



UK Health
Security
Agency

Investigation into acute hepatitis of unknown aetiology in children in England

Technical briefing

25 April 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 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 20 April 2022 to allow time for analyses. Please note more recent case numbers have been cited publicly ([114 UK cases](#) as of 21 April 2022), however the small number of new cases have not yet been included in the analyses described here.

Summary

As of 20 April 2022, there have been 111 cases of acute non-A-E hepatitis with serum transaminases greater than 500 iu/l identified in children aged under 16 years old, since 1 January 2022. This is the result of an active case finding investigation in April which identified prospective as well as retrospective cases. No cases resident in the United Kingdom (UK) have died.

Eighty-one cases are resident in England, and the rest of the investigation data concerns cases from England only. This briefing is produced to share data useful to other public health investigators and academic partners. 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.

The cases are predominantly under 5 years old. The clinical syndrome often begins with gastroenteritis-type symptoms, followed by the onset of jaundice. From the information available, 43 cases resident in England have recovered. Seven cases have received a transplant. Trawling questionnaires have not revealed any obvious common exposures. Detailed clinical case review is underway.

Fifty-three cases have been tested for adenovirus of which 40 have adenovirus detected. SARS-CoV-2 has been detected in 10 of 60 patients and other pathogens are detected at lower levels. The detection of SARS-CoV-2 at this level is not unexpected given the community prevalence across the period of the investigation and based on the limited available information there is no evidence implicating a new variant of SARS-CoV-2.

Preliminary typing of the adenovirus has been consistent with type 41F where data is available from blood samples, however other adenovirus types have also been identified in non-blood samples. Whole genome sequencing from multiple cases is essential before the

characterisation of the virus can be confirmed. This is in process although the low level of adenovirus present in blood means that data quality has been challenging.

There is also a marked exceedance of adenovirus in routine laboratory data, primarily driven by enteric samples and the 1 to 4 year old age group, although there are also exceedances seen in many other common gastrointestinal and respiratory viral infections at present, likely due to behavioural change and population susceptibility after a period of low incidence during the pandemic.

The leading hypothesis at present is that the hepatitis is linked to adenovirus. The mechanism of liver injury may be virally mediated or may be an immunopathology.

There may be a cofactor causing a normal adenovirus to produce a more severe clinical presentation in young children, such as increased susceptibility due to reduced exposure during the pandemic, prior SARS-CoV-2 or other infection, or a yet undiscovered coinfection or toxin. Alternatively, there may have been emergence of a novel adenovirus strain with altered characteristics.

UKHSA has convened an expert group of NHS and academic partners to steer a comprehensive investigation. Rapid pathogen, toxicology and host investigations are underway, including in partnership with the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) Clinical Characterisation Protocol for those investigations where a research framework is appropriate.

Part 1. Case definitions and summary data for cases in the UK

1.1 Case definitions

A case definition has been agreed across England, Wales and Northern Ireland and discussions are ongoing to align with the Scottish case definition.

England, Wales, Northern Ireland case definitions

Confirmed

A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 iu/l (Aspartate Transaminase-AST or Alanine Transaminase -ALT), who is 10 years old and under, since 1 January 2022.

Possible

A person presenting with an acute hepatitis (non hepA-E*) with serum transaminase >500 iu/l (AST or ALT), who is 11 to 16 years old, since 1 January 2022.

Epi-linked

A person presenting with an acute hepatitis (non hepA-E*) of any age who is a close contact of a confirmed case, since 1 January 2022.

*If hepatitis A-E serology results are awaited, but other criteria met, these are 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, who is 10 years of age and under or a contact of any age of a possible or confirmed case, since 1 January 2022.

Possible

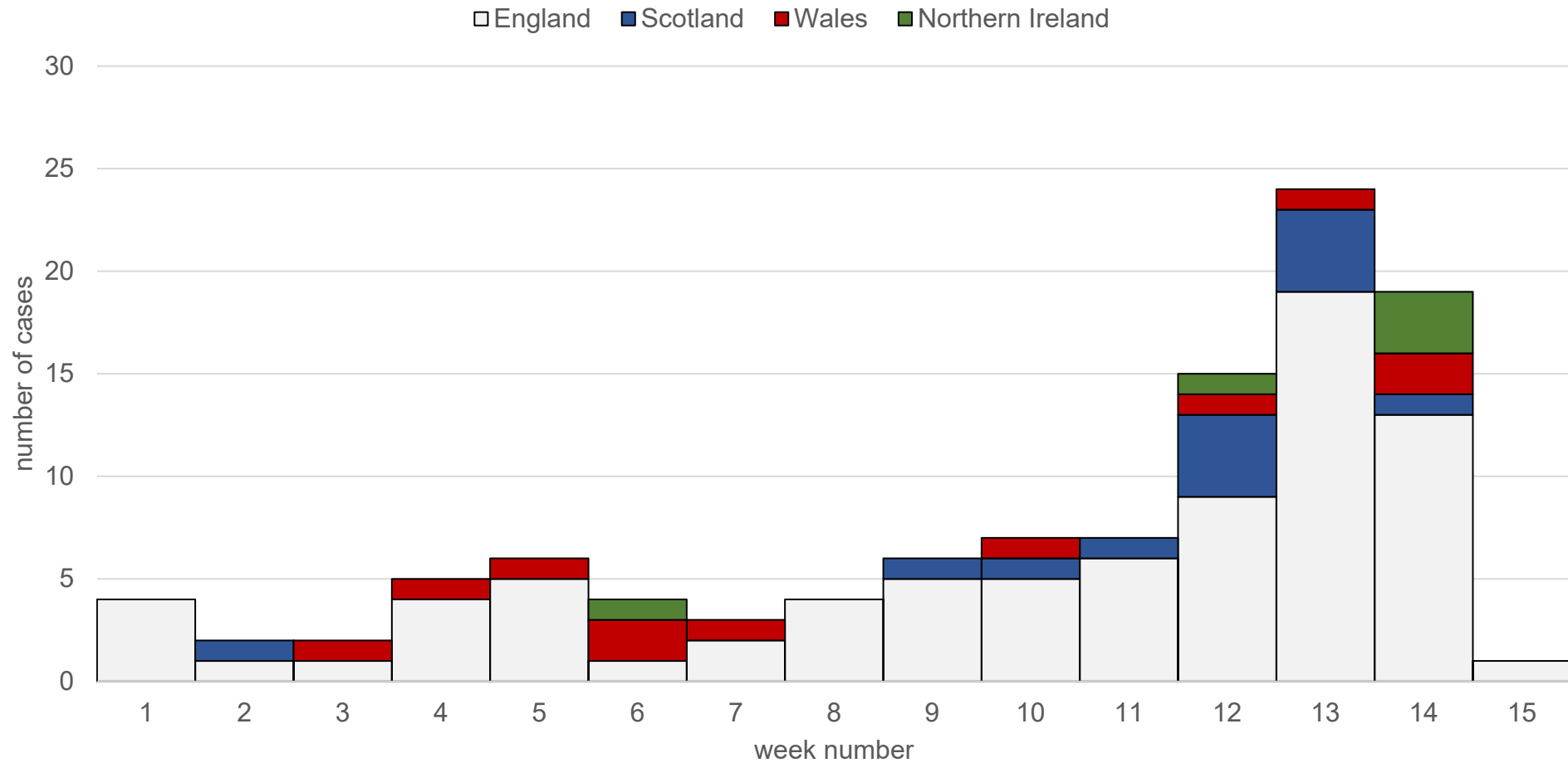
A person presenting with jaundice without any known cause, who is 10 years and under or contact of any age to a possible or confirmed case, since 1 January 2022.

1.2 Summary data on cases in the UK

As of 20 April 2022, there are 111 confirmed and possible cases in the UK. Of these, 81 cases are resident in England, 14 in Scotland, 11 in Wales and 5 in Northern Ireland (Figure 1). Between 21 January and 18 April 2022, 10 children in the UK meeting the case definition have required liver transplantation. From here on all confirmed and possible cases will be referred to as cases.

Figure 1. Cases by week and UK nation*, 1 Jan 2022 to 20 April 2022

Supplementary data is not available for this figure.



*Data for week 15 are not full week.

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

Part 2. Cases in England: descriptive epidemiology and clinical data

2.1 Cases in England

As of 20 April, there are 81 cases in England. There are no epidemiologically linked cases in England. Thirty-four potential cases in England are awaiting classification pending further data. Cases are predominantly aged between 3 to 5 years old (53: 65.4%), median age 3 (Interquartile range 3 to 4.5) and 54.3% are female. The majority are of white ethnicity (49 out of 56: 87.5%) where information was available.

2.2 Outcomes

Clinical outcomes for the 81 cases in England (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. Seven of the 81 cases 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. This possibility is being explored through alternative datasets.

Table 1. Outcomes for 81 cases in England on 20 April 2022

| | Number | Percentage |
|--|--------|------------|
| Died | 0 | 0.0 |
| Discharged or fully recovered* | 43 | 53.1 |
| Currently hospitalised or unknown discharge status | 38 | 46.9 |
| Total cases | 81 | 100 |

*Includes 3 transplanted cases

2.3 Clinical features

The most common presentation reported in cases was jaundice (60 out of 81: 74.1%) followed by vomiting (59 out of 81: 72.8%). Pale stools were also frequently reported (58.0%). Gastro-intestinal symptoms were commonly reported at presentation including diarrhoea (49.4%), nausea (39.5%). Additionally, lethargy (55.6%), fever (29.6%) and less frequently, respiratory symptoms (19.8%) were reported. Note that the denominator includes those who have reported the symptom, absence of symptom and unknown (missing information). Clinical case data including histopathology is being gathered and reviewed by an expert group.

2.4 Trawling questionnaires for exposures

Investigations have included interviews of parents conducted by health protection teams and other specialists in UKHSA to assess different exposures as potentially associated with the syndrome. These are commonly described as trawling questionnaires. These are designed to cover a broad range of potential hypotheses as to the cause or source of the condition, in a sufficiently thorough manner, and covering the pertinent period of risk.

Areas covered in this investigation included demographics, disease symptoms, medical and medication history, family structure, recent household/close contact illness, parental occupations, food and water consumption, health service utilisation, travel, animal exposure, and potential exposures to toxicants. In the first 60 case patients with data available, demographics were consistent with that of the overall hepatitis cohort and no notable features or common exposures were observed in travel, family structure, parental occupation, diet, water source, exposure to animals or potential exposures to toxicants, and no association with prior immunosuppression.

While paracetamol is an important hepatotoxic agent in overdose, there have been no reports of paracetamol hepatotoxic presentations or histories from any of the clinical units, including on toxicological screening or other diagnostic investigations. The prevalence of paracetamol use is considered consistent with guidance on management of acute illness in children.

