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Title page

Title

Relationship between receipt of self-paid surrogate vaccines and completion of the national immunization program vaccine series

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ABSTRACT

Objective: Administration of self-paid surrogate vaccines (SPSV) instead of the national immunization program vaccines (NIPV) is common but controversial in China. We evaluated the relationship between receipt of the SPSV and completion of the NIPV series.

Design and settings: A cross-sectional study was conducted in Fujian province, China.

Participants: Children who were born from September 1, 2009 to August 31, 2011, and who had been residing in the township for at least three months, were randomly recruited from 34 townships.

Main outcomes measures: Outcomes were completion rate of the NIPV series and coverage rate of the SPSV.

Results: The study included 1,428 children, of whom 282 (19.7%) received with at least one dose of the SPSV. Administration of the SPSV was associated with an increase likelihood of completing the NIPV series (OR= 3.2, 95% CI: 1.3-7.6 in the total sample, and OR=4.0, 95% CI: 1.7-9.6 in the subsample of children in regions with the SPSV accessibility). Interactions analysis further showed that children without the SPSV in regions with the SPSV supply were less likely to complete the NIPV series when comparing with those in regions without the SPSV(OR=0.5, 95% CI: 0.2-0.8). The impact of the SPSV administration on completion of the NIPV series was larger among children whose parents with junior school or less (97.8% and 97.9% vs. 92.5% and 91.9%, both P<0.001) and among those with a timely hepatitis B vaccine first dose (98.5% vs. 94.0%, P<0.001).

Conclusions: The SPSV inoculation effectively promoted the completion of the NIPV series in children. Vaccine providers should pay more attention to the vulnerable children for completing

the NIPV series, such as children without receipt of the SPSV, especially among those whose parents with a lower education level.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study exploring the association between self-paid surrogate vaccines (SPSV) administration and the national immunization program vaccines (NIPV) series completion in China.
- Our study also reveals firstly the impact of the SPSV supply on the NIPV series completion.
- The subjects were selected randomly by lot quality assurance sampling from townships which were randomly extracted by the probability proportional to size sampling method, therefore, the sample had a good representation.
- The findings were important for vaccine policy makers to correctly view and manage the SPSV in the country.
- The sample size was not large enough, and we were not able to control all potential confounding factors (e.g. percentage of floating children, the level of regional economic development) in the analyses, both may limit the interpretation of some results.

INTRODUCTION

In China, there are two types of vaccines for children, the national immunization program vaccines (NIPV) and non-NIPV.[1] The NIPV series vaccination is free and compulsory (e.g. oral live attenuated polio vaccine, OPV), while the non-NIPV inoculation is chargeable and optional.[2] There is a special vaccine series in the non-NIPV, the self-paid surrogate vaccines (SPSV), which can be replaced of the corresponding NIPV. For example, children don't need to receive 3 doses of OPV if they had administrated the inactivated polio vaccine (IPV) series.

Whether to carry out service of the SPSV for children has been controversial in China. On the one hand, given worries about that the SPSV service may cause social injustice and affect the completion of the NIPV, the National Health and Family Planning Commission of the People's Republic of China (NHFPC) opposed the SPSV service.[3] In some areas, the Health Bureau even prohibited staff in immunization clinics (IC) from the SPSV vaccination for children. On the other hand, parents always think the SPSV was better than the NIPV (e.g. safer and more effective), the opinions has been strengthened since adverse events after the NIPV immunization had been reported.[4,5] Hence, parents may select the SPSV once they can afford the fee, and/or they think it's necessary (e.g. children are not in good condition for the NIPV). Moreover, staff of centers for disease control and prevention (CDC) and IC were willing to supply the SPSV services for children to reduce the troubles caused by adverse event following immunization (AEFI) (e.g. vaccine-associated paralytic poliomyelitis [VAPP] after OPV immunization)[6] and to create income for the unit.[7] Therefore, the SPSV immunization was widely performed in China, it was estimated that 18.05% of children had received at least one dose of the SPSV nationally.[1]

Previous studies primarily focused on describing coverage of self-paid vaccines (such as pneumococcal conjugate vaccine and influenza vaccine) and their determinants,[7,8,9] and

investigating coverage of the SPSV and/or its substitution rate to the NIPV.[1,10,11] However, no studies to date were conducted to probe the relationship between the SPSV vaccination and the NIPV series completion. Knowing the relationship is important for guidance and management of the SPSV service.

Furthermore, parents who choose to have their children been vaccinated the SPSV might not only show a better economic capacity (because the SPSV is charged),[1] but also have higher awareness of immunization (because they chose the SPSV instead of the NIPV). Better economic capacities and higher vaccination awareness were good for the NIPV series completion.[12,13] Moreover, previous studies had revealed that children who had initiated a delayed first dose of hepatitis B vaccine[14] and whose parents with lower educational levels were less likely to complete the NIPV series.[15] Therefore, it is reasonable to hypothesize that: (1) children receiving the SPSV might promote their completion of the NIPV series, and (2) the relationship between the SPSV administration and the NIPV completion might be modified by parents' education level and initiation time of the hepatitis B vaccine first dose. We aimed at assessing coverage rates of the SPSV and verifying the hypotheses.

METHODS

Participants and design

The survey was conducted in December 2013 in Fujian, China. Our study subjects were randomly recruited from those Chinese children who were born from September 1, 2009 to August 31, 2011 and who had been residing in the township for at least three months. Firstly, a township with a population less than 10,000 was combined with an adjacent township to ensure adequate sample for survey, resulting in 1,004 combined townships with a population of ≥

10,000 from the 1,058 townships in Fujian province. Secondly, 34 townships were randomly selected by the probability proportional to size sampling (PPS) method from the 1,004 townships. For each township sampled, five villages (the village where the township government was located and another four randomly selected villages) were sampled as village-level survey sites. Finally, at the village-level survey sites, lot quality assurance sampling (LQAS) was used to sample households for survey questionnaires and house visits. If no children of an appropriate age were available in the sampled households, neighboring households would be then selected as an alternative subject.

A total of 42 children were surveyed in each township, including 10 from the village where the township government was located and 8 each from the remaining four villages. At last, a total of 1,428 children were selected in the province. Records on vaccination certificates kept by parents or vaccination cards kept in IC were used as evidence of vaccine immunization. Children were considered unvaccinated if both the vaccination certificate and vaccination card were absent.

Outcomes

The primary outcome was completion rate of the NIPV series. Completion of the NIPV series was defined as children completed the NIPV series with correct/appropriate intervals for different vaccines and/or doses, in which children should finish 1 dose of Bacille Calmette-Guerin vaccine (BCG), 3 doses of hepatitis B vaccine (HBV), 3 doses of OPV, 4 doses of acellular pertussis-diphtheria-tetanus vaccine (DTaP), 2 doses of measles-containing vaccine (MCV), 2 doses of group A meningococcal polysaccharide vaccine (MPSV-A), 1 dose of HepA-L, and the first dose of attenuated Japanese encephalitis vaccine (JEV-L) by 3 years of age, and

complete the second dose of JEV-L by 4 years of age. Children who had received the SPSV were identified as completion of the corresponding NIPV. For example, children who finished two doses of inactivated Japanese encephalitis vaccine (JEV-I) by 3 years of age were identified completing the first dose of JEV-L.

The secondary outcome was coverage of the SPSV, which was defined as the percentage of children who had accepted one or more doses of the SPSV. In this study, the SPSV mainly included IPV (surrogate for OPV), DTaP and Haemophilus influenzae type B (HIB) conjugate vaccine (surrogate for DTaP), DTaP/IPV/HIB conjugate vaccine (surrogate for OPV and DTaP), group A/C meningococcal conjugate vaccine (surrogate for MPSV-A), hepatitis A and B combination vaccine (surrogate for HepA-L and HBV), HepA-I (surrogate for HepA-L), and JEV-I (surrogate for JEV-L).

Statistical analyses

Data were double entered using EpiData 3.1 software to ensure the consistency. Chi-square tests were performed to compare the distribution of categorical variables between children who completed the NIPV series and those with incompletion of the NIPV series. Multivariate logistic regression models were fitted to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for completion of the NIPV series. Pearson's correlation coefficient was evaluated the correlation between the NIPV series completion rate and the SPSV coverage rate in regions with the SPSV supply.

We run an interaction analysis to compare the completion rates among children in regions without the SPSV access (all without the SPSV vaccination) with children who had received the SPSV and those without the SPSV administration in regions with the SPSV supply. To examine

whether the relationship between receipt of the SPSV and completion of the NIPV series was modified by parents' education level and initiation time of the HBV first dose, we performed cumulative completion rate stratification analysis based upon parents' education level (Junior school or less vs. High school or above) and initiation time of the HBV first dose (> vs. ≤ 24 hours) by Kaplan-Meier analyses, in which the NIPV completion time (months) was set as "survival time", and Log rank was tested for each stratum.

All statistical tests were conducted using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). A P-value of <0.05 was considered as statistically significant.

RESULTS

Characteristics of the study population

In total, 1,428 children of an appropriate age were surveyed, of whom 282 (19.7%) received at least of one dose of the SPSV. Most of the children were of Han ethnicity (97.8%) and were local children (89.6%). More than half of the children were boys (54.0%) and two-year-olds (56.2%); and most children (85%) were born in hospitals at the county level and above.

Table 1 shows the population characteristics of the entire sample and the selected children in regions with the SPSV access, stratified by children with and without completion of the NIPV series. Children who had completed the NIPV series were more likely to have a history of the SPSV vaccination in the entire sample (20.4% *vs.* 7.7%, P=0.006) and in the selected sample (29.2% *vs.* 9.5%, P=0.001). Significant differences were observed in the age of child, ethnicity, and initiation time of the HBV first dose between the two groups in both the total and the selected samples (Table 1).

Receipt of the SPSV and completion of the NIPV series

Compared with children who didn't receive the SPSV, children who had administrated the SPSV were more likely to complete the NIPV series [OR, 3.2; 95% CI, 1.3 to 7.6; P=0.009] in the total sample. The OR rose to 4.0 (95% CI 1.7-9.6) in the subgroup of children in regions with the SPSV supply (Table 2). Children of three-year-olds and with timely initiation of the HBV first dose (<24 hours after birth) were more likely to complete the NIPV series than those of two-year-olds and with a delayed HBV first dose. The minority children were less likely to complete the NIPV series than the Han children (Table 2). Educational level of the child's father also affected completion of the NIPV series in the total sample, but insignificant in the subgroup sample (Table 2). The SPSV coverage was correlated with the NIPV series completion rate in children from regions with the SPSV access (correlation coefficient= 0.689; P=0.059) (Figure 1).

Interaction analysis results

Interestingly, interactions analysis showed that, after controlling for potential factors (child's gender, age, and nationality, parents' education level, etc.), compared with children in regions without the SPSV access, children who had received the SPSV were more likely to complete the NIPV series (OR,1.8; 95% CI 0.7-4.8, P=0.25), while those without the SPSV administration were less likely to complete the NIPV series (OR,0.5; 95% CI, 0.2-0.8, P=0.01), in regions with the SPSV supply.

We observed significant interactions between parents' educational level (Junior school or less vs. High school or above), initiation time of the HBV first dose (> vs. ≤ 24 hours after birth) and the SPSV administration in the NIPV series completion. Children with the SPSV receipt had a significant higher cumulative completion rate than those without the SPSV administration in

the subgroup of children whose parents with education level of junior school or less (97.8% vs. 92.5% for father's education level, and 97.9% vs. 91.9% for mother's education level, both P<0.001) (Figure 2 B, D). Similarly, children with timely initiation of a HBV first dose were more sensitive to the SPSV vaccination, the cumulative NIPV completion rate was higher among children receiving the SPSV than that among those without the SPSV administration (98.5% vs. 94.0%, P<0.001) (Figure 2 E). No significant was observed for children whose parents with education of high school and above and who with a delayed HBV first dose (Figure 2 A, C, F). However, the cumulative NIPV completion rate was significantly lower among children with a delayed HBV first dose irrespective of whether they received the SPSV than that among those with a timely HBV first dose (Chi-square value=29.99, P<0.001).

