



RESEARCH ARTICLE

REVISED Increasing Epstein-Barr virus infection in Chinese children: A single institutional based retrospective study. [version 2; peer review: 2 approved, 1 approved with reservations]

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Abstract

The Epstein-Barr virus (EBV) is a common virus in humans and the most common causative agent of Infectious Mononucleosis. EBV primary infection has recently risen in some countries and children below 2 years of age are highly susceptible. The clinical manifestations in children with EB virus infection involve multiple systems, causing severe illness, meaning attention should be paid during diagnosis and treatment.

Objective: This single institution based retrospective study was carried out with the aim of estimating the overall prevalence of EBV infection and identifying high-risk age group among children.

Methods: This study include total 253 patients under 15 years of age found to be positive for EBV DNA by serum PCR who were admitted to the Pediatrics Department of Renmin Hospital,(Shiyan, China) during a 4-year period from 2014 to 2017. Patients were divided into three groups; 0-<4years, 4-<6years and 6-<15years. We then calculated the percentage and prevalence of EBV DNA-positive cases.

Results: The yearly EBV prevalence rate was 4.99 per 1000 admissions in 2014, 6.97 per 1000 admissions in 2015, 10.42 per 1000 admissions in 2016, and 12.16 per 1000 admissions in 2017. Out of 253 EBV-positive cases, those under 4 years had the highest rate of EBV infection (74.7%). The rate drops to 11.06% in the 4-6 years group, and was 14.22% in the 6-15 years group. Those between 6 months and 1 year are those at the highest risk.





Conclusion: The rate of hospital admission of children due to EBV infection is increasing day by day. Children under 4 years of age are highly susceptible to infection and children of age between 6 months and 1 year are the high-risk group for EBV infection.




Keywords

Infectious mononucleosis; Prevalence; EBV DNA; Epstein-Barr virus

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REVISED Amendments from Version 1

We have tried to clarify some queries of reviewer and added few points:

1. Regarding the type of the specimen – we have done Serum PCR
2. We have expanded the Assessment section
3. We have reviewed and corrected a citation in the Discussion section

See referee reports

Introduction

The Epstein-Barr virus (EBV) is the most common herpesvirus in humans and the most common causative agent of infectious mononucleosis¹. It is also known as the “kissing disease”². EBV is an acute infection with a characteristic symptomatic triad of fever, sore throat and lymphadenopathy. Sprunt and Evans in 1920 coined the term infectious mononucleosis to describe an acute infectious disease accompanied by atypical large peripheral blood lymphocytes². EBV primary infection has recently risen in some countries³ and children below 2 years of age are highly susceptible^{4,5}. EBV is transmitted primarily via oral secretions and may be transmitted via penetrative sexual intercourse⁶. Transmission may occur by the exchange of saliva among children. EBV is not spread by non-intimate contact, environmental sources, or fomites⁶. During late adolescence 50–70 percent of teenagers get infected with infectious mononucleosis². Though it has a self-limiting course, it may sometimes lead to numerous rare, atypical and threatening manifestations. The clinical manifestations in children with EBV infection involve multiple systems and can cause severe illness, meaning that attention should be paid during diagnosis and treatment. The diagnosis of EBV infection is based on clinical features such as- fever, pharyngitis, lymphadenopathy, hepatomegaly, and splenomegaly along with leukocytosis with a predominance of lymphocytes, >10% atypical lymphocytosis, heterophile antibodies (assessed via monospot test), serum PCR for EBV DNA and serological testing including antibodies for viral capsid antigens, early antigens, and Epstein-Barr nuclear antigen.

EBV DNA PCR has high specificity and sensitivity for identifying patients with infectious mononucleosis⁷.

