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The global burden of Hepatitis A: Challenges, and future strategies

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Abstract
Hepatitis A, a positive-sense RNA virus, belongs to the Picornaviridae family that affects the liver and is transmitted via contaminated food and water. There are vaccines available that can effectively cure, but it is still a major health concern globally, specifically in areas with poor sanitation and low vaccination rates. In exploring HAV, it's very important to understand the structure, its replication strategy, and transmission. The virus continues to affect communities globally, causing acute liver inflammation and leading to various clinical symptoms. This review focuses on how the virus operates, its epidemiology, and present methods for diagnosis and treatment. One of the focal points is the development of vaccines. Both Formalin-inactivated and live attenuated vaccines have promising results, and it is crucial to understand how our immune system responds to the infection. Additionally, socioeconomic factors play a significant role in how prevalent the disease is; limited access to healthcare can amplify the risk of transmission, especially in developing nations. Despite the availability of vaccines, there are significant hurdles to overcome. Vaccine hesitancy, where individuals are reluctant to get vaccinated, complicates efforts toward control and eradication. Additionally, unequal access to vaccines creates disparities that leave the most vulnerable populations at heightened risk. This situation is worsened by underdiagnosis, which means many cases go unrecognized and untreated, making it difficult to effectively monitor and intervene. To truly combat Hepatitis A and work toward its elimination, a comprehensive strategy is essential. We need to focus on increasing vaccination coverage, improving sanitation facilities, raising public awareness about prevention and treatment options, and investing in research for more effective vaccines. By tackling these interconnected issues, we can make significant strides in controlling and ultimately eradicating Hepatitis A around the world.

Keywords: Hepatitis A Virus (HAV), Enterically transmitted virus, HAV epidemiology, Viral hepatitis prevention, Public health, HAV vaccination

1. Introduction

In 1973, Feinstone and associates described the hepatitis A virus (HAV). Hepatitis A is an enteric virus infection caused by the HAV, a single-stranded, positive-sense RNA virus belonging to the *Picornaviridae* family [1]. The HAV genome is a single-stranded, positive-sense RNA of around 7.5 kb in length, with a long 5′ noncoding region (5′NCR) covalently linked at its 5′ terminus to the VPg protein (encoded in the 3B gene), which acts as a primer in the RNA synthesis during the replication [2]. Hepatitis A virus (HAV) infection represents a disease that can be effectively prevented through vaccination [3]. Initially for personal protection, these vaccines are now being used to control hepatitis A in endemic areas, aiming for the long-term elimination of HAV. Originally designed for individual protection, these vaccines are now being utilized more broadly to manage hepatitis A in endemic regions. This shift aims to ultimately achieve the long-term goal of eliminating HAV [1].

Hepatitis A (HAV) infection is rarely fatal, with the WHO estimating 7,134 deaths globally in 2016, which accounted for just 0.5% of viral hepatitis mortality [4]. In 2010, Hepatitis A virus (HAV) was estimated to cause around 47 million infections globally (95% CI; 14-111 million), leading to approximately 94,000 deaths (95% CI; 30,000-222,000). This emphasizes the need for effective prevention and public health strategies [5]. The number of outbreak-related cases from 22 European Union countries was 4,475 in 2016, with most outbreaks linked to men who have sex with men [6]. In 2016, over 7,000 people lost their lives to hepatitis A worldwide, highlighting a significant public health challenge [7]. In response, the World Health Organization (WHO) set an goal to eliminate viral hepatitis by 2030, aiming to reduce the burden of this disease and improve global health outcomes [7]. An estimated 100 million HAV infections and 1.5 million symptomatic cases occur globally each year, and these cause between 15,000 and 30,000 fatalities annually. [8].

2. Structure and genome

HAV is a small but significant virus, measuring 27-32 nm in diameter [9]. Most members of the *Picornaviridae* family possess a single 2A protein; however, some viruses have notably evolved to acquire multiple 2A proteins [10]. The structure-based phylogenetic study confidently classifies HAV within the relationship between picornaviruses and insect viruses, leveraging the VP2 "domain swap" observed in insect picorna-like viruses [9]. The translation efficiency of HAV RNA is significantly influenced by the initiation process, which hinges on the RNA structure surrounding the initiator AUG (specifically the IRES). Additionally, the rate of translation elongation is effectively regulated by codon usage, a concept that has been well-established in cell systems [11].