DISCUSSION

We found that the SPSV administration effectively improved the probability of the NIPV series completion, where the effect may be offset by high parents' education level and the delayed initiation of the HBV first dose. In China, frequent reports of adverse events in immunization, such as the Shanxi vaccine incident[4] and the Conde HBV event,[5] had further solidified the parents' views of "cheap is dear, and dear is cheap", they would choose the SPSV even if they have to pay an extra cost (each dose costs 18 to 630 RMB Yuan, mean: 156 RMB Yuan/dose, approximately $24.6/dose[16]). Moreover, receiving the SPSV may create revenue and reduce the troubles caused by the NIPV related AEFI, [10,17] therefore, children who chose the SPSV may be more popular and better to be treated with the staff in the IC. Hence, receiving the SPSV may be an indicator of the economic conditions and vaccination awareness of children' family, and

might get better service from the IC, resulting in that children had better compliance with immunization and were more likely to complete the NIPV series.[1,8,14,18-22].

Parents with lower education level always have certain characteristics (earn less, lack of knowledge, and have multiple children) that are not conducive to complete the NIPV series for their children; they might more sensitive to the price of the SPSV.[23-25] Whether to receive the SPSV may further reflect their true economic situation and immunization awareness, which leads to the difference of the NIPV series completion between the two groups. The HBV first dose are often delayed as a result of contraindications for children born in hospitals or of low medical accessibility for those born at home,[14,26,27] which might affect their catch-up vaccination of the NIPV series even if they had received the SPSV, resulting a significantly lower completion of the NIPV series than those with timely initiation of the HBV first dose.

Interestingly, we found that compared with those in regions without the SPSV service, the SPSV vaccination may enhance completion of the NIPV series but also significantly reduce the completion of the NIPV series for those without receiving the SPSV in regions with SPSV access, which showed supply of the SPSV may play a "double-sword" role in the NIPV series completion. Children who had administrated the SPSV may be better treated while those without the SPSV were treated simply and rudely, such discriminatory treatment may affect the enthusiasm of the completion of the NIPV series for those without the SPSV administration. Moreover, the difference of completion rate of the NIPV series between regions with and without the SPSV supply may be partly explained by the percentage of non-local children, which was proved as an impact factor for the NIPV series completion.[20,27] In our study, the percentage of non-local children was significantly lower in regions without SPSV the supply than that in regions with the SPSV access (3.1 vs. 13.4%, $P<0.001$).

We also found that the NIPV series completion rate was higher in children of three-year-olds, which was differed from findings of a previous study.[27] This inconsistency maybe explained by that three-year-olds usually start to attend kindergartens, where are required to examine the vaccination certificate of children under regulations, therefore prompting children to receive their missing vaccinations[28] and effectively improving the completion of the NIPV series in three-year-old children. Minority children were less likely to complete the NIPV series, which may be related to poor economic conditions of their families[29] and the lack of vaccination awareness of their parents.[30] Similar to previous studies,[31,32] we confirmed that timely HBV first dose initiation improved the NIPV series completion in children, possibly because receiving a timely HBV first dose might help emphasize the importance of vaccination to the parents, and promote their children' completion of the NIPV series.[14]

Our study has several limitations. Firstly, we included the SPSV, but not normal non-NIPV, such as the varicella vaccine and the influenza vaccine, which may introduce certain information bias. However, most normal non-NIPV is not administered until 2 years old of children, this bias might not affect the results of this study. Secondly, the moderate sample size of this study may limit the interpretation of some results. In addition, other factors, such as regional vaccination policy, the level of regional economic development, and vaccine supply and availability, will also affect the SPSV vaccination. Unfortunately, we were not able to include all these factors in the current study.

To the best of our knowledge, this is the first study exploring the association between the SPSV administration and the NIPV series completion in Fujian, China. Receipt of the SPSV can be used as a new indicator of completing the NIPV series for children. However, supply of the SPSV service play a "double-sword" role in the NIPV completion. Therefore, the health

authorities should decide whether to carry out the SPSV service basic on the actual situation, such as the percentage of non-local children, and staff in IC where the SPSV was access should focus on children without receipt of the SPSV, especially among children whose parents with a lower education level and those with a timely HBV first dose, and on those with a delayed HBV first dose irrespective of whether they received the SPSV. Moreover, the CDC should strengthen technical guidance for the SPSV immunization (e.g., formulation of sequential vaccination schedules for SPSV alternative to the corresponding NIPV).

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Table 1. Base characteristics of children in groups with and without completion of the NIPV series in total and selected sample

Characteristics	Total sample (N = 1428)			Population in regions with the SPSV access (N = 1008)		
	Incomplete group No. (%)	Complete group No. (%)	P value	Incomplete group n (%)	Complete group n (%)	P value
History of the SPSV administration			0.006			0.001
No	72 (92.3)	1074 (79.6)		57 (90.5)	669 (70.8)	
Yes	6 (7.7)	276 (20.4)		6 (9.5)	276 (29.2)	
Gender			0.620			0.550
Males	40 (51.3)	731 (54.1)		32 (50.8)	517 (54.7)	
Females	38 (48.7)	619 (45.9)		31 (49.2)	428 (45.3)	
Age at survey (years)			0.001			0.005
2 ~	56 (71.8)	746 (53.0)		45 (71.4)	502 (53.1)	
3 ~	22 (28.2)	634 (47.0)		18 (28.6)	443 (46.9)	
Nationality			<0.001			<0.001
Han	70 (89.7)	1327 (98.3)		55 (87.3)	922 (97.6)	
Minority	8 (10.3)	23 (1.7)		8 (12.7)	23 (2.4)	
Place of birth			0.350			0.201
County hospital or above	65 (83.3)	1149 (85.1)		54 (85.7)	777 (82.2)	
Township hospital	12 (15.4)	197 (14.6)		8 (12.7)	165 (17.5)	
Home	1 (1.3)	4 (0.3)		1 (1.6)	3 (0.3)	
Hukou			0.980			0.970
Local county	69 (88.5)	1211 (89.7)		54 (85.7)	819 (86.7)	
Another county in Fujian province	4 (5.1)	66 (4.9)		4 (6.3)	61 (6.5)	
Other provinces	4 (5.1)	61 (4.5)		4 (6.3)	56 (5.9)	
No hukou	1 (1.3)	12 (0.9)		1 (1.6)	9 (1.0)	
Mother's educational level			0.008			0.003
Junior school or less	68 (87.2)	967 (71.6)		56 (88.9)	652 (69.0)	
High and technical school	8 (10.3)	240 (17.8)		6 (9.5)	189 (20.0)	
College or higher	2 (2.5)	143 (10.6)		1 (1.6)	104 (11.0)	
Father's educational level			0.001			0.002
Junior school or less	69 (88.5)	925 (68.5)		55 (87.3)	629 (66.6)	
High and technical school	7 (9.0)	261 (19.3)		7 (11.2)	197 (20.8)	
College or higher	2 (2.5)	164 (12.2)		1 (1.5)	119 (12.6)	
Initiation time of the Hepatitis B vaccine first dose			0.004			0.001
> 24 hours	9 (11.5)	59 (4.4)		9 (14.3)	42 (4.44)	
≤ 24 hours	69 (88.5)	1291 (95.6)		54 (85.7)	903 (95.6)	

Table 2. Odds ratios and 95% confidence intervals for completion of the NIPV series

Characteristics	Total sample (N = 1,428)		Population in regions with the SPSV access (N = 1,008)	
	Odds ratios (95% CI)	*P* value	OR (95% CI)	*P* value
History of the SPSV administration				
No	Reference		Reference	
Yes	3.2 (1.3-7.6)	0.009	4.0 (1.7-9.6)	0.002
Gender				
Males	Reference		Reference	
Females	0.8 (0.5-1.3)	0.46	0.8 (0.5-1.4)	0.45
Age at survey (years)				
2 ~	Reference		Reference	
3 ~	2.5 (1.5-4.3)	<0.001	2.5 (1.4-4.6)	0.002
Nationality				
Han	Reference		Reference	
She	0.2 (0.1-0.4)	<0.001	0.2 (0.1-0.5)	0.001
Place of birth				
County hospital or above	Reference		Reference	
Township hospital	1.1 (0.6-2.1)	0.77	1.9 (0.9-4.2)	0.12
Home	0.4 (0.04-5.0)	0.50	0.6 (0.04-7.9)	0.69
Hukou				
Local	Reference		Reference	
Another county in Fujian province	0.7 (0.2-2.0)	0.47	0.8 (0.3-2.6)	0.75
Other provinces	0.7 (0.2-2.1)	0.55	0.8 (0.3-2.3)	0.66
No hukou	1.4 (0.1-13.8)	0.79	1.6 (0.1-18.2)	0.73
Mother's educational level				
Junior school or less	Reference		Reference	
High and technical school	1.1 (0.5-2.5)	0.86	1.4 (0.5-3.7)	0.54
College or higher	1.7 (0.3-9.4)	0.55	2.7 (0.3-25.2)	0.39
Father's educational level				
Junior school or less	Reference		Reference	
High and technical school	2.4 (1.0-5.8)	0.05	1.9 (0.8-4.9)	0.17
College or higher	4.5 (0.8-25.1)	0.08	6.7 (0.7-63.9)	0.10
Initiation time of the hepatitis B vaccine first dose				
> 24 hours	Reference		Reference	
≤ 24 hours	2.8 (1.2-6.2)	0.01	4.1 (1.7-9.8)	0.002

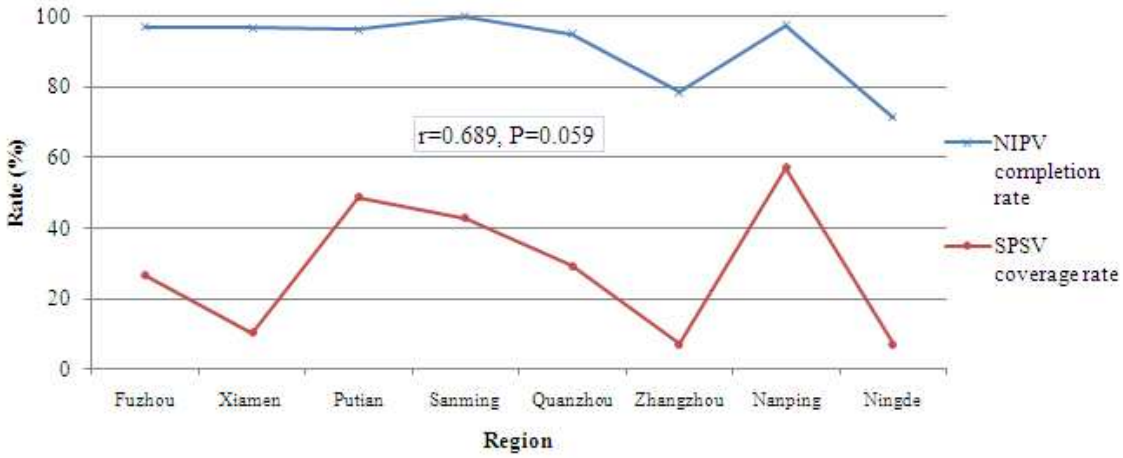

Figure 1. The correlation analysis between the NIPV series completion rate and the SPSV coverage rate in regions with the SPSV supply.

