Chapter

Epidemiology of Hepatitis A: Past and Current Trends

Anita Chakravarti and Tanisha Bharara

Abstract

Hepatitis A virus is a common infectious etiology of acute hepatitis worldwide. It was not until World War II (1973) when hepatitis A virus was first identified by an American virologist, Stephen Mark Feinstone. The virus is most commonly transmitted through contaminated food, water, or sexual contact (oral-anal sex). The discovery of hepatitis A virus vaccine is considered a milestone in the history of acute viral hepatitis. Hepatitis A occurs worldwide and frequent outbreaks have been reported over the years. Major geographic differences have existed in endemicity of the disease depending primarily upon hygiene and sanitation practices. Some countries have experienced shifting of endemicity due to improvement of environmental hygiene, swelled International travel and national recommendations for hepatitis A vaccination. The age of acquiring hepatitis A virus is also shifting toward adolescents and adults. This has led to a more symptomatic disease, since hepatitis A infection among children is usually asymptomatic; this is known as the paradox of Hepatitis A epidemiology.

Keywords: acute hepatitis, vaccine, feco-oral route, men who have sex with men, outbreak, sero-prevalence, paradox of hepatitis A

1. Introduction

The discovery of hepatitis viruses is one of the most mesmerizing scientific escapades of the last five decades. Their identification has been considered a milestone that revolutionized modern day medicine [1]. Disease outbreaks resembling hepatitis A have been known since ancient times. The earliest accounts of contagious jaundice are traced to ancient China [2]. Feinstone et al. were first to identify Hepatitis A virus (HAV) in the year 1973 [3]. Increasing globalization poses fresh challenges for prevention of HAV infections. This chapter is an attempt to decipher the evolution of the disease over the years and summaries the current HAV situation around the world.

2. The breakthrough

Outbreaks resembling hepatitis A have been reported from Europe in the 17th and 18th centuries during the period of war. The pathologists Bamberger and Virchow proposed the name "catarrhal jaundice", as they believed the disease to be caused by mucus blockage of common bile duct [4]. Viral origin of the disease was first indicated by McDonald [5]. The virus was identified when the focus of

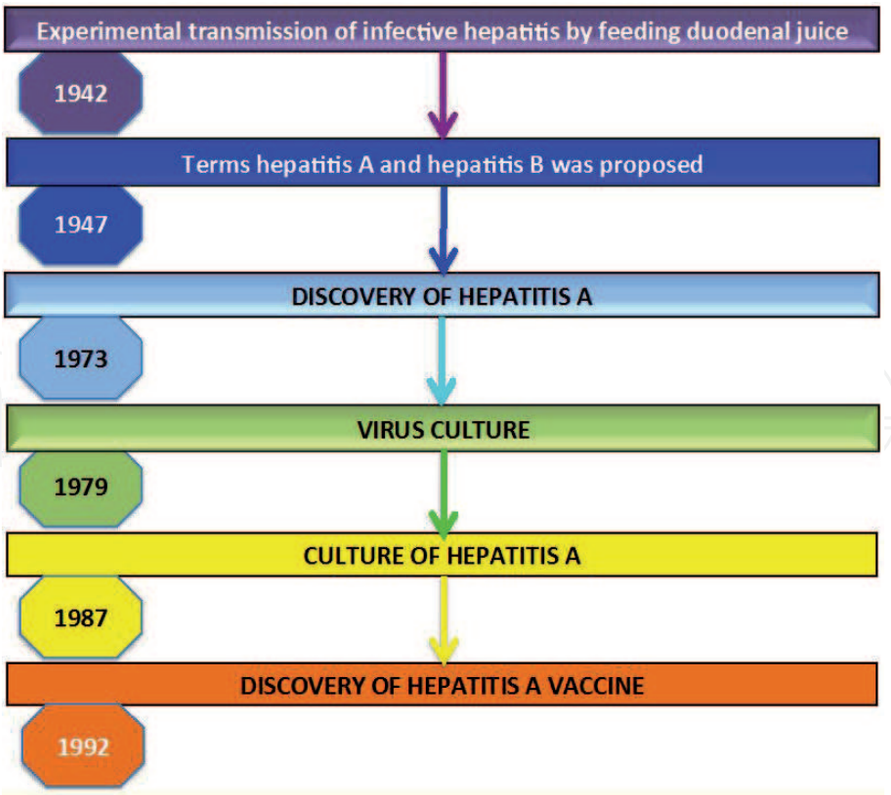

Figure 1.
The timeline of Hepatitis A virus.

investigation changed from serum to feces [6]. It was first seen under immune electron microscope in fecal suspension from infected Joliet prison inmates [3].

It was not until early 1900s that the mode of transmission of hepatitis A was identified [7, 8]. Although person-to-person contact was evident, the virus was thought to spread via droplet nuclei [9, 10]. Voegt successfully transmitted hepatitis A through duodenal juice. He published his findings in Munich Medical Weekly in 1942 [11]. Havens et al., at Yale University, United States of America, successfully transmitted jaundice by feeding serum and stool filtrate to 12 volunteers [12]. The differentiation between infectious hepatitis and serum jaundice was provided by a series of experiments carried out among mentally disabled residents at the Willowbrook State School, Staten Island [13]. While, it was MacCallum who proposed the terms hepatitis A and hepatitis B in the year 1947 [14]. The virus was first cultured in the year 1979 [15]. The viral genome was identified by reverse-transcriptase polymerase chain reaction. The cDNA copy was molecularly cloned. The RNA transcripts derived from cDNA clone proved infectious in cell cultures [16]. **Figure 1** depicts the timeline of Hepatitis A virus.

3. Hepatitis A virus – structure and mode of transmission

3.1 Structure

HAV is classified in the family Picornaviridae and genus Hepatovirus. HAV is a non-enveloped, 27- to 28-nm spherical virus with icosahedral symmetry. The virus contains a positive-sense, single stranded linear RNA. The 5′ end of the viral genome consists of a covalently bound protein termed VPg typical of picornaviridae. The viral genome consists of 60 copies each of its 3 major structural proteins, namely, VP1, VP2, and VP3 (1D, 1B, and 1C). Although a variety of genotypes

(genogroups I–VII) have been identified by analysis of genome sequences, the virus has a single serotype. Individual strains of HAV have differences at the molecular level that may be useful for epidemiologic studies; however, a high degree of identity in nucleic acid (as high as 90%) and amino acid sequence (as high as 98%) is generally seen between strains [17, 18].

