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Changes in seroprevalence of hepatitis A after the implementation of universal childhood vaccination in Shandong Province, China: A comparison between 2006 and 2014

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ABSTRACT

Objectives: The hepatitis A vaccine (HepA) has been included in the national expanded program on immunization (EPI) in China since 2008. This study was performed to evaluate the change in dynamics of the seroepidemiology of hepatitis A virus (HAV) before and after the introduction of the program.
Methods: The trends in seroepidemiology of anti-HAV antibodies were examined in Shandong Province, China, drawing on two population-based samples of persons aged 1–59 years, one obtained in the year 2006 ($n = 6682$) and the other in 2014 ($n = 5095$).
Results: A dramatic increase in seroprevalence of anti-HAV antibodies from 30.76% (95% confidence interval (CI) 26.24–35.28%) to 77.46% (95% CI 74.04–80.87%) among children aged 1.5–7 years (born after HepA was recommended for routine childhood immunization), as well as an increase from 35.32% (95% CI 29.31–41.33%) to 66.69% (95% CI 55.59–77.80%) in subjects aged 8–14 years, was observed in 2014 when compared with 2006. By contrast, a decline in seroprevalence among subjects aged 15–29 years, as seen particularly in those 20–29 years of age, from 85.72% (95% CI 80.29–91.14%) to 69.24% (95% CI 62.02–76.45%), was found in this study. There was no statistically significant difference in seroprevalence between 2006 and 2014 among the subjects older than 30 years of age.
Conclusions: The national HepA routine immunization program has had a positive effect, leading to an increase in anti-HAV seroprevalence among children in Shandong Province, China. More attention should be paid to young adults in the province.

Introduction

Hepatitis A virus (HAV) remains a global public health problem (Chi et al., 2018; WHO, 2011). An estimated 1.4 million clinical cases of hepatitis A occur each year, and some developing countries are particularly affected (Jacobsen and Wiersma, 2010; Franco et al., 2012). However, the true burden of HAV infection is considered to be 3–10 times higher, because these estimates do not include asymptomatic HAV infections in young children and there is substantial under-reporting of cases (Chodick et al., 2008; Lazcano-Ponce et al., 2013).

The degree of HAV endemicity for an area is categorized through age-seroprevalence surveys, establishing the proportion of each age group with immunity to HAV as measured by the presence of anti-HAV antibodies in the serum, whether through natural infection or immunization (Jacobsen and Wiersma, 2010). Historically, China was identified as a high-endemic region for HAV up to the mid-1990s, with cases occurring primarily in the north of the country (Xu et al., 2002). A population-based national survey conducted in 1992–1995 demonstrated that the overall seroprevalence of HAV-specific antibodies was 80.9% in China (Dai and Qi, 1997). With improvements in hygiene and socioeconomic conditions, an associated dynamic shift in HAV endemicity from high to intermediate has been documented over the past few decades in China (Chen et al., 2014).

HAV immunization has been practiced in many countries as a supplement to health education and improved sanitation, depending on the level of immunity and exposure in each setting (López

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et al., 2015; Lopalco et al., 2000; Salleras et al., 2000; Dagan et al., 2005). The World Health Organization (WHO) recommends routine childhood vaccination in countries of intermediate HAV endemicity (WHO, 2012). In China, the hepatitis A vaccine (HepA) has been available since 1992. Before 2008, HepA was self-paid, which prevented many parents from having their children vaccinated. In 2008, China integrated HepA into the national expanded program on immunization (EPI), offering one dose of live attenuated HepA (L-HepA) at the age of 18 months, or two doses of inactivated HepA (I-HepA) at the ages of 18 and 24 months, without charge (Sun et al., 2018). L-HepA was provided free of charge to the children in Shandong Province, but some parents with a better economic status preferred to choose I-HepA for their children despite the out-of-pocket payment.

