU/EEA in 2022 are described in Table 8.

Natural history of HBV infection

HBV infection may present as acute or chronic, with chronic infection resulting from persistence of the infection. The likelihood of developing chronic infection is primarily determined by the age of the individual at the time of acute infection, with a higher risk of chronic HBV infection in younger age groups: up to 90% of infants with infection develop chronic infection, 30% of children with infection after the neonatal period but before the age of five years, and up to 5% of adults [5,6].

Acute hepatitis B

Acute HBV infection may have different clinical presentations according to the age at the time of infection. During childhood, acute hepatitis B is usually asymptomatic or subclinical. However, in adults, up to 50% may develop icteric hepatitis [6].

Symptomatic cases can be described by considering three clinical phases:

- A prodromal phase lasting a few days and characterised by flu-like symptoms, nausea, vomiting, loss of appetite and upper abdominal discomfort.
- An icteric phase that can last several weeks and is characterised by jaundice, dark urine, and light-coloured stools. During this phase, liver enzymes are significantly elevated. Most children and neonates do not experience this phase, but it is reported to occur in 30 to 50% of adults [5].
- A convalescence phase following the peak of the icteric phase, characterised by recovery of all symptoms.

The majority of acute hepatitis B cases during adult age (~95%) will not progress to chronic hepatitis B even if the virus may persist lifelong in the form of covalently closed circular DNA (cccDNA) [6-8]. Individuals having recovered from acute HBV infection may develop lifelong immunisation levels of hepatitis B surface antibodies (anti-HBs). Fulminant hepatitis can occur following acute hepatitis B infection, though it is uncommon (0.1 – 0.5%). Fulminant hepatitis may be due to a heightened immune response causing massive lysis of infected hepatocytes [9].

During an acute infection, viremia increases with a doubling time of 2.0 to 2.7 days [10] during the ramp-up phase and is detectable within 15 – 20 days in the blood [11]. The Hepatitis B surface antigen (HBsAg) increases in parallel and is detectable in the blood after four to 10 weeks [12,13]. Shortly afterwards, hepatitis B core antibodies (anti-HBc) appear, IgM anti-HBc first and IgG anti-HBc later. The evolution of HBV markers during an acute infection is displayed in Figure 1.

Chronic hepatitis B

The onset of chronic HBV infection is implied by the persistence of HBsAg, the hepatitis B e antigen (HBeAg), and detectable HBV DNA for a period of more than six months [6,14]

Chronic HBV infection results from the failure to clear the acute infection and can be divided into five phases (Table 2):

HBeAg-positive chronic HBV infection (previously called immunotolerant disease): usually asymptomatic. This phase is characterised by the presence of serum HBsAg, very high levels of HBV DNA and alanine transaminase (ALT) levels in the normal range. HBeAg can be detected during this phase, and HBV DNA levels are high, with values above 20 000 IU/mL (over 3 600 copies/mL) [12,15]. However, liver inflammation is absent or limited. This phase can last several years in children infected perinatally and is thought to usually cease during the second or third decade of life [16,17], with a study describing a median age of 30.7 years at the loss of immune tolerance [18]. Individuals in this phase are highly infectious.

HBeAg-positive chronic hepatitis B (previously called immunoreactive disease): characterised by high levels of HBV DNA, positive HBeAg, and elevated ALT, with symptoms during this phase ranging from asymptomatic to liver failure with jaundice. HBeAg remains detectable during this phase, and HBV DNA levels remain high, though not as high as in the HBeAg-positive chronic HBV infection phase. During this phase, immune-mediated liver damage will occur and can be identified through necroinflammation on biopsy and varying degrees of fibrosis. Spontaneous flares representing an intensification of the immune response are a typical feature of this phase. Most flares are asymptomatic, but symptoms of acute hepatitis may accompany some and may even, rarely, result in cirrhosis and death. This phase can last several years and varies according to the age of initial HBeAg positivity, with shorter durations among those below 30 years old and longer durations among those more than 40 years old [19].

HBeAg-negative chronic HBV infection (previously called inactive carrier phase): usually an asymptomatic phase. During this phase, HBeAg becomes undetectable and antibodies to HBeAg (anti-HBe) appear, with low (<2 000 IU/mL) or undetectable levels of HBV DNA, as well as normalisation of liver transaminase levels, indicating clinical remission [12,20]. Individuals in this phase have a low risk of progression to cirrhosis, but progression to HBeAg-negative chronic hepatitis B (CHB) is still possible for a minority of patients. The risk of progression decreases with time and becomes negligible after 20 years [12,19,21]. During this phase, HBsAg loss may occur spontaneously, usually in cases with low levels of HBsAg, typically in around 1% of cases annually [15].

HBeAg-negative chronic hepatitis B: symptoms during this phase range from asymptomatic to liver failure with jaundice. This stage is characterised by active liver disease, loss of HBeAg and persistent or fluctuating moderate to high levels of HBV DNA [12,15]. In this phase, liver damage is evidenced by necroinflammation of the liver and fibrosis and is due to the patient's immune response. Patients in this phase have a very low rate of spontaneous disease remission [15].

HBsAg-negative phase or 'occult HBV infection' phase: this phase is characterised by negative HBsAg and usually positive anti-HBc; there may also be detectable anti-HBs. Patients with an occult HBV infection (OBI) usually have low or undetectable serum HBV DNA (DNA levels below 200 IU/mL), but covalently closed circular DNA (cccDNA) can be detected in the liver [15,22].

Chronic HBV infection progresses to liver cirrhosis in up to 40% of untreated patients [14]. Chronic HBV infection accounts for at least 50% of hepatocellular carcinoma cases, though this proportion varies by region [23].

Table 2. Chronic hepatitis B virus infection markers by disease phase

Marker	HBeAg-positive chronic HBV infection	HBeAg-positive chronic hepatitis B	HBeAg-negative chronic HBV infection	HBeAg-negative chronic hepatitis B	HBsAg-negative phase (OBI)
HBsAg	+ (high)	+	+ (low)	+	-
Anti-HBs	-	-	-	-	+/-
HBeAg	+	+	-	-	-
Anti-HBe	-	-/+	+	+	-
Anti-HBc (total)	+	+	+	+	+
HBV DNA	$>10^7$ IU/mL	10^4-10^7 IU/mL	<2 000 IU/mL	≥2 000 IU/mL	± Undetectable

OBI: Occult hepatitis B virus infection.
Adapted from EASL 2017 [15].

Treatment for hepatitis B

For patients with acute hepatitis B, the goal of treatment is a reduction in the risk of acute or subacute liver failure. The vast majority of adults with acute infection will recover spontaneously and do not require treatment. Severe or fulminant acute hepatitis B is a serious complication of acute hepatitis B infection. In these cases, for those who develop a coagulopathy or protracted course (persistent jaundice or other symptoms over four weeks), there is some evidence that treatment with antiviral therapy (nucleoside/nucleotide analogues) may be beneficial. If used, this treatment should be continued until loss of HBsAg. If patients with severe or fulminant acute hepatitis B do not recover following treatment with nucleoside/nucleotide analogues, they should be considered for liver transplantation [15].

The management of CHB is complex and aims to improve survival and quality of life by preventing the disease progression to cirrhosis and hepatocellular carcinoma. The two main treatment options for CHB are nucleoside/nucleotide analogues or pegylated interferon alfa. The long-term suppression of HBV DNA is the main endpoint for all treatments, and the normalisation of transaminase levels is considered an additional endpoint. While nucleoside/nucleotide analogues have a favourable safety profile, pegylated interferon alfa is associated with considerable side effects and an unfavourable safety profile. as The HBV DNA integrates into the hosts' genome and reactivation of HBV replication is possible and a cure for CHB is not achievable with the available treatments.

Patients with infections undergoing immunosuppressive therapies are evaluated for the risk of HBV reactivation. The risk depends on the serologic status of the patient and the potency of immunosuppressants. Patients at risk for reactivation include those with a resolved infection, those with inactive CHB (detectable HBsAg, undetectable HBV DNA), and those with untreated chronic active hepatitis B (detectable HBsAg and HBV DNA). Prophylaxis is recommended in patients with a higher risk of HBV reactivation due to immunosuppressive therapies. Similarly, prophylaxis is also recommended for women identified as having chronic HBV infection during pregnancy to prevent vertical transmission (also known as mother-to-child transmission) [15].

Infectious dose and viraemia

The risk of not identifying an HBV infection that could be transmitted through SoHO is related to infectious window periods (iWP) for the screening tests applied, i.e. HBsAg serological tests and nucleic acid tests (NAT) detecting HBV DNA. For HBV DNA, two potential window periods can be considered: a first initial window period (prior to HBsAg appearance) and a possible second window period during occult infection (i.e. after loss of HBsAg), where HBV DNA is no longer detectable, but the risk of transmission is still present.

An analysis of 84 acute viraemic infections in repeat blood donors identified with individual-donation (ID) NAT estimated a first iWP pre-HBsAg at 15.3 days using HBV DNA NAT with a 95% limit of detection (LOD) of 98.5 copies/mL and at 12.6 days with a 95% LOD of 46.9 copies/mL. A second iWP corresponding to the disappearance of HBsAg and the decline of HBV DNA was estimated at 1.3 and 0.7 risk-days for 95% LODs of 98.5 and 46.9 copies/mL, respectively [24]. Relying only on HBsAg detection, the first iWP is estimated at 32.5 days and the second at 9.9 days; see Figure 1.

Infectious dose and infectivity during the pre-HBsAg window period

During this initial pre-HBsAg window period, several reports have shown that HBsAg-negative donors can transmit HBV. A review of human transmission cases and experimental animal data published in 2009 by Kleinman and colleagues suggested a 50% minimum HBV infectious dose of 8.2 HBV DNA copies [25], a number later revised to 3.2 copies (between one and 10 copies) [26]. Transmission events and look-back studies indicate the lack of a clear relationship between infectivity and viral load. The immune status of the recipients as well as the amount of plasma transfused largely affect this relationship [27]. As a result, the viral load may differ only marginally between infectious and non-infectious blood: across 17 samples of anti-HBs negative blood products, the viral load transfused leading to infection in nine patients was estimated around 1 500 copies/mL (180 – 56 000) and around 900 copies/mL (200 – 19 800) to eight patients that were not infected [28].

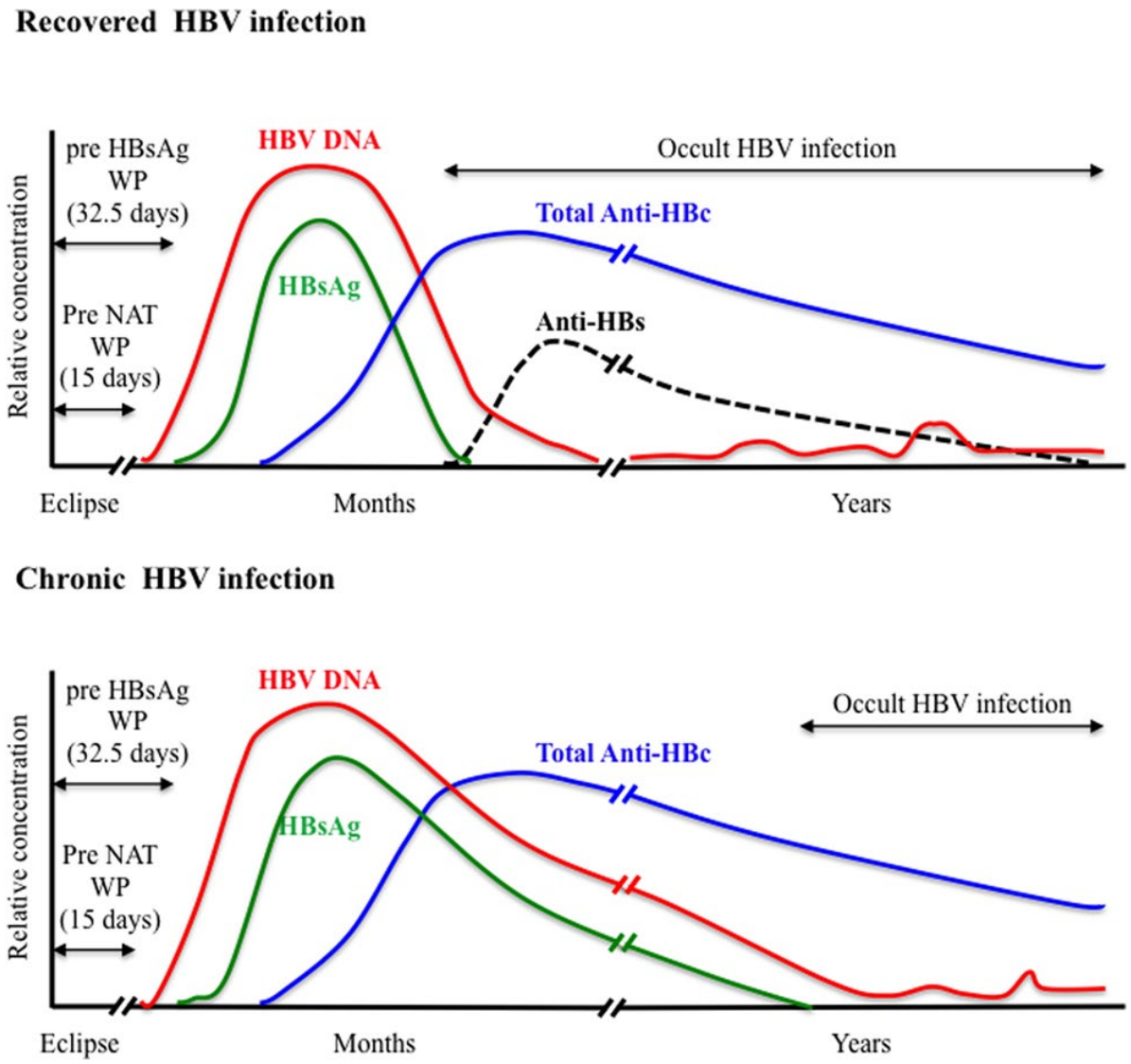
Infectious dose and infectivity after loss of HBsAg

During this period, reports indicate that donors with negative HBsAg and positive anti-HBs may still transmit HBV. The review by Kleinman and colleagues concludes that the likelihood of transmission from donations during this period is substantially lower than during the initial window period [25]. Later look-back studies following transfusion-transmission infections of HBV led to an estimated 50% minimum HBV infectious dose of 1049 HBV DNA copies (range: 117-3441 HBV DNA copies) or 187 IU, considering 1 IU corresponds to 5.6 HBV DNA copies [29]. This 50% minimum HBV infectious dose was further revised through mathematical modelling to 316 HBV DNA copies. T This model estimated that 3.3% of OBI donations would remain undetected by HBV DNA NAT with a 95% LOD of 43.1 copies/mL and could lead to transmission through transfusion of a blood component containing 20mL of plasma. This proportion was estimated at 14.0% for a volume of 200 mL of plasma [30].