3.2 Mode of transmission

3.2.1 Feco-oral

HAV is a common infectious etiology of acute hepatitis worldwide. It is most commonly transmitted through the feco-oral route. Although, HAV contamination of food material can occur anytime during cultivation/preparation/distribution, it occurs most commonly during food distribution due to infectious food handlers [19]. Virtually any food may be contaminated with the virus. HAV is relatively resistant to extremes of temperature and pH. Hepatitis A virus is omnipresent; it can perpetuate on environmental surfaces, hands of food handlers, sewage as well as in a variety of food products [20].

3.2.2 Parenteral

Rare reports of transfusion related hepatitis A have been published over the years. Transmission is via blood/blood products (Factor VIII and IX) collected from an infected donor during the phase of viremia [21–23].

3.2.3 Sexual transmission

Studies have found that people who engage in sex with casual partners, sex in gay saunas, oral-anal intercourse and household or sexual contact with acute hepatitis A (AHA) patients are at increased risk of HAV infection. Several reports of HAV infections have been reported among men who have sex with men (MSM) [24–28].

4. HAV vaccine – the holy grail

The discovery of hepatitis A virus, its propagation in cell culture and cloning of its genome culminated almost two decades later in the development and licensing of an effective vaccine [29, 30]. According to the WHO, the most effective way to prevent HAV infection is to improve sanitation and immunization. Gamma globulin was found to be effective in prevention of measles in susceptible household contacts in the year 1944 [31]. Joseph Stokes, a pediatrician working at the University of Pennsylvania School of Medicine, used the knowledge in curtailing hepatitis A outbreak among children by administering gamma globulins [32].

First HAV vaccine was developed in early 1900 [33, 34]. In 1991, a preliminary study was published among vaccinees, demonstrating neutralizing antibodies following the administration of formalin-inactivated vaccines [35]. Live attenuated hepatitis A vaccine was developed subsequently [36].

By 1992, the clinical efficacy of two formalin-inactivated hepatitis A vaccines HAVRIX (Smith-Kline Beecham) and VAQTA (Merck, Sharpe and Dohme) became obvious [30, 33]. Two laboratory-attenuated strains HM175 and CR326F respectively were used for vaccine production. The adverse reactions following vaccination were minimal, and seroconversion after two doses was found to be quite high (99.8%) [30]. Other monovalent formalin inactivated HAV vaccines available in market today

Vaccine	Virus strain	Route of administration	Adjuvant	HAV antigen dose / injection Pediatric	Adult	Manufacturer
I. Formalin inactivated						
1. HAVRIX	HM-175	i.m	Aluminium hydroxide	720 ELU	1440 ELU	GlaxoSmithKline
2. VAQTA	CR-326	i.m	Aluminium hydroxide	25U	50U	Merck, Sharpe and Dohme
3. AVAXIM	GBM	i.m	Aluminium hydroxide	80U	160 U	Aventis Pasteur
4. HEALIVE	TZ84	i.m	Aluminium hydroxide	250 U	500U	Sinovac Biotech Co LTd
5.Weisairuian	Lv-8	i.m	Aluminium hydroxide	320 ELU	640 ELU	Institute of Medical Biology of the
						Chinese Academy of Medical Sciences; Kunming
6.Veraxim	YN5	i.m	Aluminium hydroxide	800 ELU	1600 ELU	Shanghai Wison Bioengineering Inc
7. EPAXAL	RG-SB	i.m	Virosomes	24U	24U	Crucell/ Berna Biotech
8. TWINRIX	HM-175	i.m	HM-175	-	1 ml (720 ELU HAV+ 20μg HBsAg)	GlaxoSmithKline
II. Live attenuated						
1. Freeze-dried live HAV vaccine	H2	s.c	None	0.5 ml	1ml	Zhejiang Pukang Biotech company
2. HAVAC Freeze-dried live HAV vaccine	LA-1	s.c	None	-	1ml	Changchun Institute of Biologic Products

Table 1.
List of HAV vaccines available in market.

include AVAXIM (Aventis Pasteur), HEALIVE (Sinovac Biotech Co Ltd), Weisairuian (Institute of Medical Biology of the Chinese Academy of Medical Sciences; Kunming), Veraxim (Shanghai Wison Bioengineering Inc) and EPAXAL (Crucell/Berna Biotech). Hepatitis A vaccine is also available as a combined preparation with Hepatitis B vaccine in the form of TWINRIX (GlaxoSmithKline) **Table 1** [37–39].

The Food and Drug Administration (FDA) licensed HAVRIX in February 1995 for children (≥2 years), adults and travelers [34]. Centers for Disease Control and Prevention recommends vaccination for children 12 months or older, travelers to endemic countries, gays, illegal drug users, individuals with occupational risk exposure and chronic liver disease patients. The American College of Physicians too also recommends vaccination of high-risk groups [40].

In the United States, vaccination against hepatitis A is available as inactivated, monovalent vaccines (HAVRIX and VAQTA) or in combination with hepatitis B (TWINRIX). These vaccines are highly efficacious with seroconversion rates approaching 100% [41]. With the implementation of vaccination, the incidence of HAV in the United States has shown a drastic decline of 92% (12 cases per 100,000 in 1995 to 1 case per 100,000 in 2007) [42].

Among the developing nations, Indian Academy of Pediatrics (IAP) recommends two doses of vaccine for children (≥1 year). The recommended dose is 720 ELISA Units (ELU) for <19 years and 1440 ELU for ≥19 years. Protective antibody titers are seen in almost 100% vaccinees following the second dose [43]. No major adverse reactions have been associated with vaccine use.

