



A Surveillance of Differences in Transmission Rates of Varicella-Zoster Virus from Individuals with Herpes Zoster and Varicella

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Abstract

Varicella is highly contagious disease that spreads by airborne route from person-to-person. Varicella-zoster virus vaccination has been proven to be successfully declining the morbidity and mortality associated with varicella. However, many cases of varicella have been reported in vaccinated as well as unvaccinated individuals who had history of contact with individuals with either herpes zoster (HZ) or varicella. Surveillance was done during January 2011 to July 2014 in dermatological clinic at Shanghai Tenth People's Hospital, Shanghai, China and the collected data were analyzed. In this study, analysis of varicella vaccination status and history of contact with individuals with either herpes zoster or varicella in 994 varicella patients was done. Subjects were classified into two groups based on the history of exposure. The risk differences of varicella on exposure to herpes zoster and varicella patients; and role of varicella vaccination in decreasing that difference were evaluated. Nine hundred and eighty four individuals were identified with varicella diagnosis. Of these 994, history of contact with Varicella-Zoster Virus (VZV) infected individuals was unknown in 67 subjects. Of the remaining 927 subjects, 264 (28.48%) had history of exposure to individuals with HZ infections among which 61 (6.58%) were vaccinated and 203 (21.9%) were unvaccinated. The remaining 663 (71.52%) had history of exposure to individuals with varicella infections among which 65 (7%) were vaccinated and 598 (64.52%) were unvaccinated. Varicella-Zoster Virus (VZV) transmission from individuals with herpes zoster as well as varicella contributes to varicella morbidity. Transmission from varicella group is remarkably higher compared with herpes zoster group. The high incidence of VZV transmission from varicella infected individuals can be due to high infectivity of varicella, age of transmitting group, the immunization status and age of transmitted individuals.

Keywords: chickenpox, herpes zoster, shingles, vaccination, varicella, varicella-zoster virus

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Introduction

Varicella-zoster virus (VZV) is a human α -herpesvirus that causes two diseases: varicella (chickenpox) and herpes zoster (shingles). Varicella is mild, self-limiting and highly contagious disease that is common in children and young adults. It is transmitted by airborne route from person-to-person [1, 2]. The virus spreads easily from people with varicella to others who have never had the disease or vaccine and even to the vaccinated individuals. It can spread from breathing in the air contaminated with sneezing or coughing of infected person or through direct contact with virus particles that come from varicella blisters. A person with varicella is infectious from 1 to 2 days before the appearance of rash until all the varicella blisters have formed crusts [3, 4]. After varicella infection, the virus remains dormant in sensory dorsal root ganglia. Reactivation of this latent VZV results in herpes zoster (HZ) and is

manifested as cutaneous disease occurring in ≥ 1 dermatomes. It is commonly seen in adults [5, 6]. Herpes zoster cannot be transmitted from one person to another. However, a person with active herpes zoster can transmit the varicella-zoster virus through direct contact with fluid from the rash blisters (when the rash is in the blister-phase) [7]. In such cases, the person exposed to the virus might develop varicella, but they would not develop herpes zoster. A person with herpes zoster is infectious after the appearance of blisters and before the development of crusts on rashes. Herpes zoster is less contagious than varicella and the risk of a person with herpes zoster transmitting the virus is low if the rash is covered [8]. It takes 10 to 21 days exposure to a person with varicella or herpes zoster for someone to develop varicella.

