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REVIEW

# Increasing Burden of Hepatitis A in Adolescents and Adults and the Need for Long-Term Protection: A Review from the Indian Subcontinent

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**Abstract**: Hepatitis A, an acute inflammatory liver disease caused by hepatitis A virus (HAV) infection from close contact with infected people, is highly endemic in the Indian subcontinent. Due to poor sanitary conditions, most of the population is exposed to the virus in childhood. At this age, the disease is asymptomatic and provides life-long protection against the disease. Due to rapid socioeconomic development in some areas, however, pockets of the population are reaching adolescence/adulthood without prior exposure to the virus and are thus susceptible to infection. At these ages, infection carries a higher risk of symptomatic disease and complications including mortality. This review of epidemiology and burden of disease studies in the Indian subcontinent, published since 2005, shows increasing evidence of a shift from high to intermediate endemicity in high-income—typically urban—populations. The prevalence of anti-HAV antibodies (previously reported at > 90%) is lower now in adolescents and young adults (e.g., around 80% in Bangladesh and 55% in 5–15 years in India). As a result, HAV is responsible for more acute viral hepatitis predominantly in this age group (e.g., > 15 years: 3.4% in 1999 to 12.3% in 2003 or high socioeconomic status 13–20 years: 27% in 1999 to 62% in 2003), with a greater clinical and economic burden. Numerous outbreaks due to HAV have been reported [e.g., Sri Lanka (2009–2010): > 13,000 affected; Kashmir (2015–2017): 12 outbreaks; Kerala (2012–2016): 84 outbreaks] from water or food contamination. Due to current shifts in endemicity, a growing proportion of the population is no longer exposed in childhood. As the disease remains highly endemic, it also provides a source for more severe disease in susceptible people at an older age and for outbreaks. Well-tolerated and effective vaccines are available and help prevent disease burden and provide long-term protection. These should now be used more widely to protect more patients from the growing disease burden of hepatitis A.
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***Plain Language Summary***: Plain language summary available for this article—please see Fig. 1 and the following link: https://doi.org/10.6084/m9.figshare.9963044.


**Fig. 1** Plain Language Summary. Highlights the context of the article, the endemicity shift and the burden of hepatitis A in adolescents and adults and steps to be taken to address the impact of this disease

**Keywords:** Adolescent; Adult; Asia; Burden; Cost; Epidemiology; Hepatitis A; India; Seroprevalence; Vaccination

**Key Summary Points**

This literature review provides an update of the epidemiology and burden of hepatitis A in adolescents and adults in the Indian subcontinent since 2005

There is a shift from high to intermediate hepatitis A endemicity, evident from the decreasing numbers of adolescents and young adults with prior exposure and from the increasing numbers of infections (immunoglobulin G and M prevalence, respectively)

Hepatitis A remains highly endemic in rural areas and is a potential source of infection and outbreaks in the growing pockets of susceptible populations

There are more complications, hospitalizations and deaths in adolescents and adults than in children

There is a need for long-term protection, which can be achieved through available effective and well-tolerated hepatitis A vaccination

## INTRODUCTION

Hepatitis A virus (HAV) accounts for most acute viral hepatitis (AVH) globally, with around 1.5 million clinical cases each year and a rate of infection likely to be ten times higher because of underreporting [1]. The Global Burden of Disease study estimated that acute hepatitis A infections increased by 4.2% between 2005 and 2015 (from 109.6 to 114.2 million cases) [2].

Hepatitis A, an acute self-limiting inflammatory disease of the liver, is typically asymptomatic in children, while symptomatic infection including jaundice is common in adolescents and adults. Clinical disease can be severe, leading to acute liver failure [ALF, or fulminant hepatic failure (FHF)] and death in some cases, with severity strongly age-dependent [1, 3]. As affected individuals can take weeks or months to recover, there is an impact on ability to go to work or school and on quality of life, which can have important economic and social consequences in communities [4].