Part 3. Cases: pathogen investigations

3.1 Potential pathogens detected through routine clinical testing

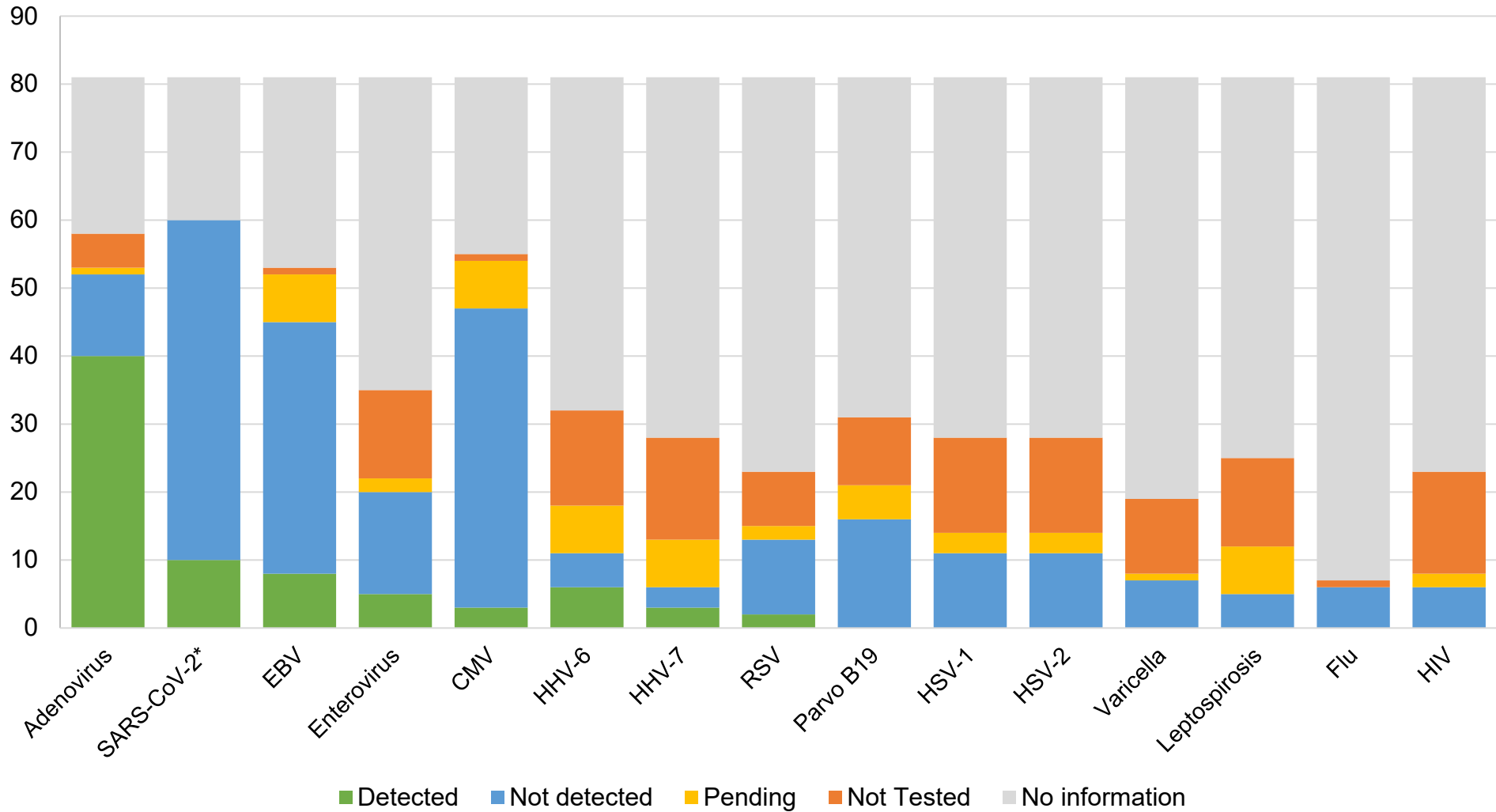
Cases have been tested for pathogens at or around the time of admission. Test choice is a local clinical decision and not all cases have been tested for the same pathogens (from [8 April 2022](#), UKHSA recommended a panel of tests to perform on all cases). However, SARS-CoV-2 should be tested on all hospital admissions. 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.

Testing patterns vary by pathogen, with more testing information being available for adenovirus, SARS-CoV-2, Epstein-Barr Virus and Cytomegalovirus. Adenovirus was the most common pathogen detected in 40 of 53 cases which have been tested, followed by SARS-CoV-2 (Figure 2).

The proportion of cases (January to April) with SARS-CoV-2 positive at admission amongst those tested was 16%, compared to approximately 5 to 8% community positivity per week in 2 to 6 year olds in March to April 2022 ([Office for National Statistics \(ONS\)](#)). The population cumulative seropositivity is likely to be much higher in the age groups we are investigating, noting it was 47% in 1 to 4 year olds and 67% in 5 to 11 year olds in January through February 2022 (UKHSA Paediatric sero-surveillance data - unpublished). There are no equivalent community prevalence data for adenovirus. Figure 3 shows the epidemic curve of adenovirus and SARS-CoV-detections in cases.

Figure 2. Pathogens tested for and results in cases in England

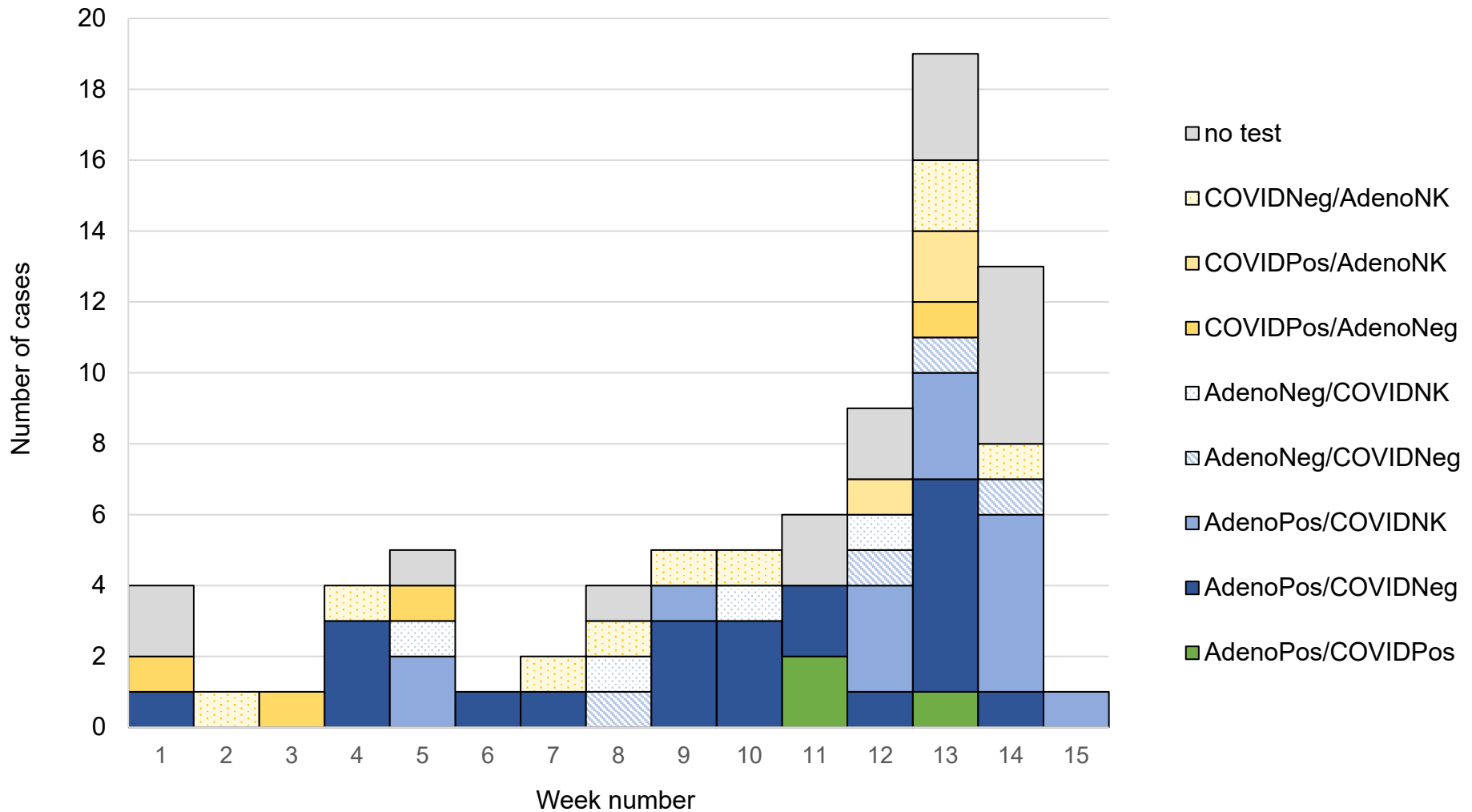
Supplementary data is not available for this figure.



*SARS-CoV-2 testing is based on testing on admission date rather than in the 6 weeks prior to admission.

Figure 3. Epidemic curve of cases, by adenovirus and SARS-CoV-2 result in England

Supplementary data is not available for this figure.



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

3.2 Adenovirus

Adenovirus was the most common pathogen detected in 40 of 53 cases which have been tested. The acute hepatitis pattern is not known to be typical of adenovirus infection in immunocompetent children, although testing for adenovirus may not be routinely undertaken.

By sample type based on the data report, adenovirus was detected more commonly in blood /serum samples, then in stool or respiratory samples, however, a consistent sample set has not been tested for most cases.

Eleven cases with adenovirus in blood have been successfully subtyped, and all of these are type 41F. Typing was not successful in all samples, and other adenoviruses were detected in some non-blood samples from cases. Further investigative work, including whole genome sequencing of multiple cases, is required before any firm conclusions can be drawn on characterisation of the adenoviruses involved.

Adenovirus DNA levels in blood/serum samples were noted to be approximately 12-fold higher in those who had received a liver transplant versus those who did not receive a liver transplant, although timing of the samples is variable with respect to onset and deterioration.

Adenovirus whole genome sequencing 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.

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 whole genome sequencing 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.

3.3 SARS-CoV-2

Ten cases tested positive for SARS-CoV-2 on admission, of 61 cases with available test data (16%). Seven of those had also tested positive in the 6 weeks prior to admission. Serology is being undertaken to explore prior infection further. However, the high population cumulative prevalence of SARS-CoV-2 will make the interpretation of this data challenging. Three cases were co-infected with adenovirus and SARS-CoV-2.

SARS-CoV-2 result is based on polymerase chain reaction or lateral flow device results. Information on antibody testing for SARS-CoV-2 is currently pending.

Four cases that have a positive test result for SARS-CoV-2 also have associated variant information. In 2 cases, genotyping indicated a probable Omicron lineage and in a further 2 cases whole genome sequencing identified VOC-22JAN-01 by the UKHSA definition (BA.2 and sublineages).

Acute hepatitis is not a common feature of SARS-CoV-2 infection in children. Data provided by ISARIC's COVID-19 Clinical Information Network - CO-CIN (February 2020 to March 2022) shows of 8,883 children admitted to hospital with SARS-CoV-2 infection 2,171 (24%) had ALT measured during admission. The decision to test was based on clinical assessment that is, missing data is not random. A grossly elevated ALT was not a typical feature of SARS-COV-2 infection, and only 13 of the 2,171 children tested had an ALT greater than 500 iu/ml.

Data source: Professor Calum Semple, University of Liverpool and Prof Ewen Harrison, University of Edinburgh on behalf of The International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) UK.

Part 4. Cases: Toxicology investigations

Ninety-seven samples from cases and 75 healthy age matched control samples have been received. A selection of serum samples 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 16 controls and 11 cases have gone through full Liquid Chromatography/Mass Spectrometry and 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 are related to the pathophysiology such as bile acids and bile salts. 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.

A small number of urines and whole bloods have been analysed by ICPMS for metals and these have not shown any metals of interest 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.

Part 5. Relevant surveillance data

This section contains extracts from surveillance data which are relevant to the investigation. In summary, whilst specialist paediatric liver units report increased activity, data from wider NHS settings and notification systems does not show a large change in presentations or inpatient diagnoses, though there are possible small increases visible in the 1 to 4 year age group in some datasets with a high level of uncertainty attached. There is no signal in adult age groups. NHS data is affected by lag and requires continued monitoring.

There are statistical exceedances in the detection of many viruses since the start of 2022, likely related to increased social mixing and behavioural change. This includes a marked exceedance in adenovirus in this period, driven primarily by detection in faecal samples and in children aged 1-4. This also coincides with a period of very high prevalence of SARS-CoV-2 infection in the UK (please see [UKHSA surveillance reports](#)).

5.1 Trends in hepatitis or associated clinical syndromes

Specialist paediatric liver care unit admissions

Specialist paediatric liver care and transplantation is provided by 3 NHS liver units in England (Birmingham, Leeds and Kings London) – 2 of 3 liver units have provided data on urgent admissions for acute hepatitis of unknown cause. While these data cannot be presented due to small numbers, these data show that the number of admissions in 2022 to date is equivalent or greater than the number of admissions annually in previous years.

Super urgent liver transplants

Using NHS Blood and Transplant coding to exclude acute liver failure due to known causes, the number of super urgent transplants in children 10 years and under reported in the first quarter of 2022 is greater than previous annual counts in 2009 to 2019. Data cannot be presented due to small numbers. No increase in liver transplants in older children has been seen.

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

During mid-late 2020 and 2021 the effect of the pandemic on healthcare seeking behaviour is reflected in lower numbers of all age emergency department attendances and admissions and for liver disease. Amongst inpatients, there has been an 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 (from 0 to 8 cases per month between November 2020 – January 2021, rising to 14 in February and 15 in March 2022). There is no signal in the other paediatric or 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 [Appendix](#)) completed by a care professional when a patient is discharged, and therefore is subject to a significant time lag.

Syndromic surveillance of liver disease emergency department attendances

Clinical codes related to 'liver disease' that are routinely used and captured in emergency departments have also been grouped together and reviewed across 122 emergency departments in England for attendances between 2018 and 2022. In children the number of liver disease attendances is low and there does not appear to be any major shift in trends so far in 2022 in line with previous years' numbers or trends (see Figure a in [Appendix](#)). A caveat in interpreting this data is that the codes used will capture hepatitis with known causes.