Methods

Assessment

We retrospectively collected 253 EBV infection with serum EBV DNA positive cases from those who were symptomatically suspected as infectious mononucleosis from symptoms such as fever, pharyngitis, cervical lymphadenopathy and other lymph nodes enlargement on hospitalized patients <15 years old at Renmin Hospital, 3rd Affiliated Hospital of Hubei University of Medicine, Shiyan, (Hubei, China) during the 4-year period from January 1, 2014, to December 31, 2017. At birth, neutrophils make up around 61% of total leukocytes and lymphocytes make up around 31%. After birth, the number of neutrophils goes down and the lymphocyte number goes up, with both reaching about 45% around the 1st week of life. This process continues and by the age of 4 years, lymphocytes reaches around 50% and

neutrophils reach around 42%. On growing older, the proportion of lymphocytes starts to fall and that of neutrophils start to increase. By the age of 6 years, the proportion of neutrophils reaches up to 51% and that of lymphocytes falls to 42%⁸. Owing to this age-specific leukocytes differential, we divided patients into three age groups: <4 years, 4–<6 years and 6–<15 Years. We also made further age-specific groupings, as follows: <30 days, 1–<6 months, 6–<12 months, 1 year, 2 years, 3 years, 4 years, 5 years, 6 years, 7 years, 8 years, 9 years, 10 years, 11 years, 12 years, 13 years, and 14 years to find out the risk group for EBV infection. A diagnosis of EBV infection was achieved using real time PCR at the Pathology Department at Renmin Hospital.

Analysis

Real-time PCR ABI iiA7 was used for quantitation of serum EBV DNA. The primers used, targeting the EBNA-1 fragment of EBV, were as follows: 5'-GTAGAAGGCCATTTTTCCAC-3' (forward) and 5'-TTTCTACGTGACTCCTAGCC-3' (reverse). PCR was conducted using the following thermocycling conditions: 93°C for 2 min, followed by 10 cycles of 93°C for 45 sec and 55°C for 60 sec, and then 30 cycles of 93°C for 30 sec and 55°C for 45 sec.

All data were analyzed using Microsoft Excel 2010. Age-specific prevalence was calculated. Prevalence was calculated as follows:

$$\text{Prevalence} = \frac{\text{number of EBV-positive children under 15 years admitted to hospital}}{\text{number of total hospital admissions for children under 15 years}}$$

Results

Out of the total of 253 patients, 151 (60%) were male and 102 (40%) were female. The male to female ratio was 3:2 (Figure 1).

The number of serum EBV DNA-positive cases observed increased each year. There were 36 EBV DNA positive cases in 2014 (total admissions, 7202) with a prevalence of 5.00 per 1000 admissions, 43 on 2015 (total admissions, 6163) with a prevalence of 6.98 per 1000, 77 on 2016 (total admissions, 7384) with

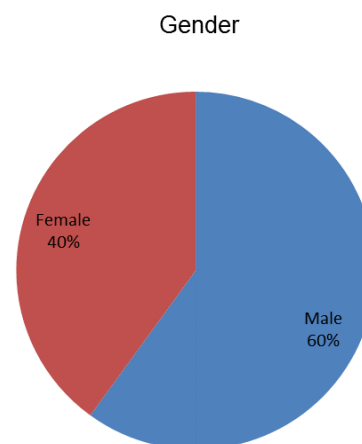


Figure 1. Sex distribution.

prevalence of 10.43 per 1000 and 97 on 2017 (total admissions, 7972) with prevalence of 12.17 per 1000 admissions (Figure 2, Figure 3).

Over the 4 years studied here, the numbers of hospitalized children were highest in the 0 to < 4 years group. Of 253 EBV-positive patients, 189 (74.70%) were in group 0 to less than 4 years, 28 (11.06%) in the group of children aged 4 to <6 years, and 36 (14.23%) in those aged 6 to <15 years. Each year, in the group of children under 4 years the percentage of EBV positive cases were more and rate were in increasing trend (Figure 4, Figure 5).

We calculated the age-specific prevalence of EBV infection to identify the high-risk group. The number of positive cases was highest in the age group 6 months- <1 year, which decreased as age increased. Prevalence is also high in this age group (Table 1 and Figure 6, Figure 7).

Dataset 1. The number of total admissions and admissions of Epstein-Barr virus (EBV)-positive children under 15 years of age for each of the years 2014–2017

<http://dx.doi.org/10.5256/f1000research.15544.d212141>

This dataset also contains stratifications of EBV-positive individuals by age and sex.