The incidence of hepatitis A is associated with socioeconomic status, sanitation and lack of access to safe drinking water [1, 5]. Low endemicity regions are high-income countries with good sanitation and hygienic conditions (infection rates are low, i.e., $< 50\%$ by age 30 years). Due to poor sanitary conditions and access to clean water, most of the population in developing countries is infected in early childhood (i.e., seroprevalence up to about 90% in children), classifying the regions as highly endemic [1, 6]. In some countries, like India, parts of the populations have recently undergone rapid socioeconomic development, which may have an impact on endemicity shift and the resulting burden of disease [1].

Many seroepidemiologic studies and reviews of hepatitis A exist up to the early 2000s; however, there is a lack of recent data to assess the endemicity level and its impact in older age groups. A fresh look at the up-to-date epidemiology of HAV in this older age group, including its complications, is warranted. This is to assess the potential shift in endemicity and increased risk of HAV infection and also the need for enhanced prevention strategies (e.g., vaccination) in the Indian subcontinent.

### HAV and its Important Features

HAV is a nonenveloped single-stranded ribonucleic acid virus belonging to the genus *Hepatovirus* of the *Picornaviridae* family. A single HAV serotype exists. Thus, HAV infection in any part of the world results in protection from reinfection globally [7], and so does vaccination. [8].

Transmission is via close contact with an infected person, primarily via the fecal-oral route or ingestion of contaminated food or

water [9]. The virus can survive in contaminated media for months as it remains stable and is resistant to acid, heat (60 °C for 60 min) and freezing environments [8, 10].

Following oral ingestion, the virus may enter the gut mucosa and replicate in intestinal cells, after which it reaches the liver via the portal blood. Here, viral replication occurs in hepatocytes; viral progeny is released into bile where it reaches the intestines and is shed in feces, weeks before the onset of symptoms. The mechanism of hepatocyte injury is thought to be immune mediated [1, 8, 9]. The average incubation period is around 30 days (range 15–50 days), with signs and symptoms appearing within 3–5 weeks of exposure [8, 10]. HAV viremia is followed by shedding in feces, increases in serum alanine aminotransferase level, a short-term increase in immunoglobulin (Ig) M antibody level and a gradual long-term increase in IgG antibody response (Fig. 2) [10].

## METHODS

A comprehensive literature review was conducted to identify studies on the seroepidemiology and burden of hepatitis A in the Indian subcontinent countries (India, Bangladesh, Nepal, Pakistan, Sri Lanka, Bhutan and Maldives). PubMed and Embase databases and the Cochrane Library were searched in April 2019. Search terms were combined to identify (1) seroprevalence of hepatitis A, (2) outbreaks of hepatitis A and (3) burden (complications, hospitalization, mortality and costs) of acute liver failure. The following keywords were used in PubMed: ((((((((((“complications” [Subheading]) OR “Hospitalization”[Mesh]) OR “Mortality”[Mesh]) OR “Economics”[Mesh]) OR “Cost of Illness”[Mesh])) AND “Liver Failure, Acute”[Mesh])) OR ((seroprevalence) AND ((((“Seroepidemiologic Studies”[Mesh]) OR “Global Burden of Disease”[Mesh]) OR “Disease Outbreaks”[Mesh]) OR “Epidemiology”[Mesh]))) AND ((“Hepatitis”[Mesh]) OR “Hepatitis A”[Mesh])) AND (((((((“India”[Mesh]) OR “Bangladesh”[Mesh]) OR “Nepal”[Mesh]) OR “Pakistan”[Mesh]) OR “Sri Lanka”[Mesh]) OR “Bhutan”[Mesh]) OR “Maldives”[Mesh]).

The search identified 335 publications. Titles and abstracts were screened for studies with data on hepatitis A in adolescents and adults on the outcomes of interest above. Reviews and vaccination studies were excluded. Publications from 2005 onwards were included. This cutoff was selected to provide an update of the large amount of data available up to the early 2000s and because recent epidemiologic data are more relevant to healthcare policy and decision-making. Full-text articles selected during screening were reviewed, and reference lists were hand-searched for additional publications of interest. There were 38 publications included in this review: 19 on seroprevalence, 10 on

