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Vaccines and the risk of acute disseminated encephalomyelitis

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ABSTRACT

Background: It is important to examine the risk of Acute disseminated encephalomyelitis (ADEM) after vaccination.
Methods: We conducted a nested case–control study between January 2011 and December 2015. Four controls per case were matched for age, gender, address. An independent expert committee validated the diagnoses of cases and controls. Data on vaccinations were obtained from computerized vaccination records. The analyses were conducted with the use of conditional logistic regression.
Results: The analyses include 272 cases of ADEM and 1096 controls. No increase in the risk of ADEM was observed for vaccination against hepatitis B, influenza, polio(live), diphtheria, pertuss(acellular), tetanusis, measles, mumps, rubella, Japanese Encephalitis, meningitis, hepatitis A, varicella and rabies vaccines. Vaccine was associated with a statistically significant increase in risk in the 31–60-day exposure interval (OR, 4.04 [95% CI, 1.07–12.69]), but not the 0–30 and 61–180-day interval. There was no association between vaccine received and the recurrence of ADEM.
Conclusions: Findings from the present study do not demonstrate an association of vaccines with an increased risk of ADEM and its recurrence among either paediatric (≤18 years) or adult (>18 years) individuals within the 180 days after vaccinations. The finding in children in the 31–60 day risk interval is likely coincidental and was not confirmed in separate self-control analyses.

1. Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated central nervous system disorder, characterized by an acute encephalopathy with polyfocal neurological deficits [1]. The pathogenesis of ADEM is not known clearly, but adhesion molecules, chemokines, matrix metalloproteinase, and other cell factors are thought to be important in its occurrence and development [2].

In addition to a known association with infections, vaccinations also have been suggested to induce a small increased risk of ADEM [3]. In an American study, vaccination was found to precede ADEM in about 5% (2/42) of cases [4]. Several cases of young females presenting with onset of ADEM approximately 1 month following the administration of human papillomavirus (HPV) vaccine have been reported [5,6]. In Langer-Gould et al, a higher risk of CNS demyelinating disease was only observed in those less than 50 years at first 14 and 30 days, but not further longer period, following any vaccination (a "temporal shift" phenomenon) [7].

In recent years, the Expanded Program on Immunization (EPI) has been carried out in China. The type and number of vaccines administered to residents increased. The probability of having a severe abnormal reaction such as ADEM to vaccines is small, but the onset of such reactions usually cause widespread public concern. This may reduce public confidence in vaccines [8]. Vaccines available for use in Jiangsu Province was presented in Supplementary material Table 1.

The purpose of this study was to examine in more detail the association between the risk of ADEM including disease recurrence and vaccines.

2. Materials and methods

2.1. Setting

In China, most people get medical technology and specialized neurological care from public hospitals. Generally, patients who

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get suspected ADEM are admitted in hospital as emergencies, and soon after, a neurologist will be invited to take care of them. Patients no more than 16 years old who are affected by neurological diseases are usually taken in pediatric hospitals.

The province of Jiangsu is located in the east of China. It covers a surface of 107.2 thousand km^2 and the mean population density is 767 inhabitants/km^2. Nantong, Yancheng and Xuzhou, which are three cities in Jiangsu province, were involved in this study. Totally, 74 hospitals were involved, 21 in Nantong, 20 in Yancheng and 33 in Xuzhou, and they all provided inpatient services. In these hospitals, any departments that might have received patients meeting the case definition were involved, including neurology, internal medicine, pediatrics, and inpatient wards. The research was approved by the institutional review board of the Jiangsu Provincial Center for Disease Control and Prevention (JSCDC). Informed consent was waived because this was a medical records review study without direct patient contact.

2.2. Case identification

We searched the Hospital Information Systems (HIS) for first mention of International Classification of Diseases, Tenth Revision (ICD-10), diagnostic codes (G04.001, G04.002, G04.051, G04.903, and G04.912) for ADEM from January 1, 2011, to December 31, 2015, for persons of any age.