Discussion

The incidence of EBV infection is higher in male children in Northern China⁹ and Turkey¹⁰. In India, the male to female ratio of EBV infection in hospitalized children is 2:1^{11,12}. A Korean study found the overall male-to-female ratio of EBV infection to be 1.53:1¹³. Our study had a male to female ratio of 3:2. During adolescence, women acquire before men the first infection by EBV¹⁴. In the US EBV antibody titers were significantly higher for females¹⁵.

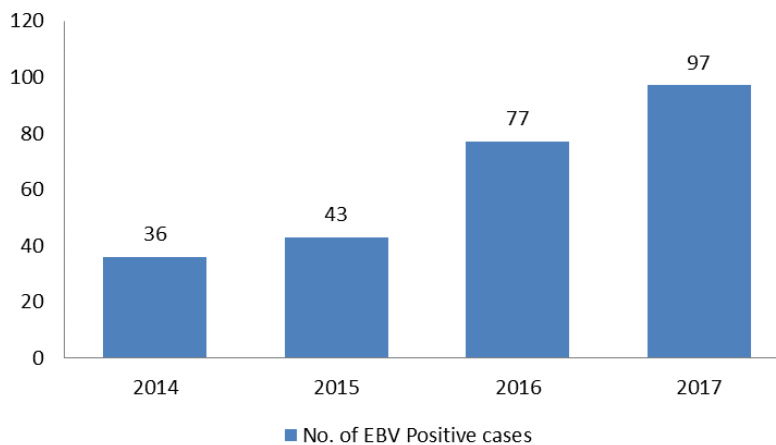


Figure 2. Yearly distribution of Epstein-Barr virus-positive patients.

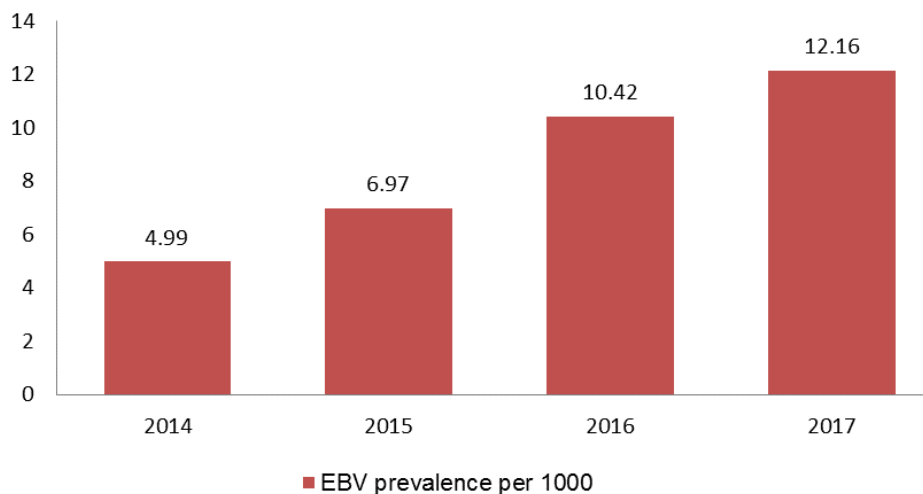


Figure 3. Prevalence of Epstein-Barr virus-positive patients per 1000 hospital admissions by year.

