



Global Clinical Data Platform

Severe acute hepatitis of unknown aetiology in children CASE REPORT FORM (CRF)

INTRODUCTION

Multiple countries are reporting severe acute cases of hepatitis of unknown aetiology in children, in several regions of the world. WHO has developed this clinical case report form (CRF) to support and facilitate reporting of anonymized, patient-level data of acute hepatitis of unknown aetiology. This form is intended to support standardized data collection in support of the following objectives:

- To understand the clinical characterization of disease, its natural history and severity.
- To understand risk factors for severe disease, including which children may be at highest risk of the disease and severe outcomes.
- To generate hypotheses about disease aetiology.
- To better characterize the scale of this public health threat to guide the public health response and the development of clinical management guidance including approaches to investigations and infection prevention and control interventions.

HOW TO REPORT

Any Member State or institution is encouraged to use this form to report anonymized clinical data on patients with severe acute hepatitis of unknown aetiology meeting the WHO working case definition (consistent with the European Centre for Disease Prevention and Control current case definition). The data can be shared and uploaded to the <u>WHO Global Clinical Platform</u>

Member States can also report cases of severe acute hepatitis through other surveillance mechanisms, e.g. IHR or the TESSy platform in the European Region.

WHO WORKING CASE DEFINITION (published 23 April 2022)

Confirmed: N/A at present.

Probable: A person presenting with an acute hepatitis (non-hepatitis A-E*) with serum transaminase > 500 IU/L aspartate transaminase (AST) or alanine aminotransaminase (ALT), who is aged 16 years and younger, since 1 October 2021

Epi-linked: A person presenting with an acute hepatitis (non-hepatitis A-E*) of any age who is a close contact of a probable case, since 1 October 2021.

* Cases of hepatitis with known aetiology such those due to specific infections, drug toxicity, metabolic inherited/genetic, autoimmune disease or acute on chronic hepatitis presentation should not be reported.



HOW TO USE THIS CASE REPORT FORM (CRF)

The CRF is designed to collect data obtained through examination, interview with parents/caregivers and review of clinic and hospital notes. Data may be collected prospectively or retrospectively. This CRF has two modules that capture different periods in the clinical course and hospital stay:

Module 1: Covering period from initial symptoms to hospital admission

 1a clinical inclusion criteria;
 1b demographics;
 1c date of onset of symptoms/signs;
 1d admission vital

 1e symptoms/signs on admission; signs;
 1f existing medical conditions;
 1g COVID-19 infection status;
 1h cOVID-19 vaccination status;
 1i childhood vaccination status;
 1j exposure to medications;
 1k other
 exposures

Module 2: To be completed at discharge from hospital or death 2a routine lab tests; 2b diagnostic tests; 2c pathologic liver tissue findings; 2d medications; 2e supportive care received; 2f outcomes

WHO encourages the use of the CRF to collect data on cases meeting the WHO case definition, even if the form cannot be fully completed.

CONSIDERATIONS TO GUIDE PRIORITY CLINICAL WORK-UP IN RESOURCE-LIMITED SETTINGS

WHO recognizes that it may not be feasible to collect every data element outlined in this CRF. Evaluation of a child with hepatitis of unknown aetiology can require extensive investigations, which may not be readily available in resource-limited settings. The following list outlines some of the known causes to consider in the clinical work-up and **should not be taken as exclusion criteria for reporting cases**.

Consider investigating for recognized causes of acute hepatitis in children other than hepatitis A-E:

See Module 1, section 1f (existing medical conditions) and sections 1j and 1k (exposure history) of the CRF.

- Autoimmune hepatitis (total IgG, anti-nuclear antibody [ANA], anti-smooth muscle antibody [ASMA], anti-liver kidney microsomal [LKM-1] antibody, anti-soluble liver antigen, anti-neutrophil cytoplasmic antibody [ANCA]). See Module 2, section 2b for a list of diagnostic tests for autoimmune disease.
- Metabolic liver diseases due to genetic/inherited disorders, e.g. Wilson's disease (serum caeruloplasmin and 24-hour urine for copper), Alpha -1 antitrypsin deficiency (alpha-1 antitrypsin level). Points in history that may raise suspicion (e.g. family history of metabolic disorder, unexplained infant deaths, miscarriages neurodevelopmental impairment and seizures).
- Medications/toxin ingestion (serum paracetamol level, urine screen for toxins/drugs).
- Chemotherapy-induced hepatitis with active malignancy.
- Other viral infections, e.g. herpes (HSV), Epstein-Barr virus (EBV), cytomegalovirus (CMV). See Module 2, section 2b for a list of diagnostic tests for investigating infectious and non-infectious aetiologies.

Laboratory testing

See Module 2, section 2b for a list of diagnostic tests that should be considered for investigating infectious and noninfectious aetiology.

The relevance and feasibility of these tests will vary by region and country capacity, and as investigations progress. The list includes but is not limited to viral infections (SARS-CoV-2, EBV, adenovirus, parvovirus, herpes simplex virus, HHV6 and 7, cytomegalovirus, enterovirus, rubella, paramyxoviruses), bacterial infections (salmonella species), as well as infections in certain regions only (malaria, dengue, leptospirosis, yellow fever).

