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Review

# Changing sero-epidemiology of hepatitis A in Asia Pacific countries: A systematic review

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ABSTRACT

*Objectives:* Hepatitis A is a viral liver disease whose prevalence is associated with low socio-economic and hygiene levels due to its faecal–oral transmission. Severity increases with age, and immunity is life-long. Decreased endemicity could result in increased age and severity of cases. A literature review was conducted to describe changes in age-stratified hepatitis A seroprevalence in Asia Pacific countries from 1980 to 2016, and to identify gaps in the literature. The PRISMA guidelines were followed.
*Methods:* The PubMed database was searched for studies on age-specific hepatitis A seroprevalence in 17 Asia Pacific countries. All studies published in the English language, reporting human hepatitis A seroprevalence levels in any age group, were included.
*Results:* Seventy-three publications from 11 countries were identified. A trend of increasing age at first exposure over time was observed, particularly in developed countries such as Japan, Taiwan, Thailand, and Korea, suggesting a transition in terms of endemicity.
*Conclusions:* Extensive gaps in the literature were identified between countries and year of publication, indicating the need for further research. Decreasing hepatitis A exposure and thus immunity conferred during childhood, may render older populations susceptible to infection. The public health and economic value of vaccination against hepatitis A should be assessed within this changing epidemiological context.


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## Introduction

Hepatitis A is a viral liver disease caused by the hepatitis A virus (HAV), a virus of the family *Picornaviridae*, genus *Hepatovirus* (Melnick, 1992). HAV is transmitted from person to person through contaminated food and sometimes water, and less often through direct contact with an infected person. The distribution of the virus is closely related to hygiene and sanitation standards, as well as socio-economic levels, with sporadic food-borne outbreaks reported in many endemic countries (Melnick, 1995). Countries have been classified as high, intermediate, and low endemicity, defined as ≥90% of the population exposed (and therefore immune) by age 10 years, ≥50% by age 15 years, and ≥50% by age 30 years, respectively (Jacobsen and Wiersma, 2010).

Close to 1.4 million infections are reported worldwide each year, of which approximately half occur in Asian countries (Martin and Lemon, 2006; David, 2004). The Global Burden of Disease project estimates that HAV causes 1 213 718 disability-adjusted life years (DALYs) (95% confidence interval 524 098–2 255 089) worldwide every year (Global Burden of Disease Database, 2013). Acute infection is clinically indistinguishable from other types of hepatitis, but unlike infections caused by hepatitis B and C viruses, HAV infection does not cause chronic liver disease. Hepatitis A is rarely fatal and most people recover with life-long immunity. However, it can take several weeks or months to recover, and severe infections, while rare, can result in fulminant hepatitis and death (World Health Organization, 2017). Laboratory confirmation of infection is typically serological, by detection of HAV-specific IgM and IgG antibodies, or through the detection of viral RNA by RT-PCR (Cuthbert, 2001).

HAV infection causes disease of variable severity with symptoms including fever, malaise, loss of appetite, diarrhoea, nausea, abdominal discomfort, dark-coloured urine, and jaundice. In young children, HAV infection is largely asymptomatic, but the severity increases with age, with jaundice occurring in more than 70% of adult cases (Melnick, 1995). Relapse can also occur (World Health Organization, 2017). As complications and death are more likely to occur in adults, a transition from high to intermediate endemicity may paradoxically increase the disease burden. Consequently, hepatitis A can have a profound economic impact on direct healthcare costs, as well as indirect costs as a result of recovery time and work absenteeism (Luyten and Beutels, 2009).

A range of HAV endemicity levels are seen in the Asia Pacific region, associated with heterogeneous developmental, hygiene, and sanitary conditions. Following economic development, an associated decline in HAV endemicity has been described in many settings (Franco et al., 2012; Barzaga, 2000). As a result, exposure in early childhood is decreasing and there has been a shift in disease burden to older age groups with a higher potential for severe disease (David, 2004). More developed countries in the region such as Singapore, Japan, and Taiwan are considered low endemic, while less developed countries such as Thailand, China, and India are seen as moderate to high endemic countries (Franco et al., 2012; Barzaga, 2000).

Hepatitis A immunization is practiced in some countries as part of prevention and control efforts, as well as to contain outbreaks, depending on the level of immunity and exposure in each setting (López et al., 2015). Currently in the Asia Pacific region, China (one dose at 18 months), Korea (two doses at 6 and 12 months), and New Zealand (two doses in risk groups) include the hepatitis A vaccine in their immunization schedule (World Health Organization, 2016).