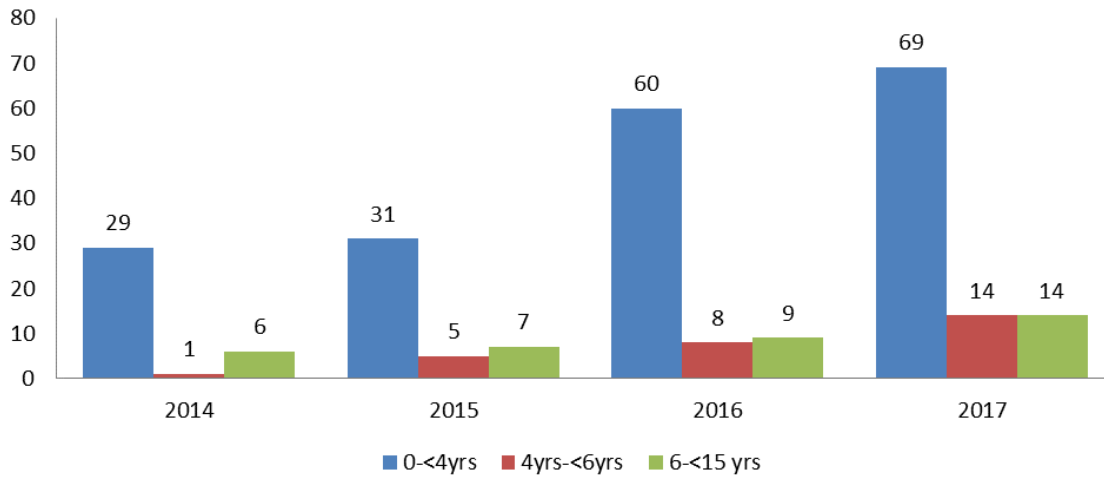


Figure 4. Age group distribution of Epstein-Barr virus-positive patients.

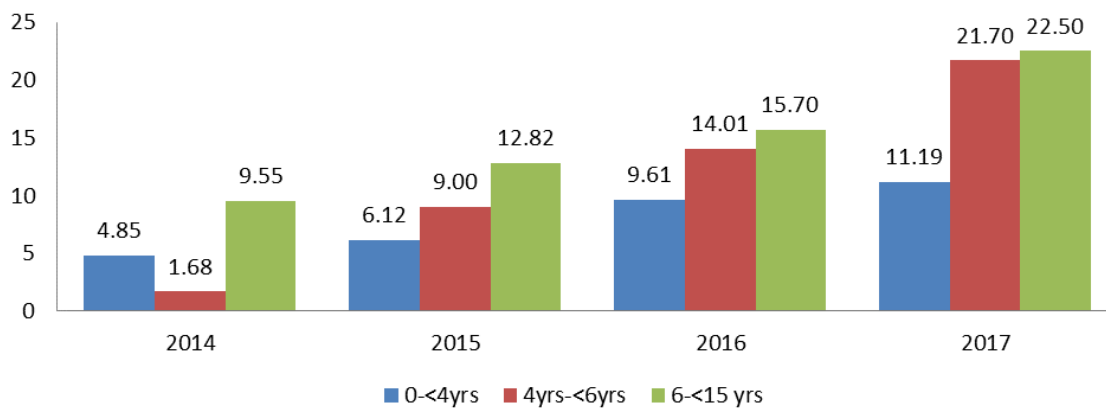


Figure 5. Prevalence of Epstein-Barr virus-positive patients cases of specific age groups per 1000 hospital admissions.

We have found that in children under 4 years, the percentage of EBV-positive cases increased each year. However, in children aged 4–<6 years this decreased, but increased in those aged 6 to <15 years. Out of the 253 EBV positive patients, those aged under 4 years made up the highest proportion (74.7%). This drops to 11.06% in those 4–<6 years, and 14.22% in those 6–<15 years. In the study done on the Northern and Southern part of China, the seroprevalence of EBV infection is more than 50% before age 3³. Serological evidence of EBV infection is found in around 84% of Chinese children aged >9 years, with peak incidence observed at age 2–3 years¹⁶. However, in a study done by Gao *et al.*, the incidence of EBV-IM peaked in children at age of 4–<6 years in Northern China¹⁰. In Taiwan, the seropositive rate of EBV is high in children aged 2 years⁴. A Danish study found that EBV infection is common in young children, and children under 3 years of age constitute the largest group of hospitalizations for acute EBV infection⁵. In a study conducted in Poland, age of infection occurred in two

peaks, i) in children aged 1 to 5 years (62%), and ii) in teenagers (24.6%)¹⁷. In most developing countries nearly 70% of patients are seropositive for EBV by the age of 2 years¹⁸. However in USA, the seroprevalence increased with age, ranging from 54.1% for 6–8 year-olds to 82.9% for 18–19 year-olds¹⁵.

