INA-RESPOND

INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

KEMENTERIAN KESEHATAN REPUBLIK INDONESIA

NEWSLETTER

May 2022

Hepatitis of unknown origin in children

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HEALTH POLICY AGENCY
MINISTRY OF HEALTH REPUBLIC OF INDONESIA
2022

INA-RESPOND newsletter

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THANK YOU

INA-RESPOND Network & Partners

INA-RESPOND Secretariat

Badan Kebijakan Pembangunan Kesehatan, Gedung 6, Lantai 3.
Jl. Percetakan Negara no.29,
Jakarta 10560
www.ina-respond.net

MASTHEAD

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FEATURES

INA-RESPOND
Newsletter

TRIPOD, PROACTIVE, & ORCHID Study Updates

By: Eka Windari R., I Wayan Adi Pranata, Lois E. Bang, Melinda Setiyaningrum, Nur Latifa Hanum, Retna Mustika Indah, Riza Danu Dewantara

INA102

We have submitted 2 papers from the TRIPOD study: #1 "The Characteristics of Drug Sensitive and Drug-Resistant Tuberculosis Cases in Indonesia" to the American Journal of Tropical Medicine and Hygiene on 22nd February 2022; and #2 "Performance of Xpert TB/RIF and Sputum Microscopy Compared to Sputum Culture for Diagnosis of Tuberculosis in Seven Indonesian Hospitals" to the Frontiers in Medicine - Infectious Diseases - Surveillance, Prevention, and Treatment on 31 March 2022. We just received comments from 1 reviewer for paper #2. Paper #1 is still under review.

The subculture isolates sent to Bandung BBLK are still ongoing, from 301 baseline samples 234 were done sub-culturing and the mTB DNA was extracted. Eight of them did not grow and the remaining 59 samples are in process.

RePORT Network call for abstracts to be presented in the upcoming Annual RePORT International meeting in Cape Town, South Africa, 7-8 September 2022 for Young Investigators. RePORT network will provide airfare, hotel expenses, as well as an invitation to participate in a poster discussion at the meeting. Young investigators defined as one of the following:

- faculty members who are no more than five years out from completion of all training; current clinical fellows,
- doctoral students or post-docs; or current medical students or residents.
- completed their last degree by 2014 or after (not more than 8 years of completion).
- The abstracts should be of high scientific quality and should describe work related to either the TRIPOD Protocol; in other words, any ongoing projects that leverage, or plan to leverage, the established RePORT platform.

INA104

As of May 17, 2022, from 4336 subjects enrolled, 46.1 % of the subjects have ended their study, and 53,09% of the subjects are still ongoing. The picture below shows the study progress from each Site.

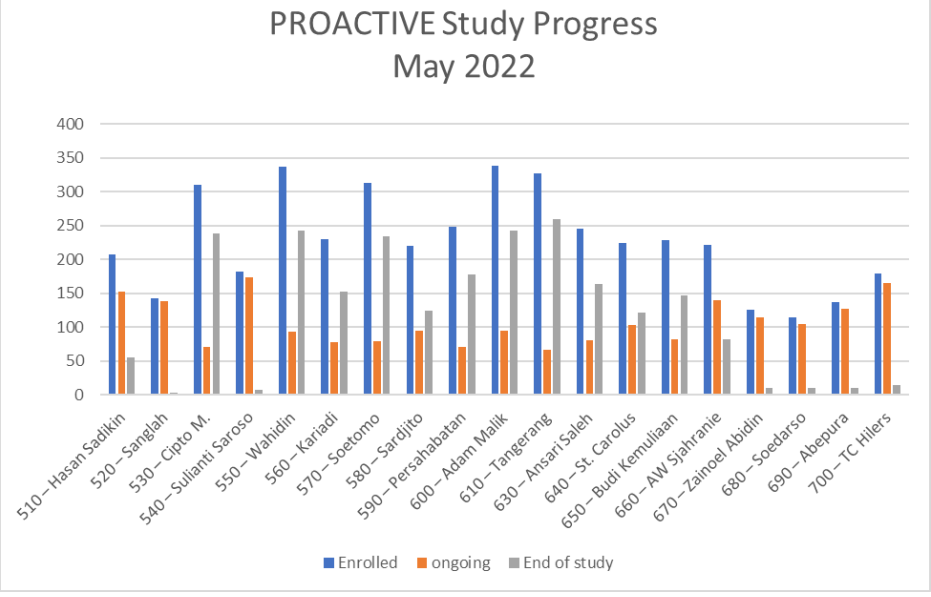


Figure 1. Site's study progress

For the end of study subjects, 1.838 subjects had already completed the study until follow up visit month 36, 233 subjects died, 162 subjects were lost to follow up, 32 subjects withdrew consent, 31 subjects moved to a city without a PROACTIVE site, five subjects with HIV negative, and one subject suspended (imprisoned). Detailed information for each site can be seen in the table below.

Below are the monitoring activities during April & May 2022:

- 5th onsite monitoring visit to site 590 RSUP Persahabatan, Jakarta, 11-13 April 2022.
- 5th onsite monitoring visit to site 580 RSUp Dr. Sardjito, Yogyakarta, 17-19 May 2022
- 4th onsite monitoring visit to RSUD Abdul Wahab Sjahranie, Samarinda, 23-25 May 2022

Table 1. Subjects' end of study reasons

No	Site	*End of Study Duration/ Complete*	Withdrew Consent	Participants with HIV negative	Moved	Death	Investigator Discretion	Lost to Follow Up	Other	Total
1.	510 – RSUP Dr. Hasan Sadikin	48	1	0	2	4	0	0	0	55
2.	520 - RSUP Sanglah	1	0	0	0	3	0	0	0	4
3.	530 – RSUPN Dr. Cipto Mangunkusumo	216	0	0	0	17	0	6	0	239
4.	540 – RSPI Dr. Sulianti Saroso	0	0	0	2	6	0	0	0	8
5.	550 – RSUP Dr. Wahidin Sudirohusodo	174	0	0	5	24	0	40	0	243
6.	560 – RSUP Dr. Kariadi	127	1	3	0	14	0	7	0	152
7.	570 – RSUD Dr. Soetomo	186	13	0	4	21	0	10	0	234
8.	580 – RSUP Dr. Sardjito	98	1	0	4	4	0	18	0	125
9.	590 – RSUP Persahabatan	129	0	1	0	37	0	11	0	178
10.	600 – RSUP Dr. H. Adam Malik	187	3	0	2	21	0	30	0	243
11.	610 – RSU Kabupaten Tangerang	214	7	0	3	19	0	16	1	260
12.	630 – RSUD Dr. M. Ansari Saleh	149	1	0	1	7	0	6	0	164
13.	640 – RS St. Carolus	119	0	0	0	1	0	2	0	122
14.	650 – RSU Budi Kemuliaan Batam	120	3	0	5	8	0	11	0	147
15.	660 – RSU A. Wahab Sjahranie	70	0	0	2	5	0	5	0	82
16.	670 – RSUD Zainoel Abidin	0	0	0	0	11	0	0	0	11
17.	680 – RSUD Soedarso	0	0	0	0	10	0	0	0	10
18.	690 – RSUD Abepura	0	1	1	1	7	0	0	0	10
19.	700 – RSUD TC Hillers	0	1	0	0	14	0	0	0	15
Total		1838	32	5	31	233	0	162	1	2302

INA107

Based on uploaded CRFs as of 10 May 2022, a total of 183 participants were enrolled in the ORCHID-COVID-19 study, with 115 from site 610 (RSU Kabupaten Tangerang, Tangerang) and 68 from site 521 (RS Universitas Udayana, Denpasar). This study had 172 (94%) participants who completed the visits, with 5 (3%) participants died during the study. In terms of deaths, 2 subjects from site 610 died because of COVID-19 and heart failure, while 3 subjects from site 521 died from thromboembolism, non-ST-segment Elevation Myocardial Infarction, and thromboembolism. On the other hand, 6 (3%) par-

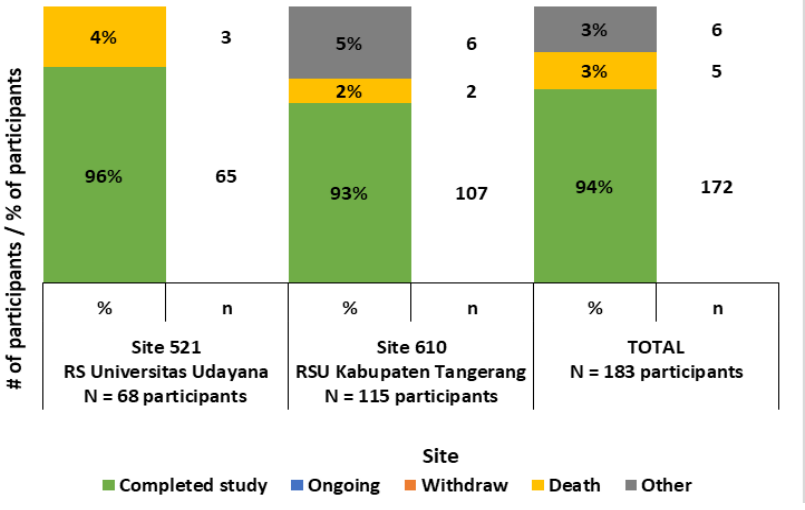


Figure 1. Participant status per site based on uploaded CRF as of 10 May 2022

ticipants decided to not continue participation to the study (categorized as other) (figure 1).

