

Acute hepatitis of unknown aetiology – Initial investigation and progress to date

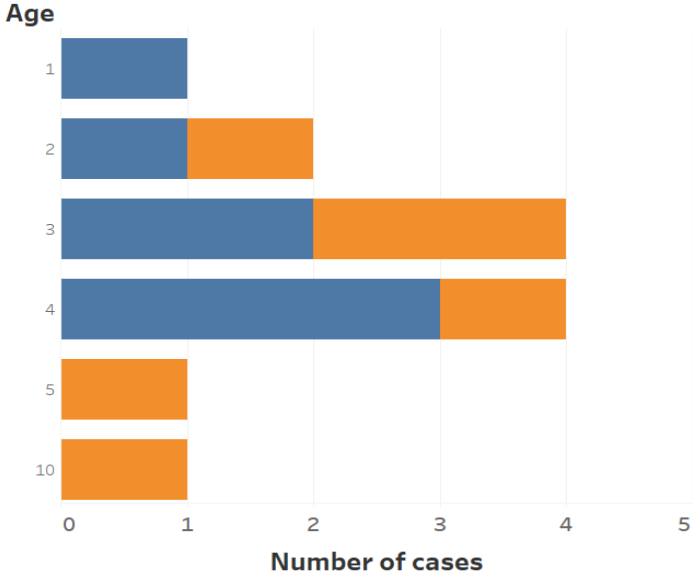
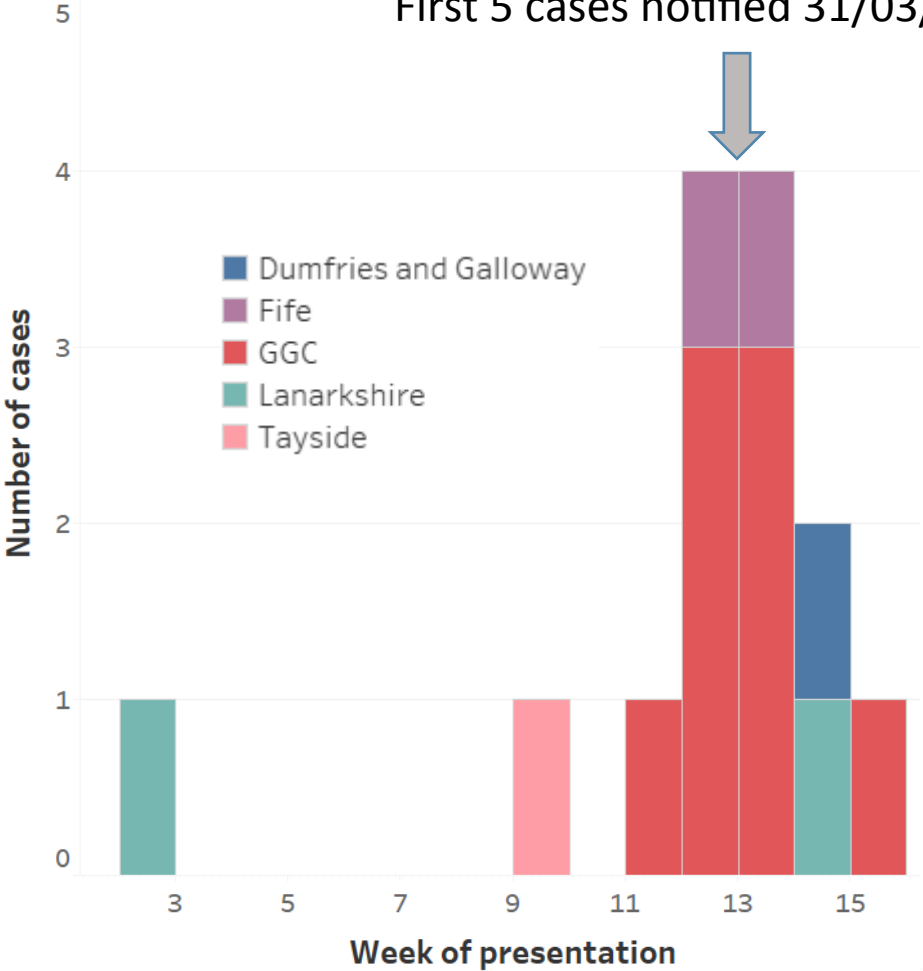
Dr Jim McMenamin, Head of Health Protection (Infection Services)
ASPHER presentation 26th May 2022

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Demographic characteristics of cases presenting with atypical non A to E hepatitis, Scotland 11 Jan - 19 Apr 2022