Where there are laboratory capacity limitations, facilities should collect and store samples for future and/or referral testing.

WHO is developing interim guidance and establishing a network of regional and global referral labs to support Member States with laboratory testing (in progress).



MODULE 1. Complete on hospital admission (within 24 hrs from hospital admission)

Facility name			_ Sta	te/Region: _		Country				
	Patient transferred to this facility from another facility? □Yes □No □Unknown If yes, name the facility									
lf yes, admiss	f yes, admission date at the first facility [_D_]/M_]/[_A_]/[_2_][_0_]_Y_][_Y_]									
Date of repor	t [_D_][_D_]/[_M_][_M_]	/[_2_][()_][_Y_]	[_Y_]						
1a. CLINICA	L INCLUSION CRITERI	A FOR L	JSE OF	CRF						
Please note	that cases that do not	meet th	e WHO	case definiti	on will not be classi	fied as a probable case:				
• Is the	patient ≤ 16 years? ⊡Yes	□No □ (Jnknowr	า						
• Does	the patient have an ALT o	r AST > {	500 IU/L1	? □Yes □No □	l Unknown					
Did th	e patient present after Oc	tober 20	21? □Ye	es ⊡No ⊡ Unk	nown					
Has the second sec	e patient been evaluated	and test	ed negat	tive for:						
a.	Hepatitis virus A	□Yes	□No	□ Pending	□ Not tested					
b.	Hepatitis virus B	□Yes	□No	□ Pending	□ Not tested					
C.	Hepatitis virus C	□Yes	□No	□ Pending	□ Not tested					
d.	Hepatitis virus E	□Yes	□No	□ Pending	□ Not tested					
Complete details in section 2b.										
1b. DEMOG	RAPHICS									

Sex assigned at birth						
Date of birth [_D_]/_M_[_M_]/[_Y_]_Y_]_Y_]						
If date of birth is unknown, record: Age []years OR [][] months OR [_][_] days						
Race/ethnicity (tick all that apply)						
□ Asian □ African/Black □ Caucasian/White □ Hispanic/Latino □ Other specify □ Unknown						

SEVERE ACUTE HEPATITIS OF UNKNOWN AETIOLOGY CASE REPORT FORM 21 June 2022 © World Health Organization 2022. Some rights reserved. This publication is available under the license <u>CC BY-SA 3.0 IGO</u>. This publication is adapted from the COVID-19 Case Record Forms (CRF) published by <u>ISARIC</u> on behalf of Oxford University. WHO Reference number: WHO/UnkHep/Clinical_CRF/2022.1



1c. DATE OF ONSET OF INITIAL SYMPTOMS

Symptom onset (date of first/earliest symptom) [D][D]/[M][M]/[2][0][Y][Y]				
Fever □Yes □No □Unknown	Scleral icterus □Yes □No □Unknown			
If yes, (max.) °C	If yes,			
Onset [D][D]/[M][M]/[2][0][Y][Y]	Onset [D][D]/[M][M]/[2][0][Y][Y]			
Decreased appetite/anorexia □Yes □No □Unknown	Jaundice □Yes □No □Unknown			
If yes,	If yes,			
Onset [D][D]/[M][M]/[2][0][Y][Y]	Onset [D][D]/[M][M]/[2][0][Y][Y]			
Fatigue □Yes □No □Unknown	Nausea □Yes □No □Unknown			
If yes,	If yes,			
Onset [][_]/[][_]/[2 _ [][Y _][Y	Onset [D][D]/[M][M]/[2][0][Y][Y]			
Rhinorrhoea □Yes □No □Unknown	Vomiting □Yes □No □Unknown			
If yes,	Onset [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]			
Onset [_][_]/[M_][M_]/[2_][0_][Y_][Y_]				
Sore throat □Yes □No □Unknown	Diarrhoea □Yes □No □Unknown			
If yes,	If yes,			
Onset [_][_]/[M_][M_]/[2_][0_][Y_][Y_]	Onset [D][D]/[M][M]/[2][0][Y][Y]			
Conjunctivitis (pink eye) □Yes □No □Unknown	Abdominal pain □Yes □No □Unknown			
If yes,	If yes,			
Onset [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Onset [D][D]/[M][M]/[2][0][Y][Y]			
Shortness of breath □Yes □No □Unknown	Dark-coloured urine □Yes □No □Unknown			
If yes,	If yes,			
Onset [_D_][_D_]/[_M_][_A_]/[_2_][_0_][_Y_][_Y_]	Onset [_D_][_D_]/[_M_]/[_2_][_0_][_Y_][_Y_]			
Wheezing □Yes □No □Unknown	Pale stool			
If yes,	If yes,			
Onset [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Onset [_D_][_D_]/[_M_][_2_][_0_][_Y_][_Y_]			
Cough □Yes □No □Unknown	Seizures			
If yes,	If yes,			
Onset [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Onset [_D_][_D_]/[_M_]/[_2_][_0_][_Y_][_Y_]			
Joint pain (arthralgia) □Yes □No □Unknown	Excessive sleepiness □Yes □No □Unknown			
If yes,	If yes,			
Onset [D][D]/[M][M]/[2][0][Y][Y]	Onset [_D_]/[_M_]/[_2_][_0_][_Y_][_Y_]			
Muscle aches (myalgia)	□ Other			
If yes,	If yes,			
Onset [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Onset [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]			