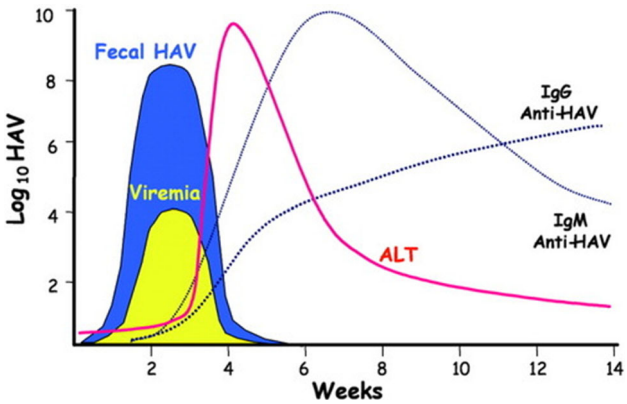


**Fig. 2** Hepatitis A infection processes over time (reproduced with permission from Martin and Lemon [10]). *ALT* alanine aminotransferase, *HAV* hepatitis A virus, *IgG anti-HAV* anti-HAV immunoglobulin G, *IgM anti-HAV* anti-HAV immunoglobulin M

outbreaks, 10 on clinical burden and 1 on economic burden.

### Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies performed by any of the authors with human participants or animals.

## RESULTS

### Seroprevalence of HAV Infection

There were 14 seroprevalence studies from India [11–24], 2 from Bangladesh [25, 26] and 1 from Pakistan [27], Sri Lanka [28] and Nepal [29] (Table 1, Table S1). The studies assessed seroprevalence of HAV antibodies (IgG and/or IgM) in healthy subjects and/or patients presenting with AVH symptoms.

In India, HAV was the most common etiology in adolescents and adults [18]. In one of the studies it was also much more common than hepatitis E infection [20]. A hospital-based study in jaundice patients (mean age 30 years) in Nepal found most of the cases were hepatitis E virus (HEV, 69.2%) and HAV (15.3%) induced [29]. Surveillance data collected between 2014 and 2017 from across India found 12.6% of suspected viral hepatitis cases were due to HAV. Among children and adolescents, most cases (29.5% and 17.9%) were caused by HAV. The majority of the cases were in the southern region (22.4%), and higher HAV positivity rates were found during the monsoon season [23]. The incidence of HAV-induced AVH increased significantly in children, adolescents and adults with time from 1999 to 2003 (Fig. 3) [11, 12]. Also, it was found that HAV-induced infections had decreased in < 5 years (75%) and increased in 6–15 years (70.8%) [15]. The pattern of decreased HAV infection in children and increased infection in adolescents and/or adults was also found in Uttar Pradesh and Rajasthan [14, 17]. In a study from Pakistan, 25% of HAV-induced AVH cases were seen in > 12 years [27]. HAV infection was the etiology in 31.2% of Indian adults with AVH or chronic or alcoholic liver disease [16]. In a study of newly diagnosed cirrhotic patients who were not vaccinated (mean age: 55.8 years) from Sri Lanka, 58% were seronegative for anti-HAV IgG and therefore susceptible [28]. In contrast, only one cross-sectional survey of healthy military trainees (mean age: 19.9 years, not vaccinated) from across India found high levels of immunity to HAV in which the majority (78.5%) of study participants were from rural areas [22].

