ECDC SUPPLEMENTARY MATERIAL

Pathogen data sheet: HCV

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

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Abbreviations

Ab	Antibody
AER	Annual Epidemiological Report
Ag	Antigen
CI	Confidence interval
CLIA	Chemiluminescence immunoassay
CMIA	Chemiluminescence microparticle immunoassay
COVID-19	Coronavirus disease 2019
CrI	Credible Interval
DAA	Direct-acting antiviral agent
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
GT	Genotype
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
HCVAg	Hepatitis C antigen
HIV	Human immunodeficiency virus
ID	Individual donation
IU	International units
iWP	Infectious window period
JPAC	Joint United Kingdom Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee
LOD	Limit of detection
mITT	Modified intention-to-treat
MP	Mini pool
MSM	Men who have sex with men
NA	Not applicable
NAT	Nucleic acid test
NC	Not calculated
ND	No data reported
NR	Not reported
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PLHIV	People living with HIV
PrEP	Pre-exposure prophylaxis
PWID	People who inject drugs
PY	Person-years
RAS	Resistance-associated substitutions
RNA	Ribonucleic acid
RP	Repeat donors
RR	Residual risk
SoHO	Substances of human origin (excluding solid organs)[1]
SVR	Sustained virologic response

[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.

STI	Sexually transmitted infection
TESSy	The European Surveillance System
TTI	Transfusion- transmissible infection
UV	Ultraviolet
WHO	World Health Organization
WP	Window period

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 C 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 C virus (HCV) are described in Table 1.

Table 1. Hepatitis C virus classification

Feature	Value
Realm	*Riboviria*
Family	*Flaviviridae*
Genus	*Hepacivirus*
Characteristics	Positive single-strand ribonucleic acid (RNA) virus
Cell tropism	– Hepatocytes – Peripheral blood mononuclear cells
Receptors on host cell	Hepatocytes (all are necessary for entry): – Cluster of differentiation 81 (CD81) – Scavenger receptor class B type I (SR-BI) – Claudin-1 (CLDN1) – Occludin (OCLN) Immune cells: – B7.2 – CD5

Source: [1,2].

2 Description of the disease

Modes of transmission

Hepatitis C virus (HCV) is transmitted through exposure to infected bodily fluids, including blood, semen, and vaginal fluids [3]. HCV 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.
- Unprotected sexual contact with a partner with an infection.
- Needlestick injuries or other injuries occurring outside a healthcare setting (e.g. bites, tattoos, piercings).
- 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 C cases in the EU/EEA in 2022 are described in Table 6.

Natural history of HCV infection

HCV infection can present as acute or chronic, with chronic infection resulting from the persistence of the infection over time. There are eight genotypes of HCV, labelled from 1 to 8, with subtypes labelled with letters (a, b…). The different genotypes represent the genetic variations of the virus and are associated with different geographical distributions. In Europe, the dominant genotypes are genotypes 1 and 3 [4], although other genotypes can also be prevalent in specific populations, such as genotype 4 among intravenous drug users [5]. Distinct subtypes (genotype 1 non-1a/1b, genotype 2 non-2a/2b, genotype 3 non-3a, genotype 4 non-4a/4d, and subtypes of genotypes 5 to 8) are infrequent in Europe and more prevalent in Africa and Asia [6]. Genotypes can affect the natural history of the disease and can significantly impact treatment outcomes [6,7].

Acute hepatitis C

Acute HCV infection can have different clinical presentations, ranging from asymptomatic (approximately 40-50% of cases) or subclinical to icteric hepatitis [8]. Symptoms of acute hepatitis C encompass jaundice, nausea, abdominal discomfort, and flu-like symptoms. These symptoms are accompanied by an elevation of liver transaminases [8]. Detection of HCV RNA is usually possible within a week after exposure, although serum HCV RNA levels can fluctuate considerably. Anti-HCV antibodies will only appear after 10 to 12 weeks, or perhaps even longer, in some reports [9]. Spontaneous resolution occurs in approximately 15 to 25% of cases, and can be more frequent in specific groups [10]. Certain genetic factors, such as polymorphisms in the IL28B gene and natural killer cell receptor genes, are associated with higher rates of spontaneous clearance [11,12].

Chronic hepatitis C

Failure to clear HCV RNA after six months following acute infection onset characterises chronic hepatitis C. Once it has reached the chronic phase, the disease can lead to progressive fibrosis, cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). If left untreated, 20-30% of chronic patients will eventually develop cirrhosis. The rate of progression is associated with various factors, including coinfections (e.g. hepatitis B virus (HBV), human immunodeficiency virus (HIV)), alcohol consumption, obesity, older age at infection, and male sex [7]. Fibrosis progression is a key indicator of disease course, with cross-sectional biopsy studies suggesting a 30-year period to develop cirrhosis. Cirrhosis increases the risk of complications such as ascites, spontaneous bacterial peritonitis, variceal haemorrhage, and hepatic encephalopathy, which in turn elevate the risk of death and the need for liver transplantation due to liver disease or HCC.

HCV infection is also associated with numerous extrahepatic manifestations [13]. People with infections are more at risk of mixed cryoglobulinemia and B-cell non-Hodgkin lymphoma [14,15]. Other manifestations, such as cardiovascular disease, insulin resistance and renal insufficiency, have also been associated with HCV infection [15].

Treatment for hepatitis C

The main goal of HCV therapy is the cure of the infection. The primary endpoint for treatment is a sustained virological response (SVR) defined by undetectable HCV RNA at 12 weeks (SVR12) and 24 weeks (SVR24) after the end of therapy, assessed by HCV RNA nucleic acid test (NAT) with a lower limit of detection ≤15 IU/ml [6].

The current treatment for HCV is based on direct-acting antiviral agents (DAA), used alone or in combination with ribavirin [6]. These DAAs can usually be given as short courses (eight to 12 weeks) of treatment, are well tolerated, and, when used with full adherence, result in cure rates upwards of 90% [16,17]. The most recent DAAs can be used across all genotypes and are recommended as first-line treatment [6].

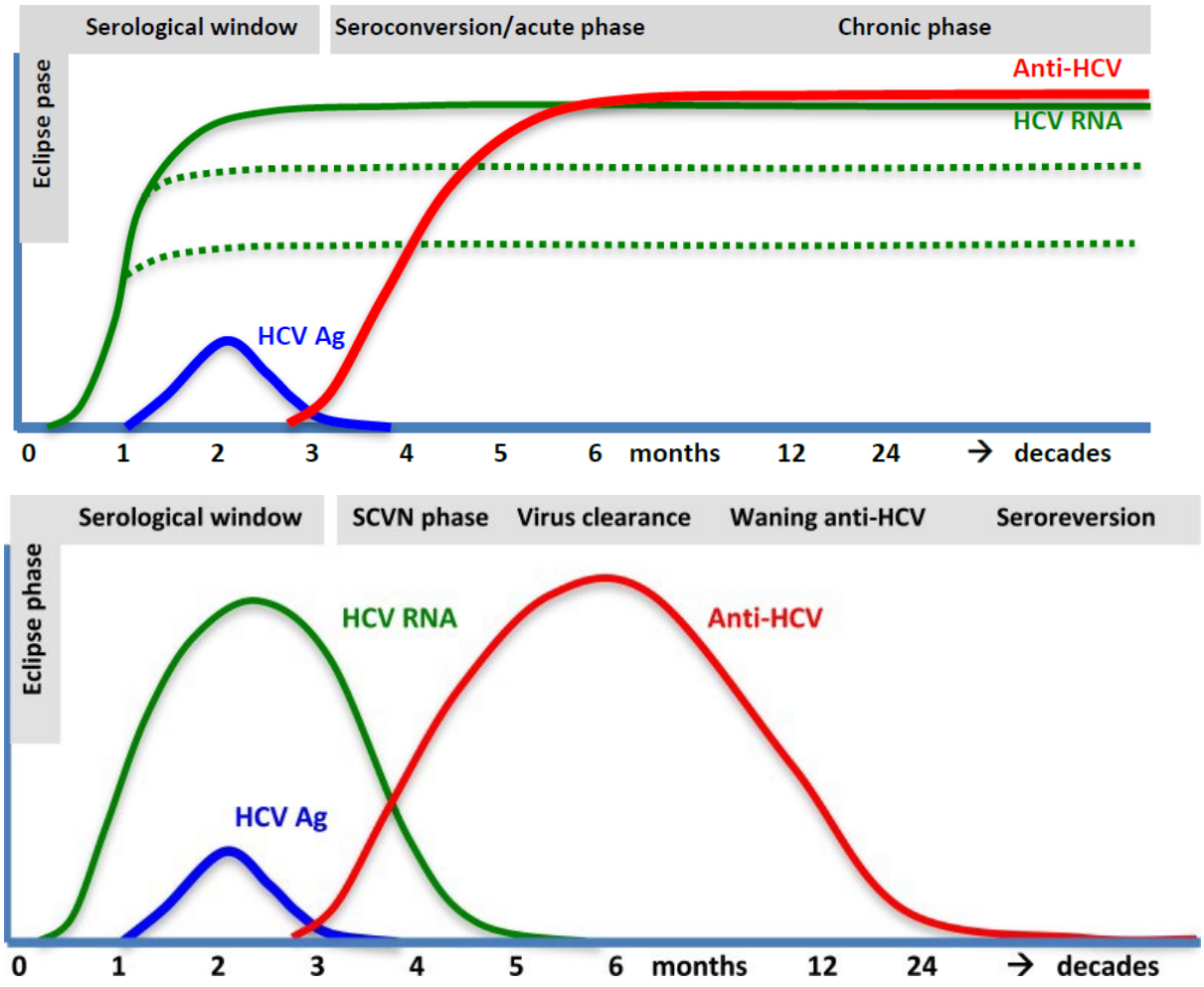
Antiviral therapy also positively impacts extrahepatic manifestations, with SVR being associated with an improvement of extrahepatic morbidity and mortality or a reduction of the risk of developing these diseases [18,19].

HCV reinfection can occur after HCV clearance, whether spontaneous or following successful treatment. Reinfection is defined by the reappearance of HCV RNA after being undetectable for more than 12 weeks (i.e. an SVR) or infection with a different HCV strain: either a different genotype or a distant strain.