First 5 cases notified 31/03/22



8 females, 6 males

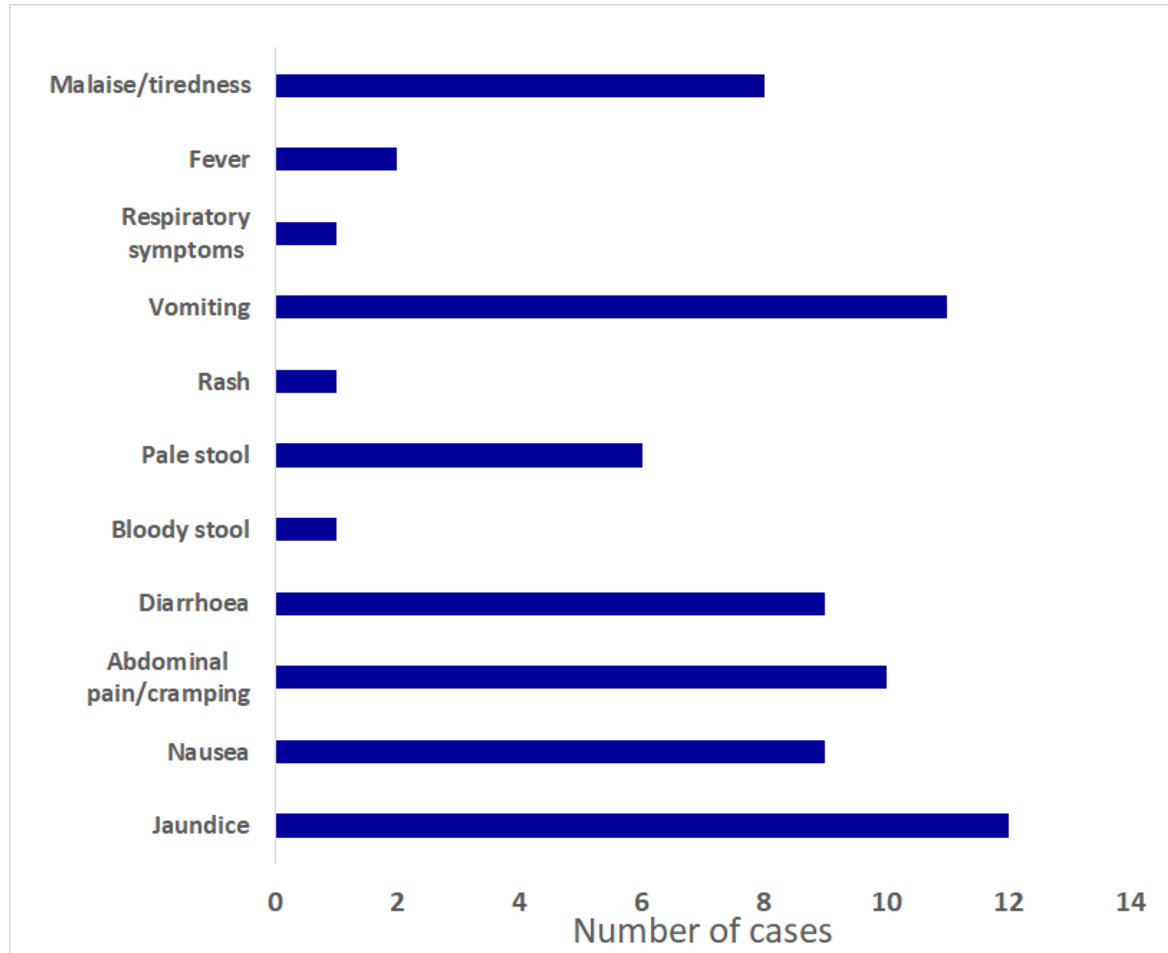


Geospatial distribution



* Data as of 1700, 18 April 2022

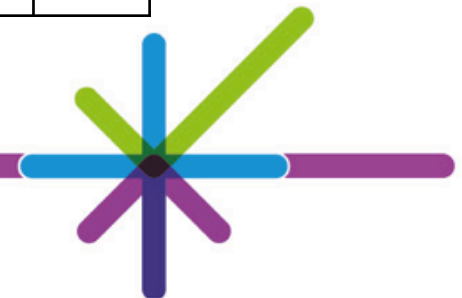
Clinical characteristics of cases presenting with atypical non A to E hepatitis, Scotland 11 Jan - 19 Apr 2022



