Author’s response to reviews

Title: Epidemiological Characteristics of Acute Disseminated Encephalomyelitis in Nanchang China: A Retrospective Study.

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Author’s response to reviews: see over
Cover letter

Dear Rita:

Thank you very much for your letter and advice. We have revised the manuscript, and would like to resubmit it for your consideration. We have asked American Journal Experts (AJE) for editing the manuscript. The certificate verification key that was provided by AJE is 9D49-8B5E-40C7-3AB2-C671. The editorial certificate was uploaded as an attachment. We have addressed the comments raised by the reviewers, and the amendments are highlighted in red in the revised manuscript. Point by point responses to the reviewers’ comments are listed in this following letter. We hope that the revised version of the manuscript is acceptable for publication in our journal.

I look forward to hearing from you soon.
With best wishes,
Yours sincerely,

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Name: Yan Yan
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We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

Replies to reviewer 1: Anannit Visudtibhan.

1. It is justified that the authors provide the detail of medical service in China where the hospitals are classified according to the level of cares. This definitively affects the data for analysis. However, it is not necessary to mention all every hospital as shown in the second paragraph of Material & Method section.

Answer:

We have provided the details of health service in China, and deleted the part of name of every hospital shown in manuscript. Added contents are the followings.

In the Chinese health service system, hospitals are divided into three levels. The higher-level hospitals have greater medical service capabilities. First-level hospitals are basic hospitals and primary health care institutions that mainly provide primary prevention services to community residents or referrals for serious or rare diseases. The second-level hospitals are regional hospitals and regional medical prevention technology centres. Their main functions include disease treatment, acceptance of referrals and technical guidance for medical services provided by primary hospitals. Third-level hospitals are general hospitals with the greatest ability to provide comprehensive medical treatment and to engage in teaching and scientific research, especially treatment of serious and rare diseases.

2. Clarification of diagnosis of ADEM should be mentioned. As being stated by International Pediatric MS Study Group, criteria of diagnosis of ADEM must be solid. The authors were able to access to the medical record of each patient, therefore, it is possible to obtain the patients with definitive diagnosis with ADEM. The result of this study will be more convincible than it is as present.

Answer:

We have added content about definitions of ADEM.

Consensus definition of ADEM was proposed by International Pediatric MS Study Group. Definitions of ADEM mainly included the followings.

The first clinical event is the symptom of infection. It occurs acutely or subacutely and indicates that an illness is severe or dangerous.

With regard to the clinical presentation, the brain or spinal cord usually suffers multifocal damage. The cerebral symptoms are predominantly mental symptoms, disturbances of consciousness and meningeal irritation; pyramidal tract and cerebellar signs can appear. The myelopathic symptoms include paraplegia, rising palsy and urinary disorders, etc.

The cerebrospinal fluid (CSF) pressure is normal or higher, CSF-monocytes rise, immunoglobulin G rises, and the electroencephalo-graph is abnormal. Computed tomography (CT) and magnetic resonance imaging (MRI) show scattered lesions on the brain and spinal cord.

3. There are many Tables and data which are not relevant and might not be included into the manuscript. Table 3 does not provide any information to the reader. Distribution of occupations is concordant to the findings and does not affect the
occurrence of ADEM. Table 4 demonstrates residential area of ADEM without further correlation to the prevalence of ADEM in Nanchang. Table 5 should provide more information regarding preceding illness prior the onset of ADEM. In addition, the last paragraph in Result mentions on immunization vaccine campaigns does not relevant to the result. The authors mentioned already in the last sentence of previous paragraph that “No patient received vaccination within two months before the onset”.

Answer:

We have deleted the contents of the Table 3 and Table 4. Because we are not able to get the number of different occupations, and the same person can be engaged in different occupations, so the number of people in each occupation is difficult to obtain. The incidence of ADEM in different occupations can not be calculated. With developing of Chinese economy and mass flow of people, boundaries between rural and urban has become increasingly vaguer. It is very difficult to tell a person lived in the rural area or urban area.

We have enriched the contents of Table 5. Serial number of Table 5 was changed into Table 3. The changed contents include the followings.

In this study, all 15 patients who fell ill within 2 months before the onset (6 cases: < 14 years old; 5 cases: 15-59 years old; 4 cases: > 60 years old) had a history of precursor infection and had symptoms of a respiratory tract infection. Among the 15 patients, 7 patients were given an antigen antibody test. One patient had the Epstein-Barr virus and Coxsackie virus, 2 patients had cytomegalovirus, 1 patient had cytomegalovirus and herpes simplex virus, 1 patient had Gram-positive bacteria, and three patients received negative results. Among the 15 patients, 2 patients had co-morbid chronic bronchitis, 1 patient had severe pneumonia, and 1 patient had high blood pressure.

