UK Health Security Agency

Investigation into acute hepatitis of unknown aetiology in children in England

Technical briefing 2

6 May 2022

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Introduction

The UK Health Security Agency (UKHSA) is working with the National Health Service (NHS) and the public health agencies of the 4 nations of the UK to investigate the potential cause of an unusually high number of acute hepatitis cases being seen in children in the past few weeks. There is no known association with travel, and hepatitis viruses (A to E) have not been detected in these children.

Unless otherwise stated this technical briefing uses data cut-off of 3 May 2022 to allow time for analyses. More recent case numbers may be cited in other UKHSA public updates but are not included in the analyses presented here. The 4 UK nations are conducting a coordinated investigation and data is in the process of being reconciled across the UK. For this reason, summary epidemiology data is presented for all 4 nations, whilst some detailed analyses can only be presented for single countries at present.

Summary

This briefing is produced to share data useful to other public health investigators and academic partners undertaking related work. Although a detailed clinical case review is also taking place, that data is not shared here as, given the small number of cases, there are some risks to confidentiality.

Cases

As of 3 May 2022, there have been 163 cases of acute non-A-E hepatitis with serum transaminases greater than 500 IU/l identified in children aged under 16 years old in the UK since 1 January 2022. This is the result of an active case finding investigation commencing in April which identified retrospective as well as prospective cases. Eleven cases have received a liver transplant. No cases resident in the UK have died.

New cases continue to be identified. Whilst there is some apparent reduction in confirmed cases in the past 2 weeks overall in the UK, there are continued new case reports in Scotland, the number of cases pending classification in England is substantial and the likely reporting lags mean that we cannot yet say there is a decrease in new cases. Cases pending classification are usually those in which laboratory testing to rule out known causes of hepatitis has not been completed.

Working hypotheses

The working hypotheses have been refined. The leading hypotheses remain those which involve adenovirus. However, we continue to investigate the potential role of SARS-CoV-2 and to work on ruling out any toxicological component.

Associated pathogens

Adenovirus remains the most frequently detected potential pathogen. Amongst 163 UK cases, 126 have been tested for adenovirus of which 91 had adenovirus detected (72%). Amongst cases the adenovirus has primarily been detected in blood. On review of some of the adenovirus negative cases it was notable that some had only been tested on respiratory or faecal samples, and some had been tested on serum or plasma rather than whole blood (whole blood being the optimal sample). It is therefore not possible to definitively rule out adenovirus in these cases.

SARS-CoV-2 has been detected in 24 cases of 132 with available results (18%). SARS-CoV-2 serological testing is in process. A range of other possible pathogens have been detected in a low proportion of cases and are of uncertain significance, although the inclusive nature of the

UKHSA case definition intentionally will pick up some cases of non-A-E hepatitis with recognised causes.

Adenovirus characterisation

Typing by partial hexon gene sequencing consistently shows that the adenovirus present in blood is type 41F (18 of 18 cases with an available result). Whole genome sequencing (WGS) has been attempted on multiple samples from cases but the low viral load in blood samples, and limited clinical material from historic cases, mean that it has not been possible to get a good quality full adenovirus genome from a case as yet.

Metagenomics

Metagenomics undertaken on blood and liver tissue has detected primarily adeno-associated virus 2 (AAV-2) in high quantities. Whilst contamination was originally suspected, AAV-2 is now detected in multiple samples from different hospital sources and tested in more than one sequencing laboratory. This finding is of uncertain significance and may represent a normal reactivation of AAV-2 during an acute viral infection (for example, adenovirus) or during liver injury of another cause. It is not unusual to detect bystander, reactivating or other incidental species during metagenomic sequencing. However, given the presence of AAV-2 in a number of cases, the significance will be further explored through testing of additional sets of controls.

Toxicology

Toxicological investigations continue with no positive findings to date. Detection of paracetamol is likely to be related to appropriate therapeutic use (also noted in the trawling questionnaires) which would not be a concern, however verification work is being undertaken to confirm this.

Host investigations

Host (for example, immunological) investigations require full research consent and are undertaken under the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterisation Protocol. Thirty-seven cases have been recruited to the ISARIC clinical characterisation protocol to date and retrospective and prospective recruitment continues.

Part 1. Working hypotheses

The following hypotheses are all being actively tested by the investigations in process.

There are increased paediatric acute non-A-E hepatitis presentations due to:

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.

Part 2. Update on planned investigations

The investigations include clinical case investigation in the NHS, public health pathogen investigations, and research investigations under the International ISARIC Clinical Characterisation Protocol with full appropriate consent. ISARIC is funded by UK Research and Innovation and the National Institute for Health Research.

2.1 Additional investigations and status

	Investigation	Lead	Status
Analytic epidemiology	Matched case-control study (with residual whole blood samples from hospitalised children for controls) to test association of hepatitis with adenovirus infection	UKHSA	Commenced
	Analysis to investigate co-factors associated with hepatitis in cases	UKHSA	Protocol under development
	Analysis to investigate factors (demographic and clinical features) associated with severe outcome in cases, stratified by adenovirus infection (case-case study)	UKHSA	Protocol under development
Surveillance for liver syndromes in children	Enhanced surveillance for severe acute hepatitis in children through British Paediatric Surveillance Unit, and referrals to paediatric liver units	UKHSA	Commenced
Mechanism of liver injury	Investigations on liver tissue to include electron microscopy, further histopathology review, T cell subset analysis	NHS	Histopathology review complete – additional investigations planned
Pathogen investigations	Adenovirus whole genome sequencing from cases and community samples	UKHSA and Great Ormond Street Hospital (GOSH)	Underway with first reports available

	Investigation	Lead	Status
	Metagenomic sequencing of blood and liver tissue from cases	UKHSA and GOSH	Underway with first reports available
	Viral culture of adenovirus and phenotypic characterisation including assessment of hepatotropism in vitro	UKHSA and academic partners	Viral cultures of clinical materials negative to date
	Adenovirus and SARS-CoV-2 serology of cases	UKHSA	Testing underway
	SARS-CoV-2 sequencing in positive cases	UKHSA	Reported where available
	Retrospective wastewater analysis for adenovirus	UKHSA	Under consideration
Host characterisation	Harmonised clinical data collation and analysis	ISARIC with partners	Recruiting
	Host genetic characterisation	ISARIC in partnership with GENOMICC	Recruiting
	Immunological characterisation including T cell activation studies	ISARIC with partners	Recruiting
	Transcriptomics	ISARIC with partners	Under consideration

Part 3. Case definitions and summary data for cases in the UK

3.1 Case definitions

Case definitions in all UK nations have been revised and harmonised to facilitate clinical reporting. Scotland have changed their case definition to remove possible cases and is moving towards alignment with England, Wales and Northern Ireland.

England, Wales, Northern Ireland case definitions

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 or genetic, congenital or mechanical cause* with serum transaminase greater than 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 or genetic, congenital or mechanical cause* with serum transaminase greater than 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-E) who is a close contact of a confirmed case. (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.)

*Confirmed and possible 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 or 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’.

Scotland case definition

Confirmed

A person presenting with a serum transaminase greater than 500 IU/L (AST or ALT) without any known cause (excluding hepatitis A-E, Cytomegalovirus and Epstein-Barr Virus), who is 10 years of age and under or a contact of any age of a confirmed case, since 1 January 2022.

3.2 Summary data on cases in the UK

As of 3 May 2022, there are 163 confirmed and possible cases in the UK. Of these, 118 cases are resident in England, 22 in Scotland, 13 in Wales and 10 in Northern Ireland (see Figure 1). Between 21 January and 3 May 2022, 11 children in the UK meeting the case definition have required liver transplantation. For the purposes of this summary, all confirmed and possible cases will be referred to as cases.

3.3 Outcomes

Clinical outcomes for the 163 cases (at time of clinical notification or interview with parent or guardian) are shown in Table 1. All cases are being followed up for outcome at 28 days after presentation to health services. No cases have died. Of the 163 cases, 11 have required transplantation. It should be noted that the case definitions require high transaminases, and it is possible that there are milder cases which have not been reported.

Table 1. Outcome status for UK cases (n=163) on 3 May 2022

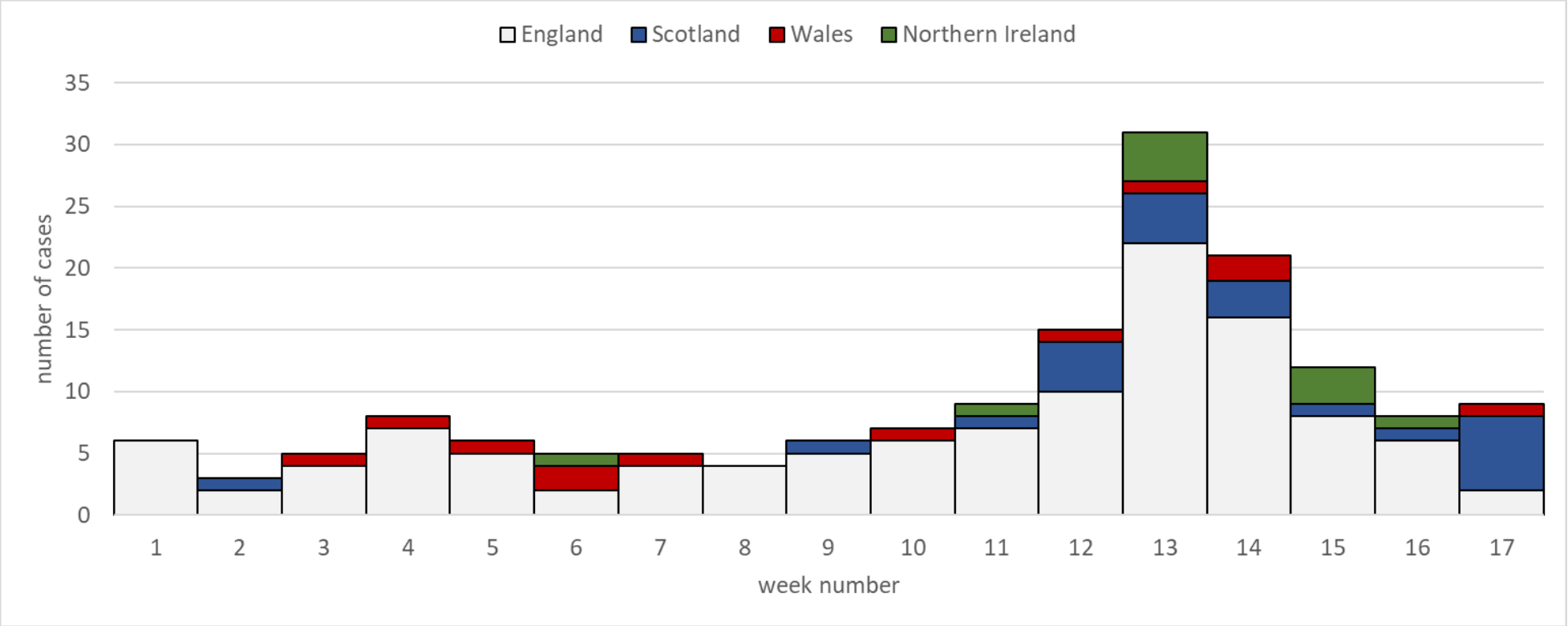
Outcome	Number	Percentage
Died	0	0.0
Hospitalisation reported		
Still in hospital^	13	8.0
Discharge status not yet ascertained^	49	30.0
up to 28 days since presentation ~	19	
29+ days since presentation ~	30	
Discharged or fully recovered	88	54.0
No information	13	8.0
Total cases	**163**	**100**

Information missing for 2 Wales cases.

^ = where hospitalised.
~ = where discharge status is unknown.

Figure 1. Cases by week and UK nation*, 1 January 2022 to 3 May 2022

Supplementary data is not available for this figure.



* Data for week 17 is not full week.

Date not available for 2 cases in England and one case in Wales.

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

3.4 Possible exposures

Investigations have included interviews of parents conducted by public health specialists to assess a broad range of different exposures (trawling questionnaires), as reported in the Acute hepatitis: technical briefing 1. In the first 60 case patients in England with data available, no notable features or common exposures were observed in travel, family structure, parental occupation, diet, water source or potential exposures to toxicants, and no association with prior immunosuppression. The public health agencies of Wales, Scotland and Northern Ireland report similar findings through their investigations. Public Health Scotland also report that there are 2 pairs of epidemiologically linked cases.

Review of UK trawling questionnaire responses has found relatively high numbers of dog-owning families or other dog exposures in cases (64 of 92 where data was available, 70%). The significance of this finding is being explored. Pet dog ownership is common in the UK. There are limited data on background rates of pet ownership in families of young children, non-household dog contact reporting may include transient non-significant contact, and the nature of trawling questionnaire investigations mean that some responses may be high through the play of chance due to the large numbers of questions asked.

Approximately three-quarters of respondents in data for England mentioned paracetamol use. Fewer reported ibuprofen use and none reported aspirin use. While paracetamol is an important hepatotoxic agent in overdose, there have been no reports of paracetamol hepatoxic presentations or histories from any of the clinical units. The prevalence of paracetamol use is considered consistent with guidance on management of acute illness in children.

COVID-19 vaccination

COVID-19 vaccinations are not recommended by the Joint Committee on Vaccination and Immunisation for children aged under 5. They are available for children aged 5 and over. There were no COVID-19 vaccinations recorded in cases aged under 5, the age group which makes up over 75% of hepatitis cases. There are fewer than 5 older case-patients recorded as having had a COVID-19 vaccination prior to hepatitis onset. There is no evidence of a link between COVID-19 vaccination and the acute hepatic syndrome.

Part 4. Cases in England: descriptive epidemiology and clinical data

4.1 Cases in England

As of 3 May, there were 118 cases in England. There are no known epidemiologically linked cases in England. Forty potential cases in England are awaiting classification pending further data (see Figure 2). Cases are predominantly aged between 3 and 5 years old (66, 56.9%), median age 3 (interquartile range 3 to 4 years) and 50% are female. The majority are of white ethnicity (92 out of 107, 86.0%) where information was available.

Figure 2. Cases by week and investigation status in England, 1 January to 3 May 2022 (n = 145)

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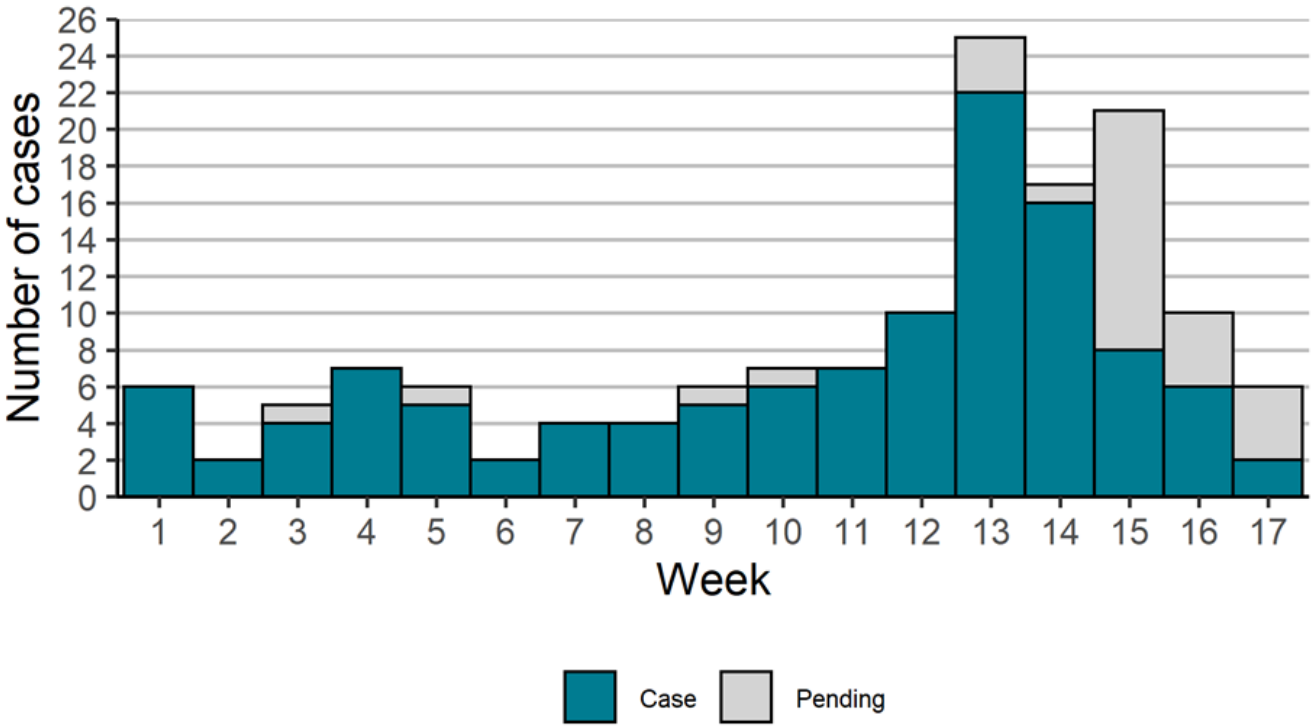

Week is based on hospitalisation date where available, then date of arrival at emergency care department where available, then date of presentation to healthcare. Fifteen cases are excluded due to date not being reported. Pending cases are those which have been notified to UKHSA but whose hepatitis A-E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

4.2 Clinical features

The most common presentation reported in cases remains jaundice (84 out of 118, 71.2%) followed by vomiting (74 out of 118, 62.7%). Pale stools were also frequently reported (50.0%). Gastro-intestinal symptoms were commonly reported at presentation including diarrhoea

(44.9%), nausea (30.5%) and abdominal pain (41.5%). Additionally, lethargy (50.0%), fever (30.5%) and less frequently, respiratory symptoms (18.6%) were reported. Note that the denominator includes those who have reported the symptom, absence of symptom and unknown (missing information).

