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 **WHO Global Clinical Platform**

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 non-infectious 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 _____ **State/Region:** _____ **Country** _____

Patient transferred to this facility from another facility? ☐Yes ☐No ☐Unknown
If yes, name the facility_____

If yes, admission date at the first facility [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Date of report [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

1a. CLINICAL INCLUSION CRITERIA FOR USE OF CRF

Please note that cases that do not meet the WHO case definition will not be classified as a probable case:

- **Is the patient ≤ 16 years?** ☐Yes ☐No ☐ **Unknown**
- **Does the patient have an ALT or AST > 500 IU/L?** ☐Yes ☐No ☐ **Unknown**
- **Did the patient present after October 2021?** ☐Yes ☐No ☐ **Unknown**
- **Has the patient been evaluated and tested negative 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. DEMOGRAPHICS

Sex assigned at birth ☐Male ☐Female ☐Transgender ☐Unknown

Date of birth [_D_][_D_]/[_M_][_M_]/[_Y_][_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

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 If yes, (max.) _____ °C **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Scleral icterus ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Decreased appetite/anorexia ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Jaundice ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Fatigue ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_	Nausea ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Rhinorrhoea ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Vomiting ☐Yes ☐No ☐Unknown **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Sore throat ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Diarrhoea ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Conjunctivitis (pink eye) ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Abdominal pain ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Shortness of breath ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Dark-coloured urine ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Wheezing ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Pale stool ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Cough ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Seizures ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Joint pain (arthralgia) ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	Excessive sleepiness ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]
Muscle aches (myalgia) ☐Yes ☐No ☐Unknown If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]	☐ Other _____ If yes, **Onset** [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

1d. CLINICAL EVALUATION ON ADMISSION: CLINICAL SYMPTOMS/SIGNS ON ADMISSION							
Decreased appetite/anorexia	☐Yes	☐No	☐Unknown	Sclera icterus	☐Yes	☐No	☐Unknown
History of fever/chills	☐Yes	☐No	☐Unknown	Skin Jaundice	☐Yes	☐No	☐Unknown
Inconsolable crying	☐Yes	☐No	☐Unknown	Nausea	☐Yes	☐No	☐Unknown
Fatigue	☐Yes	☐No	☐Unknown	Vomiting	☐Yes	☐No	☐Unknown
Inability to walk	☐Yes	☐No	☐Unknown	Diarrhoea	☐Yes	☐No	☐Unknown
Runny nose (rhinorrhoea)	☐Yes	☐No	☐Unknown	Abdominal pain	☐Yes	☐No	☐Unknown
Sore throat	☐Yes	☐No	☐Unknown	Peripheral oedema	☐Yes	☐No	☐Unknown
Conjunctivitis	☐Yes	☐No	☐Unknown	Hepatomegaly	☐Yes	☐No	☐Unknown
Shortness of breath	☐Yes	☐No	☐Unknown	Splenomegaly	☐Yes	☐No	☐Unknown
Wheezing	☐Yes	☐No	☐Unknown	Ascites	☐Yes	☐No	☐Unknown
Cough	☐Yes	☐No	☐Unknown	Petechiae/haematomas	☐Yes	☐No	☐Unknown
Muscle aches (myalgia)	☐Yes	☐No	☐Unknown	Palmar erythema	☐Yes	☐No	☐Unknown
Joint pain (arthralgia)	☐Yes	☐No	☐Unknown	Caput medusa	☐Yes	☐No	☐Unknown
Lymphadenopathy	☐Yes	☐No	☐Unknown	Pale stool	☐Yes	☐No	☐Unknown
Skin rash If yes, describe _____	☐Yes	☐No	☐Unknown	Dark-coloured urine	☐Yes	☐No	☐Unknown
Seizures	☐Yes	☐No	☐Unknown	Asterixis (flapping hands /tremor)	☐Yes	☐No	☐Unknown

Features of acute liver failure

Acute impairment of liver function (INR > 1.5) unresponsive to vitamin K, with or without (> 2) encephalopathy ☐Yes ☐No ☐Unknown

Date of onset [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Other signs/symptoms of liver failure:

- Fever ☐Yes ☐No ☐Unknown
- Presence of dehydration ☐Yes ☐No ☐Unknown; if yes, ☐severe ☐moderate ☐mild
- Inability to maintain oral hydration ☐Yes ☐No ☐Unknown
- Not passing urine ☐Yes ☐No ☐Unknown
- Severe or persistent nausea and vomiting ☐Yes ☐No ☐Unknown
- Repeated episodes of hypoglycaemia ☐Yes ☐No ☐Unknown
- Spontaneous bleeding (nasal, oral, vaginal, bloody diarrhoea and vomiting) ☐Yes ☐No ☐Unknown
- Variceal bleed ☐Yes ☐No ☐Unknown
- Mental state changes/evidence of encephalopathy: examples include excessive sleepiness, irritability, agitation, disorientation, confusion, abnormal behaviour or decreased level of consciousness: ☐Yes ☐No ☐Unknown

If yes, then grading of encephalopathy: check one that applies

Grade 1	Irritable, apathetic, behavioural and sleep disturbance
Grade 2	Drowsy, confused, but responds to commands
Grade 3	Severely confused or agitated, but response to pain
Grade 4	Unrousable, no response to pain

Multisystem involvement ☐Yes ☐No ☐Unknown

If yes, please specify

Renal failure ☐Yes ☐No ☐Unknown

Haemodynamic changes ☐Yes ☐No ☐Unknown

Pulmonary complications ☐Yes ☐No ☐Unknown

1e. VITAL SIGNS *(at admission)*

Symptom onset (date of first/earliest symptom)
[_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Admission date at this facility [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

Temperature [_][_____].[_]°C **Heart rate** [___][___][_]beats/min

Respiratory rate [_][___]breaths/min

Saturation O_2 [_][___]% on ☐Room air ☐Oxygen therapy

BP [_] [_] [_](systolic) [___][_][_](diastolic) mmHg

Severe dehydration ☐Yes ☐No ☐Unknown

Sternal capillary refill time > 2 seconds ☐Yes ☐No ☐Unknown

Jaundice: ☐Sclera ☐Skin ☐Unknown

A V P U (circle one)

Glasgow Coma Score (GCS/15) [_][_]

Malnutrition ☐Yes ☐No ☐Unknown Unknown

Mid-upper arm circumference [_][_][___]mm

Height [___] [___][___]cm

Weight [_][_][___]kg

1f. EXISTING MEDICAL CONDITIONS *(existing at admission)*

Gestational age at birth < 37 weeks? ☐Yes ☐No ☐Unknown
If yes, age when born [___][_]weeks

Chronic cardiac disease (including congenital disease)	☐Yes	☐No	☐Unknown	Diabetes mellitus If yes, ☐Type1 ☐Type2	☐Yes	☐No	☐Unknown
	☐Yes	☐No	☐Unknown				
Autoimmune disease If yes, specify: _____	☐Yes	☐No	☐Unknown	Tuberculosis (*active*) 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	☐No	☐Unknown
					☐Yes	☐No	☐Unknown
Development disorder If yes, specify: _____	☐Yes	☐No	☐Unknown	Sickle cell disease	☐Yes	☐No	☐Unknown
Chronic neurological disorder (including congenital disease)	☐Yes	☐No	☐Unknown	Thalassaemia	☐Yes	☐No	☐Unknown
	☐Yes	☐No	☐Unknown				
Rheumatologic disease	☐Yes	☐No	☐Unknown	G6P deficiency	☐Yes	☐No	☐Unknown

1g. COVID-19 INFECTION STATUS

Presence of signs or symptoms suggestive of COVID-19 within the last 3 months ☐Yes ☐No ☐Unknown

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) ☐Yes ☐No ☐Unknown

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** ☐ Pos ☐ Neg

Serology for COVID-19 antibody ☐Yes ☐No ☐Unknown

Date of test [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

SARS-CoV-2 anti-nucleocapsid ☐ Not tested ☐ Pos ☐ Neg ☐ Indeterm ☐ Pending ☐ Unknown

SARS-CoV-2 anti-spike ☐ Not tested ☐ Pos ☐ Neg ☐ Indeterm ☐ Pending ☐ Unknown

Other, specify result: _____

Exposure or high-risk contact COVID-19 in family or community ☐Yes ☐No ☐Unknown

Date of exposure D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_Y_]

1h. COVID-19 VACCINATION STATUS

Did the patient receive a COVID-19 vaccine? ☐Yes ☐No ☐Unknown

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

If yes, number of doses received ☐1 ☐ 2 ☐3 ☐ 4 ☐ > 4 ☐Unknown

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

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

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

Dose 4, Date [_D_][_D_]/[_M_][_M_]/[_2_][_0_][_Y_][_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				