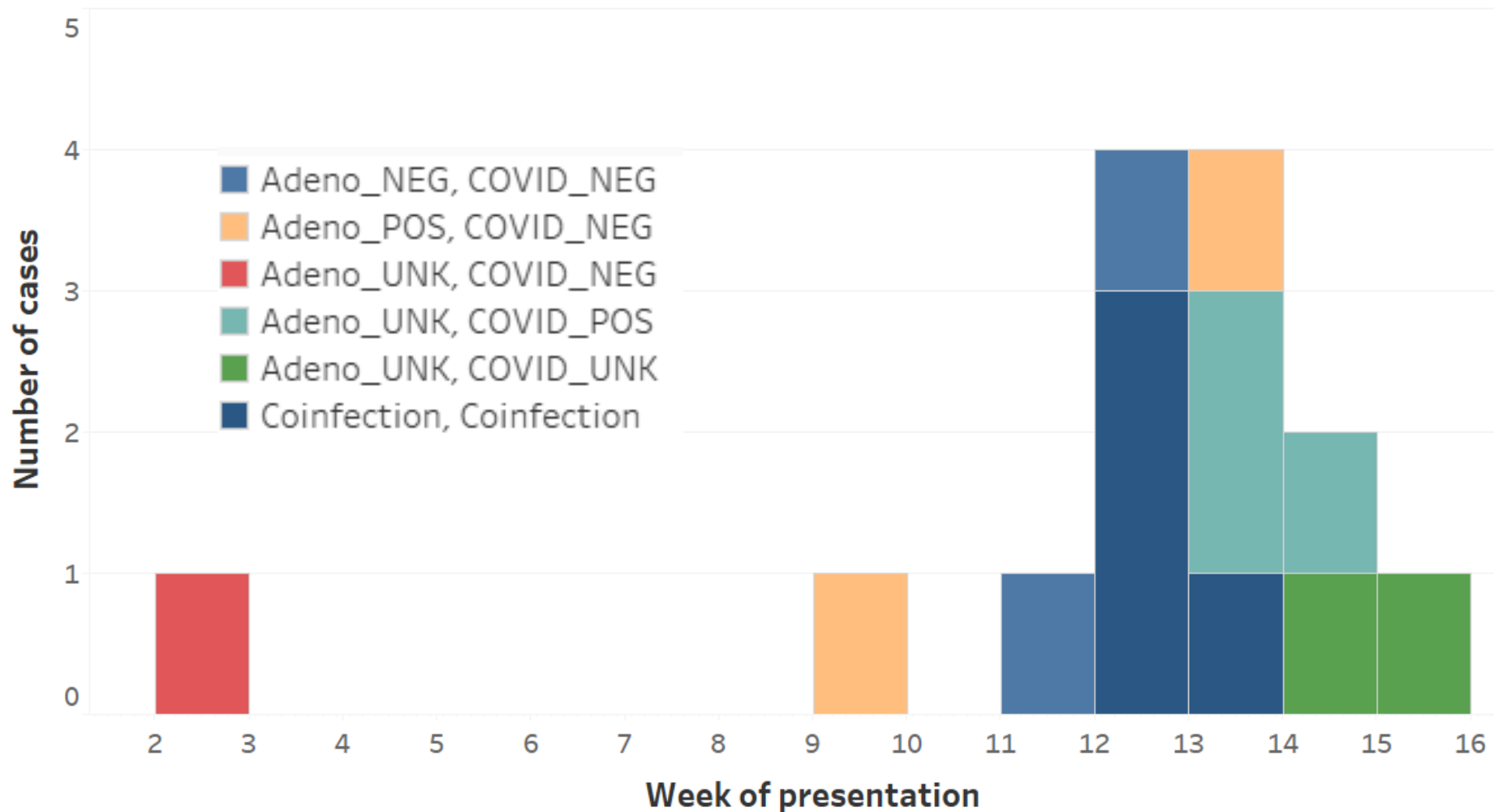
- **COVID-19 test results:** 7/12 (58%) positives, 1 unknown/missing
- **Adenovirus:** 5/8 (62%) positives, 5 unknown/missing
- **Adenovirus and SARS-COV-2 Co-infection:** 3/8 (38%)
- **EBV:** 10/10 Negative, 3 unknown
- **CMV:** 10/10 Negative, 3 unknown
- **COVID-19 Vaccine:** 0/13 vaccinated

Clinical outcomes (to be updated)

Still in hospital	1/14	7%
Discharged and well	5/14	36%
Transferred to higher facility	3/14	21%
Died	0/14	0
No outcome reported yet	4/14	29%



Epi curve of confirmed cases of atypical non A to E hepatitis (n=14), 11 Jan - 19 Apr 2022, Scotland



Known epidemiologic links:

- 2 linked cases in the same nursery in Fife
- 1 sibling pair in GGC with presentation dates of 21 and 30 March

Detected pathogens

- Adenovirus: 6 positive, 2 negative, 5 unknown
- SARS-COV-2: 7 positive, 5 Negative, 1 unknown

* Data as of 1700, 19 April 2022



UK Health
Security
Agency

Investigation into acute hepatitis of unknown aetiology in children in England

Technical briefing 3

19 May 2022



Current case definition for clinical reporting as of 26/04

Scotland

- **Confirmed:** A person presenting with a serum transaminase >500 IU/L (AST or ALT) without any known cause*, who is
 - Ages 10 years and under –
 - OR –
 - Contact of any age to a confirmed case,
 - Since 1 January 2022.

*If hepatitis A-E serology, CMV and EBV results are awaited, but other criteria met, these will be classified as “**pending classification**”. Cases that meet the initial criteria but are later found to have alternative causes will be denotified.

England (06 May 2022)

- **Confirmed:** A person presenting since 1 January 2022 with an acute hepatitis which is not due to hepatitis A-E viruses, or an expected presentation of metabolic, inherited/genetic, congenital or mechanical cause* with serum transaminase >500 IU/L (Aspartate Transaminase-AST or Alanine Transaminase -ALT), who is 10 years old and under.
- **Possible:** A person presenting with an acute hepatitis since 1 January 2022 with an acute hepatitis which is not due to hepatitis A-E viruses or an expected presentation of metabolic, inherited/genetic, congenital or mechanical cause* with serum transaminase >500 IU/L (AST or ALT), who is 11 to 15 years old.
- **Epi-linked**:** A person presenting since 1 January 2022 with an acute hepatitis (non-hepatitis A to E) who is a close contact of a confirmed case.

