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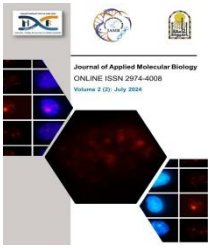

Review

Comprehensive Insights into Hepatitis A Virus

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ABSTRACT

Hepatitis A virus (HAV) infection is a global public health concern, with varying incidence and prevalence patterns across regions. This comprehensive review explores the different aspects of HAV, encompassing its virology, genetic variability, stability in the environment, global epidemiology, clinical manifestations, diagnosis, and prevention with a focus on the situation in an endemic region like Egypt. The review delves into the structure and genome of HAV, highlighting its genetic diversity and distribution of genotypes. Stability and persistence in the environment, particularly in water sources, are examined emphasizing the virus's resilience. Clinical manifestations, disease course, and extra hepatic manifestations are detailed providing insights into the diverse clinical presentations. Diagnostic methods, including serological testing and molecular diagnostics are discussed, along with surveillance strategies and outbreak investigations. The focus shifts to prevention and control measures, emphasizing the pivotal role of vaccination in reducing the overall burden of HAV. The discussion extends to hygienic practices, safe water measures, and targeted vaccination strategies for high-risk populations. This review provides valuable insights into the current understanding of HAV, informing public health strategies and guiding future research endeavors for the effective control of this viral infection.

INTRODUCTION

HAV was first identified in 1973 in a patient in the US. The discovery of HAV represented a breakthrough in understanding the mysteries of viral hepatitis, contributing to subsequent advancements in preventive measures and public health strategies **[1].**

HAV was initially detected by electron microscopy at the National Institutes of Health in a stool sample of a patient **[2].** HAV can be cultivated in primate cell cultures,

which enabled diagnostic procedures and the development of the inactive and attenuated vaccine. After serial passages, the virus showed decreased damage to hepatocytes **[3, 4].**

The virus is primarily transmitted via the fecal-oral route, with person-to-person transmission being a common mode. Nonetheless, injectable drug users, men who have sex with men (MSM), tourists visiting endemic regions, and remote villages are high-risk demographics. Unlike other hepatitis viruses such as HBV or HCV, HAV does not establish a chronic carrier state in the infected individuals **[5].** Once patients recover from acute HAV infection, they develop lifelong immunity. Following fecal-oral transmission, HAV infections range from asymptomatic to severe hepatitis with different symptoms. The severity of the condition varies according to different factors. Beyond individual health concerns, HAV has a significant impact on public health systems and the economy. Recognizing its impact highlights the significance of comprehensive preventative and control measures, including vaccination campaigns and improving hygienic habits **[6]**. This review focuses on the origin, categorization, transmission dynamics, clinical symptoms, and public health consequences of HAV.

Virology of Hepatitis A Virus

Basic Structure and Genome:

HAV belongs to the Picornaviridae, specifically the Hepatovirus genus. It is a small, icosahedral symmetric, non-enveloped virus. The genome includes a single-stranded (SS), positive sense RNA strand. The viral particle is approximately 27 - 32 nanometers in diameter, making it one of the smallest known human viruses **[7].**

The length of viral RNA reaches about 7500 nucleotides and included only one open reading frame (ORF). Approximately 38% of its total G+C content is significantly lower than that of other picornaviruses, and its codon use pattern is quite atypical. Similar to messenger RNAs in cells, the 3′ end of this molecule ends in a poly(A) tail that is comparatively long **[8].**

The ORF codes for a polyprotein which is then processed into different proteins which include both structural (SP) and non-structural proteins (NSP). The cleavage of the polyprotein into individual proteins takes place by viral proteases. The viral protease 3C is responsible for many of the cleavage events, producing mature proteins with distinct functions **[9].**

The SPs (viral capsid proteins VP1, VP2, and VP3) form an icosahedral capsid that encapsulates the viral RNA. Each of these structural proteins has 60 copies in its genome (1D, 1B, and 1C) **[10].** VP1 is located at the fivefold axis of symmetry and contains the primary neutralization epitopes responsible for inducing protective antibodies. VP2 and VP3 play an important role in maintaining the stability of the capsid **[11].**

The NSPs (2A, 2B, 2C, 3A, 3B, 3C, and 3D) play important functions, including viral replication. Proteins like 2B and 2C are associated with membrane rearrangements during viral replication. Protein 3A is a part of replication complex. Protein 3D is an RNA-dependent RNA polymerase that synthesis the new viral genome **[12].**

Interestingly, HAV utilizes an internal ribosome entry site (IRES) within its 5' UTR for translation initiation. This unique feature allows the virus to initiate protein synthesis without the need for a 5' cap structure. The IRES element is a critical component for the efficient translation of the viral RNA. In addition, the genome has a 5' untranslated region (UTR) and a 3' UTR, which are crucial for viral replication and translation initiation **[13].**