Notifiable Infectious Disease (NOIDs)

Acute infectious hepatitis is a notifiable infectious disease and is classified as A, B, C, or 'other.' NOIDs reports for 2022 were reviewed through the UKHSA health protection reporting and case management system, HPZone, to look for any increases in 'other' acute infectious hepatitis (and excluding any hepatitis E that may have been coded as 'other'). One new case for this incident was identified. No excess in NOIDs in 'other' acute hepatitis was observed.

5.2 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 is a marked exceedance of adenovirus, apparently driven by adenovirus in faecal samples and in the 1 to 4 year old age group.

Adenovirus reports from diagnostic laboratories

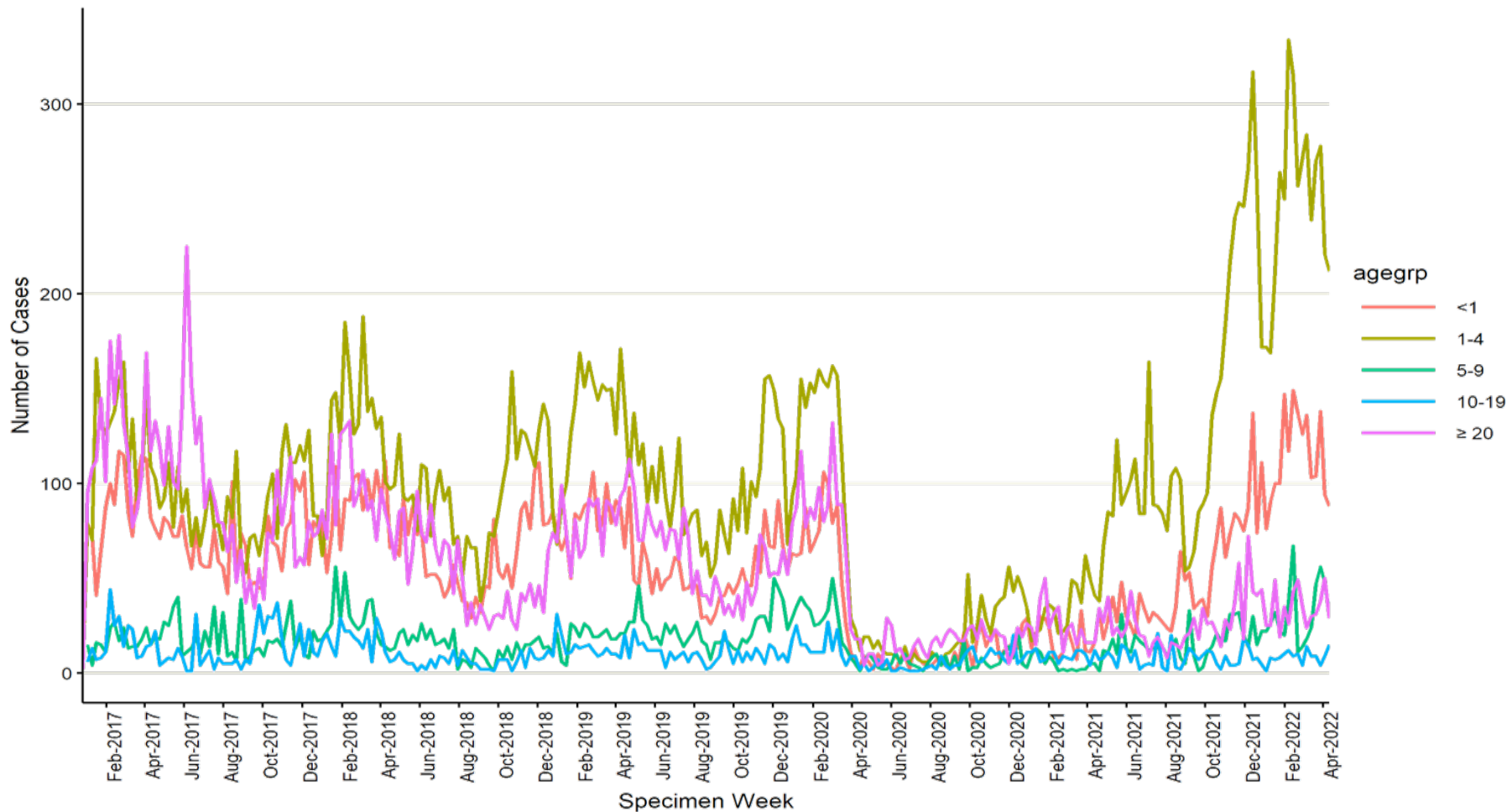
Adenovirus positive tests from routine clinical testing are recorded in SGSS and can be analysed by UKHSA. The testing patterns for adenovirus are likely to be variable and as it is not a notifiable disease there is also likely to be under reporting. Negative results are not recorded in SGSS, but a different 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 (Figure 4). Between November 2021 to March 2022, approximately 200-300

cases of adenovirus were reported into SGSS per week compared to 50-150 cases per week in the pre-pandemic period and less than 50 cases per week between March 2020 and May 2021. The increase in younger age groups begins in November 2021. This pattern is also seen specifically in enteric samples in the same age group (Figure 5).

Figure 4. Adenovirus episodes by age and week of specimen, England 1 January 2017 to 17 April 2022*

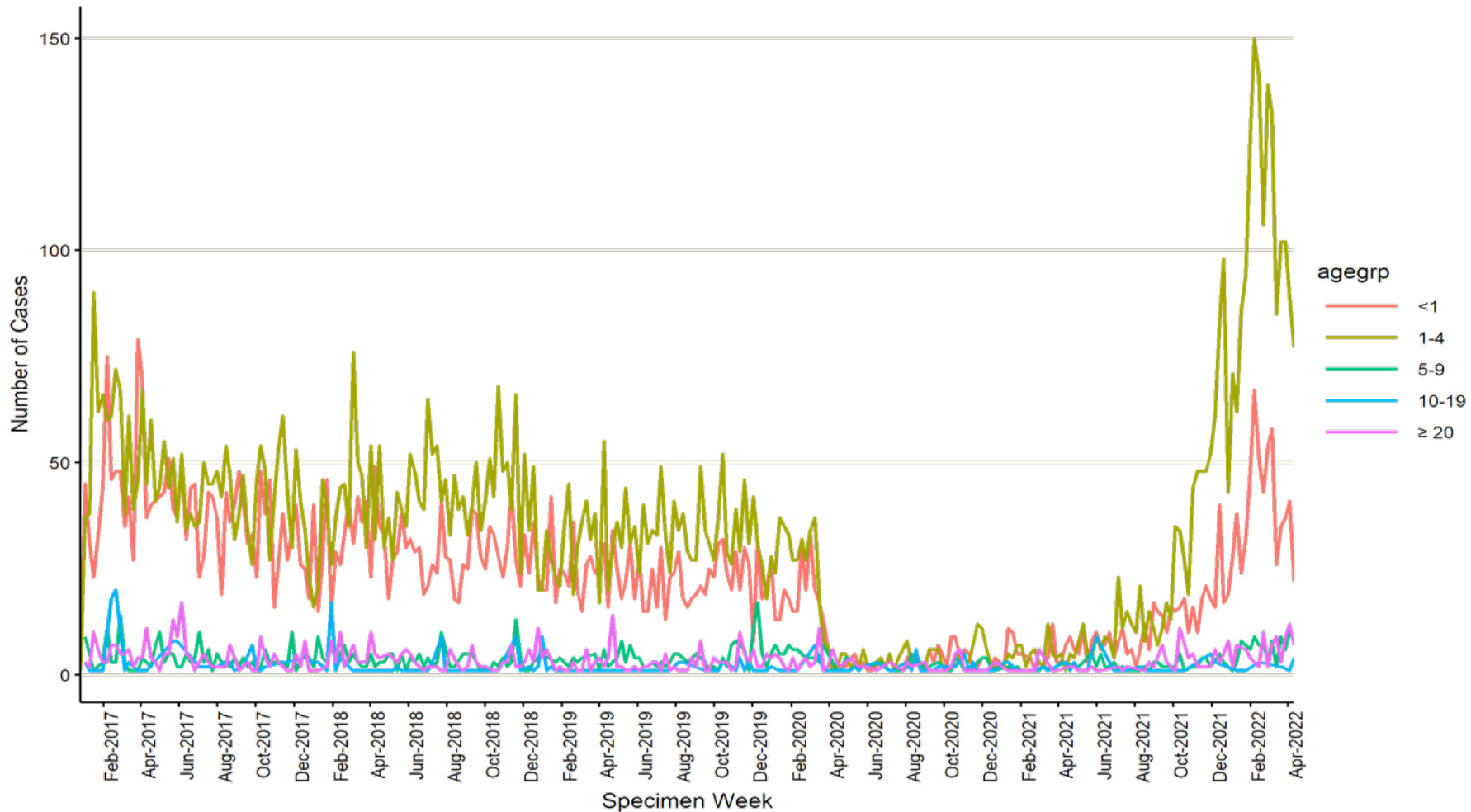
Supplementary data is not available for this figure.



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 5. Adenovirus episodes from Faecal/GI samples by age and week of specimen, England 1 January 2017 to 17 April 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](#).

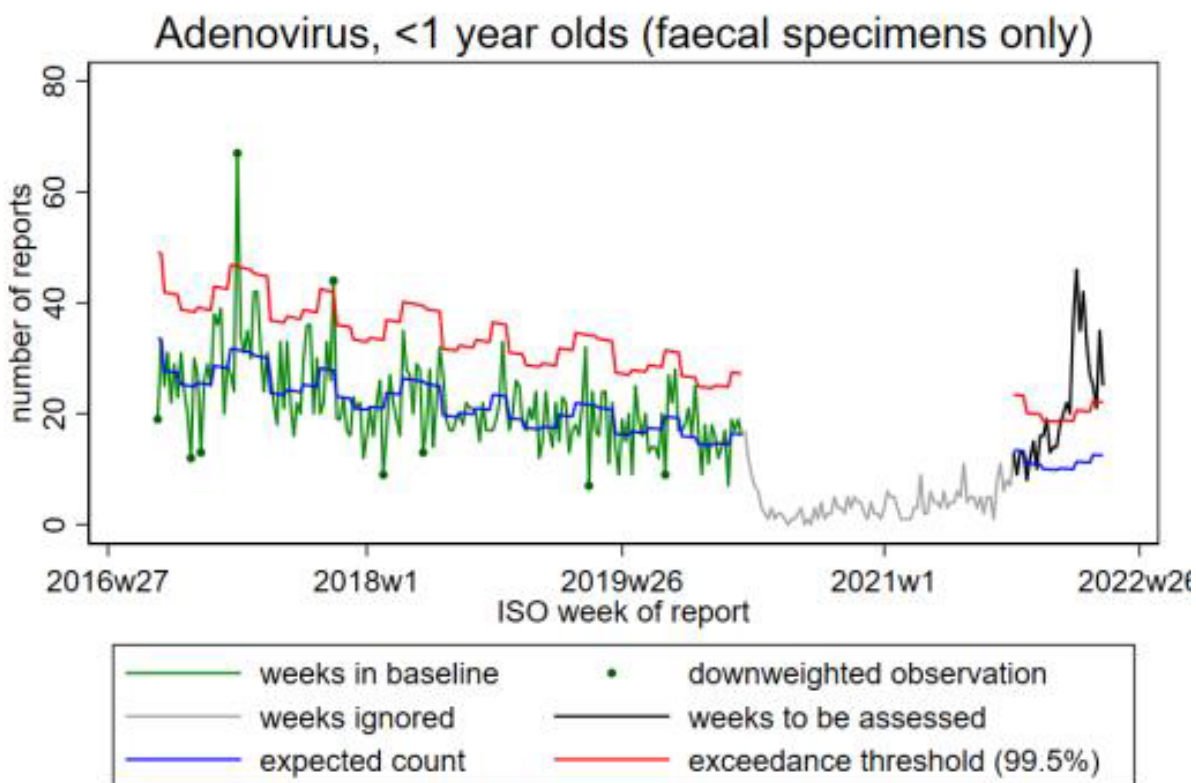
The plots in Figures 6 and 7 show trends in adenovirus reports in children from faecal and respiratory samples. The graphs compare recent data to the trends seen in previous years. Values above the red line indicate periods where the figures are higher than would be expected within the normal range.