Infectious dose and viraemia

Based on case reports and animal models, a 50% minimum infection dose between seven and 20 copies of HCV RNA has been proposed [20]. While there remains some uncertainty on these durations, detection of HCV RNA is usually possible within a week after exposure, HCV antigen (HCVAg) after 2 weeks and anti-HCV after approximately 9 weeks [21] (Figure 1).

Figure 1. Evolution of serum markers in HCV infection



Top: chronic HCV infection. Bottom: self-resolving HCV infection.
HCV: hepatitis C virus. RNA: ribonucleic acid. SCVN: seroconversion.
The eclipse phase refers to the period prior to the detection period of HCV RNA.
From World Health Organization (WHO), 2017 [22].

Survival of HCV in the environment

HCV is stable outside the human body and can maintain infectivity for up to 6 weeks between 4°C and 22°C on contaminated surfaces [23]. In contaminated syringes, HCV has been shown to remain stable in high-void-volume syringes for up to 60 days [24].

Organ systems targeted by HCV and HCV presence in different tissues

The hepatitis C virus is primarily hepatotropic. There is also evidence of extrahepatic tropism in the lymphatic system, where HCV can impact the development and function of immune cells. Immune cells (including monocytes, B cells and T cells) serve as reservoirs for the virus where it can hide from immune surveillance. The virus genome has also been documented in lymph nodes and the bone marrow [25].

3 Epidemiology

The surveillance systems across EU/EEA countries are heterogeneous [26]. These systems are based on notifications, representing the screening and testing practices instead of the actual number of infections in each country.

General population

Acute hepatitis C

The exact incidence of acute hepatitis C in the EU/EEA is not available. Given the differences in local testing practices and the possible asymptomatic course of the infection, the interpretation of the number of new acute hepatitis C cases reported per year, presented in Table 2, is limited and cannot be considered a proxy for infection incidence.

The overall notification rate for acute hepatitis C from 2013 to 2022 showed year-to-year fluctuations with no apparent long-term trend. In 2020, a substantial decrease in the notification rate was observed, probably in relation to the disruption of healthcare services and behavioural changes due to the COVID-19 pandemic. After 2020, the notification rate has increased to pre-pandemic levels (Figure 2).

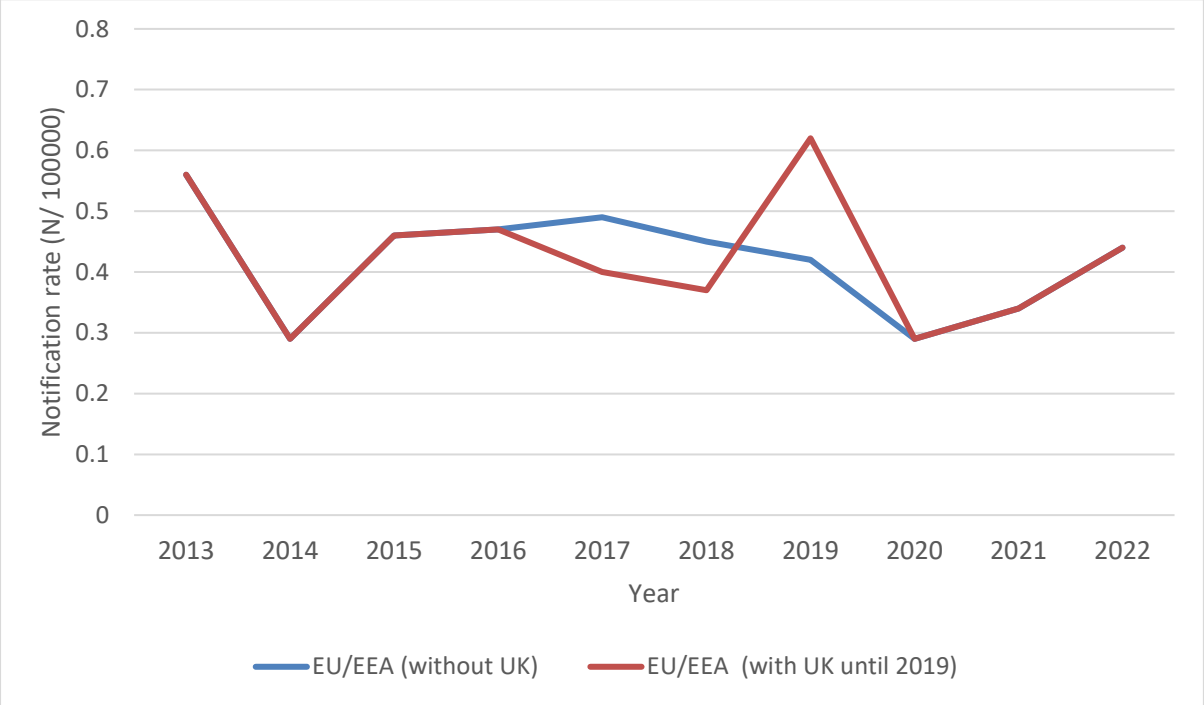
Table 2. Number of reported acute hepatitis C cases and rates per 100 000 population in the EU/EEA, by country and year (2018–2022)

Country	2018		2019		2020		2021		2022	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Austria	70	0.8	37	0.4	31	0.4	34	0.4	62	0.7
Belgium	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Bulgaria	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Croatia	1	0.0	3	0.1	1	0.0	2	0.0	0	0.0
Cyprus	1	0.1	0	0.0	0	0.0	0	0.0	0	0.0
Czechia	122	1.1	103	1.0	88	0.8	96	0.9	93	0.9
Denmark	8	0.1	11	0.2	3	0.1	4	0.1	11	0.2
Estonia	5	0.4	8	0.6	12	0.9	5	0.4	6	0.5
Finland	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
France	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Germany	590	0.7	581	0.7	360	0.4	407	0.5	679	0.8
Greece	1	0.0	2	0.0	0	0.0	0	0.0	0	0.0
Hungary	11	0.1	7	0.1	5	0.1	10	0.1	24	0.2
Iceland	0	0.0	0	0.0	0	0.0	0	0.0	ND	NR
Ireland	16	0.3	12	0.2	9	0.2	12	0.2	17	0.3
Italy	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Latvia	55	2.8	58	3.0	18	0.9	12	0.6	20	1.1
Liechtenstein	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Lithuania	25	0.9	21	0.8	8	0.3	2	0.1	14	0.5
Luxembourg	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Malta	0	0.0	0	0.0	0	0.0	0	0.0	ND	NR
Netherlands	64	0.4	76	0.4	44	0.3	30	0.2	28	0.2

Country	2018		2019		2020		2021		2022	
Norway	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Poland	14	0.0	16	0.0	0	0.0	4	0.0	9	0.0
Portugal	1	0.0	7	0.1	22	0.2	15	0.1	11	0.1
Romania	84	0.4	18	0.1	0	0.0	0	0.0	12	0.1
Slovakia	18	0.3	27	0.5	16	0.3	10	0.2	13	0.2
Slovenia	4	0.2	4	0.2	2	0.1	2	0.1	6	0.3
Spain	66	0.1	82	0.2	59	0.1	152	0.3	121	0.3
Sweden	173	1.7	157	1.5	171	1.7	202	1.9	182	1.7
United Kingdom (UK)	19	0.0	1 016	1.5	NA	NA	NA	NA	NA	NA
Total EU/EEA	**1 348**	**0.4**	**2 246**	**0.6**	**849**	**0.3**	**999**	**0.3**	**1 308**	**0.4**

Case definition remains difficult, with most cases being reported as "unknown" by the countries.
NA: Not applicable. ND: no data reported. NR: no rate calculated.
Adapted from ECDC Surveillance Atlas of Infectious Diseases [27].

Figure 2. Notification rates of acute hepatitis C per 100 000 population by year in EU/EEA countries, 2013–2022



Adapted from ECDC Surveillance Atlas of Infectious Diseases [27].

Chronic hepatitis C

The prevalence of chronic hepatitis C is often estimated based on the prevalence of anti-HCV in the general population. However, these estimates might represent an overestimation of the observed burden of the disease because patients treated for chronic hepatitis C can be considered in these numbers, given that they remain ani-HCV-positive [28].

A recent epidemiological study reports an estimated chronic hepatitis C prevalence of 0.50% [95% Credible Interval (CrI): 0.46-0.55] by the end of 2019 in 29 EU/EEA countries (except Liechtenstein). From these 29 EU/EEA countries, 25 had a prevalence of chronic hepatitis C inferior to 1%. The estimated number of people with chronic hepatitis C across these 29 countries at the end of 2019 was 1 782 923 (95% CrI: 1 638 132 – 1 941 583) (Table 3) [28].

In a previous systematic review including data from 2005 to 2015, the estimated anti-HCV prevalence based on studies conducted in the general population in the EU/EEA was 1.1% (95% CI 0.9-1.4), ranging from 0.1% in Belgium, Ireland and the Netherlands to 5.9% in Italy. The estimated number of individuals with positive anti-HCV was approximately 5.6 million [29].

Table 3. Prevalence and absolute numbers of chronic hepatitis C cases, EU/EEA, 2019

Country	Median prevalence (%)	95% CrI (%)	Number of cases (n)	95% CrI (%)
Austria	0.33	0.29-0.38	23 860	20 931-26 854
Belgium	0.18	0.09-0.36	16 178	7 737-31 562
Bulgaria	1.11	0.83-1.60	62 610	47 032-90 766
Croatia	0.74	0.46-1.11	24 274	15 060-36 404
Cyprus	0.19	0.15-0.25	1 353	1 035-1 756
Czechia	0.78	0.55-1.11	66 794	46 853-94 196
Denmark	0.27	0.25-0.30	12 423	11 262-13 621
Estonia	1.71	1.49-2.06	17 634	15 413-21 306
Finland	0.59	0.53-0.66	25 650	22 801-28 477
France	0.29	0.16-0.46	142 921	77 226-227 201
Germany	0.30	0.21-0.42	196 671	137 554-279 639
Greece	0.55	0.36-0.80	46 260	30 310-67 042
Hungary	0.23	0.20-0.25	17 984	15 962-20 101
Iceland	0.10	0.05-0.20	279	151-547
Ireland	0.21	0.13-0.35	7 844	4 711-13 035
Italy	0.96	0.80-1.15	459 000	379 172-549 698
Latvia	0.77	0.68-0.87	11 640	10 236-13 090
Liechtenstein	NR	NR	NR	NR
Lithuania	1.01	0.94-1.09	22 410	20 761-24 139
Luxembourg	0.25	0.15-0.39	1 243	760-1 894
Malta	0.27	0.20-0.35	1 083	812-1 398
Netherlands	0.04	0-0.16	6 183	0-21 759
Norway	0.22	0.14-0.30	9 164	5 954-12 631
Poland	0.36	0.27-0.45	108 210	82 261-137 566
Portugal	0.50	0.37-0.78	41 161	30 370-64 216

Country	Median prevalence (%)	95% CrI (%)	Number of cases (n)	95% CrI (%)
Romania	2.26	2.11-2.41	348 939	326 554-372 034
Slovakia	0.62	0.47-0.78	27 407	20 658-34 501
Slovenia	0.07	0.02-0.14	1 078	317-2 319
Spain	0.15	0.06-0.27	54 676	21 352-101 774
Sweden	0.16	0.07-0.31	12 758	5 174-24 732
Total EU/EEA	**0.50**	**0.46-0.55**	**1 782 923**	**1 638 132 – 1 941 583**

Estimates of prevalence and absolute numbers were approached by a multi-parameter evidence synthesis method.
CrI: Credible Interval. NR: not reported.
Adapted from Thomadakis et al., 2024 [28].