Quasi-Enveloped Virions (eHAV)

HAV is excreted in a naked, nonenveloped form, while in serum the quasi-enveloped eHAV form can be detected **[14].** During the release of eHAV into the proximal biliary canaliculi, bile salts separate the membrane from the capsid. Additionally, most HAV in the supernatants of infected cell cultures are in the eHAV form **[14-16].** The diameter of Naked virions is about 27 nm, while the diameter of eHAV is about 50 -110 nm **[14].**

eHAV virions have an exosomal appearance and do not contain viral glycoproteins. However, in cultivated cells, their specific infectivity is comparable to that of naked virions. Extraction of eHAV with organic solvents like CHCL3, dissolves the lipid membranes and diminishes the infectivity **[17].**

Genetic Variability and HAV genotypes:

Although HAV has a relatively stable genome, compared to other RNA viruses, it still can undergo genetic changes. The virus exists as a single serotype, but multiple genotypes with distinct genetic variations have been identified. HAV has a relatively low mutation rate compared to other RNA viruses. However, the absence of a proofreading mechanism in the viral RNA polymerase allows for some genetic changes over time. HAV is classified into 7 genotypes (I to VII) based on genetic differences a 168-base region spanning the VP1/2A region **[18].** Although there are molecular changes between individual HAV strains that could be valuable for epidemiologic studies, most strains have a high degree of commonality in amino acid sequence (up to 98%) and nucleic acid sequence (up to 90%) **[19].**

Within genotypes, HAV strains can further be classified into subtypes based on sequence variations. Subtypes are designated using letters (e.g., IA, IB, IIIA), representing distinct genetic lineages within a genotype. The distribution of HAV genotypes can vary widely from region to another, reflecting diverse epidemiological patterns. Certain genotypes, such as subtype IA of genotype I, are often associated with large outbreaks in various parts of the world. Genomic surveillance of HAV helps to monitor changes in genotype prevalence over time. Subsequently, understanding the distribution of genotypes is crucial for tailoring public health measures, including vaccination strategies and outbreak response **[20].**

Generally speaking, genotypes I and III are primarily human pathogens, with genotype I is being more prevalent globally. Genotype II is found in African non-human primates, while genotypes IV to VI are considered simian strains. The predominant genotype of HAV cases in the US is IA, identified in 88% of cases, while IB is observed in 11% and IIIA is present in 0.7% **[21].**

Genotype I: This is the most prevalent genotype globally and is associated with both human and simian strains. Subtypes IA and IB are commonly found in human infections. Subtype IA, particularly, is frequently linked to large outbreaks and is often associated with poor sanitation and hygiene **[22].**

Genotype II: Primarily associated with African non-human primates. While genotype II is mainly considered non-human primate-specific, occasional human infections have been reported, although they are rare **[23].**

Genotype III: Found in both human and simian strains. Subtype IIIA is commonly associated with human infections. Genotype III is prevalent in South America, contributing to a significant portion of hepatitis A cases in the region **[24].**

Genotype IV: Initially identified in northern India, genotype IV strains have been found in several regions, including Asia, Europe, and North America. In some regions, genotype IV is associated with endemic transmission and may contribute to a substantial number of cases **[25].**

Genotype V: Was first identified in South Africa, this genotype is primarily associated with simian strains and is not commonly linked to human infections **[26].**

Genotype VI: Genotype VI was commonly found in Vietnam and other parts of Southeast Asia. Both human and simian strains of genotype VI have been identified in the region **[27].**

Stability in the Environment:

One distinctive feature of HAV is its remarkable stability in the environment. The virus can withstand a wide range of pH levels and is resistant to detergents, common disinfectants, and low temperatures. This resilience contributes to the ease of HAV transmission through contaminated food, water, or fomites. The stability of HAV in the environment contributes to the potential for large-scale outbreaks, especially in settings with poor sanitation and inadequate hygienic practices. Outbreaks are often associated with contaminated food or water supplies, and the virus can persist in these sources for an extended period, leading to multiple cases of infection. Understanding the environmental stability of HAV is crucial for implementing effective preventive measures **[28].** Here are details about the stability of HAV in different environmental settings:

Resistance to pH and Temperature:

HAV is relatively stable across a broad range of pH levels, surviving in acidic conditions, such as those found in the stomach, as well as in more alkaline environments. In addition, HAV is resistant to extreme temperatures. It can withstand freezing conditions and remains viable even after exposure to temperatures as high as 60°C (140°F) for several hours. Compared to other picornaviruses, the HAV capsid is noticeably more stable at high temperatures and low pH **[29].**