As of 10 May 2022, a total of 153 (84%) participants were identified as positive COVID-19 while 30 (16%) participants were identified as negative COVID-19. In site 610, the number of participants identified as positive COVID-19 was 105 (91%) and 10 (9%) participants identified as negative COVID-19. On the other hand, in site 521, there were 48 (71%) participants identified as positive COVID-19 and 20 (29%) participants identified as negative COVID-19 (figure 2).

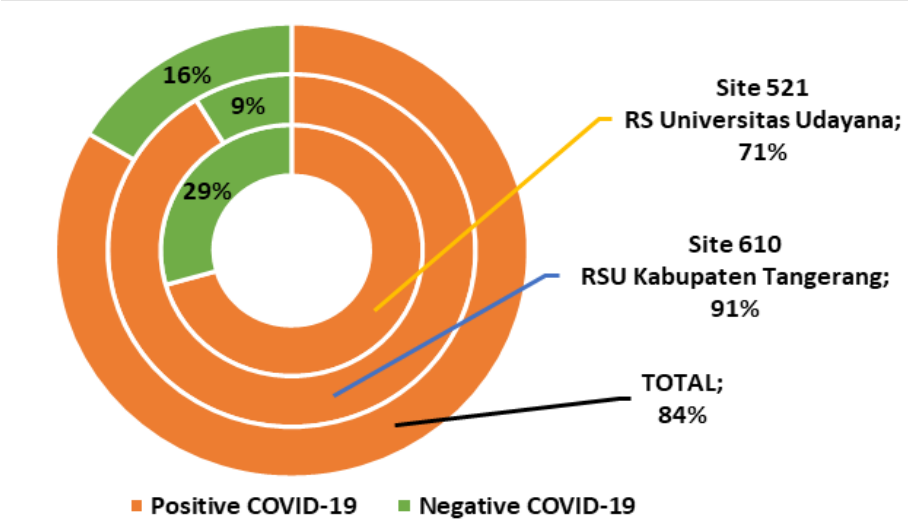


Figure 2. COVID-19 identification at enrolment based on uploaded CRF per 10 May 2022

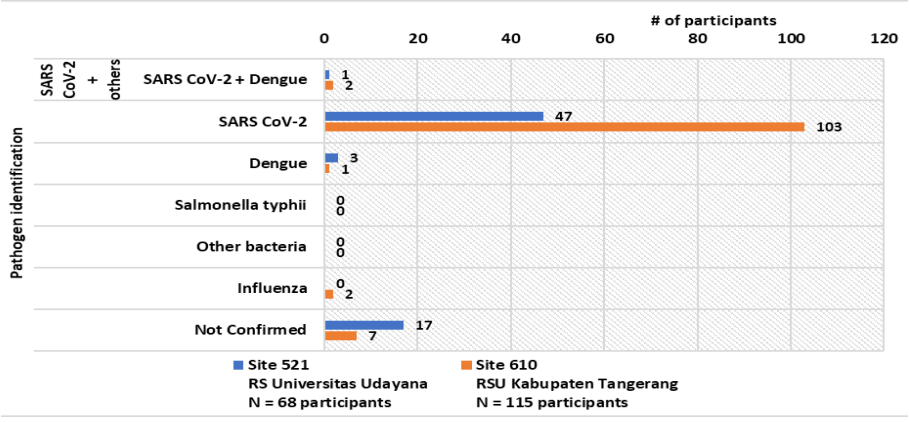


Figure 3. Pathogen identification based on uploaded CRF per 10 May 2022

In site 521, SARS-CoV-2 was identified in 47 (69%) participants based on the pathogen identification data. SARS-CoV-2 and Dengue (confirmed by PCR SARS-CoV-2 and RDT Dengue IgM) co-infection were identified in 1 (1%) participant. Dengue (confirmed by RDT Dengue NS-1) was also identified in 3 (5%) participants. Based on the data from site 610, SARS-CoV-2 was identified in 103 (90%) participants. SARS-CoV-2 and dengue (confirmed by PCR SARS-CoV-2, RDT Dengue NS-1, and RDT Dengue IgM IgG) co-infection were identified in 2 (2%) participants. Influenza (confirmed by PCR) was identified in 2 (2%) participants. Dengue (confirmed by RDT Dengue NS-1 and RDT Dengue IgM IgG) was also identified in 1 (1%) participant. Overall, the pathogen was unidentifiable among 24 (13%) participants, 17 were from Site 521 and 7 from site 610 (figure 3).

The annual report for notifying study progress was submitted to local IRB RSU Kabupaten Tangerang on May 13, 2022. Since NIHRD IRB may not be able to receive a new/extension of ethical clearance, we will submit the annual report by the end of this month while preparing the submission to the other IRBs in parallel. The current ORCHID-COVID-19 study will continue to recruit additional patients. However, we plan to shift to the ORCHID general protocol when the preparation is finished.

Several calls with NIAID will be held to discuss manuscripts based on the ORCHID-COVID-19 study results. The analysis of data from the FluPRO questionnaire is of particular interest. The FluPRO preliminary analysis was presented and discussed with John Powers. Inputs will be factored into the analysis.

INA-RESPOND Newsletter

SCIENCE CORNER

HEPATITIS OF UNKNOWN ORIGIN IN CHILDREN - WHAT WE KNOW, AND WE DON'T KNOW (YET) FOR NOW

By: Yan Mardian

1. Event Background

On 31 March 2022, Public Health Scotland was alerted to five children aged 3–5 years at Glasgow children's hospital with severe hepatitis of unknown etiology within three weeks. This cluster exceeded the expected number of cases of hepatitis of unknown etiology, fewer than four per year. The United Kingdom (UK) informed these cases to the World Health Organization's International Health Regulations (IHR) notification system on 5 April 2022 (testing had excluded viral hepatitis types A, B, C, D, and E and other known causes of acute hepatitis). Following this alert, the USA and several European Union, European Economic Area (EU/EEA), and other countries reported suspected 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 **under 16 years old in the UK** since 1 January 2022. This resulted from an active case-finding investigation commencing in April, which identified retrospective and prospective cases.

As of **21 April 2022**, at least **11 countries** in the WHO European Region and one country in the WHO Region of the Americas have reported the cases. Cases are **aged one month to 16 years old**. Seventeen children (approximately 10%) required liver transplantation; at least one death was reported. In November 2021, clinicians at a large children's hospital in **Alabama, US,** notified the Centers for Disease Control and Prevention (CDC) of five pediatric patients with significant liver injury, including three with acute liver failure. All five patients had tested positive by blood PCR for adenovirus, and all were previously healthy. None had COVID-19 or common hepatitis viruses detected on testing. Case-finding efforts at this hospital identified four additional pediatric patients with hepatitis, all with adenovirus DNA identified in the blood by PCR, for **a total of nine patients** admitted during the five months from October 2021 through February 2022. A multi-disciplinary expert team reviewed clinical and epidemiological data from the first five children: vomiting in preceding weeks, jaundice, and exceptionally high levels of transaminases, often greater than 2000

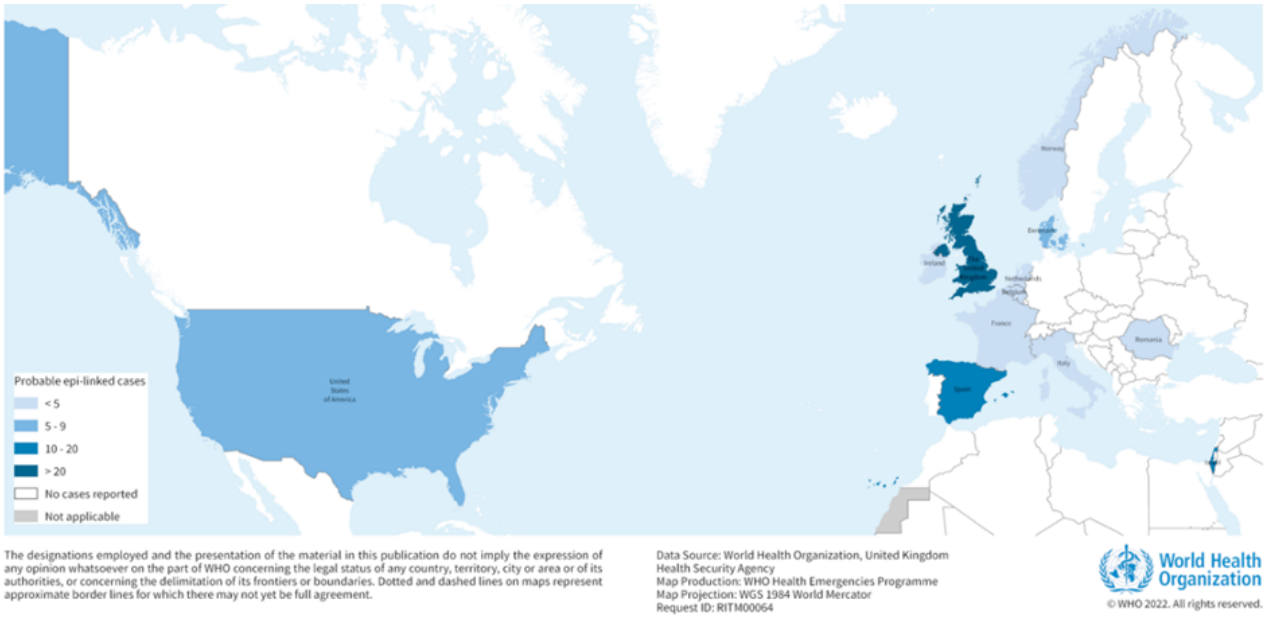


Figure 1. Distribution of cases of acute severe hepatitis of unknown origin by country (WHO)

international units per liter (IU/L; n.v. <40 IU/L), were the main features.

