

## Hepatitis A virus

Hepatitis A virus (HAV) infects the liver, with disease characterised by liver inflammation and the development of jaundice. HAV infection can be asymptomatic (no clinical symptoms), mild, or lead to severe illness in those with underlying liver disease. Hepatitis A is endemic in many developing countries, while in developed countries sporadic cases occur.

### Description of the organism

HAV belongs to the Picornaviridae family of viruses and the genus *Hepatovirus*. The *Picornaviridae* family consists of small (25–28 nm) non-enveloped viruses which are generally more robust and survive better in the environment compared to enveloped viruses, such as herpes simplex virus. HAV particles consist of a single strand of RNA contained within an icosahedral shaped protein shell (Schoub 2003; Cook and Rzezutka 2006; Rozenberg et al. 2011).

HAV has one known serotype and six genotypes (I–VI). Genotypes I–III have been associated with human illness, while genotypes IV–VI are found in Old World monkeys. Genotypes I–III are further divided into A and B. The majority of human strains of HAV belong to genotype I or III (Hollinger and Emerson 2007; FDA 2012). Isolates from a particular HAV outbreak are usually of the same genotype (Normann et al. 2008).

### Growth and survival characteristics

HAV requires specific living cells (host cells) in order to replicate. This means that the level of HAV in contaminated food will not increase during processing, transport or storage (Koopmans and Duizer 2004). While not able to replicate outside the host, HAV has been shown to survive in the environment for extended periods of time (Schoub 2003; Cook and Rzezutka 2006). The survival of HAV is influenced by environmental factors such as temperature, pH, chemicals and food composition.

It has been demonstrated that under conditions simulating typical environmental exposure, HAV remains infectious after being dried and stored for 30 days (McCaustland et al. 1982). HAV has also been shown to survive on various non-porous surfaces such as aluminium, china and latex for 60 days, however, it does not survive as well on porous materials (Abad et al. 1994). A study by Mbithi et al. (1992) demonstrated that HAV survives and remains infectious on human hands after 4 hours and can be transferred between hands and inanimate surfaces.

HAV has been shown to survive in fresh river water, seawater, groundwater and untreated tap water (Enriquez et al. 1995; Rzezutka and Cook 2004; Cook and Rzezutka 2006). However, without a standard protocol to determine virus survival it is difficult to compare the survival time of the virus in different environments. An investigation by Arnal et al. (1998) using artificial sterile seawater contaminated with HAV demonstrated that the genetic material of HAV was stable and remained in the water for 232 days, although no infectious HAV particles were detected by 35 days. In general, survival of HAV in water is enhanced at low temperatures (<4°C) (Rzezutka and Cook 2004).

Croci et al. (2002) demonstrated that when fresh produce was stored at 4°C, HAV survived and remained infective on: carrots for 4 days, fennel for 7 days and on lettuce for the study duration of 9 days. The differing survival rates observed on fresh produce may be due to the difference in surface texture of the produce and the presence of anti-viral substances. Shieh et al. (2009) showed that when spinach was stored at 5.4°C a 1 log<sub>10</sub> reduction in the level of

HAV occurred over a 28.6 day period. These studies imply that HAV can persist under normal domestic storage conditions for extended periods of time.

Chemical and physical factors can affect the heat resistance of HAV. Deboose et al. (2004) investigated the inactivation of HAV in strawberry puree and found that increasing the sucrose concentration resulted in increased heat resistance of HAV. Conversely, lowering the pH was found to decrease the heat resistance of HAV. Changing the calcium concentration had no effect. Bidawid et al. (2000b) demonstrated that increases in fat content also increased the heat resistance of HAV. Dairy products with higher fat content required longer times of exposure to heat than lower fat products to achieve the same level of HAV reduction.

HAV has been found to be resistant to temperatures up to 60°C. The temperature at which 50% of HAV particles disintegrate and release their viral RNA is 61°C (10 minutes). When stabilised by 1 mol/L MgCl<sub>2</sub>, 50% disintegration of HAV occurs at 81°C (Hollinger and Emerson 2007). In food, complete inactivation of HAV has been observed in shellfish when heated to 85°C for 3 minutes or 95°C for 2 minutes (Millard et al. 1987). These conditions are known to inactivate HAV in shellfish while maintaining a commercially acceptable product (Appleton 2000). For milk and cream, heating to 85°C for 30 seconds is sufficient to cause a 5 log<sub>10</sub> reduction in HAV titre (Bidawid et al. 2000b).