A recent update based on transmissions from OBI donations remaining undetected by highly sensitive NAT led to revising the infectious dose of 16 HBV DNA copies in negative anti-HBs donors, similar to the infectious dose in the pre-HBsAg phase. This revision was determined by a Probit analysis estimating an infectious HBV DNA concentration of 0.8 copies/mL or 0.15 IU/mL [31]. It should be noted this estimation is based on a single donation.

Strong evidence suggests that the infectivity of OBI donations is significantly reduced for donors with anti-HBs titres above 300 IU/L [24,31].

Figure 1. Serum markers in HBV infection and length of viraemia and window periods



From Candotti and Laperche, 2018 [32].

Survival of HBV in the environment

HBV has high environmental stability, and virus particles retain infectivity for at least 28 days outside the human body at room temperature. Lower temperatures increase this infectivity duration, and HBV has been shown to maintain infectivity until at least 180 days at 4°C [33].

Organ systems targeted by HBV and HBV presence in different tissues

HBV is primarily hepatotropic, and hepatocytes serve as the reservoir for the virus. In addition to hepatocytes, HBV can infect lymphoid cells. Replicative intermediates and proteins of HBV have been detected in the spleen, lymph nodes, and bone marrow. In OBI with undetectable HBV DNA in the serum, HBV DNA can still be detected in the liver and peripheral blood mononuclear cells [2,34].

HBV-HDV co-infection

Hepatitis delta virus (HDV) is a small RNA virus that depends on HBV for its propagation. Its viral envelope coat is composed of HBsAg, and it shares the same hepatocyte receptor [35,36]. HDV can only be transmitted in the presence of an HBV infection, either a simultaneous transmission of both viruses or superinfection of a patient with chronic hepatitis B [36]. HDV infection, either due to co-infection or superinfection, is an important cause of fulminant viral hepatitis [37].

3 Epidemiology

The surveillance systems for hepatitis B across EU/EEA countries are heterogeneous [38]. These systems are based on notifications, representing the screening and testing practices instead of the actual number of infections in each country. As a result, the limitations of surveillance data, such as incompleteness and underreporting, may be considered in the interpretation of results and comparison between countries within the EU/EEA.

General population

Acute hepatitis B

While the exact incidence of acute hepatitis B is not available, it can be approached through the number of newly diagnosed acute hepatitis B cases reported per year, as presented in Table 3.

The overall notification rate for acute hepatitis B declined continuously from 0.7 in 2013 to 0.4 per 100 000 population in 2019 within the 23 countries that reported consistently during this period. In 2020, the lowest notification rate since 2013 was observed: 0.3 cases per 100 000 individuals. This finding is probably in relation to the disruption of healthcare and prevention services and behavioural changes due to the COVID-19 pandemic [39]. Restrictions in travel and migration may also have impacted these numbers. After 2021, the number of notifications of acute hepatitis B has increased to pre-pandemic levels (Table 3 and Figure 2).

Table 3. Number of reported acute hepatitis B cases and rates per 100 000 population in the EU/EEA, by country and year (2018–2022)

Country	2018		2019		2020		2021		2022	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Austria	65	0.7	45	0.5	36	0.4	31	0.3	54	0.6
Belgium	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Bulgaria	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Croatia	10	0.2	17	0.4	0	0.0	0	0.0	2	0.1
Cyprus	2	0.2	0	0.0	0	0.0	1	0.1	7	0.8
Czechia	54	0.5	41	0.4	27	0.3	17	0.2	48	0.5
Denmark	9	0.2	6	0.1	15	0.3	6	0.1	10	0.2
Estonia	4	0.3	3	0.2	2	0.2	3	0.2	2	0.2
Finland	4	0.1	5	0.1	4	0.1	40	0.7	99	1.8
France	84	0.1	88	0.1	61	0.1	82	0.1	94	0.1
Germany	712	0.9	536	0.6	379	0.5	481	0.6	915	1.1
Greece	17	0.2	13	0.1	14	0.1	10	0.1	25	0.2
Hungary	35	0.4	17	0.2	14	0.1	14	0.1	23	0.2
Iceland	4	1.1	1	0.3	1	0.3	0	0.0	0	0.0
Ireland	23	0.5	22	0.4	10	0.2	11	0.2	12	0.2
Italy	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Latvia	29	1.5	35	1.8	16	0.8	12	0.6	17	0.9
Liechtenstein	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Lithuania	13	0.5	14	0.5	10	0.4	9	0.3	7	0.2
Luxembourg	0	0.0	NR	NC	NR	NC	NR	NC	NR	NC

Country	2018		2019		2020		2021		2022	
Malta	4	0.8	0	0.0	0	0.0	0	0.0	0	0.0
Netherlands	99	0.6	106	0.6	94	0.5	71	0.4	84	0.5
Norway	12	0.2	23	0.4	4	0.1	4	0.1	4	0.1
Poland	40	0.1	45	0.1	14	0.0	10	0.0	29	0.1
Portugal	32	0.3	34	0.3	30	0.3	15	0.1	34	0.3
Romania	118	0.6	94	0.5	21	0.1	18	0.1	47	0.2
Slovakia	46	0.8	49	0.9	18	0.3	10	0.2	98	1.8
Slovenia	9	0.4	9	0.4	2	0.1	6	0.3	15	0.7
Spain	404	0.9	346	0.7	202	0.4	261	0.6	318	0.7
Sweden	45	0.4	30	0.3	27	0.3	30	0.3	27	0.3
United Kingdom (UK)	515	0.8	286	0.5	NR	NC	NA	NA	NA	NA
Total EU/EEA	**2 389**	**0.6**	**1 865**	**0.4**	**1 001**	**0.3**	**1 142**	**0.3**	**1 971**	**0.5**

NA: Not applicable. NR: not reported. NC: not calculated.
Adapted from ECDC Surveillance Atlas of Infectious Diseases [40].

Chronic hepatitis B

The prevalence of chronic hepatitis B is often estimated based on the prevalence of HBsAg in the general population [41,42]. A recent systematic review of HBV prevalence estimates in the EU/EEA and the UK between 2005 and 2021 indicated a low HBV prevalence (≤ 2%) among the general population in all regions, with exceptions in Bulgaria, Greece, Italy and Romania, as seen in Table 4. Regarding countries reporting more recent estimates, a decrease in prevalence was observed when comparing with previous results [42].

Table 4. Weighted HBV prevalence in the general population in the EU/EEA, 2005-2021

Country	Number of studies	Total sample	Prevalence (%)	95% CI (%)
Austria	NR	NR	NR	NR
Belgium	2	3 326	0.69	0.69-0.69
Bulgaria	1	865	3.93	3.91-3.94
Croatia	2	2 268	0.92	0.92- 0.93
Cyprus	NR	NR	NR	NR
Czechia	1	2 644	0.34	0.33-0.34
Denmark	NR	NR	NR	NR
Estonia	NR	NR	NR	NR
Finland	NR	NR	NR	NR
France	4	38 767 987	0.80	0.80-0.80
Germany	3	30 311	0.47	0.47-0.48
Greece	4	6 346	2.44	2.44-2.45
Hungary	1	1 066	0.38	0.37-0.38
Iceland	NR	NR	NR	NR
Ireland	2	4 013	0.10	0.10-0.10
Italy	13	42 263	2.06	2.05-2.06
Latvia	NR	NR	NR	NR
Liechtenstein	NR	NR	NR	NR
Lithuania	NR	NR	NR	NR
Luxembourg	NR	NR	NR	NR
Malta	NR	NR	NR	NR
Netherlands	4	10 464	0.25	0.25-0.25
Norway	NR	NR	NR	NR
Poland	3	13 601	0.92	0.92-0.92
Portugal	2	2 158	1.23	1.22-1.23
Romania	2	14 386	4.49	4.49-4.50
Slovakia	4	8 503	0.56	0.56-0.56
Slovenia	NR	NR	NR	NR
Spain	8	65 529	0.69	0.69-0.69
Sweden	NR	NR	NR	NR

Prevalence estimates were weighted by study population size to determine the weighted country prevalence and attenuated for the high prevalence reported from smaller population size estimates in each country. NR: not reported.
Adapted from Bivegete et al., 2023 [42].

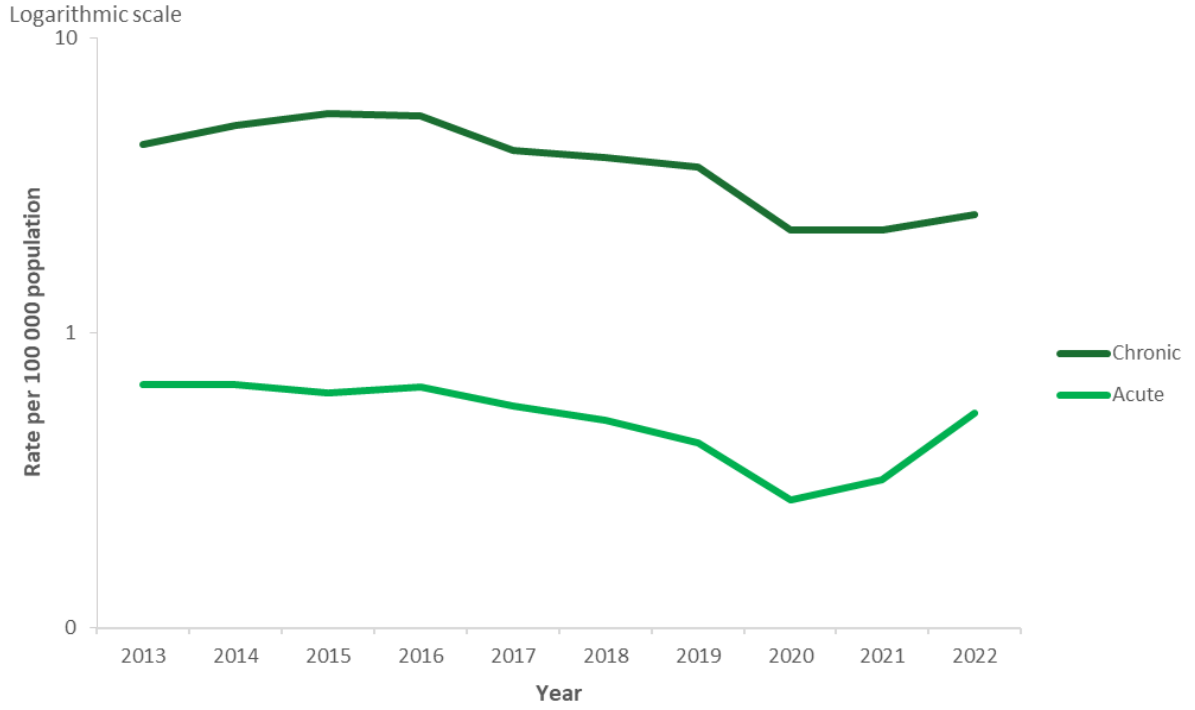
Among the 17 countries that reported consistently between 2013 and 2022, the overall notification rate for chronic hepatitis B in the EU/EEA increased from 4.4 in 2013 to 5.6 per 100 000 population in 2015, declining from 5.5 to 2.2 per 100 000 population between 2016 and 2020. In 2022, an increase of 13% was observed, up to 2.5 per 100 000 population (Table 5 and Figure 2). This increase might be associated with the end of national and international restrictions due to the COVID-19 pandemic, the reinstitution of regular contact with healthcare, higher migrant inflow in some countries, changes in surveillance and testing, as well as possible increases in transmission. Variations in reporting practices, testing strategies, and inherent epidemiological settings may explain the differences in notification rates between countries [43].