The aim of this study was to evaluate the change in dynamics of the seroepidemiology of anti-HAV before and after the introduction of HepA into the national childhood immunization program, drawing on the two population-based serosurveys conducted in 2006 and 2014 in Shandong Province, China.

Materials and methods

Study population and sampling method

Shandong Province is located in the eastern part of China and covers an area of 156,700 km^2; it is inhabited by a population of over 99 million. Stored serum samples and data were obtained from the two provincial serosurveys conducted in 2006 and 2014 (Zhang et al., 2010; Liu et al., 2017). The primary purpose of the two serosurveys was to evaluate the progress made in the prevention of hepatitis B in the province.

The 2006 survey used a three-stage cluster sampling method, in which 12 counties in the province were chosen (Zhang et al., 2010), following which two or three towns from each county were selected by systematic sampling. The 2014 survey used a two-stage cluster random sample from the same 12 counties, following which 24 villages were identified in the 12 counties (two per county) by probability proportional to size (PPS) sampling. In both surveys, the study populations were aged 1–59 years. The sampling method used in these surveys has been described previously (Zhang et al., 2010; Liu et al., 2017). Basic information including age, sex, and place of residence was investigated in both surveys, while HepA immunization history was collected only in the 2014 survey, according to the immunization records for children under 15 years old. The final sample size was 7601 in 2006 and 5528 in 2014.

Laboratory testing

All blood samples were centrifuged and the separated serum was stored at −70 °C until use. Due to an insufficient volume of serum, 6682 (87.91%) samples from 2006 and 5095 (92.17%) samples from 2014 were finally eligible for the data analysis of HAV-specific antibodies.

In the 2006 serosurvey, serological tests for the total HAV-specific antibodies were performed using a domestic ELISA kit (Wantai Biological, Beijing, China) (Zhou et al., 2013; Kong et al., 2017). As the Wantai ELISA kit was no longer available at the time of the 2014 survey, anti-HAV antibodies were determined using an automated chemiluminescent microparticle immunoassay (CMIA) on an Architect i2000SR instrument (Architect HAVAb-IgG; Abbott, Wiesbaden, Germany). The specificity and sensitivity of the CMIA test were >99.17% and >98%, respectively (Sanguanmoo et al., 2016). Samples with a signal-to-cut-off (S/CO) ratio ≥1.00 were considered CMIA-positive for anti-HAV antibodies. All tests were completed according to the manufacturers' instructions. Since the samples were tested using different kits in the two surveys, 100 serum samples from the 2006 survey were chosen at random and re-tested with the Abbott CMIA system, yielding 91% concordance.

Table 1
Characteristics of the study populations in the 2006 and 2014 serosurveys.

Category	2006		2014	
	Frequency	Proportion	Frequency	Proportion
Overall	6682	100.00	5095	100.00
Age (years)				
1–4	1085	16.24	1251	24.55
5–14	2002	29.96	1075	21.10
15–59	3595	53.80	2769	54.35
Sex				
Male	3167	47.40	2481	48.69
Female	3515	52.60	2614	51.31
Place of residence				
Urban	2167	32.43	1503	29.50
Rural	4515	67.57	3592	70.50
Region				
Eastern	2063	30.87	1693	33.23
Central	2250	33.67	1676	32.89
Western	2369	35.45	1726	33.88
Occupation (18–59 years)				
Student	234	6.51	86	3.33
Farmer	2615	72.80	1540	59.69
Worker	370	10.30	375	14.53
Manager	120	3.34	167	6.47
Service people at public facilities	63	1.75	70	2.71
Other	190	5.29	342	13.26

