Length of stay and hospitalisation rates in Indonesian patients with paediatric hepatitis A: 2015-2021

***Andraina[1], Andry Juliansen[1], Maria Gabrielle Vanessa[1], Gilbert Sterling Octavius[1], Rivaldo Steven Heriyanto[1], Michelle Patricia Muljono[1], Charista Lydia Budiputri[1]**

Sri Lanka Journal of Child Health, 2023: **52**(4): 444-450
DOI: https://doi.org/10.4038/sljch.v52i4.10616

Abstract

Objective: To describe the trend in hepatitis-A virus (HAV)-related hospitalisations in children and analyse the association of demographic, clinical and laboratory manifestations with length of stay (LOS) of HAV infection.

Method: A retrospective study was conducted in Siloam Hospitals Indonesia. Inclusion criteria were hospitalised paediatric hepatitis A patients aged 3-17 years from 2015-2021. Another viral hepatitis was excluded. Total 58 samples were divided into non-prolonged group (LOS<5 days) and prolonged group (LOS≥5 days). Demographic data, clinical manifestations and laboratory parameters were collected and analysed using SPSS. Correlations with $p < 0.05$ were considered significant.

Results: Hospitalisation rate pattern showed two peaks in 2016 and in 2019. The monocyte-to-leucocyte ratio (MLR), blood urea nitrogen (BUN), and creatinine were significantly associated with LOS in bivariate analysis. Medians of MLR and BUN were higher in the prolonged group (0.23; 17) than in the non-prolonged group (0.19; 15.98). Median of creatinine was lower in the prolonged group (0.55) than in the non-prolonged group (0.74). Multivariate analysis found that dark urine was less likely to have a prolonged LOS (OR: 0.23; 95% CI 0.06-0.91, p = 0.04).

Conclusions: Dark urine was a protective factor for prolonged LOS. Independently, higher BUN and higher MLR were risk factors for prolonged LOS.

[1]*Department of Paediatrics, Universitas Pelita Harapan, Tangerang, Banten, Indonesia*
**Correspondence:* andraina.ina@gmail.com
https://orcid.org/0000-0002-2550-2045
(Received on 09 June 2023: Accepted after revision on 21 July 2023)
The authors declare that there are no conflicts of interest
Personal funding was used for the project.

(Key words: Hepatitis A, Paediatric, Hospitalisation rates)

Introduction

Hepatitis A, the commonest form of acute viral hepatitis worldwide, is caused by the hepatitis A virus (HAV) and mostly transmitted through the faecal-oral route[1]. HAV remains a significant cause of deaths, there being over 3.93 thousand deaths in 2019[2]. In Indonesia, hepatitis A often occurs in school-aged students related to ingesting contaminated food or water; most students did not wash their hands after defaecating or before eating, there were poor hand washing facilities, water sources were located near a septic tank, poor hygiene and sanitation of food sellers (dirty food utensils), raw food consumption such as eating *pecel* and *lalapan*, sharing cutlery, and eating or drinking together during extracurricular activities[3].

Prevalence of hepatitis A in Indonesia is high and it occurs commonly in children. There were 6 outbreaks with 279 sufferers in 2019, 9 outbreaks with 550 sufferers in 2011, 8 outbreaks with 369 sufferers in 2012, and 13 outbreaks with 504 sufferers in 2013[3]. Fortunately, data show that prevalence of Hepatitis A in Indonesia has decreased in the last 30 years. However, the lower prevalence of anti-HAV antibodies among school children makes it possible for the occurrence of an outbreak[4]. Most Indonesian parents are unaware of children's self-administered Hepatitis A vaccination as it is not included in the Indonesian national immunisation programme[5]. Vaccination rate information is also limited because of lack of routine surveillance, availability and quality of existing data regarding viral hepatitis across Indonesia[6].

Clinical manifestations of hepatitis A include jaundice, abdominal pain, abdominal discomfort, vomiting, dark urine, sub-febrility and fever[7]. Most children under 6 years of age are asymptomatic or have non-specific symptoms. Older children are typically symptomatic with jaundice occurring in more than 70%[8]. It was found that hepatitis A patients with cirrhotic hepatitis and prolonged length of stay (LOS) have a significantly higher risk of death[9]. Therefore, precisely identifying variables related to cirrhosis and prolonged LOS in HAV infection is vital for rapid diagnosis and utilizing

limited hospital resources. A long-term trend in HAV hospitalisation would give valuable information on rates of hepatitis A developing into severe illness.