Among the countries with consistent reporting between 2013 and 2022, the overall notification rate for hepatitis C showed year-to-year fluctuations with no clear long-term trend. In 2020 and 2021, a substantial decrease in the notification rate was observed, probably in relation to the disruption of healthcare services and behavioural changes due to the COVID-19 pandemic. The increase in the notification rate after 2021 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 (Table 4 and Figure 3). Nevertheless, the interpretation of these data is limited, considering the differences in notification rates between countries due to variations in reporting practices, testing strategies, and inherent epidemiological settings.

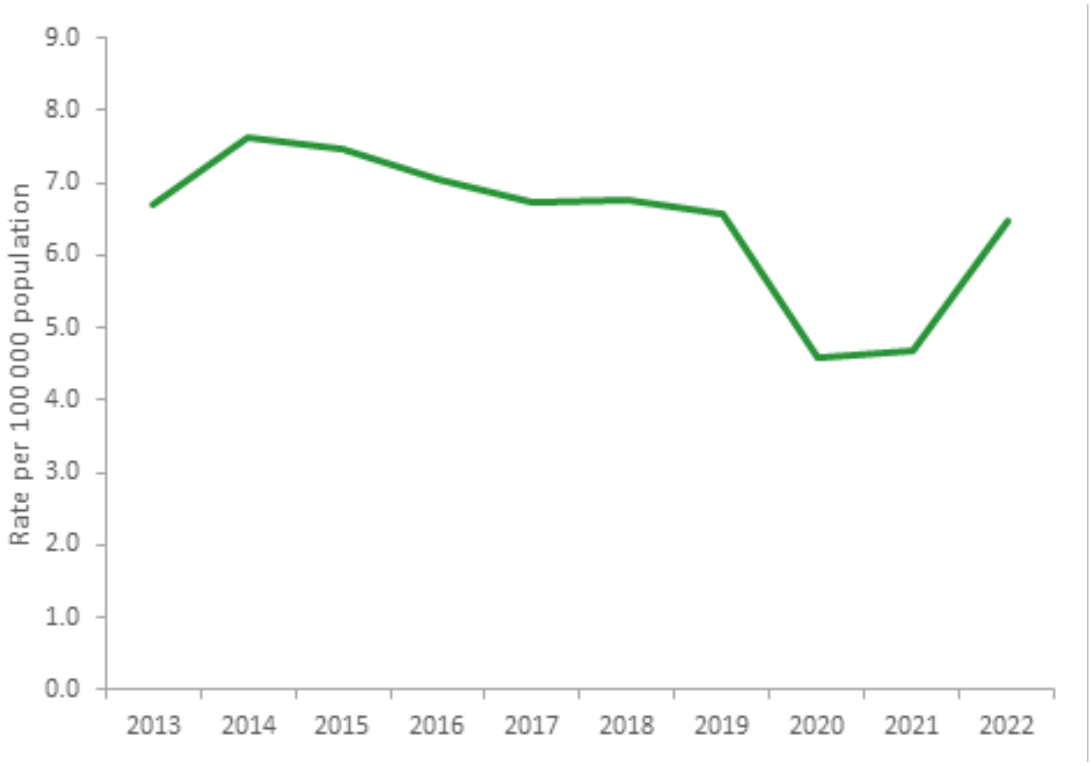
Table 4. Number of reported chronic hepatitis C cases and rates per 100 000 population in the EU/EEA, by country and year (2018–2022)

Country	2018		2019		2020		2021		2022	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Austria	452	5.1	359	4.1	173	1.9	175	2.0	275	3.1
Belgium	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Bulgaria	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Croatia	37	0.9	89	2.2	41	1.0	44	1.1	14	0.4
Cyprus	39	4.5	27	3.1	8	0.9	7	0.8	7	0.8
Czechia	928	8.7	1035	9.7	682	6.4	573	5.4	727	6.9
Denmark	175	3.0	111	1.9	158	2.7	145	2.5	194	3.3
Estonia	144	10.9	133	10.0	123	9.3	128	9.6	107	8
Finland	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
France	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Germany	2 328	2.8	2 299	2.8	1 555	1.9	1 674	2.0	3 052	3.7
Greece	124	1.2	22	0.2	19	0.2	43	0.4	99	0.9
Hungary	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Iceland	0	0.0	0	0.0	0	0.0	0	0.0	ND	NR
Ireland	106	2.2	94	1.9	25	0.5	45	0.9	69	1.4

Country	2018		2019		2020		2021		2022	
	N	Rate	N	Rate	N	Rate	N	Rate	N	Rate
Italy	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Latvia	1 414	73.1	1 322	68.9	1 004	52.6	673	35.5	688	36.7
Liechtenstein	ND	NR	ND	NR	ND	NR	ND	NR	1	2.5
Lithuania	ND	NR	ND	NR	65	2.3	57	2.0	833	29.7
Luxembourg	ND	NR	ND	NR	ND	NR	ND	NR	0	0
Malta	0	0.0	0	0.0	0	0.0	0	0.0	ND	NR
Netherlands	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Norway	ND	NR	ND	NR	ND	NR	ND	NR	ND	NR
Poland	585	1.5	501	1.3	102	0.3	0	0.0	0	0
Portugal	79	0.8	71	0.7	41	0.4	44	0.4	73	0.7
Romania	3	0.0	4	0.0	0	0.0	0	0.0	2	0
Slovakia	207	3.8	220	4.0	188	3.4	172	3.2	309	5.7
Slovenia	108	5.2	66	3.2	44	2.1	28	1.3	35	1.7
Spain	764	1.6	741	1.6	391	0.8	546	1.2	595	1.3
Sweden	1 084	10.7	916	9.0	672	6.5	675	6.5	762	7.3
United Kingdom (UK)	1 490	2.2	851	1.3	NA	NA	NA	NA	NA	NA
Total EU/EEA	**10 136**	**3.1**	**8 861**	**2.7**	**5 291**	**2.0**	**5029**	**1.9**	**7 842**	**2.9**

Case definition remains challenging, with the majority of cases being reported as "unknown" by the countries.
NA: Not applicable. ND: no data reported. NR: no rate calculated.
Adapted from ECDC Surveillance Atlas of Infectious Diseases [27].

Figure 3. Notification rates of hepatitis C (overall) per 100 000 population by year in EU/EEA countries reporting consistently, 2013–2022



Countries that reported only acute cases were excluded.
Sources: country reports from Austria, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, Luxembourg, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, and Sweden.
From ECDC Annual Epidemiological Report (AER) 2022 [3].

SoHO donors

Data reported by countries on positive findings in first-time blood donors (prevalence of HCV infections) and positive findings in repeat donors (incidence of HCV infections), and published by the European Directorate for the Quality of Medicines & HealthCare of the Council of Europe (EDQM) [30] is presented in Table 5. The overall prevalence of anti-HCV in first-time blood donors, among the countries with consistent data reporting from 2017 to 2019, showed year-to-year fluctuations with no clear trend: 974.4 per 100 000 donors in 2017, decreasing to 887.1 in 2018 and an increase to 950.2 per 100 000 donors in 2019. The interpretation of these data should consider that the definition of positive donors can vary across countries, depending on the screening strategy in each country (see test methods in use as reported to EDQM in 2021 in Table 11).

Table 5. Prevalence and incidence of HCV per 100 000 donors, per country, 2017-2019

Country	2017		2018		2019	
	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	39.4	3.8	53.9	2.5	48.4	1.5
Belgium	ND	ND	ND	ND	ND	ND
Bulgaria	184.1	265.7	116.3	124.9	NA	116.2
Croatia	0.0	0.0	0	0	8.5	1.1
Cyprus	ND	ND	ND	ND	200.6	4.7
Czechia	244.3	14.5	ND	ND	ND	ND
Denmark	ND	ND	ND	ND	6.4	0.5
Estonia	354.3	22.5	353.1	11.4	387.9	7.6
Finland	26.8	0.0	19.5	0.9	48.6	0.9
France	ND	ND	ND	ND	ND	ND
Germany	49.4	1.7	41.7	2.1	40.5	1.8
Greece	96.6	8.8	98.9	10.2	104.2	10.8
Hungary	109.3	5.2	109.9	5.2	0	0
Iceland	ND	ND	ND	ND	ND	ND
Ireland	8.0	0.0	15	0	99.7	7.7
Italy	75.2	1.5	55.5	1.4	55.7	1.2
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	6.7	0.0	27.1	0	ND	ND
Norway	10.5	1.0	9.7	1.1	10.7	0
Poland	119.7	4.1	105.6	5.2	94	2.6
Portugal	85.2	0.5	24.3	1.7	52	1.1
Romania	ND	ND	217.8	2.7	ND	ND
Slovakia	14.8	2.7	ND	ND	ND	ND
Slovenia	10.5	0.0	ND	ND	0	0
Spain	ND	ND	ND	ND	ND	ND
Sweden	28.5	1.1	ND	ND	23.5	0.6

NA: not applicable. ND: no data reported.
Adapted from table 7.2 from the 2017, 2018 and 2019 EDQM reports [30].