Statistical analysis

Data were double-entered into EpiData version 3.02 and then analyzed using SAS version 9.13. The statistical methods used for the two surveys were identical. To ensure the representativeness of post stratification adjustments, appropriate sampling weights were constructed for the count sample dataset. The weight for each person i was $w_i = w_1 \times w_2 \times w_3 \times w_{adj}$, where w_1 is the reciprocal of the inclusive probability of county, w_2 is the reciprocal of the inclusive probability of village, w_3 is the reciprocal of the inclusive probability of person i from the selected village, and w_{adj} is an adjustment factor for person i so that the sum of weights equaled the actual size of the population of Shandong in 2010. Similar to the previous serosurvey, 12 counties were divided into three regional groups (eastern, central, and western) and two types of residential area (urban and rural) (Zhang et al., 2010; Liu et al., 2017). Data on HepA coverage in the target population of children during 2008–2014 were collected from the Children Immunization Information System (CIIMS) managed by Shandong Center for Disease Control and Prevention. The SAS procedure survey was used to calculate point estimates and 95% confidence intervals (CIs) of anti-HAV prevalence by using weighting adjustments. Taylor series linearization was used for variance estimations. The 95% CI for anti-HAV prevalence were compared for each variable, and in the event that these did not overlap, the difference was considered statistically significant.

Results

Demographic characteristics

Overall, a total of 6682 samples from the 2006 survey and 5095 samples from the 2014 survey were analyzed. The male-to-female ratio was 0.90:1 in 2006 and 0.95:1 in 2014. The proportions of persons by age group, occupation group, and residential area were similar in the two surveys (Table 1).

Prevalence of anti-HAV by age in 2006 and 2014

The overall weighted anti-HAV seroprevalence was 83.54% (95% CI 81.34–85.74%) in the 2014 survey and 80.56% (95% CI 77.34–83.78%) in the 2006 survey, showing no statistically significant difference. However, compared with 2006, a dramatic increase in anti-HAV seroprevalence from 30.76% (95% CI 26.24–35.28%) to 77.46% (95% CI 74.04–80.87%) among children aged 1.5–7 years (born after HepA was recommended for routine childhood immunization) was observed in 2014, as well as an increase from 35.32% (95% CI 29.31–41.33%) to 66.69% (95% CI 55.59–77.80%) among subjects aged 8–14 years. By contrast, a decline in seroprevalence was found among subjects aged 15–29 years, as seen particularly in those 20–29 years of age, from 85.72% (95% CI 80.29–91.14%) to 69.24% (95% CI 62.02–76.45%). There was no statistically significant difference in the prevalence of anti-HAV between the two surveys for the subjects older than 30 years of age (Figure 1).

In 2006, anti-HAV seroprevalence increased with age in subjects younger than 20 years old. However, HAV seroprevalence was highest among those aged 1.5–7 years in 2014, following which it decreased gradually among the children and adolescents under 20 years of age. The seroprevalence of HAV increased with age among subjects older than 20 years of age in both surveys.

Prevalence of anti-HAV by sex, residential area, and occupation in 2006 and 2014

The prevalence of anti-HAV was similar by sex, place of residence (urban/rural), and geographic area (eastern, central, and western) in the two surveys. In the 2014 survey, the highest weighted prevalence was identified in farmers (92.04%, 95% CI 88.58–95.49%) and the lowest in students (67.17%, 95% CI 61.14–73.20%). Similar trends in anti-HAV prevalence were seen in the 2006 survey. The anti-HAV prevalence was higher in the 2014 survey compared with the 2006 survey, regardless of sex, place of residence, or geographic area, but the difference was not statistically significant (Table 2).

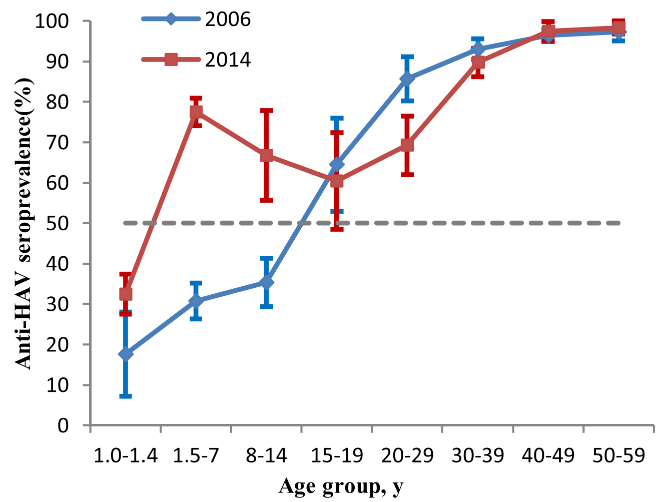

Figure 1. Age-specific prevalence of anti-HAV among persons participating in the 2006 and 2014 surveys. The dotted line denotes 50% anti-HAV prevalence. Bars indicate the 95% confidence interval.