SEVERE ACUTE HEPATITIS OF UNKNOWN AETIOLOGY CASE REPORT FORM 21 June 2022



1d. CLINICAL EVA	LUATION								
Decreased					Sclera icterus	□Yes	□No	o 🗆]Unknown
appetite/anorexia	□Yes	□No		known					
History of fever/chills	□Yes			known	Skin Jaundice	□Yes			Unknown
Inconsolable crying				known	Nausea	□Yes			Unknown
Fatigue Inability to walk	□Yes □Yes	□No □No		known	Vomiting Diarrhoea	□Yes			Unknown
Runny nose (rhinorrho				known known	Abdominal pain	□Yes □Yes	⊡No ⊡No]Unknown]Unknown
					-				
Sore throat	□Yes			known	Peripheral oedema	□Yes			Unknown
Conjunctivitis	□Yes	□No	LUNK	known	Hepatomegaly	□Yes			Unknown
Shortness of breath	□Yes	□No		known	Splenomegaly	□Yes	□No		Unknown
Wheezing	□Yes	□No		known	Ascites	□Yes	□No		Unknown
Cough	□Yes	□No		known	Petechiae/haematon	nas	□Yes	□No	□Unknown
Muscle aches (myalgi	a) ⊡Yes	□No	□Un	known	Palmar erythema	□Yes	□No	o ⊑	Unknown
Joint pain (arthralgia)	□Yes	□No		known	Caput medusa	□Yes	□No		Unknown
Lymphadenopathy	□Yes	□No		known	Pale stool	□Yes			Unknown
Skin rash If yes, describe	□Yes	□No	□Un	known	Dark-coloured urine	□Yes	□No	o □	lUnknown
Seizures	□Yes	□No	□Unl	known	Asterixis (flapping hands /trem	nor) □]Yes	□No	□Unknown
Acute impairment of live with or without (> 2) end	ephalopath	iy	์⊡Ye	s ⊡No ⊡Ur	iin K, iknown				
 with or without (> 2) end Date of onset [_D_][_D_ Other signs/symptoms Fever □Yes 1 Presence of dehydra Inability to maintain Not passing urine Severe or persistent Repeated episodes Spontaneous bleedi Variceal bleed □Ye Mental state change confusion, abnormal 	Pephalopath]/[_M_][_M s of liver fai]No □Ur ation □ oral hydrat □Yes t nausea ar of hypoglyo ng (nasal, es □No es/evidence I behaviour	IJ I_]/[_2_] ilure: hknown Yes □ ion □ Un caemia oral, vag oral, vag of ence or decr	□Yes □No □Yes □Unl ting □Yes ginal, blo nknown ephalopa reased le	S ONO OUR OUNKNOWN; if yes NO OUNKNO KNOWN Yes NO S NO OUR S NO OUR S ONO OUR S	nknown s, ⊡severe □moo wn o □Unknown nknown nd vomiting) □Yes clude excessive sleepi	□No ness, irr	⊡mi ⊡Unkr itability, Inknown	nown agitati	on, disorientatio
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World Health Organization

1e. VITAL SIGNS (at admission)							
Symptom onset (date of first/earliest symptom)							
Admission date at this facility [_D_]/[_M_]/[_2_][_0_](_Y_][_Y_]							
Temperature [][].[]°C Heart rate [][]beats/min							
Respiratory rate [][]breaths/min							
Saturation O₂ []% on □Room air □Oxygen therapy							
BP [] [](systolic) [][](diastolic)mmHg							
Severe dehydration □Yes □No □Unknown							
Sternal capillary refill time > 2 seconds							
Jaundice:							
A V P U (circle one) Glasgow Coma Score (GCS/15) [][]							
Malnutrition Description Description Description Mid-upper arm circumference [][]mm							
Height [] []cm							