Persistence in Water:

HAV can survive in various types of water, including freshwater, seawater, and chlorinated water. Improper disposal of sewage or wastewater can introduce HAV into water supplies, leading to environmental contamination. Contaminated water sources such as rivers, lakes, and wells are common causes for the transmission of HAV. The virus has been shown to remain infectious in water for extended periods, making waterborne transmission a significant concern. For , an outbreak in Shanghai, China, where the contamination of a municipal water supply led to widespread transmission of HAV **[30].**

Shellfish, such as clams and oysters, are filter feeders that can accumulate HAV if they are harvested from polluted waters. Eating raw or undercooked shellfish from contaminated areas has been associated with HAV outbreaks **[31].**

Resistance to Detergents and Disinfectants:

HAV is resistant to many common detergents and disinfectants. Therefore, traditional cleaning agents may not effectively eliminate the virus from contaminated surfaces or objects **[32].**

Stability on Surfaces and Fomites:

HAV can persist on surfaces and fomites (inanimate objects that can harbor the virus) for an extended period. The virus can remain infectious on surfaces such as countertops, utensils, and bathroom fixtures, posing a risk of transmission through contact with these contaminated objects **[33].**

Epidemiology and Global Impact

Understanding the epidemiology and global impact of Hepatitis A is essential for designing effective prevention and control strategies.

Epidemiology; Incidence and Prevalence:

HAV is found worldwide, with varying levels of endemicity. Regions with lower socioeconomic conditions often experience a higher incidence. In certain areas, HAV is endemic, meaning the virus circulates regularly in the population. In other regions, it may cause periodic outbreaks **[20].**

Every year, HAV infects about 1.5 million cases **[34].** In 2016, 7134 patients died of HAV which represents 0.5% of the total mortality caused by viral hepatitis infections. Areas of HAV geographical distribution can be classified as having high, intermediate, or low hepatitis A virus infection. However, infection does not always imply sickness, as infected young children do not exhibit any visible signs **[35].**

Turkey is regarded as a moderately endemic area for HAV, and the prevalence of anti-HAV immunoglobulin G (IgG) was reported as 64.4% in a study conducted in five different Turkish regions **[36].**

The most extensive outbreak of hepatitis A globally occurred in Shanghai, China, in 1988, resulting in over 310.000 reported cases and hospitalization of more than 8.000 individuals. **[37]**.

As for the age distribution in endemic regions, most individuals are infected in childhood, often without symptoms. This contributes to the development of immunity, and subsequent infections are generally milder. In areas with improved sanitation and hygiene, a shift in the age distribution of HAV cases may occur, with more cases occurring in older individuals. Living in crowded areas with poor sanitation, increases the risk of transmission **[38].**

Mode of transmission of hepatitis A:

Feco-oral

The virus is mostly transmitted through the feco-oral route. Contamination of the food can occur at any stage, including cultivation, preparation, or distribution, however it usually happens during food distribution because of infected food handlers **[39].**

The virus could contaminate almost any meal. HAV can withstand relatively high and low pH levels and can survive on surfaces in the environment, on food handlers' hands, in sewage, and in a range of food products **[40].**

Numerous instances of HAV genotype IB outbreaks linked to Middle Eastern food have been documented, such as outbreaks in Europe which were associated with frozen strawberries from Egypt and Morocco, frozen pomegranate seeds from Egypt in Canada, semidried tomatoes from Turkey in Europe and Australia, and pomegranate arils from Turkey in the US **[41-46].**

In the US, prior to the widespread vaccine availability, the country experienced significant outbreaks approximately every ten years. Up until 2001, children had the highest rates of HAV infection, constituting about 1/3 of cases, with the western and southwestern states having the highest rates and the majority of cases **[47, 48].** In 2022/2023, different outbreaks of HAV were reported in the US. The incident was traced down to eating infected frozen strawberries from a specific Baja California, Mexico **[20].**

Parenteral

Over the years, sporadic instances of hepatitis A linked to blood transfusions have been made public. Blood or blood products (Factor VIII and IX) obtained from an infected donor during the viremia phase are the means of transmission **[49].**

Sexual transmission

There is a higher risk of HAV infection in those who have oral-anal sex, MSM, sex with casual partners, and household or sexual contact with individuals who have acute HAV **[50].**

Infection in immunocompromised patients

HAV infections or even outbreaks were reported among MSM and drug abusers. Infections are connected with oral-anal sex and the number of sexual encounters and partners. Human immunodeficiency virus (HIV)/HAV coinfections were reported in different countries including Italy and Poland **[51].** HIV/HAV co-infection results in longer duration of HAV viremia and stool release than HIV negative persons, posing an additional risk of transmission to contacts of these cases **[52].**

