HUMAN VACCINES & IMMUNOTHERAPEUTICS
2020, VOL. 16, NO. 7, 1574–1578
https://doi.org/10.1080/21645515.2019.1688034

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RESEARCH PAPER

Vaccination coverage and its determinants of live attenuated hepatitis A vaccine among children aged 24–59 months in 20 rural counties of 10 provinces of China in 2016

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ABSTRACT

Objective: To understand one single dose coverage of live attenuated hepatitis A vaccine and its determinants among children aged 24–59 months in 20 rural counties of 10 provinces of China in 2016.
Methods: In 20 counties, using three-stage probability proportion to size sampling, 1979 children aged 24–59 months with a vaccination card were selected from 20 rural counties in 2016. Socio-demographic and socio-economic characteristics of children and their caregivers were acquired from face-to-face questionnaire survey and copies of the vaccination cards. We used multivariate logistic regression models to identify the determinants of one single dose coverage of live attenuated hepatitis A vaccine.
Results: In 2016, the overall one single dose coverage of live attenuated hepatitis A vaccine among children aged 24–59 months in rural areas of China was 77.1%. The adjusted analysis showed that being in second birth order (adjusted OR: 1.40; 95%CI: 1.03–1.90), being in third birth order or more (adjusted OR: 2.10; 95%CI: 1.26–3.51), being born at home (adjusted OR: 2.01; 95%CI: 1.04–3.88) and having the lowest per capita income of household (adjusted OR: 2.36; 95%CI: 1.11–4.99) were significantly related to being unvaccinated one single dose coverage of live attenuated hepatitis A vaccine against hepatitis A virus.
Conclusion: one single dose coverage of live attenuated hepatitis A vaccine was still at a low level in 20 rural counties of 10 provinces in China. To improve the coverage of live attenuated hepatitis A vaccine, the government should pay more attention to the disadvantaged groups, especially the children who were in second birth order or higher, or delivered at home, or who have the lowest per capita income of household.

ARTICLE HISTORY
Received 9 July 2019
Revised 5 October 2019
Accepted 21 October 2019

KEYWORDS
China; children; coverage; live attenuated hepatitis A vaccine; cross-section study

1. Introduction

Hepatitis A virus (HAV) infection is a significant health issue worldwide leading to significant economic and social consequences in the world. HAV attacks the liver and causes debilitating symptoms with the degree ranging from mild to severe level including fever, malaise, loss of appetite, diarrhea, nausea, abdominal discomfort, dark-colored urine, and jaundice.[1] In addition, HAV infection is the predominant etiology of acute hepatitis and fulminant hepatitis among children. HAV is transmitted through ingestion of contaminated food and water or direct contact with infected person by the fecal-oral route. Young children are at high risk of infection and play a vital role in transmission. Severely infected children may develop jaundice, which seriously endangers children's health. Globally, HAV infection causes approximately 1.5 million clinically evident cases of hepatitis A (HepA) each year and the majority of those cases occur in children.[2] World Health Organization (WHO) estimates that HepA caused approximately 11,000 deaths worldwide in 2015.[3] China is an endemic area for HepA. Although the overall incidence of HepA in China has declined significantly from 3.6/100,000 person/year in 2004 to 1.6/100,000 person/year in 2016, the incidence of HepA in children was still as high as 3.7/100,000 in 2016.[4] Therefore, HepA is a significant disease that deserves additional attention, especially among children.

The vaccination of children with HepA vaccine is considered to be the most effective means for prevention of HepA virus infection. The evidence has shown that inactivated and live attenuated hepatitis A vaccines are highly immunogenic and provide long-term protection.[5] In a clinical trial, a single dose of an inactivated or live attenuated hepatitis A vaccine at the age of 18–60 months resulted in high hepatitis A virus seropositive rate and anti-HAV antibody concentrations that could last for at least 5 years.[6] A longitudinal cohort study that followed recipients with a live attenuated HAV vaccine for 17 years after the initial administration showed that live attenuated hepatitis A vaccine (L-HepA) has long-term immunity, including antibody persistence and immunological memory.[7] In view of the high infectivity and viability of HAV, HepA vaccine

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should be given to children with poor immunity to prevent HepA.

