

## SPECIAL ARTICLE

# Changing Hepatitis A Epidemiology and the Need for Vaccination in Korea

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Hepatitis A is a vaccine-preventable disease of the liver caused by the hepatitis A virus (HAV). It is the most common viral hepatitis infection.<sup>1</sup> Humans are the only natural host and as the virus is excreted in high concentrations in the stool, transmission is primarily by the fecal-oral route and associated with poor sanitary conditions. Young children, in whom the infection is usually asymptomatic, play an important part in the transmission of HAV.<sup>2</sup> There is no effective treatment for this disease and the morbidity and mortality in older children and adults, and the resulting economic burden, is often underestimated and can be substantial. The incidence of HAV infection is closely related to socio-economic development and general public health measures;<sup>3</sup> and hygiene and adequate sanitation are the most important tools to prevent the spread of HAV.<sup>4</sup>

World-wide approximately 1.5 million people are infected annually,<sup>3</sup> but the true incidence is probably much higher because of

**SUMMARY** Hepatitis A is a vaccine-preventable disease with 1.5 million people infected world-wide annually. Improvement in the socio-economic status and general public health measures of Asian countries over the last 20 years has led to a shift in the seroprevalence of hepatitis A in many of these countries. In Korea, like in many other developed countries, this lowered endemicity has caused an upward shift in the average age of infection, resulting in larger numbers of individuals at risk of clinically significant hepatitis A infection. Sporadic outbreaks increase the public health burden of the disease. Inactivated hepatitis A vaccines are an effective prevention measure and have been shown to be safe, efficacious and well-tolerated in Korean children. Given this changing epidemiology of the disease and the associated increase in morbidity, vaccination of young children who are not immune, as well as other high risk groups, should be recommended.

non-recognition and under-reporting, as well as the usually asymptomatic nature of the infection in children under the age of 6 years.<sup>5-7</sup> In the United States of America (USA), it has been estimated that the number of HAV-infected individuals can be 10 times higher than the number of cases reported to the Centers for Disease Control and Prevention (CDC) each year.<sup>8</sup>

The seroprevalence of HAV antibodies is used as a marker of viral transmission in different communities. In the general population the prevalence of anti-HAV antibodies varies between 15 and 100% in different parts of the world.<sup>3</sup> This antibody prevalence can also

vary considerably between countries and different regions within countries depending on the social circumstances, environmental hygiene, public health measures and health education.

Endemicity of hepatitis A infection is categorized according to the annual incidence and the immunoserological status of different

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age groups: high endemicity, almost all children are infected before the age of 10 years<sup>3</sup> and clinically apparent hepatitis A infection is rarely seen; intermediate endemicity, seroconversion occurs predominantly in adolescents and during young adulthood<sup>9</sup> and more than 90% of individuals over the age of 30 years are seropositive as well as the incidence of clinical disease increases;<sup>10</sup> and low endemicity, the overall seroprevalence is low. Cases occur more in the form of outbreaks and 20 to 30% of the clinical cases of HAV infection are children and adolescents as well as adults in high-risk groups (injection drug users, travellers to regions with a higher prevalence, men who have sex with men).<sup>3,9</sup>

As social and economic circumstances improve, a reduction in hepatitis A disease is observed with a corresponding shift in the age-specific prevalence of hepatitis A infection. In communities with inadequate sanitation and hygiene, infections occur in infants and young children. As general health measures improve, primary infection increasingly occurs in older children, adolescents and young adults. During the last 20 years there has been a trend world-wide for many countries to move from high to intermediate and intermediate to low endemicity for hepatitis A. However, regional variation still occurs within countries and the seroprevalence has not changed to the same extent in all countries.<sup>10</sup> In the Asia-Pacific region areas of high endemicity include India, China, Nepal, Bangladesh, Pakistan, Myanmar and the Philippines, with Japan, Taiwan, Singapore and Hong Kong having low endemicity.<sup>11</sup>