CDC recommends vaccine instead of immunoglobulin for exposure to HAV in healthy individuals aged 1 to 40 years. Standard adult dosing recommends administration of two doses of the vaccine 6–12 months apart. For individuals 41 years and older, immunoglobulin administration is preferred due to the risk of more severe clinical presentation and limited evidence of vaccine efficacy in this age group. Immunoglobulins are also recommended for children less than 12 months, individuals with chronic liver disease, and immunocompromised patients [44–46].

5. HAV epidemiology – pre-vaccine era and the paradox of vaccine era

5.1 The pre-vaccine era

In the pre-vaccine era, hepatitis A occurred in cycles, every 10–15 years, with majority of cases reported among children (≤15 years) [47, 48]. Most cases (12–25%) of hepatitis A in the United States occurred as communitywide epidemics in which infection was transmitted from person to person among household or sexual contacts. International travel and foodborne outbreaks accounted for a small percentage of cases [49]. Asymptomatic infections among children played an important role in sustaining transmission. According to a survey conducted in the United States of America (1988–1994), a third of the population were sero-positive for anti-HAV IgG antibodies [50]. In the developing part of the world, majority of the population acquires asymptomatic hepatitis A infection early in life, such that large proportion of population is immune to HAV [51, 52].

HAV infection resulted in devastating consequences in susceptible populations. An outbreak in Shanghai, China in 1988 affecting over 300,000 people due to consumption raw clams represents an example of the magnitude problem in the pre-vaccine era [53].

5.2 The vaccine era

5.2.1 The world scenario – HAV sero-prevalence

WHO estimates that approximately 1.5 million people are infected with HAV each year [54]. The incidence of HAV in a given population correlates with socioeconomic properties such as income, density of housing, sanitation, and water quality. Endemic rates are high in developing countries with poor sanitation and hygiene practices. HAV endemicity is classified into low, intermediate, and high based on the sero-prevalence of anti-HAV IgG (<15%, 15–50% and >50%) [37]. High sero-prevalence reflects that majority of the population is immune to HAV [55]. HAV in children is usually asymptomatic, while frank hepatitis is seen when HAV infection occurs in adults. Since 1999 several countries including, southern Asia, Latin America, and Europe, have experienced a decline in the incidence of HAV infection due to improved sanitation and routine vaccination. This has resulted in a higher incidence of HAV infection among adult population [56–61]. The shift in age group, which acquires hepatitis A, towards adolescents and adults has amplified the incidence of symptomatic disease, since childhood HAV infection is usually asymptomatic [51, 52].

Since the availability of HAV vaccine, an overall increase in the incidence of reported HAV cases has been observed from European Union countries [62]. This points to new risks associated with globalization and population migration [62, 63]. According to a health survey conducted in the USA, a significant decrease in HAV immunity among adult population was noted between 1988–1994 and 1999–2006 [64]. The survey also demonstrated rise in the rate of hospitalization among HAV infected individuals, consequent to a higher percentage of symptomatic infection among adult population over the last decade [65]. This is known as the "paradox of hepatitis A risk" [55].

Prognosis of HAV is usually good among younger population, with low mortality rates (0.1%). The mortality rate increases proportionately with age, to as high as 2.1% among ≥40 years old [66]. In developing world, including Asia, Africa and South America, evidence of past infection is nearly universal. Juxtapose to this, infection rates are low in developed countries such as the United States, Canada, and Europe. High-risk groups in these regions comprise of injection drug users, homosexuals, people traveling to endemic regions, and among isolated communities such as nursing homes etc. [67].

In the USA, HAV outbreaks were common among illicit drug users in the pre-vaccine era. Drug users accounted for over 20% of all HAV cases as reported by the CDC during mid-1980s [68, 69]. Since 1999, with the implementation of routine HAV vaccination program, hepatitis A incidence has shown a steady decline until 2011 [70, 71]. The incidence has stabilized at an annual average of over a 1000 cases per year. Most cases were reported among international travelers returning from countries endemic for HAV [72].

In a sero-prevalence study conducted among military personals in France, Lagarde found the prevalence of HAV antibodies as 16.3% [73]. Another study conducted in Korea found the overall HAV sero-prevalence of 63.8% [74]. Japan has been conducting sero-prevalence studies over the years. The overall HAV sero-prevalence has dramatically decreased from 96.9% in 1973 to 96.9% in 1984 and 12.2% in 2003. Notably, the population susceptibility increased annually [75]. A sero-prevalence survey in Taiwan during 2009–2010 showed that only 10% of MSM aged 18–40 years in Taiwan had anti-HAV antibodies [76]. HAV vaccination program was implemented in Taiwan in 2016. Although this lead to decline in the frequencies of both human cases and positive sewage samples, no substantial increase in vaccination coverage was seen among high risk groups like MSM and HIV-infected patients [77].

Exposure to HAV is virtually universal before the age of 10 years in most developing countries [78]. In a study conducted in rural Liberia, an annual incidence of HAV was reported to be 45% among children aged 1–5 years [79]. In Indonesia, 95% of children, under the age of 10 years, were naturally immune to HAV infection [80]. Above-mentioned studies point towards the fact that, mass HAV vaccination might not be necessary in highly endemic regions.

In India, the sero-prevalence of anti-HAV antibodies exceeds 90% among adults [81]. However, there have been recent reports of a decreasing sero-prevalence across the country, paralleling with the industrialized world [82, 83]. Accordingly, HAV vaccination has been recommended for school children as well as adults [84]. Another study conducted among children found the age-related sero-prevalence of HAV to be 50.3% in the age group of 6–10 years and 30.3% among 18 months to 6 years of age. The HAV prevalence correlated strongly with the child's education and socioeconomic status [85]. In another Indian study, the HAV prevalence was found to be 97.2% [78]. These findings were in agreement with the expected pattern of HAV sero-prevalence in an area of high endemicity. Similar findings have been reported from other parts of the country as well [86–88].

About 90% of Indian children acquire protective antibodies against HAV by the age of 10 years. Similar patterns of endemicity have been found in other developing countries, with high sero-prevalence of anti-HAV antibodies [89]. Surveys conducted among children in Egypt have also reported almost 100% sero-prevalence rates [90].