Histopathology

In addition to local assessments, an additional review of all available liver samples was undertaken by a single expert histopathologist. These specimens included 6 explanted (removed) livers and 8 biopsies from a combination of English and Scottish cases. The specimens demonstrated variable severity ranging from mild hepatocellular injury to massive hepatic necrosis. The overall pattern seen is non-specific and there is no clear identifiable cause from the histopathology results.

On hematoxylin and eosin (H and E) staining, the inflammatory response was variable throughout the specimens reviewed. Further immunohistochemistry for lymphocytic subpopulations is planned.

Adenovirus immunohistochemistry has been reported from 9 of the 14 samples to date and showed immunoreactivity in the intrasinusoidal lumen but not in residual hepatocytes. This is likely a non-specific finding. One case underwent adenovirus PCR of liver tissue which was negative.

Part 5. Cases: pathogen investigations

5.1 Potential pathogens detected through routine clinical testing: all UK cases

Cases have been tested for pathogens at or around the time of admission. Test choice is a local clinical decision and not all cases have been tested for the same pathogens (from 8 April 2022 UKHSA recommended a panel of tests to perform on all cases). All hospital admissions would have SARS-CoV-2 tests. Testing information is gathered from a variety of sources, including direct reports from clinicians, direct reports from laboratories, information from UKHSA reference laboratories and from linkage to data sources including Second Generation Surveillance System (SGSS) and the COVID-19 Unified Sample Dataset.

Adenovirus remains the most common pathogen detected (see Figure 3). Of 163 UK cases, adenovirus was detected in 91, a further 35 were tested but adenovirus was not detected, 4 cases have results pending, and for 33 there is no test or no information available. On a review of some of the cases tested for adenovirus which were negative, it was apparent that several had not been tested in blood, and additional retrospective testing is being explored.

A more detailed breakdown of cases' adenovirus and SARS-CoV-2 results over time has been provided for England cases (see Figure 4).

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

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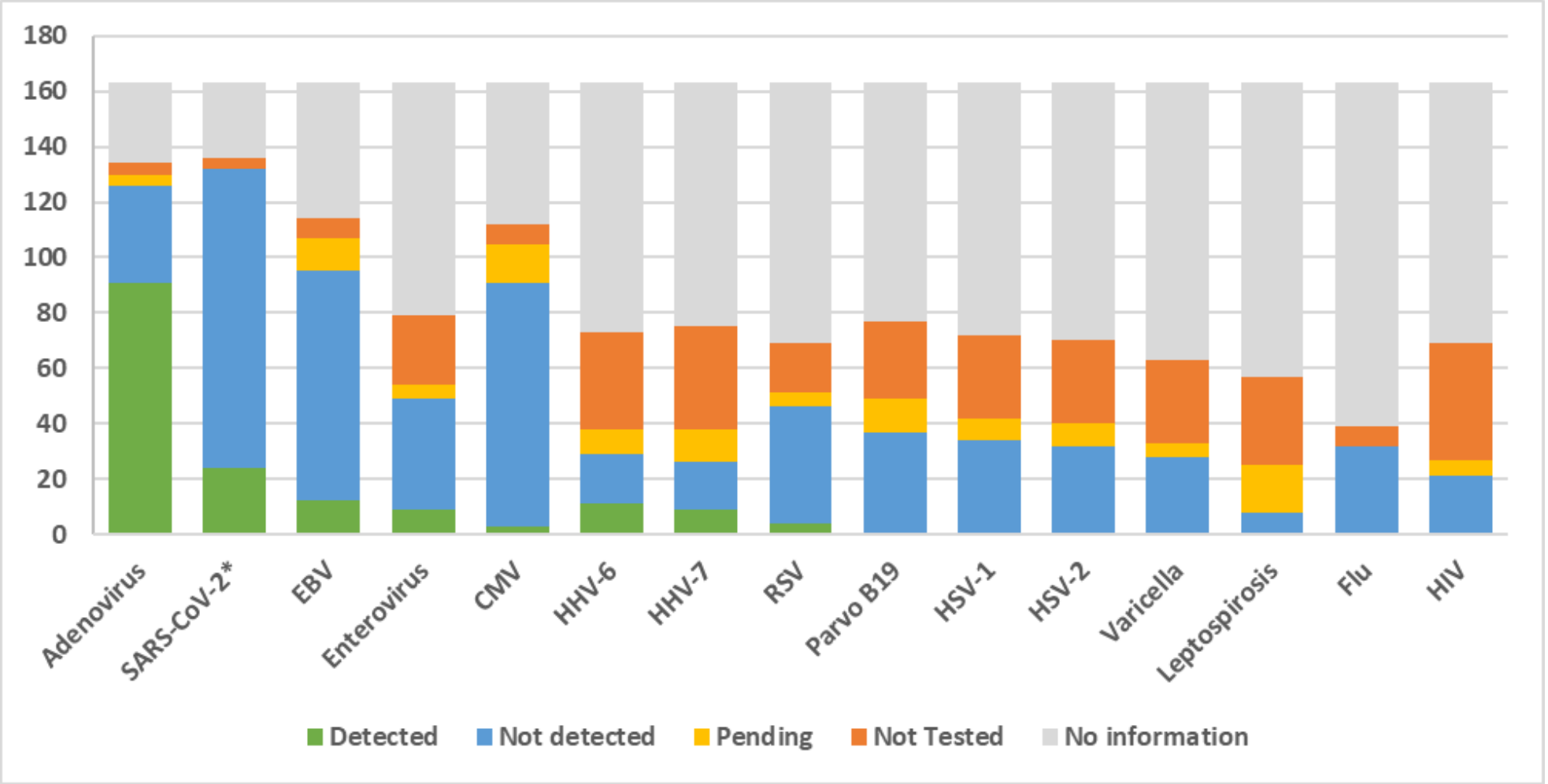

* SARS-CoV-2 testing is based on testing around hospital admission or attendance.

Figure 4. Epidemic curve of confirmed and possible cases, by adenovirus and SARS-CoV-2 result in England (n=116)

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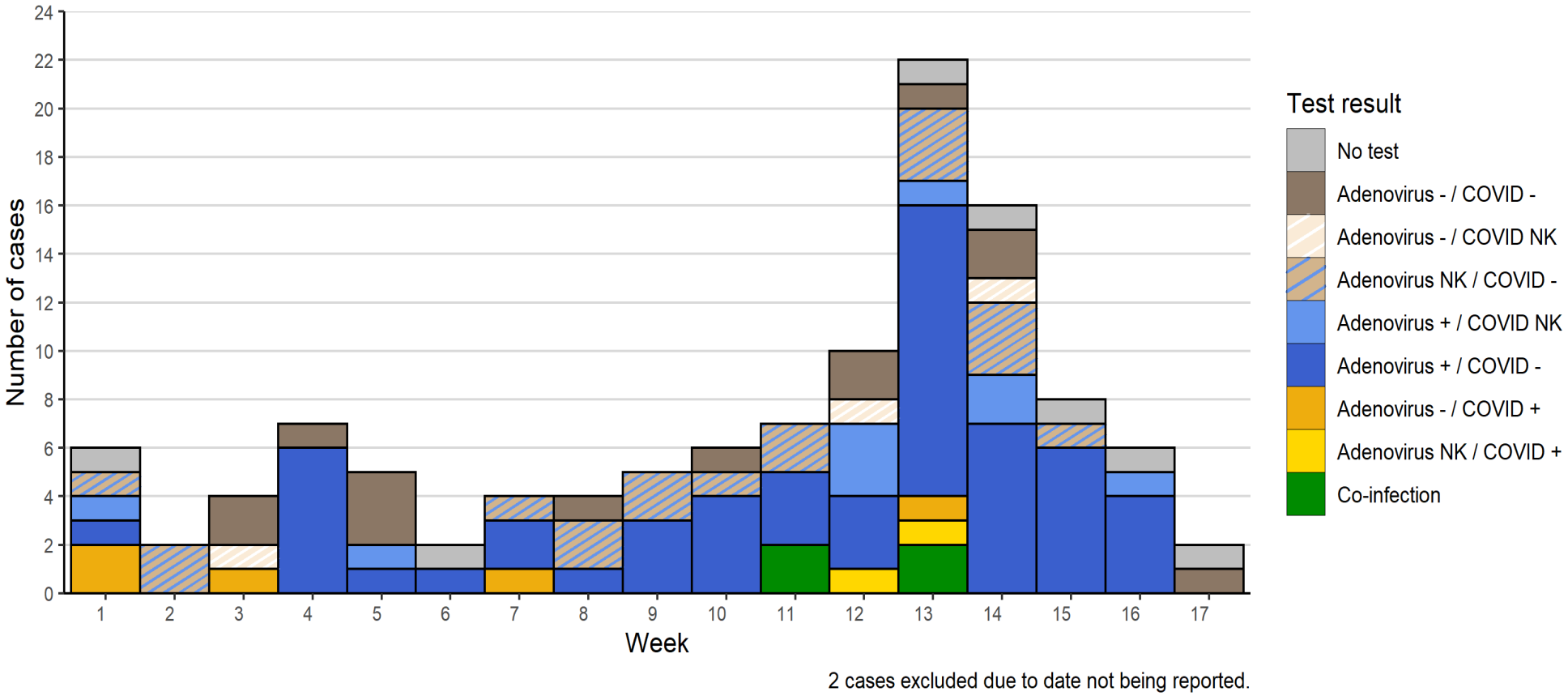


Adenovirus noted as Adeno, SARS-CoV-2 noted as COVID-19, detected noted as Pos, not detected noted as Neg, not known or not tested noted as NK.

5.2 Adenovirus

Adenovirus was the most common pathogen detected. Amongst 163 UK cases, 126 have been tested for adenovirus of which 91 had adenovirus detected.

Further analysis relates to cases from England, of which adenovirus was detected in 67 of 89 cases which have been tested. 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.

Adenovirus testing is delivered in hospital trusts through a wide range of commercial and in-house testing arrangements, and current testing algorithms rarely include the testing of whole blood for immunocompetent patients with any presenting syndromes. Ascertainment of adenovirus testing arrangements is incomplete, either because of variation in local testing arrangements, sample types tested, or platforms used, which themselves may vary in detection sensitivity. Typically, the detection of adenovirus uses a highly conserved target, but subtyping into adenovirus species requires further specific PCRs or sequence confirmation

For cases in England, by sample type based on the data report, adenovirus was detected more commonly in blood or serum samples from cases (51 out of 62, 82.2%), than in stool (44.0%) or respiratory (28.6%) samples. However, a consistent sample set has not been tested for most cases (see Table 2). We can say that the picture of detection of enteric adenoviruses in blood is not so far accompanied by detection of enteric adenovirus in stool at the same time, but in a handful of cases an enteric adenovirus has been found in blood, with a different adenovirus found in faecal or respiratory materials, indicating a possible mixed infection.

Of the 22 cases where adenovirus was not detected, 6 had not had testing on blood which appears to be the most relevant sample type for the syndrome, 5 were tested on plasma not whole blood, and a further 9 of unknown sample type had been tested in a hospital laboratory but not retested by the reference laboratory, although we are aware of potential performance differences between assays in clinical use. For 20 of the 22 cases where adenovirus is reported as not detected, we therefore cannot definitively exclude the presence of adenovirus.

Eighteen of the 33 cases with adenovirus in blood have been successfully subtyped, of which all 18 are type 41F, including 4 out of 6 transplanted cases.

Table 2. Adenovirus testing and typing of cases, England residents (n=118)

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		
		Any lab	VRD*	Typed (of which 41F)	Any lab	VRD*	Typed (of which 41F)	Any lab	VRD*	Typed (of which 41F)	Any lab	VRD*	Typed (of which 41F)
Positive (% positivity, excluding pending)	67 (75.3%)	51 (82.2%)	33	18 (18)	11 (44.0%)	4	3 (0)	6 (28.6%)	3	0 (0)	18 (72.0%)	3	0 (0)
Negative	22	11	12	-	14	7	-	15	10	-	7	2	-
Pending	4	6	-	-	7	-	-	8	-	-	1	-	-
Total tested	**93**	**68**	**45**	**-**	**32**	**11**	**-**	**29**	**13**	**-**	**26**	**5**	**-**

Notes on table:

Non 41F subtypes were identified in stool samples: 1x 1C, 1x 2C, 1x 5C.

*Testing locations: ‘Any lab’ = a clinical or regional laboratory. VRD = UKHSA Virus Reference Department.

Further investigative work, including WGS of multiple cases, is required before any firm conclusions can be drawn on characterisation of the adenoviruses involved.

Adenovirus WGS as well as metagenomic sequencing have commenced on case samples. The low levels of adenovirus present in blood are challenging for recovery of high-quality genomes. For blood samples with attempted WGS, cycle threshold values range from 32 to 37.

There are currently very limited whole genome adenovirus sequence data available in the public domain, particularly for enteric adenoviruses. Academic and clinical centres which have or can generate adenovirus WGS data are asked to share consensus genomes to an International Nucleotide Sequence Database Collaboration such as GenBank to assist characterisation of circulating adenovirus strains internationally.

5.3 SARS-CoV-2

For cases resident in England, 11 cases tested positive for SARS-CoV-2 on admission (PCR or lateral flow device), of 97 cases with available test data (11.3%). An additional 3 tested positive in the 8 weeks prior to admission (for a total period prevalence of 14 out of 100, 14%).

Serological testing is in process to explore prior infection further, however, the high population cumulative prevalence of SARS-CoV-2 will make the interpretation of this data challenging. Four cases were co-infected with adenovirus and SARS-CoV-2.

Five cases with a positive test result for SARS-CoV-2 also have associated variant information from WGS. All 5 sequences are classified as VOC-22JAN-01 (lineage BA.2). Four of the 5 sequences contain mutations in addition to those expected to be present in all BA.2 sequences, but the mutations do not occur in more than one sequence. Two of the 6 sequences are from the time of hepatitis presentation, the remaining 4 sequences are from 3, 8, and 15 days post hepatitis presentation.

5.4. Metagenomic sequencing

Blood and liver analyses

Metagenomics has been performed on 19 samples: 14 samples from 11 English cases (6 blood, 4 liver, 2 serum and 2 EDTA-Plasma) and 5 Scottish samples from 5 Scottish cases (all sera)

Three testing laboratories have been involved: GOSH, Medical Research Council Centre for Virus Research (MRC-CVR) in Glasgow and UKHSA. UKHSA analysis of this data is in process, and only provisional results are reported here. Updates will be provided.