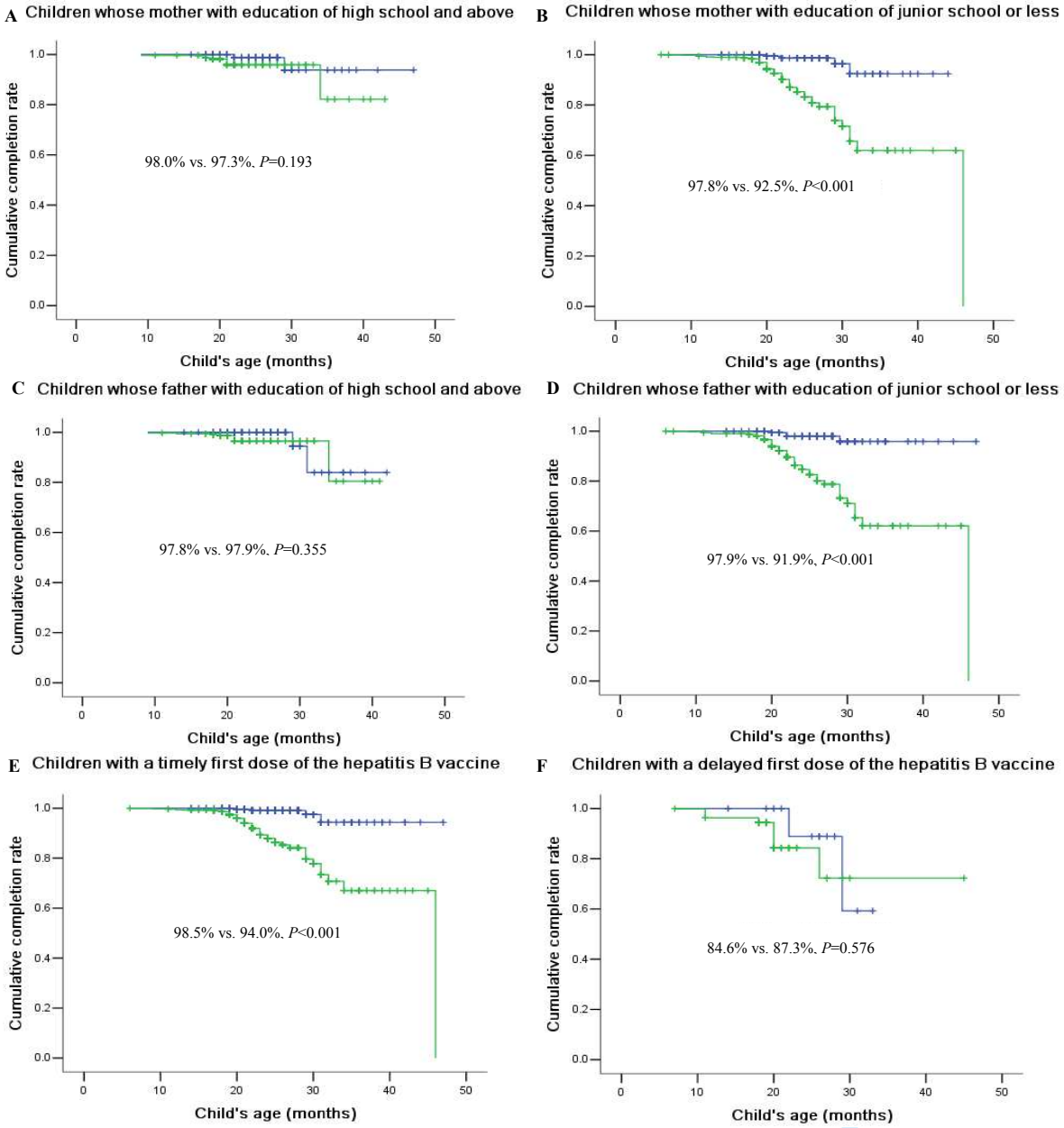

Figure 2. Kaplan-Meier estimates of the NIPV series cumulative completion rate according to the receipt of the SPSV, stratified by parents' education level and initiation time of the hepatitis B first dose.

Checklist report

(manuscript ID bmjopen-2016-015666)

	Item No	Recommendation	Page in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6-7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	---
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls	---
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	6-7
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	---
		Case-control study—For matched studies, give matching criteria and the number of controls per case	---
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8
Bias	9	Describe any efforts to address potential sources of bias	6, 8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9

		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	no missing data(7)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	---
		Case-control study—If applicable, explain how matching of cases and controls was addressed	---
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	6-7
		(*e*) Describe any sensitivity analyses	8-9

BMJ Open

Relationship between receipt of substitutable for-fee vaccines and completion of the expanded program on immunization: a cross-sectional study in Fujian, China

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Title page

Title

Relationship between receipt of substitutable for-fee vaccines and completion of the expanded program on immunization: a cross-sectional study in Fujian, China

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ABSTRACT

Objective: To evaluate the relationship between receipt of the substitutable for-fee vaccines (SFV) and completion of the expanded program on immunization (EPI).

Design and settings: A cross-sectional study was conducted in Fujian province, China.

Participants: Children who were born from September 1, 2009 to August 31, 2011, and who had been residing in the township for at least three months, were randomly recruited from 34 townships.

Main outcomes measures: Outcomes were completion rate of the EPI and coverage rate of the SFV.

Results: The study included 1,428 children, of whom 1350 (94.5%) finished the EPI and 282 (19.7%) received at least one dose of the SFV. Administration of the SFV was associated with an increased likelihood of completing the EPI (OR= 3.2, 95% CI: 1.3-7.6 in the total sample, and OR=4.0, 95% CI: 1.7-9.6 in the subsample of children in regions with the SFV accessibility). The impact of the SFV administration on completion of the EPI was larger among children whose parents have junior school education or less (97.8% and 97.9% vs. 92.5% and 91.9%, both P<0.001) and among those with a timely hepatitis B vaccine first dose (98.5% vs. 94.0%, P<0.001).

Conclusions: The SFV inoculation effectively promoted the completion of the EPI in children.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study exploring the association between substitutable for-fee vaccines (SFV) administration and the expanded program on immunization (EPI) completion in China.
- The subjects were selected randomly by lot quality assurance sampling from townships which were randomly extracted by the probability proportional to size sampling method, as well as a high response rate (100%) in the survey, therefore, the sample had a good representation.
- The findings may help target vulnerable children and improve the implementation of the SFV policy in China.
- The sample size was not large enough, and we were not able to control all potential confounding factors in the analyses, both may limit the interpretation of some results.

INTRODUCTION

China has an expanded program on immunization (EPI) which includes 1 dose of Bacille Calmette-Guerin vaccine (BCG), 3 doses of hepatitis B vaccine (HepB), 4 doses of oral live attenuated polio vaccine (OPV), 4 doses of acellular pertussis diphtheria tetanus vaccine (DTaP), 2 doses of measles-containing vaccine (MCV), 2 doses of group A meningococcal polysaccharide vaccine (MPSV-A), 2 doses of live-attenuated Japanese encephalitis vaccine (JE-L), 1 dose of live-attenuated hepatitis A vaccine (HepA-L), 1 dose of diphtheria tetanus vaccine (DT), and 2 doses of meningococcal A+C polysaccharide vaccine (MPSV-AC).[1] All of these vaccines are provided to the public as free vaccines. In addition, parents can choose to purchase variants that are for-fee vaccines, including normal and substitutable for-fee vaccines (SFV).[2-3] For example, pneumococcal conjugate vaccine is a normal for-fee vaccine, while inactivated polio vaccine (IPV) is a substitutable for-fee vaccine and can be a substitute for OPV.

Whether to carry out service of the SFV for children has been controversial in China. On the one hand, given worries that the SFV service may cause social injustice and affect the completion of the EPI, the National Health and Family Planning Commission of the People's Republic of China (NHFPC) opposed the SFV service.[4] In some areas, the Health Bureau even prohibited staff in immunization clinics (IC) from administering the SFV vaccination to children. On the other hand, parents always think the SFV was better than the free vaccines (e.g. safer and more effective), the opinions have been strengthened since the adverse events after the EPI immunization was reported.[5,6] Hence, parents may select the SFV once they can afford the fee, and/or they think it's necessary (e.g. children are not in good condition for the free vaccines). Moreover, vaccine providers may recommend the SFV once they thought the SFV was safer than free vaccines, worried about the troubles caused by adverse events following immunization

(AEFI) (e.g. vaccine-associated paralytic poliomyelitis [VAPP] after OPV immunization)[7], and were under pressure to create income for the unit.[8] Therefore, the SFV immunization was widely performed in China, it was estimated that 18.05% of children had received at least one dose of the SFV nationally, and the coverage of the SFV was higher among children in eastern areas than that in western regions.[2]

Previous studies primarily focused on describing coverage of normal for-fee vaccines (such as pneumococcal conjugate vaccine and influenza vaccine) and their determinants,[8-10] and investigating coverage of the SFV and/or its substitution rate to the free vaccines.[2,11,12] However, no studies to date were conducted to probe the relationship between the SFV vaccination and the EPI completion. Knowing the relationship is important for guidance and management of the SFV service, such as, if the SFV were conductive to complete the EPI for children, the NHFPC may improve the policy of SFV and encourage vaccination with the SFV for children who can afford the vaccine fee.

Furthermore, parents who choose to have their children vaccinated, the SFV might not only show a better economic capacity (because the SFV is charged),[2] but also have higher awareness of immunization (because they chose the SFV instead of the free vaccines). Better economic capacities and higher vaccination awareness were good for the EPI completion.[13,14] Moreover, previous studies had revealed that children who had initiated a delayed first dose of hepatitis B vaccine[1] and whose parents have lower educational levels were less likely to complete the EPI.[15] Therefore, it is reasonable to hypothesize that: (1) children receiving the SFV might promote their completion of the EPI, and (2) the relationship between the SFV administration and the EPI completion might be modified by parents' education level and initiation time of the hepatitis B

vaccine first dose. We aimed at assessing coverage rates of the SFV and verifying the hypotheses.

METHODS

Participants and design

The cross-sectional study was part of a national EPI coverage rate investigation which was set by the China CDC and was conducted in December 2013 in Fujian, China. Details of the national survey have been described elsewhere.[16,17] In brief, Chinese children aged 2 to 4 years old at the time of the survey (born from September 1, 2009 to August 31, 2011) and who had been residing in the township for at least three months were included as target subjects, and were randomly selected for the survey. Firstly, a township with a population less than 10,000 was combined with an adjacent township to ensure adequate sample for survey, resulting in 1,004 combined townships with a population of ≥ 10,000 from the 1,058 townships in Fujian province. Secondly, 34 townships were randomly selected by the probability proportional to size sampling (PPS) method from the 1,004 townships. For each township sampled, five villages (the village where the township government was located and another four randomly selected villages) were sampled as village-level survey sites. Finally, at the village-level survey sites, lot quality assurance sampling (LQAS) was used to sample households for survey.

Parents or guardians of the children were interviewed by a standardized questionnaire which was set by China CDC. The questionnaire contained 2 major items, including basic information and vaccination history. Measures of family socioeconomic situations (home address, types of living areas, and education level of the parents) and child's information (name, gender, birth date, place of delivery, ethnicity, and types of household register) were collected and included in the

analyses as potential confounding factors. Records on vaccination certificates kept by parents or vaccination cards kept in IC, rather than parents' memories of vaccination, were extracted as evidence of vaccine immunization to avoid possible recall bias. Children were considered unvaccinated if both the vaccination certificate and vaccination card were absent. It took about 10 minutes to complete a questionnaire. Newborns who received a HepB in the first and second day of birth were deemed to finish the vaccine within 24 hours and have a timely HepB first dose in our analysis,[1] because it's hard to calculate the exact hours that the babies receive the vaccine.

A total of 42 children were surveyed in each township, including 10 from the village where the township government was located and 8 each from the remaining four villages. Ultimately, a total of 1,428 children were selected in the province. Because this was part of regular national public health evaluation of EPI coverage by the township level, all selected subjects should be surveyed, therefore the response rate in our study was 100%.[18] The sampling method was identified as a suitable method for evaluation of the EPI coverage rate by the township level, and the sample (42 children) of each township had a power of 90% to detect whether the coverage rate of EPI reached 90% with a 0.05 significance level.[18] The study was part of a national EPI coverage rate investigation and was approved by the China CDC.