Several studies from India have recently reported a significant sero-epidemiological shift, with increasing incidence of infection among adults and adolescents. Recently in New Delhi, anti-HAV antibody prevalence among adults was reported to be as low as 36.7% [82].

Chile and Jordan have reported a decrease in anti-HAV sero-prevalence over the years [89, 91]. The study conducted in Jordan showed a continual rise of the sero-prevalence rates with rise in age. While, sero-prevalence was 26% among <2 years old, the rate increased to a whooping 94% for >20 years old [91]. A study conducted in Western Brazil revealed overall sero-prevalence among children as 16.7% in the year 2011, which significantly increased to 70.45% in a recently conducted survey [52, 91]. This high prevalence might be attributed to disease outbreaks in few parts of the district of Gampaha.

5.2.2 HAV outbreaks over the last decade

Over the last 10 years, several outbreaks have been reported throughout the world **Table 2** and **Figure 2** [92–107].

Although feco-oral route has been implicated in most of the cases, sexual mode of transmission among high risk groups is the second most prevalent route of transmission [104, 105].

In 2016, about 2000 cases of HAV were reported in the United State [92]. CDC and FDA investigated two major HAV outbreaks due to consumption of contaminated foods (strawberries imported from Egypt and scallops from Philippines). The first outbreak affected 134 people, with two hospitalization while, the second outbreak affected 292 individuals with 94 hospitalizations [93, 94]. An HAV outbreak in California in 2017 encompassed homelessness individuals and illicit drug users with poor sanitation practices. The outbreak spread to several other states as well. A total of 694 individuals were infected, with 45 hospitalizations and 21 deaths [95].

A sizeable hepatitis A outbreak was reported in Australia in 2009, resulting in a 2-fold increase in the number of cases reported to the state health departments. Surveillance data suggested infection due to contaminated semidried tomatoes [96].

S. No.	Year	Geographical Location	No. of documented cases	Route of transmission	Source of infection
1.	2009	Autralia	Not specified	Feco-oral	Semi-dried tomatoes
2.	2010	London	5	Feco-oral	-
3	2011	Korea	16	Feco-oral	-
2.	2013	India (Lucknow)	267	Feco-oral	-
3.	2014	India (Mylapore village)	45	Feco-oral	Contaminated water
4.	2015	Taiwan	Not specified	Sexual	MSM
5.	2016	USA (9 states)	134	Feco-oral	Strawberries
6.	2016	USA (Hawaii)	292	Feco-oral	Scallops
7.	2016	Europe	Not specified	Sexual	MSM
8.	2016	India (Kerala)	223	Feco-oral	Food from newly opened hotel
9.	2017	USA (California)	694	?Feco-oral	Illicit drug users/homeless
10.	2018	Europe	163	? Feco-oral	Travel

Table 2.
Hepatitis A outbreaks around the world over the last decade.

Figure 2.
Hepatitis A outbreaks throughout the world over the last decade.

A total of 32 outbreaks of water/food-borne disease outbreaks were reported from Kerala, India alone, in the same year, involving 2421 cases. All these outbreaks were attributable to feco-oral route [97]. Around 223 hepatitis A cases were identified in a HAV outbreak in Kerala. Attack rate was found to be highest among the age group of 16–30 years (1.44%). Food/water from a newly opened hotel in the area was the possible source of the outbreak [101]. In another study, authors reported

HAV outbreak in the medical college area in Kottayam [100]. Another outbreak of acute hepatitis was reported from Mylapore village, Kollam district, southern India during February to June 2013. A total of 45 cases were affected, pipe water contamination from a bore well was identified as the source [101].

In a study conducted among acute viral hepatitis patients in North India, hepatitis A virus was identified as the most common etiological agent (26.96%) followed by hepatitis E virus [99].

Gassowski et al. reported two hepatitis A outbreaks in Europe. One affecting travelers returning from Morocco and the other among European residents without travel history. The outbreaks lasted from January to June 2018, affecting 163 patients in eight European countries. The HAV was genotypically identified as belonging to subgenotype IA DK2018-231 and subgenotype IB V18–16428. Common risk factor among the cases was found to be unvaccinated travel due to lack of awareness [102].

In July 2010, five cases of HAV infection were reported among the Orthodox Jewish (OJ) community in London, United Kingdom. Two of the cases gave history of travel to Israel for the same event a few days back. A total of 900 contacts of the cases were traced and vaccinated [106].

Cyclic outbreaks of HAV among high-risk groups (MSM and/ HIV) have been described in several reports. Outbreak strains among MSM across countries were found to be genetically alike and circulated for over a decade [104, 105]. In June 2015, a considerable increase in reports of AHA infection was noted in Taiwan mostly affected MSM and patients with HIV or other STI. The strain was later identified as TA-15 strain. In 2016, multi-country HAV outbreaks predominately affecting MSM were observed in Europe. The EuroPride strain (RIVM-HAV16–090) detected was genetically quite similar to the TA-15 strain identified earlier [87, 108]. A similar outbreak strain was also reported in the United States in 2017 [103], which suggests a global pattern of increased risk among susceptible male adults, with possible transmission through sexual contacts at MSM events.

6. Conclusion

HAV adversely affects the economy of a country by decreasing productivity of its citizens due to absenteeism from work, adding to medical costs and the effect on tourism. Improving sanitary conditions and providing clean drinking water are imperative pillars in curtailing spread of HAV. Simple method like hand hygiene is an effective way to prevent virus transmission. Vaccination forms the foundation in prevention of HAV. Both inactivated and live attenuated vaccines are licensed and available for use. Improved sanitation and vaccination although prevents Hepatitis A infection, it paradoxically increases the susceptibility of adult population towards a more symptomatic disease. This vicious cycle is the dilemma of HAV control and prevention program.

Conflict of interest

The authors declare no conflict of interest.