Adeno-associated virus 2 (AAV2) was detected in both DNA and RNA fractions through metagenomic analysis, in samples from cases in England and Scotland.

Provisional metagenomic analysis on English blood and liver samples has been performed by GOSH using methods available online.

This has identified 9 samples (8 cases) containing more than 50 reads that have been identified as AAV2. These have been analysed using the GOSH pipeline: 4 samples (4 cases) contain over 1,500 reads mapping to AAV2 reference sequences, with consensus sequences generated. Three of these consensus sequences are from liver tissue samples, the remaining sequence is from a blood sample. A further consensus sequence from a liver sample with more than 450 reads was also generated by GOSH.

AAV2 was detected in metagenomic analysis of serum from a further 5 cases in Scotland. Sequencing and analysis of this data was undertaken by the (MRC-CVR, Glasgow) in collaboration with ISARIC Clinical Characterisation Protocol. Three AAV2 consensus sequences have been provided for this analysis.

AAV2 consensus sequences from metagenomic analysis of cases have been aligned and placed in a phylogenetic tree (Figure 5). Consensus sequences generated by GOSH are labelled GOSH 1-5, whilst MRC-CVR consensus sequences are labelled as CVR 1-3.

Whilst there is very little background data, none of the AAV2 consensus sequences generated to date are identical, and sequences do not share a recent common ancestor. Consensus genomes will be uploaded to Genbank and accession numbers included in subsequent briefings.

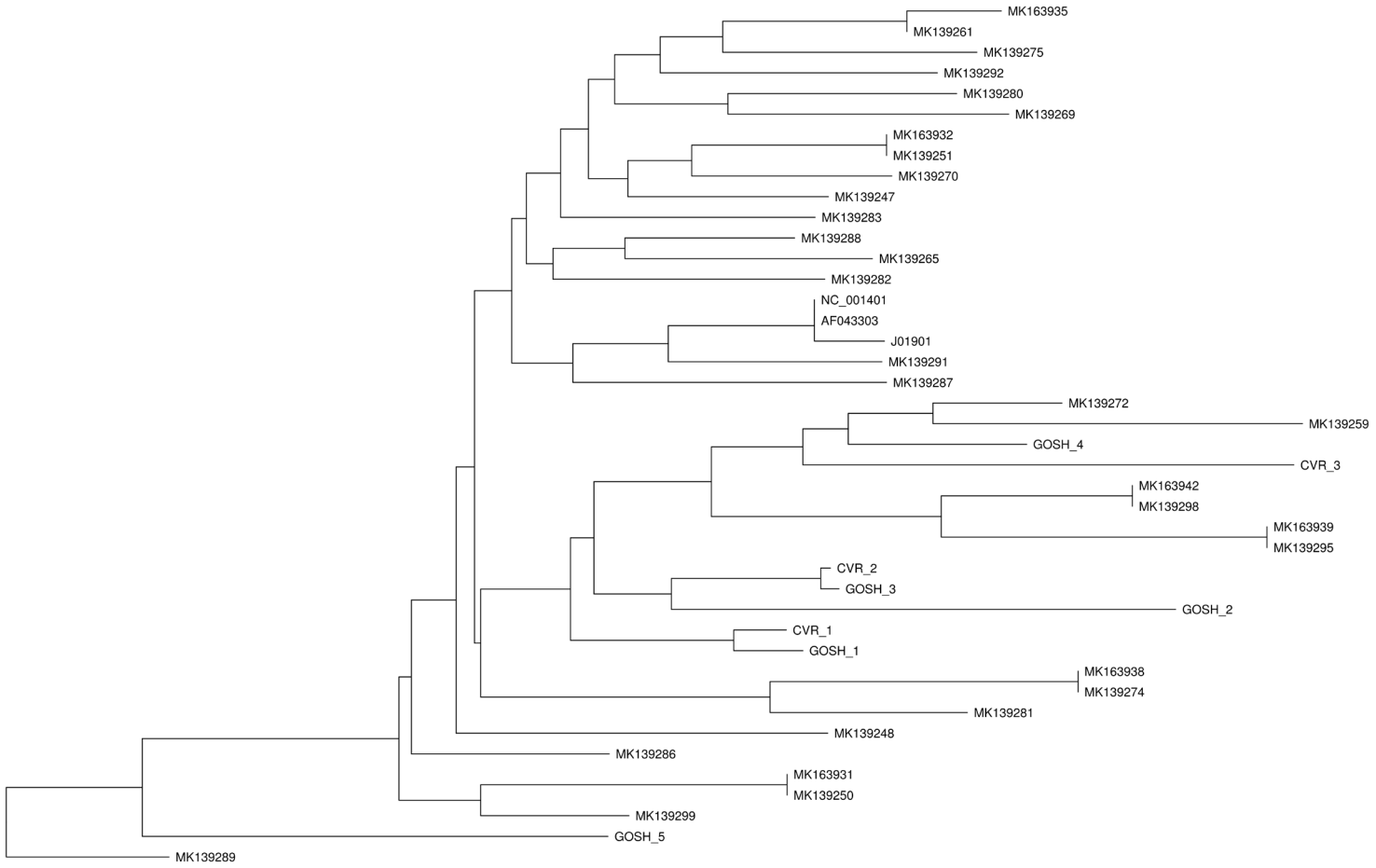
AAV2 is a dependoparvovirus which is typically dependent on other viruses including adenovirus and herpesviruses to replicate. Non-pathogenic human infection is common and latent virus may reactivate in some circumstances, again with no clinical consequence.

The hypotheses which are under consideration to explain detection of AAV2 in metagenomic data are:

1. Upregulation of AAV2 due to adenovirus or another acute viral infection.
2. Upregulation of AAV2 due to liver injury.
3. Contamination (for example of a reagent). Laboratory contamination is now considered less likely given that AAV2 has been detected in 2 testing laboratories with the appropriate negative assay controls but remains a possible explanation.
4. Undetermined role in pathogenesis of the syndrome.

Figure 5. Phylogenetic tree containing 9 UK AAV-2 consensus sequences from metagenomics analysis. Background AAV-1 and AAV-2 sequences gathered from GenBank. UK sequences labelled CVR 1-3 (Scotland) and GOSH 1-5 (England). This tree has been rooted using 2 AAV-1 genome sequences (GenBank accession numbers NC_002077 and AF063497) not shown in this image.

Supplementary data is not available for this figure.



Part 6. Cases: Toxicology investigations

One hundred and eighty-seven samples from 35 individuals and 77 healthy age-matched control samples have been analysed. A selection of serum and urine were analysed for organic compounds and whole blood and urines for metals. Four analysis protocols are being undertaken utilising Liquid Chromatography/High Resolution Mass Spectrometry (LC/HRMS) to target substances with different chemistries: polar and nonpolar, each with positive and negative ionisation for organic molecules and metabolites. Gas Chromatography/Mass Spectrometry (GC/MS) is being used for volatile and semi-volatile organics and Inductively Coupled Plasma Mass Spectrometry (ICPMS) for metals. The LC/HRMS gives a qualitative report of the organic masses which are compared against a variety of databases to derive possible substance identification. Identified substances are compared between healthy controls and cases to determine potential substances of interest. Potential acute hepatotoxic substances identified can then be compared to a reference standard, if this is available, for confirmation of identification and quantitative assessment.

To date 23 controls and 33 cases have gone through full LC/HRMS, and 28 cases and 23 controls have gone through GC/MS data acquisition in all modes and the data is currently being analysed against the databases. The first samples were from late illness and yielded hundreds of organic substances consistent across patient samples, but many (such as bile acids, bile salts and therapeutics) are related to the pathophysiology or management of acute hepatitis. The samples now under analysis are from earlier stages of illness. These are likely to be more informative with greater likelihood for causative substances still being present and less ‘interference’ from pathophysiological biochemistry.

Sixteen urine and 7 whole blood samples have been analysed by ICPMS for metals and these have not shown any metals of interest above expected levels in the cases.

Some toxicants are well known for causing liver toxicity, in particular paracetamol and aflatoxin B1. Standards have been obtained to facilitate investigation. Paracetamol or its metabolites have been detected in 12 cases and 1 control. It is probable that the levels being detected are related to normal therapeutic use but a review of the clinical history to aid interpretation is ongoing. Paracetamol remains under consideration as a potential causative agent, although currently the lines of evidence for this are weak.

Part 7. Relevant surveillance data

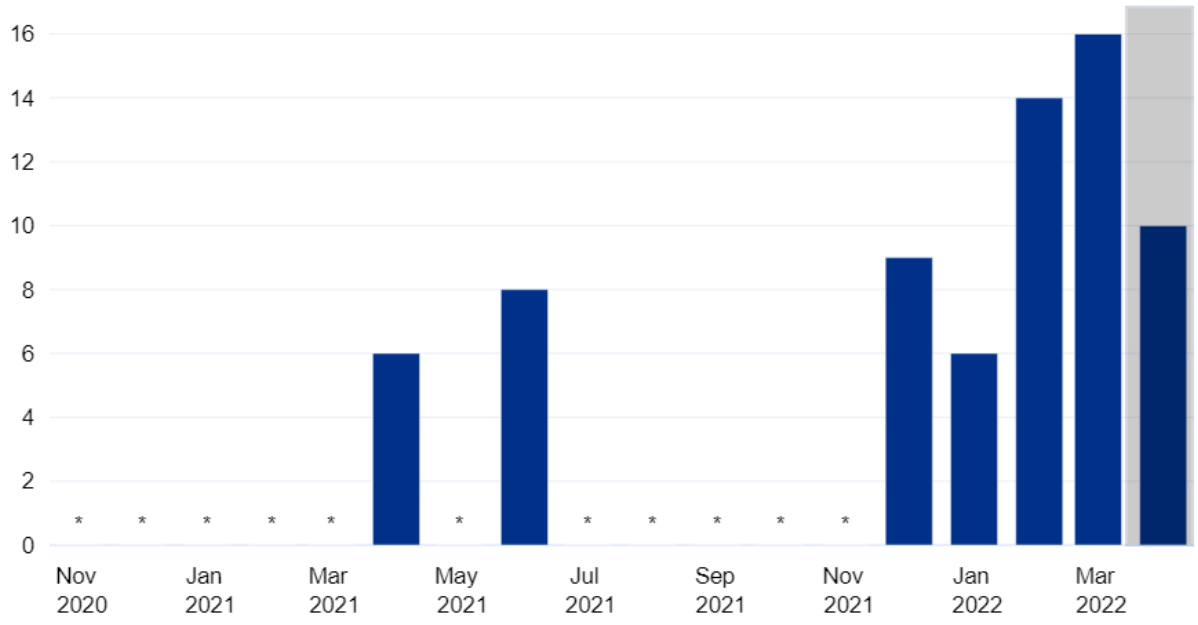
7.1 Trends in hepatitis or associated clinical syndromes

Emergency admissions of children with liver-related illnesses (non A-E hepatitis)

Amongst inpatients, there has been a small increase in the number of diagnoses in children aged 1 to 4 years with codes which may represent non-A-E hepatitis in February and March 2022 (see Figure 6). Data from April is incomplete, though is above levels seen during 2021. There is no signal in the other paediatric or in adult age groups. This data uses the primary or secondary diagnosis codes from the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) (see Table a in the Appendix) completed by a care professional when a patient is discharged, and therefore is subject to a significant time lag.

These data should be interpreted cautiously, particularly in the absence of data from before the COVID-19 pandemic and due to potential lower than usual health seeking behaviour and lower admissions due to infectious causes due to reduced social mixing during the pandemic.

Figure 6. Monthly Hepatitis Admissions for ages 1 to 4 year olds
Supplementary data is not available for this figure.



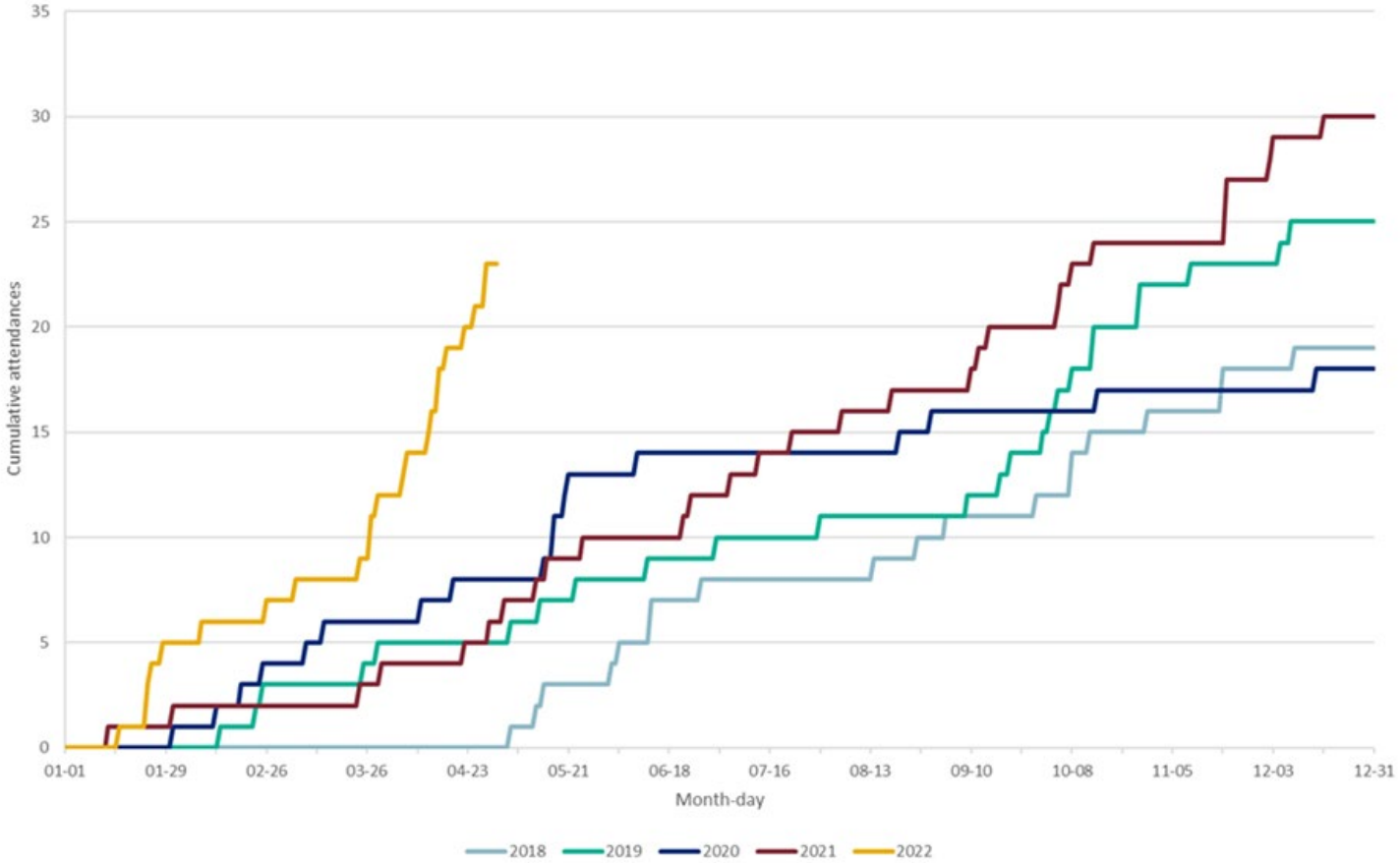
Source: APC data, produced by UKHSA
Data extracted on 04 May 2022 with data from 01 November 2020 to 25 April 2022
Bars with counts of 5 or below have been redacted and are indicated by a star (*)
The following primary or secondary diagnosis codes were used to link hepatitis:
B178, B179, B190, B199, K716, K720, K752, K759

Syndromic surveillance of liver conditions emergency department attendances

Clinical codes related to ‘liver disease’ that are routinely used and captured in emergency departments (ED) have also been grouped together and reviewed across 99 emergency departments in England which have contributed syndromic surveillance data on attendances between 2018 and 2 May 2022. Note that methods have been refined between Technical briefing 1 and this briefing, which has increased signal detection.