Faecal specimens adenovirus exceedance

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

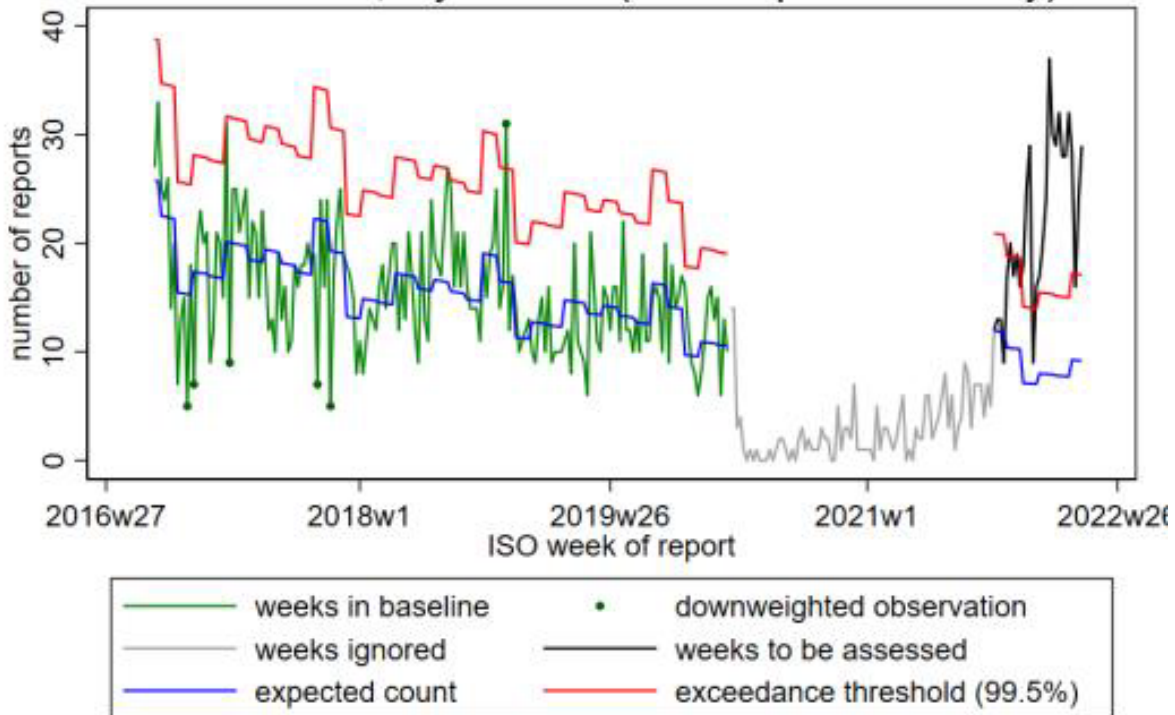
Figure 6. Exceedance for faecal specimen adenovirus as seen in less than 1 year to 9 years old

Supplementary data is not available for these figures.



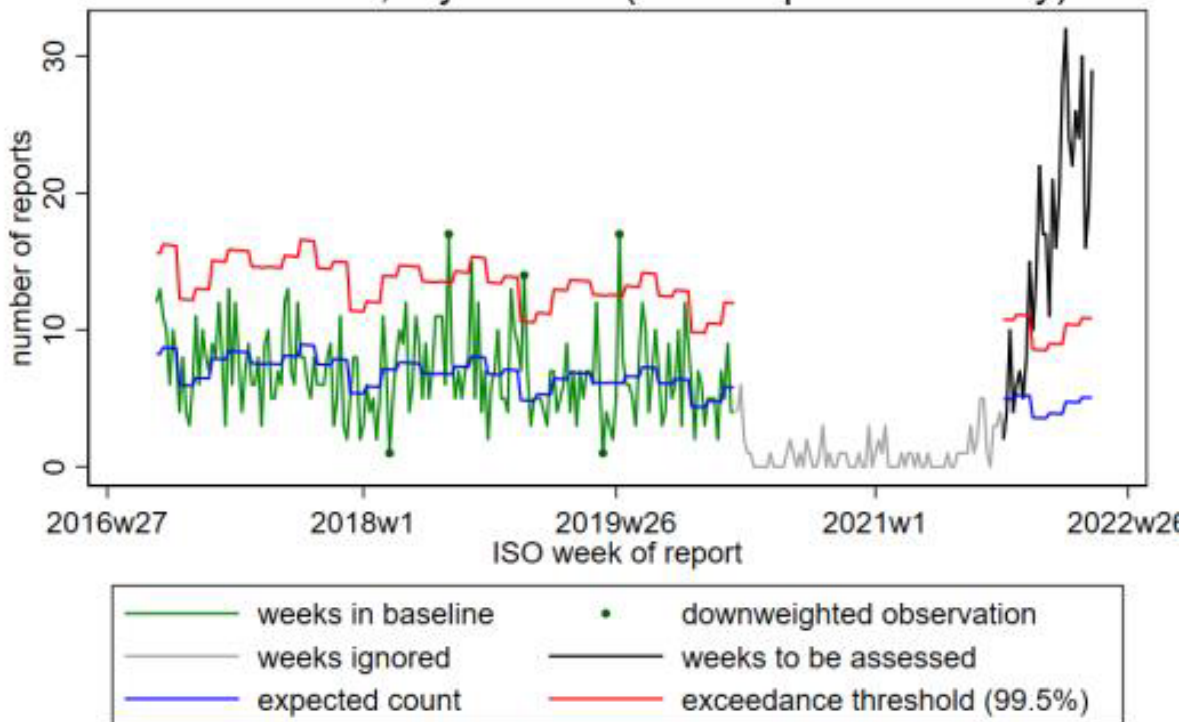
Data source : SGSS vw_Weekly_Exceedance table

Adenovirus, 1 year olds (faecal specimens only)



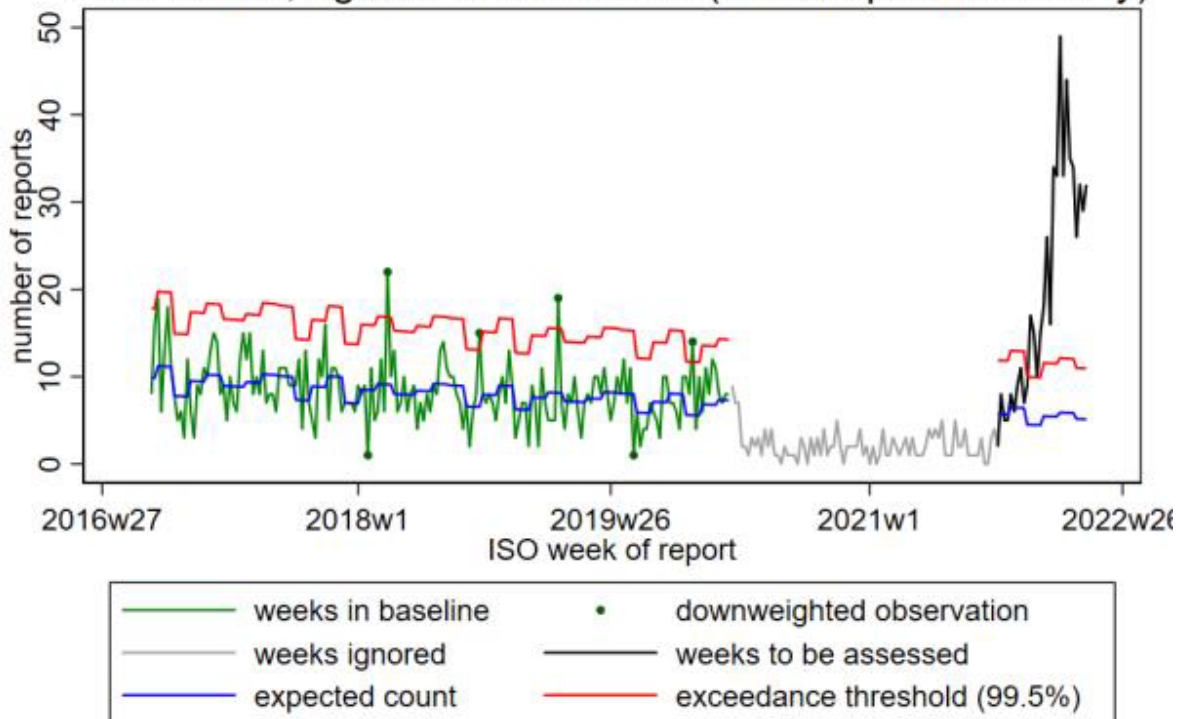
Data source : SGSS vw_Weekly_Exceedance table

Adenovirus, 2 year olds (faecal specimens only)



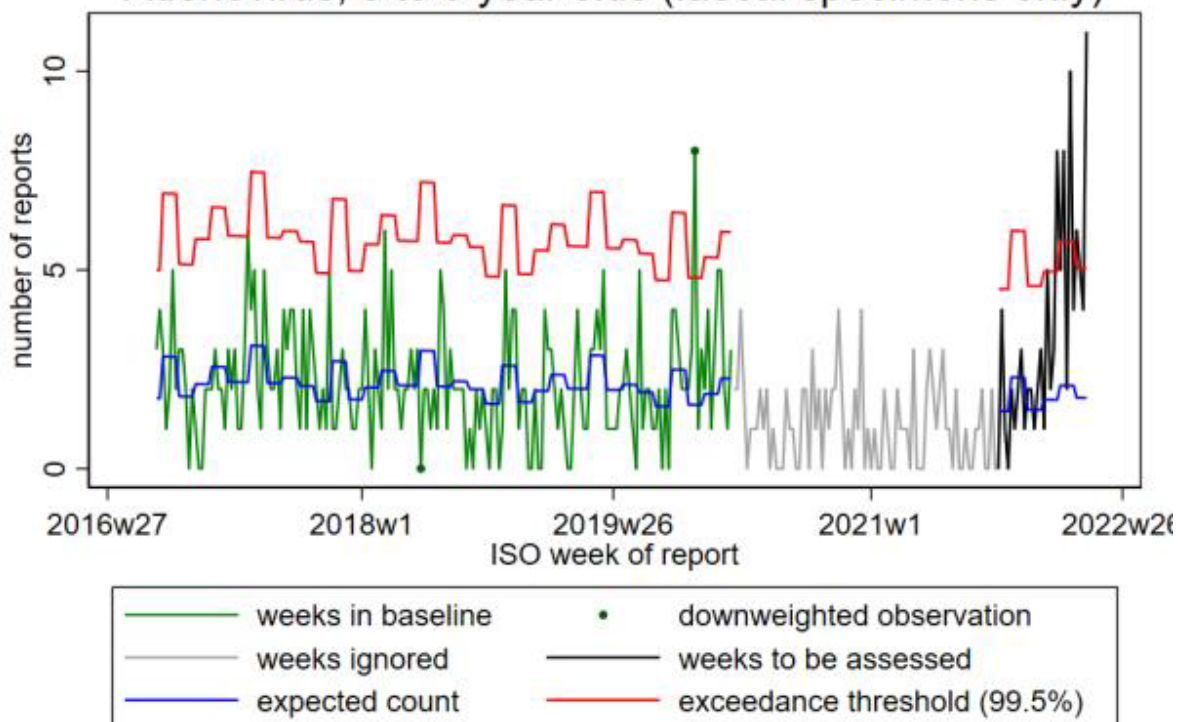
Data source : SGSS vw_Weekly_Exceedance table

Adenovirus, aged 3 to 5 inclusive (faecal specimens only)



Data source : SGSS vw_Weekly_Exceedance table

Adenovirus, 5 to 9 year olds (faecal specimens only)