1f. EXISTING MEDICAL CONDITIONS (existing at admission)							
Gestational age at birth < 37 w If yes, age when born [][□Yes	□No □Unkno	wn			
Chronic cardiac disease (including congenital disease)	⊡Yes ⊡Yes		□Unknown □Unknown	Diabetes mellitus If yes, ⊡Type1 ⊡Type2	□Yes	□No	□Unknown
Autoimmune disease If yes, specify:	□Yes	□No	□Unknown	Tuberculosis (<i>active</i>) If yes, □active □previous	□Yes	□No	□Unknown
Chronic pulmonary disease or asthma If yes, specify:	□Yes	⊡No	□Unknown	HIV If yes, ⊡on ART ⊡No ART	□Yes	□No	□Unknown
Acute or chronic kidney disease If yes, specify:	□Yes	□No	□Unknown	Asplenia	□Yes	□No	□Unknown
Chronic liver disease If yes, specify:	□Yes	□No	□Unknown	Malignancy (lymphoma, leukaemia/chemotherapy	□Yes	□No	□Unknown
Metabolic disease If yes, specify:	□Yes	□No	□Unknown	Other immunosuppressive condition (including primary ID) If yes, specify:	□Yes	□No	□Unknown
Mitochondrial disease If yes, specify:	□Yes	□No	□Unknown	History of any transplant If yes, specify:	□Yes -	□No	□Unknown
Chronic haematologic disease	□Yes	□No	□Unknown	Haemochromatosis (GALD) – neonatal	□Yes □Yes	□No □No	□Unknown □Unknown
Development disorder If yes, specify:	□Yes	□No	□Unknown	Sickle cell disease	□Yes	□No	□Unknown
Chronic neurological disorder (including congenital disease)	□Yes □Yes		□Unknown □Unknown	Thalassaemia	□Yes	□No	□Unknown
Rheumatologic disease	□Yes	□No	□Unknown	G6P deficiency	□Yes	□No	□Unknown

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1g. COVID-19 INFECTION STATUS								
Presence of signs or symptoms suggestive of COVID-19 within the last 3 months								
Date of onset of symptoms: [D][D]/[M][M]/[2][0][Y][Y]								
If yes, specify clinical features:								
Were there features of COVID-19 MIS-C (multisystem inflammatory syndrome in children)?								
(requires fever, elevated inflammatory markers, at least two signs of multisystem involvement, evidence of SARS-CoV-2								
infection or exposure, and exclusion of other potential causes)								
If yes, specify clinical features:								
Laboratory confirmation of COVID-19 (antigen test or molecular test)								
Antigen test □Yes □No □Unknown								
Molecular test □Yes □No □Unknown								
If positive, date of most recent test [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]								
Previous laboratory tests for COVID-19 (antigen test or molecular test)								
Date of previous tests [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Result □ Pos □ Neg								
Date of previous tests [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Result □ Pos □ Neg								
Date of previous tests [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] Result								
Serology for COVID-19 antibody Yes No Unknown								
Date of test_[_D_][_D_]/[_M_][_A_]/[_2_][_0_][_Y_][_Y_]								
SARS-CoV-2 anti-nucleocapsid 🛛 Not tested 🗆 Pos 🖾 Neg 🗀 Indeterm 🖾 Pending 🗔 Unknown								
SARS-CoV-2 anti-spike								
Other, specify result:								
Exposure or high-risk contact COVID-19 in family or community Ues Unknown								
Date of exposure D_[_D_]/[_M_]/[_2_][_0_][_Y_][_Y_]								

1h. COVID-19 VACCINATION STATUS

Did the patient receive a COVID-19 vaccine?
Ures
Unknown

Source of information Documented evidence (vaccine card/vaccine passport/facility-based record/other) DRecall

If yes, number of doses received $\Box 1 \Box 2 \Box 3 \Box 4 \Box > 4 \Box$ Unknown

Dose 1, Date [_D_]/[_M_][_M_]/[_2_][_0_][_Y_] **specify** □Pfizer □Moderna □Janssen □AZ □Sinovac □Sinopharm □Bharat (Covaxin) □Sputnik □Other □Unknown

Dose 2, Date [_D_][_D_]/[_M_][_4_]/[_2_][_0_][_Y_]**specify** □Pfizer □Moderna □Janssen □AZ □Sinovac □Sinopharm □Bharat (Covaxin) □Sputnik □Other □Unknown

Dose 3, Date [_D_]/[_M_]/[_2_][_0_]/Y_] **specify** Pfizer DModerna Janssen AZ Sinovac Sinopharm Bharat (Covaxin) Sputnik Other Unknown

Dose 4, Date [_D_]/[_M_]/[_2_][_0_]/Y_] **specify** Pfizer Moderna Janssen AZ Sinovac Sinopharm Bharat (Covaxin) Sputnik Other Unknown



1i. CHILDHOOD VACCINATION STATUS

Vaccination	Date Dose 1 (dd/mm/yyyy)	Date Dose 2 (dd/mm/yyyy)	Date Dose 3 (dd/mm/yyyy)	Date Dose 4 (dd/mm/yyyy)
Hepatitis A virus				
Hepatitis B virus				
Rotavirus				
DTaP/Tdap				
Hib				
IPV				
MMR				
Varicella				
Influenza				
BCG				
Yellow fever				
PCV 13				
Meningococcal B				
HPV				