Low temperature has little effect on HAV survival. Butot et al. (2008) showed that frozen storage of HAV contaminated berries and herbs had little effect on HAV survival over the study period of 3 months.

HAV is highly resistant to acidic conditions and solvents. Scholz et al. (1989) demonstrated that at pH 1 (24°C) HAV retained high infectivity after 2 hours and was still infectious after 5 hours. Under conditions that simulate the acidity of the human stomach (38°C, pH 1) HAV remained infectious for 90 minutes. Also, being a non-enveloped virus, HAV is resistant to solvents such as 20% ether and chloroform (ether destroys the envelop of some viruses) (Hollinger and Emerson 2007).

## Symptoms of disease

HAV infection often causes mild illness in humans, or results in no clinical disease at all. In children this is particularly common, with most children under 6 years of age showing no symptoms (asymptomatic infection) (FDA 2012). For those individuals in which clinical disease occurs, initial symptoms include sudden onset of fever, nausea, anorexia, malaise, vomiting, diarrhoea, abdominal pain, myalgia (muscular pain) and headache. The initial symptoms tend to abate with the onset of jaundice (yellowing of the skin and eyes and a browning of urine due to stimulation of bile pigment production) and pale clay coloured stools. Children with symptomatic infection usually develop flu-like symptoms without jaundice (Brundage and Fitzpatrick 2006; Hollinger and Emerson 2007; FDA 2012).

Most patients show complete recovery from symptoms within 3–6 months of the onset of illness. The fatality rate for HAV is approximately 2.4%, with death more likely to occur in the elderly. Acute liver failure due to severe HAV infection has been reported in children; however, it is more frequent in middle-aged and older people and those with underlying chronic liver disease. Acute liver failure is also a rare complication of HAV infection during pregnancy (Koff 1998; FDA 2012).

The incubation period before onset of disease is 15–50 days (mean time of 30 days) (FDA 2012). HAV is shed in the faeces of infected individuals for up to 2 weeks before the onset of illness. HAV is present in the blood at the same time as viral shedding starts occurring. The virus disappears from the blood shortly after symptoms of disease start, while faecal

shedding of the virus continues for another 2 weeks (Cook and Rzezutka 2006; Hollinger and Emerson 2007).

In 3–20% of cases relapses occur, generally with milder symptoms and HAV being shed in the faeces. Multiple relapses can occur (Hollinger and Emerson 2007).

### **Virulence and infectivity**

The target organ of HAV is the liver. HAV is initially ingested, infects the intestinal tract and is then transported to the liver via the bloodstream. In the liver, HAV attaches to receptors on the surface of the hepatocytes, enters these cells and replicates. Replication of HAV within the hepatocytes is not believed to result in immediate cell damage; this is thought to occur subsequent to replication and release of the virus. The host's immune response is responsible for destroying the HAV infected cells. As a consequence of this pathological damage the liver becomes inflamed (WHO 2000; Schoub 2003; Cook and Rzezutka 2006). Released viral particles enter the bile duct and pass into the gastrointestinal tract to be shed in the faeces (Cook and Rzezutka 2006). The resistance of HAV to inactivation by bile and intestinal proteolytic enzymes allows the virus to be shed in the faeces and facilitates faecal-oral transmission (Koff 1998).

### **Mode of transmission**

HAV is transmitted via the faecal-oral route by either person-to-person contact or consumption of contaminated food or water (Guillois-Becel et al. 2009). Person-to-person transmission can involve young children with unrecognised HAV infection (asymptomatic infection) (Brundage and Fitzpatrick 2006).

In contrast to person-to-person transmission, outbreaks of HAV infections usually result from faecal contamination of a single source of food or water. Foods may become contaminated in their growing areas (e.g. shellfish), or during irrigation (e.g. crops), usually by coming into contact with sewage polluted water. Food can also be contaminated by infected food handlers. Infected food handlers may contaminate foods directly or contaminate surfaces on which foods are prepared. A major issue with infected food handlers is that they are often unaware they constitute a hazard, as most of the faecal shedding of HAV occurs prior to the onset of clinical symptoms (Cook and Rzezutka 2006; Hollinger and Emerson 2007). Food establishments with poor sanitary conditions and inadequate treatment and/or disposal of human waste (sewage), along with unsatisfactory manufacturing practices may also contribute to food contamination (Sattar et al. 2000).