In 2008, Chinese Ministry of Health integrated HepA vaccine into the National Immunization Program (NIP), providing free vaccinations for children under 7 years old in the whole country.[8] The competent health authorities of the local people's government at or above the county level shall appoint qualified community health service centers to carry out the vaccination programs within their responsibility areas. The community health service center receives or purchases the vaccine and assigns a professional to supervise and manage the vaccine administration. At present, vaccination service providers in China are doctors, nurses or village doctors who have been professionally trained and tested for vaccination. Disease Control and Prevention Center (CDC) shall provide technical guidance on vaccination and supervise the use of the vaccines. China attaches great importance to the vaccination of children and implemented a vaccination card system for them. Within 1 month after birth of the child, the caregivers are required to visit the local community health center or the birth hospital within their residential regions to apply for a vaccination card. Then vaccination is performed at the local community health center according to schedule of the NIP. For missed vaccinations, there is a catch-up plan. China currently uses two types of HepA vaccine: inactivated hepatitis A vaccine (I-HepA), which is globally available, and a live attenuated hepatitis A vaccine (L-HepA) which is produced only in China and available in several developing countries including India. According to the catch-up schedule, HepA unvaccinated children under the age of 14 should receive one dose of L-HepA vaccine or two doses of I-HepA vaccine at least 6 months apart, depending on the vaccine chosen in the respective county of birth. he strengths of L-HepA vaccine include low cost, single dose injection, high protection and increased duration of immunity. As a result, 27 of the 31 provinces and cities in China select L-HepA vaccine for routine child immunization programs. A disadvantage of L-HepA vaccine is the theoretical possibility of the occurrence of reverse mutations of live vaccine strains. Therefore, for safety reasons, the health departments of Shanghai, Beijing, Tianjin, and Jiangsu that are the most affluent in China have purchased I-HepA vaccine for the regular childhood immunization program, which is safer, but more expensive compared with L-HepA vaccine. In conclusion, children born in Beijing, Shanghai, Tianjin, and Jiangsu are given one dose of I-HepA vaccine at the age of 18th and 24th month, respectively, while those born in other 27 provinces are given one dose of L-HepA vaccine at the age of 18th month. Data from Children Immunization Information Management System (CIIMS) shows that the HepA vaccine coverage is 98.8% among target children and 98.7% in L-HepA vaccine region. However, the denominator in CIIMS might be under-registered and will lead to overestimate of HepA coverage. Moreover, the provinces applying L-HepA vaccine vary in implementation of NIP, which could influence the effect of L-HepA vaccine, for example, the rural areas of China usually have low-quality implementation of NIP.

Since the 1990s, the socioeconomic development, improvement in environment hygiene and sanitation, large-scale provision of safe drinking water, and the application of HepA vaccine have led to a declined incidence of HepA in China. However, there are still some outbreaks of HepA in some parts of China, especially in rural areas of China. In May 2011, a HepA outbreak happened at an elementary school in rural area of Anhui province, and 28 pupils aged 7–13 years old were serologically confirmed HAV infection.[9] On August 10, 2013, an outbreak of HepA was reported in rural area of Jiangxi Province in southern China, and a total of 22 cases had been identified in the village (15 confirmed cases and 7 cases of asymptomatic infection). All cases were children aged below 15 years old, and their mean age was 8.5 years old.[10] It is important to emphasize that majority of the HepA outbreaks occurred in L-HepA vaccine regions, which proposes the doubt on vaccination coverage of L-HepA vaccine in those areas. This study attempted to estimate the vaccination coverage of L-HepA vaccine in 2016 among children aged 24–59 months in rural areas of China and identify the factors hindering the high vaccination coverage in those areas.