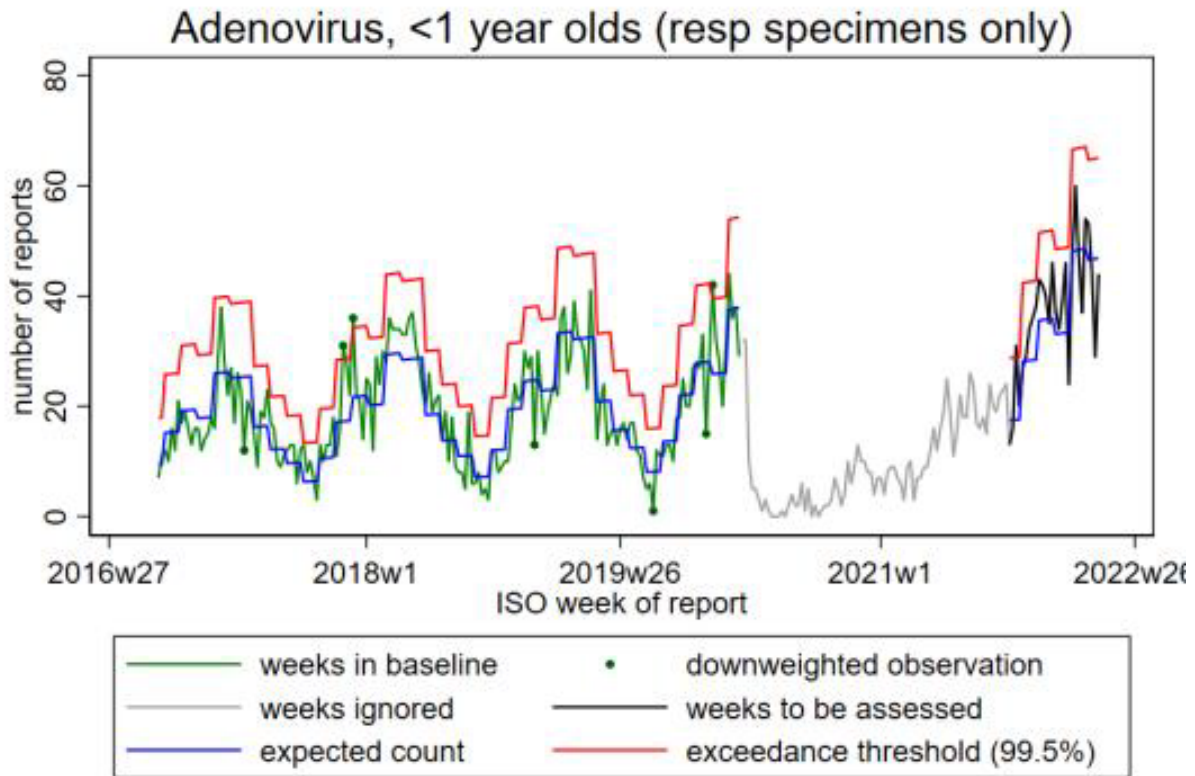


Data source : SGSS vw_Weekly_Exceedance table

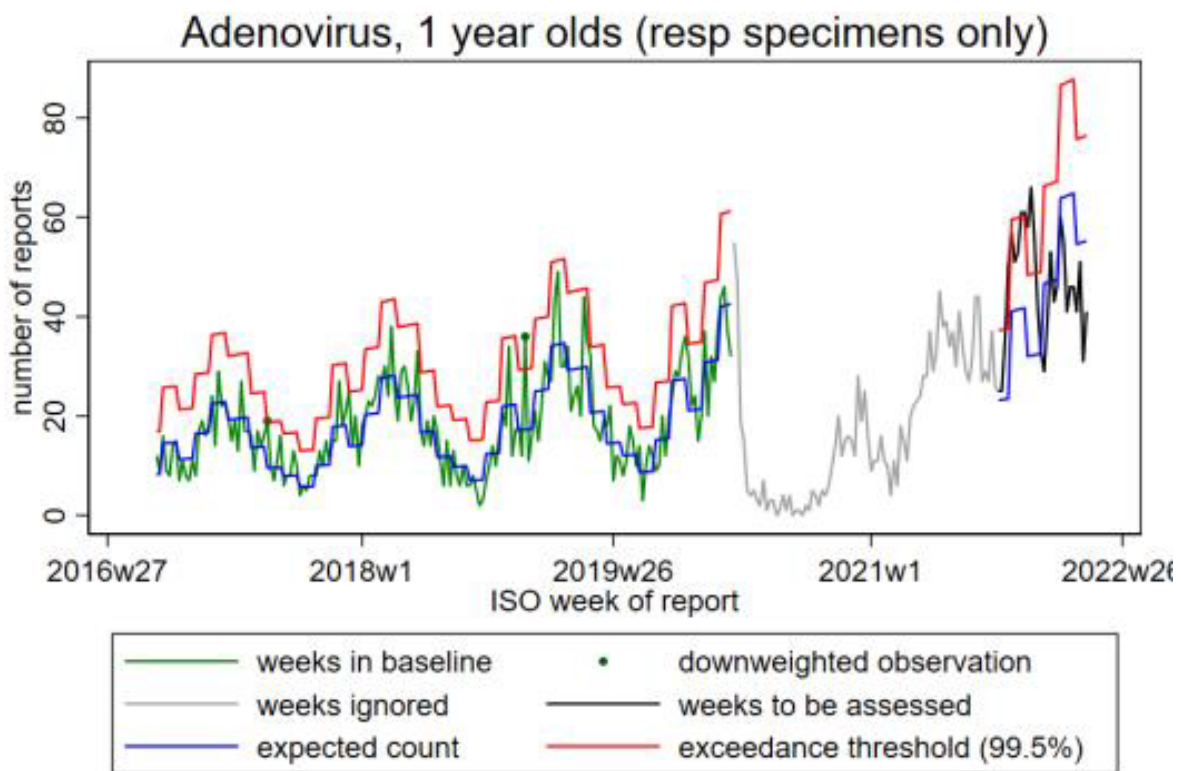
Respiratory specimens adenovirus exceedance

Exceedance is seen for respiratory adenovirus among younger children, predominantly 2 to 5 year olds and 5 to 9 year olds but not older children or adults.

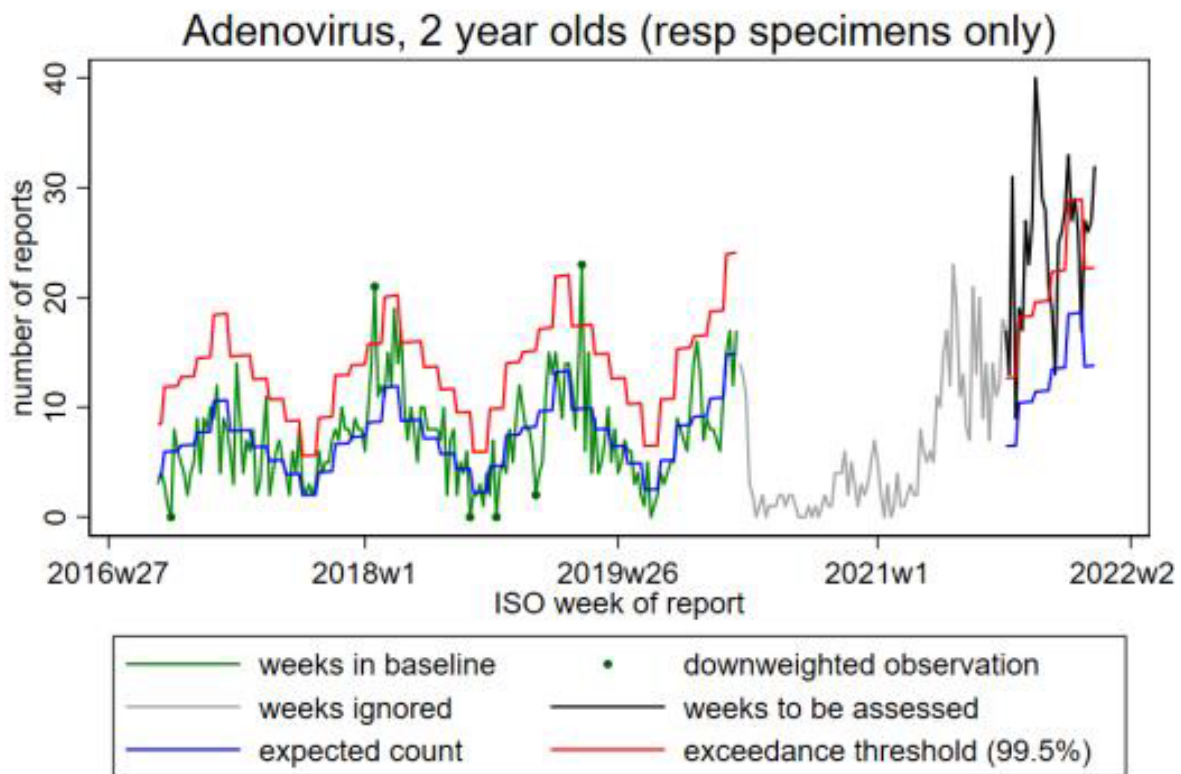
Figure 7. Exceedance for respiratory adenovirus among under 1 year olds to 9 year olds
 Supplementary data is not available for these figures.



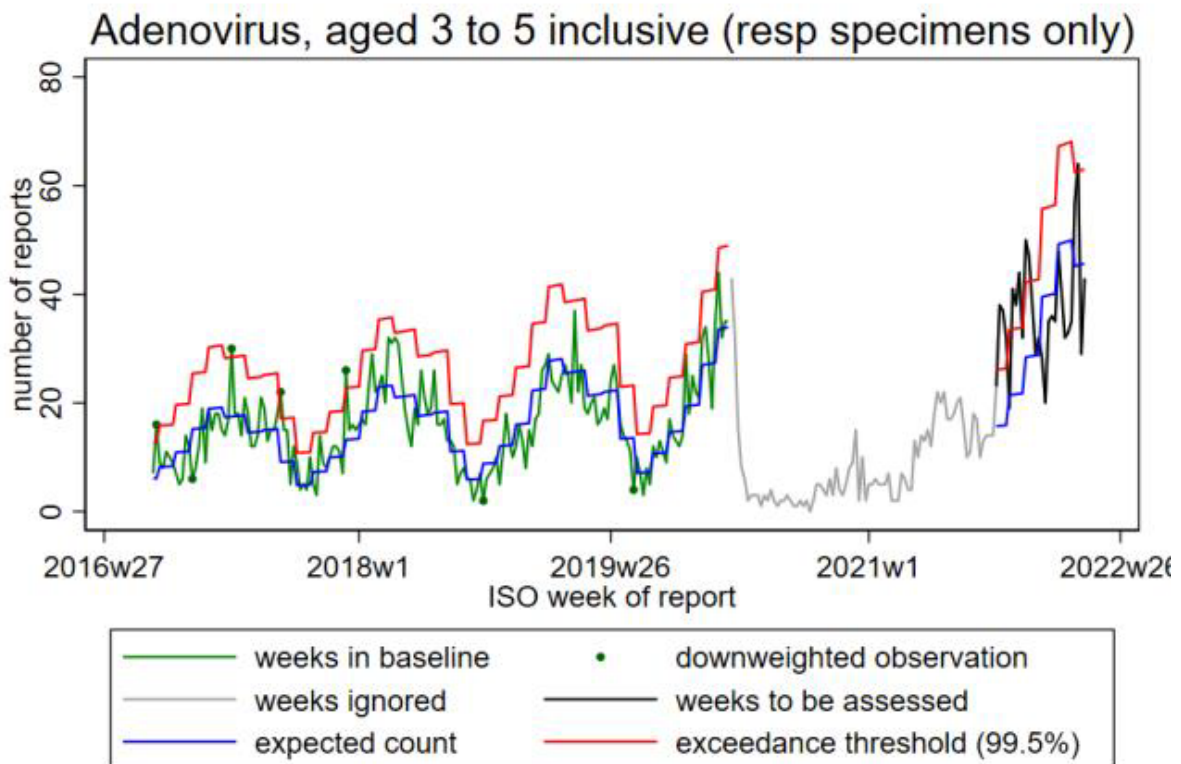
Data source : SGSS vw_Weekly_Exceedance table