People living with HIV (PLWH) have lower total bilirubin, AST, and ALT compared to HIV-negative individuals, which were attributed to suppressed immune responses against the virus and the viral infected hepatocytes. In addition, regulatory T cells (Tregs) which suppress T-cell responses are decreased during HAV infection leading to marked haptic damage **[53, 54].**

Although, HAV vaccination is recommended in these high-risk population, the seroconversion rates are lower among PLWH (after 2 doses), and an additional dose in recommended at week 4 after the first dose to boost the immune responses **[55, 56].**

Clinical Manifestations and Disease Course

Understanding the clinical manifestations and course of HAV is crucial for healthcare professionals, public health officials, and the general public.

Pathogenesis

There is no clear cytopathic alterations in infected cell cultures and damage to hepatocytes in mainly caused by the cellular immunity **[57].** There are several immunological processes involved in acute HAV infection that cause liver damage. It has been demonstrated that T-cells specific to the virus trigger the release of cytotoxic interferon-gamma in patients with acute HAV. Furthermore, mouse models have shown that hepatocellular apoptosis and inflammation were linked to responses from the innate immune cells **[58].**

Incubation Period and Prodromal Phase:

The incubation period for HAV is typically 15 to 50 days, with an average of 28 days. During this period, individuals infected with the virus may not exhibit symptoms but can still transmit the virus to others. This is followed by prodromal phase, this phase marks the onset of symptoms and includes non-specific symptoms such as fatigue, malaise, anorexia, and low-grade fever. Some individuals may experience symptoms reminiscent of a respiratory or gastrointestinal infection **[12]**.

Disease Severity:

HAV infection ranges in severity from asymptomatic or mild cases to severe cases with fulminant course. Severity is influenced by factors such as age, underlying health conditions, and host immune response. Children often experience asymptomatic, subclinical, or mild infections, and jaundice is less common., However, about 30% of patients > 6 years would show symptoms such as abdominal pain and jaundice. In addition, adults, especially over 50, are more likely to develop symptomatic and severe disease, including jaundice [59]**.**

Symptoms and Signs:

Infection with HAV may present in various forms, including asymptomatic cases (lacking an increase in serum hepatic enzymes), subclinical cases (asymptomatic but exhibiting elevated hepatic enzymes), anicteric cases (displaying symptoms without jaundice), or icteric cases (manifesting symptoms along with jaundice). As the disease progresses, the hepatic phase begins, characterized by jaundice. HAV infection leads to liver inflammation, impairing the normal processing and excretion of bilirubin. Jaundice typically becomes noticeable during the hepatic phase of HAV infection, marking a more advanced stage of the disease. As a result of liver cell damage, there is a release of liver enzymes, including ALT and AST, into the bloodstream, which are usually > 1000 IU/L. Increased levels of these enzymes are correlated with liver injury **[60].** The most common symptoms in this stage include the following:

a) Jaundice: Yellowing of the skin and sclera due to bilirubin accumulation.

b) Dark Urine: Bilirubin, not properly processed by the liver, is excreted in the urine, leading to dark-colored urine (bilirubinuria).

c) Pale Stools: Reduced bilirubin excretion into the intestines can result in pale or clay-colored stools. Although HAV in transmitted fecal oral, diarrhea occurs in < 25% of the cases.

d) Abdominal Pain: Discomfort or pain in the upper right quadrant of the abdomen may be experienced due to inflammation of the liver (hepatomegaly).

e) Fatigue and malaise, reflecting the overall impact of liver inflammation on the body. Anorexia is also common, contributing to weight loss and nutritional deficiencies.

Resolution and Recovery phases of HAV:

The majority of HAV infections are self-limiting, and the immune response typically results in resolution and recovery. The acute phase of illness may last weeks to few months, but most individuals recover fully without long-term consequences. Unlike HBV and HCV, HAV does not establish a chronic infection. Once resolved, individuals develop lifelong immunity to the virus. Recovery from HAV infection involves a dynamic process where the body's immune system responds to the virus, clears the

infection, and restores normal liver function, unless the case in complicated and coinfection with another hepatotropic virus is observed **[61, 62].** Here are more details about the recovery phase from HAV:

Resolution of Acute Phase:

The acute phase of HAV infection is characterized by symptoms such as jaundice, fatigue, and abdominal pain. As the immune response becomes activated, there is spontaneous improvement in these symptoms. Liver enzymes, including ALT and AST, which are elevated during infection, start to normalize as the liver heals. Resolution of the enzymes generally occurs within 1-6 weeks of the disease onset **[63].**

Duration of Recovery:

The duration of recovery can vary among individuals. Some patients may experience a relatively rapid improvement in symptoms, while others may have a more prolonged recovery. The acute phase of HAV infection may last for several weeks, during which symptoms may gradually subside. Approximately 85% of patients achieve full recovery within three months and almost all cases show full recovery by six months **[64].**

Monitoring and Follow-up:

Individuals recovering from HAV infection may be monitored clinically to assess the progress of recovery. Follow-up liver function tests helps gauge the extent of liver healing and the resolution of inflammation **[65].**

Complete Resolution:

In the majority of cases, individuals experience a complete resolution of symptoms and a return to normal health. The liver has a remarkable capacity for regeneration, and the recovery phase involves the restoration of normal liver function. Some individuals may experience lingering fatigue during the recovery phase. Adequate rest, a balanced diet, and psychosocial support contribute to overall well-being **[66].**

Long-term Immunity:

Recovery from HAV infection, the immune system produces antibodies specific to HAV which provide long-term immunity against the virus. Once resolved, individuals do not continue to carry the virus **[12].**

HAV complications

Fulminant hepatitis, characterized by severe liver failure, occurs in < 1% of patients. Moreover, HAV can manifest in various unconventional ways, such as relapsing hepatitis, cholestatic hepatitis or autoimmune hepatitis. Fulminant hepatitis, which is a rare occurrence characterized by severe liver injury and hepatic encephalopathy, represents an infrequent complication with an associated case-fatality rate of approximately 0.6% **[67].** Increased susceptibility to fulminant hepatitis is associated with factors such as advanced age (above 50 years) and the presence of underlying chronic liver disease **[68].** No link was reported between fulminant hepatitis and viral variants. In the US, Canada, and the United Kingdom, only a small proportion, specifically 0.9%, of instances of acute liver failure in children were ascribed to acute hepatitis A **[69, 70].**

Spontaneous recovery is observed in 30-60% of cases of fulminant hepatitis A infections. The prognosis is influenced by different factors such as age, coma, level of

clotting factor, and the presence of kidney complications. Moreover, around 10-15% of cases experience relapse of the hepatitis typically 1-4 months after the initial acute attack and 20% experience multiple relapses. These patients are characterized by elevated liver enzymes, viral persistence in stool and persistent IgM antibodies during the relapse period, which is followed by complete recovery within several weeks in most cases **[69].** In severe cases, liver transplantation may be necessary to replace the non-functional liver with a healthy donor organ **[71]**

Extrahepatic Manifestations

While HAV primarily targets the liver, it can rarely lead to extrahepatic manifestations, affecting organs and systems outside the liver. Extrahepatic manifestations are not a consistent feature of HAV infection and occur in a minority of cases. The severity and duration of extrahepatic manifestations can vary widely among affected individuals **[72].** Here are details about some of the extrahepatic manifestations associated with HAV infection:

Kidney Involvement

There have been reports of HAV infections associated with glomerulonephritis marked by changes in kidney function. Similar observations have been reported for HEV infections **[73, 74].**

Acute Pancreatitis

HAV infection can lead to acute pancreatitis. presented by severe abdominal pain, nausea, and vomiting **[75].**

Immune System Activation

The immune response triggered by HAV infection can lead to systemic effects, affecting various organs and tissues. The release of pro-inflammatory cytokines during the immune response may contribute to extrahepatic manifestations **[76].**

Neurological Manifestations

While uncommon, there have been isolated reports of neurological complications associated with HAV infection. In some instances, HAV has been temporally linked to the development of Guillain-Barré Syndrome. **[77].**

Myocarditis

Although rare, cases of myocarditis or complete heart block with fatal outcome have been reported in association with HAV. Myocarditis may present with symptoms such as chest pain, shortness of breath, and palpitations **[78].**

Diagnosis and Surveillance of HAV

Diagnosing and surveilling of HAV involve a combination of clinical evaluation, laboratory testing, and public health monitoring. Timely and accurate diagnosis, along with effective surveillance, are crucial for implementing targeted interventions, preventing outbreaks, and assessing the impact of vaccination programs. International collaboration enhances the understanding of global trends and supports coordinated efforts to control HAV **[12].**

Clinical Evaluation:

A thorough medical history is obtained, including information about the onset and duration of symptoms, recent travel, and exposure to potential sources of infection. Specific symptoms related to hepatitis A, such as jaundice, abdominal pain, dark urine, and fatigue, are explored. This is followed by detailed physical examination, which includes assessment of jaundice, to provide insights into the severity of liver involvement. Palpation of the abdomen helps assess for hepatomegaly and tender liver. Monitoring vital signs, including temperature, blood pressure, and heart rate, helps to assess the overall clinical status [79].