For about last two decades, universal live attenuated varicella vaccination has been implemented in many areas around the globe and this coverage has resulted in a significant reduction of morbidity and mortality attributable to varicella [9, 10]. The varicella vaccine was first developed in Japan by Takahashi in 1974 [11]. Varicella vaccination is recommended for all children between 12 and 15 months of age followed by a second dose at age four to six years. Two doses of varicella vaccine is recommended for all healthy persons aged >13 years and should be given four to eight weeks apart. A one-dose varicella vaccine was licensed in America in 1996 which was modified to a two-dose scheduled immunization in 2006 [12]. Though varicella vaccination has been implemented in China since 1998, it is not included in routine national or provincial immunization program. It is available in private sectors as a single- as well as a double-dose vaccine [13]. However, a high varicella vaccination coverage has been reported in some metropolitan cities such as Beijing, Shanghai and Guangzhou after local government approved the use of the varicella vaccine. The immune persistence of varicella vaccine is good. A study on persistence of immunity to live attenuated varicella vaccine in healthy adults by Ampofo et al. suggested that the prevalence and severity of the breakthrough in 21 years, which began in 1979, have not been significantly decreased after vaccination [14]. Increased vaccination of children has successfully lowered the overall burden of disease. Despite it, a higher proportion of reported cases can be seen among older children and adults who may have never had varicella or immunized at a younger age and thus be more vulnerable to the disease [15]. A person vaccinated for varicella can get the disease as well as can spread it to others. Varicella in vaccinated individuals (i.e., breakthrough cases) is generally milder, often with fewer than 50 skin lesions and fewer vesicles compared with moderate-to-severe varicella with 300 or more skin lesions and many vesicles which is typically seen in unvaccinated individuals. Persons with breakthrough cases have no or low-grade fever with fewer days of illness and have no complications [16]. For most people,

recovery from varicella provides lifelong immunity. However, in some cases, varicella can recur more than once, although this is not common [1]. Post-licensure studies showed that 2 doses of varicella vaccine can prevent 80 to 85% of any varicella diseases and 95% of severe diseases. Therefore, in about 15 to 20% of healthy vaccinated children, there is chance of breakthrough varicella. However, it is not known how long a vaccinated person remains immune to varicella [2, 17].

Despite high varicella vaccine coverage, varicella outbreaks in Shanghai have been increasing with escalation in the breakthrough cases. Breakthrough cases may spread the disease quickly due to the atypical clinical symptoms. These cases might be caused by wild virus infection due to the vaccination failure or immunization fading instead of potential vaccine strain. Several analytical studies were carried on epidemiology of varicella outbreaks in different districts of Shanghai. In an analytical study, Du Yan et al. [18] reported a total of 9968 varicella cases in Minhang district of Shanghai from 2008 to 2012 including a total of 124 local varicella outbreaks with 1225 cases. Breakthrough cases showed an uprising trend with the incidence of 21.47% in 2008 and 46.85% in 2012. The study revealed that peak seasons for varicella were March to May and October to December in both vaccinated and unvaccinated individuals and the interval period between vaccination and disease onset was found to be decreasing with time. In another study, a total of 902 cases in 112 varicella outbreaks were reported from 2005 to 2010 in Zhabei district of Shanghai [19]. In a study by Huang Jin et al., the incidence rate of varicella increased from 5.58% in 2005 to 8.58% in 2006 in local residents over 20 years old in Zhabei district of Shanghai among which a total 8.27% of the cases had been vaccinated before. There was decline in age of the highest incidence rate which was 7-9 years age-group in 2005 and 4-6 years age-group in 2006 with seasonal peaks of varicella during winter and spring and male to female ratio was 1.3:1 [20]. Liu Jing Yi et al. [21] demonstrated an increased varicella outbreaks in Xuhui district of Shanghai with a prevalence in primary and high

school. A total of 177 varicella outbreaks were reported from 2006 to 2010 with an increasing rate yearly. Most of the cases were diagnosed from April to June and from October to December. The ratio of male to female was 1.27:1. Another study on coverage and protective effects of varicella vaccination among the students in Xuhui district of Shanghai during the 2010-2011 school-year showed that immunization rate of varicella vaccine was 78.35% and the prevalence of varicella was 13.07% [22]. Qian Xiao-hua et al. reported an outbreak in Hongkou district of Shanghai from October 2011 to January 2012 in which a total of 36 cases of varicella was observed among which 95.48% cases were previously vaccinated with single dose varicella vaccine. The ratio of male to female was 1.1:1. The study recommended that second dose of varicella vaccine might prevent the outbreak of varicella [23].