Table 5. Number of reported chronic hepatitis B cases and rates per 100 000 population in the EU/EEA, by country and year (2018–2022)

Country	2018		2019		2020		2021		2022	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Austria	714	8.1	591	6.7	329	3.7	324	3.6	343	3.8
Belgium	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Bulgaria	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Croatia	46	1.1	40	1.0	7	0.2	5	0.1	5	0.1
Cyprus	81	9.4	108	12.3	29	3.3	13	1.5	24	2.7
Czechia	269	2.5	276	2.6	142	1.3	127	1.2	218	2.07
Denmark	155	2.7	164	2.8	136	2.3	118	2.0	92	1.6
Estonia	15	1.1	15	1.1	21	1.6	20	1.5	32	2.4
Finland	235	4.3	233	4.2	162	2.9	196	3.5	280	5.0
France	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Germany	36	0.0	4 297	5.2	3 146	3.8	3 720	4.5	7 454[a]	9.0[a]
Greece	NR	NC	NR	NC	5	0.0	155	1.5	158	1.5
Hungary	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Iceland	40	11.5	47	13.2	32	8.8	30	8.1	52	13.8
Ireland	468	9.7	427	8.7	252	5.1	353	7.1	483	9.5
Italy	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Latvia	299	15.5	260	13.5	206	10.8	133	7.0	174	9.3
Liechtenstein	NR	NC	NR	NC	NR	NC	2	5.1	1	2.5
Lithuania	NR	NC	NR	NC	15	0.5	18	0.6	20	0.7
Luxembourg	47	7.8	52	8.5	0	0.0	0	0.0	0	0.0
Malta	15	3.2	0	0.0	0	0.0	0	0.0	27	5.2
Netherlands	1 023	6.0	1 041	6.0	695	4.0	734	4.2	815	4.6
Norway	353	6.7	370	6.9	221	4.1	253	4.7	363	6.7
Poland	819	2.2	669	1.8	156	0.4	0	0.0	0	0.0
Portugal	98	1.0	58	0.6	46	0.4	53	0.5	61	0.6
Romania	1	0.0	9	0.0	0	0.0	0	0.0	4	0.0
Slovakia	85	1.6	92	1.7	71	1.3	67	1.2	0	0.0
Slovenia	69	3.3	51	2.5	26	1.2	32	1.5	36	1.7
Spain	NR	NC	NR	NC	NR	NC	NR	NC	NR	NC
Sweden	1 053	10.4	1 037	10.1	679	6.6	645	6.2	746	7.1
UK	6 953	11.4	4 873	8.0	NR	NC	NA	NA	NA	NA
Total EU/EEA	**12 874**	**4.5**	**14 710**	**5.0**	**6 376**	**2.5**	**6 998**	**2.8**	**11388**	**4.6**

NA: Not applicable. NR: not reported. NC: not calculated. UK: United Kingdom.
[a] Increase in Germany's cases may been related to the introduction of HBV and HCV screening for individuals over 35 years old, the implementation of electronic laboratory reporting, and the migration from Ukraine (Epidemiologisches Bulletin 31/2023 (rki.de)).
Adapted from ECDC Surveillance Atlas of Infectious Diseases [40].

Figure 1. Notification rates of acute and chronic hepatitis B per 100 000 population by year in EU/EEA countries reporting consistently, 2013–2022



From ECDC [43].

SoHO donors

A systematic review of HBV prevalence estimates in the EU/EEA and the UK between 2005 and 2021 reported a low HBV prevalence (< 1%) among first-time blood donors in all regions except Bulgaria, Greece and Romania (Table 6) [42]. These prevalence estimates were based on the prevalence of HBsAg in this population.

Table 6. Weighted HBV prevalence in first-time blood donors in the EU/EEA, 2005–2021

Country	Number of studies	Total sample	Prevalence per 100 000 population	95% CI (%)
Austria	7	318 919	80	80.0-80.0
Belgium	19	1 040 377	70	70.0-70.0
Bulgaria	5	163 162	3 960	3 960.0-3 960.0
Croatia	10	132 383	140	140.0-140.0
Cyprus	4	42 712	150	150.0-150.0
Czechia	11	487 040	50	50.0-50.0
Denmark	9	242 993	30	30.0-30.0
Estonia	9	64 079	140	140.0-150.0
Finland	14	228 699	70	70.0-70.0
France	24	9 998 185	30	30.0-30.0
Germany	11	5 787 918	110	110.0-110.0
Greece	11	707 697	1 330	1 330.0-1 330.0
Hungary	9	473 559	100	100.0-100.0
Iceland	5	9 265	60	60.0-60.0
Ireland	9	143 912	20	20.0-20.0
Italy	11	5 972 413	180	180.0-180.0
Latvia	3	27 644	390	390.0-390.0
Liechtenstein	NR	NR	NR	NR
Lithuania	7	446 806	180	180.0-180.0
Luxembourg	3	3 925	170	170.0-17.0
Malta	5	11 644	240	240.0-240.0
Netherlands	10	335 085	40	40.0-40.0
Norway	9	145 141	30	30.0-30.0
Poland	6	1 244 841	390	390.0-390.0
Portugal	5	198 498	100	100.0-100.0
Romania	6	568 842	2 710	2 710.0-2 710.0
Slovakia	11	353395	90	90.0-90.0
Slovenia	5	56 219	90	90.0-90.0
Spain	9	2 271 299	150	150.0-150.0
Sweden	8	339 673	30	30.0-30.0

NR: not reported. Prevalence estimates were weighted by study population size to determine the weighted country prevalence and attenuated for the high prevalence reported from smaller population size estimates in each country.
Adapted from Bivegete et al., 2023 [42].

Data reported by countries on positive findings in first-time blood donors (prevalence of HBV infections) and positive findings in repeat donors (incidence of HBV infections) and published by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM) [44] are presented in Table 7. The interpretation of these data should consider that the definition of positive donors may vary across countries depending on the screening strategy in each country (see test methods in use as reported to EDQM in 2021 in Table 14).

Table 7. Prevalence and incidence of HBV per 100 000 blood donors, per country, per year (2017–2019)

	2017		2018		2019	
Country	**Prevalence in 1st time donors**	**Incidence in repeat donors**	**Prevalence in 1st time donors**	**Incidence in repeat donors**	**Prevalence in 1st time donors**	**Incidence in repeat donors**
Austria	24.0	1.0	52.1	1.0	31.7	1.0
Belgium	ND	ND	ND	ND	ND	ND
Bulgaria	1247.3	415.0	924.8	81.5	NA	618.6
Croatia	13.4	0.0	7.8	0.0	25.5	0.0
Cyprus	ND	ND	ND	ND	346.5	9.5
Czechia	42.1	4.1	28.6	2.4	32.4	1.5
Denmark	ND	ND	ND	ND	12.8	0.5
Estonia	78.7	3.8	58.9	0.0	68.4	0.0
Finland	13.4	0.9	13.0	0.0	34.7	0.0
France	ND	ND	ND	ND	ND	ND
Germany	71.5	1.0	64.8	0.9	60.2	1.0
Greece	376.5	33.1	331.4	27.4	347.4	28.5
Iceland	ND	ND	ND	ND	ND	ND
Hungary	66.4	1.9	78.2	2.8	0.0	0.0
Ireland	24.0	0.0	7.5	1.5	86.4	4.3
Italy	135.4	2.3	112.6	2.4	97.1	1.8
Latvia	ND	ND	ND	ND	ND	ND
Liechtenstein	ND	ND	ND	ND	ND	ND
Lithuania	ND	ND	ND	ND	ND	ND
Luxembourg	ND	ND	ND	ND	ND	ND
Malta	ND	ND	ND	ND	ND	ND
Netherlands	16.7	0.9	30.1	0.0	ND	ND
Norway	10.5	0.0	24.3	0.0	5.4	0.0
Poland	140.6	0.0	126.0	0.2	132.9	0.9
Portugal	108.4	1.1	56.8	1.1	52.0	1.1
Romania	ND	ND	1394.3	5.5	ND	ND
Slovakia	74.2	7.3	83.1	3.7	68.0	1.9
Slovenia	52.6	0.0	30.5	0.0	64.4	0.0
Spain*	16.8		14.7		13.9	
Sweden	32.1	0.5	37.7	0.0	47.0	0.0

*NA: not applicable. ND: no data reported. Prevalence: positive findings in first-time donors; Incidence: positive findings in repeat donors. * Data for Spain are for all donors (first-time and repeat) combined.*
Adapted from EDQM 2022 [44] and Ministerio de Sanidad for Spain [45].

Risk factors and transmission modes

In 2022, in the EU/EEA, 22% of acute hepatitis B cases and 14% of chronic hepatitis B cases reported in The European Surveillance System (TESSy) had data available for documented transmission modes [43]. The most frequent modes of transmission are described in Table 8. Among acute hepatitis B, the most common transmission mode was sexual, while for chronic hepatitis B, the most common transmission mode was vertical (or mother-to-child) transmission; 94% of these were classified as imported, mainly from Asia (51%) and Africa (29%). Nosocomial transmission was the third most frequent mode of transmission reported for acute cases, being responsible for 15% of acute hepatitis B cases and 2% of chronic hepatitis B cases. The poor completeness of transmission data may limit the interpretation. However, this assessment is essential to raise awareness of the ongoing transmission modes in the EU/EEA (mostly from acute cases), as well as key groups capable of transmission (both acute and chronic cases).

Reports from EU blood donor populations report that the main characteristic associated with a positive screening test for HBV is being born in a highly endemic country [46-48]. A high proportion of individuals born in a highly endemic country will have acquired their infection vertically from their mother or via household transmission (i.e. horizontal transmission). The overall rate of vertical transmission of HBV during pregnancy is estimated at 40%, with higher rates in mothers with positive HBeAg status (up to 90%, compared to those with negative HBeAg (10-20%)). Maternal human immunodeficiency virus (HIV)-HBV coinfection also increases vertical transmission of HBV due to higher HBV viral loads and increased HBeAg positivity [49]. Horizontal transmission occurs mainly within households during childhood, mostly from older children with infections to children without infections [50].

HBV can be transmitted through unprotected (condomless) sex from an individual with HBV infection to an unvaccinated individual. Sexual transmission is markedly reported among men who have sex with men (MSM), heterosexual people with multiple sex partners or contact with sex workers [51,52]. Sexually transmitted infections (STIs) are also known to be associated with an increased risk of acquiring HBV [53]. MSM, especially those with HIV co-infection, have a higher seroprevalence of HBV infection than the general population [54,55].

People who inject drugs (PWID) are at high risk, considering the efficient transmission of HBV through unsafe injecting drug practices. Among EU/EEA countries with available estimates, national prevalence ranged from 0.5% in Croatia, Hungary, and Ireland to over 6% in Cyprus and Portugal [55].

Due to multiple risk behaviours for HBV infection, such as intravenous drug use, tattooing with non-sterilised material and unprotected sexual relationships, people in prison often are reported as having a high prevalence of HBV infections [54-57].

Other populations identified to be at elevated risk of exposure to HBV include haemodialysis patients, healthcare workers, diabetes mellitus patients (glucose monitoring) and recipients of SoHO [58]. Despite improvements in the safety of SoHO supplies, injection-related procedures, infection control measures and implementation of vaccination programs, these groups still show a higher prevalence of HBV infection than the general population, suggesting ongoing iatrogenic transmission in healthcare settings [58].

Table 8. Transmission category of hepatitis B cases by acute and chronic disease status, EU/EEA, 2022

Transmission mode	**Acute hepatitis B** (% among cases with available data)	**Chronic hepatitis B** (% among cases with available data)
Heterosexual transmission	20	7
Sex between men	16	3
Nosocomial*	15	2
Household	7	15
Sexual transmission (not specified)	7	1
Non-occupational injuries**	11	0
Injecting drug use	12	9
Other	6	18
Blood and blood products	3	3
Vertical/mother-to-child transmission[a]	1	41
Sex work	0	0
Organ and tissues	0	0
Haemodialysis	1	1
Needle-stick and other occupational exposure***	1	0

Adapted from: ECDC, 2024 [43].
**: Nosocomial transmission includes hospitals, nursing homes, psychiatric institutions, and dental services. This category refers mainly to patients exposed through healthcare settings, distinct from 'needle-stick and other occupational exposure', which refers to staff.*
***: 'Non-occupational injuries' include needle sticks that occur outside a healthcare setting, bites, tattoos, and piercings.*
****: 'Needle-stick and other occupational exposure' refers to occupational injuries*
[a]: 90% of vertical transmission cases were classified as imported.

Other relevant topics

Prevalence of anti-HBc in healthy populations

The prevalence of anti-HBc in healthy populations in several EU/EEA countries, from selected published reports, is presented in Table 9. The majority of reports include blood donors. The prevalence of this marker shows a large range across different countries, from below 1% in several low endemic countries (e.g. Belgium, Germany, the Netherlands) to above 25% of the studied population in Romania.