2. Methods

2.1 Data source and study design

The community-based cross-sectional study was conducted in 20 rural counties from 10 provinces (Ningxia, Hebei, Jiangxi, Qinghai, Henan, Guizhou, Yunnan, Xinjiang, Sichuan, and Tibet) in 2016. United Nations International Children's Emergency Fund (UNICEF) staffs, the research teams from Peking University Health Science Center, Lanzhou University, Guangxi Medical University, Capital Medical University and Chongqing Medical University, as well as government officials and field staff from 20 counties worked together on this survey. The survey was approved by Peking University Health Science Center's ethics committee. 20 counties of 10 provinces were selected by the Chinese Ministry of Health and UNICEF rather than sampled randomly. In our study, a three-stage probability proportion to size sampling (PPS) procedure was adopted to select target subjects. In the first stage, 15 administrative villages were randomly selected through PPS method in each identified county. In the second stage, 2 natural villages were randomly selected by PPS method in each administrative village. In the third stage, in each natural village, 8 households were selected as the target subjects by simple random sampling according to the roster of households with child under 5 years old provided by the village doctors. The questionnaire used in our study was based on UNICEF's Multiple Indicator Cluster Surveys (MICS) questionnaire.[11] Information concerning sociodemographic characteristics, socioeconomics characteristics, and the vaccination history of L-HepA vaccine were collected through the questionnaire. Additionally, field staff confirmed the date of L-HepA vaccine with the vaccination card provided by caregivers.

2.2 Measures

In our study, the primary outcome was one single dose coverage of live attenuated hepatitis A vaccine among children with a vaccination card, which is coded as "vaccinated" and "unvaccinated" according to information from vaccination card. Children born in 10 provinces we surveyed are given one dose of L-HepA vaccine at the age of 18th month, so we selected children aged 24–59 months with a vaccination card as our study subjects. The level of household income was defined based on quintiles in the distribution of income of residents in the areas. The bottom fifth of households were allocated to household income group 1 (Quintile 1), while the richest fifth of households assigned to household income group 5 (Quintile 5).

2.3 Analysis

In our analysis, we used three-stage sampling method to select children under 5 years old in 2016, which explained in details in the methodology, and then the survey data were clustered with a hierarchical structure (households nested within natural village, and natural village nested within administrative villages), so we considered the clustering effect of the survey design in the analysis. For the statistical analysis, we used STATA's SVY command to adjust for clustering. We firstly used the svyset command to define our complex sampling designs, including the three levels: administrative villages as primary sampling unit, natural villages as secondary sampling unit and households as final sampling unit. Svyset declares the data to be complex survey data, designates variables that contain information about the survey design. And then, we start to analyze the data using the corresponding commands after declare survey design for dataset. All our data analysis was conducted under the command of SVY. We firstly described the basic characteristics of children who received the one single dose of live attenuated hepatitis A vaccine, and the one single dose coverage of live attenuated hepatitis A vaccine were calculated. Difference in one single dose coverage of live attenuated hepatitis A vaccine across sub-groups stratified by basic characteristics was assessed by the Pearson chi-square tests. Then, we used logistic regression models to assess if there was an association between determinants and unvaccinated one dose coverage of live attenuated hepatitis A vaccine. The covariates assessed in above models on one dose coverage of live attenuated hepatitis A vaccine included child age, child gender, birth order, birth place, being left-behind, low birth weight, education level of caregiver, caregiver's ethnicity and level of household income. The strength of associations between one dose coverage of live attenuated hepatitis A vaccine and other covariates were estimated as odds ratios (ORs) and 95% confidence intervals (95% CI). All the statistical analyses were conducted using STATA 15.0, and the significance level were set at 0.05.

3. Results

In the 20 counties we investigated, the number of children under the age of 5 who were sampled was 5,196, and the actual number completed was 4,619, and the response rate was 88.9%. Among the 4,619 questionnaires collected, 131 unqualified questionnaires were excluded due to serious missing items, logical errors and other reasons, with a qualified rate of 97.2%. Finally, 4,488 questionnaires for children under 5 years old and their caregivers were retained for analysis.