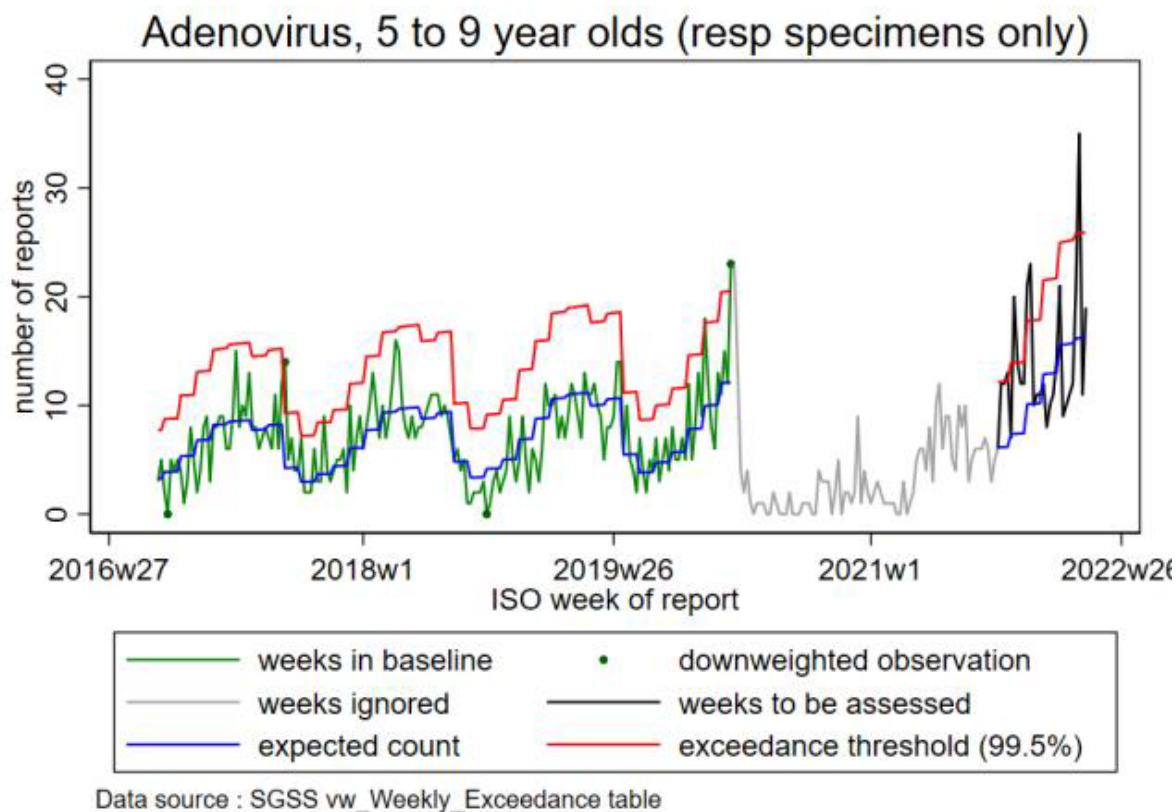
Data source : SGSS vw_Weekly_Exceedance table



Data source : SGSS vw_Weekly_Exceedance table



Data source : SGSS vw_Weekly_Exceedance table



Other pathogens showing exceedances

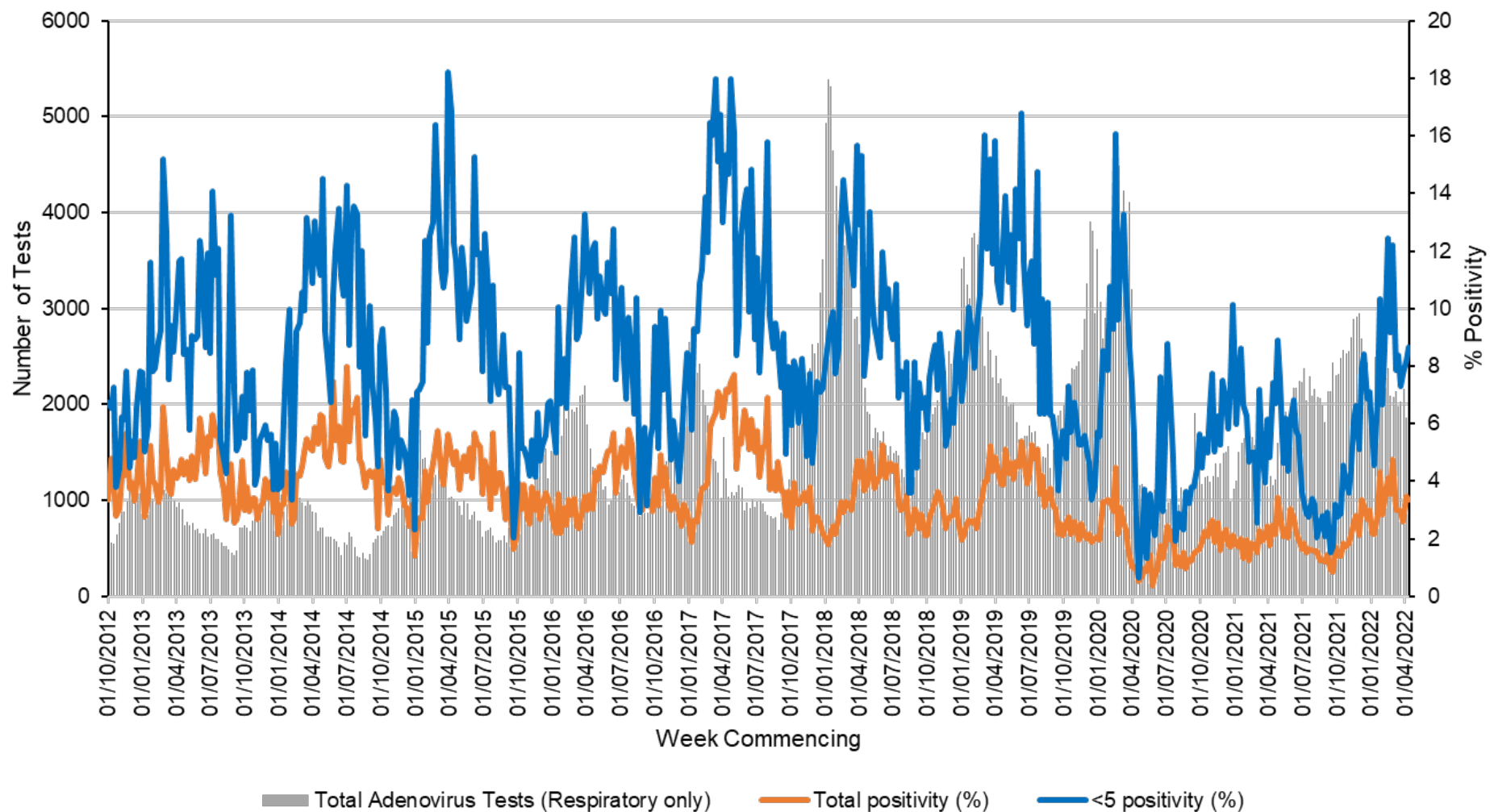
Exceedances are also seen for other respiratory and non-respiratory viruses in the period November 2021 to March 2022, which may be due to changes in behaviour and increased social mixing as restrictions eased and/or susceptibility in children due to lower levels of exposure during the pandemic. This includes norovirus, rotavirus, enterovirus, rhinovirus and human metapneumovirus. Exceedance plots are included in the [Appendix](#) (Figures b to f).

Respiratory DataMart

The Respiratory Data Mart reports adenovirus testing data from 11 sentinel laboratories across England (see Figure 8). No increase in positivity of respiratory samples was noted among all ages combined or under 5 year olds separately.

Figure 8. Respiratory Adenovirus positivity (total and under 5 year olds) by specimen week, England 2012 to 2022

Supplementary data is not available for this figure.



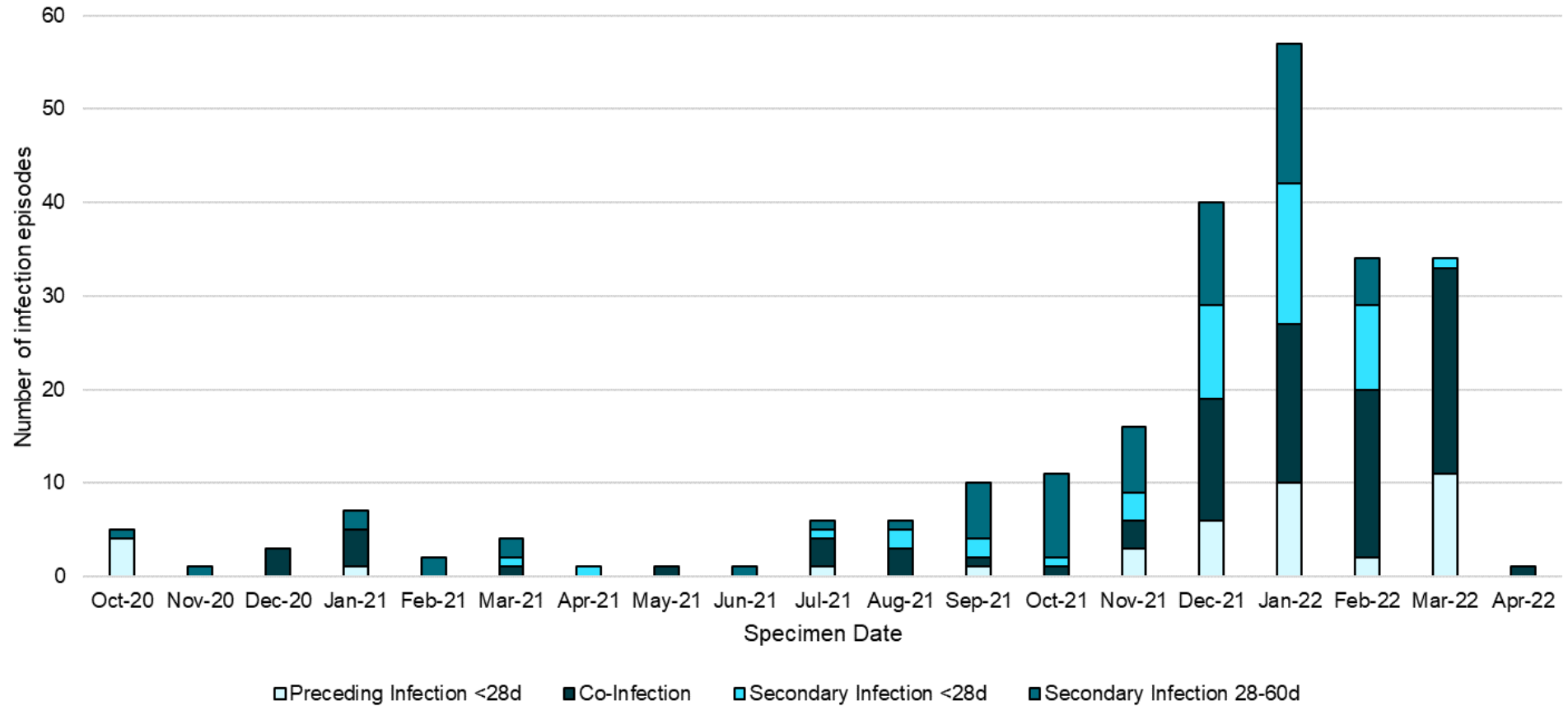
Interaction between adenovirus and SARS-CoV-2

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 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 March 2022, there has been a rise in both preceding, co- and secondary infections among children under 10. Similar rises have been seen for other childhood infections too (see Figure 9).

Figure 9. Number of adenovirus preceding, co-, and secondary infection episodes among children <10-years old with SARS-CoV-2 between October 2020 and April 2022, in England

Supplementary data is not available for this figure.



Part 6. Working hypotheses

6.1 Working hypotheses (in order of best to worst fit to data)

1. A cofactor affecting young children which is rendering normal adenovirus infections more severe or causing them to trigger immunopathology. The cofactor may be:
 - a. susceptibility, for example due to lack of prior exposure during the pandemic
 - b. a prior infection with SARS-CoV-2 or another infection, including an Omicron restricted effect
 - c. a coinfection with SARS-CoV-2 or another infection
 - d. a toxin, drug or environmental exposure
2. A novel variant adenovirus, with or without a contribution from a cofactor as listed above.
3. A drug, toxin or environmental exposure.
4. A novel pathogen either acting alone or as a coinfection.
5. A new variant of SARS-CoV-2.

Part 7. Planned investigations into aetiology

UKHSA convened a clinical and technical expert group including epidemiology, virology, hepatology, paediatrics, infectious diseases and immunology specialists. This group, led by UKHSA, will steer a comprehensive investigation and will receive and review data from the component studies. The investigations include clinical case investigation in the NHS, public health pathogen investigations, and research investigations under the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) Clinical Characterisation [Protocol](#) with full appropriate consent. ISARIC is funded by UK Research and Innovation and the National Institute for Health Research.