Diagnoses were confirmed by neurologists from clinical data, such as clinical manifestations, computed tomography (CT), electroencephalograph (EEG), cerebrospinal fluid (CSF) and magnetic resonance imaging (MRI) examinations. The consensus definitions of ADEM that were updated by the International Pediatric MS Study Group in 2013 were used [9]. The emergence of either new or old neurologic symptoms lasting more than 24 h, which stabilized or resolved either partially or completely, or lesions on MRI was defined as a relapse if it occurred >3 months after disease onset, and as a flare if it occurred ≤3 months after disease onset [10].

2.3. Control selection

For each ADEM case, 4 control individuals randomly selected from the same hospital with no history of ADEM were matched to the case according to year of birth (within 1 year), gender, and zip code (a surrogate measure for socioeconomic status) during the same period. The control participants were assigned the same index date as their matched case (symptom onset date). Controls were patients referred for headache (except trigeminal neuralgia), migraine, vascular or other diseases which were thought not to modify the probability of vaccination. Patients with chronic severe neurological diseases or autoimmune diseases were excluded.

2.4. Vaccination records

Information on vaccinations was obtained from Information Management System for Immunization Programming, in which anyone who received vaccinations would be registered, matched with ID number and verified by paper vaccination records. Any vaccination was considered to be an exposure. We collected information on all vaccinations received within 180 days.

2.5. Covariates

Other data obtained included nationality (Han and others), occupation, marital status (married and single), allergy, familial diseases, comorbid chronic diseases, and history of infectious diseases. Comorbid chronic diseases and history of infectious diseases were within 6 months before the index date.

2.6. Statistical analysis

Conditional logistic regression following univariable analysis was used to estimate the matched odds ratio (OR) and its corresponding 95% two-sided CI for the association between ADEM and vaccination. For each case, the index date was the date of onset of the first symptoms of the CNS demyelinating event. For the controls, we assigned the time of the onset of ADEM in the individual with whom the control was matched. The models were adjusted for nationality, occupation, marital status, allergy, familial diseases, comorbid chronic diseases, and history of infectious diseases within 6 months before the index date, and all variables with a P value less than 0.20 were included in the regression model [11]. To examine both the immediate and long-term effects of vaccination on ADEM, the exposure was restricted to the following different time frames before the index date: 14 days, 30 days, 60 days, 90 days, and 180 days. Additional analyses were stratified by subintervals 0–14, 15–30, 31–60, 61–90, and 91–180 days. To determine whether the paediatric was associated with any vaccine-associated ADEM, the study population was stratified according to age (≤18 years and >18 years) at the index date.

To examine whether or not each case was vaccinated in the 31–60 interval or the remainder of the 1 to 180 post-vaccination time interval, self-controlled case series (SCCS) analyses were used. To avoid the confounding by infection, we looked at cases without a history of infection in the prior 6 months separately. The risk interval was the 31–60 day interval and the comparisons interval included the remainder of the 1 to 180 post-vaccination time interval. We do the analysis for receipt of any vaccine and as many specific vaccines as possible. We also conducted separate analyses for children and adults.

The means (SDs) of normally distributed variables were compared using 2-sample t tests; for binary or categorical variables, χ^2 analysis with the Fisher exact test was used. We defined a P value less than 0.05 as statistically significant. All analyses were conducted in 2017.

3. Results

Totally, 272 patients with newly diagnosed ADEM were included in the study after an independent diagnosis of two neurologists (Fig. 1). A summary of selected characteristics of the cases (272) with ADEM and the controls (1096) is presented in Table 1.

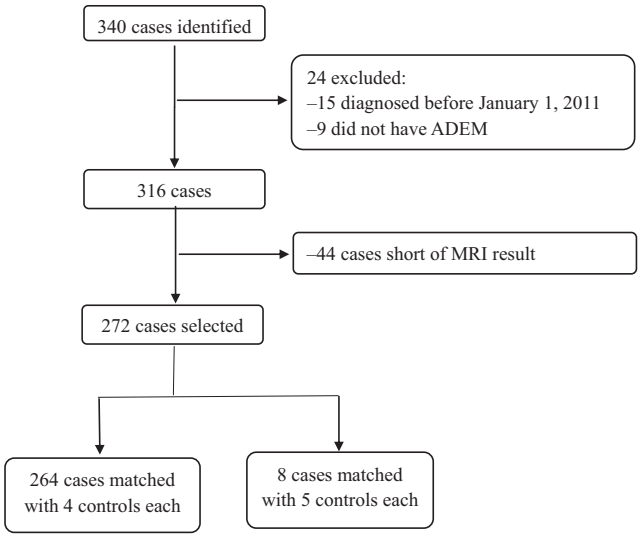

Fig. 1. Case classification flow.