Travel to areas in which HAV is endemic from low prevalence areas is known to be a risk factor for HAV infection. The likelihood of becoming infected with HAV depends on local hygienic and sanitary conditions, which vary from country to country (Koff 1998). In 2010, 55.1% of HAV cases reported in Australia were acquired overseas (OzFoodNet 2012).

HAV transmission through blood and blood products is rare. While HAV is present in the blood of infected individuals, this is only for approximately a 2 week period. However, post-transfusion HAV infection has occurred, as have outbreaks of HAV in haemophiliacs who received contaminated blood plasma-derived factor VIII concentrate (Mannucci et al. 1994; Hollinger and Emerson 2007).

## Incidence of illness and outbreak data

HAV has a worldwide distribution; however, the prevalence of infection is related to the quality of the water supply, level of sanitation and the age of the individual when infected. In most developing countries, where HAV infection is endemic, the majority of people are infected in early childhood and virtually all adults are immune. In developed countries, HAV infections are less common due to improved sanitation. As a result very few people are infected in early childhood and the majority of adults remain susceptible to infection. Hence in developed countries the risk of epidemics and the occurrence of severe disease may increase as the majority of people infected during an outbreak would be adults (children are often asymptomatic) (Conaty et al. 2000; Issa and Mourad 2001; Koopmans and Duizer 2004).

Hepatitis A is a notifiable disease in all Australian states and territories. The incidence of HAV infection notified in Australia in 2012 was 0.7 cases per 100,000 population (164 cases). This was a decrease from the previous 5 year mean of 1.3 cases per 100,000 population per year (ranging from 0.6–2.6 cases per 100,000 population per year) (NNDSS 2013).

In north Queensland in 1996–1999 the average annual HAV notification rates in Indigenous and non-Indigenous people were 110 and 25 cases per 100,000 population, respectively. In 1999 a HAV vaccination program for Indigenous children in north Queensland was introduced. Consequently, in 2000–2003 the average annual HAV notification rates for Indigenous and non-Indigenous people were 4 and 2.5 cases per 100,000 population, respectively (Hanna et al. 2004). HAV is now included as part of the National Immunisation Program Schedule for Aboriginal and Torres Strait Islander children younger than 5 years of age living in Queensland, the Northern Territory, Western Australia and South Australia (DOHA 2011). HAV vaccination is also recommended for travellers to endemic areas and those at increased risk because of lifestyle or occupation (DOHA 2008).

The notification rate for HAV in New Zealand in 2011 was 0.6 cases per 100,000 population (26 cases), which was a decrease from the 2010 rate of 1.1 cases per 100,000 population (Lim et al. 2012). The incidence of HAV in the United States (US) has declined from 12 cases per 100,000 population in 1995 to 0.54 cases per 100,000 population in 2010. This reduction has followed the 1999 recommendation for routine vaccination of children in areas of the US with consistently elevated rates of HAV (CDC 2009; CDC 2012). In the European Union there was one strong evidence foodborne HAV outbreak in 2011 and also one in 2010 (EFSA 2012; EFSA 2013).

Foodborne outbreaks of HAV have been recognised for over 40 years, but are infrequently reported. This is because the 2–6 week incubation period for HAV makes it more difficult to associate the source of infection with a particular food (Appleton 2000).

Cold cuts and sandwiches, fruits and fruit juices, milk and milk products, vegetables, salads, shellfish and iced drinks have been implicated in HAV outbreaks (FDA 2012) (refer to Table 1).

**Table 1:** Selected major foodborne outbreaks associated with HAV (>50 cases and/or ≥1 fatality)

Year	No. cases (fatalities)	Food	Country	Comments	Reference
2009-2010	392 (1)	Semi-dried tomatoes	Australia	Imported product from endemic HAV countries likely source of contamination. Semi-dried tomatoes contaminated with the identical HAV strain associated with illness in the Netherlands	(OzFoodNet 2010; Donnan et al. 2012)
2004	351	Orange juice	Egypt	Significant hygiene problems at the production plant; no heat treatment of the finished product	(Frank et al. 2007)
2004	269	Raw beef	Belgium	Infected food handler identified at the meat distribution plant	(Robesyn et al. 2009)
2003	601 (3)	Green onions	US	Green onions contaminated before or during packing on the farm in Mexico	(Wheeler et al. 2005)
1997	444	Oysters	Australia	The lake from which the oysters were harvested was polluted by sewage from a local town and boats	(Conaty et al. 2000)
1997	254	Frozen strawberries	US	Consumption of items from school cafeterias containing frozen strawberries was associated with HAV infection	(Hutin et al. 1999)
1996	5620	Raw seafood	Italy		(Lopalco et al. 1997)
1988	300,000+ (47)	Raw clams	China		(Cooksley 2000)