Table 9. Prevalence of anti-HBc in healthy populations of EU/EEA countries, from selected published reports

Country (region)	Time period	Population (n)	Positive anti-HBC definition	Age, in years	Prevalence (%) (n)
Belgium (Flanders) [46]	2010-2018	First-time blood donors (n=209 193)	Repeat reactive in duplicate	25 (median)	0.86 (1802)
Bulgaria [59]	2018-2019	General population sample (n=2 140)	Initially reactive	53 (average)	27.10 (582)
Croatia [60]	2004	Blood donors (all) (n=7 561)	Repeat reactive in duplicate (separate assays)	Not specified	5.24 (396)
Croatia [60]	2013	Blood donors (all) (n=7 318)	Repeat reactive in duplicate (separate assays)	Not specified	2.56 (187)
Croatia [60]	2017	Blood donors (all) (n=5 090)	Repeat reactive in duplicate (separate assays)	Not specified	1.32 (67)
Croatia (Primorje Gorski Kotar County) [61]	2014-2018	Hospital samples from routine clinical testing (n=24 900)	Repeat reactive in additional separate assay	Not specified	7.02 (1749)
Croatia [62]	2010-2011	General population sample (n=1552)	Not specified	20-83 (range)	7.00 (109)
Denmark (County of Funen) [63]	1997	Blood donors (all), HBsAg negative (n=10 862)	Repeat reactive in duplicate	43 (median, estimated)	1.07 (116)
France [64]	1998	First-time blood donors (n=12 456)	Repeat reactive in one additional test	Not specified	1.30 (163)
France [65]	2004	General population sample (n=14 416)	Not specified	18-80 (range)	7.30
Germany [66]	2008-2011	General population sample (n=7 047)	Repeat reactive in one additional test	18-79 (range)	5.10
Germany [67]	2006-2015	Blood donors (all), HBsAg negative (n=31 562 556)	Repeat reactive, not specified	49 (median)	0.22 (70671)
Greece (Epirus) [68]	1995-1997	First-time blood donors (n=6 696)	Not specified	36 (median)	14.90 (998)
Greece (Epirus) [69]	2018-2022	First-time blood donors (n=699)	Not specified	61 (median)	20.5 (144)
Greece (Thessaloniki) [70]	2018	Blood donors (all) (n=620)	Repeat reactive in duplicate	Not specified	3.9 (24)
Italy (Piedmont) [71]	2005	First-time blood donors, HCV and HIV negative (n=6 313)	Repeat reactive in duplicate (separate assays)	34 (average)	4.85 (305)
Italy [72]	2004-2005	First-time blood donors, non-vaccinated (n=31 190)	Not specified	Not specified	8.31 (2593)
Luxembourg [73]	2001-2002	General population sample, anti-HBs positive (n=765)	Not specified	Not specified	6.40 (49)
Netherlands [74]	2011-2013	First-time blood donors (n=70 914)	Repeat reactive, not specified	Not specified	0.79 (559)
Netherlands [74]	2011-2013	Repeat blood donors (n=311 529)	Repeat reactive, not specified	Not specified	0.75 (2331)
Netherlands [75]	2011-2018	First-time blood and plasma donors (n=249 874)	Repeat reactive in duplicate	Not specified	0.66 (5224)

Country (region)	Time period	Population (n)	Positive anti-HBC definition	Age, in years	Prevalence (%) (n)
Netherlands [75]	2011–2018	First-time blood and plasma donors, HBsAg and DNA negative (n=249 874)	Repeat reactive in duplicate	Not specified	0.74 (5224)
Poland (Kuyavia and West Pomerania) [76]	2016–2018	Hospital staff (n=306)	Repeat reactive in one additional test	48 (average)	12.09 (36)
Poland (Krakow) [77]	Ca. 2006	Blood donors (n=920), private communication	Not specified	Not specified	7.00
Portugal [78]	2001–2002	General population sample (n=1 051)	Not specified	Not specified	4.90 (51)
Portugal [79]	2012–2014	General populations sample (n=1 627)	Not specified	50 (average)	9.24
Portugal [80]	2015–2016	General population data (n=2 959)	Initially reactive	Not specified	3.50
Romania [81]	2006–2008	General population sample, HBsAg negative (n=12 470)	Not specified	45 (median, estimated)	27.00 (3370)
Romania [82]	2013	General population sample (n=3 266)	Not specified	34 (median, estimated)	27.89 (911)
Slovenia [83]	Ca. 2007	Blood donors, not otherwise specified (n=5 959)	Repeat reactive in duplicate	45 (median, estimated)	3.00 (179)
Spain [84]	1999–2007	Living tissue donors (n=3 357)	Not specified	65 (average)	17.84 (599)
Spain [84]	1999–2007	Heart-beating organ donors (n=618)	Not specified	42 (average)	12.94 (80)
Spain [84]	1999–2007	Cord blood donors (n=2 880)	Not specified	31 (average)	3.57 (103)
Spain [85]	2017	Deceased tissue donors, HBsAg negative (n=1 753)	Not specified	64 (average)	10.00 (175)
Sweden (Uppsala and Linköping) [86]	2002–2003	Blood donors (all) (n=22 964)	Confirmed positive by blood centre	Not specified	0.43 (98)

HBV-HDV coinfection

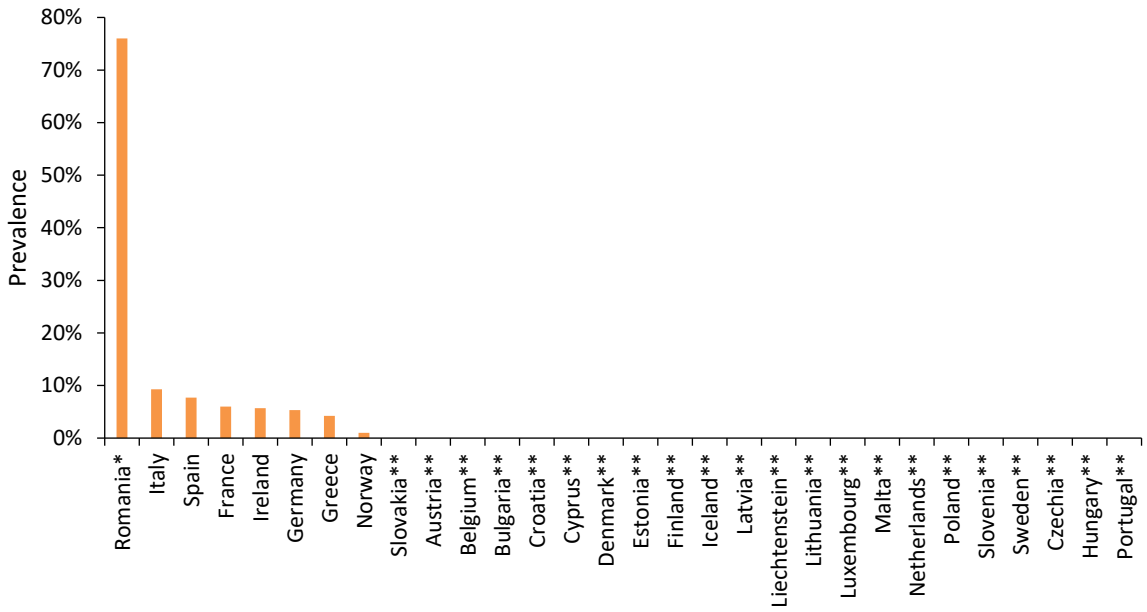
Estimating hepatitis Delta virus (HDV) prevalence or incidence can be challenging due to the large sample sizes needed to identify HBsAg-positive individuals, the criteria for HBsAg and HDV testing possibly resulting in non-representative samples, and variations in methodologies and epidemic patterns [87].

A meta-analysis from 2020 reported a global prevalence of antibodies against HDV (anti-HDV) of 4.5% (95% CI 3.6–5.7) among HBsAg-positive people, with an estimated anti-HDV prevalence of 3.0% for HBsAg-positive people in the World Health Organization (WHO) European Region. Prevalence estimates of anti-HDV in HBsAg-positive general population in some EU/EEA countries ranged from 2.0% in France to 7.0% in Romania [87].

A recent study reported the prevalence of HDV based on several publicly available national datasets, with less than 2% of HDV infections among people with HBV infections in most countries, except for Norway and Sweden (2.47% and 2.78% respectively). Of the seven EU/EEA countries included, a significant increase in the incidence of HDV cases was observed in four of them (Bulgaria, the Netherlands, Norway, and Sweden) [88].

Up to the end of 2022, nine countries in the EU/EEA had available data on estimated HDV prevalence among HBsAg-positive individuals (diagnosed and undiagnosed). Prevalence estimates ranged from 1% in Norway to 76% in Romania (Figure 3).

Figure 2. Estimated HDV prevalence among HBsAg-positive individuals, by country, 2022[a]

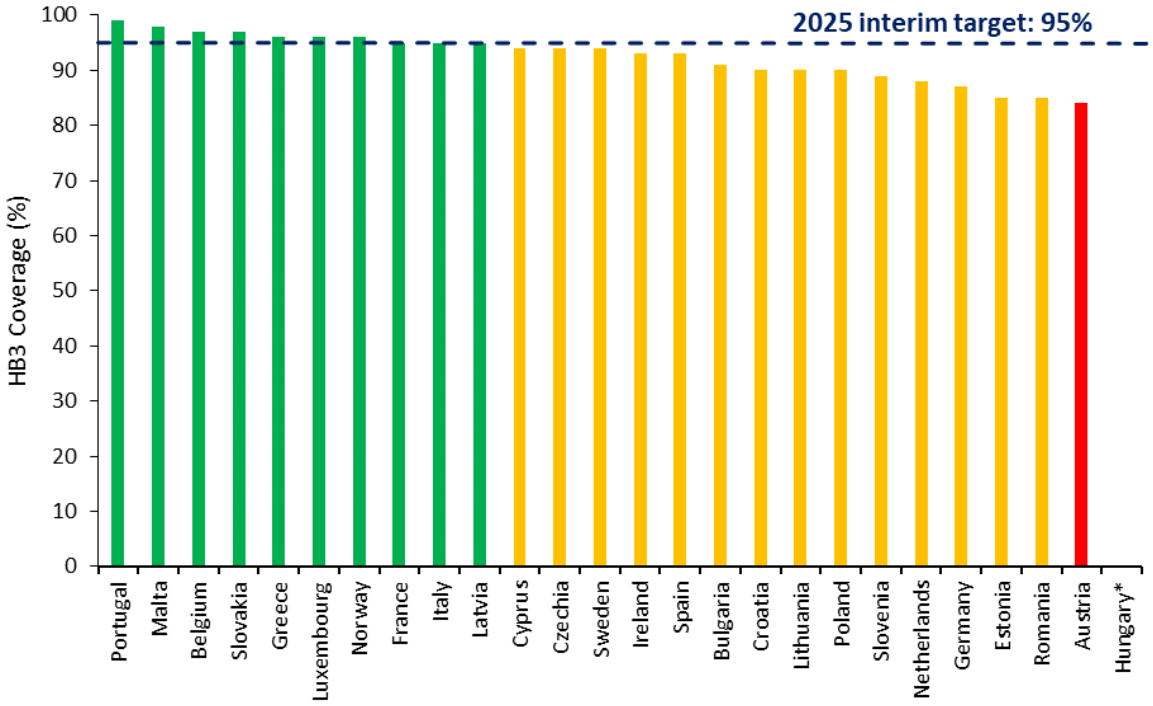


[a]2022 or most recent year with available data.
** Regional data from a sample of 100 HBsAg-positive samples tested for HDV RNA.*
*** Indicator could not be calculated due to lack of available data.*
From ECDC [unpublished data].

Vaccination against hepatitis B virus

Effective vaccines are available to protect against hepatitis B infection. The long-term effectiveness of hepatitis B vaccination is well described, and lifelong protection against hepatitis B is conferred following a full course of vaccination. Adequate anti-HBs levels, i.e. above 100 milli-international units per millilitre (mIU/mL), are achieved in most vaccinated individuals. Booster vaccination may be necessary for individuals with poor initial responses or specific risk factors. In Europe, 27 EU/EEA countries have implemented a universal childhood vaccination programme. Three countries have a selective vaccination policy targeting high-risk individuals (Denmark, Finland, and Iceland) [89]. Data on vaccine coverage in 2020 are available from 23 countries and are presented in Figure 4.

Figure 3. Coverage (%) of three doses of HBV vaccine (HB3) in EU/EEA countries implementing universal HBV vaccination, 2022



** Country did not provide data.*
NB. Denmark, Finland and Iceland do not have a national policy for universal childhood vaccination against hepatitis B, and Hungary has a universal vaccination programme targeting school-aged children.
From ECDC [89].

The impact of HBV vaccination is reflected in the reduction of new acute hepatitis B cases notified in the EU/EEA (56.2% from 2006 to 2014), with a larger reduction in countries that implemented an HBV vaccination programme before or in 1995 (-61.1%) compared to the group of countries that started the vaccination after 1995 (-50.0%). The overall (EU/EEA) acute HBV incidence rate ratio (IRR) decreased by 10% for each 1% increase in vaccine coverage (IRR: 0.90; 95% CI: 0.86 to 0.92; $p < 0.01$) [90]. There is also strong evidence for the prevention of vertical transmission of HBV through newborn vaccination and administration of hepatitis B immunoglobulin within 12 to 24 hours of birth [91,92].

However, note that breakthrough infections are possible in vaccinated individuals that may result in HBsAg-negative and HBV DNA-positive profiles [93].