Table 1
Distribution of baseline characteristics between cases and controls.

Characteristic	No. (%)		*P* value
	Cases (n = 272)	Controls (n = 1096)	
Age at onset			
0–20 years	138(50.74)	556(50.73)	1.00
21–40 years	44(16.18)	177(16.15)	
41–60 years	63(23.16)	254(23.18)	
>61 years	27(9.92)	109(9.94)	
Mean (range)	15.42(2.00–86.00)	15.43(2.00–86.00)	
Sex			
Male	149(54.78)	599(54.65)	0.97
Female	123(45.22)	497(45.35)	
Nationality			
Han	269(98.90)	1076(98.18)	0.41
Others	3(1.10)	20(1.82)	
Marital status			
Married	177(65.07)	693(63.23)	0.57
Single	95(34.93)	403(36.77)	
Place of residence			
Urban	62(22.79)	304(27.74)	0.09
Rural	210(77.21)	792(72.26)	
Allergy history			
No	260(95.59)	1024(93.43)	0.19
Yes	12(4.41)	72(6.57)	
Family history			
No	264(97.06)	1037(94.62)	0.10
Yes	8(2.94)	59(5.38)	
Comorbid chronic diseases			
No	220(80.88)	884(80.66)	0.93
Yes	52(19.12)	212(19.34)	
History of infectious diseases within 6 months before the index date			
No	40(14.71)	573(52.28)	0.00
Yes	232(85.29)	523(47.72)	

Because of matching, cases and controls had similar distributions of sex and age (Table 1). Cases and controls also had similar levels of nationality, marital status, place of residence, allergy history, family history of demyelinating diseases or other autoimmune diseases, and comorbid chronic diseases. Compared with controls, the cases were more likely to have had a visit for an infectious illness in the 6 months before symptom onset ($P < 0.05$), and 88.36% cases and 79.34% controls were upper respiratory tract infections.

The analyses of the association between any vaccination and the risk of ADEM by age and time since vaccination are presented in Table 2. Among paediatric population (≤18 years), the adjusted OR of ADEM for cases as compared with controls within 180 days before the index date was 1.19 (95% CI, 0.78–1.74). Vaccine was associated with a statistically significant increase in risk in the 31–60-day exposure interval (OR, 4.04 [95% CI, 1.07–12.69]), but not the 0–30 and 61–180-day interval. Among adult population (>18 years), the corresponding OR was 1.22 (95% CI, 0.23–4.76). When the data were pooled, the adjusted OR for cases as compared with controls was not statistically significant.

No increase in the risk of ADEM was observed for vaccination against hepatitis B, influenza, polio(live), diphtheria, pertuss(acellular), tetanusis, measles, mumps, rubella, Japanese Encephalitis, meningitis, hepatitis A, varicella and rabies vaccines (Table 3). The number of Japanese Encephalitis vaccinated individuals 180 days before symptom onset for the cases was too low to draw any conclusions. The adjusted ORs for cases as compared with controls did not materially change when additional analyses were stratified by subintervals 0–14, 15–30, 31–60, 61–90, and 91–180 days (Supplementary material Table 2). There were no statistically significant interactions by sex for any of the associations between specific vaccines and ADEM, indicating that the results were not different between male and female (Supplementary material Table 3).

23 cases without a history of infection in the prior 6 months were included in the SCCS analyses. Tables 4 show the results of the SCCS analyses using the 31–60 day exposure interval. There was no statistically significant increased risk of any vaccination or specific vaccines, and also in either children or adults.