*Cases should be reported based on clinical judgement if some hepatitis A-E virus results are awaited, or if there is an acute on chronic hepatic presentation with a metabolic, inherited/genetic, congenital, mechanical or other underlying cause. If hepatitis A-E serology results are awaited, but other criteria met, these will be classified as “pending classification”.

** A person who is epi-linked but also meets the confirmed or possible case definition will be recorded as a confirmed or possible case and their epi-link noted in their record. This prevents double-counting of cases.



Working hypotheses

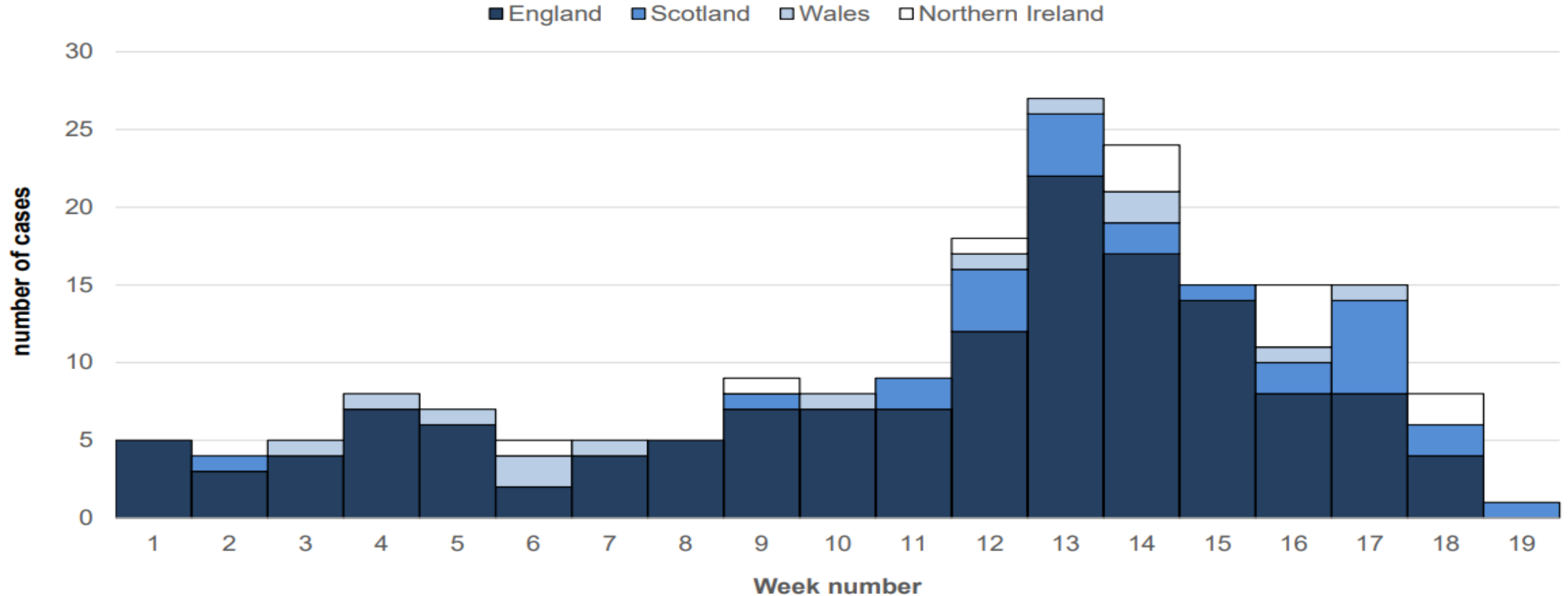
In order of fit with the current data, from best fit to poor

1. A normal adenovirus infection, due to one of:
 - a. Abnormal susceptibility or host response which allows adenovirus infection to progress more frequently to hepatitis (whether direct or immunopathological), for example from lack of exposure during the coronavirus (COVID-19) pandemic.
 - b. An exceptionally large wave of normal adenovirus infections, causing a very rare or under-recognised complication to present more frequently.
 - c. Abnormal susceptibility or host response to adenovirus due to priming by a prior infection with SARS-CoV-2 (including Omicron restricted) or another infection.
 - d. Abnormal susceptibility or host response to adenovirus due to a coinfection with SARS-CoV-2 or another infection.
 - e. Abnormal susceptibility or host response to adenovirus due to a toxin, drug or environmental exposure.
2. A novel variant adenovirus, with or without a contribution from a cofactor as listed above.
3. A post-infectious SARS-CoV-2 syndrome (including an Omicron restricted effect).
4. A drug, toxin or environmental exposure.
5. A novel pathogen either acting alone or as a coinfection.
6. A new variant of SARS-CoV-2.