IntechOpen

Author details

Anita Chakravarti* and Tanisha Bharara
Department of Microbiology, Shree Gurugobind Singh Tricentenary University, Gurugram, Haryana, India

*Address all correspondence to: anitachakravarti@gmail.com

IntechOpen

References

[1] Trepo C. A brief history of hepatitis milestones. Liver International. 2014;**34**:29-37

[2] Zuckerman AJ. The history of viral hepatitis from antiquity to the present. In: Deinhardt F, Deinhardt J, editors. Viral Hepatitis: Laboratory and Clinical Science. New York: Marcel Dekker; 1983. pp. 3-32

[3] Feinstone SM, Kapikian AZ, Purcell RH. Hepatitis A: Detection by immune electron microscopy of a virus like antigen associated with acute illness. Science. 1973;**182**:1026-1028

[4] Gruber W, Virchow R. Occurrence and diagnosis of the hepatic, and in particular, the catarrhal icterus. Virchows Archiv. 1865;**32**:117-125

[5] McDonald S. Acute yellow atrophy of the liver. Edinburgh Medical Journal. 1907;**1**:83

[6] Feinstone SM. History of the discovery of hepatitis A virus. Cold Spring Harbor Perspectives in Medicine. 2019;**9**(5):9-22

[7] Cockayne EA. Catarrhal jaundice, sporadic and epidemic, and its relation to acute yellow atrophy of the liver. QJM: An International Journal of Medicine. 1912;**6**:1-29

[8] Willcox WH. The epidemic jaundice of campaigns. British Medical Journal. 1916;**1**:297-300

[9] Blumer G. Infectious jaundice in the United States. JAMA. 1923;**81**:353-358

[10] Cullinan ER. The epidemiology of jaundice. Proceedings of the Royal Society of Medicine. 1939;**32**:933-950

[11] Voegt H. Zur aetiologie der hepatitis epidemica. Munchener medizinische Wochenschrift. 1942;**89**:76-79

[12] Havens WP, Ward R, Drill VA, Paul JR. Experimental production of hepatitis by feeding icterogenic materials. Proceedings of the Society for Experimental Biology and Medicine. 1944;**57**:206-208

[13] Krugman S, Ward R, Giles JP. The natural history of infectious hepatitis. The American Journal of Medicine. 1962;**32**:717-728

[14] Anonymous.Homologous serum hepatitis. Lancet. 1947;**ii**:691-692

[15] Provost PJ, Hilleman MR. Propagation of human hepatitis A virus in cell culture *in vitro*. Proceedings of the Society for Experimental Biology and Medicine. 1979;**160**:213-221

[16] Cohen JI, Ticehurst JR, Feinstone SM, Rosenblum B, Purcell RH. Hepatitis A virus cDNA and its RNA transcripts are infectious in cell culture. Journal of Virology. 1987;**61**:3035-3039

[17] Nainan OV, Xia G, Vaughan G. Diagnosis of hepatitis A virus infection: A molecular approach. Clinical Microbiology Reviews. 2006;**19**:63-79

[18] Lemon SM, Jansen RW, Brown EA. Genetic, antigenic and bio- logical differences between strains of hepatitis A virus. Vaccine. 1992;**10**(1):40-44

[19] Acheson D, Fiore AE. Hepatitis A transmitted by food. Clinical Infectious Diseases. 2004;**38**(5):705-715

[20] Sattar SA, Jason T, Bidawid S, Farber J. Foodborne spread of hepatitis A: Recent studies on virus survival, transfer and inactivation. Canadian Journal of Infectious Diseases. 2000;**11**:159-163

[21] Mannucci PM, Gdovin S, Gringeri A. Transmission of hepatitis A to patients with hemophilia by factor VIII concentrates treated with organic solvent and detergent to inactivate viruses. The Italian collaborative group. Annals of Internal Medicine. 1994;**120**:1-7

[22] Lemon SM. The natural history of hepatitis A: The potential for transmission by transfusion of blood or blood products. Vox Sanguinis. 1994;**67**(4):19-23

[23] Soucie JM, Robertson BH, Bell BP. Hepatitis A virus infections associated with clotting factor concentrate in the United States. Transfusion. 1998;**38**:573-579

[24] Henning KJ, Bell E, Braun J, Barker ND. A community-wide outbreak of hepatitis A: Risk factors for infection among homosexual and bisexual men. The American Journal of Medicine. 1995;**99**(2):132-136

[25] Kuijpers LA, Kool JL, Veugelers PJ, Coutinho RA, Griensven GJ. An outbreak of hepatitis A among homosexual men in Amsterdam, 1991- 1993. International Journal of Epidemiology. 1995;**24**(1):218-222

[26] Bell A, Ncube F, Hansell A, Davison KL, Young Y, Gilson R, et al. An outbreak of hepatitis A among young men associated with having sex in public venues. Communicable Disease and Public Health. 2001;**4**(3):163-170

[27] Beebeejaun K, Degala S, Balogun K, Simms I, Woodhall SC, Heinsbroek E, et al. Outbreak of hepatitis A associated with men who have sex with men (MSM), England, July 2016 to January 2017. Euro Surveillance. 2017;**22**(5):304-354

[28] Mazick A, Howitz M, Rex S, Jensen IP, Weis N, Katzenstein TL, et al. Hepatitis A outbreak among MSM linked to casual sex and gay saunas in Copenhagen, Denmark. Eurosurveillance. 2005;**10**(5):536

[29] Maynard JE, Lorenz D, Bradley DW. Review of infectivity studies in nonhuman primates with virus-like particles associated with MS-1 hepatitis. The American Journal of the Medical Sciences. 1975;**270**:81-85

[30] Andre FE, D'Hondt E, Delem A. Clinical assessment of the safety and efficacy of an inactivated hepatitis A vaccine: Rationale and summary of findings. Vaccine. 1992;**10**(1):160-168

[31] Ordman CW, Jennings CG, Janeway CA. Chemical, clinical, and immunological studies on the products of human plasma fractionation. XII. Use of concentrated normal human serum gamma globulin (human immune serum globulin) in the prevention and attenuation of measles. Journal of Clinical Investigation. 1944;**23**:541-549