2. World Health Organization (WHO) and Joint European Centre for Disease Prevention and Control (ECDC) Working Case Definition

a. **Confirmed**: N/A at present

b. **Probable**: A person presenting with acute hepatitis* with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021.

c. **Epi-linked**: A person presenting with acute hepatitis* of any age who has had close contact with a probable case, since 1 October 2021.

*(non-hep A-E (If hepatitis A-E serology results are awaited, but other criteria are met, can be reported, and will be classified as "pending classification." Cases with other explanations for their clinical presentation are discarded))

a. 3. Case definition used by the European Union, European Economic Area (EU/EEA)

b. **Confirmed**: A person presenting with acute hepatitis* with serum transaminase >500 IU/l (Aspartate Transaminase-AST or Alanine Transaminase-ALT), who is 10 years and under, since 1 January 2022.

c. **Possible**: A person presenting with acute hepatitis* with serum transaminase >500 IU/l (AST or ALT), who is 11 to 16 years, since 1 January 2022.

d. **Epi-linked**: A person presenting with acute hepatitis* of any age who has had close contact with a confirmed case, since 1 January 2022.

*(non hep A-E or an expected presentation of metabolic, inherited or genetic, congenital or mechanical cause**) **Confirmed and possible cases should be reported based on the clinical judgment 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 are met, these will be classified as 'pending classification.'

4. What Have We Learned, So Far?

1) Epidemiology and Clinical Features

Hepatitis is a condition characterized by the inflammation of the hepatic parenchyma. The inflammation may be acute, lasting typically less than six months with subsequent normalization of liver function, or it may be chronic. Non-infectious causes of hepatitis in children include immunologic conditions (e.g., autoimmune diseases), metabolic diseases (e.g., Wilson's disease, tyrosinemia), and exposure to toxins or drugs (e.g., acetaminophen). The most common infectious agents are the primary hepatotropic viruses (Hepatitis A, B, C, D, E). Other viruses that may cause acute hepatitis include Epstein-Barr virus (EBV), cytomegalovirus (CMV), parvovirus, enteroviruses, adenoviruses, rubella virus, herpesviruses (HHV-1, HHV-2, HHV-6, HHV-7) and human immunodeficiency virus (HIV). Other infectious agents include Brucella spp, Coxiella burnetii, and Leptospira.

Common symptoms of acute hepatitis (myalgia, nausea, vomiting, lethargy, fatigue, fever, abdominal pain, and diarrhea) sometimes persist for several weeks. A high proportion of acute infections with the hepatitis viruses are asymptomatic. For hepatitis A and B, the infection is much more likely to produce a minor or asymptomatic illness among children than among adults. Jaundice is commonly associated with acute hepatitis but may not show in many viral hepatitis cases. Death from acute viral hepatitis is rare and usually results from the development of fulminant hepatitis, acute liver failure (ALF) with hepatic encephalopathy. The risk of ALF resulting from fulminant viral hepatitis is associated with increasing age and preexisting liver disease. Impaired coagulation with a prolonged prothrombin time is one of the classic markers of ALF. Hepatic encephalopathy can be subtle, especially in infants. Bone marrow failure occurs in a few children with ALF, ranging from mild pancytopenia to aplastic anemia. Without liver transplantation, mortality in children with ALF is very high. In up to 50% of ALF cases in children, the cause cannot be identified, and they are classified as indeterminate. The treatment of indeterminate ALF cases is general supportive measures and liver transplantation.

As of 3 May, there were **118 cases** of hepatitis of unknown origin in children in **England**. No known epidemiologically linked the cases in England. Forty potential cases in England are awaiting classification pending further data. Cases are **predominantly aged between 3 and 5 years old** (66, 56.9%), a median age of 3 (interquartile range 3 to 4 years), and 50% are female. The majority are of white ethnicity (92 out of 107, 86.0%) where infor-

mation was available. Many cases had gastrointestinal symptoms in the weeks preceding the onset of jaundice. Of the 118 cases investigated in England as of 3 May, 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%). Gastrointestinal symptoms were commonly reported at presentation, including diarrhea. (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. These clinical findings are consistent with those described among cases reported by Scotland, although none of the Scottish cases were reported to have had a fever. Although all cases had high transaminase levels in line with the case definition, most of the children reported from Scotland had transaminases over 2000 IU/L. **Eleven cases** have received a **liver transplant**. No cases resident in the UK has died.

Nine patients with hepatitis of unknown etiology at Children's of Alabama **in Alabama, US,** were recorded from October 2021 to February 2022. These patients were from geographically distinct parts of the state; no epidemiologic links among patients were identified. The **median age** at admission was **two years, 11 months** (IQR = 1 year, 8 months to 5 years, nine months), and seven patients were female. All patients were **immunocompetent** with no clinically significant medical comorbidities. Before admission, seven, six, and three patients reported vomiting, diarrhea, and upper respiratory symptoms, respectively. Eight patients had scleral icterus at admission, seven had **hepatomegaly**, six had **jaundice**, and one had encephalopathy. Elevated transaminases were detected among all patients§ (alanine aminotransferase [ALT] range = 603–4,696 U/L; aspartate aminotransferase [AST] range = 447–4,000 U/L); total bilirubin ranged from normal to elevated (range = 0.23–13.5 mg/dL, elevated in eight patients). **Three patients** developed **acute liver failure**. Two of them were treated with cidofovir (off-label use) and steroids and were transferred to a different medical facility where they **underwent liver transplantation**. All patients have recovered or are recovering, including the two transplant recipients.

In **Israel**, **12 cases** came in the last four months; five were hospitalized in Shaare Zedek Medical Center in Jerusalem and seven in Schneider Children's Medical Center in Petah Tikva. **Two** of the children in Schneider suffered from **liver failure**, prompting doctors to carry out liver transplants. The condition of the other children improved quickly after treatment with steroids, and they were released from the hospitals. **11** out of the 12 children were **infected with the coronavirus** in the last year.

2) Histopathological examinations

In addition to local assessments, an additional review of all available liver samples was undertaken by a single expert histopathologist. These specimens included **six explanted (removed) livers and eight 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** and shown 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. Liver biopsies from **six Alabama patients** demonstrated **various degrees of hepatitis** with no viral inclusions observed, **no immunohistochemical evidence of adenovirus**, or **no viral particles identified** by electron microscopy.

3) Microbiological

Most testing information available from cases reported to date is from England. However, not all cases have been tested for the same set of pathogens, at or around the time of admission. **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 the cases, adenovirus has **primarily been detected in the blood**. Further analysis relates to cases from England, of which adenovirus was detected in 67 of 89 cases that have been tested. Of the 8 England-resident patients who required a liver transplant, seven were tested for adenovirus in blood samples and the virus was detected in all 7. 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 types 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. It is therefore not possible to definitively rule out adenovirus in these cases.

Typing by partial hexon gene sequencing consistently shows that the adenovirus present in the 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**.**

SARS-CoV-2 has been detected in **24 cases of 132** with available results (18%). **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. **Serological testing is in the 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. A range of other possible pathogens have been detected in a low proportion of cases and are of uncertain significance. However, the inclusive nature of the UKHSA case definition intentionally will pick up some cases of non-A-E hepatitis with recognized causes.

In US cases, **Adenovirus** was detected in whole blood specimens from **all patients** by real-time PCR testing (initial viral load range = 991–70,680 copies/mL). Hexon gene hypervariable region sequencing was performed on specimens from five patients, and **adenovirus type 41** was detected in all **five specimens**. Plasma specimens from two patients who underwent liver transplantation were negative for adenovirus by real-time PCR testing upon arrival at the receiving medical facility, but both patients received positive test results when retested by the same real-time PCR test using a whole blood specimen. Low viral loads precluded sequencing among three patients, and residual specimens were not available for sequencing for one patient. **Seven patients** were **coinfected with other viral pathogens**. Six received positive test results for Epstein-Barr virus (EBV) by PCR testing but negative test results for EBV immunoglobulin M (IgM) antibodies (one patient did not have IgM testing), suggesting that these were likely not acute infections but rather low-level reactivation of pre-

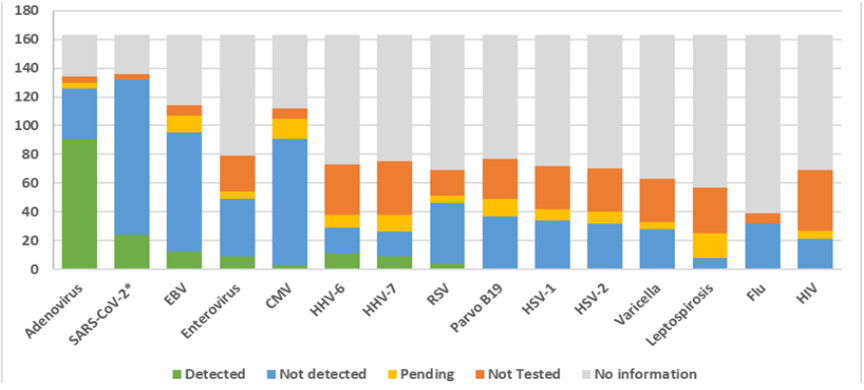


Figure 2. Pathogens tested for and results in cases in UK
* SARS-CoV-2 testing is based on testing around hospital admission or attendance.