Risk factors and modes of transmission

In 2022, in the EU/EEA, 45% of acute hepatitis C and 44% of chronic hepatitis C cases reported in the European Surveillance System (TESSy) had data available for documented transmission modes. The most frequent modes of transmission are described in Table 6. For both acute and chronic hepatitis C, the most reported mode of transmission was injecting drug use (53% and 64%, respectively), followed by nosocomial transmission for acute cases and transmission through blood and blood products for chronic cases. Despite the limitations in the interpretation of routine surveillance data, this assessment is essential to raise awareness of the ongoing different ways of transmission in the EU/EEA (mostly from acute cases), as well as key groups capable of transmission (both acute and chronic cases).

Vertical transmission of HCV is uncommon. Overall estimates of vertical transmission of HCV are inferior to 5%, and they go close to 0% if maternal HCV viral load is negative. HIV-HCV coinfection in the mother is estimated to nearly double the risk of vertical transmission (mother-to-child transmission) of HCV in relation to maternal HCV and HIV viral loads [31,32].

Like HIV and HBV, although less effective, the sexual transmission of HCV is associated with disruption of mucosal integrity with exposure to infected body fluids, which could arise through mucosal traumatic sexual practices. High-risk sexual practices more common among men who have sex with men (MSM), such as increased numbers of sexual partners, group sex, and unprotected anal sex, are associated with a higher risk of HCV infection [33]. MSM show higher seroprevalence of HCV infection than the general population, especially those living with HIV (seroprevalence up to 25% in some series) [34,35].

Tattooing and piercing have also been associated with a higher risk of HCV transmission in both EU/EEA and non-EU/EEA countries [36,37], especially in unregulated settings where practices such as the reuse of non-disposable needles, inadequate sterilisation of equipment, or use of ink contaminated with infected blood can occur [38].

People living with HIV (PLHIV) and people in prison, often populations with multiple risk factors for HCV, including needle-sharing in the context of intravenous drug use, tattooing with non-sterilised material and unprotected sexual relationships, are at increased risk of infection [34,35].

Population groups reported as being at risk of iatrogenic exposure to HCV include haemodialysis recipients, recipients of SoHO and people who had medical and dental procedures, especially in the 1990s and early 2000s, and patients with diabetes, even though the number of studies is limited and conducted in populations with overlapping risks. Healthcare workers, especially those performing exposure-prone procedures such as contact with sharp instruments or needle tips, are also at risk of occupational transmission [39]. A recent systematic review of healthcare-associated hepatitis infections reported in the medical literature between 2006 and 2021 in the EU/EEA reported 48 outbreaks related to hepatitis C mostly associated with breaches in standard infection prevention and control measures with no specifications (n=16), transfusions of blood and blood products (n=6), multi-dose vial contamination (n=4), haemodialysis machines (n=3), contrast media injector (n=3) and organ donors (n=1). The most common settings for HCV-related events were dialysis units (n=15), followed by inpatient wards (n=7), haematology/oncology units (n=6) and CT/MRI scanning units (n=6). Italy (n=12), Spain (n=8) and Poland (n=7) were the countries with the highest number of events [40].

Increasing implementation of infection prevention and control measures and screening protocols for HCV in SoHO has contributed to a decrease in the risk. However, healthcare-associated transmission is still reported, as seen in Table 6.

Table 6. Transmission category of hepatitis C cases by acute and chronic disease status, EU/EEA, 2022

Transmission mode	Acute hepatitis C (% of cases with available data)	Chronic hepatitis C (% of cases with available data)
Injecting drug use	53	64
Sex between men	8	1
Nosocomial*	17	6
Heterosexual transmission	6	4
Non-occupational injuries**	5	7
Blood and blood products	3	9
Sexual transmission (not specified)	1	2
Vertical/mother-to-child transmission	0	1
Other	1	4
Needle-stick and other occupational exposure	2	1

Adapted from ECDC AER 2022 [unpublished data].
**: 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 needlesticks that occur outside a healthcare setting, bites, tattoos and piercings.*

Other relevant topics

HCV reinfections

HCV reinfection can occur after spontaneous or treatment-induced clearance of the virus when re-exposure to HCV has occurred in individuals with ongoing risk factors. Reinfection should be suspected in case of reappearance of detectable HCV RNA or HCV core antigen after an SVR and confirmed by the demonstration that infection is caused by a different genotype or, using sequencing and phylogenetic analysis, by a distantly related strain of the same genotype from the initial infection [6]. An anti-HCV antibody test is not helpful in establishing if there is a reinfection because anti-HCV antibodies persist after viral clearance (spontaneous or treatment-induced).

Estimates of posttreatment HCV reinfection have been assessed in different populations [41,42]. In a cohort of patients who have been recently treated for HCV infection, the reinfection incidence rate was 14.2 per 100 person-years (PY). In this study, reinfection was associated with injectable drug use, unprotected anal sex with casual partners, and geographic region [43]. A study from the UK reports an overall reinfection rate of 7.91 per 100 PYs (95% confidence interval [CI] 7.37-8.49), with the highest rates among current PWID (22.55 per 100 PYs, 95% CI 19.98– 25.46) and people who had been in prison (20.42 per 100 PYs, 95% CI 17.21– 24.24). The median time to reinfection in this cohort was nine months [44]. A lower overall estimate of HCV reinfection rate – 4.13 per 100 PYs (95% CI: 3.45– 4.81) – was reported in a recent meta-analysis, with the highest reinfection incidence being reported among MSM (7.37 per 100 PYs (95% CI: 5.09– 9.65)) [45].

Regarding the comparison of reinfection rates between different treatment strategies, different results have been reported. HCV reinfection rates following interferon-based and direct-acting antiviral therapy are described as comparable [41,42].

HCV infection relapse

The general risk of recurrence of HCV infection in patients who completed the treatment for HCV infection and achieved SVR is <0.5% and is related to either reinfection or late relapse [46].

Reinfection is primarily described in high-risk populations and can be differentiated from a late relapse by genotype identification or sequencing [47,48]. Based on available data stratified by risk group, higher estimates of a 5-year recurrence risk period post-SVR are described for high-risk populations and are mainly driven by reinfection rather than late relapse [49].

HCV infection relapse should be considered when HCV RNA is detected during follow-up after negative HCV NAT results at the end of treatment and prior to SVR. Genetic sequencing techniques, like next-generation sequencing (NGS), can be useful in identifying relapses (even late relapses), with the identification of a similar viral strain during follow-up suggesting a relapse [49,50].

Resistance-associated substitutions (RASs) can be identified in the DAA-target genes in the HCV genome of individuals who fail SVR and relapse after DAA treatment [51]. They can be present at baseline or emerge due to the treatment, contributing to the persistence of HCV-resistant strains and relapse of the infection [52].

A comprehensive analysis of the risk of HCV recurrence, including interventional and observational studies [53] identified 16 studies with low-risk populations (with no recognised risk factors for reinfection) and 19 studies with high-risk populations (at least one identified risk factor for reinfection). Among the 16 017 low-risk patients, 36 late relapses (0.2%) were identified. Among the 7 932 high-risk patients, no late relapse was identified: all recurrences reported in this population were reinfections.

Further real-world data on the relapse of HCV infection after the end of treatment are summarised in Table 7. Considering the widespread use of DAA in the last few years, only studies reporting data from patients treated with interferon-free DAA regimens were included. Studies assessing only patients with HIV/HCV co-infection were not included. Among the 19 studies identified, relapse rates ranged from 0.2% to 8.0% with a median value of 2.5%.

Table 7. Relapse of chronic hepatitis C after treatment with direct antiviral agents, summary of published studies

Author, Year	Country	Study type	Population (n of patients who completed DAA treatment)	Relapse (%) (n)	Time to relapse (post-end of treatment, in weeks)	NS5A/NS5B RASs identified in patients with relapse (Yes/No/NR)
Akiyama, 2020 [54]	US	Prospective study	Chronic hepatitis C (n=150)	4.7 (7)	12 (n=6) 24 (n=1)	Yes
Bachofner, 2018 [55]	Switzerland	Retrospective multicentre study	Chronic hepatitis C (n=565)	5.7 (32)	4-12	Yes
Berg, 2019 [56]	Germany	Prospective multicentre study	Chronic hepatitis C (n=537)	mITT: 0.2 (1)	12	NR
Chiu, 2020 [57]	Taiwan	Retrospective multicentre study	Chronic hepatitis C, mixed GTs – two to three, from 1a, 1b, 2, 3 and 6 (n=116)	1.7 (2)	12	NR
D'Ambrosio, 2018 [58]	Italy	Retrospective multicentre study	Chronic hepatitis C (n=723)	0.7 (5)	4 (n=1) 12 (n=4)	Yes
Fernández Carrillo, 2017 [59]	Spain	Retrospective multicentre study	Advanced liver disease due to chronic hepatitis C (n=843)	mITT: 6.7 (45/673)	12	NR
Halfon, 2018 [60]	France	Retrospective multicentre study	Chronic hepatitis C (n=2995)	2.7 (80)	NR	Yes
Hill, 2023 [61]	US	Retrospective multicentre study	Chronic hepatitis C GT1a with baseline NS5A RASs (n=93)	1.2 (8)	12	Yes
Lashen, 2019 [62]	Egypt	Retrospective study	Chronic hepatitis C GT4 (n=648)	0.3 (2)	12	NR
Lin, 2021 [63]	Taiwan	Prospective multicentre study	Chronic hepatitis C (n=1080)	1.0 (11)	4 (n=7) 12 (n=3) 24 (n=1)	NR
Ogawa, 2017 [64]	Japan	Prospective multicentre study	Chronic hepatitis C (n=772)	1.2 (9)	4 (n=8) 12 (n=1)	Yes
Osawa, 2019 [65]	Japan	Prospective multicentre study	Chronic hepatitis C with previous DAA failure (n=30)	6.7 (2)	4	Yes
Papaluca, 2019 [66]	Australia	Prospective multicentre study	Chronic hepatitis C with previous DAA failure (n=40)	2.5 (1)	12	Yes
Sanai, 2018 [67]	Saudi Arabia	Prospective multicentre study	Chronic hepatitis C GT4, including patients with cirrhosis (n=213)	5.2 (11)	12	NR

Author, Year	Country	Study type	Population (n of patients who completed DAA treatment)	Relapse (%) (n)	Time to relapse (post-end of treatment, in weeks)	NS5A/NS5B RASs identified in patients with relapse (Yes/No/NR)
Trabut, 2018 [68]	France	Retrospective multicentre study	Chronic hepatitis C in PWID (n=50)	6 (3) (all non-active PWID)	<12	NR
Visco-Comandini, 2018 [69]	Italy	Retrospective study	Chronic hepatitis C, including patients with cirrhosis (n=337)	4.7 (16)	4 (n=14) 4-12 (n=2)	NR
von Felden, 2017 [70]	Germany	Prospective multicentre study	Chronic hepatitis C GT3, including patients with cirrhosis (n=293)	mITT: 0.4 (1/222)	4	NR
Wedemeyer, 2017 [71]	Global	Meta-analysis	Chronic hepatitis C GT1 or 4, including cirrhotic patients (n=5158)	GT1: 1.3 (45/3524) GT4: NR	NR	NR
Willemse, 2016 [72]	The Netherlands	Retrospective multicentre study	Chronic hepatitis C GT4 with advanced liver disease or cirrhosis (n=53)	8 (4)	12	NR

DAA: direct-acting antiviral agent; GT: genotype; HCV: hepatitis C virus; mITT: modified intention-to-treat; NR: not reported; PWID: people who inject drugs; RAS: resistance-associated substitutions; US: United States.