4 Laboratory testing approaches

Interpretation of hepatitis B virus screening test results

Donor screening tests include tests detecting HBV DNA, HBsAg, total anti-HBc, and, in specific situations, anti-HBs. Donor screening algorithms in use rely on a combination of at least two, three, or all four markers. The interpretation of the screening test results is described in Table 10.

Acute HBV infection

Detection of HBV in a donor with an acute infection may be impacted by the window period (WP) of serological tests detecting HBsAg and NAT detecting HBV DNA, as described in Figure 1. The infectious WP before NAT detection is estimated to be around 10-15 days for highly sensitive NAT (<20 IU/mL) and around 30 days for HBsAg detection [24,94].

Occult HBV infection

Occult HBV infection (OBI) is defined by the presence of cccDNA in the liver and/or HBV DNA in the blood in individuals who have cleared HBsAg and test negative for this marker. In individuals with an OBI, HBV DNA and total anti-HBc are usually detectable (Figure 1), though viraemia may fluctuate and a short WP of a few days may occur for NAT [24]. Donors testing negative for HBsAg and with a low-level viraemia can still transmit HBV and transmission cases from donors found to be HBV DNA negative in minipool (MP) testing have been reported [24,94,95]. However, the infectivity of OBI is considered lower than for donors with an acute HBV infection [96]. Evidence from blood donations suggests that the infectivity of OBI donations is reduced for donors with high anti-HBs titres (see Infectious dose and viraemia). A large multicentric study in Spain did not find an association of anti-HBs titres (or presence) and circulating HBV DNA in deceased tissue donors and the authors conclude this marker should not be considered for decision-making in tissue donation.

A small proportion of cases with undetectable HBsAg could be due to escape variants of the antigen which are sometimes described as 'false OBI' due to the high levels of HBV DNA [29].

Early infection detection is feasible using ID-NAT or 6–16 MP-NAT (Figure 1) during the HBsAg WP. As the characteristic of OBI is the negativity of HBsAg with low-level viraemia and the presence of anti-HBc, there are questions on the added value of using HBsAg for donor screening in low endemic settings, as it does not appear to increase the safety of blood supply compared to the combined use of HBV DNA NAT and anti-HBc testing. The reports of donors exclusively HBsAg reactive are rare and most frequently associated with recent vaccination [26,32,75,97–100].

The prevalence of OBI in the general population is uncertain as studies are usually performed in anti-HBc-positive individuals [101]. The prevalence of OBI in the general population was estimated at around 0.1–0.3% and less than 0.05% in European blood donors. The low prevalence in blood donors is likely impacted by the inclusion of repeat donors in studies reporting these values [101,102].

HBV vaccination

Detection of transient HBsAg has been reported in cases of recent vaccination against HBV. In these cases, HBsAg is unlikely to persist for more than 14 days [103-105].

Table 10. Interpretation of hepatitis B virus screening test results

Marker	Result	Interpretation
HBsAg	Positive	Acute or chronic infection: risk of transmission.
HBV DNA	Positive	
Total anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Negative	Occult HBV infection: risk of transmission.
HBV DNA	Positive, low viraemia	
Total anti-HBc	Positive	
Anti-HBs	Negative or Positive	
HBsAg	Negative	Breakthrough infection after vaccination: risk of transmission.
HBV DNA	Positive	
Total anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Resolved infection (immune through infection): possibly not infectious if detection of DNA is highly sensitive. Rare cases of transmission have occurred.
HBV DNA	Negative	
Total anti-HBc	Positive	
Anti-HBs	Positive	
HBsAg	Negative	Inconclusive: risk of transmission low but not null. Occult HBV infection is possible. May indicate past infection with waning of anti-HBs. May be due to false positive test results.
HBV DNA	Negative	
Total anti-HBc	Positive	
Anti-HBs	Negative	
HBsAg	Negative	Prior vaccination: not infectious.
HBV DNA	Negative	
Total anti-HBc	Negative	
Anti-HBs	Positive	
HBsAg	Negative	Naïve: not infectious.
HBV DNA	Negative	
Total anti-HBc	Negative	
Anti-HBs	Negative	

DNA: desoxyribonucleic acid. HBsAg: Hepatitis B surface antigen. HBV: hepatitis B virus.
Adapted from CDC, 2023 [106].

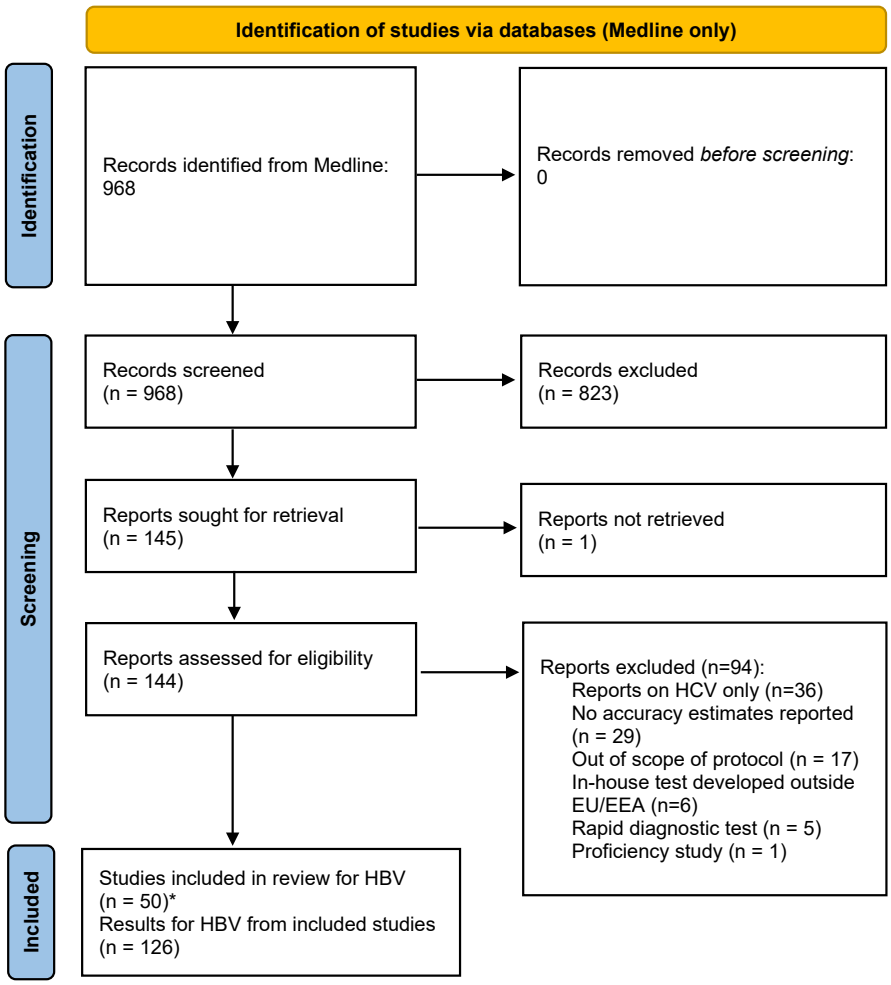
Search results

This section aims to present the performance characteristics of laboratory tests that are approved and potentially used to screen HBV in SoHO donors (living and deceased). The results summarised in this document are based on a structured but non-systematic search of Medline from January 2001 to November 2023. Studies were included if the test was described as being used or potentially used for screening SoHO donors. This included in-house (i.e. non-commercial) tests, if they were used in EU/EEA countries. In-house tests used outside the EU/EEA were excluded. Studies that only included results for rapid diagnostic tests were excluded as considered not relevant for donor screening, and accuracy metrics for rapid diagnostic tests were not extracted from included studies that reported on such tests. No other exclusion criteria were applied, and results are summarised by test method and by target. For categories with two or fewer results, medians are not reported.

The search methods are described in detail in Annex 1.

Five studies were identified that reported results on samples procured post-mortem. These results are described separately from those conducted on living donor samples.

Figure 4. Number of records identified, screened and included for laboratory test methods for HBV



** Including 6 studies on post-mortem testing.*
Note: A joint search and screening process was performed for both hepatitis B virus (HBV) and hepatitis C virus (HCV)

Summary of data

Table 11. Summary of 44 studies on available methods for hepatitis B virus (HBV) laboratory testing in samples from living donors [107-148]

Test Method (n of studies)	Range clinical sensitivity	Median clinical sensitivity	Average clinical sensitivity	Range analytic sensitivity (IU/mL)	Median analytic sensitivity (IU/mL)	Average analytic sensitivity (IU/mL)	Range specificity	Window period reported
EIA								
HBsAg (8)	43.8% - 100.0%	98.5%	94.7%	0.03 - 0.63	0.13		99.1% - 100.0%	
n reports		13			8		13	
CLIA								
HBsAg (16)	70.0% - 100.0%	100.0%	95.2%	0.01 - 0.10	0.02		99.1% - 100.0%	Estimated time to 1st reactive result: 32.2-36.8 days
n reports		19			16		31	
Anti-HBc (7)	78.9% - 100.0%	99.8%	95.3%	NR	NA		99.0% - 100.0%	
n reports		12			0		11	
HBV DNA NAT								
Overall (22)	84.8% - 100.0%	99.5%	97.2%	1.4 - 20.0	5.6	7.6	99.7% - 100.0%	
n reports		8			31		6	
ID (19)	97.7% - 100.0%	99.5%	99.4%	1.4 - 14.7	4.9	6.8	99.7% - 99.9%	14-24 days reduction from HBsAg Estimated iWP of 8.6-13.8 days
n reports		6			28		2	
MP6 - MP16 (4)	98.3%	NA	NA	11.0 - 15.7	13.3	13.3	100.0%	7 days reduction from HBsAg
n reports		1			2		1	
Pool >16 (3)	84.8%	NA	NA	20.0	NA	100.0%	100.0%	4 days reduction from HBsAg
n reports		1			1		3	

Note: all analytic sensitivity values for HBV DNA in copies/mL have been converted to IU/mL based on the conversion 1 IU = 5.3 copies. All analytic sensitivity values for HBsAg in ng/mL have been converted to IU/mL based on the conversion 1 IU = 0.98 ng. CLIA: chemiluminescent immunoassay (includes chemiluminescent microparticle immunoassays [CMIA] and electrochemiluminescence immunoassays [ECLIA]). EIA: Enzyme immunoassay (includes enzyme-linked immunosorbent assays [ELISA]). HBc(Ag): HBV core antigen. HBsAg: Hepatitis B surface antigen. ID: individual donations. iWP: infectious window period.MP: minipool. NA: not applicable. NAT: nucleic acid test. NR: not reported.

Deceased donors

Five studies evaluating laboratory test methods for the detection of HBV on post-mortem blood samples were identified in the search [149-153], of which four studies evaluated chemiluminescent immunoassays (CLIA) for the detection of anti-HBc [149,151-153], four studies evaluated CLIA for the detection of HBsAg [149,151-153], and two studies evaluated NAT for the detection of HBV DNA [150,151].

All studies evaluated the performance of the test methods on post-mortem samples relative to their performance on samples from living individuals. All studies reported no differences in the sensitivity or specificity of the evaluated test methods in samples procured post-mortem compared to those retrieved on living individuals.

In all but one report, sampling was performed within 24 hours of circulatory death. One study obtained samples between 11-54 hours after death (average: 31.5 hours). This study evaluated a NAT detecting HBV DNA and concluded on comparable analytical sensitivity in post-mortem samples but found a higher coefficient of variation in samples collected more than 24 hours post-mortem, indicating higher variability of results in these samples [150].

One study did not evaluate test methods on post-mortem blood samples but aimed to describe the risk of HBV transmission associated with different serologic profiles in organs, tissues, and cells donors [154]. This study identified two organ and two cornea donors with detectable anti-HBc and HBV DNA but negative for HBsAg, concluding that testing for HBV DNA could be a relevant screening test in these donors. The timing of sampling is not indicated for these donors.

Residual risk of HBV

The residual risk (RR) of HBV infection in SoHO donation is defined as the probability of having a donation from an asymptomatic viraemic donor not being detected by the screening assays [155]. The undetected infected donation may transmit the infection to a recipient if the blood components are not pathogen-inactivated or the inactivation is insufficient to render the donation non-infectious. Non-detection of HBV may be attributed to test failures, donors being in the diagnostic window period, or transient antigenemia or low-level viraemia. For current modern test methods, the contribution of assay failures to the residual risk is considered negligible and usually not considered in the residual risk. Table 12 presents the RR per million blood donations according to different incidence rates and test methods. An incidence adjustment factor has been used for HBV to account for transient antigenemia or low-level viraemia according to WHO guidelines on the estimation of residual risk [155]. It is important to note this adjustment factor is based on data from a dating from the 1990s finding that 25% of HBV infections have no detectable HBsAg [156]. Of note, these RRs are based on the incidence rate-window period risk day equivalent model, which has been shown to give reliable estimates for the RR of HBV in low prevalence regions [157].

Residual risks calculated in various studies conducted in EU countries are presented in Table 13. These residual risks are provided as illustrations for different test methods and are not meant to provide a comprehensive overview of the residual risk of HBV transmission in the EU/EEA. The calculation methods differ across studies, and comparisons of residual risks between countries should be interpreted cautiously.