7.1 Additional investigations and status

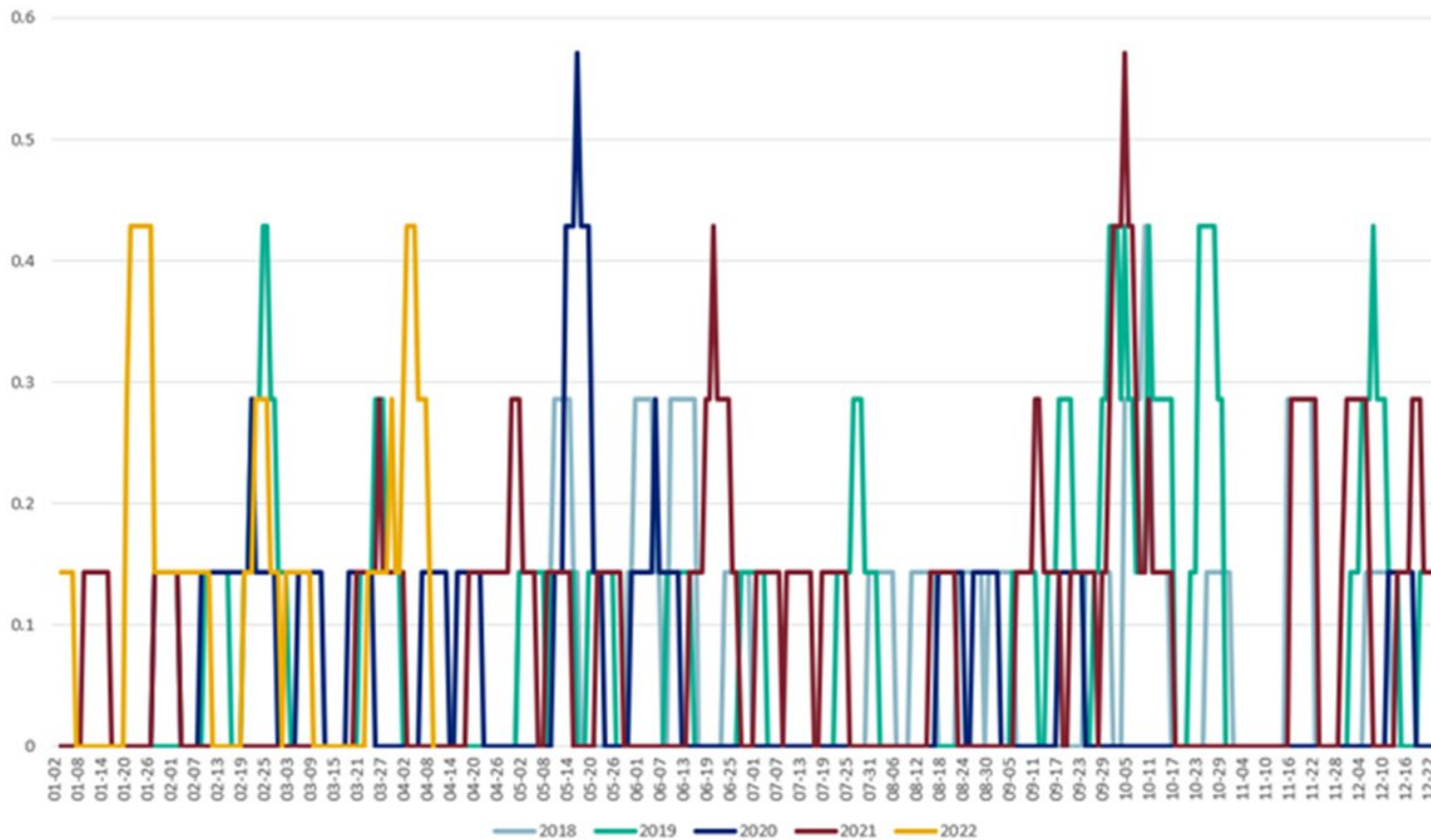
| | Investigation | Lead | Status |
|--|---|-------------|----------------------------|
| Analytic epidemiology | Matched case-control study (with residual whole blood samples from hospitalised children for controls) to test association of hepatitis with adenovirus infection | UKHSA | Protocol under development |
| | 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 | Underway |
| Mechanism of liver injury | Investigations on liver tissue to include electron microscopy, further histopathology review, T cell subset analysis | NHS | Underway |

| | Investigation | Lead | Status |
|-------------------------|--|--|---|
| Pathogen investigations | Adenovirus whole genome sequencing from cases and community samples | UKHSA and Great Ormond Street Hospital | Underway |
| | Metagenomic sequencing of blood and liver tissue from cases | UKHSA and Great Ormond Street Hospital | Underway |
| | Viral culture of adenovirus and phenotypic characterisation including assessment of hepatotropism in vitro | UKHSA and academic partners | Clinical materials in culture; no isolate yet available |
| | Adenovirus and SARS-COV-2 serology of cases | UKHSA | Samples requested |
| | SARS-COV-2 sequencing in positive cases | UKHSA | Underway |
| | Retrospective wastewater analysis for adenovirus | UKHSA | Under consideration |
| Host characterisation | Harmonised clinical data collation and analysis | ISARIC with partners | Underway |
| | Host genetic characterisation | ISARIC in partnership with GENOMICC | Planned |
| | Immunological characterisation including T cell activation studies | ISARIC with partners | Planned |
| | Transcriptomics | ISARIC with partners | Under consideration |

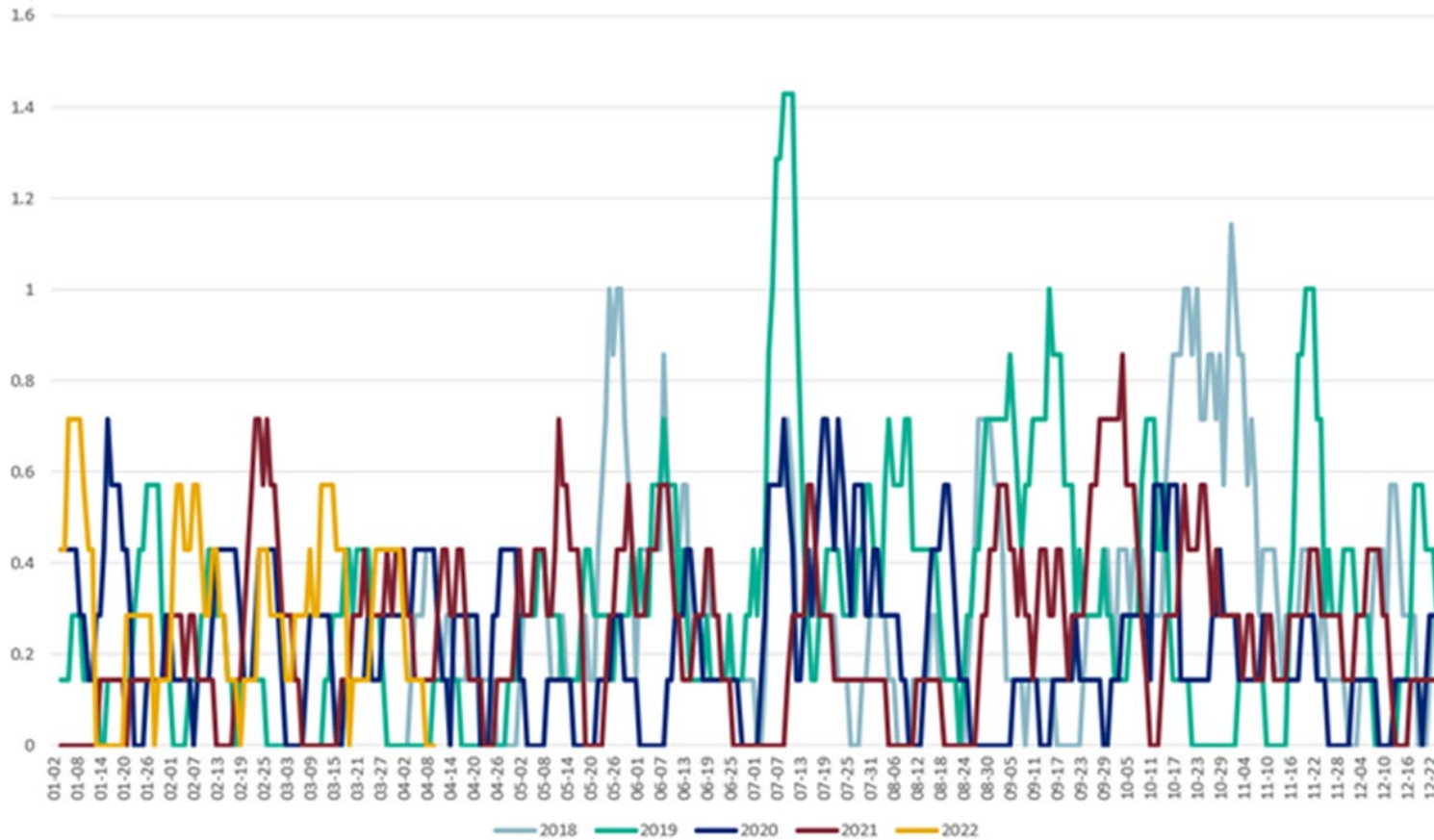
Appendix 1. Additional data

Relevant surveillance data

Figure a. Seven day moving average of ED attendances with a 'liver disease*' primary diagnosis by (i) age 1 to 4 years
Supplementary data is not available for these figures.



(ii) age 5 to 14 years



*'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 c. Rotavirus reported through SGSS

Supplementary data is not available for this figure.

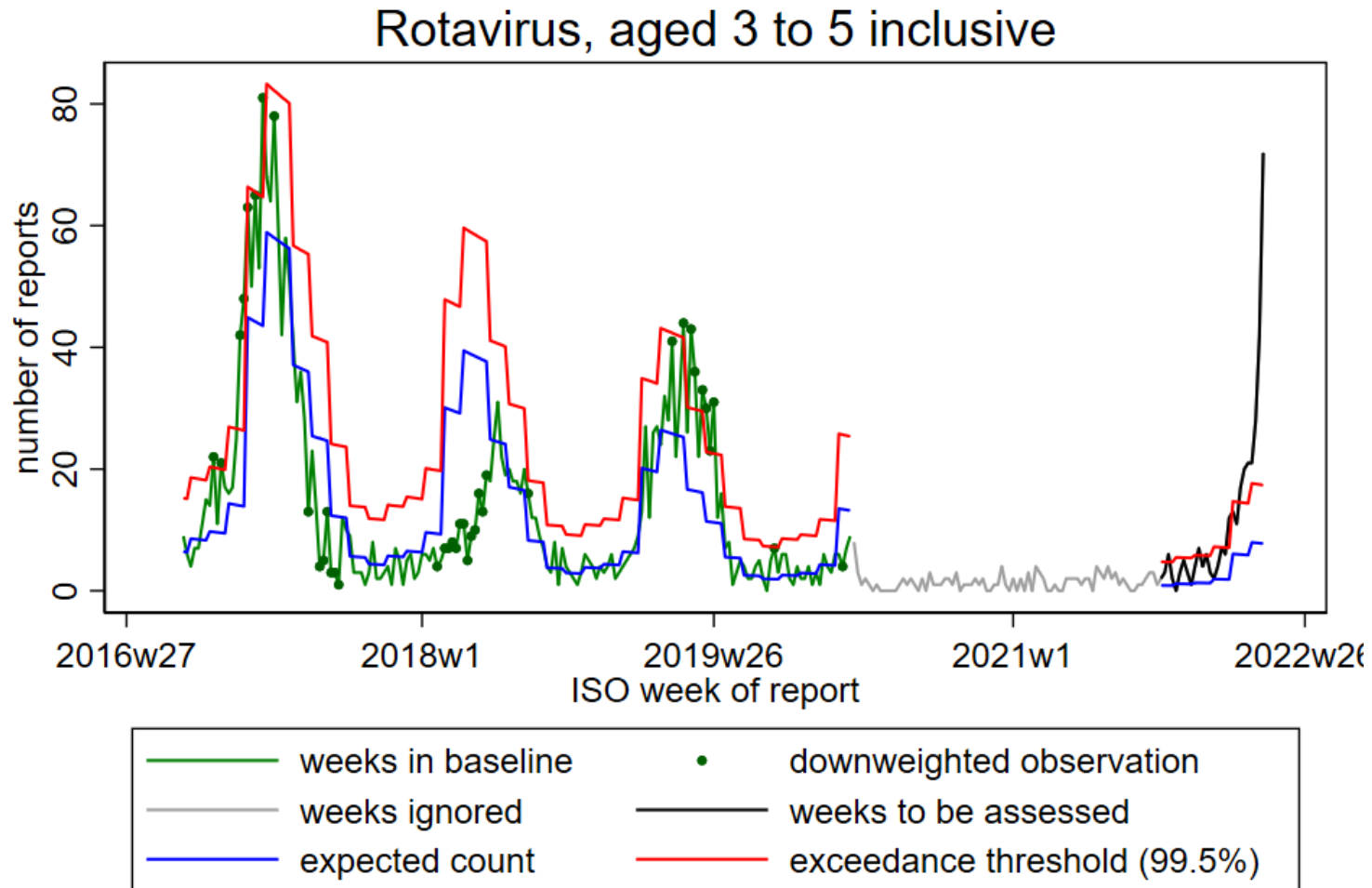


Figure d. Rhinovirus reported through SGSS

Supplementary data is not available for this figure.