In Hong Kong the prevalence

of anti-HAV antibodies in the under 30 age group decreased significantly between 1979 and 1989 (37.2 to 24.0%).<sup>12</sup> In Bangkok, Thailand, the prevalence of anti-HAV antibodies in adolescents between the ages of 10 and 19 years of age declined from 31.4% to 14.6% to 12.7% in 1987, 1993 and 1996, respectively. The decline was even more pronounced in the youngest age groups.<sup>13</sup> By 2000 the overall seroprevalence in tested Thai children and adolescents was 7.9%.<sup>14</sup> In Thailand 100% of the adults were seropositive in 1976, 90 to 100% in 1983 and 60 to 68% in 1991.<sup>10</sup> In Singapore, where vast socio-economic changes occurred over the last few decades, 60% of 10 to 19 year olds were seropositive for HAV in 1975,<sup>15</sup> 13.2% of the 10 to 24 year olds were seropositive in 1985,<sup>15</sup> and less than 1% of the 10 to 19 year olds were seropositive in 1991.<sup>10</sup> The prevalence of anti-HAV antibodies showed the same decreasing trend in children, adolescents and young adults in Taiwan during the past 25 years with 0 to 4.9% of 1 to 19 year olds being seropositive in a 1998 study.<sup>16,17</sup>

Hepatitis A infection is recognized as a major public health problem in developed countries.<sup>19,20</sup> In the USA, a country with relatively low hepatitis A endemicity, annual medical and work loss costs have been estimated at more than US\$ 300 million.<sup>20,21</sup> Outbreaks can occur with serious results. The economic impact of the 1996 outbreak in Puglia, Italy, associated with consumption of seafood, has been estimated at US\$ 43.5 million.<sup>1</sup> In 1988 an outbreak of hepatitis A occurred in Shanghai, China, when 292,301 cases and 47 (0.015%) deaths were attributed to the eating of raw and inadequately cooked clams. The

epidemic primarily affected the 20 to 40 year age group and 90% of the hospitalized cases were between 20 and 40 years old.<sup>22,23</sup> Contaminated strawberries and green onions in the USA<sup>24-26</sup> and shellfish in Spain,<sup>27</sup> Italy<sup>28</sup> and Singapore<sup>29</sup> have caused other food-related outbreaks.

Travel to Southeast Asia, the Indian subcontinent and Africa from countries with low endemicity increases the risk of imported cases.<sup>30,31</sup> In Singapore, 42.6% of the 512 cases of hepatitis A reported from 1997 to 2001 occurred in Singaporean residents who had become infected overseas.<sup>31</sup> Similarly in England and Wales, travel abroad has been identified as a significant risk factor for hepatitis A infection.<sup>32</sup>

### Hepatitis A in Korea

Economic progress and the resulting increase in sanitation and living standards that has taken place over the past 20 years in Korea, has led to better environmental health and a decrease in hepatitis A endemicity from high to intermediate and low levels. Fewer young children are being infected and this can be seen by the smaller number of children who have antibodies to HAV.<sup>7</sup> In Taejeon, the age-related prevalence of anti-HAV antibodies has been reported as follows: 8.7% in 1 to 5 year olds; 0% in 6 to 10 year olds; 1.7% in 11 to 15 year olds; 29.4% in 15 to 20 year olds, 63.6% in those in their 20s and more than 90% in all the older age groups.<sup>18</sup> Seroprevalence data from different regions in Korea reviewed by Sohn *et al.*<sup>7</sup> revealed that in young people aged 19 years and younger, more than 60% of the youngsters had antibodies to HAV in 1979 and less than 10% in 1996 (Table 1). In the

Gyeongin region the anti-HAV antibody prevalence in elementary students was found to be 0.51% during 1996.<sup>18</sup>

Therefore, although hepatitis A infection in adults has not been a large public health problem in Korea during the past 2 decades,<sup>7</sup> the risk is now increasing due to the decreasing HAV immunity in the population. In Kyung-gi Province the incidence of symptomatic hepatitis A infections in children has been reported to be on the increase. From 1988 to 1998, 46 children, mainly of middle socio-economic status, were diagnosed with hepatitis A and admitted to hospital. Of these children, 8 (17.4%) had been admitted between 1988 and 1995 and 28 (60.1%) were hospitalized in 1998. The majority of the children were between the ages of 10 and 15 years (80.4%) and the infections primarily occurred from March to July.<sup>9</sup> In the Gyeongin area a gradual increase in hepatitis A cases has been documented. Almost no cases of hepatitis A were reported before 1993, but 4 cases were reported in 1994, 10 cases in 1995 and 23 cases in 1996.<sup>18</sup>

As is seen in other countries with intermediate and low endemicity, several outbreaks of hepatitis A have been observed in Korea since 1996.<sup>7</sup> An outbreak occurred in Taejon, during the summer of 1996, after drinking water was contaminated. Of the approximately 61 patients with hepatitis A who were hospitalized, 31 pediatric patients were in the 4 to 15 year age range, and with the exception of a 44-year-old, the rest were between the ages of 16 and 26 years.<sup>18</sup> This observation confirms that few children and young adults in this region had HAV

immunity prior to the outbreak.