Laboratory Tests:

Liver function test

Measurement of liver enzymes, including ALT and AST, helps to assess the extent of liver damage. Also, elevated bilirubin levels are indicative of liver dysfunction. Serial monitoring of liver enzymes, bilirubin levels, and clinical symptoms helps to assess the progress of the infection and recovery [80].

Serologic Tests:

This involves testing for the presence of specific antibodies against HAV. The presence of anti-HAV IgM antibodies in the blood is a hallmark of acute HAV infection, indicating recent exposure. However, detection of anti-HAV IgG antibodies suggests past infection or vaccination. **[81].**

Molecular Diagnostics:

Molecular techniques, like polymerase chain reaction (PCR), or amplicon-based nanopore sequencing can detect HAV RNA in blood or stool, providing a direct confirmation of ongoing infection. Furthermore, genotyping may be performed for research or epidemiological purposes to determine the specific HAV genotype involved **[82].**

Treatment of HAV

The main treatment strategy involves providing supportive care. Hospitalization may be necessary for individuals facing dehydration that results from prolonged nausea and vomiting or those suffering from fulminant hepatitis. No particular dietary or activity constraints are mandated. Caution is recommended when using medications that could potentially harm the liver or are metabolized by the liver, which is already inflamed. While corticosteroid therapy has been suggested as beneficial in mitigating symptoms and hastening recovery in uncommon cases of cholestatic or relapsing hepatitis, it's important to note that this approach lacks evaluation through controlled trials **[83, 84].** Liver transplantation, while successful in some cases of acute liver failure, faces challenges in establishing criteria for patient selection due to high survival rates (50%-70%) without transplantation, even for the comatosed patients, with no single predictive factor for poor outcomes **[85].**

Prevention and Control Measures

Prevention and control measures for HV are multifaceted, involving vaccination, public health education, hygiene practices, and international collaboration. A comprehensive approach, including routine vaccination, targeted vaccination strategies,

and timely outbreak response, is essential for reducing the burden of HAV and preventing its spread within communities and across borders **[86].** Here are details about various prevention and control measures:

Hepatitis A Vaccination:

Development of the vaccine

HAV viral vaccine was first licensed in 1992 and was propagated in cell culture. There are 2 different forms of the vaccine; the inactivated (HepA-I) and attenuated (HepA-L) **[87].** HAV vaccines are typically inactivated, and are safe for most individuals, including those with weakened immune systems. A 2-dose schedule is commonly recommended separated by several months. HAV vaccines are available as single-dose or in combination with other vaccines, such as HBV (Twinrex) or enteric fever (typhoid) vaccines **[88].** Combination of HAV and HBV vaccines has the advantages of providing double protection against both viruses, cost-effective and is highly immunostimulant **[89].**

Administration of hepatitis A vaccine

HepA-I is approved for IM use in a 2-dose regimen. There is flexibility in receiving the second dose (ranging from 6 months to 4-5 years). It is also possible to use the two-doses from different manufacturers **[90, 91].** Although anti-HAV antibodies could be initiated by a single dosage of HepA-I or HepA-L, the second dose produced prolonged and stronger immunity. HepA-L is mostly utilized in China and India and is given as a single SC **dose [92].**

HepA-I vaccine targets children of one year or older, but Hep A-L vaccination starts at 18 months. Vaccination can be also used as postexposure prophylaxis (PEP) for adults. It is recommended to administer vaccinations to infants between 6 and 11 months of age before starting a travel to regions where the disease is prevalent **[93].**

How effective is HAV vaccination?

HAV vaccines provide a high level of protection against symptomatic infection and help prevent severe cases. The duration of immunity following vaccination is long-lasting, and booster doses are not routinely recommended. When taken as a pre-exposure prophylactic, HAV is extremely successful in preventing clinically infections. Randomized controlled trials in immunocompetent individuals showed that efficacies the vaccine were 95% and up to 100% **[93].**

A cross-sectional epidemiological study conducted in a tertiary care center in eastern Turkey between 2008 and 2019 revealed that the overall immunity to HAV among the studied patients was 81.6% **[94] .**

Moreover, observational research from China examined the efficacy of HepA-L and reported that the incidence of infection was lower by 94.5%. Of note, HepA-L is available in a few countries, therefore, additional data about efficacy is required **[95] .**

Improvements in hygienic measures and the application of HAV vaccine played important roles in decreasing the incidence rates of HAV infection, decreased incidence of outbreaks and increased the average age of infection **[96].** For example, in Turkey, the frequency of infections has decreased since 2007, decreasing to less than 5/100,000 by 2015. At the same time, the peak age for exposure has shifted to adolescence and young adulthood **[36]**