A systematic literature review was conducted to describe the changes in age-specific HAV seroprevalence in selected Asia Pacific countries over the last few decades, and to identify gaps in the published literature.

## Methods

A review of the literature was performed in August 2016, following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Moher et al., 2009). As study populations were not comparable, a meta-analysis was not conducted.

### *Study eligibility criteria*

Studies published in the English language between 1980 and 2016, reporting human HAV seroprevalence levels in any age group, were included in the review. Studies reporting data from acutely ill patients or those with liver disease, or data from non-indigenous populations or populations from outside the predetermined countries, were excluded. Reviews, mathematical modelling studies, interventional vaccine studies, and publications for which the full text was unavailable for retrieval were also excluded.

### *Search strategy*

The United States National Library of Medicine and the National Institutes of Health Medical Database (PubMed) was searched with the following combination of search terms: “hepatitis A”[MeSH Terms] AND (“seroepidemiologic”[All Fields] OR “seroprevalence”[All Fields]) AND “Asia”[All Fields]. “Asia” was consecutively replaced by 17 Asia Pacific country names: “Australia”, “Brunei”, “Cambodia”, “China”, “India”, “Indonesia”, “Japan”, “Korea”, “Laos”, “Malaysia”, “New Zealand”, “Myanmar”, “Philippines”, “Singapore”, “Taiwan”, “Thailand”, and “Vietnam”. Countries were selected based on Association of Southeast Asian Nations (ASEAN) membership, with the addition of Australia, China, India, Japan, Korea, New Zealand, and Taiwan, selected to provide low and high endemicity perspectives.

### *Data extraction and analysis*

Two authors independently reviewed all titles and abstracts to assess their inclusion. Duplicates were removed. Full texts for all eligible studies were reviewed and any discrepancies between the results of the two authors were discussed. For all eligible studies, the year of publication, country, age group, and seroprevalence data were extracted and recorded on a series of Microsoft Excel (Microsoft Corp., Redmond, WA, USA) spreadsheets. The age of study participants was allocated to standardized, 10-year categories according to the median of the reported age groups. If the reported age range included more than two categories, the corresponding seroprevalence data were allocated to all categories that contained more than 4 years of age data. Final reported age (e.g., 60+ years) was categorized into the equivalent highest age group (e.g., 61–70 years). Averages were calculated for each subpopulation and year if data were reported from different provinces of the same country. Data were used to produce country-specific line graphs describing hepatitis A seroprevalence by age group over the past four decades. All studies included were categorized into their respective decade by specific colour coding for each decade, in order to observe changing trends.

## Results

### *Study eligibility*

The database search yielded a total of 212 publications, from which 27 duplicates were removed. A further 75 were excluded based on the abstract, resulting in 110 publications from 12