We have adjusted the description about the results of ecological research on the relationship between vaccines and ADEM. We combined the sentence that “no patient received vaccination within two months before the onset”, the last paragraph in Result and the sentence “The vaccination doses in 2009 was 2.40 times higher than that in 2008, the number of ADEM patients decreased by 2. The vaccination dose in 2010 was 2.13 times higher than that in 2008, the number of ADEM patients of the former is only more one than the latter.” In this way, they formed the last paragraph in Result of revised manuscript.

4. Discussion and data interpretation are concordant to the result except the correlation to the vaccination campaign. Therefore, the last sentence in the abstract might be over emphasized. In addition, the authors should discuss on the result which demonstrated difference in monthly distribution of ADEM. There should be a pothesis why February and March had higher prevalence than other months.

Answer:

We have adjusted the description about the results of ecological research between vaccines and ADEM. We combined the sentence that “no patient received vaccination within two months before the onset”, the last paragraph in Result and the sentence “The vaccination doses in 2009 was 2.40 times higher than that in 2008, the
number of ADEM patients decreased by 2. The vaccination dose in 2010 was 2.13 times higher than that in 2008, the number of ADEM patients of the former is only more one than the latter.” In this way, they formed the last paragraph in Result of revised manuscript. We have adjusted the last sentence in Abstract and in Conclusion to the sentence, “An increase in the vaccination dose was not accompanied with a corresponding increase in ADEM.” and “More vaccinations did not cause more cases of ADEM in Nanchang, China”

We have added contents of monthly distribution of ADEM in Discussion. That is “It is easier for the residents to become infected with a precursor disease, such as a respiratory tract infection, because of the winter weather in Nanchang. In the northern hemisphere subtropical zone, it is coldest in January and February. In addition, the Chinese spring festival, the most important traditional festival in China, is often around February. People are often reluctant to go to hospital until spring festival is over. Thus, the number of patients may increase in March.”

5. Quality of written English needs improvement. The manuscript should be reviewed and edited by anyone who is keen in English writing. It will ease the readers if commas are added in the number. Syntax and typing errors (ie AMDE, etc.) appear in many sentences. Pattern of references are not consistency ie ref 7,9,14, 25.
Answer: American Journal Experts (AJE) have reviewed and edited the manuscript. The certificate verification key that was provided by AJE is 9D49-8B5E-40C7-3AB2-C671. The editorial certificate was uploaded as a attachment. We have made the pattern of references consistent.

Other contents were revised mainly.

We have revised some assertive statements. For example, in Introduction the sentence “Incidence rates of ADEM are not different between enders, races, or regions.” is modified into “Some researchers have noted that the incidence rates of ADEM are not different between genders, races, and regions”
We would like to express our sincere thanks to the reviewers for the constructive and positive comments.

Replies to Reviewer 2: Hiroyuki Torisu.

1 Authors should refer to the definition of ADEM and accuracy of diagnosis of ADEM.
   Answer: We have added content about definitions of ADEM. Consensus definition of ADEM was proposed by International Pediatric MS Study Group. Definitions of ADEM mainly included the followings.
   The first clinical event is the symptom of infection. It occurs acutely or subacutely and indicates that an illness is severe or dangerous.
   With regard to the clinical presentation, the brain or spinal cord usually suffers multifocal damage. The cerebral symptoms are predominantly mental symptoms, disturbances of consciousness and meningeal irritation; pyramidal tract and cerebellar signs can appear. The myelopathic symptoms include paraplegia, rising palsy and urinary disorders, etc.
   The cerebrospinal fluid (CSF) pressure is normal or higher, CSF-monocytes rise, immunoglobulin G rises, and the electroencephalo-graph is abnormal. Computed tomography (CT) and magnetic resonance imaging (MRI) show scattered lesions on the brain and spinal cord.

2 Authors should add how to find and get the information on ADEM patients to ‘method’ in abstract.
   Answer: We have added the contents to find and get the information on ADEM patients to ‘method’ in Abstract. That is “ADEM patients, defined as patients who were diagnosed according to the consensus definition of ADEM provided by the International Pediatric MS Study Group, were enrolled in the study. The data were extracted from the ADEM patients’ medical records.”

3 Authors should describe the disease corresponding to the mentioned ICD codes in ‘Materials and Methods’.
   Answer: We have deleted the contents about ICD codes. We used consensus definitions of ADEM to describe the searched disease now.