### Occurrence in food

The types of food most often implicated in HAV outbreaks are those that are either eaten raw or only slightly cooked (e.g. shellfish), or handled extensively prior to consumption (e.g. the picking and packing of raw produce in the field and the preparation of sandwiches and salads) (Koopmans and Duizer 2004; Cook and Rzezutka 2006).

Bivalve molluscs (e.g. oysters, mussels, clams and cockles) live in shallow, coastal and estuarine waters which can be polluted with human sewage. As filter feeders they collect nutrients by filtering particulate matter from the water. If molluscs are grown in water contaminated with human faeces, the molluscs can collect and concentrate HAV from the water (Appleton 2000; Moore 2001; Cook and Rzezutka 2006). HAV has been shown to be concentrated within mussels to 100-fold higher concentrations than the surrounding water and can persist for about 7 days in the mussels (Enriquez et al. 1992). HAV has been detected in oyster samples more than 2 months after the presumed contamination event; this is thought to be due to recontamination of the oysters from sediment in the water (Conaty et al. 2000).

The prevalence of HAV reported in shellfish ranges between 6–27%, depending on the location and analytical technique used. For mussels sampled from markets of major cities in south Italy, 15.6% were found to be contaminated with infectious HAV (n=180) (Croci et al. 2003). For shellfish (clams, mussels, scallops and oysters) collected from the north Adriatic sea located between the Italian and Balkan peninsulas, HAV was detected in 6% of samples (n=235) (Croci et al. 2007). For shellfish collected off the coast of Spain (cultured and wild mussels, wild clams and cockles), HAV was detected in 27.4% of samples (n=164) (Romalde et al. 2002). The methods utilised in these studies detect the genetic material of HAV and some methods are more sensitive than others under different conditions. This suggests that the level of HAV contamination could be higher than reported.

Hernandez et al. (1997) demonstrated that 20% of pooled samples of lettuce wash water collected in Costa Rica were contaminated with HAV (n=10 pools, 5 lettuces per pool), suggesting that lettuces from this region could be a vehicle for HAV transmission.

### Host factors that influence disease

People of all ages are susceptible to HAV infection (unless they have had a previous infection or vaccination). The disease is milder in young children under 6 years, with the risk of fatality increasing with age. Thus the risks are higher for unexposed older people (ESR 2001; FDA 2012).

A single HAV infection or administration of the HAV vaccine provides lifelong immunity for the individual against the virus (Leon and Moe 2006). When an outbreak of HAV occurs, if exposure can be recognised before cases begin to occur, treatment with intramuscular immunoglobulin (passive immunisation) within 2 weeks of exposure is >85% effective at preventing HAV infection. However, passive immunisation is only effective for a short time (3–6 months) and people will be susceptible to infection from another exposure (Issa and Mourad 2001; Hollinger and Emerson 2007).

### Dose response

The number of HAV particles required to cause infection is not known, however, it is presumed to be 10–100 viral particles (FDA 2012). In fact it has been suggested that a single ingested viral particle may cause infection, however, the probability of this occurring is very low (Cliver 1985). It has been estimated that up to 13,000 infectious HAV particles may be present in 1 mg of faeces (Bidawid et al. 2000a).

### Recommended reading and useful links

Cook N, Rzezutka A (2006) Hepatitis viruses. Ch 11 In: Motarjemi Y, Adams M (eds) *Emerging Foodborne Pathogens*. Woodhead Publishing, Cambridge, p. 282-308

FDA (2012) *Bad bug book: Foodborne pathogenic microorganisms and natural toxins handbook*, 2nd ed, US Food and Drug Administration, Silver Spring, p. 154–158.

<http://www.fda.gov/Food/FoodborneIllnessContaminants/CausesOfIllnessBadBugBook/ucm2006773.htm>

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Last updated May 2013 (minor editorial updates in April 2018)