Effects of the EPI with HepA

Among each age group under 15 years old, the immunized children had a much higher prevalence of anti-HAV than the unimmunized children in the 2014 survey (Figure 2). Among children with an HAV immunization history, the ratio of children immunized with L-HepA to I-HepA was 2.35:1 in the 1.5–7 years age group, while the ratio was 0.41:1 in the 8–14 years age group. Among immunized children aged 8–14 years, 28.83% were immunized after 2008.

The annual incidence of hepatitis A by specific age group, as well as the HepA coverage in the target population of children from CIIMS, mapped against the time of the immunization program, is presented in Figure 3. From 2006 to 2014, declines in the reported incidence of hepatitis A were observed in each age group in Shandong Province, China, and a sharp decline in children under 15 years of age since 2008.

Discussion

This study provided new laboratory evidence and presented a major shift in the seroprevalence of anti-HAV antibodies with the successful introduction of HepA into the universal childhood immunization program in Shandong Province, China. The 2006 survey, which reflects a fee-charging period with low coverage, indicated less than 40% seroprevalence of anti-HAV for children under 15 years of age in the present study. The results are in agreement with those of previous seroepidemiology studies conducted in Israel and Saudi Arabia before routine vaccination (Bassal et al., 2017; Almuneef et al., 2006).

As expected, the findings of this study revealed that there was a 1.5 times increase in prevalence (from 30.76% to 77.46%) in the cohorts included in the program (1.5–7 years of age) in the 2014 survey compared with the 2006 survey. This dramatic increase

Table 2
Prevalence of anti-HAV among the population aged 1–59 years by sex, occupation, and residential area in 2006 and 2014.

Variable	Number of samples tested		Weighted positive for anti-HAV, % (95% CI)	
	2006	2014	2006	2014
Sex				
Male	3167	2481	79.54 (75.94–83.13)	83.76 (81.63–85.89)
Female	3515	2614	81.59 (78.53–84.64)	83.32 (80.88–85.76)
Place of residence				
Urban	2167	1503	80.04 (79.00–81.09)	81.13 (78.70–83.55)
Rural	4515	3592	80.65 (76.78–84.52)	84.69 (81.40–87.98)
Region				
Eastern	2063	1693	79.49 (70.42–88.56)	80.58 (77.61–83.55)
Central	2250	1676	81.32 (71.38–91.26)	81.79 (72.24–91.35)
Western	2369	1726	80.04 (74.35–85.74)	86.63 (81.46–91.79)
Occupation (18–59 years)				
Student	234	86	63.47 (53.39–73.54)	67.17 (61.14–73.20)
Farmer	2615	1540	94.10 (92.65–95.55)	92.04 (88.58–95.49)
Worker	370	375	81.67 (71.64–91.71)	83.32 (80.82–85.82)
Manager	120	167	77.82 (65.06–90.57)	78.75 (68.00–89.50)
Service people at public facilities	63	70	74.93 (58.76–91.10)	85.72 (80.17–91.28)
Other	190	342	84.66 (77.36–91.96)	83.19 (80.90–85.47)