Objectives

To describe the trend in HAV-related hospitalisations in the paediatric population and analyse its correlation with the patients' demographic data, clinical manifestations, and laboratory results.

Method

A retrospective study was conducted in Rumah Sakit Umum Siloam (RSUS), a private hospital in Tangerang, Indonesia. Data were collected from each patient's medical record from 2015-2021.

We included 58 children aged 3–17 years diagnosed with hepatitis A and divided them into 2 groups based on LOS in hospital. Patients admitted for less than 5 days were in non-prolonged group and those admitted for 5 days or more were in the prolonged group. We collected demographic data (gender, age, body mass index), clinical manifestations (abdominal pain, fever, dark urine, nausea, vomiting, hepatomegaly, jaundice, dry eyes), duration of chief complaints (in days) and anti-HAV IgM results.

Laboratory parameters included haemoglobin, haematocrit, red blood cell count, total leucocyte count, differential blood count, total neutrophil count, neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio, thrombocyte count, erythrocyte sedimentation rate (ESR), mean corpuscular volume, mean corpuscular haemoglobin, total bilirubin, direct bilirubin, indirect bilirubin, aspartate transaminase (AST), alanine transaminase (ALT), glucose, sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, C-reactive protein (CRP), alkaline phosphatase, and gamma-glutamyl transferase (GGT).

Ethical issues: Study approval was obtained from the Ethical Board of Faculty of Medicine, Universitas Pelita Harapan (No. 332/SHLV-HA/V/2019). Being a retrospective study, written informed consent was not feasible.

Statistical analysis: This was done using Statistical Package for Social Sciences version 25. Data with non-normal distribution were tabulated using median and range. Chi-square test was used to analyse bivariate data. Variables with p-value less than 0.25 on bivariate analysis were further analysed in multivariate logistic regression. The receiver operating characteristic (ROC) curve was used to show the trade-off between clinical sensitivity and specificity. We evaluated calibration (goodness of fit) using the Hosmer-Lemeshow test with $p>0.05$ indicates a good fit of the model.

Results

From a total of 62 children infected with HAV, 4 were excluded based on exclusion criteria, leaving 58 paediatric patients with hepatitis A (Figure 1).

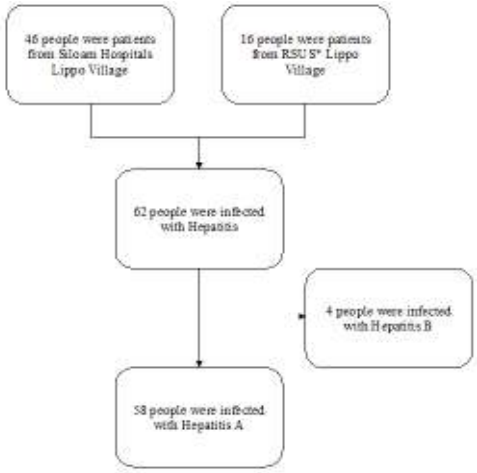
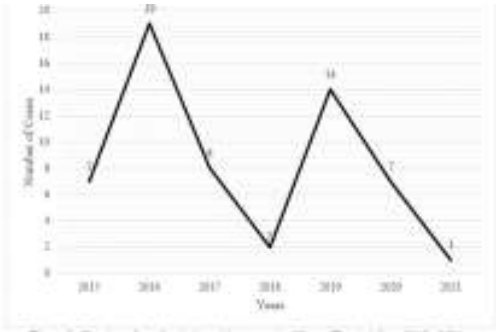


Figure 1: ***Flowchart of respondent selection***
**Rumah Sakit Umum Siloam*

Figure 2 shows the number of paediatric hepatitis A cases in Siloam Hospitals from 2015-2021. Based on this figure, the highest number of cases were found in 2016 (n= 19) and 2019 (n= 14).



Demographic factors among paediatric patients with hepatitis A are shown in Table 1.

There was male predominance. Median age was 13 years for the non-prolonged group and 14 years for the prolonged group. Most patients in both groups had good nutritional status. Abdominal pain, jaundice and vomiting were the chief complaints in the non-prolonged group, while fever and nausea were the chief complaint in the prolonged group. However, the median duration of chief complaints in both groups were the same (5 days) ($p = 0.28$).