UK cases to 16th May 2022

Figure 1. Cases by week of presentation, 1 January to 16 May 2022

Supplementary data is not available for this figure.



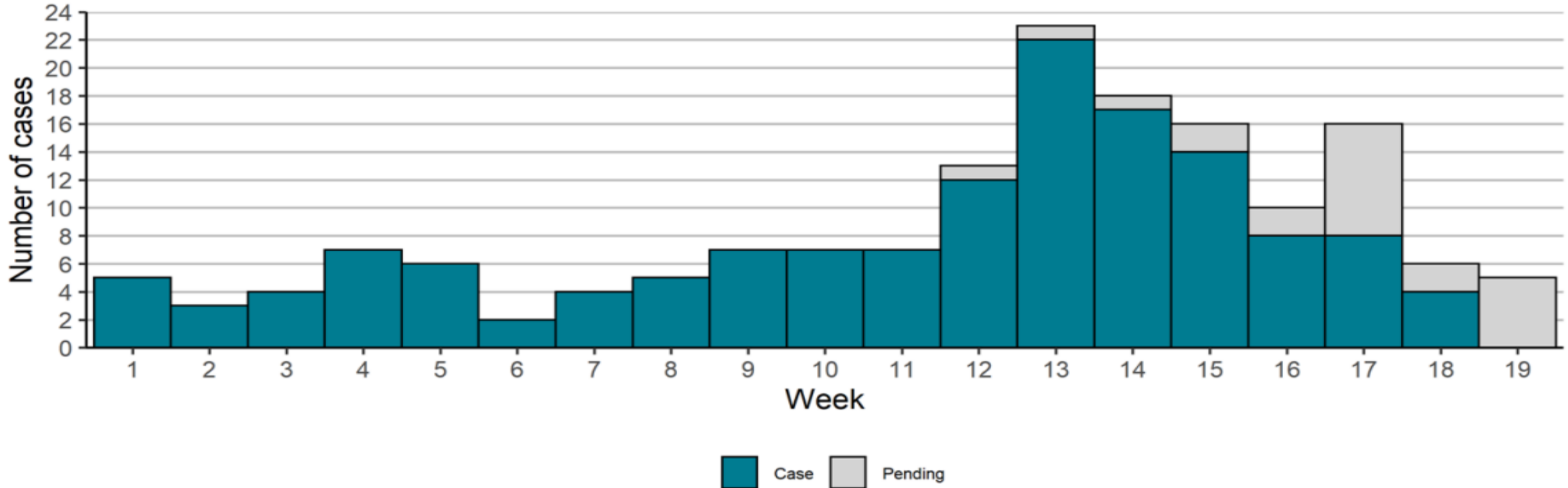
Date not available for 2 cases in England and 2 Wales possible cases.

Week is based on hospitalisation date where available, then date of arrival at emergency care department where available, then date of presentation to healthcare.

Epidemic curve - Evidence of recent slowing in new cases?

Figure 2. Notifications by week of presentation to care and investigation status (Case and pending classification) in England, 1 January to 16 May 2022

Supplementary data is not available for this figure.