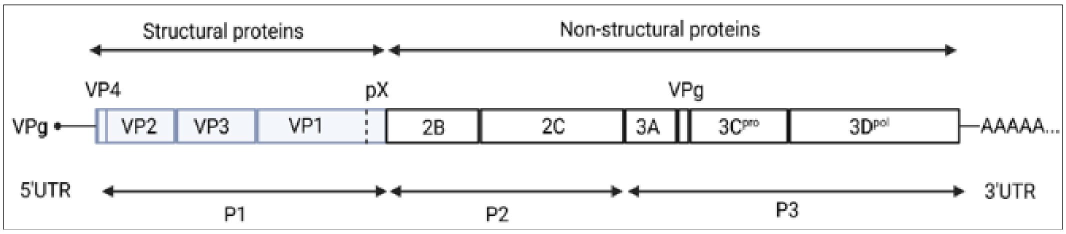

Fig 1: Genome of hepatitis A virus (created in BioRender.com)

The Genome organization of HCV shows 5' end covalently linked with the VPg protein, and 3' end has a long poly A tail. The genome produces 2 types of protein, structural proteins (VP1, VP2, VP3, VP4) and non-structural proteins (2B, 2C, 3A, $3C^{pro}$, $3D^{pol}$) [12]. HAV demonstrates a notable degree of genetic diversity, with an average nucleotide sequence divergence of approximately 10% and an amino acid sequence divergence of 2.2% among the coding region sequences of available (nearly) complete genome sequences [13]. The HAV genome consists of a single-stranded (+) RNA that is approximately 7.5 kb in length. It features a lengthy open reading frame (ORF) that encodes a single polyprotein. This polyprotein is efficiently processed by the viral protease 3Cpro into ten distinct mature proteins, highlighting the intricate nature of HAV's molecular machinery [14]. The HAV genome confidently features a single (ORF) flanked by a relatively long 5' untranslated region (UTR) and a 3' untranslated region (UTR). Notably, the 5' UTR contains an internal ribosome entry site that effectively directs the cap-independent translation of HAV proteins, ensuring efficient protein synthesis within the host cell [15].

3. Epidemiology of Hepatitis A

Hippocrates is often credited with the earliest medical records, but an illness similar to hepatitis was noted in China over 5000 years ago, showcasing the long-standing awareness of such conditions [16]. HAV is highly resilient to extreme conditions, including high temperatures, acidity, and freezing, enduring these challenges for hours or even months [8]. The recent outbreaks of the disease highlight a significant increase in infections, with a 294% rise observed from 2016 to 2018 compared to the period from 2013 to 2015 [6].

India is currently undergoing an epidemiological transition from high to intermediate endemicity of hepatitis A virus (HAV) infections, with various regions exhibiting both high and low incidence rates. Until there is significant improvement in hygiene and socio-economic conditions that can contribute to a reduction in endemicity, vaccination remains a crucial strategy to alter the epidemiological landscape of HAV infections in the country [17]. A study in India found that the hepatitis A attack rate was highest in the 15-24 age group at 4.6%. This was followed by 3.1% in the 5-14 age group and 1.2% in children under 5 [18].

The WHO estimates that there are 1.5 million cases of hepatitis A globally each year, leading to 7,134 reported deaths in 2016. In the USA, the CDC reported 12,474 cases of acute hepatitis A, resulting in an incidence rate of 3.8 cases per 100,000 people [16]. Each year, tens of millions of people globally contract the Hepatitis A virus (HAV) through fecal-oral transmission, primarily by consuming contaminated food or water or through contact with an infected individual. This highlights the need for better sanitation and hygiene awareness [19]. After fecal-oral transmission of HAV, the virus enters the bloodstream through an incompletely understood process, allowing it to reach the liver, its primary site for replication. Understanding this mechanism is crucial for addressing the virus's spread and improving treatment options [20]. HAV exclusively infects humans, and there are no known animal reservoirs for the virus [21].