### Hepatitis A vaccination

Effective vaccines against hepatitis A have been available since 1992 and they provide long-lasting immunity against infection.<sup>1,33</sup> In Korea inactivated hepatitis A vaccines have been available since 1997. Given the shift in endemicity of hepatitis A in Korea to intermediate and low levels and the increasing role for vaccination in children, the reactogenicity and immunogenicity of an inactivated hepatitis A vaccine was evaluated in healthy Korean children with no history of vaccination against hepatitis A.<sup>34</sup> It was noted that the seroconversion rate 1 month after the primary vaccination was 100%. The geometric mean of the anti-HAV antibody concentration was 263.9 mIU/ml and 2502.1 mIU/ml 1 month after the first vaccination and the booster dose respectively. After each dose of the vaccine the most prevalent local reaction was tenderness at the injection site (28.1 and 22.5% of the children, respectively). The most frequently reported general symptom after each dose was malaise that occurred in 9.4 and 4.2% of the children, respectively.

This study demonstrated that the inactivated hepatitis A vaccine, Havrix<sup>TM</sup> (GlaxoSmithKline Biologicals, Belgium), is highly immunogenic and safe in the Korean pediatric population. It confirms the international experience with this vaccine, which has demonstrated that it is efficacious, well tolerated and provides long-lasting protection in children and adults.<sup>1,35,36</sup> As observed in this study, most reactions to the vaccine are mild and non-specific, which concurs with the World Health Organization (WHO) reports that no serious adverse events have been statistically linked with inactivated hepatitis A vaccines.<sup>1,3</sup>

Passively transferred maternal antibodies may affect the response to primary infection or immunization and the decline in the maternal anti-HAV antibodies was evaluated in Korean infants in two trials. In Seoul the prevalence of HAV antibody in 60 pregnant Korean women without a history of hepatitis A infection or vaccination was 81.7% whilst the seropositivity in infants younger than 3 months was 43.3%. The seropositivity declined and the lowest values were found in infants aged 10 to 12 months and 13 to 24 months (6.7 and 3.0% re-

**Table 1** Korean anti-HAV antibody seroprevalence in under 20 years old individuals between 1979 and 1996

Seroprevalence	Place	Date	Reference
63.8% (141/221)	Seoul and Kyung-gi Province	1979	7
42.3% (169/400)	Chinju City	1988	7
50.3% (85/169)	Chonbuk Province	1989	7
11.7% (42/359)	Seoul City	1995	7
8.5% (22/256)	Daejun City	1996	7
9.5% (36/398)	Chinju City	1996	7
4.6% (15/323)	Kyung-gi Province	1996	7

spectively).<sup>37</sup> The seropositivity of 142 infants aged 1 month to 24 months was also evaluated in Taejon. Anti-HAV antibodies were present in 90.2% of the cord blood specimens and steadily declined to 8.3% in children aged between 13 and 14 months. Children tested between 17 and 20 months of age had no detectable levels of anti-HAV antibodies.<sup>18</sup>

Concerns regarding vaccination of infants with passively transferred maternal anti-HAV antibodies have been raised. Based on mathematical model estimations, vaccinated individuals, who after priming, have geometric mean concentration values greater than 200 mIU/ml, will remain seropositive for 25 years.<sup>33</sup> It has been documented that even in the presence of maternal antibodies, the anamnestic response is robust 6 years after vaccination.<sup>6,33</sup>

The duration of protection after vaccination has been shown to be at least 20 years from models of antibody decay.<sup>38,39</sup> Based on mathematical model estimations, vaccinated individuals, who after priming, have geometric mean concentration values greater than 200 mIU/ml, will remain seropositive, for 25 years.<sup>33</sup> Immune memory is important for long-term protection after vaccination as it has been shown in adults that even when there is no detectable level of antibody before the booster dose, an anamnestic response is noted.<sup>33</sup> According to the International Consensus Group on Hepatitis A Immunity, the high levels of anti-HAV antibodies found in immunocompetent adults after vaccination combined with the projected times for antibody persistence and the evidence of immune memory involvement do not lend support to

the need for booster vaccination.<sup>33</sup>

### Vaccination programs

Recognizing that hepatitis A disease can pose a significant health and economic burden, the WHO recommends that in regions with low endemicity, such as is the situation in Korea at present, high risk groups should be vaccinated. These groups include travellers to areas of higher endemicity, patients with chronic liver disease, hepatitis B and C carriers, persons engaging in high-risk sexual activity, users of illicit injectable drugs, food handlers, workers with an occupational risk of infection, recipients of therapeutic blood products, military personnel, children in day-care centers and persons living in closed communities.<sup>1,3,40</sup>