Vaccination efforts often target high-risk groups, including travelers to endemic regions. In addition, individuals in certain occupations, such as healthcare workers and workers in childcare facilities, may be at increased risk and can benefit from vaccination. HAV vaccines are generally well-tolerated, with mild and transient side effects such as soreness at the injection site or mild fever. The safety of the vaccine has been demonstrated in various populations, including pregnant women and individuals with chronic medical conditions. The vaccine is considered cost-effective, particularly when accounting for the economic burden of illness and the costs associated with outbreaks **[97].**

Immunoglobulins (Ig)

Immunoglobulins in the form of intramuscularly (IM) administered solution of plasma-derived human antibodies is available in the US (IgG anti-HAV) with an efficacy of 80-90% when administered IM before or within 2 weeks after exposure to HAV **[98].** Immunoglobulins induce rapid seroprotective anti-HAV levels (10-20 mIU/mL) within approximately 2 days post-injection, and its efficacy beyond 2 weeks after exposure remains uncertain **[99].** Indications for Immunoglobulins use include situations where the vaccine is contraindicated, as well as for travel and PEP **[100] .**

Hygiene and Sanitation Practices

Regular hand washing with soap and water is crucial in preventing the fecal-oral transmission of HAV. Adhering to proper food handling and cooking practices minimizes the risk of foodborne transmission **[101].**

Safe Water Practices

Implementing effective water treatment processes, including chlorination, reduces the risk of waterborne transmission. Public health campaigns are essential to educate individuals about the importance of avoiding drinking water from potentially contaminated sources **[102].**

Insights of HAV infection in Egypt

In Egypt, there are an estimated 8–10 million cases of viral hepatitis. The two main viruses that cause viral hepatitis in Egypt are hepatitis A and E viruses, as by the age of 15, 50% or more of Egyptians have already been exposed to HAV infection**.** The prevalence of HAV infection is elevated in developing nations owing to insufficient sanitation and poor hygienic practices. Egypt is recognized as an endemic region due to several documented outbreaks among European travelers who visited the country from November 2012 to April 2013, in addition to the previously reported outbreaks **[90]**

In Egypt, the prevalence of HAV is among the highest in the world, primarily consisting of genotypes 1A and 1B with predominance of genotype 1B. Recent investigations into HAV in sewage and the population indicate widespread circulation of the virus throughout Egypt **[103] .**

HAV in environmental samples

Hamza, Abd-Elshafy [102] investigated the presence of HAV in wastewater samples from 3 treatment plants over one year, and revealed a detection rate of 63.2%. Positive samples belonged to sub genotype IB and recombination analysis identified a rare recombination event between sub genotypes IA and IB. However, in Mansoura and Giza

regions a study investigated the presence of HAV and human norovirus genogroups I and II in surface water used for irrigation and fresh produce revealed that 41.6% of surface water samples and 27% of fresh produce samples tested positive for at least one virus. HAV was the most frequently identified virus in both surface water (23/72) and fresh produce samples (10/48), highlighting a significant concern for viral contamination in raw consumed fresh produce. The study emphasized the need for increased monitoring of viral pathogens in irrigation water and food to enhance awareness and implement control measures to mitigate the risk of illness from contaminated food **[102].**

Elmahdy, Shaheen [104] assessed the presence of HAV and norovirus genogroups I and II in green leafy vegetables such as watercress, leek, coriander, and parsley and from strawberries among Egyptian regions. The study revealed that HAV was detected in 48% of fresh strawberries and 31.2% of green leafy vegetables. Theis emphasizes the need for surveillance programs to viral persistence in fresh fruits and vegetables to decrease the potential transmission through contaminated foods **[104]**.

HAV among Egyptian patients

Another study was conducted between 2014 and 2017, involving 9321 patients found that 89.7% had markers of acute viral hepatitis, with 93.4% attributed to HAV, 3% to HCV, 2.8% to HBV, and 0.4% to hepatitis E (HEV) infections. HAV infections were most common in children <16 years, HBV infections occurred in individuals aged 16–35 years, and HCV infections were prevalent in those over 45 years. HAV infections were associated with attending nursery or pre-school, having meals outside the home, and contact with HAV cases. Compared to 2001–2004, there was a substantial increase in the proportion of HAV infections (from 40.2% to 89.7%) and significant reductions in HBV and HCV infections [105].

A cross-sectional study involving 501 refugees, the most prevalent marker was anti-HAV (96.2%), followed by anti-HBs (28.3%) and HBsAg (4.2%), with only 0.8% having positive anti-HCV IgG [106].