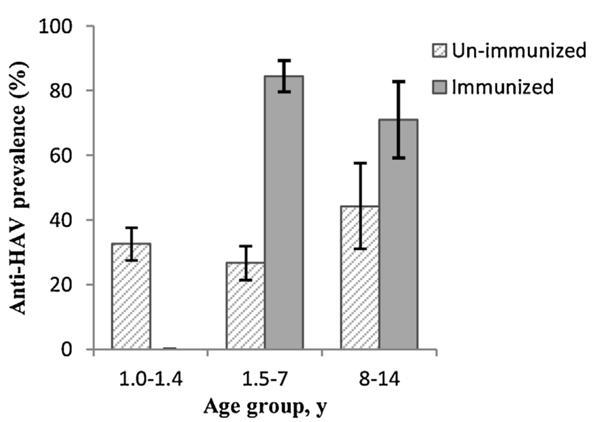

Figure 2. Prevalence of anti-HAV by hepatitis A immunization status in the age groups 1.0–1.4, 1.5–7, and 8–14 years in the 2014 survey. Bars indicate the 95% confidence interval.

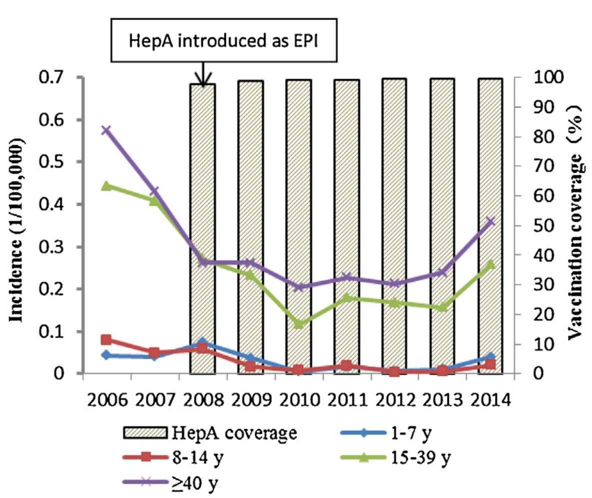

Figure 3. Annual incidence of hepatitis A by specific age and the coverage of hepatitis A vaccine in the target population of children in Shandong Province, China, 2006–2014. The annual incidence of hepatitis A is shown in four curves, one for each age group: 1–7 years, 8–14 years, 15–39 years, ≥40 years. HepA, hepatitis A vaccine; EPI, expanded program on immunization.

should be attributed primarily to a massive increase in vaccinated children, who are the primary target for universal HepA in the recommendations implemented in 2008. Compared with 2006, anti-HAV seroprevalence was also higher among children aged 8–14 years in the 2014 survey, likely reflecting a higher coverage of vaccination in these cohorts. As demonstrated by the study findings, 86.37% of children 8–14 years of age in the 2014 survey had received HepA, especially supplementing almost 30% of vaccinated cohorts in parallel with the introduction of HepA into the program. The findings of this study also demonstrated that the immunized children had a much higher prevalence of anti-HAV than the unimmunized children. The present study confirms that the universal childhood vaccination policies have had a significant impact, leading to an increase in anti-HAV seroprevalence in children, as has been found previously in population-based survey studies conducted in China – in Beijing and Shanghai city – and in studies conducted in Israel and the USA (Wang et al., 2018; Zhu et al., 2013; Bassal et al., 2017; Klevens et al., 2011).

The reduction in seroprevalence among subjects 15–29 years of age, as seen particularly in those 20–29 years of age, might be attributable in part to a decline in the circulation of HAV, because vaccination of children ultimately results in less exposure to the virus. However, it should be mentioned that natural infection has been declining with the rapid improvement in sanitation in recent years (Sa-nguanmoo et al., 2016; Franco et al., 2012), which will also have contributed to a decrease in anti-HAV seroprevalence in addition to the effects of vaccination. Nevertheless, the decline in seroprevalence will result in a higher proportion of population susceptible to HAV and should be of concern.