Outcomes

The primary outcome was completion rate of the EPI. which was defined as the percentage of children who had finished the EPI. Completion of the EPI was defined as children completing the EPI according to the recommended immunization schedule. Children aged 2 to 3 years old should finish 1 dose of BCG, 3 doses of HepB, 3 doses of OPV, 4 doses of DTaP, 2 doses of MCV, 2 doses of MPSV-A, 1 dose of HepA-L, and the first dose of JE-L, and an additional

second dose of JE-L was demanded for children of 3 to 4 ages. Vaccination earlier than the initiation schedules time of vaccines and with incorrect intervals between different doses of vaccines was defined as ineffective vaccination.

Children who had received the SFV in accordance with immunization schedule were identified as completing the corresponding free vaccines. The equivalencies between SFV and free vaccines were as follow:[19] (1) For HepB, DaTP, OPV and MPSV-A, one dose of SFV was equivalent to one dose of free vaccine. (2) For JE-L, two doses of inactivated Japanese encephalitis vaccine (JE-I) should be vaccinated for children by 3 years of age, and a third JE-I dose be given by 4 years old, which were equal to the first dose and the second dose of JE-L, respectively. (3) For HepA-L, one dose of inactivated hepatitis A vaccine (HepA-I) was equal to one dose of HepA-L for children aged less than 3 years old. However, children who had received a dose of HepA-I should accept another HepA-I dose by 4 years old, which was identified as completion of the HepA-L for children aged 3 to 4 years old.

The secondary outcome was coverage of the SFV, which was defined as the percentage of children who had accepted one or more doses of the SFV. In this study, the SFV included IPV (surrogate for OPV), DTaP and Haemophilus influenzae type B (HIB) conjugate vaccine (surrogate for DTaP), DTaP/IPV/HIB conjugate vaccine (surrogate for OPV and DTaP), group A/C meningococcal conjugate vaccine (surrogate for MPSV-A), hepatitis A and B combination vaccine (surrogate for HepA-L and HepB), HepA-I (surrogate for HepA-L), and JE-I (surrogate for JE-L).

Statistical analyses

Data was double entered using EpiData 3.1 software to ensure the consistency and avoid information bias. Multivariate logistic regression models were fitted to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for completion of the EPI, after controlling for the potential confounding factors. Pearson's correlation coefficient was evaluated to intuitively reflect the correlation between the EPI completion rate and the SFV coverage rate in regions with the SFV supply.

Due to the implementation of different policies, SFV for children were banned in some areas. To compare completion rates among children in regions with SFV access to Fujian as a whole, we also ran a multivariate logistic regression analysis in the regions of Fujian with access to the SFV. Children were further divided into three groups, including children living in areas without SFV access (these children didn't receive SFV because there was no SFV in the areas), children without history of SFV vaccination in areas with SFV access, and children who received the SFV in areas with SFV access. Logistic regression models were remodeled to compare the EPI coverage rates among the three groups.

To examine whether the relationship between receipt of the SFV and completion of the EPI was modified by parents' education level and initiation time of the HBV first dose, we performed cumulative completion rate stratification analysis based upon parents' education level (Junior school or less vs. High school or above) and initiation time of the HBV first dose (> vs. ≤ 24 hours) by Cox proportional hazards analyses, in which the EPI completion time (months) was set as "survival time".

All statistical tests were conducted using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). A P-value of <0.05 was considered as statistically significant.

RESULTS

Characteristics of the study population

In total, 1,428 children of an appropriate age were surveyed, of whom 1350 (94.5%) finished the EPI, and 282 (19.7%) received at least of one dose of the SFV. Most of the children were of Han ethnicity (97.8%) and were local children (89.6%). More than half of the children were boys (54.0%) and two-year-olds (56.2%); and most children (85%) were born in hospitals at the county level and above.

Table 1 shows the population characteristics of the entire sample and the selected children in regions with the SFV access, stratified by children with and without completion of the EPI. Children who had a history of the SFV were more likely to complete the EPI than those who hadn't received the SFV (97.9% *vs.* 93.7%) in total sample, as well as in the selected sample (97.9% *vs.* 92.1%).

Receipt of the SFV and completion of the EPI

Compared with children who didn't receive the SFV, children who had administrated the SFV were more likely to complete the EPI [unadjusted OR,3.1, 95% CI, 1.3 to 7.2, and adjusted OR, 3.1; 95% CI, 1.3 to 7.4; P=0.009] in the total sample. The adjusted OR rose to 3.9 (95% CI 1.6-9.4) in the subgroup of children in regions with the SFV supply (Table 2). Children of three-years-old and with timely initiation of the HepB first dose (<24 hours after birth) were more likely to complete the EPI than those of two-years-old and with a delayed HepB first dose. The minority children were less likely to complete the EPI than the Han children (Table 2). Educational level of the child's father also affected completion of the EPI in the total sample, but insignificant in the subgroup sample (Table 2). The SFV coverage was correlated with the EPI

completion rate in children from regions with the SFV access (correlation coefficient= 0.689; P=0.059) (Figure 1).

After controlling for potential factors (child's gender, age, and nationality, parents' education level, etc.), compared with children in regions without the SFV access, children who had received the SFV were more likely to complete the EPI (OR,1.8; 95% CI 0.7-4.8, P=0.25), while those without the SFV administration were less likely to complete the EPI (OR,0.5; 95% CI, 0.2-0.8, P=0.01), in regions with the SFV supply.

Stratified analyses

We observed significant differences of EPI coverage rates between groups of children with and without the SFV administration by stratifications of parents' educational level (Junior school or less vs. High school or above) and initiation time of the HBV first dose (> vs. ≤ 24 hours after birth). Children with the SFV receipt had a significantly higher cumulative completion rate than those without the SFV administration in the subgroup of children whose parents with education level of junior school or less (97.8% vs. 92.5% for mother's education level, and 97.9% vs. 91.9% for father's education level, both P<0.001) (Figure 2 B, D). Similarly, children with timely initiation of a HepB first dose were more sensitive to the SFV vaccination, the cumulative EPI completion rate was higher among children receiving the SFV than that among those without the SFV administration (98.5% vs. 94.0%, P<0.001) (Figure 2 E). No significant result was observed for children whose parents have education of high school and above and who had received a delayed HBV first dose (Figure 2 A, C, F).

DISCUSSION

We found that the SFV administration effectively improved the probability of the EPI completion, where the effect may be offset by high parents' education level and the delayed initiation of the HBV first dose. In China, frequent reports of adverse events in immunization, such as the Shanxi vaccine incident[5] and the Conde HBV event,[6] had further solidified the parents' views of "cheap is dear, and dear is cheap", they would choose the SFV even if they have to pay an extra cost (each dose costs 18 to 630 RMB Yuan, mean: 156 RMB Yuan/dose, approximately $24.6/dose[20]). Moreover, receiving the SFV may create revenue and reduce the incidence of AEFI caused by the free vaccines, [11,21] therefore, children who chose the SFV might be treated more enthusiastically by the staff in the IC than those who chose the free vaccines. Hence, receiving the SFV may be an indicator of the economic conditions and vaccination awareness of children' families, and might ensure better service from the IC, resulting in children having better compliance with immunization and being more likely to complete the EPI.[1,2,9,22-26].

Parents with lower education level have certain characteristics (earn less, lack of knowledge, and have multiple children) that are not conducive to complete the EPI for their children;[27,28] they might be more sensitive to the price of the SFV.[27-29] Whether to receive the SFV may further reflect their economic situation and immunization awareness, which leads to the difference of the EPI completion between the two groups. The HepB first dose are often delayed as a result of contraindications for children born in hospitals or of low medical accessibility for those born at home,[1,30,31] which might affect their catch-up vaccination of the EPI even if they had received the SFV, resulting in a significantly lower completion of the EPI than those with timely initiation of the HepB first dose.

Interestingly, we found that the supply of the SFV may play a "double-sword" role in the EPI completion. Vaccine providers may differentiate children who had received the SFV from

those with the free vaccines, which may lead to a decline in the enthusiasm of the completion of the EPI for those administrating the free vaccines.[32] Moreover, the difference of completion rate of the EPI between regions with and without the SFV supply may be partly explained by the percentage of non-local children, which was proved as an impact factor for the EPI completion.[24,31] In our study, the percentage of non-local children was significantly lower in regions without SFV supply than that in regions with the SFV access (3.1 vs. 13.4%, P<0.001).

We also found that the EPI completion rate was higher in children of three-years-old, which differed from findings of a previous study.[31] This inconsistency may be explained due to the fact that three-years-old usually start to attend kindergartens, which are required to examine the vaccination certificate of children under regulations, therefore prompting children to receive their missing vaccinations[33] and effectively improving the completion of the EPI in three-year-old children. Minority children were less likely to complete the EPI, which may be related to poor economic conditions of their families[34] and the lack of vaccination awareness of their parents.[35] Similar to previous studies,[36,37] we confirmed that timely HepB first dose initiation improved the EPI completion in children, possibly because receiving a timely HepB first dose might help emphasize the importance of vaccination to the parents, and promote their children' completion of the EPI.[1]

Our study has several limitations. Firstly, we included the SFV, but not normal for-fee vaccines, such as the varicella vaccine and the influenza vaccine, which might introduce certain information bias. However, most normal for-fee vaccines are not administered until children are 2 years old, this bias might not affect the results of this study. Secondly, the moderate sample size of this study may limit the interpretation of some results. Finally, other factors, such as access to health care, knowledge, attitudes and the practices of parents and providers, regional

vaccination policy, the level of regional economic development, will also affect the SFV vaccination. In addition, sociodemographic variables, such as the number of children, parent age, family income, etc, might be better indicators of the willingness to receive SFV than the parents' education level. Unfortunately, we were not able to include all these factors in the current study.

To the best of our knowledge, this is the first study exploring the association between the SFV administration and the EPI completion in Fujian, China. The impact of the SFV administration on completion of the EPI was larger among children whose parents have lower education level and among those with a timely Hep B first dose. Vaccine providers should focus on these vulnerable children and take measures to help complete the EPI on time. The generalizability of the results should be further studied.

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Footnotes

Contributors: JN Wu, Y Zhou and DJ Li had the initial idea for the study and designed the survey. JN Wu, MR Du and HL Piao collected and analyzed the data for this study. JN Wu wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version.

Funding: None.

Competing interests: None declared.

Data sharing statement: No additional data are available.