A total of 2,254 children aged 24–59 months and their caregivers were investigated, of which 1979 provided the vaccination cards were include in the final data analysis. As shown in Table 1, 57.3% participants were boys and 42.7% were girls. More than half of the children were in two birth order or higher (59.0%). 4.8% of children were born at

Table 1. characteristics of one single dose coverage of live attenuated Hepatitis A vaccine among children aged 24–59 months with an immunization card in 2016.

Characteristics		N	n	%	Design-based F test	P-value
Gender	Boys	1,133	866	76.4	1.456	.236
	Girls	846	660	78.0		
Age (month)	24–35	870	648	74.5	1.855	.177
	36–47	613	492	80.3		
	48–59	496	386	77.8		
Birth order of child	1	812	670	82.5	8.503	.002
	2	844	643	76.2		
	≥3	323	213	65.9		
Birth place of child	County hospital and above	1,653	1,291	78.1	4.441	.021
	Township hospital	227	178	78.4		
	At home or others	95	55	57.9		
Left-behind child	No	888	693	78.0	1.377	.249
	Yes	933	708	75.9		
Low-birth-weight child	No	1,696	1,335	78.7	0.233	.633
	Yes	114	88	77.2		
Caregiver's ethnicity	Han	1,019	801	78.6	0.244	.624
	Minority	960	725	75.5		
Caregiver's education	Illiterate	319	240	75.2	0.525	.580
	Primary school	492	375	76.2		
	Junior middle school	842	644	76.5		
	High school and above	326	267	81.9		
Per capita income of household (yuan)	Quintile 1	246	165	67.1	4.047	.009
	Quintile 2	196	149	76.0		
	Quintile 3	197	146	74.1		
	Quintile 4	333	264	79.3		
	Quintile 5	245	209	85.3		
Total		1,979	1,526	77.1		

Table 2. Factors associated with unvaccinated one dose coverage of live attenuated Hepatitis A vaccine among children aged 24–59 months with an immunization card in 2016 by multivariate logistic regression model.

Characteristics		Crude OR (95%CI)	Adjusted OR (95%CI)
Birth order of child	1	1	1
	2	1.47(1.10,1.98)	1.40(1.03,1.90)
	≥3	2.44(1.41,4.22)	2.10(1.26,3.51)
Birth place of child	County hospital and above	1	1
	Township hospital	0.98(0.64,1.51)	0.89(0.57,1.38)
	At home	2.59(1.17,5.75)	2.01 (1.04,3.88)
Per capita income of household (yuan)	Quintile 1	2.85(1.33,6.10)	2.36(1.11,4.99)
	Quintile 2	1.83(0.88,3.80)	1.57(0.75,3.27)
	Quintile 3	2.03(1.14,3.59)	1.59(0.71,3.53)
	Quintile 4	1.52(0.82,2.82)	1.46(0.77,2.77)
	Quintile 5	1	1

home. Nearly half of the caregivers belonged to a minority ethnic group (48.5%). Most of the caregivers had secondary education, but the proportion of illiteracy was as high as 16.1%.

Overall, one single dose coverage of live attenuated hepatitis A vaccine was 77.1%. The coverage was statistically different across different group of birth order, birth place and per capita income of household ($P < 0.05$). One single dose coverage of live attenuated hepatitis A vaccine was lower in children who were second or later child in the family, born at home and from household with low per capita income (Table 1).

The regression analysis showed that being second child in the family (adjusted OR: 1.40; 95%CI: 1.03–1.90), being third or later child in the family (adjusted OR: 2.10; 95%CI: 1.26–3.51), being born at home (adjusted OR: 2.01; 95%CI: 1.04–3.88) and having the lowest per capita income of household (adjusted OR: 2.36; 95%CI: 1.11–4.99) were significantly related to unvaccinated one single dose coverage of live attenuated hepatitis A vaccine (Table 2).