A study in Bangladesh found atypical manifestations of prolonged cholestasis and ascites in 15% of children under 18 with acute viral hepatitis A. This highlights the varied clinical presentations of HAV in younger populations [22].

The seroprevalence of HAV infection significantly varies across different regions of the world, and this variation is strongly linked to socioeconomic factors, as well as access to clean water and proper sanitation [23], From 1991 to 1998, a study of 2,735 acute HAV cases at a Tertiary Care Hospital in Pakistan revealed that 232 children were hospitalized, with a mortality rate of 36.7% [24].

In 2014, Germany reported 681 cases of hepatitis A to the Robert Koch Institute (RKI), marking the lowest rate since 2001. The prevalence impressively declined to 0.8 cases per 100,000 inhabitants [25]. In China, a decrease in HAV incidence was reported from 359.7/100,000 in 1992 to 17.7/100,000 in 2009, which is approximately a 93% decrease over that period [26].

Table 1: Epidemiology and key insights of hepatitis A

Region/ source	Cases/ Incidence	Key insights
USA	12474 cases 3.8/100k incidence	Moderate resurgence in recent years
India	Age-specific rates: 15-24 years: 4.6%	Transitioning from high to moderate endemicity
Pakistan	2735 acute cases;232 children hospitalized	36.7% mortality among hospitalized children
Germany	681 cases	Lowest infection rates since 2001
China	17.7 per 100k	Nearly 93% reduction due to public health measures

4. Replication of Hepatitis A

HAV replication is similar to that of other picornaviruses. It involves protein-primed RNA synthesis that creates a negative-strand intermediate, which then enables multiple rounds of positive-strand RNA synthesis [27]. The picornavirus capsid protects the genome and evades immune recognition, allowing the genome to be transported into the cellular cytoplasm for replication [28]. Quasi-enveloped HAV particles are produced in a way that closely parallels the formation of exosomes, which are small extracellular vesicles important for intercellular communication [29]. Once HAV RNA is delivered to the cytosol, the replication cycle kicks off with protein translation, resulting in the production of both structural proteins and essential nonstructural proteins that are crucial for establishing an RNA replication complex [12]. There is a clear lack of compelling evidence demonstrating that HAV replicates in the gastrointestinal epithelium [30]. HAV uses two tandem YPX3L late domains in its capsid protein VP2 to interact with the cellular protein ALIX, aiding the budding of newly assembled capsids into multivesicular bodies (MVBs) [29]. Adaptive mutations in the HAV IRES that occur during cell culture significantly enhance both replication and translation efficiency in a cell-type-specific manner [12]. The polyprotein is processed into 10 mature viral proteins, including four structural proteins—VP4, VP2, VP3, and VP1pX—that form the capsid. Six nonstructural proteins—2B, 2C, 3A, 3B (VPg), 3Cpro (a cysteine protease), and 3Dpol (RNA-dependent RNA polymerase)—are vital for RNA genome replication [31]. Genome replication adheres to the established model of positive-stranded RNA viruses. Capsid assembly is effectively guided by VP0 (which includes VP4 and VP2), VP3, and VP1pX. This process involves the cleavage of VP1pX by a cellular protease, resulting in the precise removal of pX from HAV particles [32].