In children aged 1 to 4 years (see Figure 7a), there is some signal for increased emergency department attendance for liver disease compared with previous seasons, including pre-COVID-19 years. These are small numbers in absolute terms. A less pronounced relative increase over previous seasons is seen in children aged 5 to 14 years (see Figure 7b). A caveat in interpreting this data is that the codes used will also capture hepatitis with known causes.

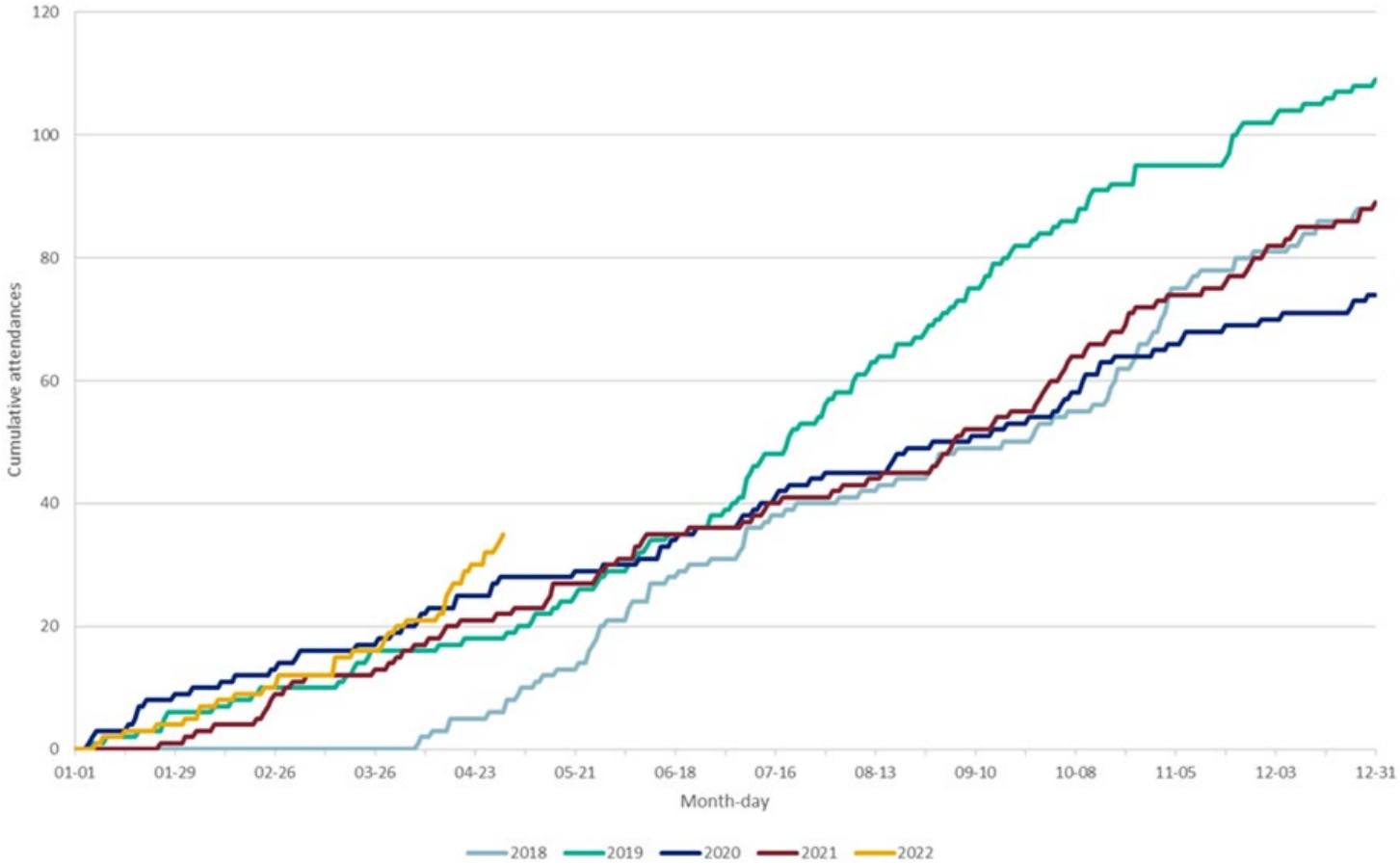
Figure 7a. Cumulative daily number of ED attendances for children aged 1 to 4 years, with a 'liver condition*' primary diagnosis, 2018 to 2 May 2022.** Supplementary data is not available for this figure.



** ED attendances as identified by syndromic surveillance, including 99 EDs:
- type 01 ED attendances only
- limited to EDs which started reporting through this route during 2018 - ED syndromic surveillance reporting through the route reported here commenced April 2018
- limited to EDs which reported quickly and frequently in the most recent week (received data for 7 out of 7 of the days 26 April to 2 May 2022, and the data arrived with the UKHSA Real-time Syndromic Surveillance Team within 2 calendar days of the patient attendance)
- EDs are excluded where historical issues with diagnosis coding have been identified

*'Liver disease' primary diagnosis includes inflammatory disease of the liver (46%), hepatic failure (33%), injury of liver (16%), acute infectious hepatitis (3%), viral hepatitis A (1%), viral hepatitis B (1%)

Figure 7b. Cumulative daily number of ED attendances for children aged 5 to 14 years, with a 'liver condition*' primary diagnosis, 2018 to 2 May 2022.** Supplementary data is not available for this figure.



** ED attendances as identified by syndromic surveillance, including 99 EDs:
- type 01 ED attendances only
- limited to EDs which started reporting through this route during 2018 - ED syndromic surveillance reporting through the route reported here commenced April 2018
- limited to EDs which reported quickly and frequently in the most recent week (received data for 7 out of 7 of the days 26 April to 2 May 2022, and the data arrived with the UKHSA Real-time Syndromic Surveillance Team within 2 calendar days of the patient attendance)
- EDs are excluded where historical issues with diagnosis coding have been identified
*'Liver disease' primary diagnosis includes inflammatory disease of the liver (46%), hepatic failure (33%), injury of liver (16%), acute infectious hepatitis (3%), viral hepatitis A (1%), viral hepatitis B (1%)

7.2 Increases in laboratory reports of new diagnoses and exceedances in potentially relevant pathogens

Laboratory data on pathogens reported by the NHS and public health laboratories through SGSS are routinely monitored for changes in trends and statistical exceedances. Increases in new laboratory diagnoses and statistical exceedances have been observed in adenovirus, enterovirus, human metapneumovirus, rhinovirus and norovirus in under 10 year olds since the end of 2021. There has been a marked exceedance of adenovirus, apparently driven by adenovirus in faecal samples and in the 1 to 4 year old age group although the number of laboratory diagnoses appear to be decreasing now. However, it is too soon to comment on any trends as random fluctuations occur and recent school holidays may have temporarily reduced social mixing.

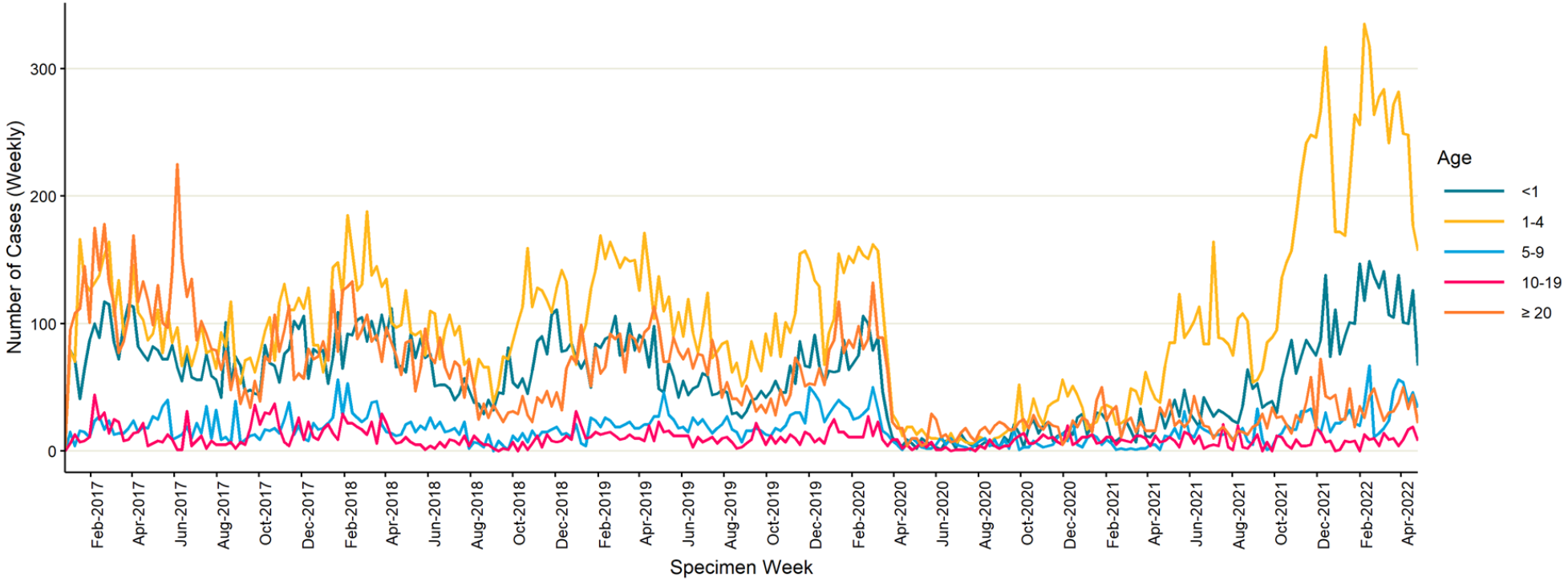
Adenovirus reports from diagnostic laboratories

Adenovirus positive tests from routine clinical testing are recorded in SGSS and can be analysed by UKHSA. The testing patterns for adenovirus are likely to be variable and as it is not a notifiable disease there is also likely to be under-reporting. Negative results are not recorded in SGSS, but a different system (Respiratory Datamart) does take positive and negative test data from a sentinel lab network only.

Reports of positive adenovirus tests from any site in 1 to 4 year olds are higher compared to the previous 5 years (see Figure 8). Between November 2021 to April 2022, approximately 200 to 300 cases of adenovirus were reported into SGSS per week compared to 50 to 150 cases per week in the pre-pandemic period and less than 50 cases per week between March 2020 and May 2021, although there has been a reduction in the number of adenovirus cases reported in the most recent week. The increase in younger age groups begins in November 2021. This pattern is also seen specifically in enteric samples in the same age group (see Figure 9).

Figure 8. Adenovirus episodes by age and week of specimen, England 1 January 2017 to 1 May 2022*

Supplementary data is not available for this figure.

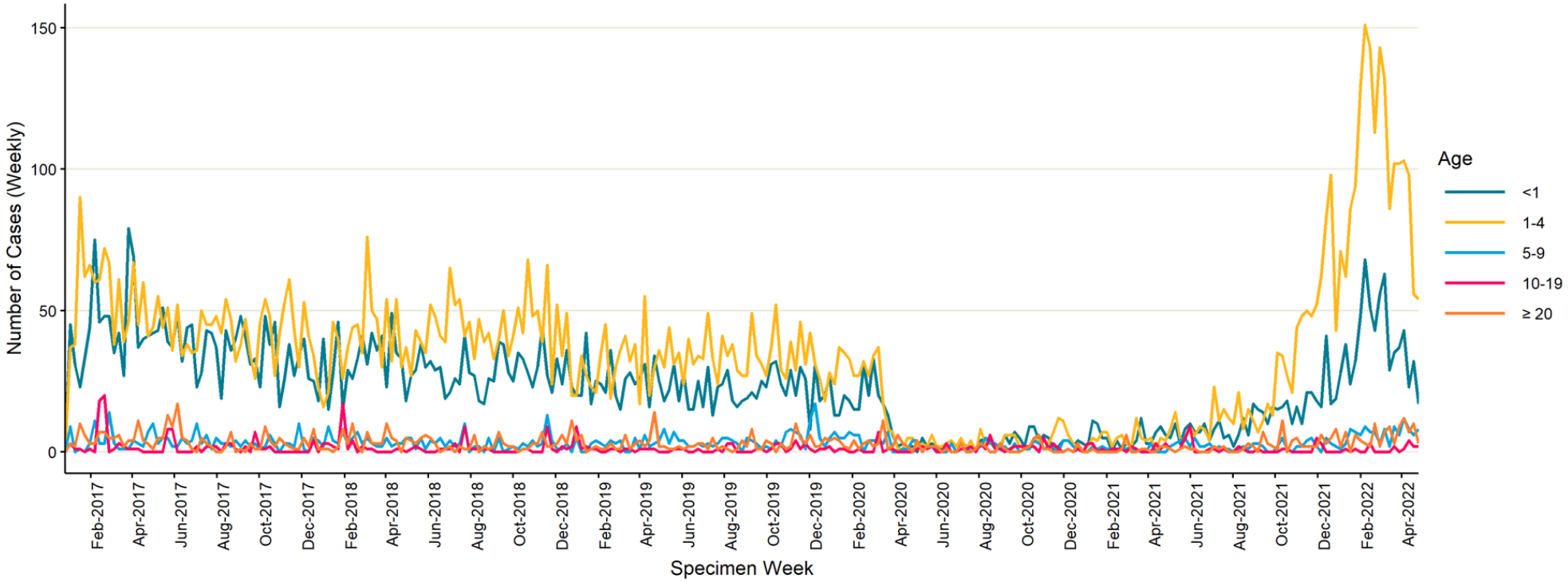


Data Source: SGSS

* The presented figures are based on laboratory reports through SGSS. Testing and reporting procedures vary by virus, UKHSA Centre and over time, including short-term trends in testing. Therefore, comparisons should be done with caution.

Figure 9. Adenovirus episodes from faecal or gastro-intestinal samples by age and week of specimen, England 1 January 2017 to 1 May 2022 *

Supplementary data is not available for this figure.



Data Source: SGSS

* The presented figures are based on laboratory reports through SGSS. Testing and reporting procedures vary by virus, UKHSA Centre and over time, including short-term trends in testing. Therefore, comparisons should be done with caution.

Exceedance monitoring

There has been an exceedance from end of 2021 in adenovirus from all sites – faecal and respiratory – in younger children but not among older children or adults. Methodology for exceedance monitoring can be found in the Sources and acknowledgements.

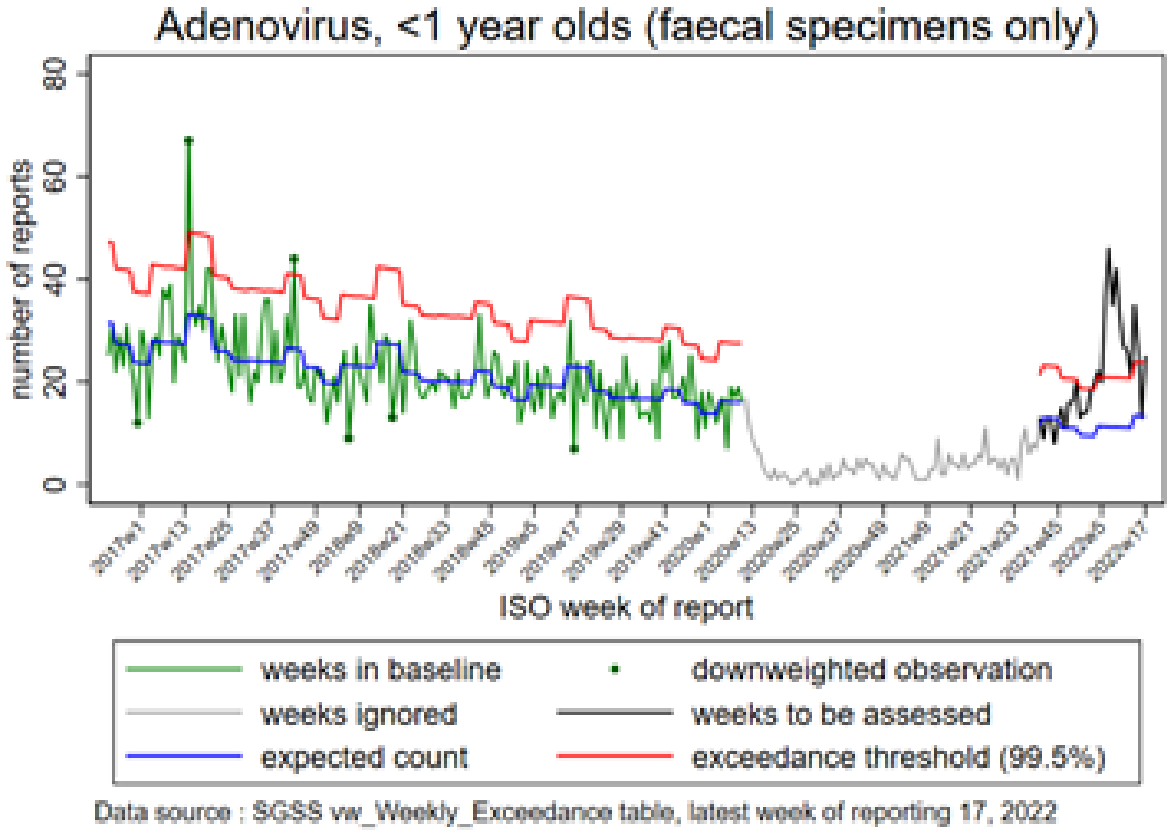
The plots in Figures 10 and 11 show trends in adenovirus reports in children from faecal and respiratory samples. The graphs compare recent data to the trends seen in previous years. Values above the red line indicate periods where the figures are higher than would be expected within the normal range.