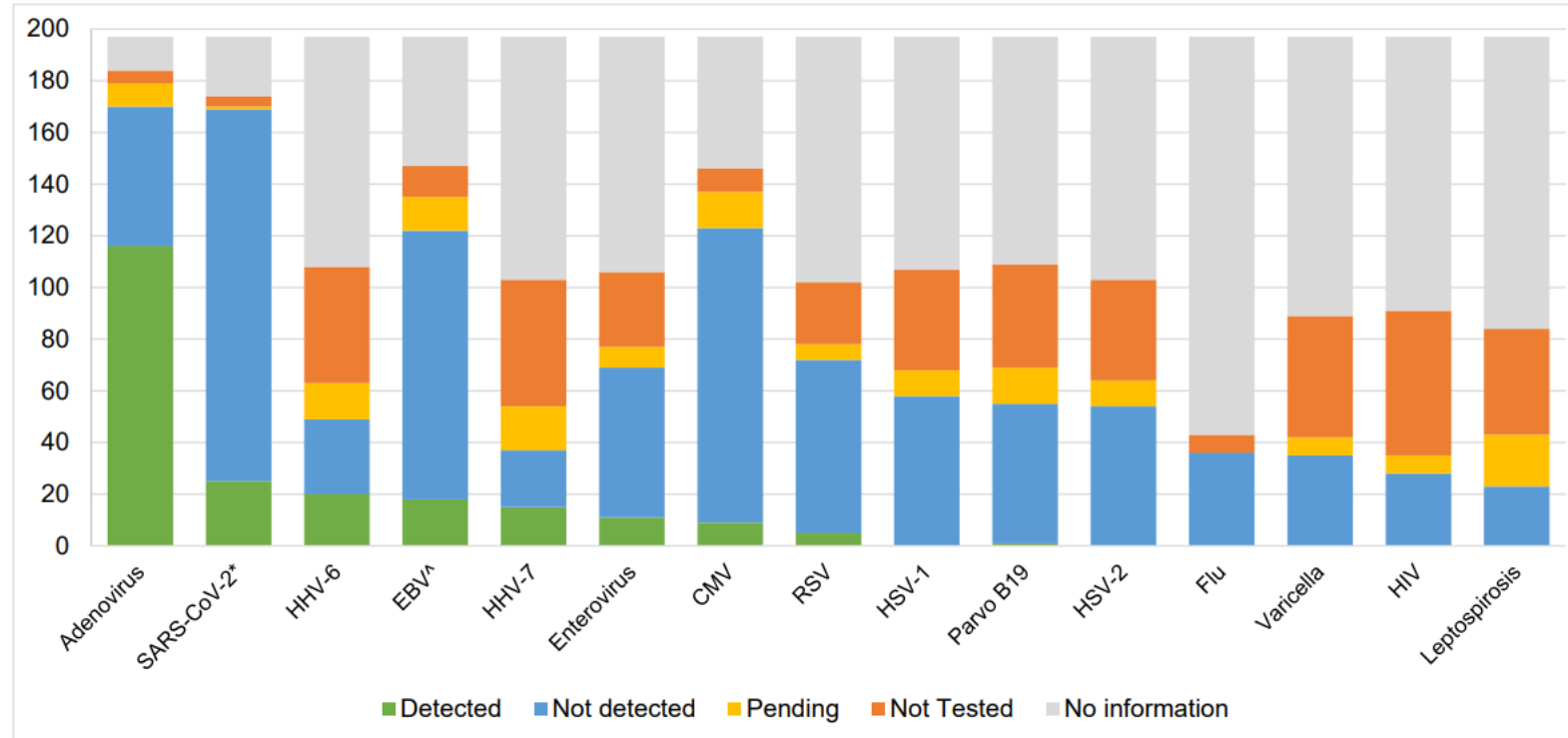


Week is based on hospitalisation date where available, then date of arrival at emergency care department where available, then date of presentation to healthcare. 28 notifications are excluded due to date not being reported. Pending cases are those which have been notified to UKHSA but whose hepatitis A-E serological results are awaited.

Pathogens Detected

Figure 3. Pathogens tested for and results in cases in UK

Supplementary data is not available for this figure.



*SARS-CoV2 testing presented here is based on testing around hospital admission or attendance (had previously included up to 2 weeks prior for England cases).

^ including one past positive.



Adenovirus detection

Of the 8 England-resident patients who required a liver transplant, 7 were tested for adenovirus in blood samples and the virus was detected in all 7. Five were successfully subtyped, as 41F.

Table 2. Adenovirus testing [note 1] results of cases resident in England

Adenovirus testing	Number of cases	Number of cases with each sample type (there may be multiple samples per case)			
		Blood	Stool	Respiratory	Other or unknown
Positive	91 (74.6%)	77 (79.4%)	18 (43.9%)	12 (27.3%)	17 (73.9%)
(% positivity, excluding pending)					
Negative	31	20	23	32	6
Pending	9	6	12	7	13
Total tested	131	103	53	51	36

[Notes on table 2](#)

[note 1] testing locations: any diagnostic laboratory.

Whole blood outperforms sera for diagnosis...

Figure 4. Ct value comparison of blood sample from cases – Hexon versus Fibre gene PCR (n=54)

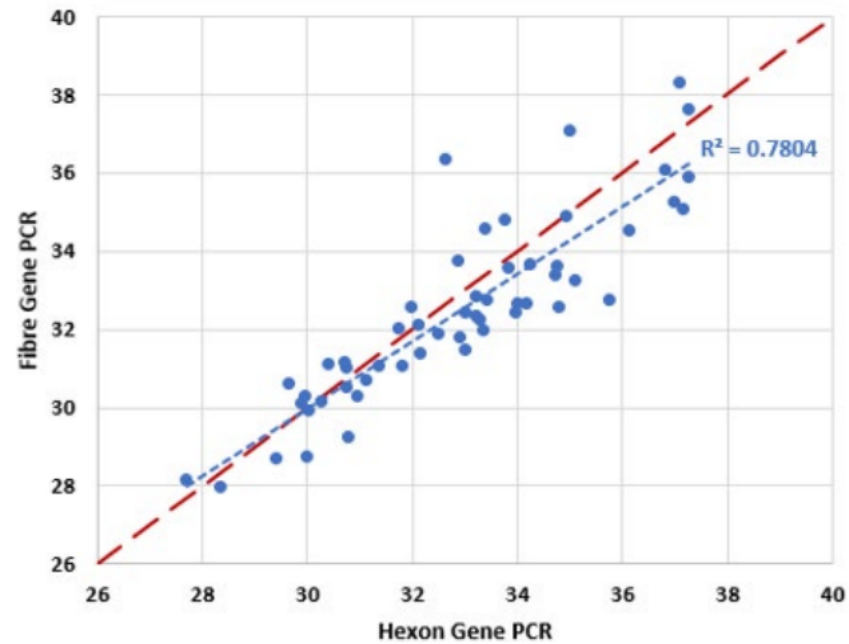
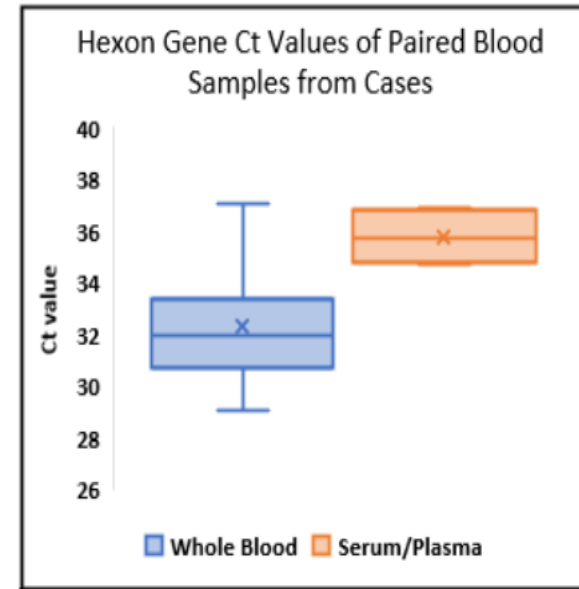