However, the WHO and other public health experts acknowledge that vaccination programs targeting specific high-risk groups may have little impact on the overall national incidence of disease and there may be a case for widespread vaccination programs in certain regions.<sup>3,20</sup> In the USA, epidemiologic data indicated that immunization of high risk adults alone is insufficient to reduce the incidence of hepatitis A and that sustained disease reduction requires routine childhood vaccination.<sup>20</sup> Therefore, it is recommended that children living in states with an average annual incidence of infection double the national average be vaccinated against hepatitis A.<sup>19</sup> Large-scale vaccination programs may be able to achieve disease control in intermediate endemicity regions where there is low prevalence of anti-HAV antibodies in childhood, but increases during adolescence

and adulthood.<sup>1,3</sup> In Israel, where infants are vaccinated against hepatitis A at 18 and 24 months of age as part of its routine infant vaccination schedule since 1999, the average annual incidence rate has successfully been reduced from 41.5 per 100,000 to less than 5 per 100,000 within 3 years.<sup>41,42</sup> Significant reductions in the incidence of hepatitis A disease have also been achieved in 11 states of the USA and in Catalonia, Spain through mass vaccination programs.<sup>43,44</sup>

Although mass vaccination programs have been shown to be effective, a concern regarding the implementation of these mass vaccination programs is the cost. In assessing the economic burden of hepatitis A infection one has to take into account the cost of symptomatic disease (such as hospitalization and medication), morbidity (in adults, the loss of income) and mortality. Other cost factors include the impact on quality of life, cost to society from periodic outbreaks as well as the cost of the vaccination program. Comparisons between different cost-benefit analyses can be difficult, as methods used to estimate the impact of vaccination programs are not standardized<sup>45</sup>.

A review by Rosenthal<sup>19</sup> of universal immunization in children, adolescents and high-risk adults against hepatitis A in developed countries comes to the conclusion that the implementation of a vaccination program in accordance with the guidelines of the Advisory Committee in Immunization Practices of the CDC would be cost-effective in the USA. Another analysis found that extending the current recommendations into a national immunization policy would provide twice

the health benefits, with a cost effectiveness similar to that of other childhood vaccines.<sup>46</sup> Israel's nationwide infant immunization program has been estimated to save US\$ 57.5 million in health service resources against a cost of US\$ 32.0 million to the health services.<sup>47</sup>

In settings where many hepatitis vaccination candidates have immunity, depending on the level of hepatitis A infection in the community, serological screening before vaccination might improve the cost-effectiveness of vaccination programs.<sup>48-50</sup> In Ireland, it was found that while vaccination alone was most cost effective when the hepatitis A immunity was 45% or less, screening before vaccination was most cost effective where prevalence of immunity was more than 45%.<sup>49</sup> While mass vaccination programs in developed countries have been shown to be cost effective, very few analyses have been performed in developing countries. In Thailand, based on their present incidence of hepatitis A infection, it has been found that a nationwide vaccination program would not be cost-beneficial at this point in time.<sup>51,52</sup>

## Conclusion

In Korea, with dramatic improvements in living standards and sanitation over the last two decades, there is evidence of a changing epidemiology of hepatitis A infection. Korean children lose the passively transferred maternal anti-HAV antibodies soon after their first birthday and as in other developed countries, where hepatitis A immunity has declined in the population, it appears that infections are occurring in late childhood or young adulthood when cases are more likely to be

symptomatic. Hepatitis A has been reported to be a major cause of acute viral hepatitis in young Koreans. Given the lower hepatitis A immunity, regional outbreaks have also been observed more often over recent years. With this pattern of low disease endemicity and periodic outbreaks, hepatitis A has the potential to create an increased public health and economic burden in Korea.

Effective and safe inactivated hepatitis A vaccines have been available in Korea since 1997. The vaccine is recommended for use in high risk groups such as persons travelling to or working in countries of intermediate or high endemicity and those working with hepatitis A patients, young children or in institutions. Immunization of children should be recommended because of their low immunity, which places them at higher risk of disease and their significant role in hepatitis A disease transmission to other children and adults, particularly when attending nurseries, schools and other institutions. As vaccine acquired immunity appears to be long lasting, the community will benefit from the increasing population immunity and reduced transmission of hepatitis A.

## ACKNOWLEDGEMENT

The authors would like to express their thanks to Roosmarie Bam for her editorial assistance in preparing this manuscript.

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