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.

Table 1. Adenovirus testing and typing of cases, England residents (n=118)

Demographic	No.
Pathogen testing result, no. positive/total no.	
Adenovirus (whole blood)	9/9
EBV¶	6/9
Enterovirus/Rhinovirus	4/8
Metapneumovirus	1/8
Respiratory syncytial virus	1/8
Human coronavirus OC43	1/8
SARS-CoV-2**	0/9
Hepatitis A/B/C	0/9

Pathogen testing performed	
Blood viral PCR	9
Hepatitis A/B/C	9
Epstein-Barr Virus, blood viral PCR	9
Epstein-Barr Virus, IgM	8
Respiratory panel testing§	8
Blood culture	4
Urine culture	4
Stool culture	1

Table 2. laboratory testing results in a cluster of pediatric patients with acute hepatitis and adenovirus infection (N = 9) — Alabama, October 2021–February 2022

vious infections. Other detected viruses included enterovirus/rhinovirus, metapneumovirus, respiratory syncytial virus, and human coronavirus OC43. All patients received negative test results for hepatitis viruses A, B, and C. Several other causes of pediatric hepatitis and infections were ruled out, including autoimmune hepatitis, Wilson disease, bacteremia, urinary tract infections, and SARS-CoV-2 infection. **None** of the children had documented history of previous **SARS-CoV-2 infection**.

4) Metagenomics Amongst the UK cases, 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). 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 acute viral infection (for example, adenovirus) or during liver injury of another cause. It is not unusual to detect bystanders, 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 the testing of additional sets of controls.

AAV2 is a dependoparvovirus that is typically dependent on other viruses including adenovirus and herpesviruses to replicate. Non-pathogenic human infection is common and latent viruses may reactivate in some circumstances, again with no clinical consequence. The hypotheses which are under consideration to explain the detection of AAV2 in metagenomic data are:

a. Upregulation of AAV2 due to adenovirus or another acute viral infection.
b. Upregulation of AAV2 due to liver injury.
c. 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.
d. Undetermined role in the pathogenesis of the syndrome.

5) 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.

6) 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 Characterization Protocol. **Thirty-seven cases have been recruited** to the ISARIC clinical characterization protocol to date and retrospective and prospective recruitment continues.

7) Possible Exposures

Investigations have included interviews of parents conducted by public health specialists to assess a broad range of different exposures (trawling questionnaires). 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.

A 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 means 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 the guidance on the management of acute illness in children.

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 acute hepatic syndrome.**

8) Working Hypothesis

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:

I. 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.

II. A **novel variant adenovirus**, with or without a contribution from a cofactor as listed above.

III. A **post-infectious SARS-CoV-2 syndrome** (including an Omicron restricted effect).

IV. A drug, **toxin** or environmental exposure.

V. A **novel pathogen** either acting alone or as a coinfection.

VI. A **new variant of SARS-CoV-2**.

5. Adenovirus: Is He Guilty?

1) Virological features and clinical presentation

Adenoviruses are a group of double-stranded DNA non-enveloped DNA (dsDNA) viruses belonging to the genus Mastadenovirus of the Adenoviridae family. Adenovirus genomes share a central conserved part that can be used for detection purposes. Human adenoviruses (HAdV) are separated into seven genetically distinguishable species (HAdV-A through HAdV-G) and are currently classified into more than **100 genotypes and 52 serologically distinct types**. Species A, B, C, D, E, and F circulate globally and have been implicated in outbreaks of infection in humans. Different genome types (or genomic variants) can be distinguished within the same serotype by restriction enzyme analysis of genomic DNA. **Different types** display **different tissue tropisms**, which may correlate with clinical manifestation and may circulate at a

HAvD subgroup	Serotype	Type of infection
A	12, 18, 31	gastrointestinal, respiratory, urinary
B, type 1	**3, 7, 16, 21**	keratoconjunctivitis, gastrointestinal, respiratory, urinary
B, type 2	11, 14, 34, 35	gastrointestinal, respiratory, urinary
C	1, 2, 5, 6	respiratory, gastrointestinal including hepatitis, urinary
D	**8–10,13,15,17,19,20,22–30,32,33,36–39,42–49**	keratoconjunctivitis, gastrointestinal
E	**4**	keratoconjunctivitis, respiratory
F	40, 41	gastrointestinal
G	52	gastrointestinal

Table 3. Adenovirus serotypes and associated clinical diseases

given time in different countries or regions causing transmission of novel strains between countries or across continents and replacement of dominant viruses with new strains.

The **incubation period** for respiratory adenoviruses is estimated to range between **two and 14 days** and for enteric ones between three and 10 days. The incidence of adenovirus infection **peaks** between the ages of **six months and five years**, but the highest incidences have been described among children under two years. The most common clinical features are keratoconjunctivitis (HAdV types 5, 8, 19, and 37), acute respiratory symptoms (HAdV types 1-5, 7, 14, and 21), urethritis in men by types 8 and 37, or gastroenteritis (HAdV-types 31, 40 and 41). More rare manifestations include kidney disease, hemorrhagic cystitis, or hepatitis. Adenovirus (**HAdV-40 and HAdV-41**) is considered one of the most important **causative agents** of **acute viral gastroenteritis in young children**. Although HAdV infections are generally self-limiting in healthy children; **immunocompromised individuals**, for example acute leukemia patients, bowel transplant patients, and stem cell and solid-organ transplant recipients, are at **higher risk** for developing **severe and disseminated disease**. **Acute liver failure** from adenovirus is **rare** and is described **especially in immunocompromised patients**. Depending on the species, these viruses may infect respiratory, conjunctival, gastrointestinal, and genitourinary sites. To note, **fulminant hepatitis is a rare complication** of adenoviral infection. Latent infection with HAdVs may occur with the virus residing in renal, lymphoid, or other tissues for many years, with reactivation sometimes occurring in severely immunosuppressed individuals.

2) Circulation

Adenoviruses **circulate throughout the year**. In the USA, the highest numbers of detections of adenoviruses associated with conjunctivitis in a 30-year study period have been from July to September and the lowest from April to June every year. Higher circulation of adenoviruses has been detected in Brazil from April-May and July to October and in China, a higher prevalence peaked in April and October. Uncertainties remain about the seasonality of adenovirus in the EU/EEA and whether it is type-specific.

3) Routes transmission

Transmission can occur by direct contact with infected individuals through **inhalation of droplets, faecal-oral** route, and **conjunctival inoculation**, or indirectly through exposure to contaminated objects (**fomites**). Infections may spread rapidly among closed populations, for example in hospitals, schools and nurseries, and severe outbreaks of respiratory infection or keratoconjunctivitis due to HAdV have been described linked to a variety of virus types. Some outbreaks of more severe disease have been reported among groups of immunocompromised people.

4) Role of Adenovirus in the landscape of viral hepatitis in children?

Adenovirus type 41, the apparently implicated adenovirus type, typically presents as diarrhea, vomiting, and fever, often accompanied by respiratory symptoms. While there have been case reports of hepatitis in immunocompromised children with adenovirus infection, **adenovirus type 41 is not known to be a cause of hepatitis in otherwise healthy children. Reports of positive adenovirus** tests from any site in 1- to 4-year-olds are **higher**

compared to the previous 5 years. 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. The increase in younger age groups **began in November 2021**.

In a recent systematic review of the global epidemiology of viral-induced acute liver failure, the burden of acute liver failure after infection with hepatitis B virus, hepatitis A virus, hepatitis C virus, hepatitis E virus, herpes simplex virus/human herpesvirus, cytomegalovirus, Epstein-Barr virus, and parvovirus B19 was estimated. The prevalence of hepatitis A-induced acute liver failure was markedly lower in countries with routine hepatitis A immunization versus no routine hepatitis A immunization. Hepatitis E virus was the most common etiological cause of viral-induced acute liver failure reported in this review. In addition, viral-induced acute liver failure had poor outcomes as indicated by high fatality rates, which appear to increase with poor economic status of the studied countries. Unfortunately, data were largely missing for acute liver failure after infection with varicella-zoster virus, human parainfluenza viruses, yellow fever virus, coxsackievirus, and/or Adenovirus.

