A study on relationship between the incidence of measles and nosocomial exposure at measles epidemic season in Chongqing

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Abstract

After measles vaccine supplementary immunization, the epidemiological characteristics of measles have changed in Chongqing, China. In addition, according to data from the National Measles Surveillance Information System, the proportion of measles cases with a history of hospital visit 7 to 21 days prior to onset of measles increased year by year to 32.1% in 2016. Further studies are necessary to eliminate the influence of nosocomial exposure on measles. We performed a case-control study in seven districts of Chongqing from June to August 2016 to identify risk factors for measles virus infection and susceptibility. Laboratory-confirmed measles who younger than 5 years old were matched with one control by age and residence. We interviewed case patients and controls regarding potential risk factors for measles virus infection and susceptibility. Unadjusted and adjusted matched odds ratios and 95% confidence intervals (CIs) were calculated using non-conditional logistic regression. After a cross-sectional analysis of the behavioral characteristics of visiting hospitals in the case and control groups, it was found that there was a difference between the two groups in the choice of hospitals visited for the first time ($\chi^2 = 35.500, P = .000$), and that nosocomial transmission risk tended to develop in outpatient services of respiratory medicine. After analysis using one-way ANOVA, the relationship between hospital visits prior to onset and the incidence risk of measles was that visiting hospitals five times within 1 to 3 weeks prior to onset affected the incidence (OR = 44.866, 95%CI = 5.938–338.981). The relationship between the number of types of hospitals visited prior to onset and the risk of nosocomial exposure to measles showed that visiting any community hospital, children's hospital, or general hospital had no risk, but visiting two or more of these hospitals affected the incidence (OR = 6.928, 95%CI = 3.849–13.754). Based on further analysis, the relationship between the number of hospital visits after onset and the risk of nosocomial exposure to measles was that the chances of visiting hospitals increased after onset. Risks of nosocomial exposure to measles and infections are high in pediatric hospitals. Nosocomial exposure risk factors should be considered when controlling measles.

Abbreviations: CI = confidence interval, WHO = World Health Organization.

Keywords: Chongqing, measles elimination, nosocomial exposure

1. Introduction

Measles is a highly contagious viral illness that contributes considerably to the mortality of children aged less than 5 years worldwide. China began to use the measles vaccine widely in 1965. By the 1990s, the morbidity and mortality of measles had declined by over 95%, compared with that of the pre-vaccine period.[1] In order to accelerate measles elimination targets initiated by Western Pacific Region of the World Health Organization (WHO), in 2010, the China Ministry of Health launched nationwide measles supplementary immunization activities for children aged from 8 months to 14 years.[2,3] The measles incidence rate sharply decreased by the end of that year and reached its historical lowest point (0.29 case/100,000 population) in 2011. Because of the lack of large-scale follow-up campaigns, national measles cases rebounded in 2013 with the accumulation of susceptible populations,[4] including Chongqing. As monitored, national epidemic characteristics of measles have evolved since 2013, mainly presented as a continuously increasing constituent ratio of adult patients in the eastern and central regions and the development of infection in unvaccinated children born after 2010 in the western regions.[5,6] It was also found that the epidemic temporal distribution of measles obviously moved forward to June to September from the traditional time of April to June in Chongqing, and that endemic distribution showed an obvious tendency of centralization presented as incidence and many outbreaks of measles, mostly in the main districts with dense populations and good economies and counties.

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According to data from the national measles surveillance information system, approximately 32.1% of measles patients had visited the hospital within 7 to 21 days prior to the onset of measles disease. In Chongqing, it was reported that the percentage was even higher with 66.4%, 54.8%, and 53.1% of measles patients visiting the hospital before the onset of measles for the last three years, respectively. These data indicate that there was an increased risk of hospital visits and measles outbreaks. In this study, epidemiological data of measles cases during the high-occurrence season of 2016 were collected, and each transmission risk factor was focused on and discussed, providing a reference basis to accelerate the formulation of control strategies for measles epidemic situations in China.

2. Methods

2.1. Data collection

During June to August 2016, among all cases reported in Chongqing, over 76% were children younger than 5 years old. For the case group, we enrolled all patients younger than 5 years old from the main seven districts of Chongqing based on the national measles information system; For the control group, patients were randomly chosen from the corresponding communities in a ratio of 1:1 to match the age and residence of the case group.

2.2. Cross-sectional study

Using a cross-sectional study one-way ANOVA, information including outpatient data, measles patients’ attitudes to visiting hospital, time of visiting hospital, etc. were collected from related departments (departments of respiratory, outpatient services of fever, emergency, infection) at all levels of hospitals, and the relevance between the situation of visiting hospitals and the epidemic situation was analyzed.