Table 1: ***Analysis of demographic factors among paediatric patients with hepatitis A (n=58)***

Characteristic	Non-prolonged (0-4 days)	Prolonged (≥5 days)	OR (95% CI)	p-value
Gender: n (%)				
Male	18 (81.8)	22 (61.1)	2.86 (0.80 - 10.24)	0.1
Female	04 (22.2)	14 (38.9)		
Age (years): Median (range)	13 (5-17)	14 (3-17)		
0-5: n (%)	01 (04.5)	02 (05.6)	Ref	Ref
6-10: n (%)	02 (09.1)	05 (13.9)	1.25 (0.68 – 22.88)	1
11-15: n (%)	16 (72.7)	15 (41.7)	0.47 (0.04 – 5.72)	1
16-17: n (%)	03 (13.6)	14 (38.9)	2 .33(0.16 – 34.51)	0.5
Body mass index (kg/m^2): Median (range)	19.48 (15.17-24.22)	17.62 (13.72-32.18)		
Healthy weight: n (%)	17 (77.3)	28 (77.8)	Ref	Ref
Underweight: n (%)	03 (13.6)	06 (16.7)	1.21 (0.27 – 5.50)	1
Overweigh: n (%)t	01 (04.5)	0 (0)	N/A	0.39
Obese : n (%)	01 (04.5)	02 (05.6)	1.21 (0.10 – 14.43)	1
Clinical manifestations*				
Abdominal pain				
Negative: n (%)	17 (77.3)	31 (86.1)	0.55 (0.14 - 2.17)	0.4
Positive: n (%)	05 (22.7)	05 (13.9)		
Fever				
Negative: n (%)	18 (81.8)	20 (55.6)	3.6 (1.10 - 12.78)	0.07
Positive: n (%)	04 (18.2)	16 (44.4)		
Dark urine				
Negative: n (%)	06 (27.3)	19 (52.8)	0.34 (0.11 - 1.05)	0.1
Positive: n (%)	16 (72.7)	17 (47.2)		
Nausea				
Negative: n (%)	04 (18.2)	05 (13.9)	1.38 (0.33 - 5.8)	0.71
Positive: n (%)	18 (81.8)	31 (86.1)		
Vomiting				
Negative: n (%)	08 (36.4)	15 (41.7)	0.8 (0.27 - 2.39)	0.90
Positive: n (%)	14 (63.6)	21 (58.3)		
Hepatomegaly				
Negative: n (%)	14 (63.6)	25 (69.4)	0.77 (0.25 - 2.36)	0.86
Positive: n (%)	08 (36.4)	11 (30.6)		
Jaundice				
Negative: n (%)	03 (13.6)	07 (19.4)	0.65 (0.15 - 2.85)	0.72
Positive: n (%)	19 (86.4)	29 (80.6)		
Dry eyes				
Negative: n (%)	22 (100.0)	35 (97.2)	N/A	1
Positive: n (%)	0 (0)	01 (02.8)		
Duration of chief complaints (days): Median (range)	3 (0-4)	7 (5-10)		0.28
Anti-HAV IgM				
Non-reactive: n (%)	01 (04.5)	03 (08.3)	0.52 (0.05 - 5.38)	1
Reactive: n (%)	21 (95.5)	33 (91.7)		

**One patient can have more than one symptoms; N/A= Not available; Anti-HAV IgM: Anti Hepatitis A Virus Immunoglobulin M*

Laboratory findings among children with hepatitis showed several abnormalities (Table 2).

The monocyte-to-lymphocyte ratio (MLR), blood urea nitrogen (BUN), and creatinine were significantly associated with the LOS. MLR had a higher median (0.23) in the prolonged group compared to non-prolonged group (0.19) and this was statistically significant (p = 0.01). BUN also had a higher median (17) in the prolonged group compared to the non-prolonged group (15.98) and this was statistically significant (p = 0.04). On the other hand, creatinine had a higher median in the non-prolonged group (0.74) compared to the prolonged group (0.55) and this was also statistically significant (p = 0.01). Other laboratory values were not significantly associated with the LOS.

Multivariate analysis showed that the paediatric hepatitis A patients with dark urine were less likely to have a prolonged LOS (OR: 0.23; 95% CI 0.06-0.91, p = 0.04) (Table 3).

The Hosmer-Lemeshow test showed a p value more than 0.05 (p= 0.3) which indicates a good fit of the model.