Further investigative work, including **WGS of multiple cases**, is required before any **firm conclusions can be drawn** on the characterization of the adenoviruses involved. Adenovirus WGS as well as metagenomic sequencing have commenced on case samples. **The low levels of adenovirus present in the blood are challenging for the 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 centers 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 characterization of circulating adenovirus strains internationally.

5) Hypothesis of AdV potentiated SARS-CoV-2 superantigen-mediated pathology

The SARS-CoV-2 has been identified in 18% of reported cases in the UK and 11 (11%) of 97 cases in England with available data tested SARS-CoV-2 positive on admission; a further three cases had tested positive within the 8 weeks prior to admission. Ongoing serological testing is likely to yield greater numbers of children with severe acute hepatitis and previous or current SARS-CoV-2 infection. Eleven of 12 Israeli patients were reported to have had COVID-19 in recent months, and most reported cases of hepatitis were in patients too young to be eligible for COVID-19 vaccinations. SARS-CoV-2 infection can result in viral reservoir formation. SARS-CoV-2 viral persistence in the gastrointestinal tract can lead to a repeated release

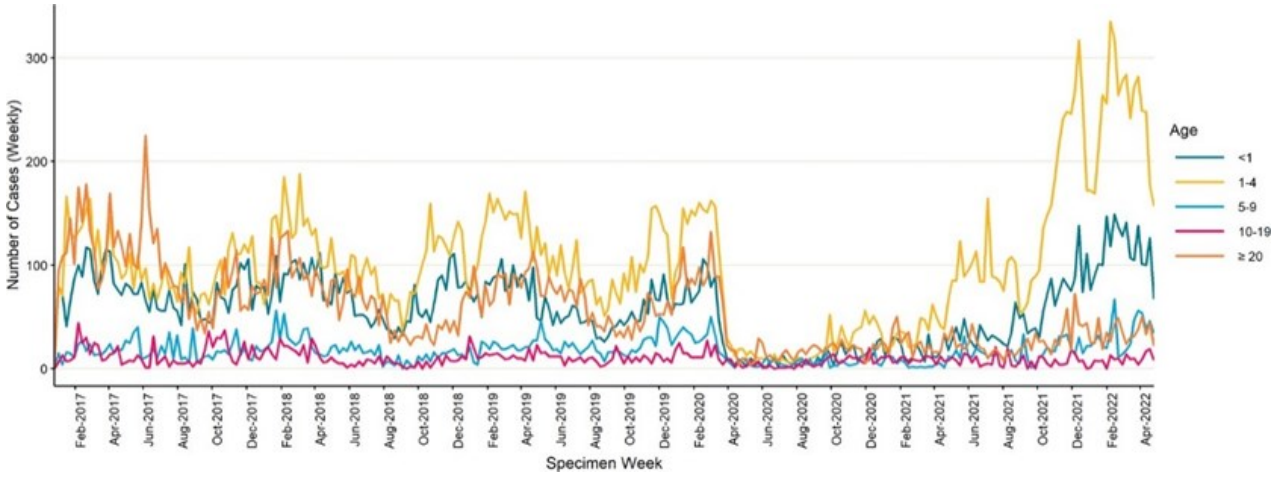


Figure 3. Adenovirus episodes by age and week of specimen, England 1 January 2017 to 1 May 2022
Data Source: SGSS
* The presented figures are based on laboratory reports through SGSS. Testing and reporting procedures vary by virus, UKHSA Centre and over time, including short- term trends in testing. Therefore, comparisons should be done with caution.

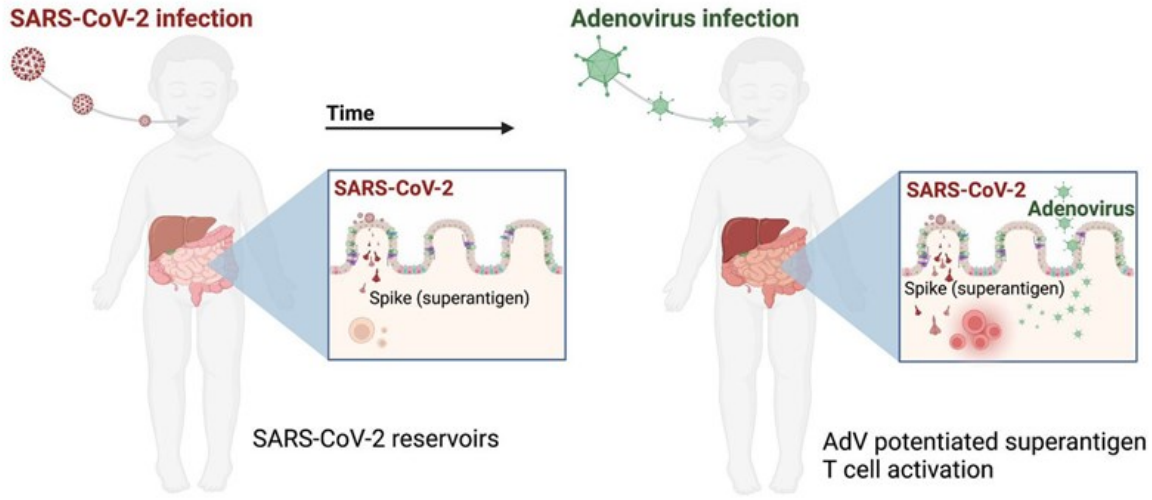
of viral proteins across the intestinal epithelium, giving rise to immune activation. Such repeated immune activation might be mediated by a superantigen motif within the SARS-CoV-2 spike protein that bears resemblance to Staphylococcal enterotoxin B, triggering broad and non-specific T-cell activation. This superantigen mediated immune-cell activation has been proposed as a causal mechanism of the multisystem inflammatory syndrome in children.

Acute hepatitis has been reported in children with multisystem inflammatory syndrome, but coinfection of other viruses was not investigated. There is a hypothesis that the recently reported cases of severe acute hepatitis in children could be a consequence of **adenovirus infection with intestinal tropism in children previously infected by SARS-CoV-2 and carrying viral reservoirs**. In mice, adenovirus infection sensitises to subsequent Staphylococcal-enterotoxin-B-mediated toxic shock, leading to liver failure and death. This outcome was explained by adenovirus-induced type-1 immune skewing, which, upon subsequent Staphylococcal enterotoxin B administration, led to excessive IFN-γ production and IFN-γ-mediated apoptosis of hepatocytes. Translated to the current situation, it is suggested that children with acute hepatitis be investigated for SARS-CoV-2 persistence in stool, T-cell receptor skewing, and IFN-γ upregulation because this could provide evidence of a SARS-CoV-2 superantigen mechanism in an adenovirus-41F-sensitised host. If evidence of superantigen mediated immune activation is found, immunomodulatory therapies should be considered in children with severe acute hepatitis.

6. Current guideline for testing

In addition to case findings, when testing probable and epidemiologically linked cases, appropriate samples should be collected to perform the tests outlined in Table 4. ECDC recommends the early collection of multiple specimen types from the cases under investigation and testing with different diagnostic methods for prompt detection of possible causative agents. Countries should include adenovirus testing for children with severe acute hepatitis, at the same time as testing for hepatitis A-E. Preliminary data indicate that **whole blood is an important sample matrix to test for viruses**. It will be important to **store specimens** (e.g., serum and EDTA blood, nasopharyngeal/throat swabs (for bacterial and viral testing), fecal, and urine specimens) for possible further diagnostic testing and typing as required. Adenovirus and/or SARS-CoV-2 positive samples should be typed.

If diagnostics are not available locally, then specimens should be referred to national laboratories, including for typing and pathogen characterization. Quantification of



Hypothesis of AdV potentiated SARS-CoV-2 superantigen-mediated pathology in severe, acute hepatitis. Following infection with SARS-CoV-2 virus, viral reservoirs have been reported and could over time lead to repeated super-antigen mediated immune cell activation as shown in Multisystem inflammatory syndrome, MIS-C. If such viral reservoirs are present and a child is subsequently infected with AdV, this superantigen-mediated effect could be much more pronounced and potentially give rise to immunopathology such as the recently reported acute, severe hepatitis which is why evidence of such immunopathology should be investigated in these cases.

Figure 4. Hypothesis of AdV potentiated SARS-CoV-2 superantigen-mediated pathology

positive PCR findings in blood samples should be conducted with cycle threshold (Ct) value as a proxy, and if possible, using sequential sampling over a longer time period. Institutes with metagenomic capacities can consider metagenomic analyses of samples for probable and epidemiologically linked cases. Samples for potential analysis can include blood and available liver biopsies but can be extended to any relevant samples. As the etiology remains unknown, relevant toxicology and environmental studies should also be considered where possible. Laboratory screening for metabolic and autoimmune diseases is recommended to exclude other non-infectious causes.

7. Situation in Indonesia

Indonesia Health Minister Budi Gunadi Sadikin in a written statement on Monday (05/10) urged the general public to be aware and take preventive measures against the threat of acute hepatitis that has been found in multiple countries across the globe and is believed to have entered Indonesia. Currently, there have been three reported cases believed to be linked to this disease **claiming the lives of three children in Indonesia**.