[32] Stokes J, Neefe JR. The prevention and attenuation of infectious hepatitis with gamma globulin (preliminary note). JAMA. 1945;**127**:144-145

[33] Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis a vaccine in healthy children. The New England Journal of Medicine. 1992;**327**:453-457

[34] Innis BL, Snitbhan R, Kunasol P, Laorakpongse T, Poopatanakool W, Kozik CA, et al. Protection against hepatitis A by an inactivated vaccine. JAMA. 1994;**271**:1328-1334

[35] Sjogren MH, Hoke CH, Binn LN, Eckels KH, Dubois DR, Lyde L, et al. Immunogenicity of an inactivated hepatitis A vaccine. Annals of Internal Medicine. 1991;**114**:470-471

[36] Midthun K, Ellerbeck E, Gershman K, Calandra G, Krah D,

Mc-Caughtry M, et al. Safety and immunogenicity of a live attenuated hepatitis A virus vaccine in seronegative volunteers. The Journal of Infectious Diseases. 1991;**163**:735-739

[37] Shouval D. The immunological basis for immunization series. In: Immunization Vaccines and Biologicals. Switzerland: World Health Organization Department of Immunization; 2010. p. 39

[38] Cui F, Liang X, Wang F, Zheng H, Hutin YJ, Yang W. Development, production, and postmarketing surveillance of hepatitis A vaccines in China. Journal of Epidemiology. 2014;**24**:169-177

[39] Sabanin IV, Rikhter VV, Kuzin SN. Assessment of effectiveness and immunogenicity of hepatitis A vaccination in servicemen of internal forces of Ministry of Internal Affairs of Russia. Zhurnal Mikrobiologii, Epidemiologii, i Immunobiologii. 2010;**1**:35-39

[40] Gardner P, Eickhoff T, Poland GA, Gross P, Griffin M, LaForce FM, et al. Adult immunizations. Annals of Internal Medicine. 1996;**124**:35-40

[41] Iorio N, John S. Hepatitis A NCBI Bookshelf. A Service of the National Library of Medicine, National Institutes of Health. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019

[42] Gingrich GA, Hadler SC, Elder HA. Serologic investigation of an outbreak of hepatitis A in a rural day-care cente. American Journal of Public Health. 1983;**73**:1190-1193

[43] Verma R, Khanna P. Hepatitis A vaccine should receive priority in National Immunization Schedule in India. Human Vaccines & Immunotherapeutics. 2012;**8**(8):1132-1134

[44] Waszczuk K, Waszczuk E, Szenborn L. Can we better protect patients with inflammatory bowel disease against infections patient attitude and personal immunization knowledge. Acta Gastroenterologica Belgica. 2018;**81**(2):257-261

[45] O'Leary ST, Kimberlin DW. Update from the advisory committee on immunization practices. Journal of the Pediatric Infectious Diseases Society. 2018;**7**(3):181-187

[46] Singh V, Crosby RA, Gratzer B, Gorbach PM, Markowitz LE, Meites E. Disclosure of sexual behavior is significantly associated with receiving a panel of health care services recommended for men who have sex with men. Sexually Transmitted Diseases. 2018;**45**(12):803-807

[47] Groseclose SL, Brathwaite WS, Hall PA, Adams DA, Connor FJ, Sharp P, et al. Centers for Disease Control and Prevention. Summary of notifiable diseases, United States, 2000. MMWR Morbidity and Mortality Weekly Report. 2002;**49**:1-102

[48] Centers for Disease Control and Prevention. Hepatitis Surveil- lance Report No. 58. Atlanta; 2003

[49] Wasley A, Feinstone SM, Bell BP. Hepatitis A. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 7th ed. Philadelphia: Churchill Livingstone; 2011. pp. 2367-2387

[50] Bell BP, Kruszon-Moran D, Shapiro CN. Hepatitis a virus infection in the United States: Serologic results from the third National Health and nutrition examination survey. Vaccine. 2005;**23**:5793-5806

[51] Mathur P, Arora N. Epidemiological transition of hepatitis A in India: Issues for vaccination in developing countries. Indian Journal of Medical Research. 2008;**128**(6):699-704

[52] Mantovani SAS, Delfino BM, Martins AC, Oliart-Guzmán H, Pereira TM, Branco FLCC, et al. Socioeconomic inequities and hepatitis A virus infection in Western Brazilian Amazonian children: Spatial distribution and associated factors. BMC Infectious Diseases. 2015;**15**(1):428

[53] Cooksley WG. What did we learn from the Shanghai hepatitis A epidemic? Journal of Viral Hepatitis. 2000;7(1):1-3

[54] World Health Organization. Hepatitis A Fact sheet No. 328. Available from: http://www.searo.who.int/thailand/factsheets/fs0030/en/ [Accessed: 31 July 2019]

[55] Mohd Hanafiah K, Jacobsen KH, Wiersma ST. Challenges to mapping the health risk of hepatitis A virus infection. International Journal of Health Geographics. 2011;**10**:57

[56] Barzaga BN. Hepatitis a, shifting epidemiology in South-East Asia and in China. Vaccine. 2000;**18**(1):61-64

[57] Poovorawan Y, Theamboonlers A, Sinalaparatsamee S, Chaiear K, Siraprapasiri T, Khwanjaipanich S, et al. Increasing susceptibility to HAV among members of the young generation in Thailand. Asian Pacific Journal of Allergy and Immunology. 2000;**18**:249-253

[58] Tanaka J. Hepatitis a shifting epidemiology in Latin America. Vaccine. 2000;**18**(1):57-60

[59] Sohn YM, Rho HO, Park MS. The changing epidemiology of hepatitis A in children and the consideration of active immunisation in Korea. Yonsei Medical Journal. 2000;**41**:34-39

[60] Dal-Re R, Garcia-Corberia P, Garcia-de-Lomas J. A large percentage of the Spanish population under 30 years of age is not protected against hepatitis A. Journal of Medical Virology. 2000;**60**:363-366