Table 1. Base characteristics of children in groups with and without completion of the EPI in total and selected sample

Characteristics	Total sample (N = 1428)		Population in regions with the SFV access (N = 1008)	
	Did not complete EPI No. (%)	Did complete EPI No. (%)	Did not complete EPI n (%)	Did complete EPI n (%)
History of the SFV administration				
No	72 (6.3%)	1074 (93.7%)	57 (7.9%)	669 (92.1%)
Yes	6 (2.1%)	276 (97.9%)	6 (2.1%)	276 (97.9%)
Gender				
Males	40 (5.2%)	731 (94.8%)	32 (5.8%)	517 (94.2%)
Females	38 (5.8%)	619 (94.2%)	31 (6.8%)	428 (93.2%)
Age at survey (years)				
2 ~	56 (7.3%)	746 (92.7%)	45 (8.2%)	502 (91.8%)
3 ~	22 (3.4%)	634 (96.6%)	18 (3.9%)	443 (96.1%)
Nationality				
Han	70 (5.0%)	1327 (95.0%)	55 (5.6%)	922 (94.4%)
Minority	8 (25.8%)	23 (74.2%)	8 (25.8%)	23 (74.2%)
Place of birth				
County hospital or above	65 (5.4%)	1149 (94.6%)	54 (6.5%)	777 (93.5%)
Township hospital	12 (5.7%)	197 (94.3%)	8 (4.6%)	165 (95.4%)
Home	1 (20.0%)	4 (80.0%)	1 (25.0%)	3 (75.0%)
Household registration				
Local registration	69 (5.4%)	1211 (94.6%)	54 (6.2%)	819 (93.8%)
Outside or no registration	9 (6.1%)	139 (93.9%)	9 (6.7%)	126 (93.3%)
Mother's educational level				
Junior school or less	68 (6.6%)	967 (93.4%)	56 (7.9%)	652 (92.1%)
High and technical school	8 (3.2%)	240 (96.8%)	6 (3.1%)	189 (96.9%)
College or higher	2 (1.4%)	143 (98.6%)	1 (1.0%)	104 (99.0%)
Father's educational level				
Junior school or less	69 (6.9%)	925 (93.1%)	55 (8.0%)	629 (92.0%)
High and technical school	7 (2.6%)	261 (97.4%)	7 (3.4%)	197 (96.6%)
College or higher	2 (1.2%)	164 (98.8%)	1 (0.8%)	119 (99.2%)
Initiation time of the Hepatitis B vaccine first dose				
> 24 hours	9 (13.2%)	59 (86.8%)	9 (17.6%)	42 (82.4%)

≤ 24 hours	69 (5.1%)	1291 (94.9%)	54 (5.6%)	903 (94.4%)

Table 2. Odds ratios and 95% confidence intervals for completion of the EPI

Characteristics	Total sample (N = 1,428)		Population in regions with the SFV access (N = 1,008)	
	Odds ratios (95% CI)	*P* value	Odds ratios (95% CI)	*P* value
History of the SFV administration				
No	Reference		Reference	
Yes	3.1 (1.3-7.4)	0.009	3.9 (1.6-9.4)	0.002
Gender				
Males	Reference		Reference	
Females	0.8 (0.5-1.4)	0.48	0.8 (0.5-1.4)	0.46
Age at survey (years)				
2 ~	Reference		Reference	
3 ~	2.5 (1.5-4.2)	0.001	2.5 (1.4-4.5)	0.002
Nationality				
Han	Reference		Reference	
She	0.2 (0.1-0.4)	<0.001	0.2 (0.1-0.5)	0.001
Place of birth				
County hospital or above	Reference		Reference	
Township hospital	1.1 (0.6-2.2)	0.74	1.9 (0.9-4.2)	0.10
Home	0.5 (0.05-5.8)	0.60	0.7 (0.06-9.2)	0.79
Household registration				
Local registration	Reference		Reference	
Outside or no registration	0.8 (0.4-1.6)	0.46	0.9 (0.4-1.9)	0.71
Mother's educational level				
Junior school or less	Reference		Reference	
High and technical school	1.1 (0.5-2.5)	0.83	1.4 (0.5-3.8)	0.50
College or higher	1.7 (0.3-9.4)	0.55	2.7 (0.3-25.8)	0.38
Father's educational level				
Junior school or less	Reference		Reference	
High and technical school	2.4 (1.0-5.7)	0.054	1.9 (0.7-4.7)	0.18
College or higher	4.5 (0.8-24.8)	0.09	6.5 (0.7-62.4)	0.10
Initiation time of the hepatitis B vaccine first dose				
> 24 hours	Reference		Reference	
≤ 24 hours	2.7 (1.2-6.0)	0.016	3.9 (1.7-9.3)	0.002

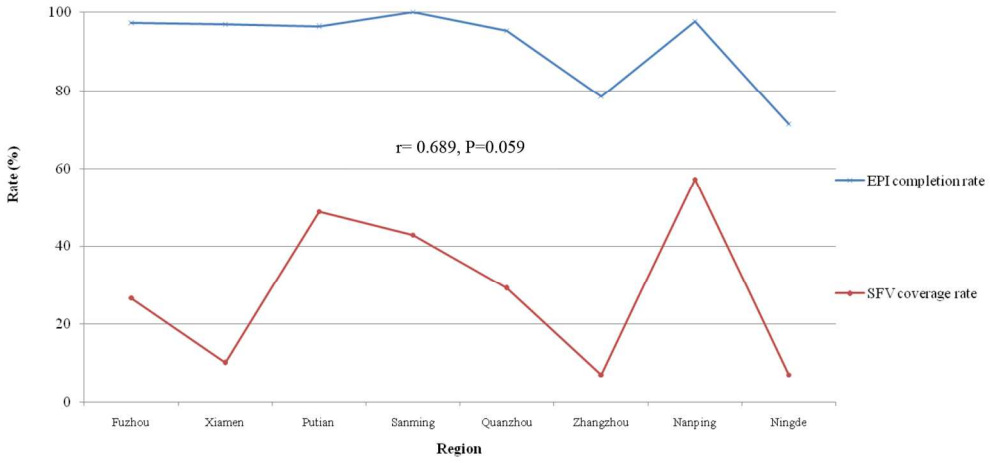
Figure Legends

Figure 1

The correlation analysis between the EPI completion rate and the SFV coverage rate in regions with the SFV supply. EPI, expanded program on immunization; SFV, substitutable for-fee vaccines.

Figure 2

Cox proportional hazards models estimates of the EPI cumulative completion rate according to the receipt of the SFV, stratified by parents' education level and initiation time of the hepatitis B vaccine first dose. A, B, C, and D show the difference of cumulative EPI completion rate between groups of children with and without the SFV vaccination by parents' education level (high school and above vs. junior school or less), as well as by initiation time of the hepatitis B vaccine first dose (timely vs. delayed initiation) in E and F. EPI, expanded program on immunization; SFV, substitutable for-fee vaccines.



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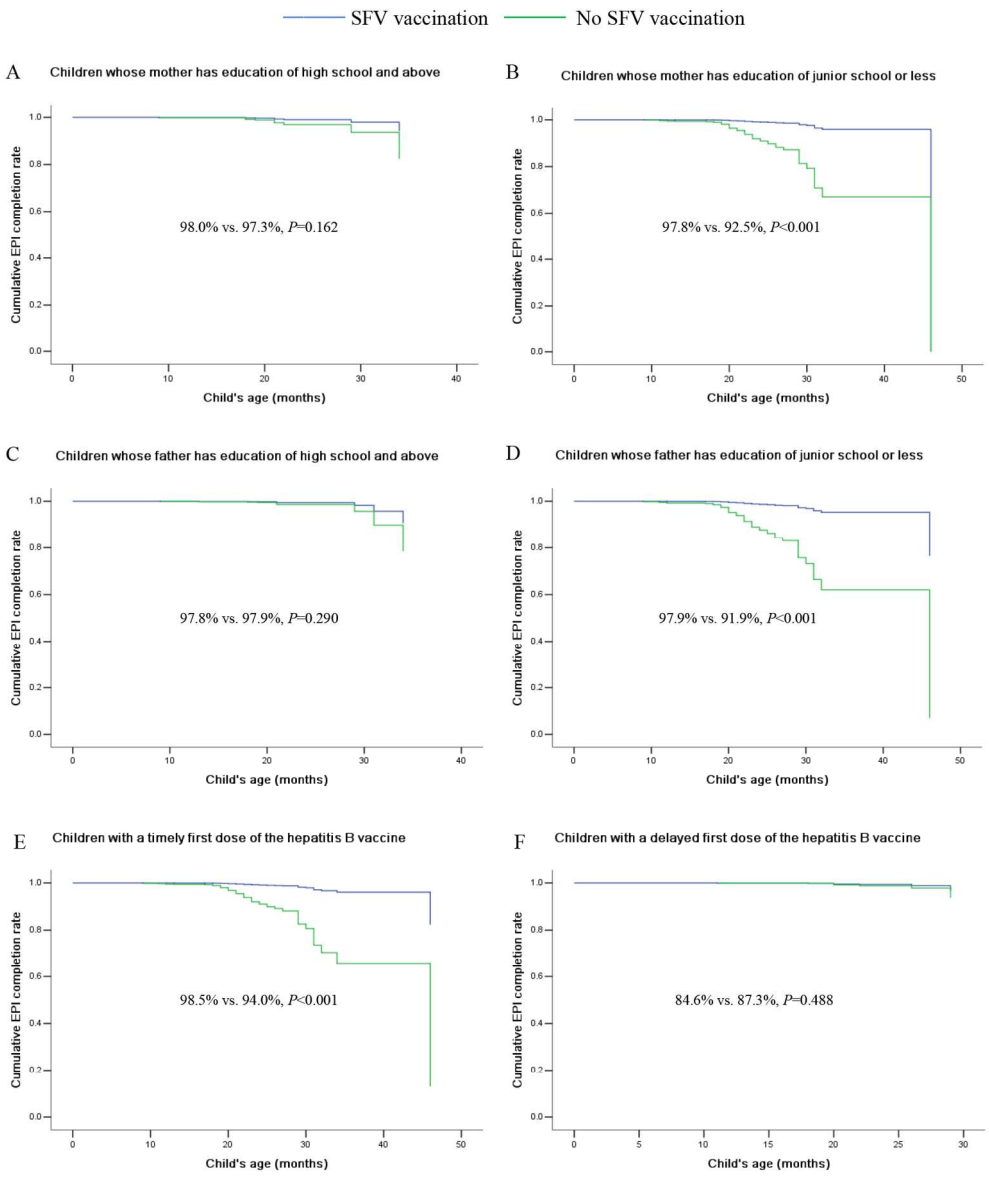

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TSROBE checklist and statement_BMJOpen-2016-015666

1. TSROSE Checklist:

	Item No	Recommendation	Meet?	Page, line in the manuscript, or illustration
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	See p1 the Title.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	See p2 the Abstract.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	See p4-5, the Introduction section.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	See p5-6, the last paragraph in the Introduction section.
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	See p6, the first sentence in "Participants and design".
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	See p6-7, the Participants and design section.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	See p6, the first paragraph in the "Participants and design" section.
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants		
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	No	Not applicable because we conducted a cross-sectional study.
		Case-control study—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	See p7-8, the Outcomes section, and see p6, potential confounders were described in the second paragraph of the Participants and design section.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	See p6-7, we collected information by a standardized questionnaire and extracted the immunization history from the vaccination cards. We mentioned these in the second paragraph of the Participants and design section.
Bias	9	Describe any efforts to address potential sources of bias	Yes	Bias of this study may contained confounding bias and recall bias, which were mentioned in the third and fourth sentences in the second paragraph of the Participants and design section (p6-7); we used the records on vaccination certificates kept by

				parents or vaccination cards kept in IC, rather than parents' memories of vaccination, to avoid the recall bias, and run multivariate logistic regression to control the potential confounders, see the Statistical analyses section.
Study size	10	Explain how the study size was arrived at	Yes	The sample size was calculated by the China CDC, we mentioned it and cited the paper probing how to calculate the sample, see the second paragraph in p7.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	We had two quantitative variables, the child's age and the inoculation time of the HepB first dose. We divided the child's age (2-4 years old) into 2 groups (2~, 3~) because definitions of the EPI completion are different between these two groups. And the China CDC demanded infants receiving the HepB first dose within 24 hours, so we created a new variable, a delayed or timely HepB first dose (> vs. ≤ 24 hours), from the inoculation time of the HepB first dose. We explained these in the Methods (p7, 8)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	See p9, the Statistical analyses section.
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	see p9, the Statistical analyses section.
		(*c*) Explain how missing data were addressed	No	Not applicable, we didn't had missing data in this study.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	No	Not applicable. We had mentioned the sampling strategy which was studied in another paper (Reference 18) .
		Case-control study—If applicable, explain how matching of cases and controls was addressed		
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses	No	Not applicable, we didn't ran any sensitivity analyses because the response rate was 100% in this study.
Results				
Participants	13*	(a) Report the numbers of individuals at each stage of the study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Yes	We selected 1428 children by the sampling strategy, and the response rate was 100% in this study, we included all the 1428 in the analysis and reported the results of the subjects, see p10 the Result section.
		(b) Give reasons for non-participation at each stage	No	Not applicable because the response rate was 100% in this study.
		(c) Consider use of a flow diagram	No	We had described the sampling process (see p6 the Participants and design section), we don't think it's necessary to draw a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders	Yes	See the Results and the Tables.