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Paracetamol/acetaminophen EVes ENo EUnknown First date given: []][]/[]][]][]][]][]][]][]][]][]][]][]][1j. EXPOSURE	TO MEDICATION in the	e 2 months prio	r to symptom onset	
Allergy medicine DYes DNo DUnknown First date given: []/ in days_ Aspirin Oves: Frequency: Route: Duration: in days_ Aspirin Oves DNo DUnknown First date given: []/	Paracetamol/ace	etaminophen ⊡Yes ⊡No	□Unknown	First date given: [_D_][_D_]/	M]/[_2_][_0_][_Y_][_Y_]
If yes, specify:	Dose:	Frequency:	Route:	Total duration:	in days
Dose: Frequency: Route: Duration: in days Aspirin EYes DNo DUnknown First date given: D) [D] [M] [M] [Z] [D] [Y] [Y] Dose: Frequency: Route: Duration: in days Cough EYes DNo DUnknown First date given: D) [D] [M] [M] [Z] [D] [Y] [Y] Dose: Frequency: Route: Duration: in days Antibiotics EYes DNo DUnknown First date given: D) [D] [M] [M] [Z] [D] [Y] [Y] Dose: Frequency: Route: Duration: in days Simethicone drops EYes DNo DUnknown First date given: D) [M] [M] [Z] [D] [Y] [Y] Dose: Frequency: Route: Duration: in days Antiepileptic medication EYes DNo DUnknown First date given: D) [M] [M] [Z] [D] [Y] [Y] Mi yes, specify:			First date giv	en: [_D_][_D_]/[_M_][_M_]/[_2	2_][_0_][_Y_][_Y_]
Aspirin D'es Dio D'Unknown First date given: D_D_V_2_0_V_2_0_V_V_1 Dose:			Route:	Duration:	in davs
Dose: Frequency: Route: Duration: in days Cough CYes No Unknown First date given: D		r roquonoy:		Buildionii	,
If yes, specify: Route: Duration: in days Duprofen IYes No Route: Duration: in days Antibiotics IYes No Route: Duration: in days Antibiotics IYes Route: Duration: in days Simethicone drops Route: Duration: in days Simethicone drops Route: Duration: in days Simethicone dropsYes Route: Duration: in days Antiopileptic medicationYes Route: Duration: in days Antiopileptic medicationYes Route: Duration: in days Herbal medicine/naturopathic/homeopathic medicine Yes Frequency: Route: Duration: in days Herbal medicine/naturopathic/homeopathic medicine IYes Frequency: Route: Duration: in days Dose: Frequency: Route: Duration: Dose: Frequency: Route: Duration: Other medication IYes Route: Duration: Other medication IYes Route: Duration: Other medication Route: Duration:					
Dose: Frequency: Route: Duration: in days Ibuprofen LYes LNo LNnknown First date given: D			First date giv	ren: [_D_][_D_]/[_M_][_M_]/[_2	2_]_0_]_Y_]_Y_]
Dose: Frequency: Route: Duration: in days Antibiotics Yes No Unknown First date given: D			Route:	Duration: i	n days
If yes, specify: Dose: Frequency: Route: Duration: in days Simethicone drops Oyes Frequency: Route: Duration: in days Antiepileptic medication Oyes Route: Dose: Frequency: Route: Duration: in days Antiepileptic medication Oyes Route: Dose: Frequency: Route: Duration: in days Antiepileptic medication Oyes Route: Dose: Frequency: Route: Duration: in days Herbal medicine/naturopathic/homeopathic medicine Oyes Outon Outon If yes, specify: Dose: Frequency: Route: Duration: Outon Unknown If yes, specify: Route: Duration: Other medication Oyes Frequency: Route: Duration: Other medication Oyes No Unknown If yes, specify: Prequency: Route:	-		-		
Dose: Frequency: Route: Duration: in days Simethicone drops UYes No Unknown First date given: D				ren: [_D_][_D_]/[_M_][_M_]/[_2	2_][_0_][_Y_][_Y_]
Dose:				Duration:	in days
Dose: Frequency: Route: Duration: in days Herbal medicine/naturopathic/homeopathic medicine "Yes No Unknown First date given: D] If yes, specify:	Dose:	Frequency:	Route: ⊒Unknown Fi	Duration: rst date given: [_D_][_D_]/[_M	in days
Image: Section of the section of th					in days
If yes, specify: Frequency: Dose: Frequency: Route: Duration: Other medication IPes INO IUnknown If yes, specify: Dose: Frequency: Route: Duration: Duration: Other medication IPes INO IUnknown If yes, specify: Other medication IPes INO IUnknown If yes, specify: Frequency: Freque	□Yes □No □ If yes, specify:	Unknown First date	given: [_D_][_D_]/		
If yes, specify:				First date given: [_D_][_□ Duration:	_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] _
If yes, specify: First date given: [_D_]/[_M_]/[_M_]/[_2_][_0_]/[_Y_][_Y_]	If yes, specify:				
Dose: Frequency: Route: Duration:				First date given: [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
	Dose:	Frequency:	Route:	Duration:	_