[61] Gdalvich M, Grotto I, Mandel Y, Mimouni D, Sherman J, Ashkenezi I. Hepatitis A antibody prevalence among young adults in Israel, the decline continues. Epidemiology and Infection. 1998;**1221**:477-479

[62] European Centre for Disease Prevention and Control. Annual Epidemiological Report Hepatitis A. Available from: https://ecdc.europa.eu/en/publications-data/hepatitis-annual-epidemiological-report-2016 [Accessed: 31 July 2019]

[63] Gozlan Y, Bar-Or I, Rakovsky A. Ongoing hepatitis A among men who have sex with men (MSM) linked to outbreaks in Europe in Tel Aviv area, Israel, December 2016–June 2017. Euro Surveillance. 2017;**22**:30575

[64] Klevens RM, Kruszon-Moran D, Wasley A. Seroprevalence of hepatitis A virus antibodies in the U.S.: Results from the National Health and nutrition examination survey. Public Health Reports. 2011;**126**:522-532

[65] Ly KN, Klevens RM. Trends in disease and complications of hepatitis A virus infection in the United States, 1999-2011: A new concern for adults. The Journal of Infectious Diseases. 2015;**212**:176-182

[66] Ariyarathna N, Abeysena C. Seroprevalence of viral hepatitis A in a district of Sri Lanka: A community based cross-sectional study. BMC Infectious Diseases. 2019;**19**:443

[67] Tan EM, Marcelin JR, Virk A. Pretravel counseling for immunocompromised travelers: A 12year singlecenter retrospective review. Infection, Disease & Health. 2019;**24**(1):13-22

[68] CDC. Viral hepatitis surveillance Atlanta, GA: US Department of

Health and Human Service. Available from: https://www.cdc.gov/hepatitis/statistics/2016surveillance/pdfs/2016HepSurveillanceRpt.pdf [Accessed: 01 August 2019]

[69] CDC. Hepatitis surveillance: Report no. 55. Atlanta, GA: US Department of Health and Human. Available from: Service https://babel.hathitrust.org/cgi/pt?id=mdp.39015026224173;view=1up;seq=24 [Accessed: 01 August]

[70] Groseclose SL, Brathwaite WS, Hall PA, Adams DA, Connor FJ, Sharp P, et al. Centers for Disease Control Prevention. Summary of notifiable diseases, United States. MMWR Morbidity and Mortality Weekly Report. 2002;**49**:1-102

[71] Wasley A, Grytdal S, Gallagher K. Surveillance for acute viral hepatitis—United States, 2006. MMWR Surveillance Summaries. 2008;**57**:1-24

[72] Centers for Disease Control Prevention. Viral hepatitis surveillance, United States 2016. Atlanta, GA: US Department of Health and Human Services, CDC. Available from: https://www.cdc.gov/hepatitis/statistics/2016surveillance/pdfs/2016HepSurveillanceRpt.pdf [Accessed: 01 August 2019]

[73] Lagarde E, Joussemet M, Lataillade J, Fabre G. Risk factors for hepatitis A infection in France: Drinking tap water may be of importance. European Journal of Epidemiology. 1995;**11**(2):145-148

[74] Yun H, Lee HJ, Yoon Y, Kim K, Kim S, Shin MH, et al. Seroprevalence of hepatitis-antibodies in relation to social factors, a preliminary study. Osong Public Health and Research Perspectives. 2012;**3**(1):31-35

[75] Kiyohara T, Sato T, Totsuka A, Miyamura T, Ito T, Yoneyama T. Shifting Seroepidemiology of hepatitis A in Japan, 1973-2003. Microbiology and Immunology. 2007;**51**(2):185-191

[76] Tseng YT, Sun HY, Chang SY, Wu CH, Liu WC, Wu PY, et al. Seroprevalence of hepatitis virus infection in men who have sex with men aged 18-40 years in Taiwan. Journal of the Formosan Medical Association. 2012;**111**(8):431-438

[77] Lee YL, Lin KY, Cheng CY, Li CW, Yang CJ, Tsai MS, et al. Taiwan HIV study group. Evolution of hepatitis A virus seroprevalence among HIV-positive adults in Taiwan. PLoS One. 2017;**12**(10):e0186338. DOI: 10.1371/journal.pone.0186338

[78] Battegay M, Gust ID, Feinstone SM. Hepatitis A virus. In: Mandel JL, Bennett JE, editors. Principles and Practices of Infectious Diseases. New York: Churchill Livingstone; 1995. pp. 1636-1656

[79] Prince AM, Brotman B, Richardson L, White T, Pollock N, Riddle J. Incidence of hepatitis A virus (HAV) infection in rural Liberia. Journal of Medical Virology. 1985;**15**:421-428

[80] Brown P, Greguer G, Smallwood L, Ney R, Moerdowo RM, Gerety RJ. Serological markers of hepatitis A and B in the population of Bali, Indonesia. American Journal of Tropical Medicine and Hygiene. 1985;**34**:616-619

[81] Tandon BN, Gandhi BM, Joshi YK. Etiological spectrum of viral hepatitis and prevalence of markers of hepatitis A and B virus in northern India. Bulletin of the World Health Organization. 1984;**62**:67-73

[82] Das K, Jain A, Gupta S, Kapoor S, Gupta RK, Chakravorty A, et al. The changing epidemiological pattern of hepatitis A virus in an urban population in India: Emergence of a trend similar to

European countries. European Journal of Epidemiology. 2000;**16**:507-510

[83] Dhawan PS, Shah SS, Alvares JF, Kher A, Shankaran KPW, et al. Seroprevalence of hepatitis A virus in Mumbai and immunogenicity and safety of hepatitis A vaccine. Indian Journal of Gastroenterology. 1998;**17**:16-18

[84] Das K, Kar P, Chakarborty A, Gupta S, Das BC. Is a vaccination programme against hepatitis A needed in India? Indian Journal of Gastroenterology. 1998;**17**:158

[85] Arankalle V, Mitra M, Bhave S. Changing epidemiology of hepatitis A virus in Indian children. Dovepress. 2014;**4**:7-13