The purpose of this study is to analyze that the incidence of transmission of varicella is higher among individuals with contact with varicella patients compared to the individuals with contact with herpes zoster patients and to document the impact of a vaccination on declining the transmission of varicella from VZV infected individuals.

Materials and Methods

A face-to-face and telephone interview-based questionnaire survey on 994 clinically diagnosed varicella cases, who visited out-patient department from 1 January 2011 to 31 July 2014, was conducted. Varicella was defined as an acute illness with generalized papulovesicular rashes without other known cause. Cases were considered as breakthrough varicella if they developed varicella within 42 days or more after the vaccination with a shorter duration of illness, fewer constitutional symptoms, and less than 50 skin lesions. The subjects were categorized on the basis of history of exposure to herpes zoster and varicella individuals. Cases were defined as vaccinated if they had documented proof (e.g., immunization record) of previous vaccination with either single or double doses of varicella vaccine and as the unvaccinated groups which included all those

who were never been vaccinated for varicella. Study was not based on age since the vaccinated individuals were children of 1 to 15 years old and unvaccinated individuals were children, adolescents, and adults (16-50 years). The time since licensure of varicella vaccination (1998 in China) accredited to the discrepancy of age among participants. All of them were interviewed about vaccination status and duration between time of vaccination and time of onset of varicella. A detailed questionnaire was carried about whether or not they were exposed to patients with herpes zoster and/or varicella. Information on severity of the disease was collected, which included the onset of skin lesions, types of skin lesion, duration of illness and whether or not it was associated with fever and/or other symptoms. The age and vaccination status of the herpes zoster and varicella patients who transmitted varicella in healthy individuals were not known. Data were analyzed using SPSS 8.1 software. Chi-square test was used to compare the risk of varicella in healthy individuals based on history of exposure and its relation to varicella vaccination.