The minister added that as of **May 11**, there are **18 cases of suspected acute hepatitis of unknown etiology**. The **first three cases** in Indonesia were reported on **April 27,**

Sample type	Test type	Pathogen
Blood	Serology	Hepatitis A, B, C, D*, E/ Cytomegalovirus (CMV)/Epstein-Barr virus (EBV), Varicella, HIV, SARS-CoV-2 anti-S, SARS-CoV-2 anti-N (only if locally available), Adenovirus**
	Serology	*Brucella* spp, *Bartnonella henselae*, *Borrelia burgdorferi* (if epidemiologically appropriate)
	Culture	If clinically indicated i.e. fever, as per routine procedures for bacterial pathogens
	Culture	Adenovirus, CMV, EBV, HSV, influenza
	PCR***	Adenovirus**, enteroviruses, CMV, EBV, HSV, HHV6 and 7, parechovirus, hepatitis A, C, E.
	Toxicological screening	Liquid Chromatography / High Resolution Mass Spectrometry (LC/HRMS), Gas Chromatography / Mass Spectrometry (GC/MS), Inductively Coupled Plasma Mass Spectrometry (ICPMS), in a case control study
Throat swab	PCR	Respiratory virus screening by multiplex assay (including influenza, adenovirus, parainfluenza, rhinovirus, respiratory syncytial virus, human bocavirus 1-3 etc), SARS-CoV-2, enteroviruses, human metapneumovirus (hMPV)
	Culture	Streptococcus group A
Stool or rectal swab	PCR	Enteric viruses screening by multiplex assay (including, norovirus, enteroviruses, rotavirus, astrovirus, sapovirus)
	PCR	Enteric bacterial pathogens (incl. *Salmonella*, if a screening panel is used)
	Culture	*Campylobacter*, *Salmonella*, *Shigella*, *E.coli* 0157
	Culture	Adenovirus, Enteroviruses, Rotavirus
Urine	PCR	*Leptospira*
	Culture	If clinically indicated, as per routine procedures for bacterial pathogens
	Toxicological screening	Inductively Coupled Plasma Mass Spectrometry (ICPMS)

Table 4. Recommended testing approach for probable (and epi-linked) cases of severe acute hepatitis

*Testing for hepatitis D only in cases positive for hepatitis B.

**Note that for adenovirus testing, detection has been found to be superior in whole blood compared to serum.

***Please provide Ct values as a proxy of nucleic acid quantification when available.

2022, a few days after the World Health Organization (WHO) reported the outbreak in Europe. The Health Ministry quickly followed up on this incident by issuing a Circular (SE) regarding the Precautions for the Discovery of Acute Hepatitis of Unknown Aetiology. The Ministry is keeping close communication with the United States CDC and Britain's government regarding the details of the acute hepatitis outbreak, though unfortunately, there are yet conclusive explanations on why this disease can spread wildly. Indonesia, in partnership with the WHO and the U.S. government, is currently conducting tests to uncover the cause of the outbreak.

As of May 4, the Indonesian Paediatric Society had issued several recommendations in response to this outbreak, adapting to formerly explained guidelines issued by ECDC and US-CDC. The screening and management algorithms are as follows (provided in Bahasa).

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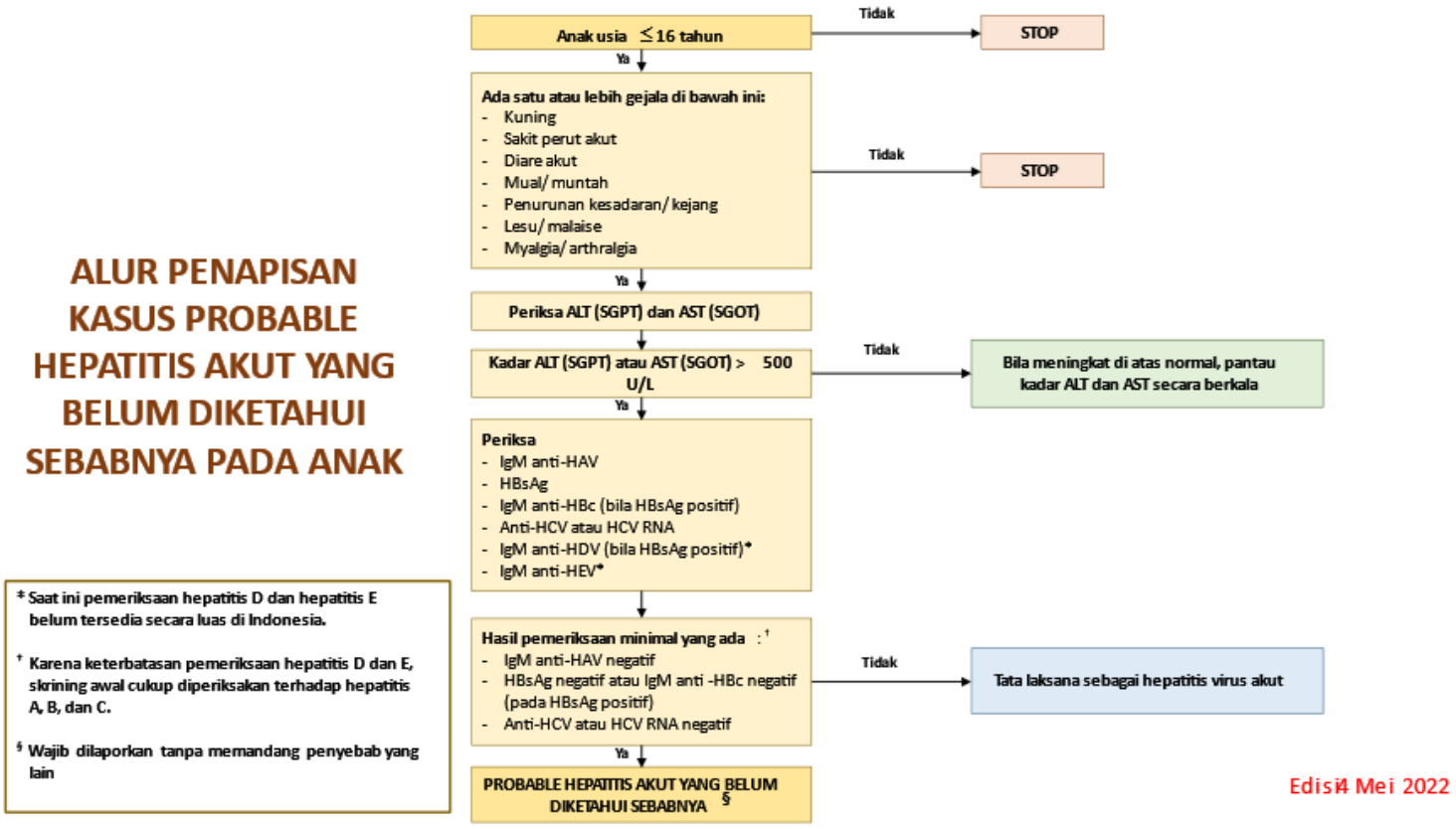
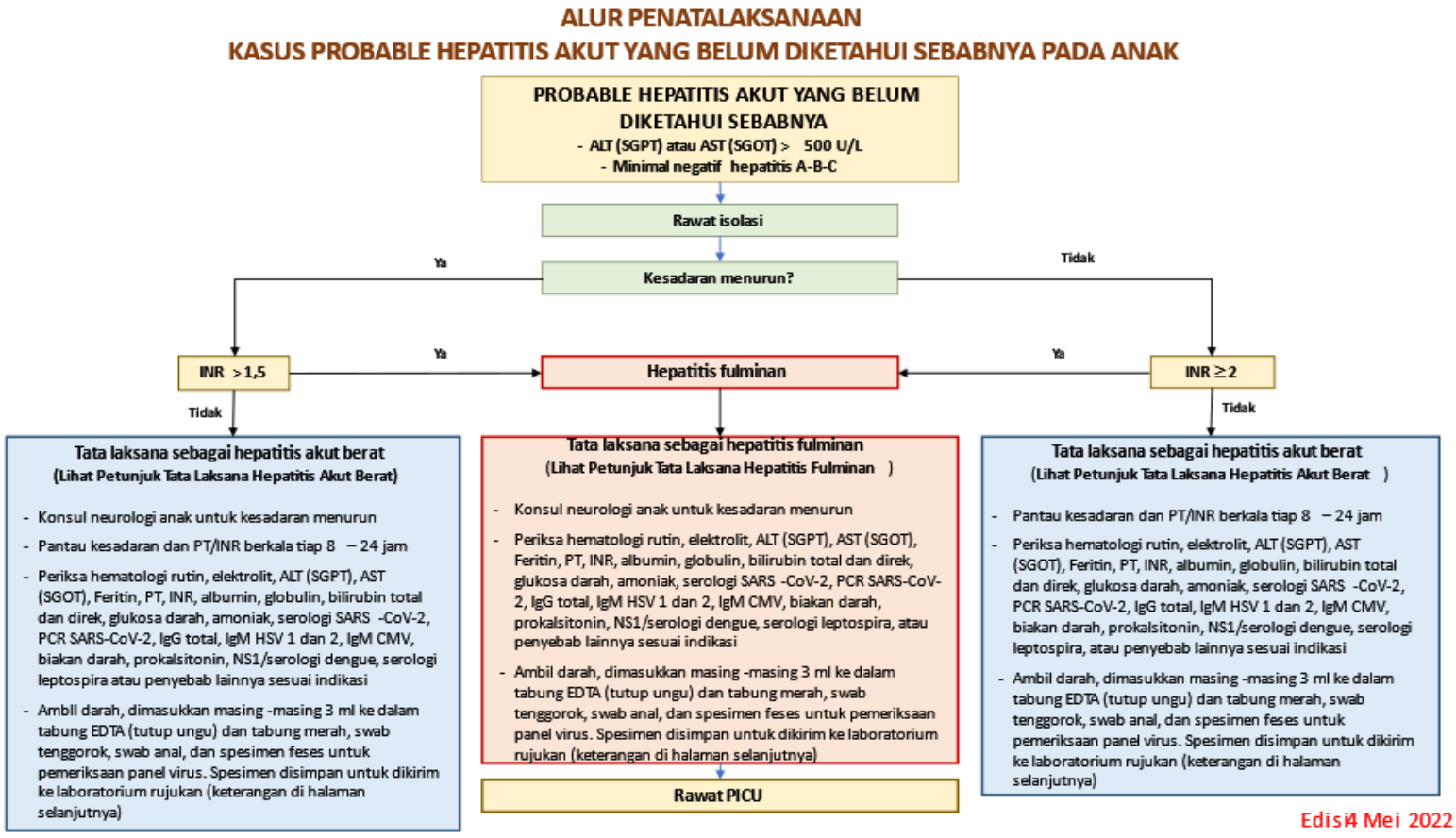
Figure 5. Demographic of 18 suspected cases in Indonesia, as of May 11.