Consistent with previous serosurveillance data (Chen et al., 2014; Lee et al., 2011; Gallone et al., 2017), a continuous high level and no change in anti-HAV seroprevalence was found for the older population (>30 years of age) in the 2006 and 2014 surveys. This is explained by the fact that these older people were more likely to have been exposed to HAV due to poorer hygiene and sanitation during early childhood, at a time when the disease was endemic in China. In addition, the lowest anti-HAV seroprevalence in both surveys was found for children under 1.5 years of age, who were under the age for HepA immunization and whose antibodies were derived from maternal antibodies. Passive antibody transfer is able to convey protection to the infants when exposed to HAV in early life. However, this protection is transient because of the rapid decline in acquired maternal antibodies with age (Chen et al., 2014).

In 2008, HepA was implemented nationwide in China as part of the EPI, and since then Shandong has progressively provided free L-HepA for the target population of children throughout the province. Data from CIIMS showed that the reported coverage of HepA was consistently greater than 90% among the target children during 2008–2016 in Shandong Province. Several countries or regions where routine vaccination is recommended have demonstrated the effectiveness of immunization on the incidence of hepatitis A (Zhu et al., 2013; Fisenka et al., 2008; Chironna et al., 2012; Zhang et al., 2014). The results of the present study also demonstrated that the reported incidence of hepatitis A had declined by up to 47% for those 1–15 years of age in 2014 when compared to 2006–2008 in Shandong Province, according to the data from the Chinese National Notifiable Disease Reporting System (NNDRS). Again, the rapid decline in incidence in the target population of children after routine HepA immunization strongly indicates that the decline was attributable to massive vaccination, although factors of economic progress and improvements in sanitation conditions during this period will also have played an important role in this decline.

HAV infection is vaccine-preventable. However, recommendations for the application of HepA vary considerably among countries. WHO guidance on HepA underlines the need to consider an estimation of the cost–benefit of various prevention strategies on the basis of the epidemiological characteristics of hepatitis A in a country or region (WHO, 2012). The implementation of HepA in the routine childhood immunization program in China was in line with the requirements of the country and the WHO for preventing hepatitis A. Changes in seroprevalence trends observed in this study should be attributed primarily to vaccine implementation, resulting in the age of the susceptible population being older and children under 15 years of age no longer being the most susceptible population.

Strengths of this study include a sound strategy, with populations from the same 12 representative counties being investigated using comparable methods, the inclusion of sufficient sample sizes, and the use of similar statistical methods by computing sampling weights across the two surveys. However, there were some limitations to this study. First, the total antibodies (IgG and IgM) for anti-HAV were detected in the 2006 survey, while HAV-specific IgG antibodies were detected in the 2014 survey. Given the fact that HAV-specific antibodies were almost exclusively IgG among the healthy population, this difference might have had only a modest influence on the results. Second, the 2006 survey used ELISA to detect anti-HAV, while the 2014 survey used CMIA. The sensitivity of the ELISA was lower than that of the CMIA for detecting anti-HAV (Zhou et al., 2013). However, the ELISA test used was considered acceptable according to a previous study (Zhou et al., 2013). Again, the consistency was more than 90% when 100 serum samples from the 2006 survey were randomly selected for evaluation with the same lot number of the Abbott CMIA kit used in the 2014 survey. Third, both of the test kits used to detect antibodies in this study were unable to distinguish whether detectable antibodies in the serum were derived from natural infection or vaccination. Nevertheless, the changes in anti-HAV seroprevalence identified in this study are consistent with the results of higher vaccination coverage through the universal childhood immunization program and the trend in incidence.

In conclusion, China has successfully integrated HepA into the routine immunization program since 2008, leading to an increase in anti-HAV seroprevalence among children in Shandong Province. The age of the population susceptible to HAV has been shifted towards an older age group and more attention should be paid to young adults. Ongoing monitoring of the serological profile is important as the epidemiology of hepatitis A changes and is required to determine the direction of future vaccination policy.

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Ethical issues

The survey was approved by the China CDC Ethics Committee. A written informed consent form was obtained from each individual or the guardian (if age <18 years) before investigation.

Conflict of interest

The authors declare that they have no conflict of interest.

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