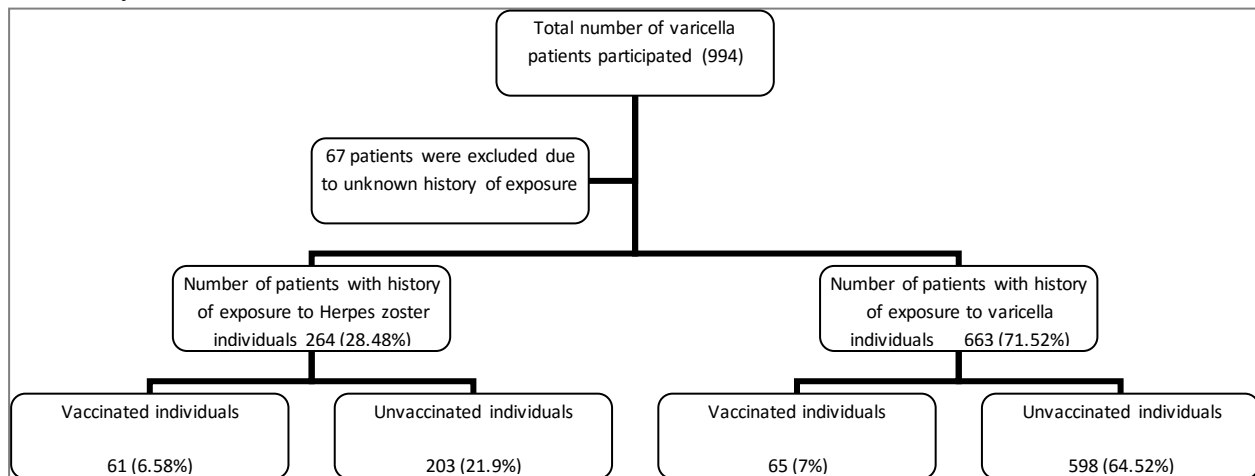
Results

A total of 994 varicella patients participated in surveillance conducted from January 2011 to July 2014. Out of 994, history of contact was unknown in 67 individuals and thus were excluded. Among 927 individuals, 264 (28.48%) had history of exposure to individuals infected with herpes zoster and 663 (71.52%) had history of exposure to individuals infected with varicella. A total of 126 (13.6%) individuals had received vaccination against varicella-zoster virus while the remaining 801 (86.4%) were unvaccinated. A total of 61 of 126 vaccinated cases and 203 of 801 unvaccinated cases had history exposure to herpes zoster infected individuals. On the other hand, numbers of vaccinated and unvaccinated individuals with exposure history of varicella were 65 and 598 respectively. In total of 801 unvaccinated cases, there was remarkable difference in transmission of varicella-zoster virus from individuals with herpes zoster (203) and varicella (598). While vaccination helped in decreasing this

difference (61 herpes zoster cases and 65 varicella cases). Among total of 126 vaccinated cases, almost equal numbers of patients had history of contact with varicella (65 cases) and herpes zoster (61 cases). Varicella in vaccinated person was mild in type with fewer skin lesions (less than 50), lasting for few days without or with a low-grade fever, and few other symptoms. A greater proportion of unvaccinated individuals with exposure to varicella was associated

with VZV transmission (598) compared with the proportion of vaccinated individuals with exposure to varicella (65) ($p < 0.001$). There was decline in age of the highest incidence rate which was 7-8 years-group in 2011 and 0-2 age-group in 2014 with seasonal peaks of varicella during January, April and May. The peak incidence among adults was found in 22-27 years age-group with overall sex ratio was 1.1:1 (484 males and 443 females) (**Figure 1**).

Figure 1: Outcome of a retrospective study of varicella patients at a government hospital in Shanghai during January 2011 to July 2014



Discussion

Both herpes zoster and varicella patients transmit varicella-zoster viruses to healthy individuals causing varicella infection. During one-dose varicella vaccine era, the risk of transmission of varicella from individuals with varicella and HZ were 90% and 10% respectively [24]. As increased two-dose varicella vaccine coverage continues to result in waning of varicella cases, HZ cases occupy a greater proportion of risk factors of varicella. In this study, the proportion of varicella cases associated with varicella and those associated with HZ were 71.52% and 28.48% respectively. Compared to previous study, the decline in disease circulation from varicella and incline in that from HZ could be due to two-dose varicella vaccine coverage.

We examined the relationship between varicella vaccination status and risk of varicella. Risk of varicella infection is higher in non-immunized

individuals in contact with varicella patients than those in contact with herpes zoster patients. In unvaccinated group, number of varicella cases due to contact with varicella patients (598, 64.52%) was about 3 folds compared to contact with herpes zoster patients (203, 21.9%). Exposure to HZ or varicella cases resulted in similar proportions of varicella cases (6.58% and 7%, respectively) in immunized individuals. In 2012, Viner et al. found similar proportions of varicella cases had past exposure to HZ or varicella in his study on transmission of varicella zoster virus from individuals with herpes zoster or varicella in school and day care settings [24]. Although children and young adults are the targets of natural and breakthrough varicella, transmission of varicella is common among adults who are mostly in close contact with the infected person as parents or as healthcare providers. In this study, fifty six percent of total cases i.e. 519 cases belonged to 21-35 years age-group with peaking of varicella in 22-27 years age-group. According to CDC (Centers for Disease

Control and Prevention) report, as high as 90% of susceptible individuals in household contacts of persons with varicella are at risk of varicella transmission [25]. This study reported a seasonal fluctuation in varicella transmission with the highest incidence occurring in January, April and May. Male-to-female ratio was 1.1:1 and that was consistent with the sex ratios of previous studies [20, 21, 23]. Vaccines are not 100% effective in preventing diseases but can prevent from severe diseases. Transmission of VZV can occur from either vaccinated or unvaccinated individuals with varicella and herpes zoster. Vaccinated people can spread as well as get to suffer from varicella and/or herpes zoster. It is not known how long a vaccinated person is protected against varicella [26]. In order to achieve and maintain high varicella vaccination coverage rates, we strongly recommend enhanced efforts to increase the uptake of varicella vaccine. In vaccinated individuals, cause of breakthrough was unknown. Investigations of breakthrough cases should be encouraged to determine whether breakthrough is occurring because of failure of vaccine (lower than expected vaccine effectiveness) or failure to vaccinate (low vaccine coverage rates therefore high susceptibility). The transmission rate in breakthrough cases with less than 50 skin lesions has been found to be remarkably low compared with the unvaccinated cases [16]. Both HZ and varicella were found to be equally infectious to transmit VZV to immunized individuals. Varicella was found to infect larger proportion of non-immunized group compared with HZ. The reasons of higher risk of transmission from varicella infected individuals are summarized below:

1) Transmitting group:

- a) High infectivity of varicella and
- b) The age group that is commonly infected with varicella- varicella is common among children which are the age-group that needs more care and attention than any other age-groups therefore more people in contacts are at risk to varicella.

2) Exposed group:

a) Vaccinated status- vaccinated individuals might have received single dose that is less protective than double dose vaccination; and a large number of participants (enrolled in this surveillance) was unvaccinated.

b) Adult age group – immunity gradually declines with age; and this age-group individuals, particularly 16-35 years, are more exposed to the infected persons as parents, healthcare providers and kindergarten staffs thus are more prone to infection.

Vaccinated individual can develop infection with the vaccine-strain varicella-zoster virus and can spread it to others. However, this happens very rarely. Age-related decline in cell-mediated immunity against VZV can be considered as an important risk factor in unimmunized population. Vaccination plays an important role in reduction of the risk for varicella infection during early childhood and the risk for HZ occurring later in life. Vaccination helps in reduction of wild-type VZV infection among vaccinated recipients and, through herd immunity, unvaccinated recipients [27]. However, VZV infection resulting from reactivation of vaccine-strain VZV has been increasing with the increase in vaccine coverage and circulation of wild-type VZV is decreasing gradually [28]. In contrast to vaccination of immunocompetent subjects, vaccination of immunocompromised subjects can result in risk of VZV transmission as they are more likely to have infection with vaccine strain VZV and to spread it to subsequent contacts. Some specific groups such as VZV-infected healthcare personnel and kindergarten staffs, due to higher exposure, can appear as risk for varicella transmission to comparatively larger groups of individuals including immunodeficient groups such as transplant recipients, HIV-positive individuals and children. Various studies reported the potential risk factors for varicella vaccine failure and disease that has impact on vaccine effectiveness among vaccinated persons. These include asthma, eczema, earlier age at vaccination, longer time since vaccination, receipt of varicella vaccine within 28 days of the measles-mumps-rubella (MMR) vaccine, and use of oral steroid proximal to the development

of breakthrough varicella. Low coverage of varicella vaccination in adolescents and adults, long duration after vaccination in children and lack of isolation policies contribute to outbreak of varicella [29, 30]. It is important to enhance coverage of varicella vaccination among adolescents and adults.

Our study has several limitations. Firstly, the sample size was small. Secondly, the study comprised clinically diagnosed cases that did not require laboratory confirmation. Thirdly, discrepancy in distribution of varicella among children and adults i.e. all infected children up to 15 years were immunized and all infected adults (16 years or older) were non-immunized. Finally, insufficient information on age of vaccination and duration between vaccination and onset of varicella in vaccinated group.

Conclusion

This surveillance provides more evidence that exposure to varicella infected individuals appears to result in high incidence of varicella infection. Varicella incidence due to exposure to HZ infected individuals was lower. Immunized individuals were found to be equally susceptible to HZ as well as varicella. Non-immunized individuals were at 3 folds risk of varicella infection transmission from varicella infected individuals compared with HZ infected individuals. Ongoing monitoring of varicella incidence will be critical for understanding the transmission of VZV from HZ and varicella infected individuals and varicella vaccination program's impact on varicella epidemiology.

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Conflicts of Interest

The authors declare no conflicts of interest in preparing this article.

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