2.3. Case-control study

The case-control method was employed to analyze the risk factors that may increase the chance of onset, including the situation of visiting hospitals within 1 to 3 weeks prior to onset, situation of visiting hospitals after onset, situation of direct contact with patients, and history of traveling to places of dense population, and to discuss the influence of nosocomial exposure on the onset of measles.

2.4. Quality control

The investigators were personnel responsible for measles surveillance and community inoculation. All were trained in field investigation skills by higher-level investigators. The follow-up loss rate for the questionnaire survey was controlled to be within 10%. The sample size was designed to be 686, with a completion rate of 99.7%. As 18 patients enrolled between June and August were lost to follow-up in the case group, the same number of cases reported by the same system in September were used as supplements. A logic check was performed on the input of the survey data. Unqualified questionnaires were identified and reinvestigated.

2.5. Ethical approval and informed consent

Approval to conduct this study was granted by the relevant departments of Chongqing Center for Disease Control and Prevention. All information was collected after permission was obtained from the participants. Verbal informed consent was obtained from all participants.

3. Results

3.1. General information of subjects

There were 384 male (56.1%) and 300 female (43.9%) subjects with a male: female ratio of 1.28:1. As of September 2016, age ranged from 1 month to 5 years, with an average of 1 year and median of 9.9 months. Of all subjects, 191 were younger than 8 months old, 493 were older than 8 months, and there was no statistically significant difference in age between the control and case groups ($t = 0.422, P = .673$) (Table 1).

According to the survey, 47.7% of parents immediately visited the hospital once their children suffered from respiratory diseases. An analysis of the selection of medical institutions found that 51.6% of the subjects preferred to choose children’s hospitals for treatment, followed by the nearest district-level general hospitals and city-level large general hospitals. A comparison of the constituent ratio of the first visited hospitals indicated that the difference in the selection of first hospital visits between the case and control groups was statistically significant ($\chi^2 = 35.500, P = .000$) (Table 2).

A total of 456 participants (66.7%) visited hospitals between June and August. In the case group, 95.0% of the subjects had visited hospitals, but only 38.3% in the control group. The difference was statistically significant ($\chi^2 = 247.605, P = .000$). Among the participants who had visited hospitals, most went to respiratory outpatient services for treatment. The constituent ratios of medical measures were as follows: outpatient treatment 55.7% (infusion, injection, atomization, etc.), taking medicines at home 30.5%, and hospitalization 28.3%. Most of these subjects stayed at hospitals for half a day or <3 hours (Table 3).

Measles patients had the highest infectiousness during the rash stage for 5 days. In this survey, patients mostly had gone to the following places during this period: hospitals (83.6%), buses and stations (19.3%), supermarkets (9.1%), playgroups (5.6%), and children’s bath centers (0.6%). Of the 342 patients, 261 (76.3%) had visited hospitals 1-3 weeks prior to onset (latent period), indicating that the difference when compared with 38.3% of patients in the control group who had visited hospitals during the entire survey was statistically significant ($\chi^2 = 100.989, P = .000$). Many patients in the case group visited hospitals not only during June to August, but also during the latent period for many times. As a susceptible person, patients who were in an early disease course were more likely to be exposed to and infected with measles in hospitals.

### Table 1

| Main characteristics of subjects and chi-square analysis results. | Case group | Control group | Subtotal | $\chi^2$ | $P$ |
|----------------------|------------|--------------|----------|---------|-----|
| **Sex** | | | | | |
| Male | 209 | 175 | 384 | 6.864 | .009 |
| Female | 133 | 167 | 300 | | |
| **If the child was older than 8 mo old** | | | | | |
| Yes | 255 | 238 | 493 | 2.099 | .147 |
| No | 87 | 104 | 191 | | |
| **History of measles immunization** | | | | | |
| Yes | 31 | 232 | 263 | 308.311 | .000 |
| No | 163 | 5 | 168 | | |
| **History of under-standing measles** | | | | | |
| Yes | 57 | 45 | 102 | 0.361 | .548 |
| No | 21 | 13 | 34 | | |
3.2. Multiple-factor analysis for the incidence of measles

Analysis of this case-control study revealed that subjects, especially those in the case group, visited hospitals not only during June to August but also during the latent period many times, indicating that most patients with measles might have been infected in the treatment of other previous diseases ($\chi^2 = 100.989, P = .000, OR = 5.19, 95\% CI = 3.71–7.17$). Further multiple-factor non-conditional logistic regression analysis showed that children older than 8 months of age and with a history of visiting hospitals prior to onset were more susceptible to measles, but those with a history of measles immunization were not susceptible to measles (Table 4).