		(b) Indicate the number of participants with missing data for each variable of interest	No	Not applicable, there was no missing data in this study.
		(c) Cohort study—Summarize follow-up time (eg, average and total amount)	No	Not applicable.
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	No	Not applicable.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	No	Not applicable.
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes	See p 10, the first paragraph of the Results.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included	Yes	See p10, the results of "Receipt of the SFV and completion of the EPI" section.
		(b) Report category boundaries when continuous variables were categorised	Yes	See p 10, timely initiation of the HepB first dose was marked with (<24 hours after birth), which was explained in the Methods.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes	The OR means the probability of completion the EPI in children receiving SFV compared with those without receiving SFV.
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses	Yes	See p11, the Stratified analyses section.
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	See p12, the Discussion section.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	See p13-14, the limitations paragraph in the Discussion section.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	See p12-14, the Discussion section.
Generalizability	21	Discuss the generalizability (external validity) of the study results	Yes	See p14, the last paragraph of the Discussion section.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No	No funding in this study, see p14, the Funding section.

*Give such information separately for cases and controls in case-control studies, and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

2. A statement to the Methods section

We had revised the Methods section of the manuscript by items of the

TSROBE (item 4-12), including the study design, setting, participants, variables, data sources, bias, study size, quantitative variables and statistical methods, if applicable. Please see the TSROBE checklist above.

BMJ Open

Relationship between receipt of substitutable for-fee vaccines and completion of the expanded program on immunization: a cross-sectional study in Fujian, China

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Title page

Title

Relationship between receipt of substitutable for-fee vaccines and completion of the expanded program on immunization: a cross-sectional study in Fujian, China

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ABSTRACT

Objective: To evaluate the relationship between receipt of the substitutable for-fee vaccines (SFV) and completion of the expanded program on immunization (EPI).

Design and settings: A cross-sectional study was conducted in Fujian province, China.

Participants: Children who were born from September 1, 2009 to August 31, 2011, and who had been residing in the township for at least three months, were randomly recruited from 34 townships.

Main outcomes measures: Outcomes were completion rate of the EPI and coverage rate of the SFV.

Results: The study included 1,428 children, of whom 1350 (94.5%) finished the EPI and 282 (19.7%) received at least one dose of the SFV. Administration of the SFV was associated with an increased likelihood of completing the EPI (OR= 3.2, 95% CI: 1.3-7.6 in the total sample, and OR=4.0, 95% CI: 1.7-9.6 in the subsample of children in regions with the SFV accessibility). The impact of the SFV administration on completion of the EPI was larger among children whose parents have junior school education or less (97.8% and 97.9% vs. 92.5% and 91.9%, both P<0.001) and among those with a timely hepatitis B vaccine first dose (98.5% vs. 94.0%, P<0.001).

Conclusions: Receipt of SFV is associated with increased likelihood of completion of the EPI in Fujian, China.

ARTICLE SUMMARY

Strengths and limitations of this study

- This is the first study exploring the association between substitutable for-fee vaccines (SFV) administration and the expanded program on immunization (EPI) completion in China.
- The subjects were selected randomly by lot quality assurance sampling from townships which were randomly extracted by the probability proportional to size sampling method, as well as a high response rate (100%) in the survey, therefore, the sample had a good representation.
- The findings may help target vulnerable children and improve the implementation of the SFV policy in China.
- The sample size was not large enough, and we were not able to control all potential confounding factors in the analyses, both may limit the interpretation of some results.

INTRODUCTION

China has an expanded program on immunization (EPI) which includes 1 dose of Bacille Calmette-Guerin vaccine (BCG), 3 doses of hepatitis B vaccine (HepB), 4 doses of oral live attenuated polio vaccine (OPV), 4 doses of acellular pertussis diphtheria tetanus vaccine (DTaP), 2 doses of measles-containing vaccine (MCV), 2 doses of group A meningococcal polysaccharide vaccine (MPSV-A), 2 doses of live-attenuated Japanese encephalitis vaccine (JE-L), 1 dose of live-attenuated hepatitis A vaccine (HepA-L), 1 dose of diphtheria tetanus vaccine (DT), and 2 doses of meningococcal A+C polysaccharide vaccine (MPSV-AC).[1] The EPI vaccines are mostly produced by state-owned pharmaceutical companies and are provided to the public as free vaccines. In addition, parents can choose to purchase variants that are for-fee vaccines, which are mostly manufactured by private enterprises based in China or are imported from abroad. The for-fee vaccines can be further divided into two types, normal and substitutable for-fee vaccines (SFV).[2-3] For example, pneumococcal conjugate vaccine is a normal for-fee vaccine, while inactivated polio vaccine (IPV) is a SFV and can be a substitute for OPV.

Whether to carry out service of the SFV for children has been controversial in China. On the one hand, given worries that the SFV service may cause social injustice and affect the completion of the EPI, the National Health and Family Planning Commission of the People's Republic of China (China NHFPC) opposed the SFV service.[4] In some areas, the Health Bureau even prohibited staff in immunization clinics (IC) from administering the SFV vaccination to children. On the other hand, parents always think the SFV was better than EPI vaccines (e.g. safer and more effective), the opinions have been strengthened since the adverse events after the EPI immunization was reported.[5,6] Hence, parents may select the SFV once they can afford the fee, and/or they think it's necessary (e.g. children are not in good condition for EPI vaccines).

Moreover, vaccine providers may recommend the SFV once they thought the SFV was safer than EPI vaccines, worried about the troubles caused by adverse events following immunization (AEFI) (e.g. vaccine-associated paralytic poliomyelitis [VAPP] after OPV immunization)[7], and were under pressure to create income for the unit.[8] Therefore, the SFV immunization was widely performed in China, it was estimated that 18.05% of children had received at least one dose of the SFV nationally, and the coverage of the SFV was higher among children in eastern areas than that in western regions.[2]

Previous studies primarily focused on describing coverage of normal for-fee vaccines (such as pneumococcal conjugate vaccine and influenza vaccine) and their determinants,[8-10] and investigating coverage of the SFV and/or its substitution rate to the EPI vaccines.[2,11,12] However, no studies to date were conducted to probe the relationship between the SFV vaccination and the EPI completion. Knowing the relationship is important for guidance and management of the SFV service, such as, if the SFV were conductive to complete the EPI for children, the China NHFPC may improve the policy of SFV and encourage vaccination with the SFV for children who can afford the vaccine fee.

Furthermore, parents who choose to have their children received the SFV might not only show a greater disposable income (because the SFV requires an out-of-pocket payment),[2] but also have higher awareness of immunization (because they chose the SFV instead of the EPI vaccines). Better economic capacities and higher vaccination awareness were significantly related to completion of the EPI vaccine series.[13,14] Moreover, previous studies had revealed that children who had initiated a delayed first dose of HepB[1] and whose parents have lower educational levels were less likely to complete the EPI.[15] Therefore, it is reasonable to hypothesize that: (1) children receiving the SFV might promote their completion of the EPI, and

(2) the relationship between the SFV administration and the EPI completion might be modified by parents' education level and initiation time of the HepB first dose. We aimed at assessing coverage rates of the SFV and verifying the hypotheses.

METHODS

Participants and design

The cross-sectional study was part of a national EPI coverage rate investigation and was conducted in December 2013 in Fujian, China. Details of the national survey have been described elsewhere.[16,17] In brief, Chinese children aged 2 to 4 years old at the time of the survey (born from September 1, 2009 to August 31, 2011) and who had been residing in the township for at least three months were included as target subjects, and were randomly selected for the survey. Firstly, a township with a population less than 10,000 was combined with an adjacent township to ensure adequate sample for survey, resulting in 1,004 combined townships with a population of ≥ 10,000 from the 1,058 townships in Fujian province. Secondly, 34 townships were randomly selected by the probability proportional to size sampling (PPS) method from the 1,004 townships. For each township sampled, five villages (the village where the township government was located and another four randomly selected villages) were sampled as village-level survey sites. Finally, at the village-level survey sites, lot quality assurance sampling (LQAS) was used to sample households for survey.

Parents or guardians of the children were interviewed by a standardized questionnaire which was set by China CDC. The questionnaire contained 2 major items, including basic information and vaccination history. Measures of family socioeconomic situations (home address, types of living areas, and education level of the parents) and child's information (name, gender, birth date,

place of delivery, ethnicity, and types of household register) were collected and included in the analyses as potential confounding factors. Records on vaccination certificates kept by parents or vaccination cards kept in IC, rather than parents' memories of vaccination, were extracted as evidence of vaccine immunization to avoid possible recall bias. Children were considered unvaccinated if both the vaccination certificate and vaccination card were absent. It took about 10 minutes to complete a questionnaire. Newborns who received a HepB in the first and second day of birth were deemed to finish the vaccine within 24 hours and have a timely HepB first dose in our analysis,[1] because it's hard to calculate the exact hours that the babies receive the vaccine.

A total of 42 children were surveyed in each township, including 10 from the village where the township government was located and 8 each from the remaining four villages. Ultimately, a total of 1,428 children were selected in the province. Because this was part of regular national public health evaluation of EPI coverage by the township level, all selected subjects should be surveyed, therefore the response rate in our study was 100%.[18] The sampling method was identified as a suitable method for evaluation of the EPI coverage rate by the township level, and the sample (42 children) of each township had a power of 90% to detect whether the coverage rate of EPI reached 90% with a 0.05 significance level.[18] The study was part of a national activity which was organized by the China NHFPC to evaluate whether the EPI coverage by the township level meets the requirements of the Twelfth Five Year Plan of Health Development and was exempt from ethical review.[16]

Outcomes

The primary outcome was completion rate of the EPI, which was defined as the percentage of children who had finished the EPI. Completion of the EPI was defined as children completing the EPI according to the recommended immunization schedule. Children aged 2 to 3 years old should finish 1 dose of BCG, 3 doses of HepB, 3 doses of OPV, 4 doses of DTaP, 2 doses of

MCV, 2 doses of MPSV-A, 1 dose of HepA-L, and the first dose of JE-L, and an additional second dose of JE-L was demanded for children of 3 to 4 ages. Vaccination earlier than the initiation schedules time of vaccines and with incorrect intervals between different doses of vaccines was defined as ineffective vaccination.

Children who had received the SFV in accordance with immunization schedule were identified as completing the corresponding EPI vaccines. The equivalencies between SFV and EPI vaccines were as follow:[19] (1) For HepB, DTaP, OPV and MPSV-A, one dose of SFV was equivalent to one dose of EPI vaccine. (2) For JE-L, two doses of inactivated Japanese encephalitis vaccine (JE-I) should be vaccinated for children by 3 years of age, and a third JE-I dose be given by 4 years old, which were equal to the first dose and the second dose of JE-L, respectively. (3) For HepA-L, one dose of inactivated hepatitis A vaccine (HepA-I) was equal to one dose of HepA-L for children aged less than 3 years old. However, children who had received a dose of HepA-I should accept another HepA-I dose by 4 years old, which was identified as completion of the HepA-L for children aged 3 to 4 years old.

The secondary outcome was coverage of the SFV, which was defined as the percentage of children who had accepted one or more doses of the SFV. In this study, the SFV included IPV (substitute for OPV), DTaP and Haemophilus influenzae type B (HIB) conjugate vaccine (substitute for DTaP), DTaP/IPV/HIB conjugate vaccine (substitute for OPV and DTaP), group A/C meningococcal conjugate vaccine (substitute for MPSV-A), hepatitis A and B combination vaccine (substitute for HepA-L and HepB), HepA-I (substitute for HepA-L), and JE-I (substitute for JE-L).