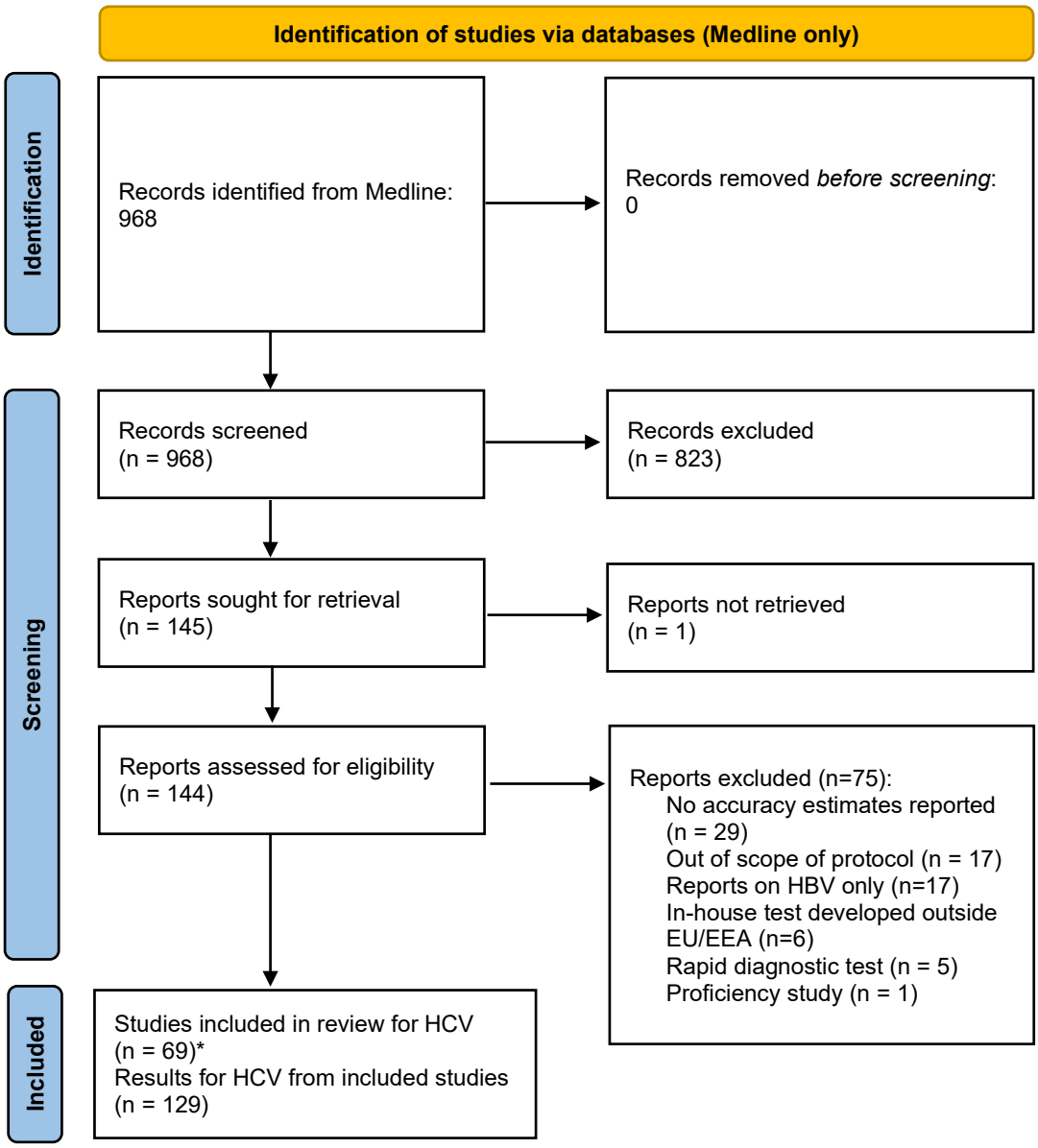
4 Laboratory testing approaches

Search results

This section aims to present the performance characteristics of laboratory tests that are approved and potentially used to screen for HCV in SoHO donors (living and deceased). The results summarised in this section 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 the screening of SoHO donors. This included in-house (i.e. non-commercial) tests, if they were used in EU/EEA countries. 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.

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



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

Summary of data

Living donors

The sensitivity and specificity of available test methods in the context of screening of SoHO donors are summarised by test category in Table 8. The reported sensitivity of screening tests was highest for NAT detecting HCV RNA. No specific differences were found for specific genotypes. These tests are considered, in the diagnostic setting, to have a very low probability of false negatives due to highly conserved regions of the virus, such as the 5'UTR (untranslated region) of the virus [6].

Deceased donors

Six studies evaluating laboratory test methods for the detection of HCV on post-mortem blood samples were identified in the search [73-78], of which four studies evaluated chemiluminescent immunoassays (CLIA) for the detection of anti-HCV and three studies evaluated NAT for the detection of HCV RNA.

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 from 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 HCV RNA 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 [75].

Table 8. Summary of 63 studies on available methods for hepatitis C virus (HCV) laboratory testing in samples from living donors [79-141]

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								
Ab HCV (6)	99.4% - 100.0%	100.0%	99.9%	NR	NA	NA	98.7% - 99.9%	
n reports	5			0			8	
HCVAg (5)	73.8% - 97.4%	94.6%	91.9%	NR	NA	NA	99.6% - 99.7%	
n reports	6			0			2	
Ag-Ab combination (6)	30.0% - 99.4%	70.0%	67.7%	NR	NA	NA	91.4% - 99.8%	10-day delay compared to HCV RNA
n reports	6			0			4	
CLIA								
Ab HCV (15)	85.2% - 100.0%	100.0%	97.3%	NR	NA	NA	99.6% - 100.0%	25-day delay compared to HCV RNA
n reports	14			0			31	
HCVAg (2)	NR	NA	NA	NR	NA	NA	99.9% - 100.0%	Mean reduction of 36 days compared to anti-HCV 2-day delay compared to HCV RNA
n reports	0			0			2	
Ag-Ab combination (1)	99.6%	NA	NA	NR	NA	NA	99.9%	
n reports	1			0			1	
HCV RNA NAT								
Overall (35)	98.1% - 100.0%	99.6%	99.4%	2.0 - 389.1	11.0	35.9	99.5% - 100.0%	
n reports	10			50			10	
ID (32)	99.0% - 100.0%	99.7%	99.7%	2.0 - 188.9	11.0	188.9	100.0% - 100.0%	Estimated iWP approx. 2-3 days HCV RNA detected 25-31 days before anti-HCV
n reports	7			44				

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
MP6 - MP16 (7)	98.1% - 99.6%	99.0%	98.9%	4.6 - 148.0	76.3	76.3	99.5% - 100.0%	
n reports	3			2			2	
Pool >16 (5)	NR	NA	NA	43.0 - 389.0	76.0	146.0	100.0% - 100.0%	
n reports	0			4			4	

Note: all analytic sensitivity values in copies/mL have been converted to IU/mL based on the conversion 1 IU = 2.73 copies.
Ag: antigen. Ab: antibody. CLIA: chemiluminescent immunoassay (includes chemiluminescent microparticle immunoassays [CMIA] and electrochemiluminescence immunoassays [ECLIA]). EIA: Enzyme immunoassay (includes enzyme-linked immunosorbent assays [ELISA]). ID: individual donations. iWP: infectious window period.MP: minipool. NAT: nucleic acid tests. NA: not applicable. NR: not reported.

Residual risk of HCV

The residual risk (RR) of HCV 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 [21]. The undetected infected donation can 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. The non-detection of HCV can be caused by test failures or donors being in the diagnostic window period. For current modern test methods, the contribution of assay failures to the residual risk is considered negligible and is usually not considered in the residual risk. Table 9 presents the RR per million blood donations according to different incidence rates and for different test methods. It should be noted that these calculations do not take into account testing strategies using more than one test method in parallel.

Residual risks calculated in various studies conducted in EU countries are presented in Table 10. These RRs are provided as illustrations for different test methods and are not meant to provide a comprehensive overview of the residual risk of HCV transmission in the EU/EEA. The calculation methods differ across studies, and comparisons of residual risks between countries should be interpreted cautiously.

Table 9. Residual risk (RR) of hepatitis C virus (HCV) transmission per million blood donations, by test method and incidence rate (in repeat donors and *first-time donors*)

Incidence rate per 100 000	ID NAT	MP-16 NAT	HCVAg EIA/CLIA	Ag-Ab combination EIA/CLIA	Anti-HCV EIA/CLIA
1	0.14	0.19	0.25	1.04	1.64
	0.41	*0.57*	*0.74*	*3.12*	*4.93*
5	0.68	0.96	1.23	5.20	8.21
	2.05	*2.87*	*3.70*	*15.61*	*24.64*
10	1.37	1.92	2.46	10.40	16.43
	4.11	*5.75*	*7.39*	*31.21*	*49.28*
30	4.11	5.75	7.39	31.21	49.28
	8.21	*11.50*	*14.78*	*93.63*	*147.84*
50	6.84	9.58	12.32	52.02	82.14
	12.32	*17.25*	*22.18*	*156.06*	*246.41*
70	9.58	13.42	17.25	72.83	114.99
	16.43	*23.00*	*29.57*	*218.48*	*344.97*
90	12.32	17.25	22.18	93.63	147.84
	20.53	*28.75*	*36.96*	*280.90*	*443.53*
100	13.69	19.16	24.64	104.04	164.27
	24.64	*34.50*	*44.35*	*312.11*	*492.81*
110	15.06	21.08	27.10	114.44	180.70
	28.75	*40.25*	*51.75*	*343.33*	*542.09*
120	16.43	23.00	29.57	124.85	197.13
	32.85	*46.00*	*59.14*	*374.54*	*591.38*

Ab: antibody. Ag: antigen. EIA/CLIA: enzyme immunoassay/chemiluminescent immunoassay. HCV: hepatitis C virus. HCVAg: hepatitis C antigen. ID-NAT: individual nucleic acid testing. MP-16 NAT: minipool nucleic acid testing of 16 donations.
RR was calculated as the product of the window period and the incidence rate. A first-time donor incidence adjustment factor of 3 was used.
The values for window periods were taken from the WHO guidelines on the estimation of residual risk using the values for the three-fold concentration of the 95% detection probability [21].