5. Pathogenesis

Marmosets (Callithrix sp.) were amongst the first species confirmed to facilitate the transmission of HAV and played a crucial role in the early studies of hepatitis A pathogenesis [5]. During infection, HAV RNA in the cytosol is detected by RNA helicases RIG-I and MDA5, and by Toll-like receptor 3 (TLR3) after it is taken up into endosomes [33]. Exosomes from damaged liver cells contain high levels of cytochrome P450. The reactive oxygen generated by CYP2E1 can lead to the production of superoxide anion-free radicals, hydrogen peroxide, and strong oxidants. Elevated CYP2E1 levels are observed in various pathophysiological conditions [34]. Early antiviral defects in CD8+ T cells likely aren't due to a lack of help, as CD4+ T cells in HAV-infected chimpanzees produced IL-2, IL-21, and IFN-γ [35].HAV can evade blood clearance mechanisms. Glycoproteins on erythrocytes act as decoy receptors, binding pathogens and stopping them from reaching target tissues [2]. Anti-HAV antibodies and HAV-specific cytotoxic T cells are consistently detected during illness. These findings strongly indicate that the pathogenesis of HAV is mediated by the immune system [36]. HAV is a hepatotropic positive-strand RNA virus that effectively employs strategies to inhibit innate immune responses, utilizing protease-mediated cleavage of innate immune adaptors [37]. It is unclear if there are two distinct stages of HAV pathogenesis in infected primates like humans and chimpanzees; however, it is likely that both mechanisms are present and may overlap in timing [33].

6. Transmission routes of Hepatitis A

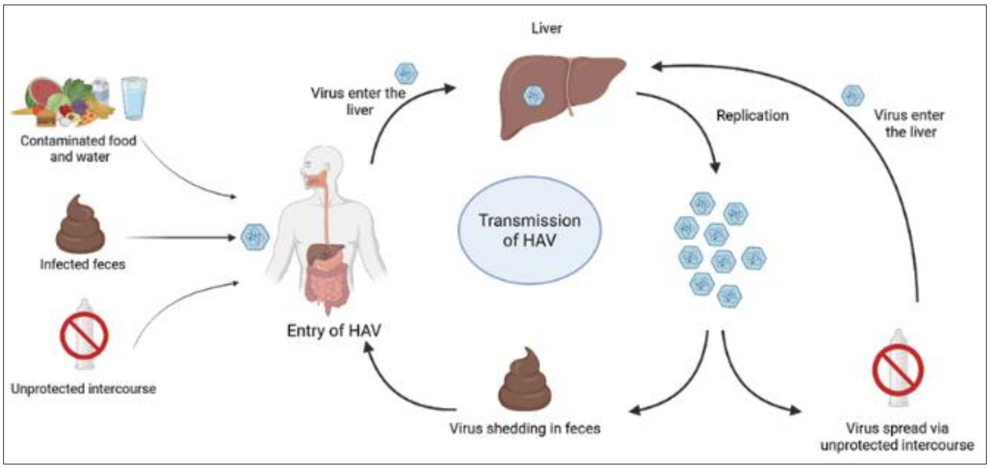

Fig 2: Transmission route of hepatitis A virus (Created with BioRender.com)

The highest rates of infection are seen in areas with poor sanitary conditions and limited access to clean water, as the virus is transmitted through person-to-person contact and contaminated food or water [38]. Closed environments and restaurant catering are the primary settings for HAV outbreaks [4]. Hepatitis A virus (HAV) is highly transmissible and can be spread by asymptomatic individuals through feces for up to two weeks before and for as long as two weeks after the onset of symptoms [39]. Following the ingestion of HAV, a notable incubation period of approximately 4 weeks occurs before symptoms of acute hepatitis manifest. These symptoms include malaise, jaundice, and a significant elevation of liver enzymes [40]. The risk of severe illness from HAV infection depends largely on age. Infections in young children are usually asymptomatic, while adults may experience severe illness, hospitalization, and, in rare cases, death [41]. Childhood vaccinations have resulted in increased susceptibility to HAV infections among young adults [42]. Subclinical infections in childhood were so widespread that nearly all children over the age of 5 exhibited anti-HAV IgG [24]. Approximately 1% of cases lead to acute liver failure in children [43].