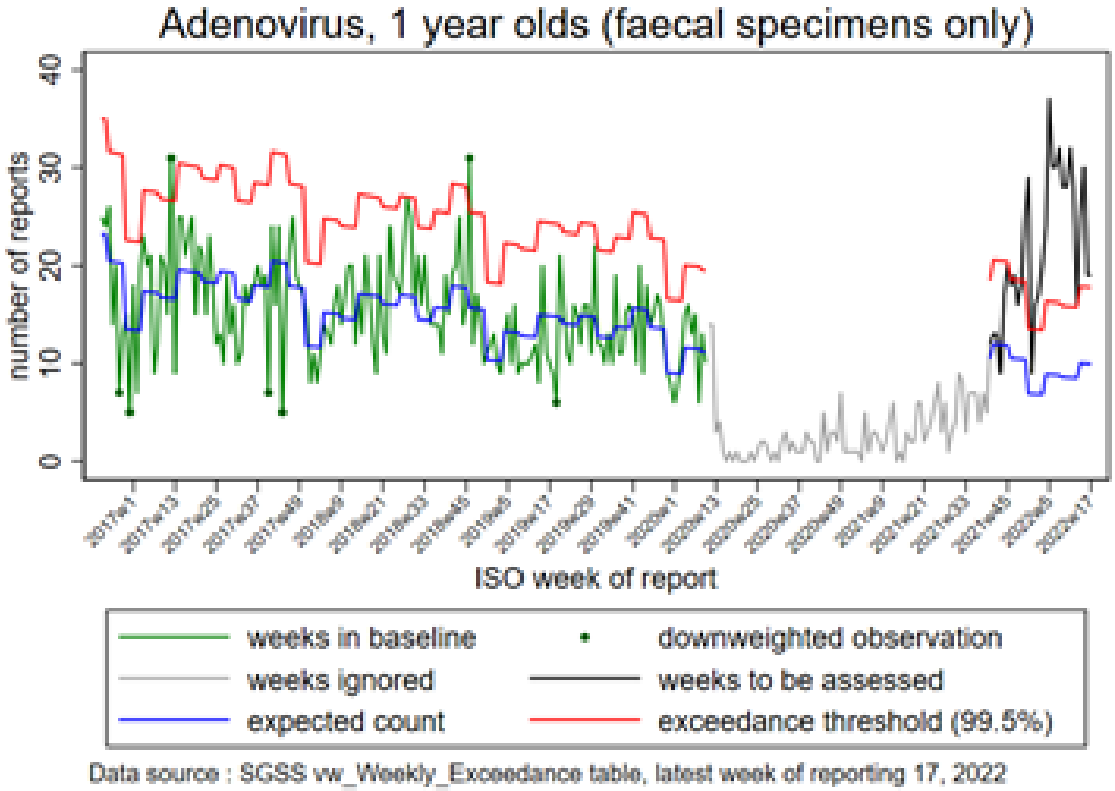
Faecal specimens adenovirus exceedance

Exceedance for faecal specimen adenovirus is seen in all younger children under 1 year to 9 years old, but not older children or adults.

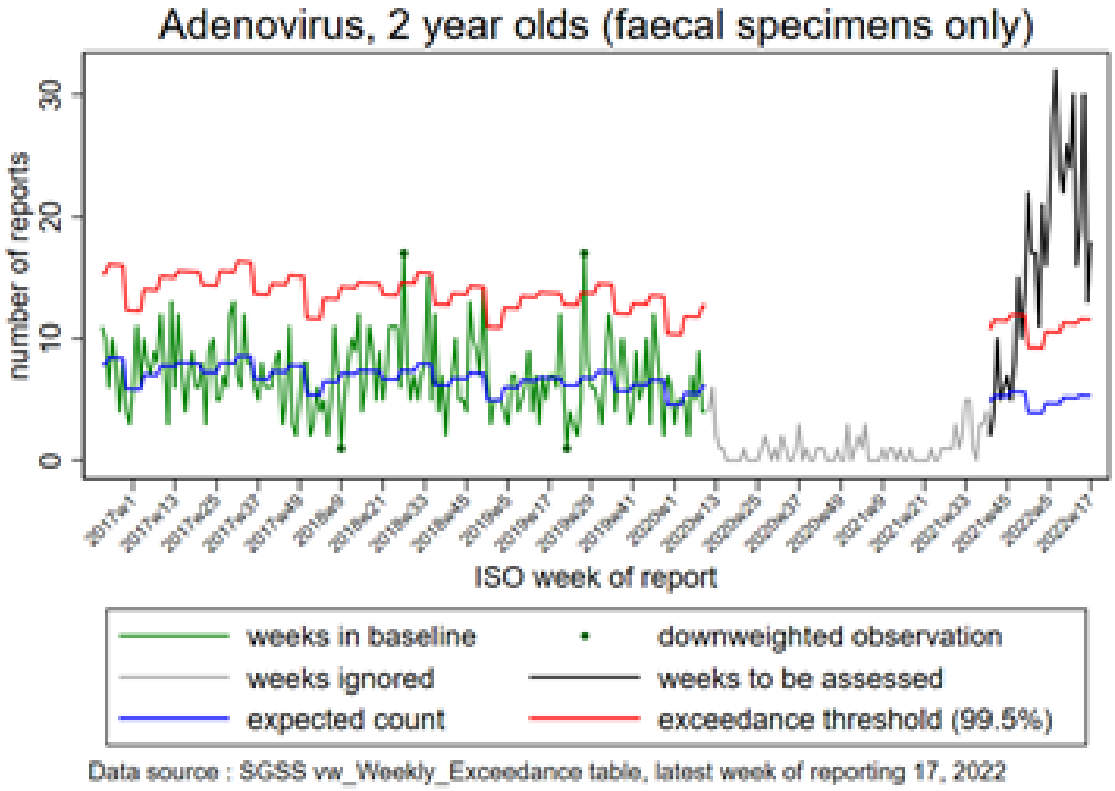
Figure 10. Exceedance for faecal specimen adenovirus as seen in under 1 year to 9 years old

Supplementary data is not available for these figures.

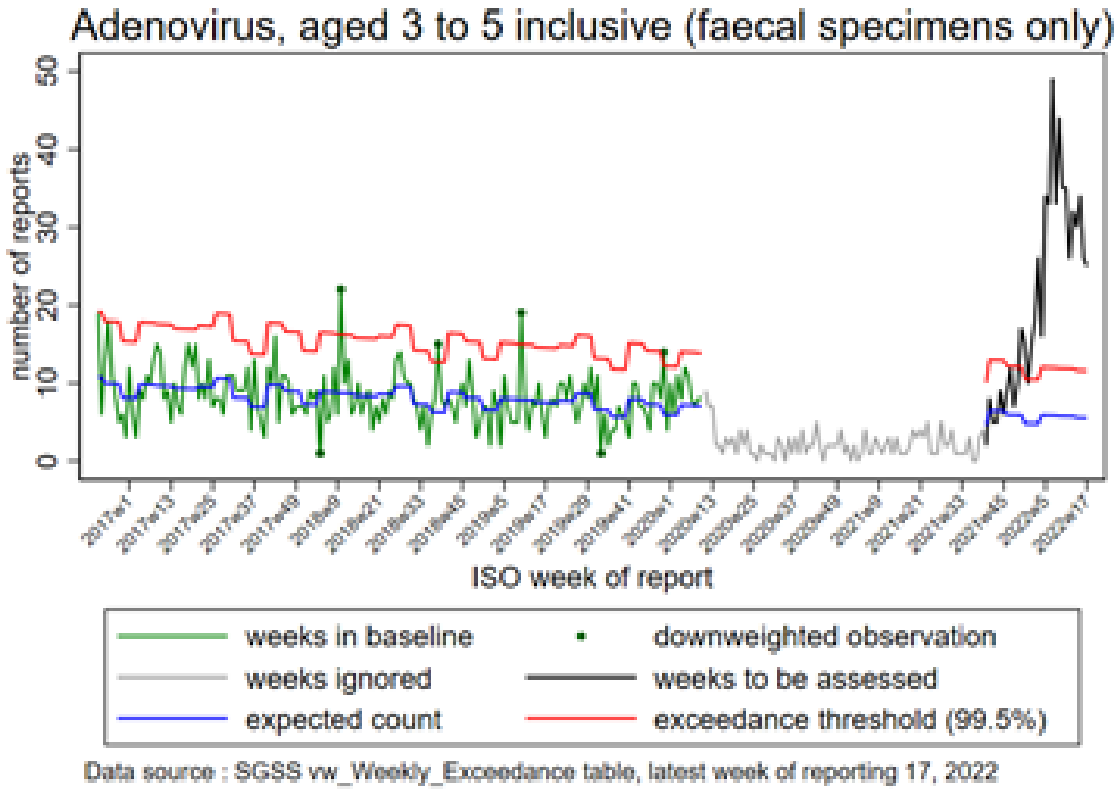




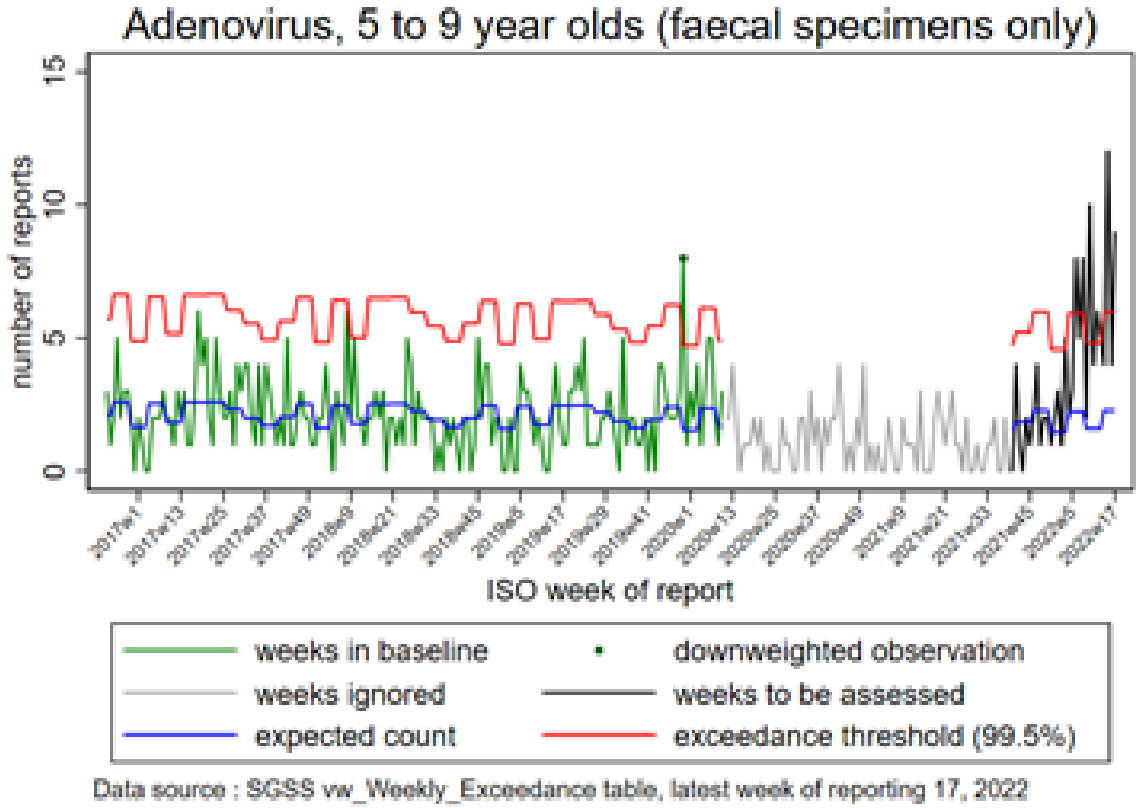
Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022



Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022



Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022

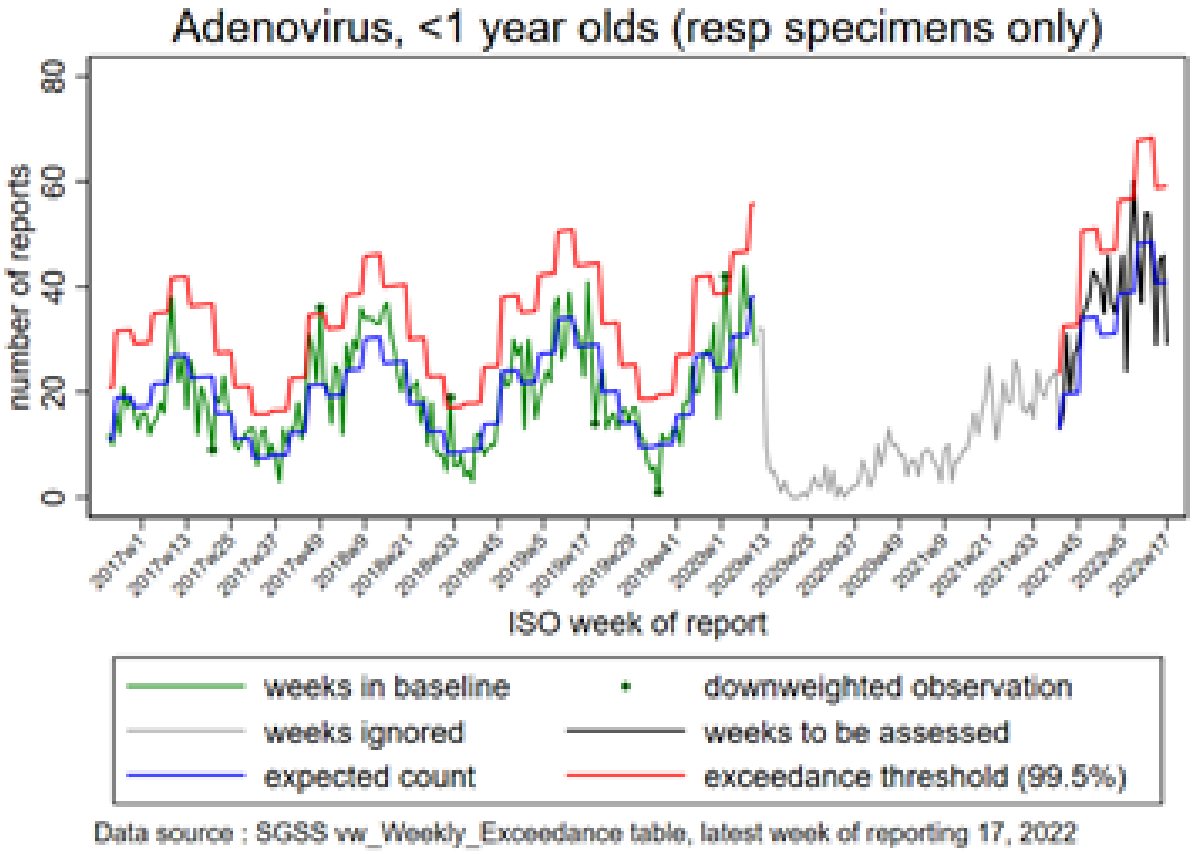


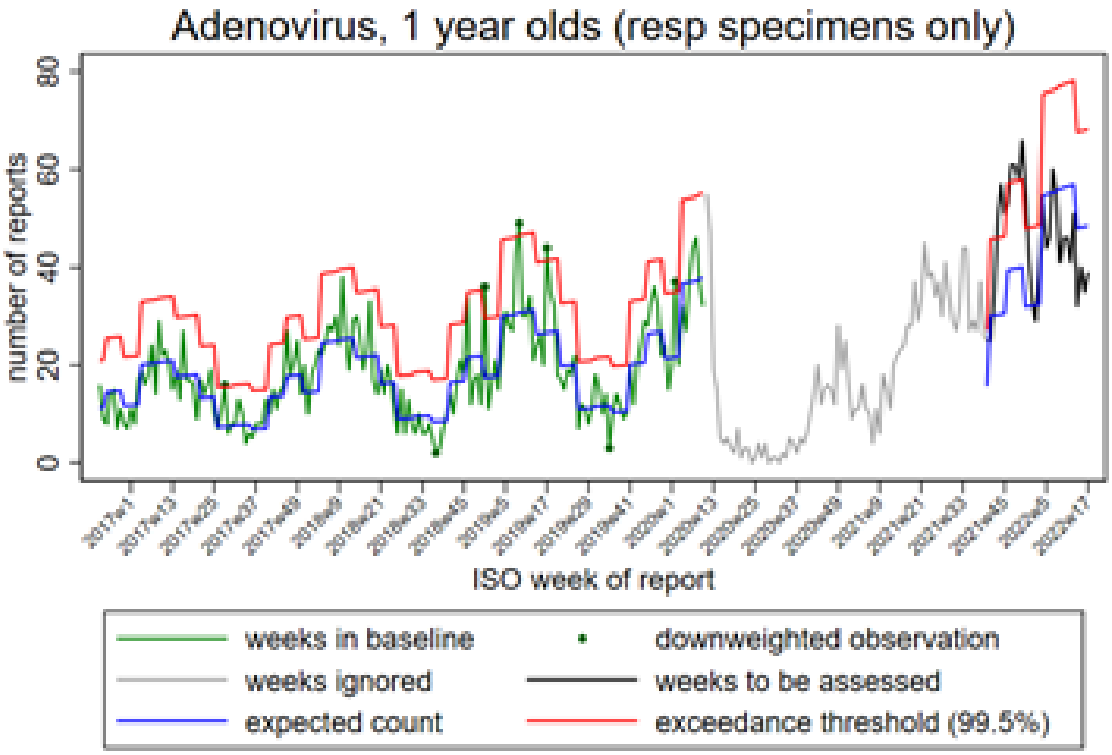
Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022

Respiratory specimens adenovirus exceedance

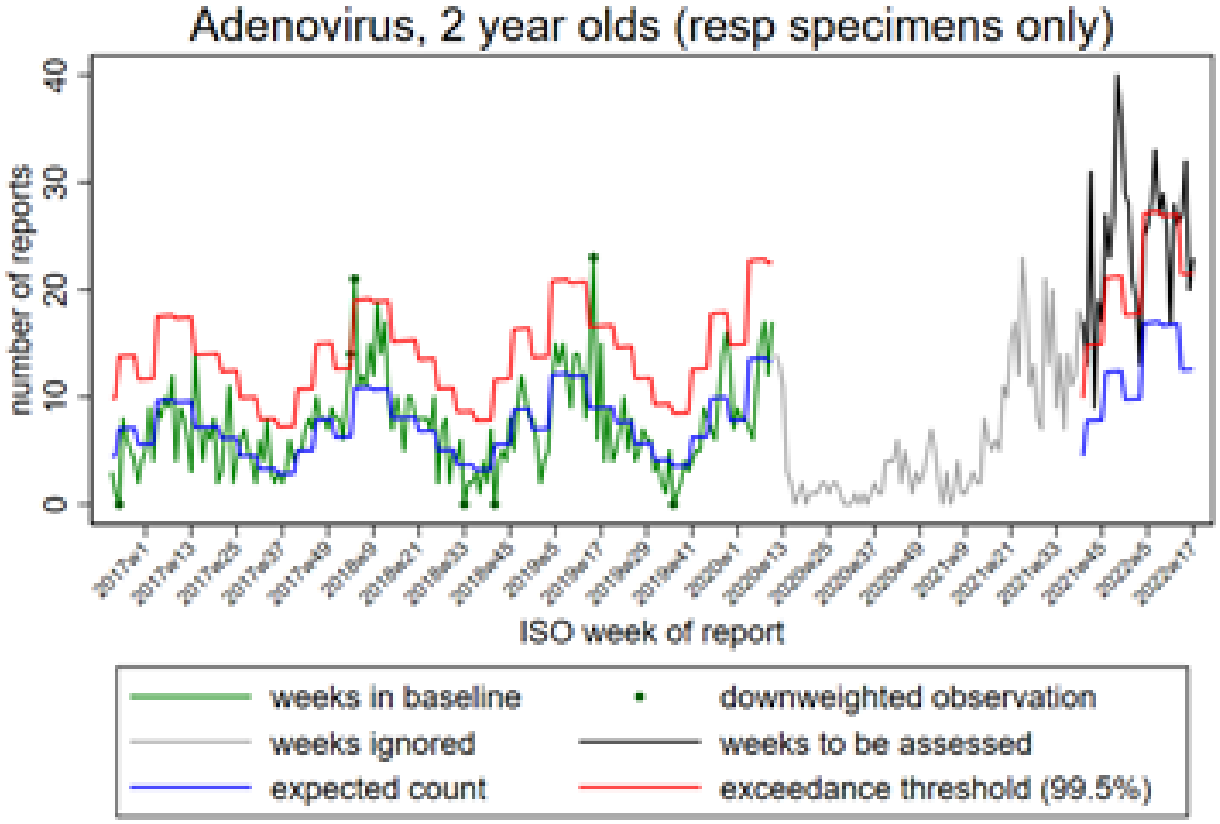
Some respiratory adenovirus exceedance was observed in 2 year olds in late 2021 and to a lesser extent in 3 to 5 year olds, but no persistence of this exceedance into 2022 has been observed, and no respiratory adenovirus exceedance observed in other age groups.

Figure 11. Exceedance for respiratory adenovirus among under 1 year olds to 9 year olds
Supplementary data is not available for these figures.

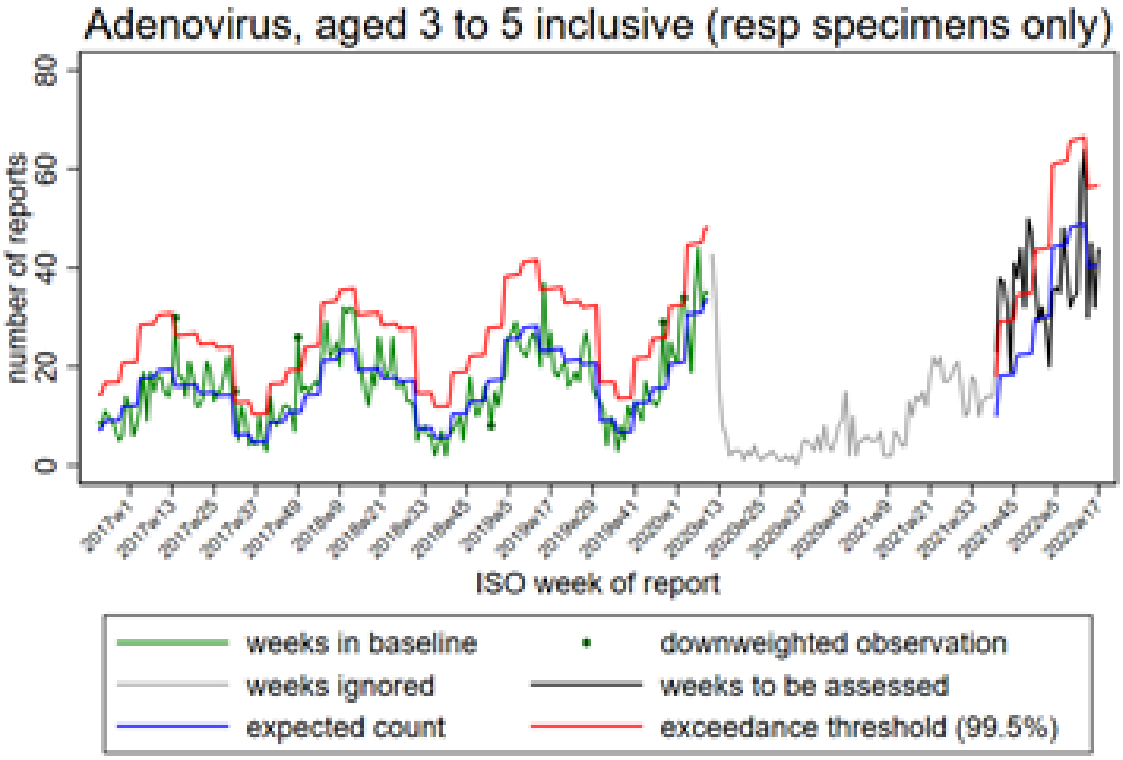




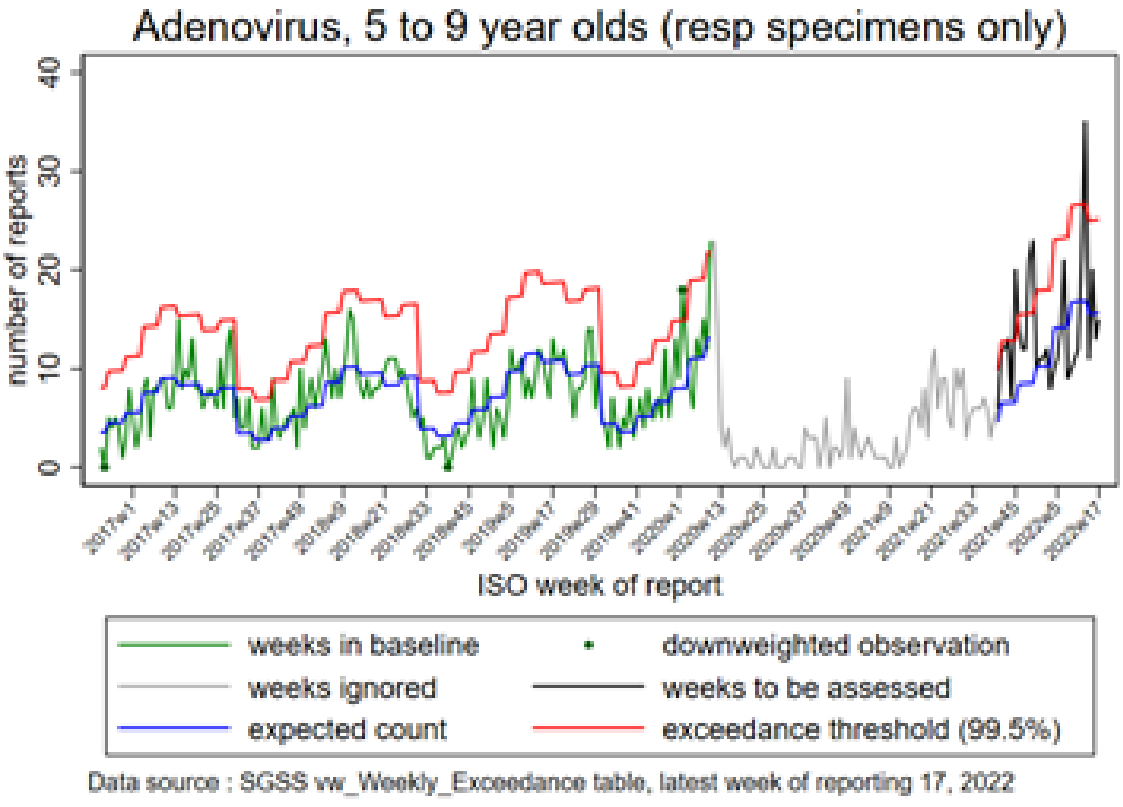
Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022



Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022



Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022



Data source : SGSS vw_Weekly_Exceedance table, latest week of reporting 17, 2022

Other pathogens showing exceedances

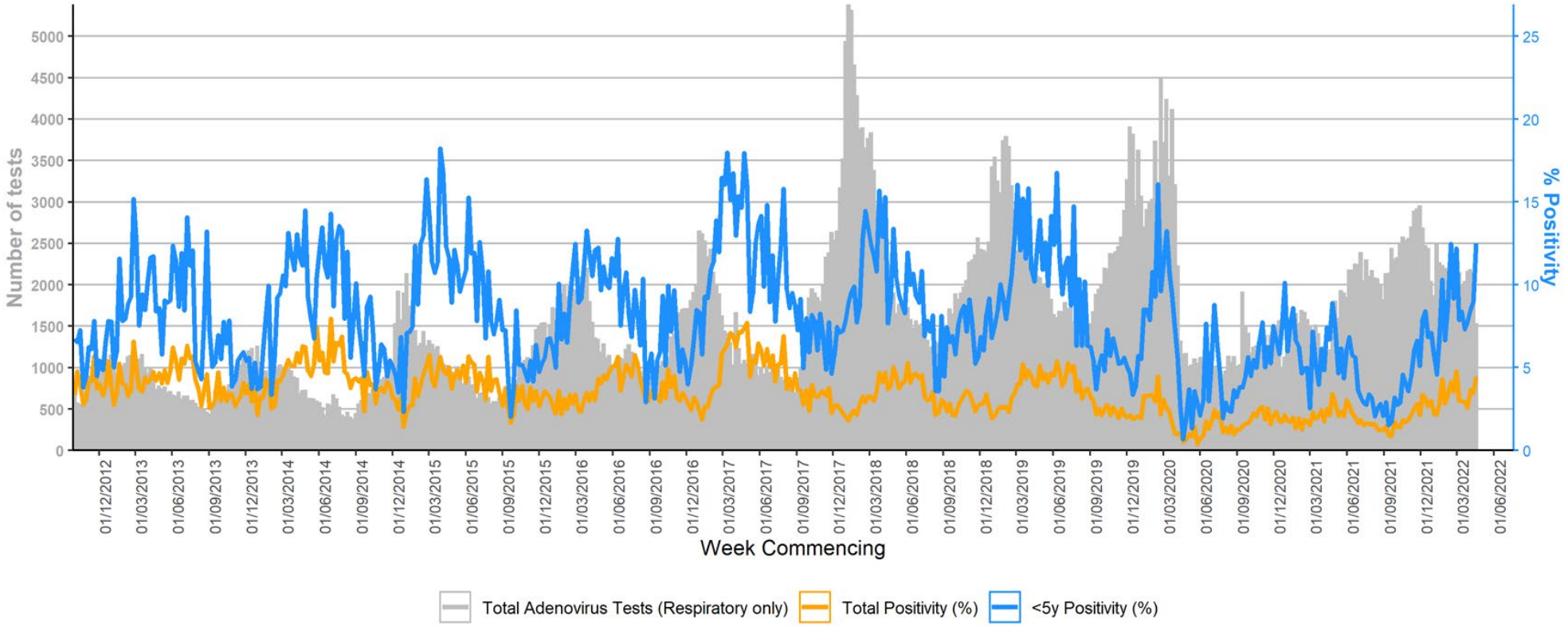
Exceedances are also currently seen for several other respiratory and non-respiratory viruses, which may be due to changes in behaviour and increased social mixing as restrictions eased and/or susceptibility in children due to lower levels of exposure during the pandemic. This includes norovirus, rotavirus, enterovirus, rhinovirus and human metapneumovirus. Exceedance plots are included in the Appendix (Figures b to d).