The AUC curve is shown in Figure 3 with a value of 0.69 (95% CI 0.52 - 0.86; p value= 0.03).

Table 2: Analysis of laboratory findings among patients with hepatitis A

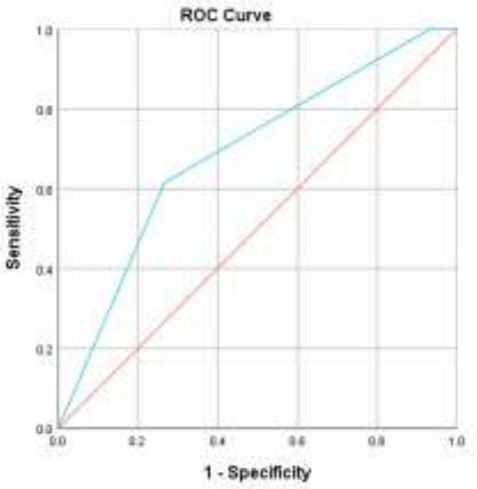
Variable	Patients with available data	Reference range	Non-prolonged	Prolonged	P value
Haemoglobin (g/dL) Male Female	53	 12.5-16.1 12-15	13.6 (7.9-16.8)	13.55 (7.9-16.8)	0.66
Haeematocrit (%) Male Female	53	 36-47 35-45	41.5 (25.2-50.2)	41.65 (25.2-50.2)	0.27
Red blood cell count (10^6 /µL)	53	4-5.5	5.3 (3.28-6.54)	5.3 (3.28-6.54)	0.90
Leucocytes (10^3 cells/mm^3)	53	4-10.5	6.81 (3.47-50.05)	6.46 (3.47-16.52)	0.12
Basophils (%)	44	0-0.75	0 (0-1)	0 (0-1)	0.45
Eosinophils (%)	44	1-3	2 (0-8)	3 (0-8)	0.42
Band neutrophils (%)	44	3-5	3 (2-5)	3 (2-3)	0.29
Segmented neutrophils (%)	44	54-62	52 (17-80)	53 (23-80)	0.40
Lymphocytes (%)	45	25-33	34 (11-73)	34 (11-65)	0.32
Monocytes (%)	44	3-7	7 (4-9)	7 (4-8)	0.56
Total neutrophils (per mm^3)	44	25-80	55 (20-83)	56 (26-83)	0.23
Neutrophil-to-lymphocyte ratio	45	N/A	1.62 (0-7.55)	1.71 (0.4-7.55)	0.15
Monocyte-to-lymphocyte ratio	45	N/A	0.22 (0-0.55)	0.23 (0.11-0.55)	**0.01**
Platelet-to-lymphocyte ratio	45	N/A	10,038.46 (1,753.42-36,363.64)	9,972.22 (2,369.23-27,181.82)	0.83
Thrombocyte count (µl/mm^3)	52	150-400	310,000 (128,000-786,000)	307,000 (154,000-786,000)	0.98
ESR (mm/hour)	44	0-10	15 (3-70)	15 (3-70)	0.88
Mean corpuscular volume (fL)	52	78-95	80.05 (54.8-90.8)	80.1 (58.3-90.8)	0.31
MCH (pg/cell)	52	26-32	26.7 (16-35.6)	26.7 (16-29.8)	0.83
MCHC (g /dL)	52	32-36	33.3 (25.9-35.9)	33.1 (25.9-35.7)	0.12
Total bilirubin (mg/dL)	51	0.1-0.7	4.94 (0.46-16.32)	5.12 (0.46-16.32)	0.87
Direct bilirubin (mg/dL) Male Female	51	 0.11-0.42 0.1-0.39	4.37 (0.26-13.97)	4.46 (0.26-13.97)	0.92
Indirect bilirubin (mg/dL)	51	0.2-0.8	0.54 (0.09-3.08)	0.56 (0.09-3.08)	0.88
Serum aspartate transaminase (U/L) Male Female	54	 9-24 8-22	362 (25-1,473)	436 (25-1,433)	0.14
Serum alanine transaminase (U/L) Male Female	55	 9-24 8-22	752 (31-2,130)	874 (31-2,009)	0.33
Glucose (mg/dL)	15	60-100	94 (71-131)	95 (71-116)	0.33
Sodium (mEq/L)	24	136-143	138 (132-144)	136.5 (132-142)	0.08
Potassium (mEq/L)	24	3.4-4.7	3.8 (3.3-4.7)	3.75 (3.4-4.7)	0.93
Chloride (mmol/L) Male Female	24	 101-106 100-107	98.5 (93-110)	98 (93-110)	0.26
Blood urea nitrogen (mg/dL) Male Female	11	 7.3-21 7.3-19	15.98 (9-20.2)	17 (9-25)	**0.04**
Creatinine (mg/dL)	17	0.45-0.81	0.67 (0.38-1.03)	0.63 (0.38-1.03)	**0.01**
C-reactive protein (mg/L)	15	0.1-1	5 (1-21.3)	4 (1-21.3)	0.36
Alkaline phosphatase (U/L) Male Female	18	 127-517 62-280	327.5 (155-759)	353 (155-759)	0.26
Gamma-glutamyl transferase (U/L)	20	7-21	163 (11-372)	173 (11-372)	0.22