[86] Aggarwal R, Naik S, Yachha SK, Naik SR. Seroprevalence of antibodies to the hepatitis A virus among children in northern India. Indian Paediatrics. 1999;**36**:1248-1250

[87] Freidl GS, Sonder GJ, Bovée LP, Friesema IH, van Rijckevorsel GG, Ruijs WL, et al. Hepatitis A outbreak among men who have sex with men (MSM) predominantly linked with the EuroPride, the Netherlands, July 2016 to February 2017. Euro Surveillance. 2017;**22**(8):30468

[88] Acharya SK, Batra Y, Bhatkal B. Seroepidemiology of hepatitis A virus infection among school children in Delhi and north Indian patients with chronic liver disease: Implications for HAV vaccination. Journal of Gastroenterology and Hepatology. 2003;**18**(7):822-827

[89] Fix AD, Martin OS, Gallicchio L, Vial PA, Lagos R. Age-specific prevalence of antibodies to hepatitis A in Santiago, Chile: Risk factors and shift in age of infection among children and young adults. The American Journal of Tropical Medicine and Hygiene. 2002;**66**(5):628-632

[90] Acharya SK, Madan K, Dattagupta S, Panda SK. Viral hepatitis in India. National Medical Journal of India. 2006;**19**(4):203-217

[91] Hayajneh WA, Balbeesi A, Faouri S. Hepatitis A virus age-specific sero- prevalence and risk factors among Jordanian children. Journal of Medical Virology. 2015;**87**(4):569-574

[92] Centers for Disease Control and Prevention. Morbidity and Mortality Weekly Report (MMWR). Provisional cases of selected notifiable diseases, and selected low frequency diseases, United States and U.S. territories, weeks ending November 11, 2017, and November 12, 2016. Available from: www.cdc.gov/mmwr/volumes/66/wr/mm6645md.htm [Accessed: 01 August 2019]

[93] Centers for Disease Control and Prevention. Viral hepatitis: 2016–Multistate outbreak of hepatitis A linked to frozen strawberries (final update). Available from: www.cdc.gov/hepatitis/outbreaks/2016/hav-strawberries.htm [Accessed: 28 July 2019]

[94] State of Hawaii, Department of Health: Disease Outbreak Control Division. Hepatitis A outbreak 2016. Available from: http://health.hawaii.gov/docd/hepatitis-a-outbreak-2016 [Accessed: 28 July 2019]

[95] California Department of Public Health. Hepatitis A outbreak in California. 2018. Available from: www.cdph.ca.gov/Programs/CID/DCDC/Pages/Immunization/Hepatitis-A-Outbreak.aspx [Accessed: 28 July 2019]

[96] Donnan EJ, Fielding JE, Gregory JE, Lalor K, Rowe S, Goldsmith P, et al. A multistate outbreak of hepatitis A associated with semidried tomatoes in

Australia. Clinical Infectious Diseases. 2012;**54**:775-781

[97] Integrated Disease Surveillance Project. Recent Weekly Outbreak. Available from: http://www.idsp.nic.in/index4.php?lang=1&level=0&linkid=406&lid=3689 [Last Accessed: 01 August 2019]

[98] Rakesh PS, Mainu TT, Raj A, Babu D, Rajiv M, Sreelakshmi K, et al. Investigating a community wide outbreak of hepatitis A in Kerala, India. Journal of Family Medicine and Primary Care. 2018;**7**:1537-1541

[99] Jain P, Prakash S, Gupta S. Prevalence of hepatitis A virus, hepatitis B virus, hepatitis C virus, hepatitis D virus and hepatitis E virus as causes of acute viral hepatitis in North India: A hospital based study. Indian Journal of Medical Microbiology. 2013;**31**(3):261-265

[100] Arankalle VA, Sarada Devi KL, Lole KS, Shenoy KT, Verma V, Haneephabi M. Molecular characterization of hepatitis A virus from a large outbreak from Kerala, India. Indian Journal of Medical Research. 2006;**123**(6):760-769

[101] Rakesh PS, Sherin D, Sankar H, Shaji M, Subhagan S, Salila S. Investigating a community-wide outbreak of hepatitis A in India. Journal of Global Infectious Diseases. 2014;**6**(2):59-64

[102] Gassowski M, Michaelis K, Wenzel JJ, Faber M, Figoni J, Mouna L, et al. Two concurrent outbreaks of hepatitis A highlight the risk of infection for non-immune travellers to Morocco, January to June 2018. Euro Surveillance. 2018;**5**(27):1-5

[103] Latash J, Dorsinville M, Del Rosso P, Antwi M, Reddy V, Waechter H, et al. Notes from the eld: increase in reported hepatitis a infections among men who have sex with men - New York City, January-August 2017. MMWR Morbidity and Mortality Weekly Report. 2017;**66**(37):999-1000. DOI: 10.15585/mmwr.mm6637a7

[104] Urbanus AT, van Houdt R, van de Laar TJ, Coutinho RA. Viral hepatitis among men who have sex with men, epidemiology and public health consequences. Euro Surveillance. 2009;**14**(47):19-21

[105] Stene-Johansen K, Tjon G, Schreier E, Bremer V, Bruisten S, Ngui SL, et al. Molecular epidemiological studies show that hepatitis A virus is endemic among active homosexual men in Europe. Journal of Medical Virology. 2007;**79**(4):356-365

[106] Edelstein M, Turbitt D, Balogun K, Figueroa J, Nixon G. Hepatitis A outbreak in an orthodox Jewish community in London, July 2010. Eurosurveillance. 2010;**15**(37):19662

[107] Lim HS, Choi K, Lee S. Epidemiological investigation of an outbreak of hepatitis A at a residential facility for the disabled. Journal of Preventive Medicine and Public Health. 2013;**46**(2):62-73

[108] European Centre for Disease Prevention and Control (ECDC). Rapid risk assessment: Hepatitis A outbreak in the EU/EEA mostly affecting men who have sex with men. Available from: https://ecdc.europa.eu/en/publications-data/rapid-risk-assessment-hepatitis-outbreak-eueea-mostly-affecting-men-who-have-sex [Accessed: 28 July 2019]