Statistical analyses

Data was double entered using EpiData 3.1 software to ensure the consistency and avoid information bias. Multivariate logistic regression models were fitted to estimate the odds ratios (ORs) and their 95% confidence intervals (CIs) for completion of the EPI, after controlling for the potential confounding factors. Pearson's correlation coefficient was evaluated to intuitively reflect the correlation between the EPI completion rate and the SFV coverage rate in regions with the SFV supply.

Due to the implementation of different policies, SFV for children were banned in some areas. To compare completion rates among children in regions with SFV access to Fujian as a whole, we also ran a multivariate logistic regression analysis in the regions of Fujian with access to the SFV. Children were further divided into three groups, including children living in areas without SFV access (these children didn't receive SFV because there was no SFV in the areas), children without history of SFV vaccination in areas with SFV access, and children who received the SFV in areas with SFV access. Logistic regression models were remodeled to compare the EPI coverage rates among the three groups.

To examine whether the relationship between receipt of the SFV and completion of the EPI was modified by parents' education level and initiation time of the HepB first dose, we performed cumulative completion rate stratification analysis based upon parents' education level (Junior school or less vs. High school or above) and initiation time of the HepB first dose (> vs. ≤ 24 hours) by cox proportional hazards analyses, in which the EPI completion time (months) was set as "survival time".

All statistical tests were conducted using SPSS 19.0 software (IBM Corp., Armonk, NY, USA). A P-value of <0.05 was considered as statistically significant.

RESULTS

Characteristics of the study population

In total, 1,428 children of an appropriate age were surveyed, of whom 1350 (94.5%) finished the EPI, and 282 (19.7%) received at least of one dose of the SFV. Most of the children were of Han ethnicity (97.8%) and were local children (89.6%). More than half of the children were boys (54.0%) and two-year-olds (56.2%); and most children (85%) were born in hospitals at the county level and above.

Table 1 shows the population characteristics of the entire sample and the selected children in regions with the SFV access, stratified by children with and without completion of the EPI. Children who had a history of the SFV were more likely to complete the EPI than those who hadn't received the SFV (97.9% *vs.* 93.7%) in total sample, as well as in the selected sample (97.9% *vs.* 92.1%).

Receipt of the SFV and completion of the EPI

Compared with children who didn't receive the SFV, children who had administrated the SFV were more likely to complete the EPI [unadjusted OR, 3.1, 95% CI, 1.3 to 7.2, and adjusted OR, 3.1; 95% CI, 1.3 to 7.4; P=0.009] in the total sample. The adjusted OR rose to 3.9 (95% CI 1.6-9.4) in the subgroup of children in regions with the SFV supply (Table 2). Children of three-years-old and with timely initiation of the HepB first dose (<24 hours after birth) were more likely to complete the EPI than those of two-years-old and with a delayed HepB first dose. The minority children were less likely to complete the EPI than the Han children (Table 2). Educational level of the child's father also affected completion of the EPI in the total sample, but insignificant in the subgroup sample (Table 2). The SFV coverage was correlated with the EPI

completion rate in children from regions with the SFV access (correlation coefficient= 0.689; P=0.059) (Figure 1).

After controlling for potential factors (child's gender, age, and nationality, parents' education level, etc.), compared with children in regions without the SFV access, children who had received the SFV were more likely to complete the EPI (OR,1.8; 95% CI 0.7-4.8, P=0.25), while those without the SFV administration were less likely to complete the EPI (OR,0.5; 95% CI, 0.2-0.8, P=0.01), in regions with the SFV supply.

Stratified analyses

We observed significant differences of EPI coverage rates between groups of children with and without the SFV administration by stratifications of parents' educational level (Junior school or less vs. High school or above) and initiation time of the HepB first dose (> vs. ≤ 24 hours after birth). Children with the SFV receipt had a significantly higher cumulative completion rate than those without the SFV administration in the subgroup of children whose parents with education level of junior school or less (97.8% vs. 92.5% for mother's education level, and 97.9% vs. 91.9% for father's education level, both P<0.001) (Figure 2 B, D). Similarly, children with timely initiation of a HepB first dose were more sensitive to the SFV vaccination, the cumulative EPI completion rate was higher among children receiving the SFV than that among those without the SFV administration (98.5% vs. 94.0%, P<0.001) (Figure 2 E). No significant result was observed for children whose parents have education of high school and above and who had received a delayed HepB first dose (Figure 2 A, C, F).

DISCUSSION

We found that children who had received SFV were more likely to complete the EPI, where the association may be offset by high parents' education level and the delayed initiation of the HepB first dose. In China, frequent reports of AEFI, such as the Shanxi vaccine incident[5] and the Conde HepB event,[6] had further solidified the parents' views of "cheap is dear, and dear is cheap", they would choose the SFV even if they have to pay an extra cost (each dose costs 18 to 630 RMB Yuan, mean: 156 RMB Yuan/dose, approximately $24.6/dose[20]). Moreover, receiving the SFV may create revenue and reduce the incidence of AEFI caused by the EPI vaccines, [11,21] therefore, children who chose the SFV might be treated more enthusiastically by the staff in the IC than those who chose the EPI vaccines. Hence, receiving the SFV may be an indicator of the economic conditions and vaccination awareness of children' families, and might ensure better service from the staff of the IC, resulting in children having better compliance with immunization and being more likely to complete the EPI.[1,2,9,22-26].

Parents with lower education level have certain characteristics (earn less, lack of knowledge, and have multiple children) that are not conducive to complete the EPI for their children;[27,28] they might be more sensitive to the price of the SFV.[27-29] Whether to receive the SFV may further reflect their economic situation and immunization awareness, which leads to the difference of the EPI completion between the two groups. The HepB first dose are often delayed as a result of contraindications for children born in hospitals or of low medical accessibility for those born at home,[1,30,31] which might affect their catch-up vaccination of the EPI vaccines even if they had received the SFV, resulting in a significantly lower completion of the EPI than those with timely initiation of the HepB first dose.

Interestingly, we found that the supply of the SFV may play a "double-sword" role in the EPI completion. Vaccine providers may differentiate children who had received the EPI vaccines

from those with the SFV, which may lead to a decline in the enthusiasm of the completion of the EPI.[32] Moreover, the difference of completion rate of the EPI between regions with and without the SFV supply may be partly explained by the percentage of non-local children, which was proved as an impact factor for the EPI completion.[24,31] In our study, the percentage of non-local children was significantly lower in regions without SFV supply than that in regions with the SFV access (3.1 vs. 13.4%, $P<0.001$).

We also found that the EPI completion rate was higher in children of three-years-old, which differed from findings of a previous study.[31] This inconsistency may be explained due to the fact that three-years-old usually start to attend kindergartens, which are required to examine the vaccination certificate of children under regulations, therefore prompting children to receive their missing vaccinations[33] and effectively improving the completion of the EPI in three-year-old children. Minority children were less likely to complete the EPI, which may be related to poor economic conditions of their families[34] and the lack of vaccination awareness of their parents.[35] Similar to previous studies,[36,37] we confirmed that timely HepB first dose initiation improved the EPI completion in children, possibly because receiving a timely HepB first dose might help emphasize the importance of vaccination to the parents, and promote their children' completion of the EPI.[1]

Our study has several limitations. Firstly, we included the SFV, but not normal for-fee vaccines, such as the varicella vaccine and the influenza vaccine, which might introduce certain information bias. However, most normal for-fee vaccines are not administered until children are 2 years old, this bias might not affect the results of this study. Secondly, the moderate sample size of this study may limit the interpretation of some results. Finally, other factors, such as access to health care, knowledge, attitudes and the practices of parents and providers, regional

vaccination policy, the level of regional economic development, will also affect the SFV vaccination. In addition, sociodemographic variables, such as the number of children, parent age, family income, etc, might be better indicators of the willingness to receive SFV than the parents' education level. Unfortunately, we were not able to include all these factors in the current study.

To the best of our knowledge, this is the first study exploring the association between the SFV administration and the EPI completion in Fujian, China. The association between the SFV administration and the EPI completion was more obvious among children whose parents have lower education level and among those with a timely Hep B first dose. Vaccine providers should focus on these vulnerable children and take measures to help them complete the EPI on time. The generalizability of the results should be further studied.

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Footnotes

Contributors: JN Wu, Y Zhou and DJ Li had the initial idea for the study and designed the survey. JN Wu, MR Du and HL Piao collected and analyzed the data for this study. JN Wu wrote the first draft of the manuscript. All authors critically revised the manuscript and approved the final version.

Funding: None.

Competing interests: None declared.

Data sharing statement: No additional data are available.

Table 1. Base characteristics of children in groups with and without completion of the EPI in total and selected sample

Characteristics	Total sample (N = 1428)		Population in regions with the SFV access (N = 1008)	
	Did not complete EPI	Did complete EPI	Did not complete EPI	Did complete EPI
	No. (%)	No. (%)	n (%)	n (%)
History of the SFV administration				
No	72 (6.3%)	1074 (93.7%)	57 (7.9%)	669 (92.1%)
Yes	6 (2.1%)	276 (97.9%)	6 (2.1%)	276 (97.9%)
Gender				
Males	40 (5.2%)	731 (94.8%)	32 (5.8%)	517 (94.2%)
Females	38 (5.8%)	619 (94.2%)	31 (6.8%)	428 (93.2%)
Age at survey (years)				
2 ~	56 (7.3%)	746 (92.7%)	45 (8.2%)	502 (91.8%)
3 ~	22 (3.4%)	634 (96.6%)	18 (3.9%)	443 (96.1%)
Nationality				
Han	70 (5.0%)	1327 (95.0%)	55 (5.6%)	922 (94.4%)
Minority	8 (25.8%)	23 (74.2%)	8 (25.8%)	23 (74.2%)
Place of birth				
County hospital or above	65 (5.4%)	1149 (94.6%)	54 (6.5%)	777 (93.5%)
Township hospital	12 (5.7%)	197 (94.3%)	8 (4.6%)	165 (95.4%)
Home	1 (20.0%)	4 (80.0%)	1 (25.0%)	3 (75.0%)
Household registration				
Local registration	69 (5.4%)	1211 (94.6%)	54 (6.2%)	819 (93.8%)
Outside or no registration	9 (6.1%)	139 (93.9%)	9 (6.7%)	126 (93.3%)
Mother's educational level				
Junior school or less	68 (6.6%)	967 (93.4%)	56 (7.9%)	652 (92.1%)
High and technical school	8 (3.2%)	240 (96.8%)	6 (3.1%)	189 (96.9%)
College or higher	2 (1.4%)	143 (98.6%)	1 (1.0%)	104 (99.0%)
Father's educational level				
Junior school or less	69 (6.9%)	925 (93.1%)	55 (8.0%)	629 (92.0%)
High and technical school	7 (2.6%)	261 (97.4%)	7 (3.4%)	197 (96.6%)
College or higher	2 (1.2%)	164 (98.8%)	1 (0.8%)	119 (99.2%)
Initiation time of the Hepatitis B vaccine first dose				
> 24 hours	9 (13.2%)	59 (86.8%)	9 (17.6%)	42 (82.4%)

≤ 24 hours	69 (5.1%)	1291 (94.9%)	54 (5.6%)	903 (94.4%)