#### *Seroprevalence in Urban vs. Rural and Based on Socioeconomic Status*

HAV exposure was also significantly different across the various study populations [urban vs. rural: 31.8% vs. 55.3%, $p = 0.005$; high/middle socioeconomic status (SES) vs. low SES: 33.3% vs. 53.9%, $p = 0.022$; family size 3–5 vs. ≥ 6: 31.6% vs. 59.1%, $p < 0.001$] [19]. A study from Pune ($N = 1065$ serum samples) found that in high SES subjects, there was a significant increase in anti-HAV positivity, while in the lower middle SES group, a significant decrease (6–25 years, $p < 0.0001$) was recorded compared with 1998 data [24]. Among healthy adult blood donors, HAV exposure was significantly lower for subjects with high vs. middle SES (89.0% vs. 95.9%, $p < 0.01$) [21]. Furthermore, two large studies from Bangladesh also compared seroprevalence in urban and rural populations and by SES. The first study ($N = 465$) found significantly lower HAV seroprevalence in urban vs. rural populations (73.3% vs. 82.2%, $p < 0.05$) as well as in urban high SES vs. urban low SES populations (68.8 vs. 79.7%, $p < 0.05$). The 11–15-year urban high SES group had the lowest seroprevalence (72.3%) compared with the urban low SES (100%) and rural (90%) groups [25]. The second study ($N = 818$) found similar trends: HAV exposure was highest in the rural lower-middle SES group (seroprevalence 96.5%) and lowest in the high SES group (49.8%); exposure among school children was lowest in urban high SES (43.0%) compared with urban low SES (76.2%) and rural (96.5%) schools ($p < 0.01$) [26].

**Table 1** Summary of data related to HAV seroprevalence in adolescents/adults

| Region, source | Study period | *N* | Subjects | Age | IgM + %(*n*) | IgG + %(*n*) |
|---|---|---|---|---|---|---|
| India [18] | 2003–2004 | 224 | AVH | Overall | 33 (74) | |
| | | | | 11–20 years | 47.3 (35) | |
| | | | | 21–30 years | 40.5 (30) | |
| | | | | 31–40 years | 4.1 (3) | |
| India [20] | 2-year study before 2014 | 958 | AVH | 11–30 years, mostly | 19.3 | |
| Nepal [29] | 2014 | 52 | AVH | Overall | 15.3 (8) | |
| India [23] | 2014–2017 | 24,000 | Suspected AVH | Overall | 12.6 (3017) | |
| | | 5060 | | ≤ 9 years | 29.5 (1493) | |
| | | 3552 | | 10–19 years | 17.9 (636) | |
| | | 12,602 | | ≥ 20 years | 5.0 (636) | |
| India [11] | 1999–2003 | 500 | Healthy controls | Overall | | 71 (356) |
| | | | | > 35 years vs. < 35 years | | 92 vs. 57 |
| | | 1932 | AVH | Overall | 11.4 (221) | |
| | | | | In 1999 | 6.0 (20) | |
| | | | | In 2003 | 15.8 (82) | |
| | | | | In 1999 > 15 years | 3.4 (7) | |
| | | | | In 2003 > 15 years | 12.3 (40) | |
| India [12] | 1999–2004 | 550 | AVH | 13–20 years | 48.0 (60) | |
| | | | | 21–30 years | 30.7 (40) | |
| | | | | > 30 years | 9.6 (15) | |
| India [13] | 2006–2009 | 370 | LD (AVH) | – | 8.1 (6) | |
| India [15] | 2014 | 89 | AVH | Overall | 33.7 (30) | |
| | | | | 6–15 years | 70.8 (17) | |
| | | | | 16–40 years | 8.7 (4) | |

**Table 1** continued

| Region, source | Study period | *N* | Subjects | Age | IgM + %(*n*) | IgG + %(*n*) |
|---|---|---|---|---|---|---|
| India [14] | 2011–2012 | 267 | AVH | Overall | 27.0 (72) | |
| | | | | Children | 27.3 (39) | |
| | | | | Adults | 26.6 (33) | |
| India [17] | 2015 | 1654 | AVH | Overall | 7.7 (127) | |
| | | | | 11–20 years | 45.6 (58) | |
| | | | | 21–30 years | 18.1 (23) | |
| | | | | 31–40 years | 3.1 (4) | |
| | | | | 41–50 years | 2.3 (3) | |
| | | | | > 50 years | 21.5 (2) | |
| Pakistan [27] | 2003–2004 | 626 | AVH | 3–27 years | 40.6 (252) | |
| India [16] | 2012–2015 | 285 | LD | 41.3 years | 31.2 (89) | |
| Sri Lanka [28] | 2013–2014 | 135 | Cirrhosis | 55.8 years | | 42.0 (45) |
| India [22] | 2010–2011 | 4175 | Healthy trainees | Overall | | 92.68 (3683) |
| India [19] | 2006–2008 | 142 | Hospital and school | 5–15 years | | 54.5 (36) |
| India [21] | 2002 vs. 2004–2005 | 1145 | Healthy volunteers | Overall | | 96.5 (689) vs. 92.1 (388) |
| | | | | 18–25 years | | 90.3 (306) vs. 90.6 (183) |
| | | | | > 25 years | | 99.5 (383) vs. 93.6 (205) |
| Bangladesh [25] | 2005 | 465 | Outpatients and healthy volunteers | 11–15 years | | 80.4 (82)[a] |
| | | | | 16–20 years | | 98.5 (64)[a] |
| | | | | 21–25 years | | 100 (60)[a] |