4 Authors described in Materials and Methods as follows; ‘The searched diseases included ADEM, acute myelitis, acute disseminated encephalitis, encephalomyelitis, and cerebrospinal meningitis.’. What does this sentence imply?
   Answer: We have added content about definitions of ADEM. Consensus definition of ADEM was proposed by International Pediatric MS Study Group. Definitions of ADEM mainly included the followings.
   The first clinical event is the symptom of infection. It occurs acutely or subacutely and indicates that an illness is severe or dangerous.
   With regard to the clinical presentation, the brain or spinal cord usually suffers multifocal damage. The cerebral symptoms are predominantly mental symptoms, disturbances of consciousness and meningeal irritation; pyramidal tract and cerebellar signs can appear. The myelopathic symptoms include paraplegia, rising palsy and urinary disorders, etc.
   The cerebrospinal fluid (CSF) pressure is normal or higher, CSF-monocytes rise, immunoglobulin G rises, and the electroencephalo-graph is abnormal. Computed tomography (CT) and magnetic resonance imaging (MRI) show scattered lesions on the brain and spinal cord.
We have deleted the sentence. We used consensus definitions of ADEM to describe the searched disease now.

5 Authors should describe the definition and specific difference of rural and urban.
Answer:
We have deleted the contents of the Table 4. With developing of Chinese economy and mass flow of people, boundaries between rural and urban has become increasingly vaguer. It is very difficult to tell a person lived in the rural area or urban area. The incidence of ADEM in different places can not be calculated.

6 In Conclusions, authors described ‘Vaccination was not directly associated with onset of ADEM.’. What does the word ‘directly’ imply?
Answer:
We have adjusted the description about the results of ecological research between vaccines and ADEM. We combined the sentence that “no patient received vaccination within two months before the onset”, the last paragraph in Result and the sentence “The vaccination doses in 2009 was 2.40 times higher than that in 2008, the number of ADEM patients decreased by 2. The vaccination dose in 2010 was 2.13 times higher than that in 2008, the number of ADEM patients of the former is only more one than the latter.” In this way, they formed the last paragraph in Result of revised manuscript. We have adjusted the last sentence in Abstract and in Conclusion to the sentence, “An increase in the vaccination dose was not accompanied with a corresponding increase in ADEM.” and “More vaccinations did not cause more cases of ADEM in Nanchang, China”.

7 The statements as below are not well sustained. The authors should show evidence or revise the expression. These statements seem too assertive.
7.1 In Abstract, “Incidences of ADEM are not different between genders, races, or regions,...”.
Answer:
In Abstract, the sentence “Incidences of ADEM are not different between genders, races, or regions,...” was deleted. In Introduction it was revised into “Some researchers have noted that the incidence rates of ADEM are not different between genders, races, and regions”.

7.2 In Introduction, “Acute Disseminated Encephalomyelitis (ADEM) which is an autoimmune disease characterized by idiopathic central nervous demyelination and inflammatory infection affects several areas in the central nervous system.”
Answer:
The upper sentence was revised into “Acute disseminated encephalomyelitis (ADEM) is a disease that is mainly characterised by an inflammatory reaction and demyelination of the central nervous system (CNS) [1]”

7.3 In Introduction, “Incidence rates of ADEM are not different between enders, races, or regions [7, 8].”
Answer:

The upper sentence was modified into “Acute disseminated encephalomyelitis (ADEM) is a disease that is mainly characterised by an inflammatory reaction and demyelination of the central nervous system (CNS) [1].”

7.4 In Introduction, “It has good prognosis and commonly occurs in the tropics, but rarely in temperate zones.”
Answer:

The upper sentence was deleted.

7.5 In Discussion, “No evidence suggests that vaccination is linked with the onset of ADEM”. Authors should add the phrase‘ in China’.
Answer:

The phrase ‘in Nanchang, China’ was added into the upper sentence.

7.6 In Discussion, “Revaccination is more risky than primary vaccination [31].”
Answer:

The upper sentence was deleted.

8 In Abstract and other parts, authors should change the expression ‘annual average incidence’ into other expression like ‘average annual incidence’.
Answer:

All the expression ‘annual average incidence’ were changed into ‘average annual incidence’.

9 The software ‘EPIDATA3.1’ needs the information of the source.
Answer: The information of source on the software ‘EPIDATA3.1’ was Chinese version EPIDATA 3.1 (270108).

Other contents were revised mainly.
We have provided the details of medical service in China, and delete the part of name of every hospital shown in manuscript. Added contents are below.

In the Chinese health service system, hospitals are divided into three levels. The higher-level hospitals have greater medical service capabilities. First-level hospitals are basic hospitals and primary health care institutions that mainly provide primary prevention services to community residents or referrals for serious or rare diseases. The second-level hospitals are regional hospitals and regional medical prevention technology centres. Their main functions include disease treatment, acceptance of referrals and technical guidance for medical services provided by primary hospitals. Third-level hospitals are general hospitals with the greatest ability to provide comprehensive medical treatment and to engage in teaching and scientific research, especially treatment of serious and rare diseases.

We have deleted the contents of the Table 3. Because we are not able to get the number of different occupations, and the same person can be engaged in different occupations, so the number of people in each occupation is difficult to obtain. The incidence of ADEM in different occupations can not be calculated.