N/A: Not Available

Table 3: ***Multivariate analysis of demographic factors and laboratory findings amongst paediatric patients with hepatitis A***

Variable	OR (95% CI)	P value	OR adj (95% CI)	p- value adj
Demographic data				
Gender	4.32 (0.91 - 20.48)	0.07	4.18 (0.92 - 18.92	0.06
Fever	3.27 (0.70 - 15.30)	0.13	3.35 (0.73 - 15.48)	0.12
Dark urine	0.22 (0.05 - 0.93)	0.04	0.23 (0.06 - 0.91)	0.04
Laboratory data				
Leucocyte (10^3 cells/mm^3)	3.63 (0.59 - 22.51)	0.17	3.51 (0.60 - 20.78)	0.17
Total neutrophils (per mm^3)	0.22 (0.01 - 5.87)	0.37	0.23 (0.01 - 5.55)	0.37
MCHC (g /dL)	6.31 (0.45 - 88.89)	0.17	6.69 (0.52 - 86.43)	0.15
Sodium (mEq/L)	1.48 (0.33 - 6.70)	0.61	-	-
Blood urea nitrogen (mg/dL)	1.02 (0.07 - 14.50)	0.99	-	-
Creatinine (mg/dL)	0.84 (0.22 - 3.12)	0.79	-	-
Gamma-glutamyl transferase (U/L)	0	1	-	-

CI: confidence interval; OR: odds ratio; OR adj: adjusted odds ratio (Adjusted by decreased sodium, blood urea nitrogen, creatinine, and gamma-glutamyl transferase)



Diagonal segments are produced by ties.

Area	95% CI	*p-value*
0.687	0.52 - 0.86	0.3

Hosmer-Lemeshow test showed p-value >0.05 (p= 0.3)

Figure 3: ***Receiver operating characteristic (ROC) curve***

Discussion

Hepatitis A predominantly infects children and adolescents. Our study comprised children aged 3-17 years. According to Centers for Disease Control and Surveillance's (CDC) data, individuals below 20 years of age accounted for approximately one-third of cases[10]. Our findings showed a spike in hospitalised paediatric hepatitis A patients in 2016 and 2019. This was in accordance with the outbreak in Pacitan district in 2016[11] and Surabaya in 2019[12], Indonesia.

Chakravarti A, *et al*[13] found that risk factors for hepatitis A were dense populations, poor sanitation, and water quality, all of which are prevalent in Indonesia. However, we could not assess these due to the retrospective nature of our study. As the world's fourth most populated country, Indonesia likely causes exposure to contaminated water and food to children[14]. The overall decreasing trend of hospitalised paediatric hepatitis A patients from 2015 to 2021 might be due to the hepatitis A vaccination programme and the low endemicity of this disease[15]. However, hepatitis A vaccination is still not included in the National Health Insurance Programme by the Indonesian Government[5].

Hepatitis A has a wide spectrum of clinical manifestations from asymptomatic to fulminant[16]. Chief complaints of abdominal pain, jaundice, and vomiting in the non-prolonged group is the classic manifestations of acute hepatitis A due to intrahepatic inflammation which impairs conjugated bilirubin transportation, leading to the accumulation of bilirubin in the skin and sclera[16]. This finding is similar to a British study that showed leading manifestations of jaundice, abdominal pain, and vomiting in hospitalized children with a median LOS of 1 day (0-7)[17]. However, we could not find a significant association in bivariate or multivariate analysis. This is probably because hepatitis A is mostly asymptomatic among children, a study by Koff RS[18] showing that less than 30% of infected young children are symptomatic.