**Table 1** continued

| Region, source | Study period | *N* | Subjects | Age | IgM + %(*n*) | IgG + %(*n*) |
|---|---|---|---|---|---|---|
| Bangladesh [26] | 2005–2006 | 818 | Patients and school children | Overall | | 69.6 (569)[a] |
| | | | | 11–20 years | | 79.8 (217)[a] |
| | | | | 21–30 years | | 91.0 (70)[a] |

*AVH* acute viral hepatitis, *Ig* immunoglobulin, *LD* liver diseases, *N* number of subjects, *n* number of seropositive subjects, *y* year

[a] Combined IgG and IgM

## Clinical Presentation and Complications of HAV Infection

### *Clinical Presentation*

Typical clinical presentation, including adolescent and adult cases, was reported in detail in five studies, from India [18, 30, 31], Pakistan [32] and Sri Lanka [33]. All of these studies reported patients with jaundice (80–100%), abdominal pain (26–82%) and fever (45–91%). Other common symptoms included nausea/vomiting, dark urine, anorexia and fatigue. The studies in older age groups reported high rates of hepatomegaly (73–100%), and a high rate of splenomegaly was reported in a small subgroup of adolescents (86%) (Fig. 4).

In a prospective study of HAV IgM-positive subjects with jaundice, 62 had AVH (mean age: 22 years) and 7 had FHF (mean age: 29 years). More males than females had HAV infection [34]. The duration of illness for HAV-induced AVH in the majority of patients (74.3%) was 1–4 weeks as seen from a study at a military hospital in Southern India [18].

Also, in a study of 221 HAV-induced AVH patients (mean age: 20.5 years), 96.3% of patients took 4–10 weeks from the onset of jaundice to recover, 18 patients (8.3%) developed ALF, of which 3 died, and the rest recovered within 16 weeks [11].

### *Complications and Deaths*

Complications following hepatitis A infection seen in the literature are acute renal injury, FHF, ALF, relapsing hepatitis A, gall bladder wall thickening, acute-on-chronic liver failure (ACLF), gastrointestinal bleeding, intracerebral bleeding, hypoglycemia, encephalopathy, acute liver cell failure, prolonged cholestasis, coagulopathy, ascites, thrombocytopenia, pleural effusion, congestive heart failure, higher creatinine levels, increased hospital stay and mortality.

In a prospective study ($N = 224$ AVH, mean age: 22.5 years) of 74 cases of HAV-induced AVH, there was 1 patient with ALF, 4 patients with relapsing hepatitis A and 2 patients with gall bladder wall thickening [18]. Data collected over the 1999–2004 period in a tertiary care

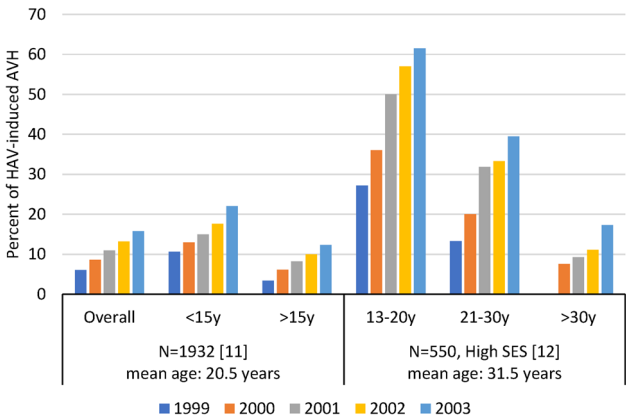


**Fig. 3** HAV-induced AVH (%) over time. *AVH* acute viral hepatitis, *HAV* hepatitis A virus; *N* number of subjects, *SES* socioeconomic status