We found hospitalization for mononucleosis in all age groups. The number of positive cases was higher in the age group >6 months but <1 year, which decreases as age increases. The prevalence is also high on age group 6 month to 1 year. This indicates that the age group 6 months to less than 1 year is a high-risk group. The most common age group for hospitalization with acute EBV infection in Denmark was 1–2 years⁵. In Asia and other developing countries most of the children are infected with EBV in early life, mostly before the age of 1 year¹⁹. According to Cocuz *et al.*, admissions for infectious mononucleosis were prevalent in young children, with most occurring in the 1–3 years age group (32.31% of the total IM Cases), followed by those

Table 1. Age-specific distribution and prevalence of Epstein-Barr virus.

Age	2014			2015			2016			2017		
	P	C	N	P	C	N	P	C	N	P	C	N
0-30 days	0	0	668	0	0	554	4.94	4	809	4.87	2	410
≥1-<6 months	1.05	1	954	0	0	984	2.66	3	1124	1.84	2	1083
≥6-<12 months	37.38	8	214	53.92	11	204	82.19	18	219	93.18	26	279
1 year	2.18	4	1837	6.28	10	1592	10.38	20	1925	7.00	15	2141
2 years	7.31	8	1094	7.46	5	670	8.05	8	869	15.47	13	840
3 years	11.44	8	699	6.20	4	645	10.21	7	685	13.33	11	825
4 years	1.94	1	514	2.42	1	413	8.21	5	609	16.97	10	589
5 years	0	0	343	12.90	4	310	8.90	3	337	9.63	4	415
6 years	11.95	3	251	8.16	2	245	17.09	4	234	21.73	5	230
7 years	5.12	1	195	6.36	1	157	11.76	2	170	18.86	3	159
8 years	0	0	144	0	0	127	0	0	128	15.87	2	126
9 years	0	0	92	11.11	1	90	10.75	1	93	10.10	1	99
10 years	14.28	1	70	15.87	1	63	27.02	2	74	9.52	1	105
11 years	16.39	1	61	16.66	1	60	0	0	50	0	0	55
12 years	0	0	40	0	0	26	0	0	34	47.61	2	42
13 years	0	0	19	142.85	2	14	0	0	11	0	0	24
14 years	0	0	7	0	0	9	0	0	13	0	0	12

P, Prevalence of Epstein-Barr virus (EBV)-positive cases per 1000; C, number of EBV-positive cases; N, total number of hospital admissions.

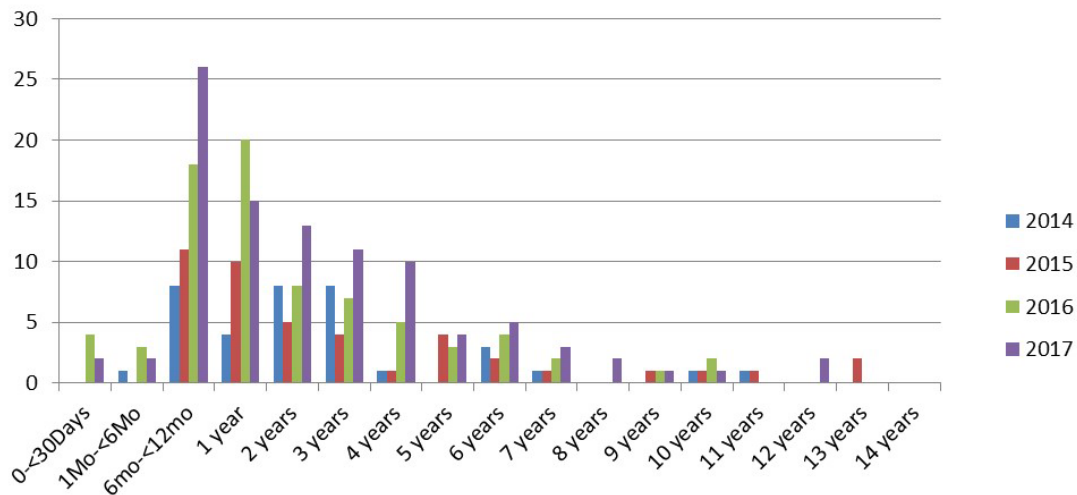


Figure 6. Age-specific distribution of Epstein-Barr virus-positive patients.