Thirty-nine patients (21 ≤ 18 year-old vs 18 >18 year-old) have experienced at least once relapse. Follow-up was a median of 25 months (25th–75th percentile 8–67), 26 months (25th–75th percentile 9–72) in children and 23 months (25th–75th percentile 5–66) in adults, $P = 0.59$. Rate of relapse was not significantly lower in patients >18 year-old than ≤18 year-old (13.43% vs 15.21%, $P = 0.68$). Among both paediatric patients (≤18 years) and adult patients, the ORs (95% CI) of the association with ADEM recurrence were not statistically significant (Table 5).

4. Discussion

In this nested case-control study, we found that the risk of ADEM was not significantly increased within the 180 days after vaccinations. We found that any vaccines are not associated with an increased risk of ADEM among either paediatric (≤18 years) or adult (>18 years) individuals except for the 31–60-day exposure interval among paediatric population (≤18 years). The finding in children in the 31–60 day risk interval is likely coincidental, perhaps from multiple comparisons. The finding is inconsistent between children and adults and in the vaccine-specific analysis, it does not appear specific to a particular vaccine, and there was

Table 2
Association between any vaccination and ADEM by age and time since vaccination.

Time of vaccination before index date	Age ≤18 y				Age >18 y			
	No. (%) of cases	No. (%) of controls	OR (95% CI)	Adjusted OR (95% CI)	No. (%) of cases	No. (%) of controls	OR (95% CI)	Adjusted OR (95% CI)
a								
14 d	4(2.90)	16(2.88)	1.01(0.33–3.06)	1.03(0.35–3.07)	3(2.24)	9(1.67)	1.35(0.36–5.06)	1.32(0.33–4.95)
30 d	7(5.07)	40(7.19)	0.69(0.30–1.57)	0.68(0.29–1.54)	5(3.73)	22(4.07)	0.91(0.34–2.46)	0.95(0.36–2.49)
60 d	20(14.49)	53(9.53)	1.61(0.93–2.79)	1.59(0.90–2.76)	11(8.21)	38(7.04)	1.18(0.59–2.38)	1.15(0.55–2.30)
90 d	30(21.74)	91(16.37)	1.42(0.89–2.26)	1.40(0.85–2.24)	18(13.43)	59(10.93)	1.27(0.72–2.23)	1.24(0.69–2.20)
180 d	56(40.58)	201(36.15)	1.21(0.82–1.77)	1.19(0.78–1.74)	24(17.91)	106(19.63)	0.89(0.55–1.46)	0.93(0.59–1.55)
b								
0–14 d	4(2.90)	16(2.88)	1.01(0.33–3.06)	1.08(0.39–3.16)	3(2.24)	9(1.67)	1.35(0.36–5.06)	1.24(0.26–6.06)
15–30 d	3(2.17)	24(4.31)	0.49(0.15–1.66)	0.65(0.35–1.86)	2(1.50)	13(2.40)	0.61(0.14–2.72)	0.71(0.23–3.72)
31–60 d	13(9.42)	13(2.34)	4.34(1.97–9.60)	4.04(1.07–12.69)	6(4.48)	16(2.97)	1.52(0.52–3.96)	1.22(0.23–4.76)
61–90 d	10(7.25)	38(6.84)	1.07(0.52–2.19)	1.10(0.32–2.59)	7(5.22)	21(3.89)	1.35(0.56–3.24)	1.25(0.26–4.24)
91–180 d	26(18.84)	110(19.78)	0.94(0.59–1.51)	0.84(0.39–1.41)	6(4.48)	47(8.70)	0.49(0.20–1.16)	0.56(0.25–3.19)

Odds ratio (95% confidence interval) from conditional logistic regression models adjusted for occupation, familial diseases, comorbid chronic diseases, and history of infectious diseases.

Table 3
Association between different vaccines and ADEM by time since vaccination.