Risk factors of Hepatitis A

In developing countries with poor sanitation, high infection rates in children foster immunity without symptoms, resulting in infrequent outbreaks [44]. Unsafe intercourse, especially men having sex with men, health care professionals like doctors and nurses, researchers, etc are Individuals who are at risk of exposure. Individuals who travel from low-prevalence nations to high-prevalence nations are also at high risk of infection, as they do not have immunity to fight against this infection [22]. Other than that, people with pre-existing chronic liver diseases due to alcohol consumption (alcoholic liver), liver cirrhosis, or liver with HBV/HCV infection are at risk. Apart from that, people who are immunocompromised, with conditions like AIDS, or infected with HIV are at high risk of HAV infection [8]

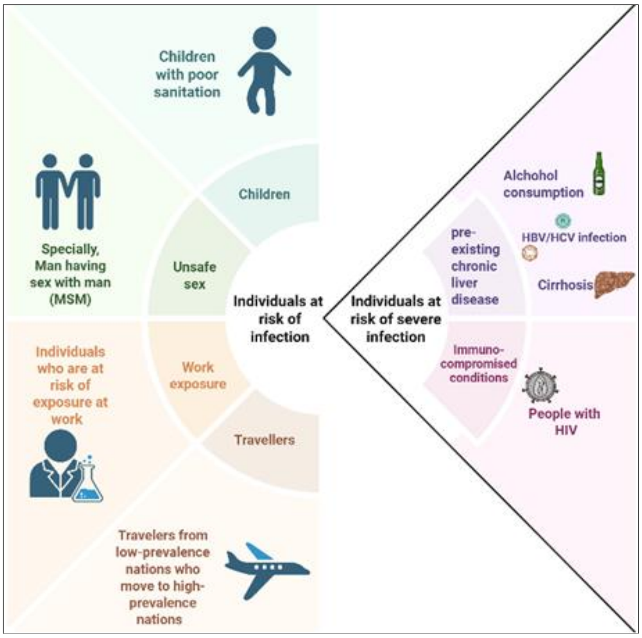

Fig 3: High-risk groups of HAV infection (Created in BioRender.com)

7. Clinical manifestation

HAV infection presents a spectrum of clinical manifestations, from asymptomatic cases to acute liver failure (ALF). Importantly, it does not progress to chronic hepatitis [45]. The development of symptomatic hepatitis is linked to the patient's age. Symptoms are less common in children, but most adults (>70%) suffer symptoms that last up to 8 weeks [23]. Once infected, most people acquire clinical indications of self-limiting icteric hepatitis; however, less than 30% of young infants suffer from clinical symptoms [46]. Blood in the urine (28%-94%), nausea or vomiting (26%-87%), stomach pain (37%-65%), and a high temperature (18%-75%), are common symptoms of hepatitis A, which can appear suddenly [46]. The following are examples of extrahepatic symptoms that have been recorded in the past: rash, kidney damage, myocarditis, and Guillain-Barré syndrome [47]. In the absence of concurrent viral hepatitis, the World Health Organization (WHO) reports that clinical manifestations of liver failure, such as asterixis, are nearly never observed [48]. There are neurological and ophthalmological symptoms that accompany the subsequent antiphospholipid syndrome that hepatitis A seems to generate [46].

8. Diagnosis and treatment

Physicians commonly diagnose Hepatitis A based on clinical and epidemiological symptoms, as well as serological tests for IgM antibodies to HAV [49]. In the laboratory, clinical materials such as blood, feces, bile, liver biopsy, and serum are used to identify HAV [9]. The diagnosis of HAV infection is often confirmed by serologic evidence of a recent infection, that is, identification of immunoglobulin M (IgM) antibodies against HAV [47]. However, because EIA testing requires infrastructure and is time-consuming, there has been a rising interest in point-of-care (POC) testing [50]. The development of anti-HAV IgM correlates with higher liver enzymes [Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] in the serum, a hallmark of liver injury [20]. Excessive serum transaminase levels (alanine transaminase higher than aspartate transaminase), total and direct bilirubin, and alkaline phosphatase levels may occur in symptomatic patients and take up to three months to resolve [51]. Molecular tests that can directly identify viral nucleic acids have the potential to enhance diagnosis (such as real-time PCR), which is critical for reducing the spread of diseases [9]. Although serum detection of HAV RNA is technically possible, it is rarely used to diagnose acute hepatitis A infection [47]. Early diagnosis allows for effective immunosuppression, limiting liver injury progression [52].