Table 2. Odds ratios and 95% confidence intervals for completion of the EPI

Characteristics	Total sample (N = 1,428)		Population in regions with the SFV access (N = 1,008)	
	Odds ratios (95% CI)	*P* value	Odds ratios (95% CI)	*P* value
History of the SFV administration				
No	Reference		Reference	
Yes	3.1 (1.3-7.4)	0.009	3.9 (1.6-9.4)	0.002
Gender				
Males	Reference		Reference	
Females	0.8 (0.5-1.4)	0.48	0.8 (0.5-1.4)	0.46
Age at survey (years)				
2 ~	Reference		Reference	
3 ~	2.5 (1.5-4.2)	0.001	2.5 (1.4-4.5)	0.002
Nationality				
Han	Reference		Reference	
She	0.2 (0.1-0.4)	<0.001	0.2 (0.1-0.5)	0.001
Place of birth				
County hospital or above	Reference		Reference	
Township hospital	1.1 (0.6-2.2)	0.74	1.9 (0.9-4.2)	0.10
Home	0.5 (0.05-5.8)	0.60	0.7 (0.06-9.2)	0.79
Household registration				
Local registration	Reference		Reference	
Outside or no registration	0.8 (0.4-1.6)	0.46	0.9 (0.4-1.9)	0.71
Mother's educational level				
Junior school or less	Reference		Reference	
High and technical school	1.1 (0.5-2.5)	0.83	1.4 (0.5-3.8)	0.50
College or higher	1.7 (0.3-9.4)	0.55	2.7 (0.3-25.8)	0.38
Father's educational level				
Junior school or less	Reference		Reference	
High and technical school	2.4 (1.0-5.7)	0.054	1.9 (0.7-4.7)	0.18
College or higher	4.5 (0.8-24.8)	0.09	6.5 (0.7-62.4)	0.10
Initiation time of the hepatitis B vaccine first dose				
> 24 hours	Reference		Reference	
≤ 24 hours	2.7 (1.2-6.0)	0.016	3.9 (1.7-9.3)	0.002

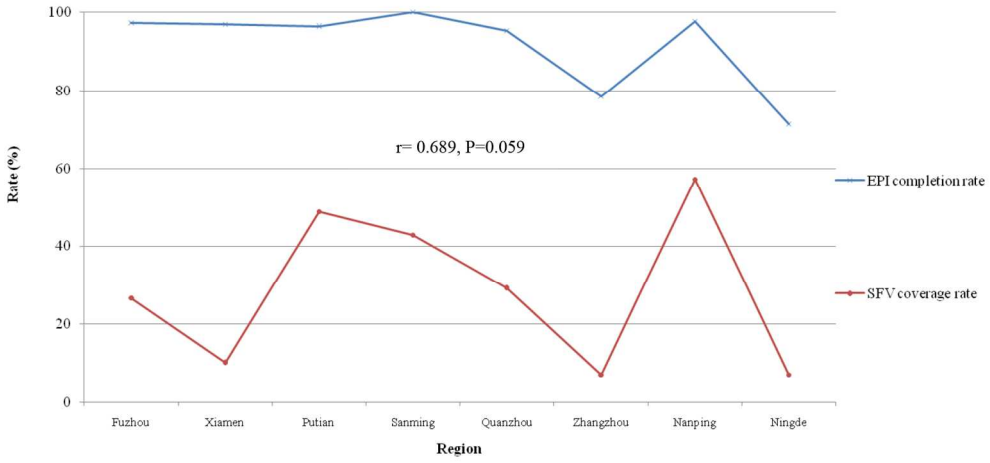
Figure Legends

Figure 1

The correlation analysis between the EPI completion rate and the SFV coverage rate in regions with the SFV supply. EPI, expanded program on immunization; SFV, substitutable for-fee vaccines.

Figure 2

Cox proportional hazards models estimates of the EPI cumulative completion rate according to the receipt of the SFV, stratified by parents' education level and initiation time of the hepatitis B vaccine first dose. A, B, C, and D show the difference of cumulative EPI completion rate between groups of children with and without the SFV vaccination by parents' education level (high school and above vs. junior school or less), as well as by initiation time of the hepatitis B vaccine first dose (timely vs. delayed initiation) in E and F. EPI, expanded program on immunization; SFV, substitutable for-fee vaccines.



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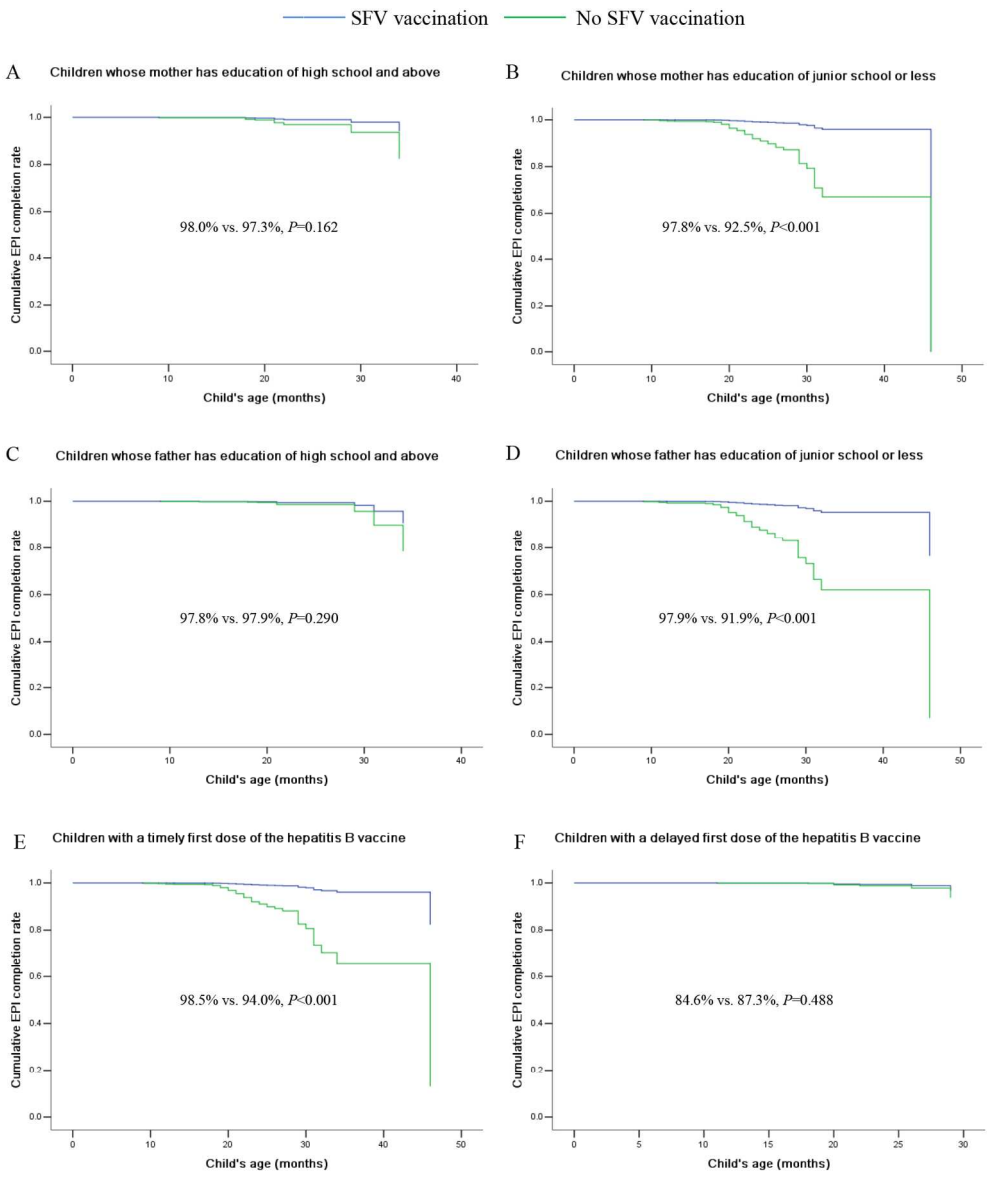

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TSROBE checklist _BMJOpen-2016-015666_R2

	Item No	Recommendation	Meet?	Page, line in the manuscript, or illustration
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Yes	See p1 the Title.
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Yes	See p2 the Abstract.
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Yes	See p4-5, the Introduction section.
Objectives	3	State specific objectives, including any prespecified hypotheses	Yes	See p5-6, the last paragraph in the Introduction section.
Methods				
Study design	4	Present key elements of study design early in the paper	Yes	See p6, the first sentence in "Participants and design".
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Yes	See p6-7, the Participants and design section.
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Yes	See p6, the first paragraph in the "Participants and design" section.
		Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls		
		Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants		
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed	No	Not applicable because we conducted a cross-sectional study.
		Case-control study—For matched studies, give matching criteria and the number of controls per case		
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Yes	See p7-8, the Outcomes section, and see p6, potential confounders were described in the second paragraph of the Participants and design section.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Yes	See p6-7, we collected information by a standardized questionnaire and extracted the immunization history from the vaccination cards. We mentioned these in the second paragraph of the Participants and design section.
Bias	9	Describe any efforts to address potential sources of bias	Yes	Bias of this study may contained confounding bias and recall bias, which were mentioned in the third and fourth sentences in the second paragraph of the Participants and design section (p6-7); we used the records on vaccination certificates kept by

				parents or vaccination cards kept in IC, rather than parents' memories of vaccination, to avoid the recall bias, and run multivariate logistic regression to control the potential confounders, see the Statistical analyses section.
Study size	10	Explain how the study size was arrived at	Yes	The sample size was calculated by the China CDC, we mentioned it and cited the paper probing how to calculate the sample, see the second paragraph in p7.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Yes	We had two quantitative variables, the child's age and the inoculation time of the HepB first dose. We divided the child's age (2-4 years old) into 2 groups (2~, 3~) because definitions of the EPI completion are different between these two groups. And the China CDC demanded infants receiving the HepB first dose within 24 hours, so we created a new variable, a delayed or timely HepB first dose (> vs. ≤ 24 hours), from the inoculation time of the HepB first dose. We explained these in the Methods (p7, 8)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Yes	See p9, the Statistical analyses section.
		(*b*) Describe any methods used to examine subgroups and interactions	Yes	see p9, the Statistical analyses section.
		(*c*) Explain how missing data were addressed	No	Not applicable, we didn't had missing data in this study.
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed	No	Not applicable. We had mentioned the sampling strategy which was studied in another paper (Reference 18) .
		Case-control study—If applicable, explain how matching of cases and controls was addressed		
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy		
		(*e*) Describe any sensitivity analyses	No	Not applicable, we didn't ran any sensitivity analyses because the response rate was 100% in this study.
Results				
Participants	13*	(a) Report the numbers of individuals at each stage of the study—eg, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	Yes	We selected 1428 children by the sampling strategy, and the response rate was 100% in this study, we included all the 1428 in the analysis and reported the results of the subjects, see p10 the Result section.
		(b) Give reasons for non-participation at each stage	No	Not applicable because the response rate was 100% in this study.
		(c) Consider use of a flow diagram	No	We had described the sampling process (see p6 the Participants and design section), we don't think it's necessary to draw a flow diagram.
Descriptive data	14*	(a) Give characteristics of study participants (eg, demographic, clinical, social) and information on exposures and potential confounders	Yes	See the Results and the Tables.

		(b) Indicate the number of participants with missing data for each variable of interest	No	Not applicable, there was no missing data in this study.
		(c) Cohort study—Summarize follow-up time (eg, average and total amount)	No	Not applicable.
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	No	Not applicable.
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	No	Not applicable.
		Cross-sectional study—Report numbers of outcome events or summary measures	Yes	See p 10, the first paragraph of the Results.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence intervals). Make clear which confounders were adjusted for and why they were included	Yes	See p10, the results of "Receipt of the SFV and completion of the EPI" section.
		(b) Report category boundaries when continuous variables were categorised	Yes	See p 10, timely initiation of the HepB first dose was marked with (<24 hours after birth), which was explained in the Methods.
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Yes	The OR means the probability of completion the EPI in children receiving SFV compared with those without receiving SFV.
Other analyses	17	Report other analyses done—eg, analyses of subgroups and interactions, and sensitivity analyses	Yes	See p11, the Stratified analyses section.
Discussion				
Key results	18	Summarise key results with reference to study objectives	Yes	See p12, the Discussion section.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Yes	See p13-14, the limitations paragraph in the Discussion section.
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Yes	See p12-14, the Discussion section.
Generalizability	21	Discuss the generalizability (external validity) of the study results	Yes	See p14, the last paragraph of the Discussion section.
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	No	No funding in this study, see p14, the Funding section.

*Give such information separately for cases and controls in case-control studies, and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.