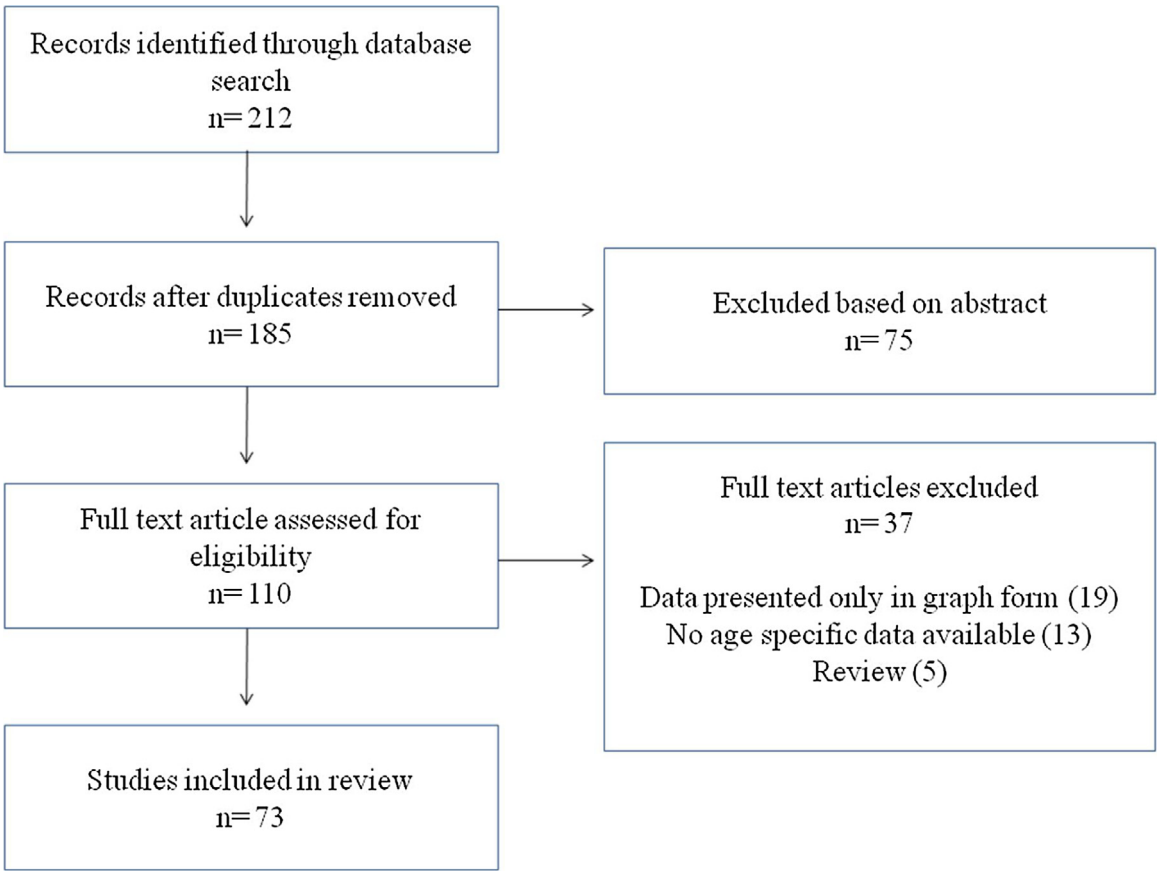


**Figure 1.** Flow diagram of the search strategy and the number of articles included and excluded at each stage.

countries that were included for full-text review. After reviewing the full texts, 37 publications were excluded because data were presented only graphically ($n = 19$) or without age-specific data ($n = 13$), or because the publication was a review or commentary ($n = 5$) (Figure 1). A total of 73 publications from 11 different countries were included in the analysis (Table 1). Seroprevalence was defined in the selected studies by the level of IgG antibodies or total anti-HAV antibodies.

Most publications were from Korea ($n = 18$), Thailand ($n = 17$), and India ($n = 14$). No data were available for Brunei, Laos, Cambodia, Philippines, or Myanmar. Only one time period was reported for Malaysia and Vietnam, therefore it was not possible to identify a change in seroprevalence over time. No publications were included from Australia.

The number of studies published over the years has been increasing: there were four eligible publications in the 1980s, 17 in the 1990s, 32 in the 2000s, and 20 in the 2010s.

**Table 1**
Number of studies included in the review per country.

| Country | Number of included publications |
|---|---|
| Korea | 18 |
| Thailand | 17 |
| India | 14 |
| Taiwan | 10 |
| Japan | 4 |
| China | 3 |
| Singapore | 2 |
| Indonesia | 2 |
| Malaysia | 1 |
| Vietnam | 1 |
| New Zealand | 1 |
| Australia | 0 |

*Trends in age-specific hepatitis A seroprevalence*

Anti-HAV seroprevalence rates increased with age in all countries, with seroprevalence often reaching 90–100% among older age groups (Figure 2). However these levels of exposure were observed at different points in history. In India, for example, studies in 2000 reported seroprevalence of 87.4% in those aged 31–40 years, while in China, Thailand, and Japan, seroprevalence of 80–90% was seen in 31–40-year-olds in 1998, 1991, and 1980, respectively. In Taiwan, a seroprevalence rate of 94.5% was seen in older age groups, such 94.5% in those aged 41–50 years in 2001.

In some countries, seroprevalence decreased over time, especially in the younger age groups, indicative of declining endemicity (Figure 2). In Thailand, for example, seroprevalence among 21–30-year-olds decreased from 84.9% in 1991 to 35.8% in 2007 and 17% in 2016. Similarly, in Japan, seroprevalence among 21–30-year-olds decreased from 87.1% in 1980 to only 1.75% in 2007, while in 61–70-year-olds it decreased from 100% in 1980 to 94.3% in 1996 and 69.4% in 2007. Similar patterns were seen in Taiwan and India. In contrast, seroprevalence increased in Korea among 1–10-year-olds from 26.8% in 1989 to 38.2% in 2003 and 63.6% in 2011. Seroprevalence in older age groups remained high over time, with 95% infected in 1989, 91.4% in 2008, and 83.2% in 2011. A similar pattern was seen in China. Data were insufficient to make longitudinal comparisons for Singapore, Indonesia, and New Zealand.