Vaccines	Vaccinated ≤14 d before index date				Vaccinated ≤30 d before index date			
	No. (%) of cases	No. (%) of controls	OR (95% CI)	Adjusted OR (95% CI)	No. (%) of cases	No. (%) of controls	OR (95% CI)	Adjusted OR (95% CI)
Hepatitis B	4(1.47)	20(1.82)	0.80(0.27–2.37)	0.75(0.17–3.39)	8(2.94)	38(3.47)	0.84(0.39–1.83)	0.82(0.35–1.78)
Influenza	4(1.47)	17(1.55)	0.95(0.32–2.84)	0.92(0.38–2.54)	9(3.31)	52(4.74)	0.69(0.33–1.41)	0.72(0.35–1.48)
Polio(live)	0(0.00)	0(0.00)	NA	NA	0(0.00)	0(0.00)	NA	NA
Diphtheria, pertuss(acellular), tetanusis	0(0.00)	0(0.00)	NA	NA	0(0.00)	1(0.09)	NA	NA
Measles, mumps, rubella	0(0.00)	0(0.00)	NA	NA	1(0.37)	3(0.27)	NA	NA
Japanese Encephalitis	0(0.00)	0(0.00)	NA	NA	0(0.00)	1(0.09)	NA	NA
Meningitis(A/C/Y/W135)	0(0.00)	1(0.09)	NA	NA	0(0.00)	2(0.18)	NA	NA
Hepatitis A	0(0.00)	0(0.00)	NA	NA	0(0.00)	1(0.09)	NA	NA
Varicella	1(0.37)	3(0.27)	NA	NA	1(0.37)	5(0.46)	NA	NA
Rabies	0(0.00)	2(0.18)	NA	NA	1(0.37)	5(0.46)	NA	NA

Vaccines	Vaccinated ≤60 d before index date				Vaccinated ≤90 d before index date			
	No. (%) of cases	No. (%) of controls	OR (95% CI)	Adjusted OR (95% CI)	No. (%) of cases	No. (%) of controls	OR (95% CI)	Adjusted OR (95% CI)
Hepatitis B	13(8.46)	51(6.48)	1.03(0.55–1.93)	1.05(0.57–1.96)	31(11.40)	117(10.68)	1.08(0.71–1.64)	1.11(0.82–2.64)
Influenza	19(6.99)	85(7.76)	0.89(0.53–1.50)	0.88(0.52–1.48)	27(9.93)	122(11.13)	0.88(0.57–1.37)	0.98(0.67–1.57)
Polio(live)	2(0.74)	15(1.37)	0.53(0.12–2.35)	0.555(0.14–2.37)	5(1.84)	23(2.10)	0.87(0.33–2.32)	0.77(0.30–2.52)
Diphtheria, pertuss(acellular), tetanusis	3(1.10)	11(1.00)	1.10(0.31–3.97)	1.15(0.38–3.46)	7(2.57)	32(2.92)	0.88(0.38–2.01)	0.82(0.30–2.21)
Measles, mumps, rubella	3(1.10)	15(1.37)	0.80(0.23–2.80)	0.85(0.28–2.85)	5(1.84)	27(2.46)	0.74(0.28–1.94)	0.72(0.38–1.84)
Japanese Encephalitis	0(0.00)	1(0.09)	NA	NA	1(0.37)	5(0.46)	NA	NA
Meningitis(A/C/Y/W135)	1(0.37)	3(0.27)	NA	NA	3(1.10)	8(0.73)	1.52(0.40–5.76)	1.55(0.45–5.78)
Hepatitis A	2(0.74)	10(0.91)	0.80(0.18–3.69)	0.83(0.21–3.72)	7(2.57)	35(3.19)	0.80(0.35–1.82)	0.85(0.38–1.86)
Varicella	3(1.10)	8(0.73)	1.52(0.40–5.76)	1.49(0.38–5.74)	7(2.57)	25(2.28)	1.13(0.48–2.65)	1.15(0.49–2.68)
Rabies	2(0.74)	7(0.64)	NA	NA	6(2.21)	28(2.55)	0.86(0.35–2.10)	0.88(0.33–2.18)