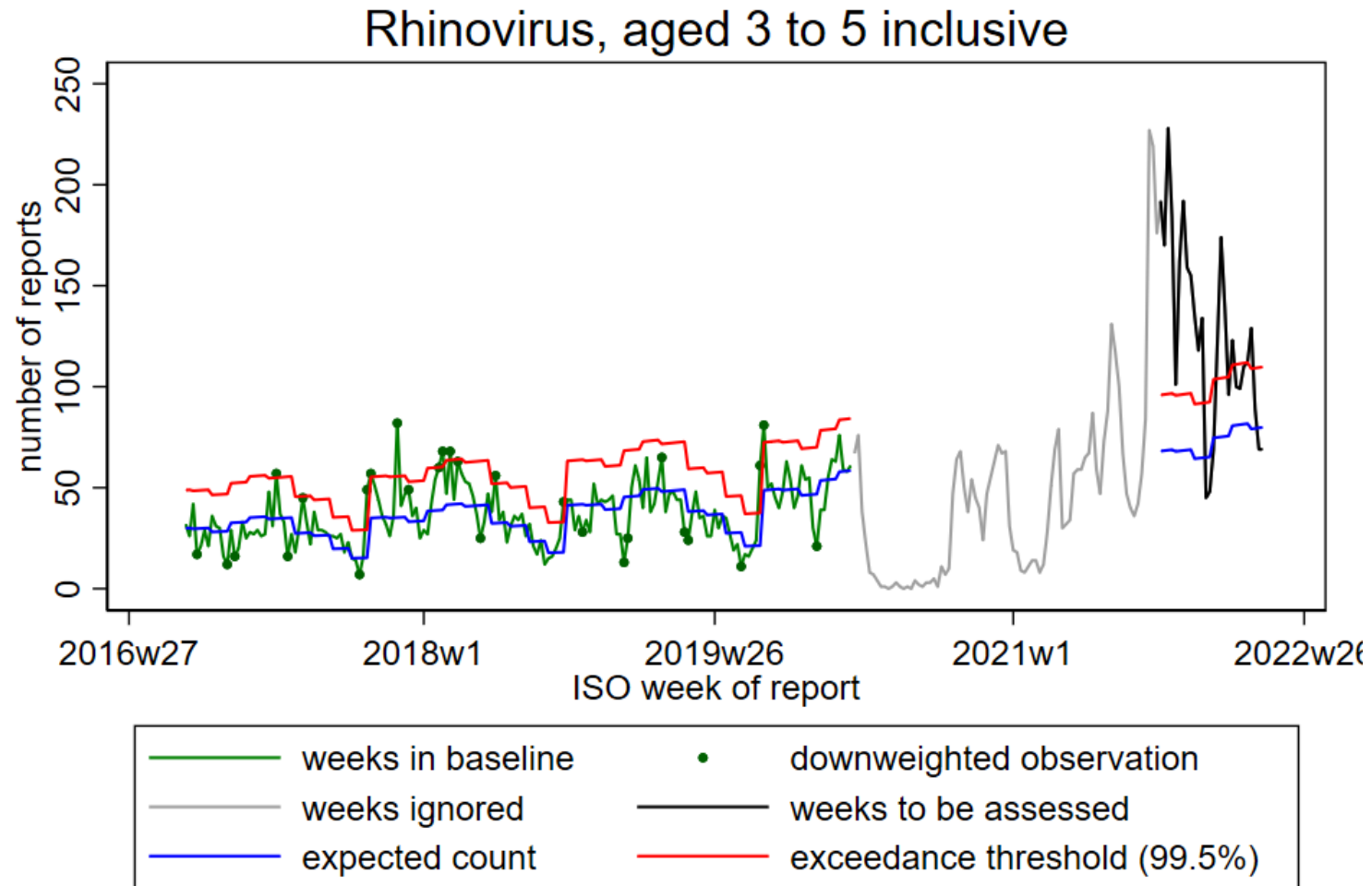
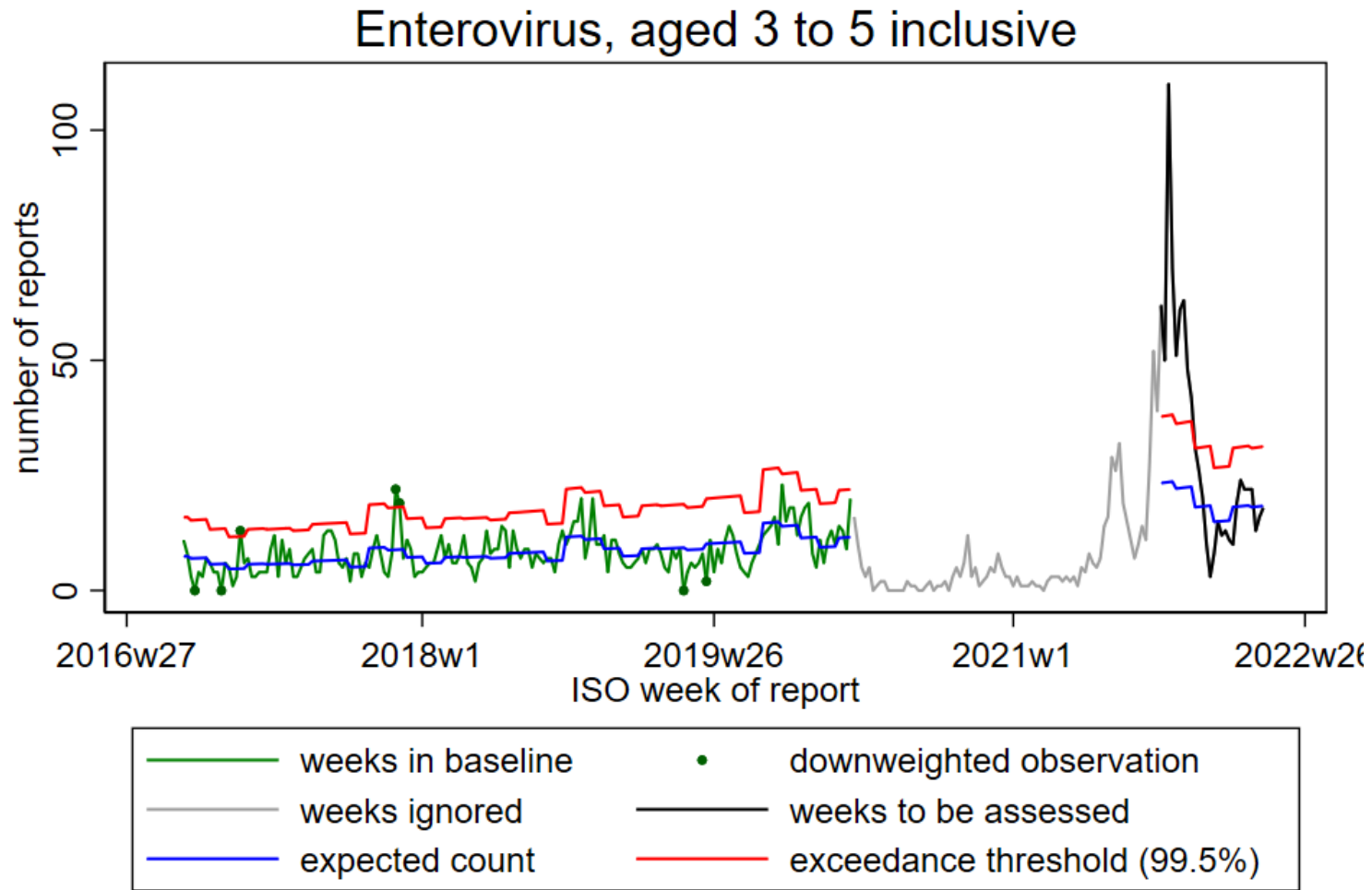


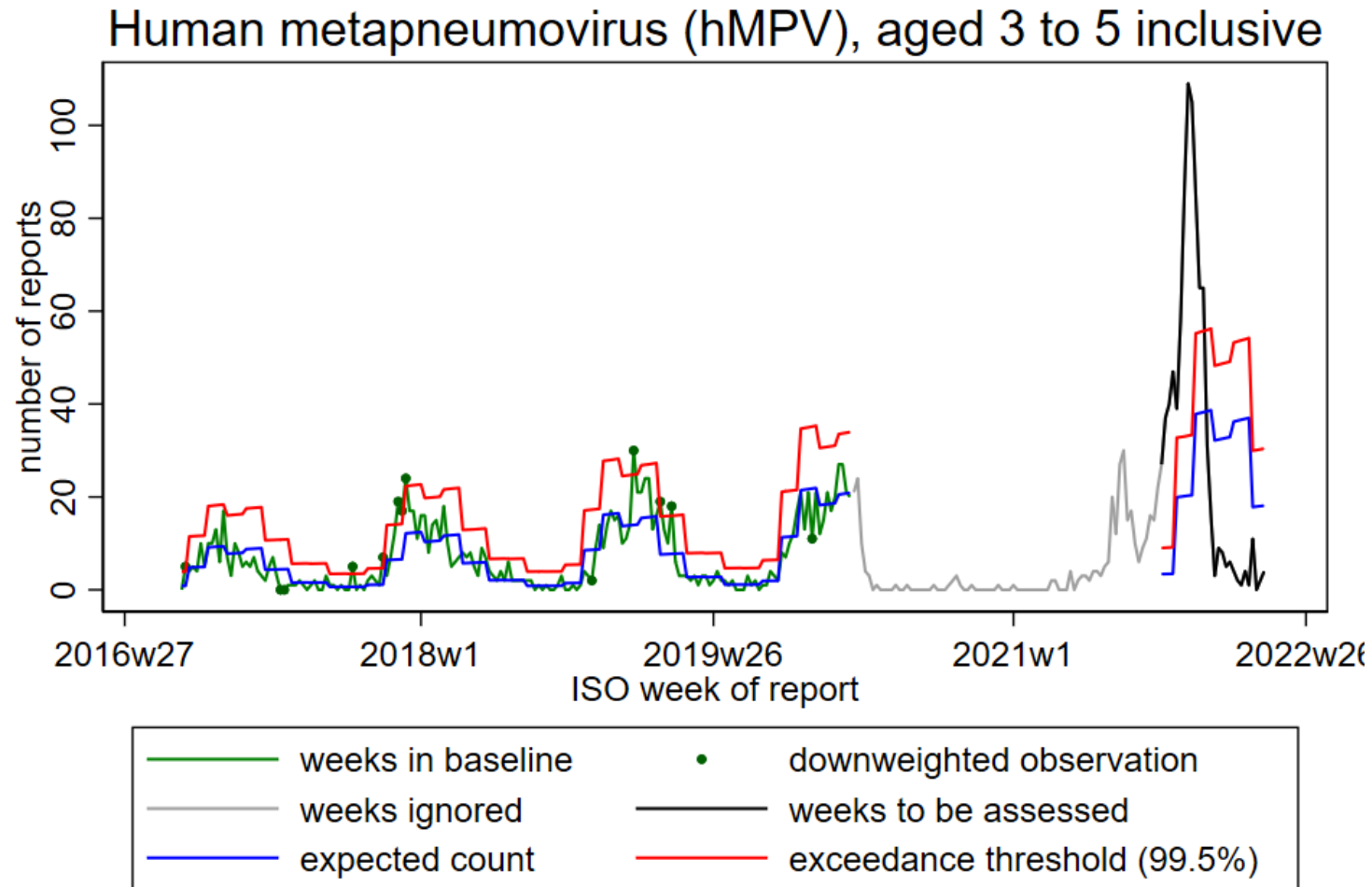
Figure e. Enterovirus reported through SGSS
Supplementary data is not available for this figure.



Data source : SGSS vw_Weekly_Exceedance table

Figure f. Human metapneumovirus reported through SGSS

Supplementary data is not available for this figure.



Data source : SGSS vw_Weekly_Exceedance table

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 used in this investigation

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-19 Unified Data Set (UKHSA)
NOIDs (UKHSA)
HPZone (UKHSA)
International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) UK

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UKHSA Epicell
UKHSA Genomics and Public Health Analysis Team
UKHSA Toxicology Cell
UKHSA Virology Cell
UKHSA Virus Reference Department
UKHSA Incident Management Team
University of Edinburgh
University of Liverpool

About the UK Health Security Agency

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 health secure.

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Version 1.0

Published: April 2022
Publishing reference: GOV-12076

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