1k. OTHER EXPOSURES in 2 months prior to symptom onset	
1a. Attendance to in-person school or day care in the 2 months prior to symptom onset □Yes □No □I Last attendance: [][]/[][]/[_2_][_0_][_Y_][_Y_] Name of school or day care:	
1b. Any outbreaks reported by school or day care in the 2 months prior to symptom onset □Yes □No □I Date [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	
2. Any new illnesses or infections in household members or other close contacts in the 2 months prior to □Yes □No □Unknown Date [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] If yes, specify:	symptom onset
3a. Any national or overseas trip In the 2 months prior to symptom onset □Yes □No □Unknown Date [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] If yes, specify location:	
3b. During the trip, did the child get sick? □Yes □No □Unknown If yes, specify symptoms:	
4. Any contact with wild animals, or a pet or animal living with the patient or any friend/relative at the time □Yes □No □Unknown If yes, specify:	of the illness
5. Any bite or reaction to any insect or animal contacts in the 2 months prior to symptom onset Date [D_][D_]/[M_][M_]/[2_][0_][Y_][Y_] If yes, specify:	No □Unknown
6. Any problem or exposure to different water in the 2 months prior to symptom onset	own
7. Any problem or exposure to different food in the 2 months prior to symptom onset	own
8. Did the child or household member start using any <u>new</u> personal care products (e.g. soaps, lotions) in the prior to symptom onset? □Yes □No □Unsure If yes, specify:	e 2 months
Other exposures: 9. For infants < 6 months, is the child: □ Exclusively breastfeeding □Mixed feeding □Replacement feeding (infant formula) If mixed feeding/formula feeding, which brand of formula? 9b. For infants and children 6–59 months	
 9. For infants < 6 months, is the child: □ Exclusively breastfeeding □Mixed feeding □Replacement feeding (infant formula) If mixed feeding/formula feeding, which brand of formula? 	
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 9. For infants < 6 months, is the child: □ Exclusively breastfeeding □Mixed feeding □Replacement feeding (infant formula) If mixed feeding/formula feeding, which brand of formula?	
 9. For infants < 6 months, is the child: □ Exclusively breastfeeding □Mixed feeding □Replacement feeding (infant formula) If mixed feeding/formula feeding, which brand of formula? 9b. For infants and children 6–59 months Is the child still receiving breastmilk? □Yes □No □Unsure Is the child still receiving infant formula? □Yes □No If yes, which brand of formula: What age did the child start complementary foods other than breastmilk/infant formula? 	
 9. For infants < 6 months, is the child: □ Exclusively breastfeeding □Mixed feeding □Replacement feeding (infant formula) If mixed feeding/formula feeding, which brand of formula? 9b. For infants and children 6–59 months Is the child still receiving breastmilk? □Yes □No □Unsure Is the child still receiving infant formula? □Yes □No If yes, which brand of formula: What age did the child start complementary foods other than breastmilk/infant formula? 	



MODULE 2. Complete at discharge/death

2a.LABORATORY TESTING

Test name	Admission value	Date [D_][D_]/[M_][M_]/ [2_][0_][Y_][Y_]	Most abnormal value	Date [][]/[_M_][_M_]/[_2 _][_0_][_Y_][_Y_]				
	HAEMATOLO	GY (specify if different	units)					
WBC (cells x 10 ⁹ /L)								
Total lymphocyte count (10 ³ /µL)								
Absolute neutrophil count (cells per mm ³)								
Haematocrit (%)								
Platelets (x 10 ⁹ /L)								
ESR (mm/h)								
CRP (mg/dL)								
Ferritin (ug/L)								
D-dimer (U/L)								
BIOCH	EMISTRY AND EL	ECTROLYTES (specify	v if different units	5)				
ALT (U/L)								
AST (U/L)								
Total bilirubin (mg/dL)								
Alkaline phosphatase (U/L)								
Sodium (mEq/L)								
Chloride (mmol/L)								
Potassium (mEq/L)								
Calcium (mg/dL)								
Glucose (mg/dL)								
Creatinine (mg/dL)								
Blood urea nitrogen (mg/dL)								
Albumin (g/dL)								
Uric acid (mg/dL)								
Ammonia (umol/L)								
Lactate (mmol/L)								
		BLOOD GASES						
Carbon dioxide (mmol/L)								
Bicarbonate (mmol/L)								
рН								
COAGULATION								
INR (International Normalized Ratio)								
Prothrombin time								
Activated partial thromboplastin time (aPTT)								
Fibrinogen (mg/dL)								

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2b. DIAGNOSTIC TESTS (to identify aetiology)

	AUTOIMMUNE MARKERS (specify units)	
Total immunogl	obulin (IgG) g/L	
Smooth muscle	antibody (SMA)	
Liver kidney mie (LKM)	crosomal antibody	
Antinuclear anti		
	METABOLIC LIVER DISEASES	
Serum caerulop		
24-hr urine for c level	copper serum ferritin	
Serum transferr	in saturation	
	MEDICATION/TOXIN SCREEN	
Serum paraceta	mol level	
Urine screen fo	r toxins/drugs	
MICROBIOLO	GY	Date
Hepatitis A	□Yes □No □Unknown	
IgM anti-HAV	□ Not tested □ Tested Lab-based EIA RDT □ Pos □ Neg □ Indeterm	
	□ Pending □ Unknown	
IgG anti-HAV	□ Not tested □ Pos □ Neg □ Pending □ Unknown	
Total anti-HAV	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
Hepatitis B		
HBsAg	□ Not tested □ Tested Lab-based EIA RDT □ Pos □ Neg □ Indeterm	
	Pending Unknown	
IgM anti-HBc	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
Total anti-HBc	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
HBeAg	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
Anti-HBeAg	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
HBV DNA	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
Hepatitis C		
Anti-HCV	□ Not tested □ Tested Lab-based EIA RDT □ Pos □ Neg □ Indeterm	
	Pending Unknown	
HCV RNA	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
Hepatitis D		
Anti-HDV	□ Not tested □ Tested Lab-based EIA RDT □ Pos □ Neg □ Indeterm	
	Pending Unknown	
HDV RNA	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
Hepatitis E		I
IgM anti-HEV	□ Not tested □ Tested Lab-based EIA RDT □ Pos □ Neg □ Indeterm	
	□ Pending □ Unknown	
IgG anti-HEV	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	
HEV RNA	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	