3.3. One-way ANOVA for incidence of measles

1. Relationship between times of visiting hospital prior to onset and incidence risk of measles

Taking whether child subjects suffered from measles during June to August ($1 = \text{yes}, 0 = \text{no}$) as the dependent variable, a single-factor non-conditional logistic regression analysis was employed to investigate the difference between the number of types of hospitals (community hospitals, children’s hospitals, and general hospitals) visited 1 to 3 weeks prior to onset in the case group and the number of types of hospitals visited during June to August in the control group on the incidence of measles (Table 6).

2. Relationship between the numbers of types of hospitals visited prior to onset and risk of nosocomial exposure to measles

Taking whether child subjects suffered from measles during June to August ($1 = \text{yes}, 0 = \text{no}$) as the dependent variable, a single-factor non-conditional logistic regression analysis was employed to investigate the difference between the number of types of hospitals visited during June to August in the control group on the incidence of measles (Table 7).
measles. Compared with the number of types of hospitals visited prior to onset (no difference in visiting one hospital; OR = 6.928 in visiting two or more hospitals), it was found that the difference in the number of types of hospitals visited between the case and control groups increased, indicating that the opportunity of visiting hospitals increased after onset, the probability of the presence of nosocomial infection source increased, and the possibility that susceptible populations were infected increased (Table 8).

4. Discussion

In medical institutions, different patients gather and sources of infection and susceptible population accumulate, making the spread of infectious diseases become easy in these places.\textsuperscript{[6–8]} Studies have shown that infectious droplets from the respiratory secretions of patients with measles can persist for >1 hour in the form of aerosol suspension.\textsuperscript{[9]} Nosocomial infection has become a serious problem, as the incidence of measles falls to a low level or measles is being eliminated, particularly when the measles epidemic rebounds.\textsuperscript{[10]}

1. Strengths and weaknesses

Strengths of the study include that measles case identification and verification was conducted by a real-time, national measles and rubella surveillance system that has met WHO quality and sensitivity standards continuously since 2011; all of the measles cases were laboratory confirmed and laboratory testing of cases and controls was performed by the National Measles and Rubella Laboratory network; one control were matched per case to provide additional sample size for analyses of controls' factors associated with immunity to measles.

Weaknesses of the study that only select a part of the southwestern of China’s 1 provinces were studied, limiting generalization to the entire country. Due to the concentration of the outbreak cases in children under 5 years of age, health workers and adult cases over 5 years of age as a risk source of nosocomial infection were not included in the analysis. Therefore, published findings from the other age group\textsuperscript{[11]} can be compared with these finding for a broader understanding of measles virus transmission in China. Even though the national measles surveillance system met and continues to meet WHO quality criteria, it is highly unlikely that all measles cases were reported, especially milder cases and those not medically-attended. Therefore, the cases cannot be said to represent all measles cases in the study provinces.

2. High risk of exposure to measles in hospitals

Nosocomial transmission of measles virus is a well-described phenomenon, as hospitals and other healthcare settings emerge as significant places of transmission when a country is at or

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### Table 4

| Factor                                      | Assignment | Partial regression coefficient | P   | OR  | 95% CI of OR  |
|---------------------------------------------|------------|-------------------------------|-----|-----|---------------|
| If the child was older than 8 months old    | 0 = no, 1 = yes | 2.479                         | 0.00 | 11.925 | 5.287–26.895  |
| Sex                                         | 0 = female, 1 = male | 0.338                         | 0.147 | 1.402 | 0.888–2.214   |
| History of measles immunization             | 0 = no, 1 = yes | -5.034                        | 0.007 | 0.003–0.015  |
| If patient had visited hospital prior to onset | 0 = no, 1 = yes | 1.283                         | 0.01 | 3.609 | 2.268–5.742   |
| Constant                                    |            | 2.1                           | 0.001 | 8.170 |               |

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### Table 5

| Factor                                      | Assignment | P   | OR  | 95% CI of OR  |
|---------------------------------------------|------------|-----|-----|---------------|
| Times of visiting children’s hospitals      | 0 = never  | 0.00 |     |               |
|                                             | 1 = once   | 0.192 | 3.950 | 0.501–31.154 |
|                                             | 2 = 2–4 times | 0.059 | 7.194 | 0.931–55.570 |
|                                             | 3 = 5 times or more | 0.000 | 44.866 | 5.938–338.981 |