Table 12. Residual risk (RR) of hepatitis B virus (HBV) transmission per million blood donations, by test method and incidence rate (in repeat donors and *first-time donors*)

Incidence rate per 100 000 donors	**ID-NAT** WP: 27	**MP-16 NAT** WP: 37	**HBsAg EIA/CLIA** WP: 42
1	1.36	2.34	3.95
	2.22	*3.04*	*3.45*
5	6.82	11.72	19.73
	11.09	*15.20*	*17.25*
10	13.65	23.43	39.45
	22.18	*30.39*	*34.50*
20	27.30	46.86	78.90
	44.35	*60.78*	*68.99*
30	40.95	70.29	118.35
	66.53	*91.17*	*103.49*
40	54.60	93.72	157.80
	88.71	*121.56*	*137.99*
50	68.25	117.15	197.25
	110.88	*151.95*	*172.48*
60	81.90	140.58	236.70
	133.06	*182.34*	*206.98*
70	95.55	164.01	276.15
	155.24	*212.73*	*241.48*
80	109.19	187.45	315.60
	177.41	*243.12*	*275.98*

EIA/CLIA: enzyme immunoassay/chemiluminescent immunoassay. HBsAg: hepatitis B surface antigen. ID-NAT: individual nucleic acid testing. MP-16 NAT: minipool nucleic acid testing of 16 donations. WP: window period.;
The RR was calculated as the product of the window period and the incidence rate. An HBV incidence adjustment factor was used, considering an average of 2.1 donations per repeat donor per year. A first-time donor incidence adjustment factor of 3 was used.
The values for window periods were taken from the WHO guidelines on estimation of residual risk using the values for the three-fold concentration of the 95% detection probability [155].

Table 13. Examples of residual risks of hepatitis B virus transmission calculated in various EU countries, by periods and test methods

Author, year	Country	Period	Test method	Window period (days)	Type of donation	Incidence rate per 100 000 donations	Residual risk per million donations
Gonzalez, 2005 [158]	Italy	1999–2001	HBsAg EIA/CLIA	59	Whole blood	44.12	69.16
do Barrio, 2005 [159]	Spain (7 centres)	2000–2002	HBsAg EIA/CLIA	59	Whole blood	11.55	18.67
Offergeld, 2005 [160]	Germany	2001–2002	HBsAg EIA/CLIA HBsAg EIA/CLIA + MP-NAT HBsAg EIA/CLIA + ID-NAT	50 45 34	Whole blood	1.31	4.37 1.62 1.22
Pillonel, 2005 [161]	France	2001–2003	HBsAg EIA/CLIA	56	Whole blood	1.02	1.57
Hourfar, 2008 [162]	Germany	1997–2005	HBsAg EIA/CLIA + MP-NAT and ID-NAT	31.4-42.8*	Whole blood	1.37	2.73-2.85*
López-Menchero, 2019 [163]	Spain (Valencia)	2003–2006	HBsAg EIA/CLIA	42	Whole blood	13.11-13.32*	13.40-13.72*
Koch, 2013 [164]	Portugal (1 centre)	2007–2010	HBsAg EIA/CLIA + MP-NAT	35	Whole blood	1.98	1.9
Grubyte, 2011 [165]	Lithuania	2004–2011	HBsAg EIA/CLIA	42	Whole blood	20.34-172.96*	13.08-270.09*
an der Heiden, 2014 [166]	Germany	2006–2012	HBsAg EIA/CLIA + anti-HBc	34	Whole blood	0.46	1.07
Scheiblauer, 2020 [94]**	Germany	2008–2015	HBsAg EIA/CLIA MP-NAT (146 IU/mL) ID-NAT	30.0 / 38.3*** 26.9 / 35.2*** 12.2 / 20.5***	Whole blood	7.51 4.86 4.17	0.6 / 0.8*** 0.4 / 0.5*** 0.1 / 0.2***
Stanic, 2017 [167]	Croatia	2013–2016	ID-NAT + anti-HBc for reactive NAT	NR	Whole blood	9.2	27.1
López-Menchero, 2019 [163]	Spain (Valencia)	2006–2017	HBsAg EIA/CLIA + ID NAT	17	Whole blood	6.77-21.08*	2.89-8.90*
Grubyte, 2011 [165]	Lithuania	2012–2018	HBsAg EIA/CLIA + ID-NAT	17	Whole blood	20.34-146.28*	13.08-103.33*

Author, year	Country	Period	Test method	Window period (days)	Type of donation	Incidence rate per 100 000 donations	Residual risk per million donations
Velati, 2019 [168] ****	Italy	2009–2018	HBsAg EIA/CLIA + MP-NAT and ID-NAT	8.6 to 27.9	Whole blood	FT: 0.11 RP: 0.41	Acute Hepatitis B donors: 0.17 (0.11–0.25) OBI donors: 0.22 (0.19–0.24) Overall HBV: 0.39 (0.30–0.49)
Cappy, 2022 [47]	France	2018–2020	ID-NAT	10	Whole blood	3.7	0.11

EIA/CLIA: enzyme immunoassay/chemiluminescent immunoassay. FT: first-time donors. HBsAg: Hepatitis B surface antigen. ID-NAT: individual donation nucleic acid test. MP-NAT: minipool nucleic acid tests. NR: not reported. OBI: occult hepatitis B infection. RP: repeat donors.
** Range over the study period.*
*** In those with negative anti-HBc.*
**** The first and second figures are based on infectious doses of 1 and 10 HBV DNA copies, respectively.*
*****Residual risk is weighted by the proportion of donations tested by each method.*

5 Current testing requirements in EU/EEA countries

Testing requirements for blood donation

Testing practices for blood donation screening are described in Table 14. Information on confirmatory algorithms is not provided in this document as it is considered out of the scope of the development of the technical guidelines.

Table 14. Reported testing practices for HBV in the EU/EEA by country for blood donations, 2021

Country	HBsAg	Anti-HBc*	HBV NAT	Comments
Austria	Yes	No	Yes	
Belgium***	Yes	NC	Yes	Anti-HBc testing is performed on first-time donors and on the next donation if the donor has not returned to donate for two years and depending on other risk factors.
Bulgaria	Yes	No	Yes	
Croatia	Yes	No	Yes	
Cyprus	Yes	No	Yes	
Czechia	Yes	Yes	Yes	If ID-NAT is reactive: anti-HBc is added to screening. The anti-HBc test is also a part of obligatory confirmatory testing for HBV.
Denmark	Yes	Yes	Yes	Anti-HBc testing is performed on first-time donors, and anti-HBc reactive donors are deferred permanently.
Estonia	Yes	No	Yes	
Finland	Yes	Yes	Yes	Anti-HBc is done on first-time donors in some establishments.
France	Yes	Yes	Yes	
Germany	Yes	Yes	Yes**	Anti HBc-only positive donations can be used if highly sensitive NAT (<5 IU/mL) is negative and anti-HBs is > 100 IU/mL.
Greece	Yes	Yes	Yes	
Hungary	Yes	No	Yes	
Iceland	Yes	NC	No	
Ireland	Yes	No	Yes	
Italy	Yes	No	Yes	
Latvia	Yes	NC	Yes	
Lithuania	Yes	NC	Yes	
Luxembourg	Yes	NC	Yes	
Malta	Yes	NC	Yes	
Netherlands	Yes	Yes	Yes	All blood donations are tested for anti-HBc; anti-HBc reactive donations can be released for clinical or manufacturing use if anti-HBs levels >200 mIU/mL. HBV-HCV-HIV NAT is routinely performed as multiplex real-time PCR testing in minipools of six donations.

Country	HBsAg	Anti-HBc*	HBV NAT	Comments
Norway	Yes	Yes	No	Anti-HBc testing is done when it is more than six months since the previous donation. Anti-HBc reactive donations can be released for clinical or manufacturing use if anti-HBs titre is >200 mIU/mL.
Poland	Yes	No	Yes	
Portugal	Yes	Yes	Yes	
Slovakia	Yes	Yes	Yes	
Slovenia	Yes	Yes	Yes	
Spain	Yes	No	Yes	Anti-HBc is performed in some establishments.
Sweden***	Yes	Yes	No	Anti-HBc only for new donors, when registering for blood donation. If anti-HBs is > 100 IU/mL, they are approved as blood donors.

HBc(Ag): HBV core antigen. HBsAg: Hepatitis B surface antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. ID-NAT: individual donation nucleic acid test. IU: international units. NAT: nucleic acid test. PCR: polymerase chain reaction.
** Data from 2019.*
*** HBV-NAT-testing is mandatory for donations from which a plasma for transfusion will be manufactured if not kept in quarantine for four months.*
**** Data amended after the initial draft of the guidelines on the prevention of HBV transmission through substances of human origin.*
From EDQM, 2021 [169].

Testing requirements for tissues and non-reproductive cells donors

Due to the unavailability of data on testing practices in EU/EEA countries, testing requirements from the mapping exercise conducted in 2015 by the European Commission are described in this section.

Table 15. Testing requirements for HBV in the EU/EEA by country: tissues and non-reproductive cells (2015)

Country	Testing requirement declared*	Tissue/cell type	Donor type	Comment
Austria	• HBsAg • Anti-HBc • HBV NAT	All	Living and deceased	If the anti-HBc test is positive and the HBsAg test is negative, further tests are required (risk evaluation) to determine the clinical use.
Belgium	• HBsAg • Anti-HBc • HBV NAT	All	Living and deceased	NAT tests are mandatory unless the processing includes an inactivation step validated for the viruses concerned. For living donors, NAT tests may be replaced by serology six months after the collection/procurement of tissues or cells.
Bulgaria	• HBsAg • Anti-HBc • HBV NAT	All	NAT for living donors	Additional testing is needed if anti-HBc is positive and HBsAg is negative. Tests for active replication and/or viral load. Anti-HBs should be > 50 IU/l.
Croatia	• HBsAg • Anti-HBc • HBV NAT	All	Living and deceased	For anti-HBc positive and HBsAg negative donors, it is necessary to provide evidence of titres of anti-HBs higher than 100 IU/mL and negative NAT to release the donation.
Cyprus	• HBsAg • Anti-HBc • HBV NAT	All	Living and deceased	NAT testing is required if tissues or cells will be issued without retesting of donors after 180 days of collection.
Czechia	• HBsAg • Anti-HBc	All	Living and deceased	
Denmark	• HBsAg • Anti-HBc • HBV NAT	All	HBV NAT for deceased donors	
Estonia	• HBsAg • Anti-HBc • HBV NAT	All	Living and deceased	Where tissues and cells of allogeneic living donors can be stored for long periods, repeated sampling and testing are required after an interval of 180 days, except if tested by HBV NAT.
Finland	• HBsAg • Anti-HBc • HBV NAT	All	Living and deceased	All deceased donors need to be tested with serological AND NAT tests for HIV, HBV and HCV. All living donors (allogeneic grafts) need to be tested with serological AND NAT tests (no quarantine applied) or a 180-day test (if serology is used).
France	• HBsAg • Anti-HBc • HBV NAT • Anti-HBs	All	Living and deceased	Anti-HBs is performed only if anti-HBc is positive.

Country	Testing requirement declared*	Tissue/cell type	Donor type	Comment
Germany	• HBsAg • Anti-HBc • HBV NAT	All Except for cornea and skin for HBV NAT	Living and deceased	Validation of the serological and NAT assays for use in cadaveric samples is required.
Greece	• HBsAg • Anti-HBc • Anti-HBs • HBV NAT	All	Living and deceased	HBV NAT is performed for living donors if requested by the Transplant Centre.
Hungary	• HBsAg • Anti-HBc	All	Living and deceased	
Ireland	• HBsAg • Anti-HBc	All	Living and deceased	
Italy	• HBsAg • Anti-HBc • Anti-HBs • HBV NAT	All	HBV NAT for living donors	HBV NAT is used in living donors of tissues if serology is not repeated after 180 days. Anti-HBs is performed if anti-HBc results are positive.
Latvia	• HBsAg • Anti-HBc	All	Living and deceased	
Lithuania	• HBsAg • Anti-HBc • Anti-HBs • HBV NAT	All	Living and deceased	HBV NAT for deceased donors only.
Luxembourg	• HBsAg • Anti-HBc	All	Living and deceased	
Malta	• HBsAg • Anti-HBc	All	Living and deceased	
Netherlands	• HBsAg • Anti-HBc	All	Living and deceased	
Norway	• HBsAg • Anti-HBc	All	Living and deceased	
Poland	• HBsAg • Anti-HBc • HBV NAT	All	Living and deceased	HBV NAT can be used as a confirmatory test.
Portugal	• HBsAg • Anti-HBc • Anti-HBs • HBV NAT	All	Living and deceased	Anti-HBs is performed when anti-HBc is positive.
Romania	• HBsAg • Anti-HBc • Anti-HBs	All	Living and deceased	

Country	Testing requirement declared*	Tissue/cell type	Donor type	Comment
Slovakia	• HBsAg • Anti-HBc	All	Living and deceased	
Slovenia	• HBsAg • Anti-HBc • HBV NAT	All	HBV NAT for deceased donors	For living donors, NAT is used if the sample is taken at the time of donation or within seven days post donation.
Spain	• HBsAg • Anti-HBc • HBV NAT	All		HBV NAT: recommended in particular if anti-HBc positive and HBsAg negative.
Sweden	• HBsAg • Anti-HBc • HBV NAT	HBV NAT: bone, tendons	Living and deceased	HBV NAT is recommended for all donors.