Respiratory DataMart

The Respiratory DataMart reports adenovirus testing data from 11 sentinel laboratories across England (see Figure 12). No increase in positivity of respiratory samples was noted among all ages combined or under 5 year olds separately.

Figure 12. Respiratory Adenovirus positivity (total and under 5 year olds) by specimen week, England 2012 to 2022

Supplementary data is not available for this figure.



Interaction between adenovirus and other pathogens

SARS-CoV-2

COVID-19 data and microbiological data for other organisms from SGSS were linked using various demographic variables. Interactions were explored to understand whether infection with adenovirus in the general paediatric population has preceded infection with SARS-CoV-2, co-infected or was a secondary infection within 27 days or more or delayed secondary infection to 59 days after a SARS-CoV-2 episode. This analysis is limited by ability to link across demographic variables but gives a sense of whether there has been a more recent increase in infection with SARS-CoV-2 and adenovirus.

The data show that between October 2020 and April 2022, there has been a rise in both preceding, co- and secondary infections among children under 10 (see Figure 13). Similar rises have been seen for other childhood infections too.

Other pathogens

Adenovirus data and microbiological data for other organisms from SGSS were linked using various demographic variables. Interactions were explored to understand whether infection with other pathogens in the general paediatric population has preceded infection with adenovirus co-infected or was a secondary infection within 27 days or more delayed secondary infection to 59 days after an adenovirus episode.

The data shows that between October 2020 and April 2022 there has been a rise in the number of adenovirus co-infections, and less so, preceding infections with another pathogen in the general paediatric population (see Figure 14). The most frequent pathogens detected between January and May 2022 were rhinovirus or enterovirus, SARS-CoV-2 enterovirus and respiratory syncytial virus, mainly as a coinfection (see Figure 15), which is not surprising considering the seasonality of these respiratory organism and high levels of community infection of SARS-CoV-2.

Figure 13. Number of adenovirus preceding, co-, and secondary infection episodes among children under 10 years old with SARS-CoV-2 between October 2020 and April 2022, in England

Supplementary data is not available for this figure.

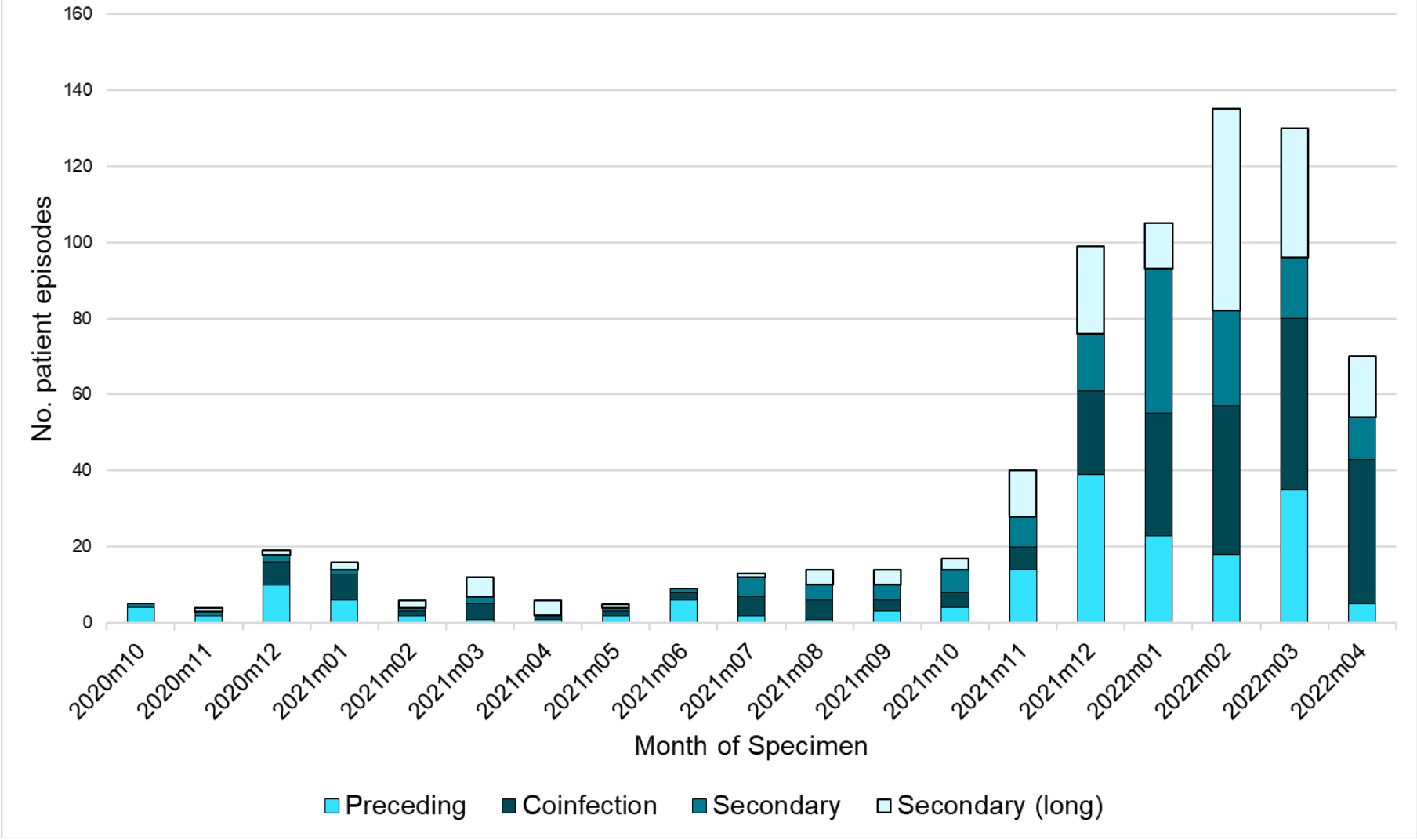


Figure 14. Number of adenovirus patient-episodes in England with a preceding, co-, and secondary infection with another pathogen among children under 10 years old between October 2020 and 3 May 2022, in England

Supplementary data is not available for this figure.

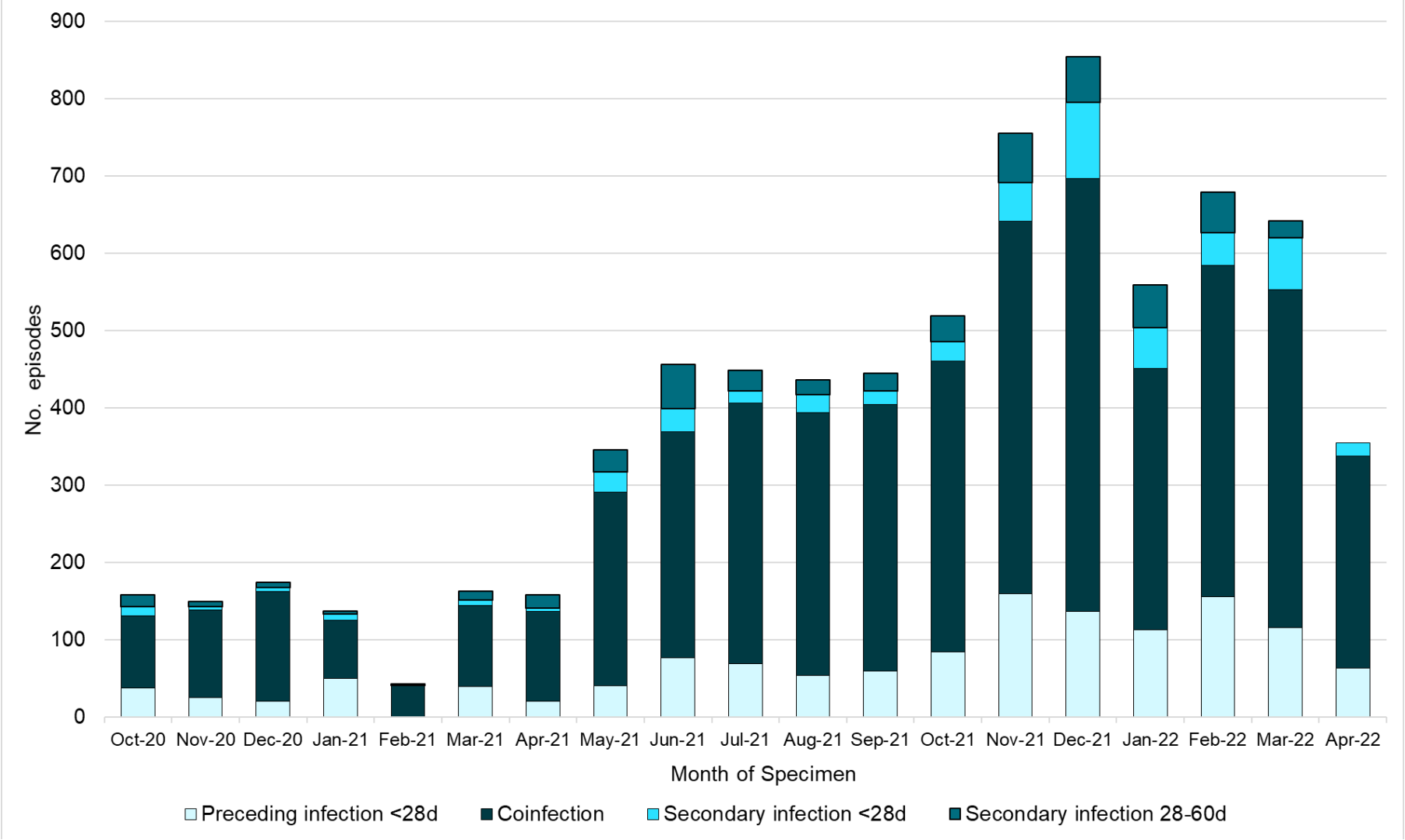
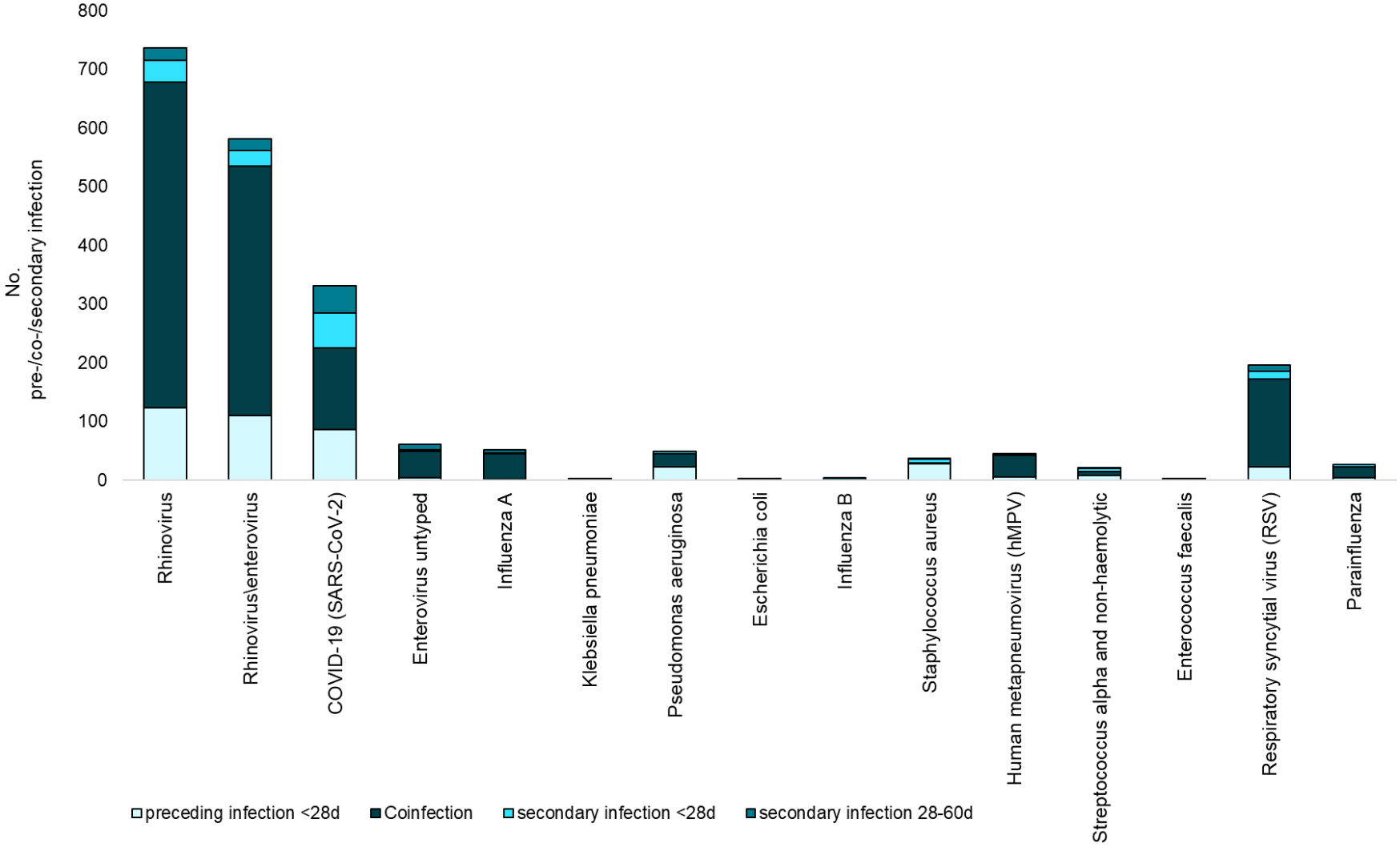


Figure 15. Most frequent pathogens identified in adenovirus patient-episodes in England with a preceding, co-, and secondary infection among children under 10 years old between October 2020 and 3 May 2022, in England

Supplementary data is not available for this figure.

