

Adenovirus Infection in Children

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SAPA ID WORKSHOP
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VACCINES & INFECTIOUS DISEASES ANALYTICS

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Presentation outline

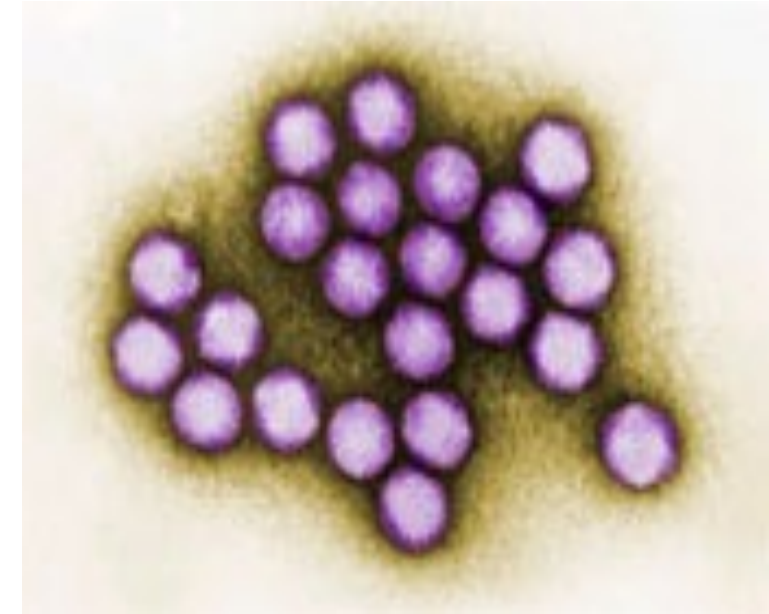
- Adenovirus
- Acute hepatitis of unknown aetiology
- Take home messages
- Q&A



ADENOVIRUS

Adenovirus: virology

- Isolation from adenoidal cells 1953
- Nonenveloped double-stranded DNA viruses
- >60 recognized (sero)types (A-G subgroups/species)
- Excellent vectors for vaccine development/cancer therapy



1. Tebruegge, M. and Curtis, N., 2012. Adenovirus: an overview for pediatric infectious diseases specialists. *The Pediatric infectious disease journal*, 31(6), pp.626-627.

2. Shieh, W.J., 2021. Human adenovirus infections in pediatric population-an update on clinico-pathologic correlation. *biomedical journal*.

Adenovirus: epidemiology

- Typically person-to-person respiratory droplets
- Less commonly conjunctival and faecal–oral route
- Incubation period 2 and 14 days
- Majority of infections in first 5 years of life
- In SA prevalence by NPA PCR testing ~ 19 - 26%

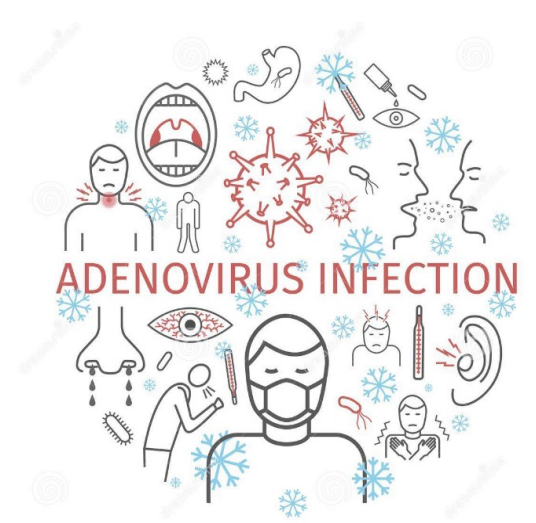


3. Cohen, C., Walaza, S., Moyes, J., Groome, M., Tempia, S., Pretorius, M., ... & Madhi, S. A. (2015). Epidemiology of viral-associated acute lower respiratory tract infection among children < 5 years of age in a high HIV prevalence setting, South Africa, 2009–2012. *The Pediatric infectious disease journal*, 34(1), 66.