All hospitalized hepatitis A paediatric patients had increased ESR, CRP, and a marked increase in total bilirubin, direct bilirubin, AST, ALT and GGT. A study from Turkey showed a significant correlation between AST, ALT, total bilirubin, direct bilirubin, and length of hospitalization in paediatric patients 1-17-year-old[10]. Our laboratory analysis found that MLR and BUN may be an indicator of hepatitis A severity as these values were significantly higher in the prolonged group. The urea synthesis capacity decreases in patients with compromised liver function, but increases in patients with inflammation[11]. The inflammation that occurs in hepatitis A patients might explain why the BUN value was high. Creatinine was significantly higher in the non-prolonged group. This is in contrast with a study from Europe with an increasing parallel of creatinine with LOS[12]. Hepatitis A patients may activate the renin-angiotensin system, induce immune complex-mediated nephritis, or induce endotoxaemia which contributes to renal injury[13]. However, in multivariate analysis, neither creatinine nor BUN were statistically significant. We hypothesized that hepatitis A may be complicated by renal disfunction yet creatinine and BUN are not better predictors for LOS in hepatitis A disorder. This is because creatinine level is influenced by muscle mass and its production by liver besides kidney function itself[14]. Low muscle mass and decreased liver function as in hepatitis A patients may lower creatinine level impairing its sensitivity or specificity[14].

Interestingly, our study showed that paediatric hepatitis A patients with dark urine were 81% less likely to have a prolonged duration of stay. Appearance of dark urine is commonly found in the acute phase (within a few days to a week) due to the presence of bilirubin in the urine[15,16] and we hypothesized that patients who presented with this symptom might had been diagnosed with hepatitis sooner, therefore could be treated sooner as well. This might explain why these patients were less likely to have a shorter period of hospitalization. One study stated that prodromal symptoms such as fever, anorexia, nausea, vomiting, abdominal discomfort, malaise, and weakness precede the onset of dark urine[16]. However in our study, no prodromal symptoms were at a significant level in the bivariate analysis. Dark urine, also was not significantly associated with LOS in the bivariate analysis.

One limitation of our study was that we did not include malaise, weakness, ascites, and cholecystitis. This was because some variables, due to the retrospective nature of the study, were not recorded in our medical records. A larger number of samples too is recommended. A similar study assessed other laboratory values, such as prothrombin time, activated partial thromboplastin time, international normalized ratio, and albumin[19]. Present study also might not be representative of the global population because only patients from 2 local hospitals were taken. However, our study also has some strengths. It included all paediatric hepatitis A patients admitted to the local hospital, giving valuable epidemiological data for hospitalized pediatric hepatitis A locally. Education about the importance of preventive measure like good personal hygiene and vaccination have to be programmed by government and conducted to citizens. Clinicians need to be aware of clinical features and laboratory investigations that might lead to prolonged hepatitis A as well as detect early and manage paediatric patients properly to prevent prolonged LOS.

Conclusions

Number of hospitalized pediatric HAV patients in this study was highest in 2016 and 2019. Paediatric HAV patients who presented with dark urine were associated with prolonged LOS. Independently, higher BUN and higher MLR were risk factors for prolonged LOS. Leading chief complaints in the prolonged group were fever and nausea.

References

1. Çetinkaya B, Tezer H, Parlakay AÖ, Sayli TR. Evaluation of paediatric patients with hepatitis A. *Journal of Infection in Developing Countries* 2014; **8**(3): 326–30. https://doi.org/10.3855/jidc.4057 PMid: 24619264

2. Cao G, Jing W, Liu J, Liu M. The global trends and regional differences in incidence and mortality of hepatitis A from 1990 to 2019 and implications for its prevention. *Hepatology International* 2021; **15**(5): 1068–82. https://doi.org/10.1007/s12072-02110232-4 PMid: 34345993 PMCid: PMC8514357

3. Martini S, Rahman FS. Determinants of hepatitis A infection among students: A case study of an outbreak in Jember, Indonesia. *Journal of Public Health Research* 2022; **11**(1): 126–9. https://doi.org/10.4081/jphr.2021.2309 PMid: 34595900 PMCid: PMC8859719