hospital in Northern India showed that HAV-induced ALF in adults increased when compared with earlier studies (22.2% vs. 4–6%) [12]. In a retrospective study of patients > 12 years, 14.5% ($n$ = 33/228) had complications: most common was acute renal injury ($n$ = 17) and FHF ($n$ = 4). Patients with complications had significantly higher mean creatinine values (3.28 vs. 1.12) and mean international normalized ratios (2.46 vs. 1.43) than patients with no complications ($p < 0.05$). Mortality (21.2%, $n$ = 7) occurred only among patients aged 20–-40 years [35]. Another study of AVH in children ≤ 15 years (N = 138) found only the 10–15-year group (5.8%, $n$ = 8/22) had complications [gastrointestinal bleeding, intracerebral bleeding and hypoglycemia in one child each, grade I encephalopathy in two children, acute liver cell failure in four children and prolonged cholestasis (> 12 weeks) in three children] [30]. A study from Eastern India reported the following complications in adolescents ($n$ = 10 aged 10–14 years): coagulopathy ($n$ = 4), ascites ($n$ = 3), two cases each of thrombocytopenia, gall bladder wall thickening and pleural effusion, and one case of congestive heart failure [36]. In a study conducted in Pakistan including 185 acute hepatitis A patients (26% > 16 years), FHF occurred in a comparable number of < 15 and > 15 year olds (2% vs. 3%, respectively) and required longer hospital stays (9 days compared with 2.9 without FHF; mean length of stay). The hospitalization rate was significantly higher for > 15 year olds (45% vs. 24% in < 15 years, $p < 0.006$) [32].

Acute hepatitis A is also known to cause severe complications such as ACLF in patients with cirrhosis. In a study of 3220 cirrhosis patients (mean age: 36.3 years), 121 cases of ACLF were reported of which 27.2% were HAV induced. ACLF was also associated with a high 3-month mortality rate (44.6%) [37].

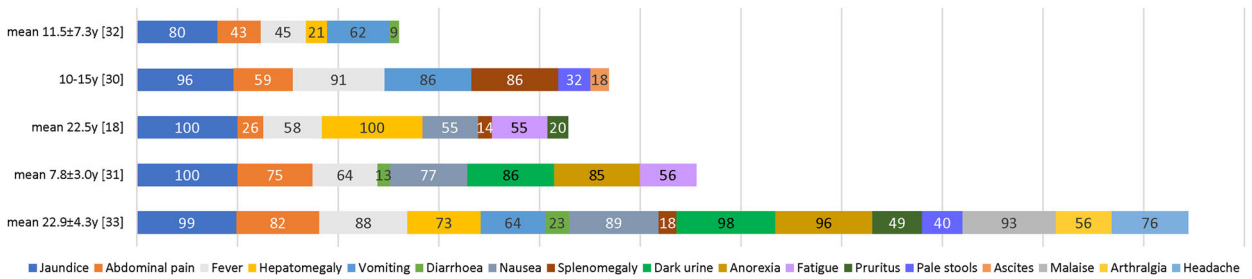


**Fig. 4** Clinical signs and symptoms reported (%) among adolescents/adults in Indian subcontinent. *y* years

### HAV Outbreaks

Several HAV outbreaks were reported across India between 2004 and 2017 [4, 31, 38–43] as well as one in Sri Lanka in 2009–2010 [33, 44] (Table S2). It was noted that men were more affected as were adolescents and young adults (16–30 years, 142 cases) [42, 43]. The highest attack rate was found among 15–24 year olds followed by 5–14 year olds [41]. Most of these outbreaks were caused by water contamination or food contamination from a hotel.