4. Zar, H. J., Barnett, W., Stadler, A., Gardner-Lubbe, S., Myer, L., & Nicol, M. P. (2016). Aetiology of childhood pneumonia in a well vaccinated South African birth cohort: a nested case-control study of the Drakenstein Child Health Study. *The Lancet Respiratory Medicine*, 4(6), 463-472.

Adenovirus: epidemiology

- Mild and self-limiting disease in immunocompetent children
- Life threatening to immunocompromised hosts, neonates and infants
- Strains causing severe and fatal necrotising pneumonia described
- Long-term sequelae following pneumonia
- Disseminated disease and increased mortality in immunocompromised



Adenovirus: diagnosis

- Antigen detection
- Polymerase chain reaction (PCR)
- Virus isolation
- Serology



Adenovirus: prevention and treatment



- Contact and droplet precautions
- Environmental cleaning
- Prompt response to clustered cases
- No approved antiviral drugs
- Treat symptoms and complications



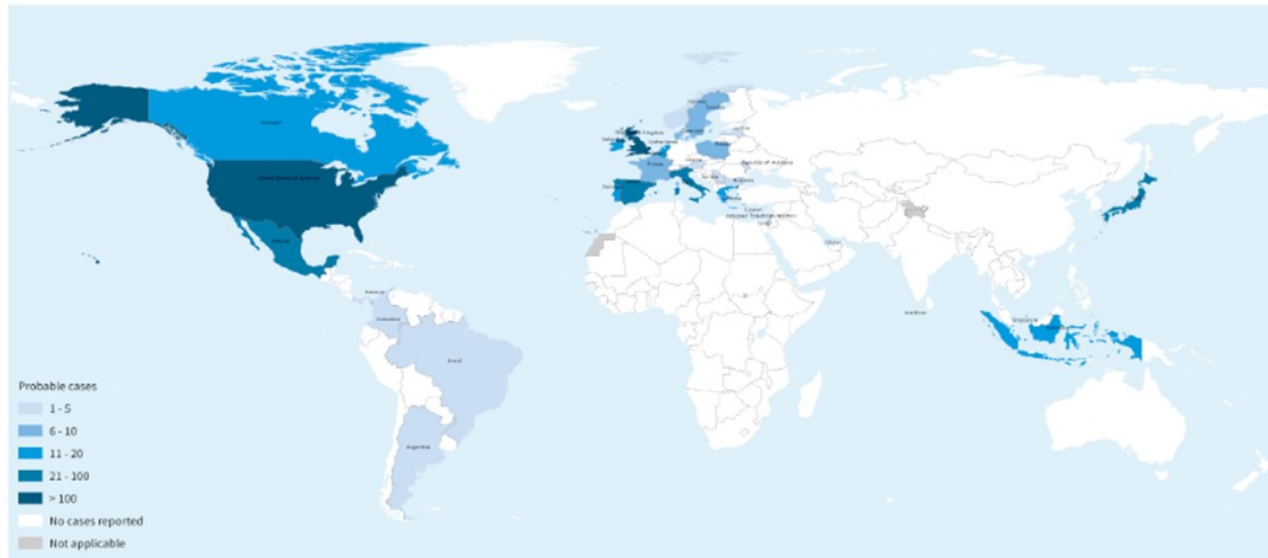
ACUTE HEPATITIS OF UNKNOWN AETIOLOGY

Background

- April 2022 WHO reported cases of acute severe hepatitis in children
- Initially 10 from UK
- Previously well young children
- Transaminases [ALT] & [AST] >500 IU/L (liver transplant/death)
- Not caused by known hepatitis viruses (??adenovirus/SARS COV2)
- No travel, diet , toxins or water source association