HBc(Ag): HBV core antigen. HBsAg: Hepatitis B surface antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. NAT: nucleic acid test.
** Minimum mandatory requirement for tissues and cells is anti-HBc and HBsAg as per directive 2004/23/EC. HBV NAT is required for living donors (except stem-cell donors) in case of storage for long periods, if no re-testing is performed or if there is no validated inactivation step for viruses.*
Tests are reported as legally binding unless specified otherwise.
From European Commission [170].

Testing requirements for reproductive cells donors

Due to the unavailability of data on testing practices in EU/EEA countries, testing requirements from the mapping exercise conducted in 2015 by the European Commission are described in this section.

Table 16. Testing requirements for HBV in the EU/EEA by country: reproductive cells (2015)

Country	Testing requirement declared*	Donation type	Comment
Austria	• HBsAg • Anti-HBc • HBV NAT	HBV NAT: all non-partner donation	
Belgium	• HBsAg • Anti-HBc • HBV NAT	HBV NAT: all non-partner donation	NAT tests are mandatory unless the processing includes an inactivation step validated for the viruses concerned.
Bulgaria	• HBsAg • Anti-HBc • HBV NAT	HBV NAT: all non-partner donation	Oocyte donors are tested at recruitment and on the day of donation, and results should be available before the transfer of the embryos. Sperm is usually quarantined for 180 days and donors retested after this period, except if NAT is used.
Croatia	• HBsAg • Anti-HBc • Anti-HBs • HBV NAT	All	For anti-HBc-positive/HBsAg-negative donors, it is necessary to provide evidence of titres of anti-HBs higher than 100 IU/mL and negative NAT to release the donation for clinical use.
Cyprus	• HBsAg • Anti-HBc • HBV NAT	All	NAT testing is required if tissues or cells will be issued without retesting of donors after 180 days of collection.
Czechia	• HBsAg • Anti-HBc	All	
Denmark	• HBsAg • Anti-HBc • HBV NAT	All	HBV NAT is mandatory for oocyte donors. NAT testing is required if non-partner donors are not retested after 180 days.**
Estonia	• HBsAg • Anti-HBc • HBV NAT	All	NAT testing is required if non-partner donors are not retested after 180 days.
Finland	• HBsAg • Anti-HBc • HBV NAT	HBV NAT: sperm in non-partner donation	NAT testing is required if non-partner donors are not retested after 180 days.
France	• HBsAg • Anti-HBc • HBV NAT • Anti-HBs	All	In non-partner sperm donation, NAT testing for HIV, HCV and HBV at the last collection will allow to avoid the 180 days of quarantine.
Germany	• HBsAg • Anti-HBc	All	
Greece	• HBsAg • Anti-HBc	All	
Hungary	• HBsAg • Anti-HBc	All	
Ireland	• HBsAg • Anti-HBc	All	
Italy	• HBsAg • Anti-HBc	All	

Country	Testing requirement declared*	Donation type	Comment
Latvia	• HBsAg • Anti-HBc	All	
Lithuania	• HBsAg • Anti-HBc	All	
Luxembourg	• HBsAg • Anti-HBc	All	
Malta	• HBsAg • Anti-HBc	All	
The Netherlands	• HBsAg • Anti-HBc	All	
Norway	• HBsAg • Anti-HBc	All	
Poland	• HBsAg • Anti-HBc • HBV NAT	All	NAT is used as a confirmatory test.
Portugal	• HBsAg • Anti-HBc • HBV NAT	All	NAT testing is required if non-partner donors are not retested after 180 days.
Romania	• HBsAg • Anti-HBc • Anti-HBs	All	
Slovakia	• HBsAg • Anti-HBc	All	
Slovenia	• HBsAg • Anti-HBc	All	
Spain	• HBsAg • Anti-HBc • HBV NAT	HBV NAT: non-partner donation	NAT testing is required if non-partner donors are not retested after 180 days.
Sweden	• HBsAg • Anti-HBc	All	Non-partner sperm donors should be quarantined for 180 days and then retested.

HBc(Ag): HBV core antigen. HBsAg: Hepatitis B surface antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HIV: human immunodeficiency virus. NAT: nucleic acid test.
** Minimum mandatory requirement for tissues and cells is HBsAg as per directive 2004/23/EC.*
*** Sperm donation may take place regularly every week or several times a week over a longer coherent period of time. In such cases, the Danish Patient Safety Authority accepts that blood sampling is performed at the time of the first donation and subsequently at least every three months.*
Tests are reported as legally binding unless specified otherwise.
From European Commission [170].

6 Recommendations from other organisations

Recommendations for blood

Table 17. Recommendations from selected organisations for HBV testing of blood donations

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
EU Commission [171-173] Directive 2002/98/EC Directive 2004/33/EC, Annex III Regulation (EU) 2017/746	Minimum requirements: HBsAg. Class D devices should be used for the detection of the presence of, or exposure to, a transmissible agent in blood, blood components, or in any of their derivatives, to assess their suitability for transfusion.	Individuals whose sexual behaviour puts them at a high risk of acquiring severe infectious diseases that can be transmitted by blood must be deferred permanently. Persons who have been in close household contact with an individual infected by HBV (acute or chronic) must be deferred for six months (four months if appropriate testing has been performed) from the time of contact, unless demonstrated to be immune.	Individuals infected with HBV must be deferred permanently, except for HBsAg-negative persons who are demonstrated to be immune.
European Directorate for the Quality of Medicines & HealthCare (EDQM) [174] The Guide to the preparation, use and quality assurance of blood components, 21st edition	Minimum requirements: hepatitis B surface antigen (HBsAg). Recommended: anti-HBc and HBV DNA NAT are also helpful in defining the infection status of the donor.	Current sexual partners of people with HBV should be deferred unless demonstrated to be immune.	Individuals should be deferred for two weeks following the administration of hepatitis B or a combined hepatitis A and hepatitis B vaccine in order to prevent vaccine-related positivity in the HBsAg test.
US Food and Drug Administration (FDA) [175,176] Adequate and Appropriate Donor Screening Tests for Hepatitis B; Hepatitis B Surface Antigen (HBsAg) Assays Used to Test Donors of Whole Blood and Blood Components, Including Source Plasma and Source Leukocytes Use of Nucleic Acid Tests on Pooled and Individual Samples from Donors of Whole Blood and Blood Components, Including Source Plasma, to Reduce the Risk of Transmission of Hepatitis B Virus	We recommend that establishments using HBsAg detection assays to test whole Blood and blood components […] use assays that have a lower limit of detection capability of 0.5ng HBsAg/mL or less. We recommend that you use an FDA-licensed donor screening test for HBV DNA by NAT in addition to testing for HBsAg and anti-HBc. If HBsAg and anti-HBc are negative or non-reactive, we recommend to further test HBV DNA with a lower limit of detection of < 100 IU/mL.		Individuals infected with HBV must be deferred permanently.

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) [177] Guidelines for the Blood Transfusion Services Donor Selection Guidelines	Minimum requirements: HBsAg 0.2 IU/mL, anti-HBc and anti-HBs. HBV DNA NAT is recommended in pools of a maximum of 24 donations.	Current sexual partner or household contact with active or recovered HBV infection. Previous contact with sexual partner (3 months) or household contact (4 months) with active or recovered HBV infection can donate.	Donations that are anti-HBc reactive and have anti-HBs >100 mIU/mL are considered suitable for release if HBsAg and ID HBV DNA NAT are negative.

DNA: desoxyribonucleic acid. HBc(Ag): HBV core antigen. HBsAg: Hepatitis B surface antigen. HBV: hepatitis B virus.ID: individual donation. IU: international units. NAT: nucleic acid test.

Recommendations for tissues and cells

Table 18. Recommendations from selected organisations for testing of tissues and cells donations

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
EU Commission [173,178] Directive 2006/17/EC Regulation (EU) 2017/746	Tissues and cells (except reproductive cells) Minimum requirements: HBsAg, anti-HBc. Reproductive cells - partner donation Minimum requirements: HBsAg, anti-HBc. Reproductive cells – non-partner donation Minimum requirements: HBsAg, anti-HBc. Class D devices should be used for the detection of the presence of, or exposure to, a transmissible agent in cells, tissues, or in any of their derivatives, in order to assess their suitability for transplantation or cell administration.	Children aged less than 18 months born from mothers with hepatitis B, or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests.	Individuals infected with acute or chronic hepatitis B must be deferred permanently. When anti-HBc is positive and HBsAg is negative, further investigations are necessary with a risk assessment to determine eligibility for clinical use. Deceased donors General criteria for exclusion: History, clinical evidence, or laboratory evidence of […] hepatitis B […]. Deceased child donors: Children aged less than 18 months born from mothers with […] hepatitis B […] or at risk of such infection, and who have been breastfed by their mothers during the previous 12 months, cannot be considered as donors regardless of the results of the analytical tests. Allogenic living donors: The same exclusion criteria must be applied as for deceased donors […].
European Directorate for the Quality of Medicines & HealthCare (EDQM) [179] Guide to the Quality and Safety of Tissues and Cells for Human Application, 5th edition	Minimum requirements: HBsAg, Anti-HBc. If anti-HBc is reactive and HBsAg is negative, HBV DNA with a limit of detection below 30 IU/mL must be used. Recommended: HBV DNA NAT.	• Injected drug use for non-medical reasons. • Tattoos, ear piercings, body piercings and/or acupuncture in non-approved settings. • Exposure to someone else's blood or other body fluids (such as needlestick injury or human bite) when that person was known to be infected with HBV (or of unknown status). • Sharing a residence with someone who has HBV. • Patients on regular haemodialysis.	Individuals infected with HBV must be deferred permanently. **Sampling:** In the case of a deceased donor, blood samples must have been obtained just before cardiocirculatory arrest or, if this was not possible, the time of sampling must be as soon as possible after death, and in any case, within 24 hours after death. In the case of living donors, blood sampling must be obtained at the time of donation or, if this is not possible, within 7 days before or 7 days after donation. Newborns and infants aged under 18 months, or children who have been breastfed by their mothers during the previous 12 months, who were born to a mother with confirmed HBV infection, cannot be considered donors, regardless of the results of analytical tests of their sample.

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
US Food and Drug Administration (FDA) [180] Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products	[…] We recommend that you test HCT/P donors for HBsAg and for total anti-HBc (IgG and IgM). In addition, FDA recommends that you test HCT/P donors for HBV using an FDA-licensed NAT donor screening test in accordance with the manufacturer's instructions.	• Men who have had sex with another man in the preceding 5 years. • Persons who have injected drugs for a non-medical reason in the preceding 5 years. • Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years. • Persons who have been in juvenile detention, lock up, jail or prison for more than 72 consecutive hours in the preceding 12 months.	Any HCT/P donor whose specimen tests positive (or reactive) using any of the assays (i.e., HBsAg, total anti-HBc (IgG and IgM), or HBV NAT) is considered ineligible.
Human Tissue Authority [181] HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient Treatment	Minimum requirements: HBsAg and anti-HBc.		Individuals with acute or chronic hepatitis B must be deferred permanently. If the original sample is additionally tested by NAT for HBV, a repeat sample does not need to be taken.
Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) [177] Guidelines for the Blood Transfusion Services	Minimum requirements: HBsAg 0.2 IU/mL, HBV DNA, anti-HBc + anti-HBs.	Current sexual partner or household contact with active or recovered HBV infection. Previous contact with sexual partner or household contact (3 months) with active or recovered HBV infection can donate. Less than 7 days after the last immunisation for HBV.	Donations that are anti-HBc reactive and have anti-HBs ≥100 mIU/mL are considered suitable for release. Donations that are anti-HBc reactive and are HBsAg and ID HBV DNA negative do not require an anti-HBs level of ≥100 mIU/mL to be considered suitable for release.

DA: desoxyribonucleic acid. HBcAg: HBV core antigen. HBsAg: Hepatitis B surface antigen. HBV: hepatitis B virus. HCT/P: human cells, tissues, and cellular and tissue-based products. ID: individual donation. IU: international units. NAT: nucleic acid test.

7 Transmission through SoHO

Evidence of transmission of HBV through SoHO

Evidence of transmission of HBV through different SoHO types is presented in Table 19. This list is intended to document evidence of transmission for each SoHO type but is not intended to present comprehensive documentation of transmission events. As a reminder, absence of evidence is not evidence of absence.

Table 19. Evidence of transmission of HBV by type of SoHO

SoHO type	Evidence of transmission
Blood components: plasma	Yes [182,183]
Blood components: platelets	Yes [183,184]
Blood components: red blood cells	Yes [24,183,185]
Blood components: whole blood	Yes [186]
Cells: human progenitor cells	Yes [187]
Cells: oocytes	None. Presence of HBsAg [188]
Cells: sperm	Yes [189]
Tissues: bone	Possible [190]
Tissues: corneas	Yes [191]
Tissues: heart valve	Yes [192]
Tissues: skin	None
Tissues: tendon or ligaments	None

Donor HBV markers for reported transmission events are described in Table 20. Several transmission events with blood components were reported with donors presenting with negative HBsAg and HBV DNA using highly sensitive NAT, in some cases below 3 IU/mL [31,193]. Some, but not all, of the transmission events could have been prevented using anti-HBc screening.