In an outbreak in Pune due to HAV in a susceptible population from the middle SES group, the overall attack rate was 55.8%. This was highest among 5–10-year-old (65.8%) children, higher than for children < 5 years (44.5%; $p < 0.001$) and comparable to the 11–15-year-old group ($p = 0.064$) [31]. In the same year, another outbreak due to water contamination was reported in adults in Kerala, Southern India. Of the 540 cases in a medical college hospital area, HAV infection was confirmed in 87% ($n = 248/285$) of patients and 39% ($n = 52/132$) of medical staff and students for whom serum samples were available. HAV was predominant among 18–20 year olds (42.5%) followed by 21–25 year olds (41.4%), 36–52 year olds (25.0%) and 26–35 year olds (20.0%). Two deaths were also reported among adults [40]. Many more HAV outbreaks were reported in Kerala between 2012 and 2016: in total, 84 outbreaks of which 2 involved > 100 people, 13 involved > 50 people and 49 involved > 20 people, with 22 deaths reported in 2015–2016 [43, 45]. In Kashmir, India, 23 outbreaks were reported between 2015 and 2017, of which 12 were due to HAV [38]. In Punjab, India, in 2011, there was an outbreak due to hepatitis E (primarily), in which nine cases were due to HAV and five to HAV and HEV co-infection. Half of the patients with HAV infection were > 20 years old compared with 17.5% of those with HEV infection [39]. A large outbreak of HAV infection ($N = 13,477$ cases) was reported in Sri Lanka in 2009, primarily in the Northern Province following civil war, which included the community and a displaced persons camp ($n = 5245$) and armed forces in the area ($n = 6622$) [44].

#### *Economic Burden of Hepatitis A Infection*

Following multiple outbreaks in Kerala, and with an average 8268 suspected cases per year, mostly affecting 15–35 year olds, one study assessed the out-of-pocket cost of hepatitis A to households in 2015 [46]. Of the 95 patients with confirmed hepatitis A interviewed, 83.2% were admitted to the hospital for 7.6 days on average and lost a median of 60 working days (range 21–180 days). The total estimated mean cost for the household due to one person with hepatitis A was 24,775 rupees (95% confidence interval: 19,426–30,123) (364 US dollars) [46].

## DISCUSSION

This review article intended to document the current status of hepatitis A epidemiology in the Indian subcontinent. The review of the epidemiology studies identified suggested a changing trend in endemicity, with more susceptible adolescents/adults than previously seen in these countries [1, 9]. As a result, higher HAV infection rates were observed in these age groups and more outbreaks than in the past (although outbreak reporting could be the result of better surveillance). The first AVH outbreak due to HAV was seen in Kerala in 2004, while previous outbreaks were due to HEV infection [40]. Another study in South India reported that HAV was responsible for more AVH than HEV among young adults [20]. It was a significant cause of AVH predominantly in young people in Pakistan [27] and in India [15–18, 20]. An increasing trend of HAV infection rates between 1999 and 2003 in both adolescent and adults in India suggests fewer children were naturally infected than before [11]. Economic progress and improvements in water supply and sanitation were likely reasons for the decrease in HAV exposure seen in some groups such as those with higher SES or living in urban areas [12, 19, 21, 25, 26]. Only two studies found levels of natural infection (and thus protection) remained high by adolescence. One was in Bangladesh, although the authors identified significant differences between urban and rural and between high and low SES groups'

seroprevalence during childhood, suggesting changes beginning in some groups [25]. The other was a study in military trainees in India where most subjects (79%) were from rural areas [22]. In other studies comparing urban and rural seroprevalence, significantly higher exposure was found in rural areas [19, 25, 26]. Therefore, there appears to be growing pockets of susceptible populations who are potentially at high risk of infection and frequent outbreaks from the rural populations where hepatitis A is still highly endemic.

Furthermore, the literature makes evident that the older age groups could present with more hepatomegaly [18, 32, 33], splenomegaly [18, 30, 33] and acute renal injury [35]. The recovery time in most cases without complications was 4–10 weeks and for acute liver failure 16 weeks [11] with extended hospital stays [32]. Deaths have been reported in young adults with HAV-induced AVH [11, 35] as well as in outbreaks [4, 40]. HAV-induced ACLF was also associated with high mortality [37].