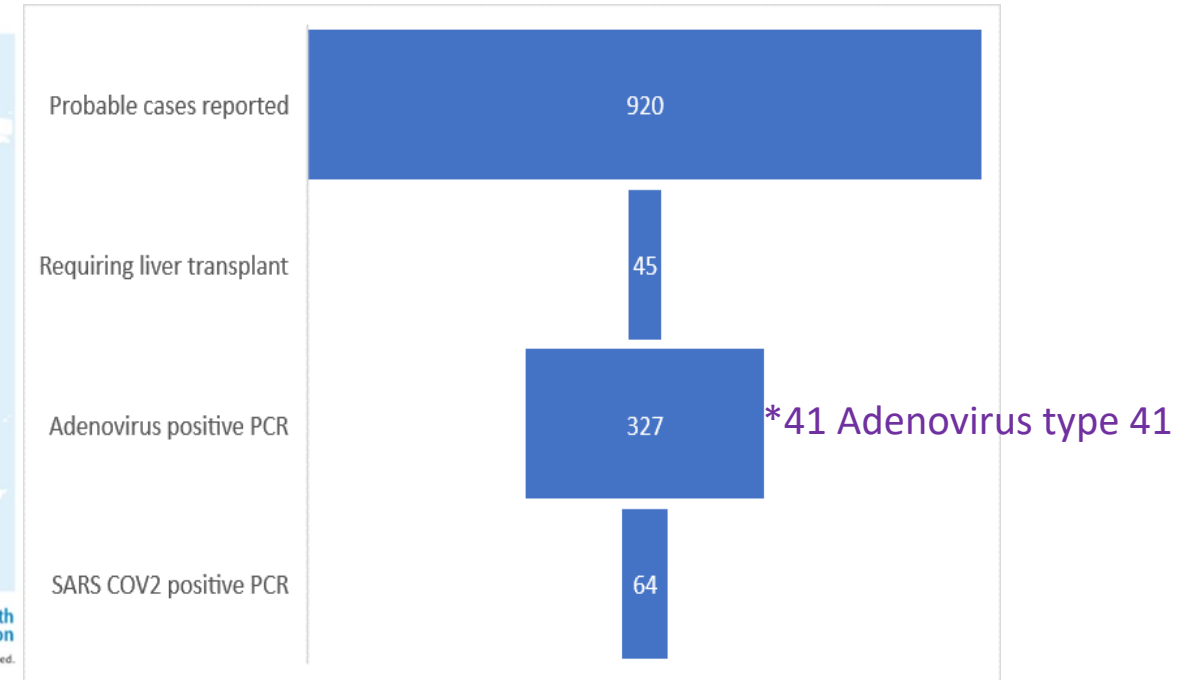
WHO disease outbreak news 24 June 2022

Figure 1. Distribution of probable cases of severe acute hepatitis of unknown aetiology in children by country, as of 22 June 2022 (n=920)



The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization, United Kingdom Health Security Agency
 Map Production: WHO Health Emergencies Programme
 Map Projection: WGS 1984
 Request ID: RITM00064



Clinical presentation

- Jaundice
- Vomiting
- Pale stools
- Gastrointestinal symptoms
- Fever and respiratory symptoms least common

7. Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin—what is known so far. *Journal of Hepatology*. 2022 May 6.

8. Kelgeri C, Couper M, Gupte GL, Brant A, Patel M, Johansen L, Valampampil J, Ong E, Hartog H, Perera MT, Mirza D. Clinical Spectrum of Children with Acute Hepatitis of Unknown Cause. *New England Journal of Medicine*. 2022 Jul 13.

What we don't know... yet

- Exact aetiology not yet determined
- Adenovirus ubiquitous
 - not in liver tissue samples analysed
 - associations co-incidental?
 - novel adenovirus? (whole genome sequencing)
- SARS-CoV-2 co-factor??
 - in isolation or with adenoviral co-infection
 - post infectious sequelae
- Currently no evidence of COVID-19 vaccination association

7. Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin—what is known so far. *Journal of Hepatology*. 2022 May 6.

Case definition

Working Case Definition for Testing

Confirmed: Not applicable at present

Probable: A child or adolescent who is 16 years and younger, presenting with acute hepatitis (non-hepatitis A, B or C) of unknown aetiology with serum transaminase >500 IU/L (AST or ALT), with no evidence of toxin ingestion, since 1 October 2021. **NICD will test these cases for adenovirus infection*

Epi-linked: A person presenting with acute hepatitis (non-hepatitis A, B or C*) of any age who is a close contact of a probable case, since 1 October 2021.

Cases with alternative diagnoses will be not be included in the dataset for evaluation.