4-<6 years old (27.69% of the total IM Cases), then those 11-16 years old (26.15% of the total IM Cases) and finally those 7-10 years old (13.84% of the total IM Cases)²⁰.

Several prior studies have reported in the last decade which shows the changes in the epidemiology of EBV infection. A Japanese study showed that the seroprevalence of EBV in 5-7 years old children was higher than 80% before the early

1990s which decreased to 59% in the years 1995¹⁹. Similarly in the USA, the study showed that the seroprevalence in 6-19 year olds declined from 72% in 2003-2004 to 65% in 2009-2010²¹. But, the EBV primary infection is increasing in England and Wales²². Therefore, we aimed to determine the epidemiological condition of EBV infection over the last years in the Pediatrics Department of Renmin Hospital, Shiyuan, China. The EBV positivity rate in hospitalized children is increasing every year.

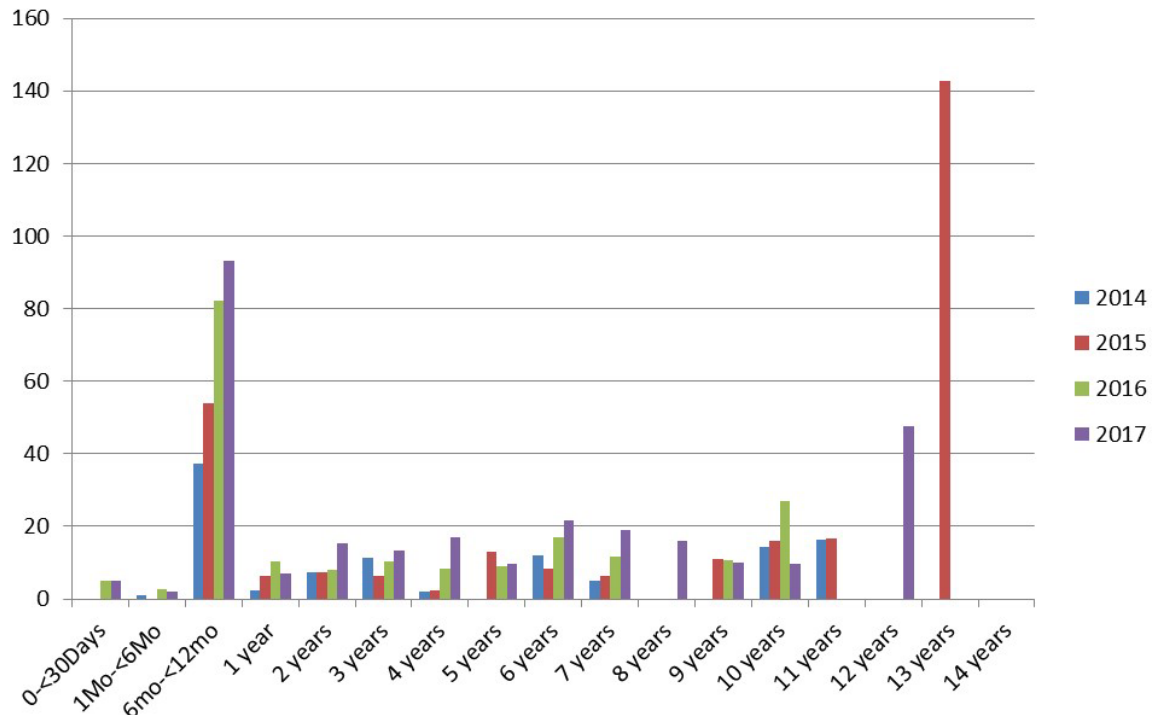


Figure 7. Age-specific distribution of Epstein-Barr virus-positive patients per 1000 hospital admissions.

Prevalence is also increased each year. In the years 2000 to 2016, the EBV infection rate in France has increased, whereas its seroprevalence has decreased³.