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OTHER MICRO	DBIOLOGICAL STUDIES	Unknown	
Test	Result	Type of test and sample	Date
SARS-CoV-2	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□PCR □Serology □Culture □Other Location: □ Whole blood □Serum □Stool □Respiratory	
	☐ Sample stored for potential future testing	□Nasopharyngeal □Urine □CSF □Liver tissue □Other	
Adenovirus	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□PCR □Serology □Culture □Other Location:	
	□Sample stored for potential future testing	□ Whole blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other	
Influenza	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□PCR □Serology □Culture □Other Location: □ Whole blood □Serum □Stool □Respiratory	
	Specify subtype (A, B or H1N1):	□Nasopharyngeal □Urine □CSF □Liver tissue □Other	
Parainfluenza	□ Not tested □ Pos □ Neg □ Indeterm	□PCR □Serology □Culture □Other	
	Pending Unknown	Location:	
	□ Sample stored for potential future testing	□ Whole blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other	
EBV	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□PCR □Serology □Culture □Other Location:	
	☐ Sample stored for potential future testing	□ Whole blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other	
CMV	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□PCR □Serology □Culture □Other Location:	
	□ Sample stored for potential future testing	□ Whole blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other	
Varicella	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□PCR □Serology □Culture □Other Location:	
	□ Sample stored for potential future testing	□ Whole blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other	



HIV	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing	□PCR □Serology □Culture □Other Location: □Blood □Serum □Other
HHV-6	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □Sample stored for potential future testing	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
HHV-7	 □ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing 	 □PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
RSV	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
Parvovirus B19	 □ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing 	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
HSV-1	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
HSV-2	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
Enteric viruses: norovirus, enterovirus, rotavirus, astrovirus, sapovirus	 □ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing 	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other

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Bocavirus	 Not tested Pos Neg Indeterm Pending Unknown Sample stored for potential future testing 	 □PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
HPeV	 Not tested Pos Neg Indeterm Pending Unknown Sample stored for potential future testing 	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue
Leptospirosis	 Not tested Pos Neg Indeterm Pending Unknown Sample stored for potential future testing 	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
Mycoplasma	 Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □ Sample stored for potential future testing 	□PCR □Serology □Culture □Other Location: □ Blood □Serum □Stool □Respiratory □Nasopharyngeal □Urine □CSF □Liver tissue □Other
Blood culture	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□Bacterial □Fungal pathogen:
Throat swab culture	Sample stored for potential future testing Not tested □ Pos □ Neg □ Indeterm Pending □ Unknown Sample stored for potential future testing	□Bacterial panel including Streptococcus gr A pathogen:
Stool culture	□ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown	□Bacterial panel including Salmonella spp. pathogen:
Urine culture	 Sample stored for potential future testing Not tested Pos Neg Indeterm Pending Unknown Sample stored for potential future testing 	□Bacterial □Fungal pathogen:



RADIOLOGY Yes No Unknown						
Imaging study Conducted			Date (mm/dd/yyyy)	Key findings		
Abdominal ultrasound with echo doppler	□Yes □No	□Unknown				
Fibroscan	□Yes □No	□Unknown				
Abdominal CT scan	□Yes □No	□Unknown				
Abdominal MRI	⊡Yes ⊡No	□Unknown				
Magnetic resonance cholangiopancreatogr aphy (MRCP)	□Yes □No	□Unknown				
Chest X-ray	□Yes □No	□Unknown				
Endoscopy (gastroscopy)	□Yes □No	□Unknown				