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INA-RESPOND

Newsletter

INA-RESPOND 4TH WEBINAR IN THE COVID-19 SERIES

By: INA-RESPOND Webinar Committee

On behalf of the committee, we would like to express our gratitude to all attendees, moderators, speakers, and participants for making the 4th webinar title "Learning lessons from two years of the pandemic; Are we getting closer to the finish line?" a success. The webinar that was held on 21 May 2022 was attended by 300 participants (international and national). We congratulate and thank everyone who contributed to the success of this webinar. Hopefully, the material from this webinar will be useful for the audience. See you in the next webinar series!

INA-RESPOND Newsletter

MEASURING THE SYMPTOMS OF COVID-19 USING PATIENT REPORTED OUTCOMES: FLU-PRO PLUS

By: John H Powers MD

Introduction

COVID-19, the disease caused by the SARS-CoV-2 virus, represents an infectious disease caused by a novel and mutating pathogen. Yet COVID-19 still falls into the category of viral respiratory tract diseases caused by a number of other respiratory pathogens including influenza. Indeed, these diseases are grouped together in what is often termed "influenza-like illness" (ILI) due to the fact that the host response, which is similar across these pathogens, results in similar symptomatic disease manifestations in humans. Conversely, the manifestations of disease caused by the same pathogen may differ in intensity and duration in different hosts (eg. older vs younger patients, immunocompetent vs immunocompromised).

Why use Patient Reported Outcomes (PROs)?

Patient-Reported Outcome (PRO) instruments are valid methods of capturing symptoms directly from patients without interpretation from anyone else. PROs are developed by interviewing patients to determine which symptoms are impactful and important for them in a given disease. This allows for comprehensive capturing of the symptoms that influence patients' lives. Furthermore, the way questions are asked and the response options to those questions are tested for patient understanding. This allows more accurate capturing of information on patients' health status.[1] In contrast, Clinician Reported Outcomes (ClinROs) based on individual investigators non-standardized questioning of patients, may be incomplete, not understood by patients. What is asked and how it is asked may vary from clinician to clinician. This may decrease accuracy and increase the variability of the information captured.[2]

FLU-PRO Plus in COViD-19

FLU-PRO is a PRO that was developed to capture symptom information on patients with influenza like illness. The concepts measured in FLU PRO were originally based on interviews of patients with influenza but have been extended to interviews in patients with other viral diseases [3,4,5] and to patients with COVID-19 (manuscript submitted). These interviews show the symptoms of viral respiratory tract viral diseases are similar regardless of viral pathogens. The symptoms of loss of taste and smell were added to FLU-PRO to develop FLU-PRO Plus given the increased incidence of these symptoms in COVID-19. The responses to questions and the response options in FLU-PRO Plus have been tested in patients to assure patient understanding of the concepts measured, the questions themselves and the response options, all of which have demonstrated clear patient understanding.

Measurement properties in COVID-19

After evaluating that a PRO measures the correct concepts with good patient understanding, the next step is to evaluate the measurement properties of the PRO under the conditions of use in which it will be used. This is similar to evaluating a laboratory test, in that the same properties of reliability, reproducibility, known groups validity and responsiveness to change are evaluated to ensure the scores captured by the instrument are accurate. A recent study performed by the Infectious Diseases Clinical Research Program (IDCRP), a collaboration between the NIH/NIAID's Collaborative Clinical Research Branch (CCRB) and the US Department of Defense (DoD), evaluated the measurement properties of FLU-PRO Plus in patients with COVID-19 seen in health facilities that were part of the DoD. The study was performed as an amendment to the IDCRP's Epidemiology, Immunology, and Clinical Characteristics of Pandemic Infectious Diseases (EpICC) study. EpICC is a prospective cohort study developed to evaluate patients with diseases with pandemic potential and was amended within weeks of the start of the COVID-19 pandemic to add in assessments such as FLU-PRO Plus to evaluate outcomes in patients with COVID-19.

The results of this evaluation were recent published in Open Forum in Infectious Diseases presented the evidence on the measurement properties of FLU-PRO Plus in COVID-19.[6] Adults with symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with FLU-PRO Plus survey information within 1 week of symp-

tom onset were included. Reliability of FLU-PRO Plus was estimated using intraclass correlation coefficient (ICC; 2 days' reproducibility). Known-groups validity was assessed using patient global assessment (PGA) of disease severity. Patient report of return to usual health was used to assess responsiveness (day 1–6/7).

Two hundred twenty-six SARS-CoV-2–positive participants were included in the analysis. Reliability among those who reported no change in their symptoms from one day to the next was high for most domains (ICC range, 0.68–0.94 for day 1 to day 2). Construct validity was demonstrated by moderate to high correlation between the PGA rating of disease severity and domain and total scores (e.g., total scores correlation: 0.69 [influenza-like illness severity], 0.69 [interference in daily activities], and –0.58 [physical health]). In addition, FLU-PRO Plus demonstrated good known-groups validity, with increasing domain and total scores observed with increasing severity ratings.

Most of the patients enrolled had mild to moderate illness as would be expected in the military population of mostly young healthier persons, so further studies are needed in patients with more severe illness and longer follow-up to evaluate the long-term symptomatic and functional consequences of COVID-19 on patients' lives.

In conclusion, FLU-PRO Plus performs well in measuring signs and symptoms in SARS-CoV-2 infection with excellent construct validity, known-groups validity, and responsiveness to change. Standardized data collection PRO instruments can facilitate meta-analyses, vaccine effectiveness studies, and other COVID-19 research activities as well as comparisons. FLU-PRO Plus is a recommended outcome measures in international COVID-19 studies.[7]

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INA-RESPOND Newsletter

SPORTS & LIFESTYLE

EXERCISE AND AUTOIMMUNE DISEASE: WHAT DO WE KNOW ABOUT IT

By: Ria Lestari

Autoimmune disease (AD) occurs when the immune system attacks self-molecules because of a breakdown of immunologic tolerance to autoreactive immune cells. It is a condition in which your immune system mistakenly attacks your body.1

The overall estimated prevalence is 4.5% – 2.7% for males and 6.4% for females. Many ADs have been strongly associated with genetic, infectious, and environmental predisposing factors. Comprising multiple disorders and symptoms ranging from organ-specific to systemic, autoimmune diseases include insulin-dependent diabetes mellitus, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, thyroiditis, and multiple sclerosis.2

Physical inactivity and sedentary behavior are highly prevalent in individuals with ADs, with current estimates indicating around 60% of individuals with an AD do not achieve the recommended amount of weekly physical activity (i.e., 150 min/week of moderate-to-vigorous physical activity). Sedentary time for this population ranges between 8.3–14.0 hours per day, which is higher than for the general population.4

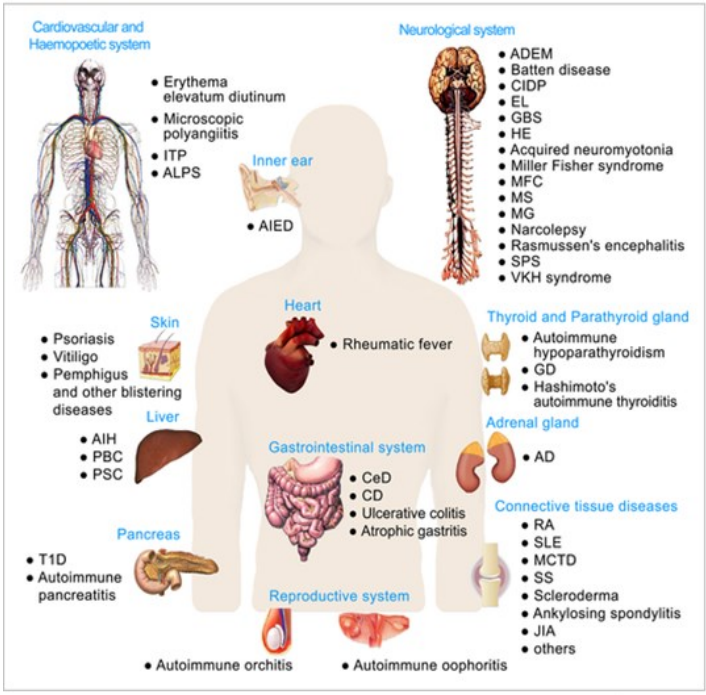

Figure 1. Representative organ-specific and systemic autoimmune diseases.3

What are the benefits of exercise?