This review provides a much needed update to document the changing situation in the Indian subcontinent and to inform policymakers about the increasing evidence that a shift in HAV endemicity is taking place in different subgroups, particularly among high SES urban populations. In 2005, Argentina was transitioning from high to intermediate endemicity, resulting in an increase in the hepatitis A burden of disease. Universal childhood vaccination was introduced, achieving high and sustained coverage. As a result, the incidence of hepatitis A decreased by nearly 90% in all age groups with no cases of FHF or liver transplants recorded up to 6 years later. The vaccination program was found to be cost-effective with one dose of inactivated vaccine. Subsequently, the World Health Organization recommended HAV universal mass vaccination (UMV) in countries where endemicity was shifting from high to intermediate levels, following epidemiology and cost-effectiveness considerations [8]. Very few countries have implemented UMV to date; however, individual protection through targeting at-risk persons is an effective interim alternative. While cost is perceived as a barrier to vaccination, the economic burden of hepatitis A to a household in India was significant at nearly 25,000 rupees due to out-of-pocket payments for medical care as well as lost wages and caregiver expenses [46].

### Necessity for Long-Term Protection?

Hepatitis A infection in early childhood, typical in high endemicity countries, provides long-term natural immunity. This review has identified a growing number of studies suggesting a shift from high to intermediate endemicity in the populations studied, with a reduction in HAV exposure in childhood, increases in outbreaks and clinical HAV-induced AVH predominantly found in adolescents and adults. Infection in these age groups is more severe with an impact on ability to work/study and an economic impact on the household. Considering these health and societal implications, there is a need to protect individuals belonging to these groups of the population.

Improving sanitation and providing access to safe drinking water will help to reduce HAV transmission [47]; however, many people in this region do not have access to safe drinking water. Some authors have proposed screening and vaccinating only those who are seronegative. For example, Hussain et al. [11] proposed screening 15 year olds and vaccinating those susceptible. Sharma et al. [16] also proposed vaccination after screening. Khanna et al. [12] and Gadgil et al. [21] proposed targeting children from high SES groups for vaccination as many remain susceptible to infection. One of the risks associated with this strategy is that the patient could be lost and not return for a follow-up visit, in which case the opportunity for vaccination in early childhood is lost. Second, India is characterized by heterogeneity, with pockets of susceptible and exposed groups and some regions with rapid developments in hygiene and living standards. Infectious diseases affect individuals irrespective of their economic status, as also seen in this review. Also, previous screening programs, for example, Papanicolaou (PAP) smears for the prevention of cervical cancer, have been unsuccessful in achieving high coverage [48]. The costs and lack

of facilities and infrastructure are also likely to make screening for HAV seroprevalence challenging on a large scale in these countries. Most vaccination programs in the region are in children, with low awareness of adolescent and adult vaccines. Childhood vaccination, therefore, provides an opportunity to offer long-term protection against hepatitis A.

Well-tolerated, highly immunogenic and effective HAV inactivated and live vaccines are available [1, 49–53]. Contrary to the belief that the immune response to an inactivated vaccine is mostly humoral with little or no cellular immunity, protein-based inactivated HAV vaccines have been able to demonstrate both humoral and cell-mediated immune responses [54, 55]. The resultant effect of this is long-term protection, as demonstrated by seroprotection of up to 40 years using a modeling study [56]. Similarly, for live vaccines, this effect has been demonstrated for up to 17 years [57]. Furthermore, evidence from infectious diseases where live vaccines are used (e.g., measles, mumps and varicella) suggests multiple doses are recommended for adequate protection. The nature of inactivated vaccines allows their use in immunocompromised subjects [51], for post-exposure prophylaxis [58] and for outbreak control as well [53].

## CONCLUSIONS

This review has highlighted the recent changes in the hepatitis A epidemiology and burden of disease in the Indian subcontinent, with a shift in epidemiology, especially in particular pockets of the population, leading to more serious hepatitis A cases in susceptible adolescents and adults. This new situation renders vaccination of individuals belonging to these groups of the population even more important than before. Further sanitation, and eventually, universal hepatitis A vaccination introduction, will contribute to lowering the burden of hepatitis A disease by protecting more patients in the Indian subcontinent.

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