Vaccines	Vaccinated ≤180 d before index date			
	No. (%) of cases	No. (%) of controls	OR (95% CI)	Adjusted OR (95% CI)
Hepatitis B	61(22.43)	255(23.27)	0.95(0.64–1.31)	0.93(0.56–1.35)
Influenza	38(13.97)	149(13.59)	1.03(0.70–1.52)	1.05(0.79–1.55)
Polio(live)	9(3.31)	28(2.55)	1.31(0.61–2.80)	1.35(0.65–2.89)
Diphtheria, pertuss(acellular), tetanusis	14(5.15)	45(4.11)	1.27(0.69–2.34)	1.41(0.55–3.38)
Measles, mumps, rubella	11(4.04)	36(3.28)	1.24(0.62–2.47)	1.03(0.68–3.75)
Japanese Encephalitis	1(0.37)	6(0.55)	NA	NA
Meningitis(A/C/Y/W135)	6(2.21)	15(1.37)	1.63(0.63–4.23)	1.56(0.55–5.38)
Hepatitis A	18(6.62)	65(5.93)	1.12(0.66–1.93)	1.44(0.85–2.98)
Varicella	17(6.25)	82(7.48)	0.82(0.48–1.42)	0.88(0.43–1.67)
Rabies	11(4.04)	35(3.19)	1.28(0.64–2.55)	1.26(0.63–2.58)

Odds ratio (95% confidence interval) from conditional logistic regression models adjusted for occupation, marital status, allergy, comorbid chronic diseases, and history of infectious diseases.

Table 4
Relative risk of ADEM in the 31–60 day risk interval following vaccines, compared to remainder of the 180 days after vaccination.

	Exposure interval	Nonexposure interval	IRR	95% CI
Vaccines				
Hepatitis B	2	7	1.64	0.43–10.59
Influenza	1	5	1.78	0.38–21.56
Polio(live)	0	1	NA	NA
Diphtheria, pertuss(acellular), tetanusis	0	2	NA	NA
Measles, mumps, rubella	0	2	NA	NA
Japanese Encephalitis	0	0	NA	NA
Meningitis(A/C/Y/W135)	0	1	NA	NA
Hepatitis A	1	2	2.38	0.28–39.42
Varicella	0	3	NA	NA
Rabies	0	2	NA	NA
Any	4	19	1.32	0.64–5.62
Age				
≤18y	3	13	0.93	0.57–6.42
>18y	1	6	0.86	0.35–19.38

Table 5
Association between any vaccination and relapse of ADEM by age.

	Age ≤18 y				Age >18 y			
	No. (%) of vaccinated	No. (%) of nonvaccinated	OR (95% CI)	Adjusted OR (95% CI)	No. (%) of vaccinated	No. (%) of nonvaccinated	OR (95% CI)	Adjusted OR (95% CI)
Relapse	8(38.10)	13(61.90)	0.89(0.34–2.30)	095 (0.52–1.68)	5(27.78)	13(72.22)	1.96(0.63–6.16)	1.32 (0.35–5.43)
Relapse-free	48(41.03)	69(58.97)			19(16.38)	97(83.62)		
Total	56(40.58)	82(59.42)			24(17.91)	110(82.09)		

Odds ratio (95% confidence interval) from conditional logistic regression models adjusted for occupation, allergy, familial diseases, comorbid chronic diseases, and history of infectious diseases.

no statistically significant increased risk in the SCCS analyses. The result could be due to residual confounding with the use of hospitalized controls, especially with the large differences in infectious diseases between the cases and controls.

Hepatitis B has been the vaccine about which there has been the greatest controversy regarding a possible association with demyelinating diseases. We found no increased risk with HepB-containing vaccine and the risk of ADEM 180 days following vaccination, which consistents with the results from most previous HepB vaccine and ADEM risk studies [7,12–14]. However, as in the previous French study [15], an association between pediatric acute CNS inflammatory demyelination and Engerix B vaccine was reported only 3 years after vaccination (OR, 2.8; 95% CI, 1.2–6.4). This finding is difficult to interpret because the study failed to find associations for other HepB vaccine brands. Our results are also different from another analysis conducted in France which found that the number of notified cases that occurred within 2 months after HepB vaccination was higher than expected [16]. There have been some case reports of central nervous system demyelination within a few weeks after the HepB vaccination, but as their authors recognize, these reports cannot demonstrate a causal or triggering association [17,18].