Figure 5. Comparison of different sample types using Hexon Gene PCR. Detection in cases (N=24)



Metagenomics

5.4. Metagenomic sequencing

Blood and liver analyses

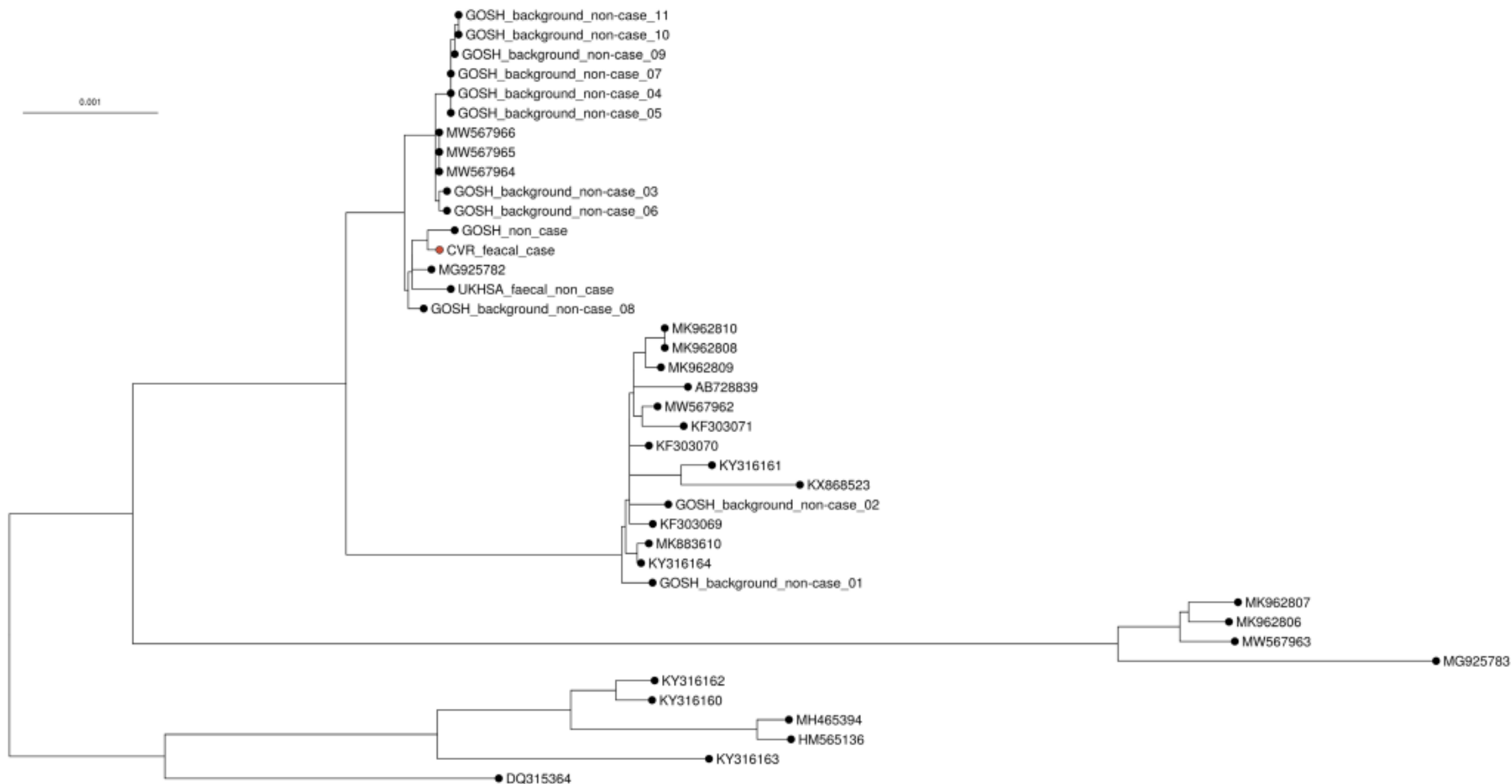
Metagenomics data from 28 UK samples, of which 10 samples (9 cases) sequenced at GOSH, and 18 samples (9 cases) from Medical Research Council-University of Glasgow Centre for Virus Research (MRC-CVR) have been analysed. Sample types include 8 liver samples, 7 faecal, 6 blood, one rectal, and 6 throat.