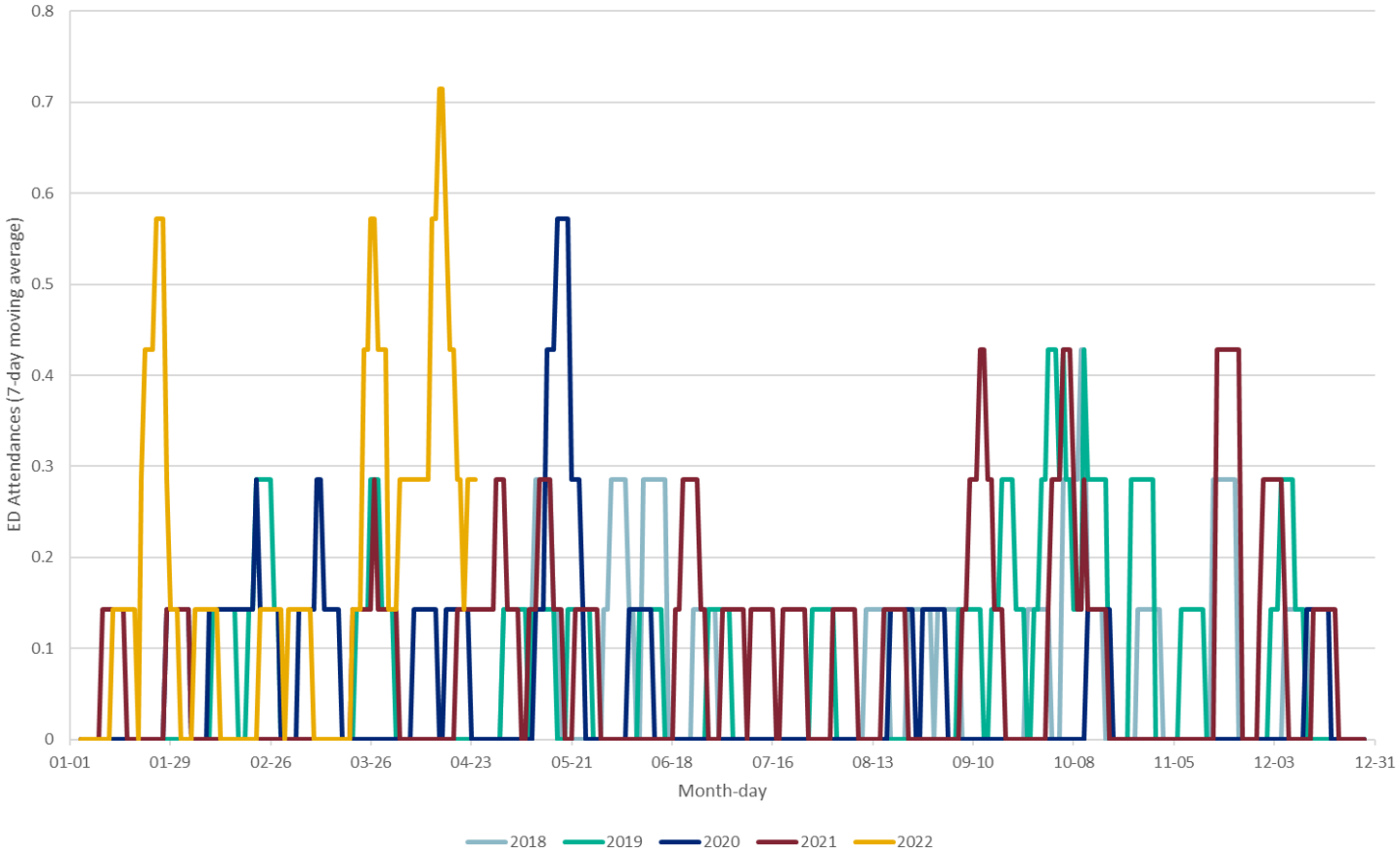


Appendix 1. Additional data

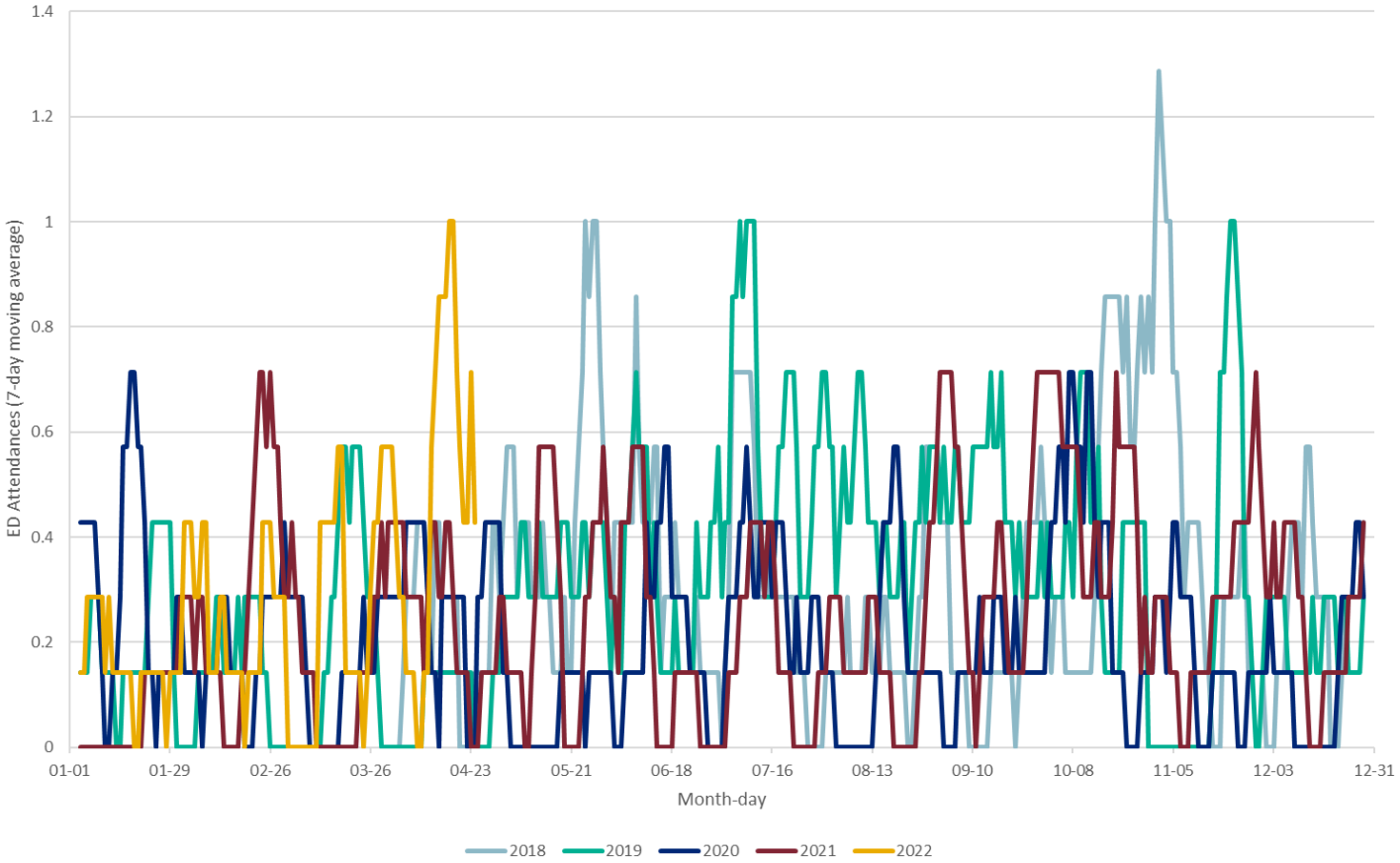
Relevant surveillance data

Figure a. Seven day moving average of ED attendances with a 'liver condition*' primary diagnosis by: (i) age 1 to 4 years**

Supplementary data is not available for these figures.



(ii) age 5 to 14 years



** ED attendances as identified by syndromic surveillance, including 99 EDs:
- data up to and including 2 May 2022
- type 01 ED attendances only
- limited to EDs which started reporting through this route during 2018
- limited to EDs which reported quickly and frequently in the most recent week (received data for 7 out of 7 of the days 26 April to 2 May 2022, and the data arrived with the UKHSA Real-time Syndromic Surveillance Team within 2 calendar days of the patient attendance)
- EDs are excluded where historical issues with diagnosis coding have been identified
*'Liver disease' primary diagnosis includes inflammatory disease of the liver (46%), hepatic failure (33%), injury of liver (16%), acute infectious hepatitis (3%), viral hepatitis A (1%), viral hepatitis B (1%).

Exceedances of other pathogens

Statistical exceedances of other respiratory and gastro-intestinal pathogens observed in 2022.

Figure b. Norovirus reported through SGSS
Supplementary data is not available for this figure.

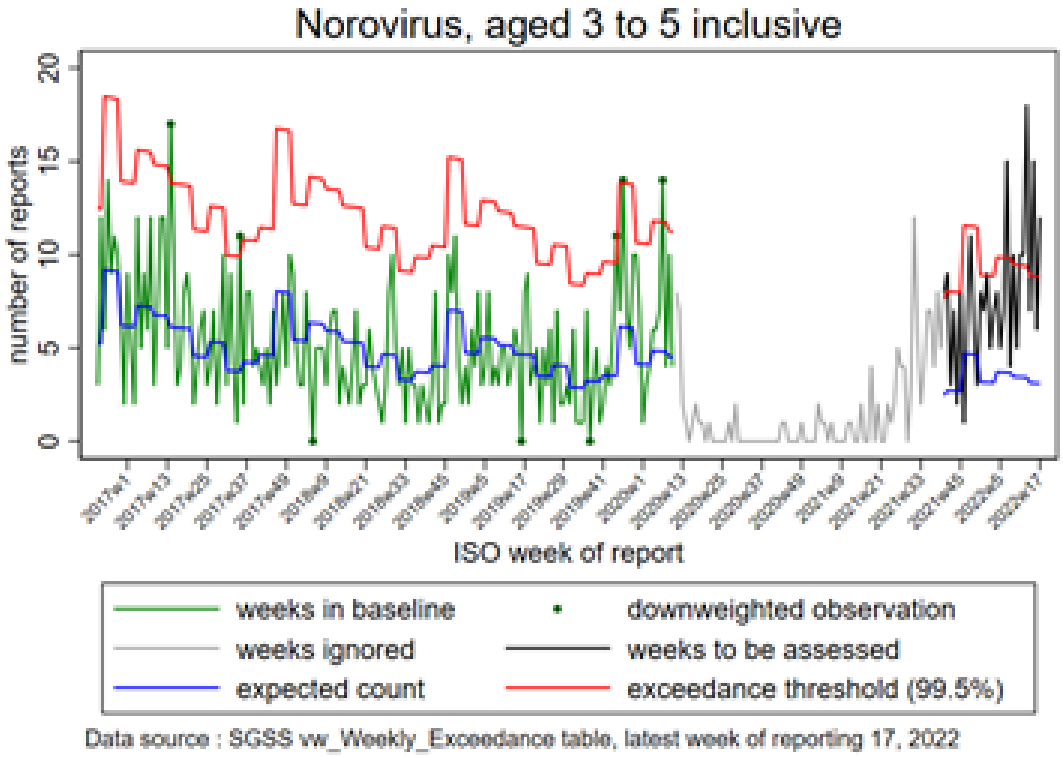


Figure c. Rotavirus reported through SGSS
Supplementary data is not available for this figure.

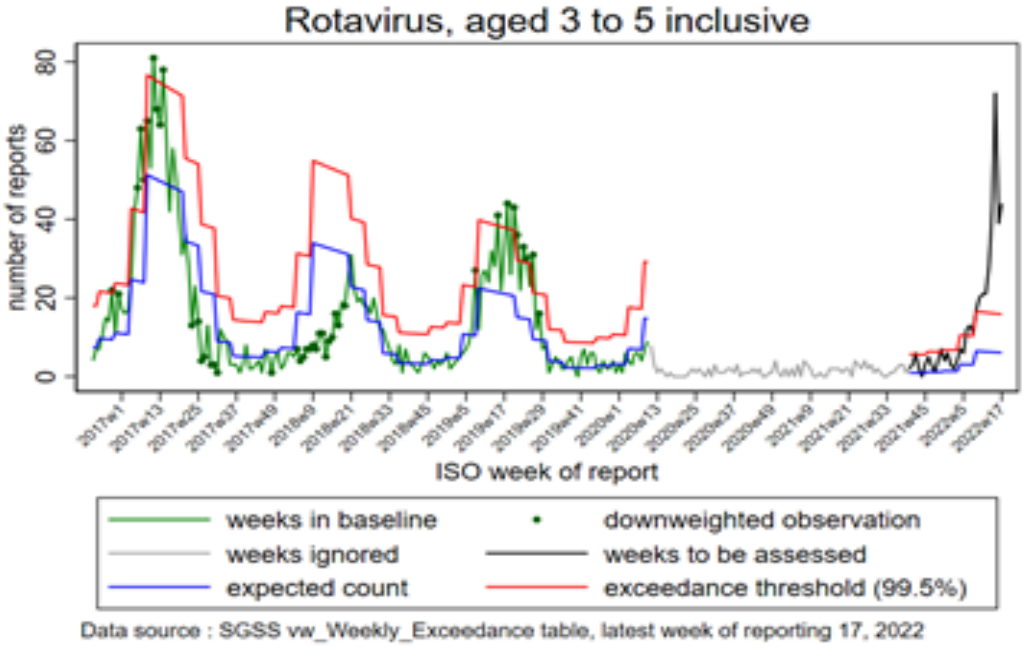
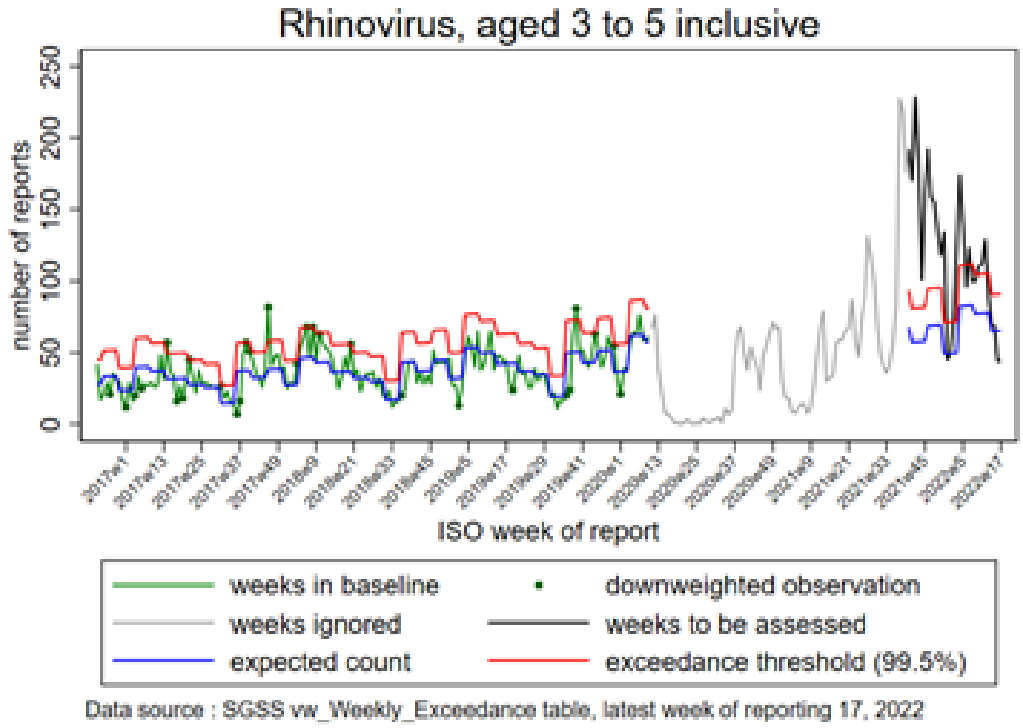


Figure d. Rhinovirus reported through SGSS

Supplementary data is not available for this figure.



Sources and acknowledgments

Data sources and methodologies

Admissions diagnoses with acute non-A-E hepatitis

The data source used for this analysis is the Secondary Uses Service (SUS) Admitted Patient Care (APC), a national data set which contains 'hospital episode' data relating to a period of care for a patient under a single consultant within one hospital provider. A stay in hospital from admission to discharge is called a 'spell' and can be made up of one or more episodes of care. Data is based on the date of the patient's admission for each spell, where the primary or secondary diagnosis was one of the below International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes.

Table a. ICD-10 codes used for in-patient admissions with acute non-A-E hepatitis

ICD-10 code	Description
K759	Inflammatory liver disease, unspecified
K752	Nonspecific reactive hepatitis
K720	Acute and subacute hepatic failure
K716	Toxic liver disease with hepatitis, not elsewhere classified
B190	Unspecified viral hepatitis with hepatic coma
B199	Unspecified viral hepatitis without hepatic coma
B179	Acute viral hepatitis, unspecified
B178	Other specified acute viral hepatitis

These diagnostic codes were chosen to identify acute non-A-E hepatitis diagnoses.
Admitted Patient Care data is completed by providers upon discharge of the patient. This means that patients still in hospital will not be present in our data set. In addition, due to variation in reporting by hospitals, data is subject to change and reporting delays. This means the most recent month of data is likely to be incomplete.

Exceedance monitoring

UKHSA monitors trends in pathogens through routine and ad hoc surveillance of laboratory notifications of positive test results undertaken as part of clinical care reported through SGSS. Exceedance monitoring is also used as part of assessing whether disease activity is above that expected. This uses a statistical threshold based on a moving average and secular trends in detection of a pathogen (thus addressing both changes in laboratory testing practices over time, and seasonal variation in disease activity). Further details of the statistical methods are described by Noufaily and colleagues.

Data sources

Data used in this investigation is derived from:

- Second Generation Surveillance System (UKHSA)
- Secondary Uses Service (NHS Digital)
- Emergency Care Data Set (NHS Digital)
- Admitted Patient Care (NHS Digital)
- Respiratory Datamart (UKHSA)
- Syndromic surveillance (UKHSA)
- NHS Blood and Transplant
- COVID Unified Data Set (UKHSA)
- NOIDs (UKHSA)
- HPZone (UKHSA)
- International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) UK

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UKHSA is responsible for protecting every member of every community from the impact of infectious diseases, chemical, biological, radiological and nuclear incidents and other health threats. We provide intellectual, scientific and operational leadership at national and local level, as well as on the global stage, to make the nation heath secure.

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