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2c. PATHOLOGIC LIVER TISSUE FINDINGS						
LIVER BIOPSY						
Specimen collected □Yes □No □Unknown Date: [D][D]/[M][M]/[2][0][Y][Y] If yes, what were the findings? □ Acute/active hepatitis □ Fibrosis □ Macrovesicular steatosis □ Granuloma						
Image: Autoimmune hepatitie Image: Harmonia Autoimmune hepatitie Image: Harmonia Bile duct injury/inflammation Interface hepatitis Microvesicular steatosis Smudge cells Chronic hepatitis Microvesicular steatosis Was there hepatocellular necrosis Yes Select type (check all that apply) Single cell						
Immunochemistry DYes No DUnknown If yes, specify results:						
Electron microscopy						
Microbiology □Yes □No □Unknown Virus □ Not tested □ Pos □ Indeterm □ Pending □ Unknown □PCR □Serology □Culture □Other Result						
Bacteria Not tested Pos Neg Indeterm Pending Unknown PCR Serology Culture Other Result						
Fungal □ Not tested □ Pos □ Neg □ Indeterm □ Pending □ Unknown □PCR □Serology □Culture □Other Result						
Parasites Not tested Pos Neg Indeterm Pending Unknown PCR Serology Culture Other Result						
LIVER TRANSPLANT Received liver transplant □Yes □No □Unknown Date [D][D]/[M][M]/[2][0][Y][Y] Did the patient have the explanted liver tissue analysed by pathology? □Yes □No □Unknown						
If yes, what were the findings?						
□ Autoimmune hepatitis □ Haemophagocytosis □ Portal inflammation/hepatitis						
□ Bile duct injury/inflammation □ Interface hepatitis □ Smudge cells						
□ Chronic hepatitis □ Microvesicular steatosis □ Viral/intranuclear inclusions						
Was there hepatocellular necrosis □Yes □No □Unknown						
Select type (check all that apply)						
Immunochemistry □Yes □No □Unknown If yes, specify results:						
Electron microscopy						
Microbiology □Yes □No □Unknown						
Virus Not tested Pos Indeterm Pending Unknown PCR Serology Other Result						
Bacteria □ Not tested □ Pos □ Indeterm □ Pending □ Unknown □PCR □Serology □Culture □Other Result						
Fungal □ Not tested □ Pos □ Indeterm □ Pending □ Unknown □PCR □Serology □Culture □Other Result						
Parasites Not tested Pos Neg Indeterm Pending Unknown PCR Serology Culture Other Result						

SEVERE ACUTE HEPATITIS OF UNKNOWN AETIOLOGY CASE REPORT FORM 21 June 2022



2d. MEDICATIONS At any time during hospital stay, did the patient receive						
Group of drugs IM = intramuscular, INH = inhaled, IV = intravenous, PO = per oral, PR = per rectal, SC = subcutaneous	Medication	Date start	Dose	Frequency	Duration (days)	
Antivirals						
Antibiotics DPO DIV DIM						
Antifungals						
Antimalarials						
Corticosteroids						
N-acetylcysteine □PO □ IV						
Lactulose						
Rifaximin □IV						
Antiepileptic medication						
Mannitol DIV						
Hypertonic saline (3%) □IV						
Pentoxifylline □IV						
Norepinephrine DIV DIM						
Albumin DIV						
Vasopressin □IV						
Terlipressin □IV						
Midodrine DIV						
Octreotide DIV						
Vitamin K						
Glucose □PO □IV						
Heparin □PO □SC □IV						
Other medications:						

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2e. SUPPORTIVE CARE At any time during this admission, did the patient receive:							
ICU or high dependency unit admission?							
Discharge date [D][D]/[M][M	Discharge date [D][D]/[M][M]/[2][0][Y][Y]						
Oxygen therapy? □Yes □No □U	nknown	D	ate [_D_][_D_]	/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]			
If yes, complete all below:							
O₂ flow: □1–5 L/min □6–10 L	./min □1	1–15 L	/min □> 15 L/	min 🗆 Unknown			
Non-invasive ventilation?	□No	□Unkn	own Speci	fy □BiPAP □CPAP □HFNO			
Invasive ventilation (any)? □Yes □!	No ⊡Unk	nown D	ate [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]			
Extracorporeal liver support/extracorporeal support (ECMO)? □Yes □No □Unknown Date: [_D_][_D_]/[_M_][_A_][_2_][_0_][_Y_][_Y_]							
Haemodialysis/peritoneal dialysis?	□Yes	□No	□Unknown	Date [_D_][_D_]/[_M_][_M_]/[_2_]	[_0_][_Y_][_Y_]		
High-volume plasma exchange?	□Yes	□No	□Unknown	Date [_D_][_D_]/[_M_][_M_]/[_2_]	[_0_][_Y_][_Y_]		
Inotropes/vasopressors?	□Yes	□No	□Unknown	Date [D][D]/[M][M]/[2]	[_0_][_Y_][_Y_]		
Liver transplant	□Yes	□No	□Unknown	Date [_D_][_D_]/[_M_][_M_]/[_2_]	[_0_][_Y_][_Y_]		
Other							

2f. DIAGNOSIS CATEGORY AND OUTCOME

□ Acute hepatitis without liver failure at presentation or during clinical course

□ Acute hepatitis without liver failure at presentation but developed liver failure during disease course but no transplantation

□ Acute hepatitis without liver failure at presentation but developed liver failure during disease course and had transplantation

□ Acute hepatitis with liver failure at presentation but without transplantation

□ Acute hepatitis with liver failure at presentation and transplantation

Outcome Discharged alive Hospitalized Transfer to other facility Death Palliative discharge Unknown

Outcome date [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_] □Unknown

If discharged alive, ability to self-care at discharge versus before illness:

□Same as before illness □Worse □Better □Unknown