Although most EBV infections are self-limiting, sometimes they may lead to rare, atypical and threatening manifestations. Although serious complications during the acute phase of primary EBV infection are rare¹, neurological complications, like meningoencephalitis, acute encephalitis, acute cerebellitis, transverse myelitis, and myeloradiculitis, occur more frequently in children under 2 years of age^{17,23,24}. Furthermore, in immunocompromised individuals, there was an association observed between EBV with several tumors following reactivation of the virus from latency²⁵.

Since this study was conducted in children admitted to hospital, the results might lack generalization to the entire population, but may indicate trends and bring up questions deserving further prospective study.

Increasing primary infection of EBV in children may be due to many reasons, including that the virus is active among the population around Shiyuan, airborne transmission²⁶ of the virus is higher in this area, multiple caregivers for each infant, bottle feeding, unnecessary kissing, feeding with chewed food to babies, or through hospital acquired EBV infection e.g. from health care personals, doctors or nurses. There are several reports on the intrauterine transmission of EBV, but none has been substantiated by appropriate viral studies^{27,28}. Besides, doctors may be more familiar and experienced with the clinical presentation, symptoms, and signs of infectious mononucleosis.

The next steps should be a focus on awareness to parents and caregivers of children, and development of a vaccine against EBV to reduce the burden of EBV infection in future.

Conclusion

The rate of hospital admission of children due to EBV infection is increasing. Children under 4 years of age are highly susceptible to infection and children of age between 6 months and 1 year are the high-risk group for EBV infection. Vaccination against EBV must be considered to reduce the burden of EBV infection in future.

Data availability

Dataset 1. The number of total admissions and admissions of Epstein-Barr virus (EBV)-positive children under 15 years of age for each of the years 2014–2017. This dataset also contains stratifications of EBV-positive individuals by age and sex. DOI: <https://doi.org/10.5256/f1000research.15544.d212141>²⁹.

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The article “Increasing Epstein-Barr virus infection in Chinese children: A single institutional based retrospective study” is a single center hospital based study which reports the rate of EBV infection in hospitalized children. Although it has reported prevalence of EBV in this group, but in real meaning it is just a rate of EBV infection in hospitalized children in a hospital. Its rate might not have much meaning in general as the findings can not be generalized due to various reasons including hospital based data and also we do not have any idea about the denominator used for the calculation purpose and this denominator might differ in different hospitals and directly affects the rate of EBV reported. The main message that can be taken from this study is that the rates of EBV infection is rising in current years and its rate is higher in less than 4 years group and thereafter there is a gradual fall in its rate among older children. As authors have discussed in discussion section, we should understand that the reason for this rising trend can be different; first, real rising in EBV infection; second, increasing awareness among people and among medicos about the disease leading to frequent diagnosis of the condition. The role of other unknown factors may also have an impact.

The study is a simple descriptive analysis, includes retrospective analysis of EBV infection from 2014 to 2017 in hospitalized children.

The introduction section highlights history, epidemiology, clinical features and diagnosis of EBV infection. It states EBV as the most common causative agent of infectious mononucleosis and does not mention other causative agent, if there are any and it does not describe other manifestation of EBV infections. Introduction section also fails to describe the gap in the current knowledge on the subject matter, rational and need of current study. It is not clear what were the objectives of the study.

Methodology section describes the design of the study to some extent. It needs more on elaboration of the methodology followed, inclusion and exclusion criteria and spectrum of the pediatric subjects admitted to the hospital. The unnecessary description of peripheral blood pictures at birth and changes thereafter can be omitted. The age-specific grouping less than 4 years, 4-6 years and 6-15 years needs explanation as it seems inappropriate and equal age interval should be selected if there is no any reason to classify as chosen.

In the result section, the word “prevalence” may not be appropriate in pertinent to this study and appropriate word should be selected. The rate of EBV infection reported is among the admitted subjects

and as the spectrum of admitted subjects is unknown, it is very difficult to understand it. For example, if all the children admitted to the hospital were febrile, the EBV infection rate would have been different and if the children admitted included non-infective conditions as well, it would have been different. Unnecessary figures and double reporting can be avoided in result section. The figures 2 and 3 basically state the same, figure 2 reports in absolute numbers and figure 3 reports the rates per 1000 admissions. Similarly, figures 4 and 5 also report the same.