4. Discussion

Our study showed that one single dose coverage of live attenuated hepatitis A vaccine was 77.1% in 20 rural counties from 10 provinces in China. Data from National Notifiable Disease Reporting System (NNDRS), which are managed by China CDC, showed that the coverage of HepA vaccine was 98.8% among target children between 2008 and 2016 in China, especially 98.7% in L-HepA vaccine regions.[12] Although the results of that national data show that the coverage of L-HepA vaccine closes to full coverage averagely across, our findings show that the coverage of L-HepA vaccine was still at a relatively low level in some areas of China, especially in rural areas of China. The Chinese government should give high priority to strengthening the vaccination of L-HepA vaccine in rural areas of China.

We found that being the second or later child in the family was significantly related to risk of missing L-HepA vaccination. One possible explanation is the uneven distribution of family resources, including parents' attention and time commitment to children. For families with 2 or more children, parents' attention and time allocated for the second or later child would be relatively reduced.[13] Another possible reason is the concern from parents on vaccination. Several adverse events of vaccines from the national routine vaccination program were reported by the media in recent years in China, which hinders the vaccination of L-HepA vaccine to some extent.

Our results showed that compared with children born in hospitals (county hospital and above: 78.1%; township hospital: 78.4%), the coverage of L-HepA vaccine for children born at home (57.9%) was lower, and being born at home (adjusted OR: 2.01; 95%CI: 1.04–3.88) was significantly related to unvaccinated proportion of L-HepA vaccine. Although China's hospital delivery rate increased significantly in the past few decades, home delivery still exists in rural areas of China.[9] In 2016, maternal hospital delivery rate reached 99.8%, but 36,920 newborns were still born at home at that year given the large population base in China.[9] It is important to point out that the families who are lack of access to hospital delivery also lack access to vaccination at same time, which can explain the lowest coverage of L-HepA vaccine for children born at home. Possible solutions to deal with this issue include continuing efforts to promote hospital delivery in rural areas of China and strengthening training for local health care workers.

In addition, our study demonstrated that the level of household income had significant effect on the coverage of L-HepA vaccine, although the hepatitis A vaccine is free to vaccinate in China. There may be some reasons for this finding. First, compared with high-income families, low-income families lack access to primary health care so that they cannot obtain basic public health services, like vaccination. Second, poorest people may be inclined to spend time on income-earning opportunities rather than access to health services whose benefits are difficult to achieve.[10] Last but not the least, HepA vaccine is vaccinated free of charge in China, but there are many indirect costs such as expenses on transportation and time cost of parents on child vaccination.[12] The high indirect costs will be a potential obstacle to L-HepA vaccination.

The main strength of our study is that we reported the coverage of L-HepA vaccine in rural areas of China, which is rarely reported in previous studies conducted in China. However, there are several limitations for our study. Firstly, our study population was not representative of the whole child population in the 10 provinces. The 20 counties of 10 provinces were decided by the Chinese Ministry of Health and UNICEF instead of random selection. In addition, since vaccination information of L-HepA vaccine should be acquired by reviewing the vaccination card, we lacked the information of L-HepA vaccine for children who cannot provide vaccination card in the interview.

Acknowledgments

This work was funded by a grant from UNICEF China ("Health, Nutrition and WASH" [NO.501]). We want to thank research teams from Peking University, Lanzhou University, Guangxi medical University, Capital Medical University, Chongqing Medical University for their contributions in orchestrating the field work and identifying study population. We also want to thank all of family members who participated in this study from the 20 counties of 10 provinces in China.

Disclosure of potential conflicts of interest

All authors approved the final manuscript as submitted and had complete access to the study data that support the publication. This manuscript, including data and tables, has not been published elsewhere in whole or part, and is not under review for publication elsewhere. There is no conflict of interest that could inappropriately influence (bias) our work.

Funding

This work was supported by the UNICEF (China) "Health, Nutrition and WASH" [NO. 501].

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