This antiviral effect is substantial, as the majority of persons treated within the first two weeks of HAV exposure do not create a de novo anti-HAV antibody response, despite the possibility that some virus replication and capsid synthesis occurred in the liver [53]. HAV treatment focuses on infection prevention and supportive measures, vaccination is an effective way to prevent Hepatitis virus infections [54]. Transplacental antibody transfer allows infants who have been exposed to HAV to develop immunity. This passive immunity gives protection for several months and has undetectable antibody levels by 12 months of age [55].

9. Vaccine

HAV vaccine is an efficient and safe way to prevent hepatitis A infection [56]. The first commercially produced hepatitis A vaccine was launched in 1992 [57]. False-negative results can be seen in early infection, while the patient is viraemic, and IgM antibodies can be detected in the context of recent HAV vaccine boosting [23]. Health officials should also investigate the prospect of eliminating hepatitis A in the region by targeted vaccination of specified age groups and special populations, particularly since the WHO has previously recommended one- or two-dose immunization [58]. Worldwide, there are two forms of HAV vaccines: formaldehyde-inactivated and live attenuated vaccinations are available [56]. Hepatitis A vaccines can protect tourists from non-endemic or low-endemicity countries from exposure to HAV during journeys to endemic areas [19]. The formalin-inactivated HAV vaccination provides protective immunity that is as effective and durable as that conferred by spontaneous infection [53]. Both inactivated and live-attenuated vaccines against the viral infection hepatitis A are currently available [57]. HAV immunization can elicit protective antibodies in 95% of vaccinees with a single dose and offer protective immunity for at least two years [59]. There are now four inactivated HAV vaccines available, each with identical efficacy and side effect profiles. However, widespread immunization campaigns are not yet universal [60]. Two weeks from the first dose of HAV vaccination, around 70% of patients generate protective levels of antibodies [61]. After getting the second dose of HAV vaccination, patients will have appropriate levels of antibodies that will most likely last for at least 10 to 29 years, or maybe for life [61]. Vaccination is regarded as the most effective technique to protect the population from viral illnesses. However, vaccinations may frequently lose effectiveness in the environment of quickly evolving pathogens [62].

10. Challenges in managing HAV

Low-income countries consistently experience elevated rates of hepatitis A virus (HAV) incidence. Monitoring new hepatitis A cases in these high-incidence regions presents challenges, primarily because many infections occur in young children who do not exhibit symptoms [19]. The risk of hepatitis A infection is closely linked to socio-economic conditions, individual hygiene practices, and the availability of safe drinking water [17]. Patients with chronic liver disease must be offered HAV vaccination because they face a higher risk of severe infection. Despite this clear need, the practice has not yet been widely adopted in clinical settings [63]. Countries with poor sanitary and socioeconomic conditions often show a high prevalence of HAV, highlighting the need for improved public health measures and infrastructure to reduce its impact [64].Despite the minimal circulation of HAV in low-endemicity countries, a significant number of adults do not possess immunity against the virus [41].

Alongside other challenges, we faced significant strains in vaccination supply and resource demands during peak periods of high demand, as well as issues related to monopolization and the scarcity of available resources [65]. The challenges presented by traditions and cultural behaviors, geographical specificities, socio-demographic disparities, the healthcare system, and unique vaccine characteristics are delineated, along with actionable opportunities to enhance public confidence [66].

11. Discussion

This review of the hepatitis A virus highlights the intricate interaction among viral structure, epidemiology, transmission patterns, and public health. While vaccination campaigns have decreased the disease impact in some parts of the world, sanitation issues, vaccine reluctance, and socioeconomic inequality still plague other areas [6]. Furthermore, it appears that research is required to improve diagnostic procedures and increase the range of antivirals due to changing clinical signs and new diagnostic technologies. To address the ongoing threat of HAV globally, integrative approaches including immunization, education, better cleanliness, and surveillance are crucial going forward [57]. Public health issues with Hepatitis A virus infection remain, particularly in regions with inadequate sanitation and low vaccination rates. Even though vaccinations have decreased the frequency globally, infrastructure and awareness shortages continue to cause outbreaks. The long-term control and eradication of HAV requires strengthening immunization programmes, enhancing hygiene, and developing diagnostic techniques [8].

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