Anti-HAV was higher in older refugees and non-working subjects. Higher seroprevalence was also reported among refuges from Sudan. On the other hand, HBs-Ag was marked among Yemeni refugees. Both anti-HAV and anti-HBs were higher among inhabitants of Dakahlia **[107].**

Another study reported that out of etiologies of acute hepatitis in 141 adult patients at Embaba Fever Hospital hepatitis A represented 0.71%. The clinical presentation ranged from mild to severe, and there were no significant differences in clinical, epidemiological, and biochemical features among the different hepatitis types. The study emphasized the importance of serological tests as the sole method for distinguishing between HAV, HBV, and non-A, non-B (NANB) hepatitis **[108].**

A cross-sectional study conducted in Cairo, involving 184 hospitalized children aimed to assess the prevalence of silent viral hepatitis (A, B, C, and E) showed that 2.71% of the children tested positive for HCV antibodies, while the remaining 179 children were negative for all hepatitis viruses **[109].**

Outbreaks among tourists

In 2004, a major HAV outbreak among European tourists returning from Egypt involved 351 case-patients staying at a specific hotel (termed hotel X) from 9 countries, with a single strain (genotype 1b) was identified. Orange juice was identified as the likely

infection source through a case-control study. This emphasized the importance of hepatitis A vaccination before traveling to endemic areas. In Germany, half of annual cases were acquired abroad, a surge in infections among tourists returning from Egypt prompted an outbreak investigation and preventive measures, including vaccination at the implicated hotel in the Red Sea resort of Hurghada **[110].**

Interestingly, RKI informed other European countries about the outbreak and reported another 60 primary cases (19 Austria, 10 Sweden, 9 Denmark 9 Netherlands, 7 Belgium, 5 UK, 2 Italy, 1 Switzerland) and 13 secondary infections (Austrian tourist that returned to her job in food preparation), which were reported via the national public health institutes of eight other European countries **[111] .**

Despite all surveyed countries recommending HAV vaccination for travelers to Egypt, 40% of annual cases (2001-2003) were linked to travel, highlighting the need for improved adherence to vaccination guidelines and a standardized case definition for reporting confirmed hepatitis A cases **[112].**

In 2008, another cluster of 10 confirmed cases of HAV infection was detected in Belgian travelers returning from Egypt in the duration of September through November 2008, revealing a common source outbreak likely linked to Nile River cruises. The age range of the cases was 23-59 years, and none was vaccinated **[113].**

On 15 October 2008, the French Institute for Public Health Surveillance warned about an increase in hepatitis A cases among individuals who had traveled to Egypt, particularly on Nile River cruises in August 2008. The alert prompted other European countries to report similar cases linked to Nile river cruises, suggesting a potential association between HAV infection and such travel **[114].**

On December 2, 2008, German public health authorities received reports of 34 symptomatic infections that met HAV specified case definition. The age range was 11-69 years and only 4 did not go on a Nile cruise. Cases originated from various regions within Germany **[114].**

Between January and April 2013, 6 cases of HAV in Norway with a travel history to Egypt was reported, and majority of the viruses belonged to genotype 1B. therefore, Norwegian Institute of Public Health posted an urgent inquiry on the Epidemic Intelligence Information System, and several European countries reported similar increases in HAV cases among travelers to Egypt, prompting a multinational investigation to identify common exposures and patterns among affected travelers from different countries in the European Union/European Economic Area. Results showed that as of 24 April 2013, 80 HAV cases (39 from Germany, 11 from England, 11 from Netherlands, 7 from Denmark, 6 from Norway, and 6 from Sweden) were reported among travels with onset of symptoms after 1 November 2012. The age range was 3-76 years. **[90].**

The marked increase in HAV cases among different travelers to Egypt lead to an outbreak investigation coordinated by the European Centre for Disease Prevention and Control (ECDC) in collaboration with different public health institutes, the World Health Organization (WHO), and Egyptian authorities. The study aimed to analyze the cases and assess the need for reinforced vaccination recommendations for travelers. The study reported 107 HAV cases among travelers from 14 European countries **[115]**.

CONCLUSION

This review provided an in-depth exploration of HAV, spanning its historical context, virology, clinical manifestations, epidemiology, and public health impact. The discovery

of HAV marked a significant milestone in the understanding of viral hepatitis, with key researchers contributing to our knowledge of its taxonomy, transmission dynamics, and clinical spectrum. The global burden of HAV remains a critical public health concern, necessitating ongoing efforts to mitigate its impact. The epidemiological landscape underscores the need for the development and implementation of vaccination programs to reduce the incidence of HAV particularly in endemic regions such as Egypt. As we move forward, it is crucial to emphasize the importance of continued research into HAV, addressing gaps in our understanding of its molecular biology, evolving epidemiological patterns, and emerging variants. Advances in antiviral therapies and ongoing efforts to improve vaccine accessibility can contribute to the ultimate goal of minimizing the global impact of HAV.

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