Discussion section is written well. It is better to avoid the use of the word “prevalence” and make comparisons with similar studies. Limitations and suggestions for further studies should also be made and discussed. Based on the study, we can not conclude that the children under 4 years of age are susceptible to EBV infections, we can only say that the rates were higher among this group.

Overall, the article is simple and provides few insights on EBV infection and highlights its rising trend from 2014 to 2017 with higher rate among children less than 4 years old.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Cardiology, Internal Medicine

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 01 April 2019

<https://doi.org/10.5256/f1000research.19928.r45221>



Michael J. Goldacre 

UK Medical Careers Research Group, Unit of Health-Care Epidemiology, Nuffield Department of Population Health, University of Oxford, Oxford, UK

It is hard to assess what the findings truly mean, because the study population is not a representative sample of the general child population of the area studied. It is a study of children admitted to hospital with clinical findings suggestive of EBV infection who are shown to have had the infection (the 'numerator'), expressed as a percentage of all children of the same age admitted to the hospital (the 'denominator'). It is therefore not true prevalence, but the prevalence in hospitalised children. The numerator is potentially affected by factors that influence the referral of children to hospital and the clinical decisions to admit them. The denominator cannot be said to be representative of the general population of children. Changes over time in the prevalence rate could be affected by changes to the numerator, which is what the authors have assumed (i.e. more children affected by EBV); or by changes in the referral or admission practices in respect of children with symptoms suggestive of EBV infection; or they could be affected by changes to the denominator population. To illustrate the latter point, an increase in admissions of children with non-infective diagnoses, eg injuries, would tend to reduce the rate of children with EBV per 100 children admitted overall.

It is also impossible to know how to interpret how the authors' data on 'prevalence' compare with those reported by other studies, because the sampled populations may be quite different. For example, reference 21 reports a study of people in the National Health and Nutrition Examination Surveys (NHANES) which comprise a representative sample of the US population (and which may therefore be quite different from a hospitalised population).

The authors cannot do anything about the nature of the subjects studied by them; but they can describe and discuss this as a potential limitation of the study.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

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Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Referee Report 22 February 2019

<https://doi.org/10.5256/f1000research.19928.r44512>



Anna Mania 

Department of Infectious Diseases and Child Neurology, Karol Marcinkowski University of Medical Sciences, Poznań, Poland

Suggested amendments were done appropriately. I have no further comments

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious diseases, pediatrics

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 12 September 2018

<https://doi.org/10.5256/f1000research.16956.r37372>**Anna Mania**

Department of Infectious Diseases and Child Neurology, Karol Marcinkowski University of Medical Sciences, Poznań, Poland

The study presents results of retrospective analysis conducted to estimate the overall prevalence of EBV infection and identify high risk groups among children.

This study included 253 patients under 15 years of age positive for EBV DNA by PCR, were admitted to the Pediatrics Department in China during a 4-year period from 2014 to 2017. Patients were divided into three groups; 0-<4years, 4-<6years and 6-<15years. The percentage and prevalence of EBV DNA-positive cases was calculated on that basis.

The highest rate of EBV infection (74.7%) was observed in the group under 4 years of age, 11.06% and 14.22% in the 4-6 years and in the 6-15 years group, respectively.

The authors mention increasing number of EBV-infected individuals in recent years. Noticing the highest number of cases in children between 6 month to 1 year.

Certain limitations of the study were visible:

1. The authors confirm EBV infection by PCR, however I could not find the information concerning the type of the specimen – blood, saliva, urine, anything else?
2. Significant proportion of EBV infected patient may be asymptomatic; the term infection is not equivalent to the disease, therefore it is a pity that data concerning clinical symptoms are not mentioned.

Minor comments:

1. Citing articles are not equivalent to given numbers e.g –study conducted in Poland is given at the 25 positions in the list, not 18;

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: infectious diseases, pediatrics

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 04 Feb 2019

Kiran Devkota, Hubei University of Medicine, China

Respected Professor

Thank you so much for your time and consideration. I have tried to make clear on the queries that you have noted.

Competing Interests: No competing interests were disclosed.

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