Table 20. Transmission events of HBV through SoHO and donor HBV marker profile

SoHO type	Donor HBV markers profile							
			HBsAg	Anti-HBc (IgM)	Anti-HBc (total)	Anti-HBs	HBeAg	Anti-HBe	HBV DNA
Blood components: plasma [182]	At donation (before transfusion):		neg	/	/	/	/	/	neg
	Posterior donation (leading to lookback procedure):		neg	neg	pos	55 IU/ml	neg	pos	57 IU/mL Donor and recipient had genotype D HBV virus, with identical prenegS/S coding region sequences.
Blood components: plasma [31]*	Possible transmission		neg	/	pos	14 IU/L	/	/	neg 95% limit of detection <10 IU/mL
	Confirmed transmission		neg	/	neg	neg	/	/	neg
	Confirmed transmission		neg	/	neg	/	/	/	/
	Confirmed transmission		neg	/	/	/	/	/	/
	Confirmed transmission		neg	/	neg	neg	/	/	/
	Probable transmission		neg	/	neg	neg	/	/	/
	Probable transmission		neg	/	neg	/	/	/	/
Blood components: red blood cells [31]*	Confirmed transmission		neg	/	/	/	/	/	/
	Probable transmission		neg	/	/	/	/	/	/
Blood components: platelets [184]	Case 1	At donation	neg	/	neg	/	/	/	neg
		Six weeks post-donation	pos	/	neg	neg	/	/	pos (estimated transfused HBV DNA <10 x 10^3 qeq)
	Case 2	At donation	neg	/	neg	/	/	/	pos (assessed retrospectively; estimated transfused HBV DNA 750 x 10^3 qeq)
		Seven weeks post-donation	pos	/	pos	neg	/	/	
Blood components: red blood cells [24,185]	[24]	Transfused donation	neg	/	/	/	/	/	neg
		Donation 60 days after	pos	/	/	/	/	/	pos
	[185]	Transfused donation	neg	/	/	/	/	/	pos (retrospectively assessed, with 253 IU/ml)
Blood components: whole blood [186]	Transfused donation		neg	/	/	/	/	/	pos (assessed retrospectively)
Blood components: platelet concentrate [193]	Confirmed transmission		neg	/	neg	0.3 IU/L	/	/	neg (retrospectively estimated at 0.06 IU/mL)
	Confirmed transmission		neg	/	neg	2.5 IU/L	/	/	neg (retrospectively estimated at 0.10 IU/mL)
	Confirmed transmission		neg	/	neg	0.5 IU/L	/	/	neg (retrospectively estimated at 0.11 IU/mL)
	Confirmed transmission		neg	/	neg	1.2 IU/L	/	/	neg (retrospectively estimated at 2.04 IU/mL)
	Confirmed transmission		neg	/	neg	1.2 IU/L	/	/	neg (retrospectively estimated at 0.02 IU/mL)
	Confirmed transmission		neg	/	neg	0.7 IU/L	/	/	neg (retrospectively estimated at 0.002 IU/mL)

SoHO type	Donor HBV markers profile							
		HBsAg	Anti-HBc (IgM)	Anti-HBc (total)	Anti-HBs	HBeAg	Anti-HBe	HBV DNA
Blood components: plasma [193]	Confirmed transmission	neg	/	neg	10.7 IU/L	/	/	neg (95% limit of detection: 3.1 IU/mL)
Blood components: platelet concentrate [27]	Confirmed transmission	neg	/	neg	/	/	/	Weakly pos
	Confirmed transmission	neg	/	neg	/	/	/	neg
	Confirmed transmission	neg	/	neg	/	/	/	pos (600 IU/L)
	Confirmed transmission	neg	/	neg	/	/	/	pos (<25 IU/mL)
	Confirmed transmission	neg	/	neg	/	/	/	pos (>500 IU/mL)
	Confirmed transmission	neg	/	neg	/	/	/	pos (171 IU/mL)
Blood components: red blood cells [27]	Confirmed transmission	neg	/	neg	/	/	/	Weakly pos
	Confirmed transmission	neg	/	neg	/	/	/	pos (<25 IU/mL)
	Confirmed transmission	neg	/	pos	12 IU/L	/	/	pos (180 IU/mL)
	Confirmed transmission	neg	/	neg	/	/	/	pos (>500 IU/mL)
Blood components: plasma [27]	Confirmed transmission	neg	/	neg	/	/	/	Weakly pos
	Confirmed transmission	neg	/	neg	/	/	/	pos (160 IU/mL)
	Confirmed transmission	neg	/	neg	/	/	/	pos (<20 IU/mL)
	Confirmed transmission	neg	/	pos	/	/	/	pos (<20 IU/mL)
	Confirmed transmission	neg	/	pos	12 IU/L	/	/	pos (180 IU/mL)
Cells: human progenitor cells [187]	Leakage from cryopreservation bag	pos	neg	neg	neg	neg	neg	pos (assessed retrospectively)
Cells: sperm [189]		pos	/	/	/	pos	/	pos
Tissues: bone [190]								
Tissues: corneas [191]		pos	/	/	/	/	/	/
Tissues: heart valve [192]		pos	/	/	/	neg	/	/

** Cases presented in this publication were specifically selected due to negative HBsAg and negative or absent HBV DNA tests.*
geq: genomic equivalent quantity

Reported transmission events of HBV infections through SoHO

Table 21. Number of SoHO-transmitted HBV infections (imputability 2 or 3*) and number of units transfused or distributed in the EU/EEA (2017–2022)

Year	SoHO	Number of transmitted HBV infections	Number of transmitted unspecified viral infections	Number of units transfused or distributed**
2022	Blood	1	0	12 653 949
	Tissues and cells	0	0	610 725
	Reproductive cells	0	0	506 429
2021	Blood	0	0	17 813 542
	Tissues and cells	0	2	NA
	Reproductive cells	0	0	NA
2020	Blood	0	0	18 881 223
	Tissues and cells	0	0	566 499
	Reproductive cells	0	0	738 282
2019	Blood	2	1	19 322 367
	Tissues and cells	1	1	523 763
	Reproductive cells	0	0	984 750
2018	Blood	2	0	19 267 785
	Tissues and cells	2	0	531 352
	Reproductive cells	0	0	746 588
2017	Blood	4	0	20 674 603
	Tissues and cells	0	0	748 757
	Reproductive cells	0	0	670 565

NA: Not available.
** 2: likely, probable; 3: certain.*
*** Not reported by all countries for each year. Units are distributed for tissues and cells and reproductive cells.*
From SARE reporting, European Commission, 2024.

8 Pathogen reduction

Search results

This section aims to present the published outcomes of pathogen reduction methods regarding HBV, including in the context of SoHO processing. The results summarised in this section are based on a structured but non-systematic search of Medline from January 2001 to March 2024. A combined search for HBV and HCV was performed.

Available commercial pathogen reduction technologies for blood components in the EU/EEA are described in Table 22.

Table 22. Available commercial pathogen reduction technologies with CE marking

Pathogen reduction method	Components
Amotosalen + UVA Light (320-400 nm)	Platelets (apheresis or whole blood-derived)
Amotosalen + UVA Light (320-400 nm)	Plasma (apheresis or whole blood-derived)
Riboflavin + UVB Light (280-360 nm)	Platelets (apheresis or whole blood-derived)
Riboflavin + UVB Light (280-360 nm)	Plasma (apheresis or whole blood-derived)
Riboflavin + UVB Light (280-360 nm)	Whole blood
UVC light	Platelets
Filtration + Methylene Blue + visible light (400-700 nm)	Fresh frozen plasma (apheresis or whole blood-derived)
Solvent/Detergent	Single donation or mini-pool of plasma (apheresis or whole blood-derived)

Adapted from Drew 2017 [194].

A total of 300 reports were screened, among which 26 were included. Individual studies and literature were included if they included measures of pathogen reduction following a processing or inactivation step for HBV in SoHO. Duplicates were removed. No other exclusion criteria were applied, and results are summarised by SoHO type in Table 23.

For tissues, thermal treatment (above 82°C), peracetic acid/ethanol sterilisation, and gamma irradiation above 35 kGy, were associated with reduction in the viral load of HBV below detection limits of tests used. For blood components, amotosalen and UV-A, methylene-blue and light, solvent/detergent, amustaline and glutathione, and PEN-110, were associated with reduction in the viral load of HBV below detection limits of tests used. Reports for riboflavin and UV-A or use of UV-C only indicated limited pathogen reduction for HBV with detectable viral load after application of the pathogen reduction method.

None of the studies identified reported results on the inactivation of HBV in the context of processing of reproductive cells.

The search methods are described in detail in Annex 1.

Summary of data

Table 23. Pathogen reduction methods for HBV by substance of human origin (SoHO) [195-207]

Author, year	Country	Publication type	SoHO type	Virus	Pathogen reduction method	Pathogen load metric	Value	Comment
Moore, 2012	NA	Review	Bone	HBV (PRV model)	Gamma irradiation (13 kGy)	Log reduction	3.8	Viral above LoD
Pruss, 2001	Germany	Study	Bone	HBV (PRV model)	Gamma irradiation (35 kGy)	Log reduction	>5.6	
Pruss, 2003	Germany	Study	Bone	HBV (PRV model)	Peracetic acid/ethanol	Log reduction	>4.1	
Pruss, 2001	Germany	Study	Bone	HBV (PRV model)	Thermal treatment (82.5C, 15 min)	Log reduction	>4.1	
Moore, 2004	US	Study	Musculoskeletal grafts	HBV (DHBV model)	Terminal ethylene oxide	Viral titres	<10^0.5	No infectivity
Allain, 2005	NA	Review	Plasma	HBV	Amotosalen + UV-A	Log reduction	>4.5	
Bryant, 2007	NA	Review	Plasma	HBV	Amotosalen + UV-A	Log reduction	>5.5	
Lanteri, 2020	NA	Review	Plasma	HBV (DHBV model)	Amotosalen + UV-A	Log reduction	4.4	Viral above LoD
Seghatchian, 2011	NA	Review	Plasma	HBV (PRV model)	Methylene Blue + Light	Log reduction	>5.5	
Seghatchian, 2011	NA	Review	Plasma	HBV (DHBV model)	Methylene Blue + Light	Log reduction	>6	
Allain, 2005	NA	Review	Platelets	HBV	Amotosalen + UV-A	Log reduction	>5.5	
Irsch, 2011	NA	Review	Platelets	HBV	Amotosalen + UV-A	Log reduction	>5.5	
Irsch, 2011	NA	Review	Platelets	HBV (DHBV model)	Amotosalen + UV-A	Log reduction	>6.2	
Lanteri, 2020	NA	Review	Platelets	HBV	Amotosalen + UV-A	Log reduction	>5.5	

Author, year	Country	Publication type	SoHO type	Virus	Pathogen reduction method	Pathogen load metric	Value	Comment
Lanteri, 2020	NA	Review	Platelets	HBV (DHBV model)	Amotosalen + UV-A	Log reduction	>6.7	
Lanteri, 2020	NA	Review	Platelets	HBV (DHBV model)	Amotosalen + UV-A	Log reduction	≥4.8	
Schlenke, 2014	NA	Review	Platelets	HBV (PRV model)	Riboflavin + UV-A	Log reduction	2.5	Viral above LoD
Schlenke, 2014	NA	Review	Platelets	HBV (PRV model)	UV-C	Log reduction	2.8	Viral above LoD
Kleinman, 2015	NA	Review	RBC	HBV (DHBV model)	Amustaline + glutathione	Log reduction	>5.1	
Aytay, 2004	US	Study	RBC	HBV	PEN110	Log reduction	>7.2	
Moore, 2012	NA	Review	Tendons	HBV (PRV model)	Gamma irradiation (13 kGy)	Log reduction	3.8	Viral above LoD
Schmidt, 2012	Germany	Study	Tendons	HBV (PRV model)	Gamma irradiation (35 kGy)	Log reduction	4	Modelled value.

HBV: Hepatitis B Virus; DHBV: Duck Hepatitis B Virus; PRV: Pseudorabies Virus; NA: not applicable; kGy: kiloGray; LoD: limit of detection.
Note: log reductions with "> " or "≥" indicate viral loads below limit of detection after pathogen reduction.

9 Public health resources

ECDC

- Hepatitis B
- Surveillance and disease data for hepatitis B
- Hepatitis B and C prevalence database

US Centers for Disease Control (CDC)

- CDC HBV professional resources

US Food and Drug Administration (FDA)

- Complete List of Donor Screening Assays for Infectious Agents and HIV Diagnostic Assays
- FDA Blood Guidances
- FDA Tissue Guidances

European Directorate for the Quality of Medicines & HealthCare (EDQM)

- EDQM Guide to the preparation, use and quality assurance of blood components
- EDQM Guide to the quality and safety of tissues and cells for human application

World Health Organization (WHO)

- Hepatitis
- Blood transfusion safety
- Transplantation

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Annex 1. Search strategies

Available on request.

Annex 2. Laboratory testing approaches and pathogen inactivation methods: data extraction tables

Available on request.