For those with rheumatoid arthritis, activity has been shown to improve heart health and joint mobility. It's also been proven to improve the disease course. For those living with lupus, physical activity has been shown to improve heart health, psychological health, and quality of life. Additionally, a systematic review and meta-analysis that looked at the effects of exercise in those with lupus showed that exercise is beneficial to help curb fatigue. Fibromyalgia, another autoimmune disease that causes painful flares, has also been studied. Aerobic exercise improves pain, physical health, mental health, and quality of life. It helps that aerobic exercise, such as running, walking, or cycling, can be easily adjusted to fit your tolerance.5

How much is too much?

One of the most common mistakes people make is to push themselves too hard and over-exercise. Overtraining spikes inflammation and can make an autoimmune condition worse. Also, when you have an inflammatory condition, you must realize your immune system is never at a constant. Stress, viruses, diet, and myriad other factors keep our immune systems in a constant state of fluctuation.6

People with AD must always tweak and adjust their activity level to not overburden their immune system or neurological health. If you are used to working out at a certain level and then suddenly notice your workout makes you feel worse, it could be an outside factor flaring up inflammation. So, you need to dial it down or even take some time off.

For instance, someone who does high-intensity intervals (HIIT) and weight training four or five days a week suddenly feels fatigued and lethargic the day after each class. They may need to reduce the duration, intensity, or frequency of those workouts or substitute with something that doesn't push their inflammation over the edge, like a brisk walk.7

Autoimmune disorder exercise recommendations

It can become quite challenging to make clear exercise recommendations for autoimmune disorders, as the disease does present itself in so many different forms. It is still in your best interest to strive for the physical activity recommendations made by the World Health Organization (WHO)8, which suggest you maintain:

- A minimum of 150 minutes of moderate-intensity aerobic exercise per week
- A minimum of two sessions of resistance training per week that focuses on all major muscle groups per session

It is shown that both aerobic exercise and resistance training have been shown to improve immune system function, boost health, enhance the quality of life, and reduce symptoms in people suffering from autoimmune disorders.9

Now, how you achieve this is dictated by your capabilities at an individual level. If you have been training for quite some time and have a good fitness level and a solid foundation of strength, you might be perfectly fine with jumping into some moderate-intensity exercise. This could mean consistent aerobic activity and some moderately heavy strength training.10

However, if you have not exercised in quite some time, your approach should be different. In this scenario, you might start with light walking and bodyweight strength training and see how you respond. You would then build up this intensity and volume as your fitness increases.10

Conclusion

Patients with autoimmune diseases are much more sedentary and less active than the healthy population. Accumulated evidence supports the integral role of physical activity and exercise in the management regimens for various autoimmune diseases.

Exercise can be just as safe for people with an autoimmune disease as it is for people without if there is a good understanding of the disease, symptoms, any side effects to medications, and the person. It is essential that if you have an autoimmune disease, your exercise program is supervised by a sports medicine doctor who can tailor the exercise program to your individual needs.

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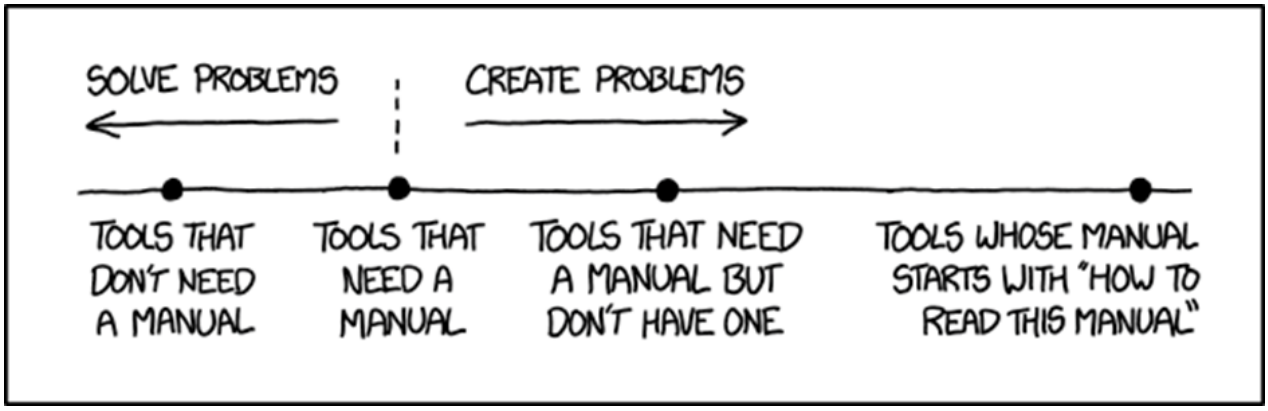
RAPID QUALITATIVE RESEARCH: ANOTHER THING TO ADD TO OUR TOOLKIT?

By: Aly Diana

COMIC CORNER



Source: https://xkcd.com/1343/

Just recently, I came across something called rapid qualitative research. As the interest in applied research is increasing and social and political landscapes are changing rapidly, many qualitative researchers have tried to search for ways to deliver research findings in time to inform decision-making processes. Rapid qualitative analysis can inform near real-time intervention development and ensure relevant content creation while setting the stage for stakeholder buy-in. Rigorous and timely analyses support the delivery of contextually appropriate, efficient, high-value health care. Although I just recently heard about it, the field of rapid qualitative research has grown tremendously over the past decade.

In a nutshell, rapid qualitative research techniques have been modified to decrease the length of studies. The main approaches used to date have included: 1) bypassing the transcription of interview audio recordings to analyse data directly from the recordings; 2) reliance on interview or focus group notes instead of audio recordings and transcription; 3) the use of techniques such as mind maps as focus groups are ongoing to summarise emerging findings; 4) the implementation of structured observation guides to focus on the development of field notes during participant observation; and 5) the development of rapid data analysis techniques through the use of frameworks, tables or targeted coding techniques.

To do the rapid qualitative research approaches, in general, the following characteristics are required: 1) iterative design, often carrying out data collection and analysis in parallel; 2) involve at least some degree of participatory research (including relevant stakeholders in the design and/or implementation of the study); 3) combine multiple methods of data collection and carry out triangulation during analysis; 4) can rely on the use of teams of researchers to cover more ground during data collection or contribute to data analysis; and 5) are normally carried out within short study timeframes (a few weeks to a few months) or might include multiple data collection exercises of short duration (i.e. rapid feedback evaluations that run for a few years, but include short and intensive periods of data collection and analysis to share emerging findings as the evaluation is ongoing). Due to the focus on delivering findings in a timely way, collaboration becomes one of the important factors. Stakeholders need to be actively involved in the design

and implementation of the study to ensure the findings are delivered in a format and at a time when they can be used to make changes.

Some examples of study objectives that may need rapid qualitative research design are to: 1) rapidly diagnose or capture a snapshot of current activity (i.e. services already being delivered, needs of a particular population) to inform service development; 2) rapidly evaluate interventions or services that have already been implemented, capturing experiences of delivering and receiving services and considering how these are shaped by contextual factors; 3) develop an in-depth focused analysis of individuals' experiences or practices; and 4) capture events or situations that will change or disappear rapidly (this includes research we have carried out during infectious epidemics or other complex health emergencies).

However, rapid research continues to be regarded as research of lower quality than long-term traditional qualitative research. In part, this is due to evident gaps in the reporting of research methods and findings in published rapid studies. The situation is further complicated by the lack of quality standards for rapid research and lack of consensus on terminology. Researchers also face challenges when designing and implementing rapid studies such as ensuring consistency in data collection and analysis across team members, biases in sampling, balancing the breadth and depth of data, allowing time for critical reflection, time pressures for data access, and barriers produced by ethical review processes. Many researchers also feel ready to implement rapid studies, without learning from approaches developed previously (leading to "reinventing the wheel" scenarios) or considering the limitations and benefits of short-term research.

The method certainly has some rooms for improvement. To decide whether we want to add or not to add it to our toolkit certainly required more exploration. QSR International, the company that develop NVivo (software for qualitative data analysis), has offered free webinar: An Introduction to Rapid Qualitative Research for people who might be interested (https://go.qsrinternational.com/rapid-qualitative-research?plt=1.1.1.1.0).

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