4. Mulyanto. Viral hepatitis in Indonesia: Past, present, and future. *Euroasian Journal of Hepato-Gastroenterology* 2016; **6**(1): 65–9. https://doi.org/10.5005/jp-journals-10018-1171 PMid: 29201730 PMCid: PMC5578564

5. Ahmad I, Endarti D, Andayani TM. Analysis of community's knowledge level of hepatitis A disease and vaccines in Indonesia. *J Farm Galen (Galenika J Pharmacy)* 2020; **6**(2): 221–8. https://doi.org/10.22487/j24428744.2020.v6.i2.15028

6. Jonathan S, Jack W, Suzanne W. Situation analysis of viral hepatitis in Indonesia : A policy report. *Coalition to Eradicate Viral Hepatitis in Asia Pacific* 2018; **3**(2): 10.

7. Blechová Z, Trojánek M, Kynl J, Částková J, John J, Malý M, *et al.* Clinical and laboratory features of viral hepatitis A in children. *Wien Klin Wochenschr* 2013; **125**(3–4): 83–90. https://doi.org/10.1007/s00508-012-0316-9 PMid: 23358879

8. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recommendations and Reports* 2006; **55**(RR-7): 1–23.

9. Chen CM, Chen SCC, Yang HY, Yang ST, Wang CM. Hospitalization and mortality due to hepatitis A in Taiwan: a 15-year nationwide cohort study. *Journal of Viral Hepatitis* 2016; **23**(11): 940–5. https://doi.org/10.1111/jvh.12564 PMid: 27386835

10. CDC. Hepatitis surveillance report no. 57, issued September 2000.

11. Lukmitarani R, Ardiyah M, Azizah R. The outbreak of hepatitis A: Evidence in Pacitan District. Journal Kesehat Lingkung 2021; **13**(1): 35. https://doi.org/10.20473/jkl.v13i1.2021.35-40

12. Juniastuti, Wahyuddin D, Nihayatussa'adah, Amin M, Yamani LN, Utsumi T, *et al*. Analysis of genetic and serology of hepatitis A virus infection during and after outbreak in two junior high

schools in Surabaya, Indonesia. *Journal of Medical Virology* 2019; **91**(6): 1048–55. https://doi.org/10.1002/jmv.25403 PMid: 30659645

13. Chakravarti A, Bharara T. Epidemiology of hepatitis A: Past and current trends. In: Streba CT, Vere CC, Rogoveanu I, Tripodi V, and Lucangioli S, editors. Hepatitis A and Other Associated Hepatobiliary Diseases 2020;1–17. https://doi.org/10.5772/intechopen.89248

14. Haryanto B. Indonesia: Country report on children's environmental health. *Reviews on Environmental Health* 2020; **35**(1): 41–8. https://doi.org/10.1515/reveh-2019-0088 PMid: 32134738

15. Hernandez-Suarez G, Saha D, Lodroño K, Boonmahittisut P, Taniwijaya S, Saha A, *et al.* Seroprevalence and incidence of hepatitis A in Southeast Asia: A systematic review. *PLoS One* 2021; **16:** 1–19. https://doi.org/10.1371/journal.pone.0258659 PMid: 34851983 PMCid: PMC8635355

16. Adiwinata R, Kristanto A, Richard T, Edbert D, Angelina F, Eppy E, *et al.* A clinical profile of hepatitis A patients in Jakarta, Indonesia. *Makara Journal of Health Research* 2017; **21**(1): 79807880. https://doi.org/10.7454/msk.v21i1.4610

17. Braccio S, Irwin A, Riordan A, Shingadia D, Kelly DA, Bansal S, *et al.* Acute infectious hepatitis in hospitalised children: A British Paediatric Surveillance Unit study. *Archives of Disease in Childhood* 2017; **102**(7): 624–8. https://doi.org/10.1136/archdischild-2016-311916 PMid: 28377449

18. Koff RS. Clinical manifestations and diagnosis of hepatitis A virus infection. *Vaccine* 1992; **10**(Suppl. 1): 15–7. https://doi.org/10.1016/0264410X(92)90533-P PMid: 1335649

19. Glavind E, Aagaard NK, Grønbæk H, Møller HJ, Orntoft NW, Vilstrup H, *et al.* Alcoholic hepatitis markedly decreases the capacity for urea synthesis. *PLoS One* 2016; **11**(7): 1–13. https://doi.org/10.1371/journal.pone.0158388 PMid: 27379798 PMCid: PMC4933397