## Discussion

This review provides further evidence to show that for many Asia Pacific populations, the risk of exposure to HAV has changed over time, an effect that will result in clinical infections seen in older age groups. The increasing number of publications identified

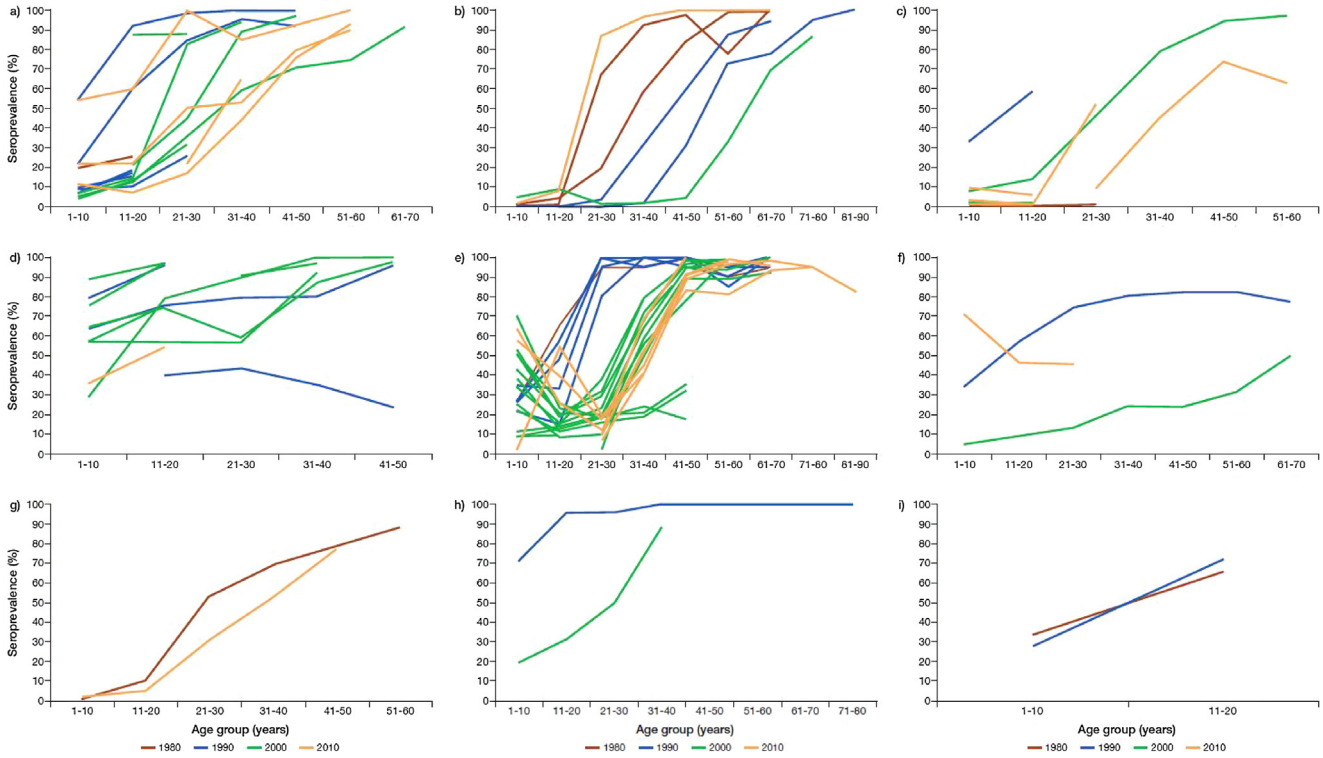


**Figure 2.** Age-specific hepatitis A seroprevalence in (a) Thailand ($n = 17$), (b) Japan ($n = 4$), (c) Taiwan ($n = 10$), (d) India ($n = 14$), (e) Korea ($n = 18$), (f) China ($n = 3$), (g) Singapore ($n = 2$), (h) Indonesia ($n = 2$), (i) New Zealand ($n = 1$). Each line of the same colour represents results from a single study.

in more recent years indicates that the surveillance of hepatitis A exposure through seroprevalence surveys seems to have gained more attention. Nevertheless, significant gaps in the literature were identified, particularly for Laos, Cambodia, Philippines, and Myanmar.