Analysis of metagenomics data from blood and liver samples (n=14) has been initially performed using Kraken2. One sample contained insufficient viral reads for further analysis. Viral reads in the remaining 13 samples show adeno-associated dependoparvovirus A in all samples. Four samples contain reads mapping to human adenovirus, which includes viruses such as Adenovirus 41F. All samples also contain reads identifying as Human Herpes Virus, including viruses such as HHV6. Work is ongoing to determine sub-types. Four of 8 liver samples also contain Human Polyomavirus. The classifier used in initial analysis does not have the specificity required to identify species and subspecies. Work is ongoing.

It was previously reported that adeno-associated virus 2 (AAV2) was detected in both deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) fractions through metagenomic analysis, in samples from cases in England and Scotland. Analysis is ongoing.



Figure 6. Whole genome phylogenetic tree containing ADV 41F consensus sequence generated from metagenomics of faecal sample by MCR-CVR. Background ADV 41F sequences gathered from GenBank, and GOSH. This tree has been rooted using ADV C genome sequences from GenBank not shown in this image. Case sequences are shown in red, background sequences shown in black. Supplementary data is not available for this figure.



Toxicology

Extensive investigation – 145 pts and 77 age/sex matched controls

- Liquid Chromatography/High Resolution Mass Spectrometry (LC/HRMS)
 - targets substances with different chemistries: polar and nonpolar, each with positive and negative ionisation for organic molecules and metabolites
- Gas Chromatography/Mass Spectrometry (GC/MS)
 - used for volatile and semi-volatile organics
- Inductively Coupled Plasma Mass Spectrometry (ICPMS)
 - for metals/elemental analyses

- Paracetamol – detections in line with appropriate clinical use
- Fluconazole – detections in line with appropriate clinical use



International reporting



COMMUNICABLE DISEASE THREATS REPORT

CDTR
Week 20, 15-21 May 2022

All users

This weekly bulletin provides updates on threats monitored by ECDC.

In excess of 600 cases have been officially reported to date from more than 30 countries

I. Executive summary

Increase in hepatitis cases of unknown aetiology in children – Multicountry – 2022

Opening date: 13 April 2022

Latest update: 20 May 2022

On 5 April 2022, an increase in cases of acute hepatitis of unknown aetiology among previously healthy children aged under 10 years was reported by the United Kingdom (UK). Most cases identified by the UK presented with symptoms from March 2022 onwards. Since then, additional cases have been reported from the EU/EEA and globally.

→ Update of the week

EU/EEA:

As of 19 May 2022, 125 cases of acute hepatitis among children aged 16 years and under have been reported from 14 EU/EEA countries ([Austria](#) (2), [Belgium](#) (9), [Cyprus](#) (2), [Denmark](#) (6), [France](#) (2), [Greece](#) (3), [Ireland](#) (6), Italy (35), the [Netherlands](#) (6), [Norway](#) (4), [Poland](#) (3), [Portugal](#) (12), [Spain](#) (26) and [Sweden](#) (9)). Among these cases, six required a liver transplant.

Outside of the EU/EEA:

As of 12 May 2022, the UK Health Security Agency (UKHSA) has identified a total of 176 children aged under 10 years with acute hepatitis of unknown aetiology. Of these, 11 have received a liver transplant. The most recent technical briefing on investigations into the cases in the UK presents data as of 6 May 2022.

Outside of EU/EEA and the UK, as of 19 May 2022, there are at least 313 cases of acute hepatitis among children. Cases have been reported by 16 countries: Argentina (9), Brazil (44), Canada (11), Costa Rica (2), Indonesia (14), Israel (12), Japan (12), Malaysia (1), Mexico (21), Moldova (1), Palestine* (1), Panama (2), Serbia (1), Singapore (1), South Korea (1) and the United States (180).

The total number of cases reported worldwide is 614, including 14 deaths reported from Ireland (1), Indonesia (6), Mexico (1), Palestine* (1) and the United States (5).

**This designation shall not be construed as recognition of a State of Palestine and is without prejudice to the individual positions of the Member States on this issue.*

Disclaimer: Data presented in this update are compiled from official national reports or, if not available, from public sources quoting national authorities. Where possible, cases are classified according to the EU/EEA case definition. Media reports might not include complete information on testing, so classification of cases is not always possible. These are presented as 'cases under investigation'. Data include both probable cases, according to the case definition used in the EU/EEA, and cases under investigation. In some cases, the testing strategy has not been officially confirmed.

Working hypotheses

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Adenovirus +/- cofactor seems likeliest explanation...But investigation continues!