WHO working case definition

- **Confirmed case:** Not available at present
- **Probable case:** A person presenting with an acute hepatitis (non hep A-E¹) with serum transaminase >500 IU/L (AST or ALT), who is 16 years and younger, since 1 October 2021
- **Epidemiologically linked:** A person presenting with an acute hepatitis (non hep A-E¹) of any age who is a close contact of a probable case, since 1 October 2021

¹ If hepatitis A-E serology results are pending, but other criteria are met, these can be reported and will be classified as "pending classification". Cases with other explanations for their clinical presentation are discarded. Delta testing is not required, as it is only undertaken in persons who are HBsAg positive to establish presence of co-infection.

6. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON394>

9. [https://www.nicd.ac.za/diseases-a-z-index/hepatitis-of-unknown-aetiology/#:~:text=Acute%2C%20severe%20hepatitis%20of%20unknown,\(which%20causes%20acute%20gastroenteritis\).](https://www.nicd.ac.za/diseases-a-z-index/hepatitis-of-unknown-aetiology/#:~:text=Acute%2C%20severe%20hepatitis%20of%20unknown,(which%20causes%20acute%20gastroenteritis).)

What to do

The differential diagnosis of acute hepatitis in children

- Viral hepatitis due to hepatitis A, B+/-D, C or E
- Hepatitis secondary to a viral infection with CMV, HSV, EBV, HHV-6, HHV-7, or more rarely due to influenza or respiratory syncytial virus, and possibly adenovirus
- Hepatitis due to overwhelming systemic bacterial or fungal infection of any kind, more commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*, and enteric bacteria
- Toxin ingestion should be ruled out, especially paracetamol overdose. Some traditional herbal medications have been implicated
- Current infection with SARS-CoV-2 should be ruled out.

NB: All tests for these conditions should be submitted to usual testing laboratory (NHLS in public sector, or private laboratories in the private sector).

The NICD will test the following sample types for adenovirus.

(Sample collection instructions may be found on the NICD website, 'Diseases A-Z, under 'Hepatitis of uncertain aetiology')

- Stool – submit a 'brown swab' or stool specimen in a sealed jar
- Blood – submit whole blood in an EDTA tube (purple top)
- Throat swab – collect a swab
- Tissue (e.g liver biopsy – please consult laboratory)

Specimen submission instructions:

1. Label all samples 'NICD/CVI laboratory - Attention Jayendrie Thaver,' (jayendriet@nicd.ac.za/ 011 386 6419/ 083 266 3323).
2. For every patient, please complete a case investigation form (CIF) and submit it along with the specimens to the NICD.
3. CIFs are available on the NICD website and also from NICD Centre for Vaccines and Immunology (CVI) (epidemiologist Chenoa Sankar (chenoas@nicd.ac.za/ 078 371 0927).

Take home messages

- Adenoviruses cause mainly mild self-limiting infections in young children
- Young infants and immunocompromised prone to severe infections with long term sequelae
- Adenovirus implicated in emerging acute severe hepatitis in children
- Aetiology of acute hepatitis still unknown
- Early case identification of hepatitis important

References

1. Tebruegge, M. and Curtis, N., 2012. Adenovirus: an overview for pediatric infectious diseases specialists. *The Pediatric infectious disease journal*, 31(6), pp.626-627.
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5. Khanal, S., Ghimire, P., & Dhamoon, A. S. (2018). The repertoire of adenovirus in human disease: the innocuous to the deadly. *Biomedicines*, 6(1), 30.
6. <https://www.who.int/emergencies/disease-outbreak-news/item/2022-DON394>
7. Mücke MM, Zeuzem S. The recent outbreak of acute severe hepatitis in children of unknown origin—what is known so far. *Journal of Hepatology*. 2022 May 6.
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9. [https://www.nicd.ac.za/diseases-a-z-index/hepatitis-of-unknown-aetiology/#:~:text=Acute%2C%20severe%20hepatitis%20of%20unknown,\(which%20causes%20acute%20gastroenteritis\)](https://www.nicd.ac.za/diseases-a-z-index/hepatitis-of-unknown-aetiology/#:~:text=Acute%2C%20severe%20hepatitis%20of%20unknown,(which%20causes%20acute%20gastroenteritis)).

THANK YOU



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