Table 10. Examples of residual risks (RR) of hepatitis C 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 [142]	Italy	1999–2001	Anti-HCV	70	Whole blood	9.26	16.74
do Barrio, 2005 [143]	Spain (7 centres)	2000–2002	MP-NAT and anti-HCV	38-94 (range)	Whole blood	2.18	3.94
Offergeld, 2005 [144]	Germany	2001–2002	MP-NAT and anti-HCV Anti-HCV	10 66	Whole blood	0.83	0.23 1.50
Pillonel, 2005 [145]	France	2001–2003	MP-NAT and anti-HCV	10	Whole blood	0.35	0.10
Hourfar, 2008 [146]	Germany	1997–2005	MP-NAT and anti-HCV	6.3	Whole blood	0.53	0.09
López-Menchero, 2019 [147]	Spain (Valencia)	2003–2006	MP-NAT and anti-HCV	5	Whole blood	3.00 - 9.65*	0.37 - 1.18*
Koch, 2013 [148]	Portugal (1 centre)	2007–2010	MP-NAT and anti-HCV	5	Whole blood	1.98	0.30
Grubyte, 2011 [149]	Lithuania	2004–2012	Anti-HCV	60	Whole blood	147.6 - 2310.2*	242.7 - 3797.6*
an der Heiden, 2014 [150]	Germany	2006–2012	MP-NAT and anti-HCV	8	Whole blood	0.72	0.35
Stanic, 2017 [151]	Croatia	2013–2016	ID-NAT and anti-HCV	3	Whole blood	NR	0.07
López-Menchero, 2019 [147]	Spain (Valencia)	2006–2017	ID-NAT and anti-HCV	3	Whole blood	1.37 - 8.33*	0.10 - 0.63*
Grubyte, 2011 [149]	Lithuania	2012–2018	ID-NAT and anti-HCV	3	Whole blood	31.7 - 362.2*	2.6 - 29.8*
Velati, 2018 [152]	Italy	2009–2015	ID-NAT and anti-HCV	Method 1[a]: 4.7 Method 2[b]: 8 Method 3[c]: 5	Whole blood	Incidence: 2.3 Prevalence: 85.7	Method 1[a]: 0.077 Method 2[b]: 0.034 Method 3[c]: 0.021
Himmelsbach, 2022 [153]	Germany	2019	ID MP16-NAT MP96-NAT	5 7 NR	Whole blood	NR	0.15 0.25 0.35

Author, year	Country	Period	Test method	Window period (days)	Type of donation	Incidence rate per 100 000 donations	Residual risk per million donations
Bruhn, 2015 [154]	Europe	2005–2011	ID-NAT and anti-HCV ID-NAT MP8-NAT and anti-HCV MP16-NAT and anti-HCV HCV-Ag and anti-HCV Anti-HCV	1.9 1.9 3.3 3.7 40.5 64.5	Whole blood	Incidence: 1.3 Prevalence: 33.2	0.10 0.11 0.18 0.21 1.94 3.61
Van De Laar, 2006 [155]	Netherlands	2000–2002	MP-NAT	10	Whole blood	Incidence: 0.12 Prevalence: 18.4	0.03

HCV: hepatitis C virus. ID-NAT: individual donation nucleic acid test. MP-NAT: minipool nucleic acid test.
a. RR estimated according to Busch, 2005 [156]. b. RR estimated according to EMA, 2016 [157]. RR estimated according to WHO [21].
** Range over the study period.*

5 Current testing requirements in EU/EEA countries

Testing requirements for blood donation

Testing practices for blood donation screening are described in Table 11. 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 11. Reported testing practices for HCV in the EU/EEA by country: blood donations, 2021

Country	Anti-HCV	HCVAg	HCV NAT	Comments
Austria	Yes	Yes	Yes	
Belgium	Yes	No	Yes	
Bulgaria	Yes	Yes	Yes	
Croatia	Yes	No	Yes	
Cyprus	Yes	No	Yes	
Czechia	Yes	No	No	NAT and HCVAg are not mandatory, but are done in some establishments.
Denmark	Yes	No	Yes	
Estonia	Yes	No	Yes	
Finland	Yes	No	Yes	
France	Yes	No	Yes	
Germany	Yes	No	Yes	
Greece	Yes	NR	Yes	
Hungary	Yes	No	No	
Iceland	Yes	No	No	
Ireland	Yes	No	Yes	
Italy	Yes	No	Yes	
Latvia	Yes	No	Yes	
Lithuania	Yes	No	Yes	
Luxembourg	Yes	Yes	Yes	
Malta	Yes	No	Yes	
Netherlands	Yes	No	Yes	HBV-HCV-HIV NAT routinely performed as a multiplex in minipools of 6 donations.
Norway	Yes	No	No	
Poland	Yes	No	Yes	HCV core antigen is recommended.
Portugal*	Yes	No	Yes	
Romania	Yes	Yes	Yes	Use of antibody-antigen combination tests.
Slovakia	Yes	No	No	NAT is not mandatory but is performed in most establishments.
Slovenia	Yes	No	Yes	
Spain	Yes	No	Yes	
Sweden	Yes	No	No	

Ag: antigen. HBV: hepatitis B virus. HCV: hepatitis C virus. HCVAg: hepatitis C virus antigen. HIV: human immunodeficiency virus. NAT: nucleic acid test.
**Data amended after the initial draft of the guidelines on the prevention of transmission of HCV through SoHO.*
From EDQM [158].

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 12).

Table 12. Testing requirements for HCV in the EU/EEA by country: tissues and non-reproductive cells (2015)

Country	Testing requirement declared*	Tissue / cell type	Donor type	Comment
Austria	• Anti-HCV • HCV NAT	All	Living and deceased	NAT is mandatory if no re-testing is performed
Belgium	• Anti-HCV • HCV 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	• Anti-HCV • Recommended: HCV NAT	All	HCV NAT for living donors	
Croatia	• Anti-HCV • HCV NAT	All	Living and deceased	
Cyprus	• Anti-HCV • HCV 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	• Anti-HCV	All	Living and deceased	
Denmark	• Anti-HCV • Recommended: HCV NAT	All	HCV NAT for deceased donors	
Estonia	• Anti-HCV • HCV 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 HCV NAT.
Finland	• Anti-HCV • HCV NAT	All	Living and deceased	All deceased donors need to be tested by serological **AND** NAT tests for HIV, HBV and HCV. All living donors (allogeneic grafts) need to be tested by serological AND NAT tests (if no quarantine is applied) or 180-day-test (when quarantine is applied).
France	• Anti-HCV • HCV NAT	All	Living and deceased	
Germany	• Anti-HCV • Recommended: HCV NAT	All Except for skin, for HCV NAT.	Living and deceased	

Country	Testing requirement declared*	Tissue / cell type	Donor type	Comment
Greece	• Anti-HCV • Recommended: HCV NAT	All	Living and deceased	NAT performed if requested by the transplant centre.
Hungary	• Anti-HCV	All	Living and deceased	NAT testing can be done, but it is not compulsory.
Ireland	• Anti-HCV	All	Living and deceased	
Italy	• Anti-HCV • HCV NAT	All	Living and deceased	HCV NAT is used in living tissue donors if serology is not repeated after 180 days
Latvia	• Anti-HCV	All	Living and deceased	
Lithuania	• Anti-HCV • HCV NAT	All	HCV NAT for deceased donors	
Luxembourg	• Anti-HCV	All	Living and deceased	
Malta	• Anti-HCV	All	Living and deceased	
Netherlands	• Anti-HCV	All	Living and deceased	
Norway	• Anti-HCV	All	Living and deceased	
Poland	• Anti-HCV	All	Living and deceased	
Portugal	• Anti-HCV • HCV NAT	All	Living and deceased	
Romania	• Anti-HCV	All	Living and deceased	
Slovakia	• Anti-HCV • HCV NAT	All	Living and deceased	

Country	Testing requirement declared*	Tissue / cell type	Donor type	Comment
Slovenia	• Anti-HCV • HCV NAT	All	HCV 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	• Anti-HCV • HCV NAT	All	HCV NAT recommended for stem-cell donors	
Sweden	• Anti-HCV • Recommended: HCV NAT	HCV NAT: bone, tendons	Living and deceased	

** Minimum mandatory requirement for tissues and cells is anti-HCV as per directive 2004/23/EC. HCV 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.*
NAT: nucleic acid test. HCV: hepatitis C virus.
Tests are reported as legally binding unless specified otherwise.
From European Commission [159].

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 13).