Influenza vaccine is another commonly administered to people. The null result that we found in this investigation is consistent with the recent observation that there was no increase in the risk of neurological disorders after the pandemic influenza A(H1N1) vaccination of more than one million people in Sweden [19].

For the other vaccines, individual cases with demyelinating diseases that followed shortly after a vaccination were reported [20–28]. Based on 2 exposed cases, the odds ratio for Tdap exposure 5–28 days prior to ADEM onset was 15.8 (95% CI, 1.2–471.6) [29]. However, it is difficult to interpret these associations because it is not possible to distinguish whether the observed event was causal or coincidental. Our study evaluated several vaccines, and the results indicate that the observations in the published case reports probably represent coincidental temporal associations rather than causal associations. Another epidemiologic study about central nervous system demyelinating diseases after the adult vaccines also suggested that the findings may be due to chance [12].

Recurrence after an initial ADEM diagnosis was in about 14% of patients in our study, which is higher than reported in Argentina (10%, follow up 80 months)[30], and lower than in France (18%, follow up 65 months)[31], Italy (30.5%, follow up 69 months)[32] and United States (24%, follow up 24 months)[10]. Children and adults experienced demyelinating relapses in similar proportions in our study, consistent with prior research [10]. We did not find any significant association between ADEM recurrence and vaccination.

Many identifiable infections are well known risk factors for ADEM [33]. Most cases (85.29%) in our study had signs of infection 6 months prior to the neurologic symptoms. It is likely that the infectious agents trigger an autoimmune response against the CNS antigens, which leads to the CNS pathology. In theory, vaccines could increase the risk of ADEM through mechanisms similar to those induced by infections. However, even in animal models, these mechanisms are complex and depend on the timing of exposure, antigen type, genetic background, and coadministration of adjuvants [34]. The hypothesis was that the vaccine could cause an acute autoimmune reaction in susceptible persons soon after administration [35]. This hypothesis may seem plausible given what we know about adverse reactions to other drugs, but its appropriateness to ADEM is questionable.

Our study was a large population-based case-control study that included both male and female. It adds to existing knowledge by providing information on several vaccines that had not previously been studied. The retrospective nature of the case-control design may be subject to recall bias, but recall bias was avoided through the use of computerized vaccination records.

Our study has several limitations. We could not evaluate the association between ADEM and HPV vaccine, because no HPV vaccine is available in Jiangsu, although it has been reported that several young females presented with fulminant onset of ADEM 2 to 4 weeks following administration of HPV vaccine [5,6]. We could not

detect associations with small select subgroups (symptom onset within 14 days following Rabies vaccine, etc). Lack of association of vaccines with ADEM in our study is also probably because there are not enough numbers of subjects regarding a rare event. Studies with larger sample size are required to further validate the results. We could not examine the potential influence of vaccine preservatives and adjuvants. Further studies are needed to completely rule out an effect. Residual confounding(s) may be another limitation. We collected only information on vaccinations received within 180 days, instead of vaccinations beyond the risk period. Otherwise, use of "case-only" analysis (e.g., self-controlled case series/interval or case-crossover) could eliminate measured and unmeasured fixed confounding.

5. Conclusions

In summary, findings from the present study do not demonstrate an association of vaccines with an increased risk of ADEM and its recurrence among either paediatric (≤18 years) or adult (>18 years) individuals within the 180 days after vaccinations except for the 31–60-day exposure interval among paediatric population (≤18 years). The finding in children in the 31–60 day risk interval is likely coincidental and was not confirmed in separate self-control analyses. We found no association between HepB vaccination and an increased risk of ADEM up to 180 days after vaccination, which is reassuring. Our results also indicate that previous case reports of ADEM shortly after administration of several other vaccines probably represent coincidental temporal associations and not true causal associations.

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Disclosure of conflict of interest

None.

Author contributions

Yong Chen, study concept and design, analysis and interpretation of data.

Fubao Ma, study concept and design, study supervision.

Yuanling Xu, acquisition of data, interpretation of data.

Xuhua Chu, acquisition of data, interpretation of data.

Jinlin Zhang, study concept and design, acquisition of data.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.05.063.

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