Changing government policy and increased trade and foreign investment have helped several countries such as Thailand, Singapore, Korea, Japan, and China to grow their economies during the last quarter century. This growth has been associated with an increase in healthcare expenditure and improvements in sanitation and hygiene levels, and increasing age at first HAV exposure (Sa-nguanmoo et al., 2016; Kiyohara et al., 2007). Korea is a good example. In the early 1980s the country was considered to have high HAV endemicity (Lee et al., 2011). Hepatitis A vaccine was introduced in Korea in 1997, recommended for high-risk groups, and was introduced into the national immunization programme in a two-dose schedule in May 2015 (Kim et al., 2017). Even before this time, immunization rates were probably high: one study conducted in 2005 estimated a vaccination rate of 42.3% for one or more doses and 24.7% for two doses in children aged 12–35 months (Kim et al., 2009). A recent nationwide study by Lee et al. (2011) explored the change in HAV sero-epidemiology over 30 years in Korea and concluded that the most vulnerable population in 2008–2010 was those aged 20–29 years; this is in contrast to 30 years earlier, when children under 10 years of age were most at risk. In this review, increasing seropositivity in Korean 1–10-year-olds was also observed – likely a consequence of vaccine introduction – from 26.8% in 1989 to 63.6% in 2011; this was accompanied by a decreasing seroprevalence in those aged 21–30 years, from 95% in 1989 to 18.8% in 2011 (Hong et al., 2013).

Hepatitis A vaccine was first introduced in China in 1992 and included in the national immunization programme in 2007 with a single dose of a live attenuated vaccine at age 18 months; more than 10 million doses were administered annually (World Health Organization, 2010). Several of the studies from China included in this review reported an increase in seroprevalence in the young age groups over time. A study of anti-HAV IgM levels from Shanghai, testing for IgG levels in the population, showed a 36.6% increase in seropositivity among 1–10-year-olds between 1998 and 2013, indicating a protective effect resulting from the vaccine. Now at 25 years following the introduction of the vaccine, China is coming close to eliminating hepatitis A (Xu and Wang, 2014).

India is one of the most populous and heterogeneous countries in the region and has an expanding economy. Similar to Taiwan and Thailand, HAV seroprevalence decreased in children but increased in older age groups between 1992 and 2010, which perhaps reflects historical exposure in early childhood prior to this period of economic development. However, it is important to note that such studies were conducted in different geographical areas with consequent variation in development. Since 2005, a live hepatitis A vaccine has been registered in India and is available only in the private market (World Health Organization, 2010).

While this review identified countries that have shifted from a developing to a more developed level and undergone a change in HAV endemicity, there are countries in the region that are still largely developing and from where available data are very limited. Myanmar was under military rule between 1962 and 2011, during which time travel and tourism, as well as foreign investment, were restricted (McGann, 2013). Cambodia is a country with a similar history, and rapid development has only occurred in the last decade or so (Khmer Rouge History). In contrast, in developed countries such as New Zealand and Australia, hepatitis A research might be limited due to low infection rates and other public health priorities (Martin and Lemon, 2006). Studies have shown that underreporting of hepatitis A exists in countries including New Zealand and the USA, with large variations in reporting completeness (Savage et al., 2016).

This study has some limitations. Firstly, only one database was searched for publications, and the language of these publications was restricted to English. It is plausible that increasing the search

to other databases and searching for surveillance data would yield more publications on age-specific seroprevalence in the target area. The study method of standardizing all reported age groups into 10-year categories may have resulted in the loss of precision of some of the age-reported seroprevalence. Finally, the studies reviewed used different sampling methods and diagnostic techniques and are therefore representative of the published literature, which may over-represent high-risk or other subgroups, limiting the generalizability of the results.

The Asia Pacific region includes countries at different stages of development, several of which are likely to transition to a more developed status in the coming decades. As a result, several countries in this region will likely observe a shift in hepatitis A endemicity from moderate to low. Decreasing endemicity could be associated with a higher burden of disease in older age groups in the absence of vaccination programmes. Studies of symptomatic disease burden would further help to determine the economic value of vaccination and to inform hepatitis A vaccination policy.

## Author contributions

JN conceived the study. MG and JN planned the study and reviewed the literature. MG prepared graphs and drafted the manuscript. SD, ML, GM, and NA provided technical support and gave iterative comments on the manuscript. All authors contributed to defining the inclusion/exclusion criteria and guided the search and selection process. All authors modified and approved the final manuscript.

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## Conflict of interest

MG was under contract with Sanofi Pasteur at the time this work was undertaken. NA is a full-time employee of Shantha Biotechnics Pvt Ltd (a Sanofi company). ML, SD, GM, and JN are full-time Sanofi Pasteur employees and stockholders.

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