Table 13. Testing requirements for HCV in the EU/EEA by country: reproductive cells (2015)

Country	Testing requirement declared*	Donation type	Comment
Austria	• Anti-HCV • HCV NAT	HCV NAT: all non-partner donation	
Belgium	• Anti-HCV • HCV NAT	HCV NAT: all non-partner donation	NAT tests are mandatory unless the processing includes an inactivation step validated for the viruses concerned.
Bulgaria	• Anti-HCV • Recommended: HCV NAT	HCV 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 embryos. Sperm is usually quarantined for 180 days and donors are retested after this period.
Croatia	• Anti-HCV	All	
Cyprus	• Anti-HCV • HCV NAT	All	NAT testing is required if tissues or cells will be issued without retesting of donors after 180 days of collection.
Czechia	• Anti-HCV	All	
Denmark	• Anti-HCV • HCV NAT	All	HCV NAT is mandatory for oocyte donors. NAT testing is required if non-partner donors are not retested after 180 days.**
Estonia	• Anti-HCV • HCV NAT	All	NAT testing is required if non-partner donors are not retested after 180 days.
Finland	• Anti-HCV • HCV NAT	HCV NAT: sperm in non-partner donation	NAT or 180-day retesting.
France	• Anti-HCV	All	In non-partner sperm donation, NAT testing for HIV, HBV and HCV at the last collection is possible to avoid the 180 days of quarantine (after 2015).
Germany***	• Anti-HCV	All	
Greece	• Anti-HCV	All	180-day retesting from the time of donation for all sperm donors, excluding partners.
Hungary	• Anti-HCV	All	
Ireland	• Anti-HCV	All	
Italy	• Anti-HCV • HCV NAT	All	
Latvia	• Anti-HCV	All	
Lithuania	• Anti-HCV	All	

Country	Testing requirement declared*	Donation type	Comment
Luxembourg	• Anti-HCV	All	
Malta	• Anti-HCV	All	
The Netherlands	• Anti-HCV	All	
Norway	• Anti-HCV	All	
Poland	• Anti-HCV	All	
Portugal	• Anti-HCV	All	NAT testing is required if non-partner donors are not retested after 180 days.
Romania	• Anti-HCV	All	
Slovakia	• Anti-HCV	All	
Slovenia	• Anti-HCV	HCV NAT: mandatory for oocyte donors	HCV NAT testing allows for the release of sperm without repeat testing 180 days after donation.
Spain	• Anti-HCV • HCV NAT	HCV NAT: mandatory for sperm donors	HCV NAT testing allows for the release of sperm without repeat testing 180 days after donation.
Sweden	• Anti-HCV	All	Non-partner sperm donors should be quarantined for 180 days and then retested.

HCV: hepatitis C virus. 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-HCV 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.*
****Data amended after the initial draft of the guidelines on the prevention of transmission of HCV through SoHO.*
Tests are reported as legally binding unless specified otherwise.
From the European Commission [159].

6 Recommendations from other organisations

Recommendations for blood

Table 14. Recommendations from selected organisations for HCV testing of blood donations

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
EU Commission [160-162] Directive 2002/98/EC Directive 2004/33/EC, Annex III Regulation (EU) 2017/746	Minimum requirements: anti-HCV. 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, in order 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. Individuals at risk of acquiring a transfusion-transmissible infection, namely those exposed to: Endoscopic examination using flexible instruments; Mucosal splash with blood or needlestick injury; Transfusion of blood components; Tissue or cell transplant of human origin; Major surgery; Tattoo or body piercing; Acupuncture, unless performed by a qualified practitioner and with sterile single-use needles, shall be deferred for six months or for four months provided a NAT test for HCV is negative.	Individuals infected with hepatitis C must be deferred permanently.
European Directorate for the Quality of Medicines & HealthCare (EDQM) [163] The Guide to the preparation, use and quality assurance of blood components, 21st edition	Minimum requirements: antibody to hepatitis C virus (anti-HCV). Recommended: The application of NAT techniques shortens the window period compared with serological testing and therefore has a positive impact on blood safety.	All blood donors should be provided with information about behaviours associated with an increased risk of blood-borne infectious agents, such as HIV and hepatitis transmission, and be given the opportunity for self-exclusion so that those persons refrain from donating. 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.	Individuals infected with HCV or history thereof must be deferred permanently.

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
US Food and Drug Administration (FDA) [164,165] Nucleic Acid Testing (NAT) for Human Immunodeficiency Virus Type 1 (HIV-1) and Hepatitis C Virus (HCV): Testing, Product Disposition, and Donor Deferral and Reentry Recommendations for Evaluating Donor Eligibility Using Individual Risk-Based Questions to Reduce the Risk of Human Immunodeficiency Virus Transmission by Blood and Blood Products	Minimum requirements: test of each donation intended for transfusion or for use in manufacturing a product, with an anti-HCV screening test. Recommended: Use of licensed HCV NAT on units that are non-reactive on donor-screening anti-HCV test.	Factors associated with an increased risk of a relevant transfusion- transmissible infection (TTI): - Behaviours associated with a relevant TTI; - Receipt of blood or blood components or other medical treatments and procedures associated with possible exposure to a relevant TTI; - Signs and/or symptoms of a relevant TTI; - Institutionalization for 72 hours or more consecutively in the past 12 months in a correctional institution; - Intimate contact with risk for a relevant TTI; - Nonsterile percutaneous inoculation; - Travel to, or residence in, an area endemic for a transfusion-transmitted infection, when such screening is necessary to assure the safety, purity, and potency of blood and blood components due to the risks presented by donor travel and the risk of transmission of that transfusion-transmitted infection by such donors; - Exposure or possible exposure to an accidentally or intentionally released disease or disease agent relating to a transfusion-transmitted infection, if you know or suspect that such a release has occurred;	In individuals with repeatedly reactive anti-HCV screening tests or a positive HCV NAT with negative anti-HCV, it is recommended to take a follow-up sample after a minimum period of 6 months from the original donation for testing by an HCV ID-NAT and two different, licensed anti-HCV screening tests. If the ID-NAT is non-reactive and both of the licensed anti-HCV tests are repeatedly reactive after a 6-month waiting period, we recommend that you defer the donor permanently.
Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) [166] Guidelines for the Blood Transfusion Services Donor Selection Guidelines	Minimum requirements: anti-HCV (mandatory) and HCV RNA (mandatory). RNA screening in pools of a maximum of 24 donations. The UK requirement for the minimum level of sensitivity for the performance of HCV RNA screening is 5000 IU/mL in an individual donation.	Individual risk criteria: Injectable drug use (active or past); Working as a sex worker; Chemsex activity; Number of sexual partners; Type of sexual contact (anal sex); Use of PrEP or PEP. Partner risk criteria: Hepatitis C carrier; Partner who has received money or drugs for sex. Injectable drug use (active or past, including	Donors whose blood samples are confirmed positive cannot normally be reinstated, even after successful treatment, as screening test reactivity will persist in serological assays, for example anti-HCV […].

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
		chemsex drugs).	
World Health Organization (WHO) [167]	Testing at the BE should be performed on fully automated platforms. Minimum testing should include [..] testing for transmissible infectious agents: serological screening for […] anti-hepatitis C virus.		It is strongly recommended that, where feasible, the following are considered: nucleic acid testing to further reduce the risk of transfusion-transmissible infections.

HCV: Hepatitis C virus. ID: individual donation. IU: International units. PrEP: pre-exposure prophylaxis. PEP: post-exposure prophylaxis. RNA: ribonucleic acid. TTI: transfusion-transmissible infection. UK: United Kingdom.

Recommendations for tissues and cells

Table 15. Recommendations from selected organisations for testing of tissues and cells donations

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
EU Commission [162,168] Directive 2006/17/EC Regulation (EU) 2017/746	Tissues and cells (except reproductive cells) Minimum requirements: anti-HCV Reproductive cells - partner donation Minimum requirements: anti-HCV. Reproductive cells – non-partner donation Minimum requirements: anti-HCV. 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.		Deceased donors: General criteria for exclusion: History, clinical evidence, or laboratory evidence of […] hepatitis C […]. Deceased child donors: Children aged less than 18 months born from mothers with […] hepatitis C […] 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) [169] Guide to the Quality and Safety of Tissues and Cells for Human Application, 5th edition	Minimum requirements: anti-HCV HCV RNA assay (LOD ≤50 IU/mL) is strongly recommended. Molecular assays from deceased donors should be performed in individual samples (see current legislation of each country), not in pooled samples. Reproductive cells Minimum requirements: Partner donation: anti-HCV Non-partner donation: anti-HCV. For the safe use of fresh oocytes, additional NAT testing at the time of donation is needed.	Behavioural risk factors: Injected drug use for non-medical reasons; Tattoos, ear piercings, body piercings and/or acupuncture in non-approved settings; New diagnosis or treatment for sexually transmitted diseases (STIs); Sexual contacts in exchange for money or drugs; Sexual behaviour associated with risk of acquiring STIs. Personal risk/exposure events: Persons from a high-risk region for endemic disease, as well as the risk of vertical transmission […]; Exposure to someone else's blood or other body fluids […] when that person was known to be infected with […] HCV; Sharing a residence with someone who has […] clinically active HCV;	Individuals infected with HCV 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 h 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. If tissues and cells of allogeneic living donors can be stored for long periods before use, repeat sampling and testing are required after 180 days, unless specific exemption criteria are met.

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
		Patients on regular haemodialysis; People who have been in a lockup, jail, prison or juvenile correctional facility for more than 72 consecutive hours should be carefully evaluated for the risk of high-risk behaviours. If a child donor is 18 months old or younger or has been breastfed in the 12 months before death, the birth mother should be evaluated for risks associated […] HCV […].	Reproductive cells Sperm donations must be quarantined for ≥ 180 days after the last collection, after which repeat testing is required. If, at each donation, serology testing is combined with NAT for […] HCV, quarantine is not necessary.
US Food and Drug Administration (FDA) [170] Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products	Minimum requirements: FDA-licensed screening test for anti-HCV and FDA-licensed screening NAT test for HCV, or combination NAT. If a donor is one month of age or younger, you must collect and test a specimen from the birth mother instead of the donor. The specimen for testing from the birth mother must be collected within seven days of donation by the infant.	Any potential donor who exhibits one or more of the following should be determined to be ineligible: Persons who have injected drugs for a non-medical reason in the preceding 5 years, including intravenous, intramuscular, or subcutaneous injections; Persons who have engaged in sex in exchange for money or drugs in the preceding 5 years; Persons who have had sex in the preceding 12 months with any person described above or with any person who has […] clinically active (symptomatic) hepatitis C infection; Persons who have been exposed in the preceding 12 months to known or suspected […] HCV-infected blood through percutaneous inoculation (e.g., needle stick) or through contact with an open wound, non-intact skin, or mucous membrane; Persons who have been in juvenile detention, lock up, jail or prison for more than 72 consecutive hours in the preceding 12 months; Persons who have undergone tattooing, ear piercing or body piercing in the preceding 12 months, in which sterile procedures were not used, e.g., contaminated instruments and/or ink were used, or shared instruments that had not been sterilized between uses were used.	Individuals with a positive anti-HCV test must be considered ineligible.
Human Tissue Authority [171] HTA Guide to Quality and Safety Assurance for Human Tissues and Cells for Patient	Minimum requirements: anti-HCV		If the original sample is additionally tested