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### Table 6

| Factor                                      | Assignment | P   | OR  | 95% CI of OR  |
|---------------------------------------------|------------|-----|-----|---------------|
| The number of types of hospitals visited    | 0 = never  | 0.00 |     |               |
|                                             | 1 = 1 hospital | 0.316 | 1.412 | 0.719–2.772  |
|                                             | 2 = 2 hospitals or more | 0.000 | 6.928 | 3.489–13.754 |

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### Table 7

| Factor                                      | Assignment | P   | OR  | 95% CI of OR  |
|---------------------------------------------|------------|-----|-----|---------------|
| Times of visiting children’s hospitals      | 0 = never  | 0.00 |     |               |
|                                             | 1 = once   | 0.036 | 8.727 | 1.149–66.261  |
|                                             | 2 = 2–4 times | 0.001 | 28.045 | 3.755–209.467 |
|                                             | 3 = 5 times or more | 0.000 | 513.829 | 69.108–3820.387 |

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### Table 8

| Factor                                      | Assignment | P   | OR  | 95% CI of OR  |
|---------------------------------------------|------------|-----|-----|---------------|
| The number of types of hospitals visited    | 0 = never  | 0.000 |     |               |
|                                             | 1 = 1 hospital | 0.000 | 3.332 | 1.787–6.214  |
|                                             | 2 = 2 hospitals or more | 0.000 | 78.449 | 36.841–167.046 |
near the elimination of measles.[12,13] Another case-control study conducted in China showed that visiting a hospital was a significant risk factor and demonstrated nosocomial transmission in an intravenous drip treatment room.[14] Patients with measles had the highest infectiousness during the rash appeared for 7 days. In this survey, the proportion of patients who had visited hospitals during the rash appeared ± 5 days was the highest, followed by bus stops, supermarkets, and playgrounds. Of these, the risk of exposure to measles was the highest in hospitals. In the case group, 76.3% of patients had visited hospitals 1-3 weeks prior to onset (latent period), which was statistically different from the proportion of patients who had visited hospitals in the control group ($\chi^2 = 100.989, P = .000$; OR = 5.19, 95%CI = 3.71–7.17). The number of visits to children’s hospitals (with a median of 2 and an average of 2.24) was higher than that of visits to general or community hospitals during the latent period for patients in the case group, indicating that patients in the case group had visited hospitals many times during the latent period. As susceptible individuals in the early disease course, these patients were more likely to be exposed to and infected with measles in hospitals.[15]

The Department of Respiratory Medicine (53.0%), Outpatient Service of Fever (21.3%), and Department of Pediatrics (11.8%) were preferred by patients with measles. The constituent ratios of nasal diseases taken were outpatient treatment 55.7% (injection, infusion, atomization, etc.), taking medicines at home 30.5%, and hospitalization 28.3%. Since child patients from the main districts were usually near homes, their lengths of stay at hospitals were mostly half a day or <3 hours, even for those hospitalized. Only 17.5% of patients were hospitalized. As infection sources in the late disease course, patients’ lengths of hospital stay, frequency of hospital visits, and isolation methods inevitably influenced the probability of nosocomial exposure in other patients.

3. Particularly high risk of exposure to measles in children’s hospitals

The risk of measles attributable to visiting hospitals in six provinces was 43% among children aged <8 months (too young to vaccinate in China) and 32% among children aged 8 months to 14 years.[11,13] Due to these specialties, children’s hospitals attracted the attention of child patients and their parents. In subjects from the 7 main districts, 47.7% of parents immediately went to hospitals for treatment after child patients suffered from respiratory diseases, of whom 51.6% preferred children’s hospitals. On the other hand, monitoring data from China Information System for Disease Control and Prevention showed that constituent ratios of measles and hand-foot-and-mouth disease reported by children’s hospitals were in a larger proportion and that Children’s Hospital of Chongqing Medical University was the primary pass all over the city and had more particularly concentrated infection sources than other hospitals.

5. Conclusion

Whether the patients visited hospitals was a risk factor for the incidence of measles. Children older than 8 months and a history of visiting hospitals prior to onset were more susceptible to measles,[6,7] but those with a history of measles immunization were not susceptible to measles. Similarly, the number of types of hospitals visited influenced the incidence of measles; namely, patients with more types might be more susceptible to measles. For susceptible people, the number of visits to hospitals, especially children’s hospitals, during the latent period obviously influenced the incidence of measles. After onset, the frequency of visiting hospitals increased the opportunities for nosocomial exposure to measles, since patients with measles were the source of infection. In the control stage of measles, nosocomial exposure is an important transmission factor, which usually becomes an important risk factor to cause the lasting of measles epidemic situation, especially at high-occurrence season.

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Author contributions

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