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
Treatment			by NAT for HCV, a repeat sample need not be taken. Deceased donors General criteria for exclusion: History, clinical evidence, or laboratory evidence of […] hepatitis C […], transmission risk or evidence of risk factors for this infection. Deceased child donors: Children aged less than 18 months born from […] hepatitis C […], 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. Living donors: The same exclusion criteria must be applied as for deceased donors.
Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation Services Professional Advisory Committee (JPAC) [166] Guidelines for the Blood Transfusion Services Donor Selection Guidelines	<u>Tissues</u> Minimum requirements: anti-HCV (mandatory) Optional: HCVAg and/or HCV Ag/Ab, HCV RNA <u>Stem cells</u> Minimum requirements: anti-HCV (mandatory) and HCV RNA (mandatory). RNA screening in pools of a maximum of 24 donations. The UK requirement for the minimum level of sensitivity for the performance of HCV RNA screening is 5000 IU/mL in an individual donation.	<u>Tissue – Live Donors</u> Individual risk criteria: Injectable drug use (active or past); Exchange of sex for money or drugs; Chemsex drugs use/chemsex activity; Number of sexual partners; Type of sexual contact (anal sex); Use of PrEP or PEP. Partner risk criteria: Hepatitis C carrier Partner who has received money or drugs for sex. Injectable drug use (active or past, including chemsex drugs). Tissue – Deceased Donors Same as above.	For allogeneic donors the concluded result of HCV microbiological assays, must be negative for a tissue to be released from quarantine for issue. Living tissue donors' samples: Living tissue donors can be tested by either a single sample taken at the time of donation where testing includes a NAT for […] HCV, or by two samples including a post 180-day quarantine sample where additional NAT testing is not required. Where only a single sample is tested the 'donation sample' must be obtained at the time of donation or, if not possible, within 7 days post-donation.

Institution	Minimum requirements and recommended tests	Risk groups	Additional information
		Stem cells: Same as above. Deceased donors: Where the deceased donor is less than 18 months of age, or breast fed within the 12-month period prior to donation, the mother's risk for transmissible disease must also be evaluated.	<u>Deceased tissue donor samples:</u> An ante-mortem blood sample, up to 7 days preceding death, is always preferable to a post-mortem sample for testing. Where no ante-mortem sample is available, then a post-mortem sample can be used. Samples for testing must not be taken more than 24 hours post-mortem […]. For post-mortem samples, concluded test results other than negative for current infection will debar tissues from release unless a superior sample can be obtained (e.g., obtained ante-mortem or closer to the time of death), and this sample is tested, and negative results are obtained.
European Society of Human Reproduction and Embryology (ESHRE) [172]	Minimum requirements: anti-HCV Recommended: confirmatory testing with HCV NAT.		After advanced semen processing, PCR testing for HCV in sperm is not necessary.

Ab: antibody. Ag: antigen. HCV: hepatitis C virus. HCVAg: HCV antigen. LOD: limit of detection. NAT: nucleic acid test. PCR: polymerase chain reaction. PrEP: pre-exposure prophylaxis. PEP: post-exposure prophylaxis. STI: sexually transmitted infection. UK: United Kingdom.

7 Transmission through SoHO

Evidence of transmission of HCV through SoHOs

Reminder: absence of evidence is not evidence of absence.

Table 16. Evidence of transmission of HCV by type of SoHO

SoHO type	Evidence of transmission
Blood components: plasma	Yes [173]
Blood components: platelets	Yes [174]
Blood components: red blood cells	Yes [175]
Blood components: whole blood	Yes [176]
Cells: human stem/progenitor cells	Yes [177]
Cells: oocytes	None. Presence in follicular fluid [178]
Cells: sperm	None. Transmission is biologically plausible [179]
Tissues: bone	Yes [180]
Tissues: corneas	None. Presence in corneas [181-183]
Tissues: skin	None
Tissues: tendon or ligaments	Yes [184]

Reported transmission events of HCV infections through SoHO

Table 17. Number of SoHO-transmitted HCV infections (imputability 2 or 3*) and number of units transfused or distributed in the EU/EEA (2017 – 2022)

Year	SoHO	Number of transmitted HCV infections	Number of transmitted unspecified viral infections	Number of units transfused or distributed**
2022	Blood	1	0	12 653 949
	Tissues	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	1	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	0	0	531 352
	Reproductive cells	0	0	746 588
2017	Blood	1	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 HCV, 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 18.

Table 18. 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 [185].

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 HCV in SoHO. Duplicates were removed. No other exclusion criteria were applied, and results are summarised by SoHO type in Table 19.

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 HCV below detection limits of tests used. For blood components, amotosalen and UV-A, methylene-blue and light and PEN-110, were associated with reduction in the viral load of HCV below detection limits of tests used. Reports for riboflavin and UV-A or use of UV-C only indicated limited pathogen reduction for HCV with detectable viral load after application of the pathogen reduction method.

Three studies investigated transmission of HCV following sperm washing in the context of medically assisted reproduction for couples. Transmission of HCV to the serodiscordant partner was assessed in two studies and the transmission of HCV to the offspring was assessed in all three studies. No transmission event was reported across all studies.

The search methods are described in detail in Annex 1.

Summary of data

Table 19. Pathogen reduction methods for HCV by substance of human origin (SoHO) [186-205]

Author, year	Country	Publication type	SoHO type	Virus	Method	Pathogen load metric	Value	Comment
Moore, 2012	NA	Review	Bone	HCV (BVDV model)	Gamma irradiation (13 kGy)	Log reduction	4.6	Detected
Pruss, 2001	Germany	Study	Bone	HCV (BVDV model)	Gamma irradiation (35 kGy)	Log reduction	>5.5	
Pruss, 2003	Germany	Study	Bone	HCV (BVDV model)	Peracetic acid/ethanol	Log reduction	>4.1	
Pruss, 2001	Germany	Study	Bone	HCV (BVDV model)	Thermal treatment (82.5C, 15 min)	Log reduction	>5.5	
Moore, 2004	US	Study	Musculoskeletal grafts	HCV (BVDV model)	Terminal ethylene oxide	Viral titres	<10^0.5	No infectivity
Allain, 2005	NA	Review	Plasma	HCV	Amotosalen + UVA	Log reduction	>4.5	
Bryant, 2007	NA	Review	Plasma	HCV	Amotosalen + UVA	Log reduction	>4.5	
Lanteri, 2020	NA	Review	Plasma	HCV (BVDV model)	Amotosalen + UVA	Log reduction	>4.3	
Seghatchian, 2010	NA	Review	Plasma	HCV (BVDV model)	Methylene Blue + Light	Log reduction	>5.4	
Steinmann, 2012	Germany	Study	Plasma	HCV (BVDV model)	Methylene Blue + Light	Log reduction	>3.6	
Steinmann, 2012	Germany	Study	Plasma	HCV	Methylene Blue + Light	Log reduction	>3.8	
Keil, 2015	International	Study	Plasma	HCV	Riboflavin + UVB	Log reduction	>4.1	
Chou, 2015	Taiwan	Study	Plasma	HCV	Solvent/detergent (tri-n-butyl phosphate/Triton X-45)	Relative light units	0	Total loss of infectivity
Steinmann, 2012	Germany	Study	Plasma	HCV (BVDV model)	UV-C	Log reduction	2.7	Viral load above LoD

Author, year	Country	Publication type	SoHO type	Virus	Method	Pathogen load metric	Value	Comment
Steinmann, 2012	Germany	Study	Plasma	HCV	UV-C	Log reduction	>5.0	
Allain, 2005	NA	Review	Platelets	HCV	Amotosalen + UV-A	Log reduction	>4.5	
Irsch, 2011	NA	Review	Platelets	HCV	Amotosalen + UV-A	Log reduction	>4.5	
Irsch, 2011	NA	Review	Platelets	HCV (BVDV model)	Amotosalen + UV-A	Log reduction	>6.0	
Kwon, 2014	Korea	Study	Platelets	HCV (BVDV model)	Amotosalen + UV-A	Log reduction	>6.0	
Lanteri, 2020	NA	Review	Platelets	HCV	Amotosalen + UV-A	Log reduction	>4.5	
Lanteri, 2020	NA	Review	Platelets	HCV (BVDV model)	Amotosalen + UV-A	Log reduction	>4.1	
Lanteri, 2020	NA	Review	Platelets	HCV (BVDV model)	Amotosalen + UV-A	Log reduction	>6.5	
Corbin, 2002	NA	Review	Platelets	HCV (BVDV model)	Riboflavin + UVB	Log reduction	5.57	Viral load above LoD
Goodrich, 2006	NA	Review	Platelets	HCV (WNV model)	Riboflavin + UVB	Log reduction	5.1	Viral load above LoD
Kwon, 2014	Korea	Study	Platelets	HCV (BVDV model)	Riboflavin + UVB	Log reduction	1.8	Viral load above LoD
Ruane, 2004	US	Study	Platelets	HCV (WNV model)	Riboflavin + UVB	Log reduction	5.2	Viral load above LoD
Schlenke, 2014	NA	Review	Platelets	HCV	Riboflavin + UVB	Log reduction	>4.1	
Schlenke, 2014	NA	Review	Platelets	HCV	UV-C	Log reduction	>5.0	
Kleinman, 2015	NA	Review	RBC	HCV (BVDV model)	Amustaline + glutathione	Log reduction	>4.8	
Bryant, 2007	NA	Review	RBC	HCV (BVDV model)	PEN110	Log reduction	>5.0	

Author, year	Country	Publication type	SoHO type	Virus	Method	Pathogen load metric	Value	Comment
Bourlet, 2009	France	Study	Sperm	HCV	Sperm washing	HCV transmission to the offspring	0	No transmission reported (n=76)
Cassuto, 2002	France	Study	Sperm	HCV	Sperm washing	HCV transmission to the partner or the offspring	0	No transmission reported (n=5)
Savasi, 2013	Italy	Study	Sperm	HCV	Sperm washing	HCV transmission to the partner or the offspring	0	No transmission reported (n=35)
Moore, 2012	NA	Review	Tendons	HCV (BVDV model)	Gamma irradiation (13 kGy)	Log reduction	2.6	Detected

HCV: Hepatitis C Virus; BVDV: Bovine Viral Diarrhoea Virus; WNV: West Nile 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 C
- HCV surveillance and disease data

US Centers for Disease Control (CDC)

- CDC HCV 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 (DQM)

- 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.