Special Issue: Infectious Disease and Mathematical Modelling

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(3) 1–12

DOI: 10.1177/0300060519887847
journals.sagepub.com/home/imr
SAGE

A persistent outbreak of varicella in a primary school in Dongguan City, Guangdong Province, China

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Abstract

Objectives: To describe the epidemiological features of a school varicella outbreak in Dongguan City, China, to identify the reasons underlying persistent spread, and to assess the effectiveness of the varicella vaccine.

Methods: We identified all cases during the outbreak. We described the outbreak epidemic course and examined the influence of the following variables on the outbreak: sleeping in the dormitory, eating in school, taking school transportation, hand-washing habits, morning examinations, and effectiveness of case isolation. Logistic regression was used to estimate the odds ratio and 95% confidence interval (CI) of contracting varicella.

Results: A total of 92 varicella cases were reported, accounting for 5.53% (92/1663) of all students. Among cases, 64.13% (59/92) were vaccinated. The outbreak lasted for 93 days and occurred in six generations. Vaccination coverage was between 78.05% and 85.67%. The varicella vaccine was effective in 56.63% of recipients (95% CI: 35.49–70.84%). Vaccine effectiveness significantly decreased after 4–6 years.

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Conclusions: The varicella vaccine was unable to prevent virus spread even with high vaccination coverage. Delayed and inefficient isolation of cases was the primary cause of the persistent outbreak.

Keywords
Varicella, outbreak, vaccination effectiveness, morning examination, isolation, field investigation

Date received: 29 May 2019; accepted: 21 October 2019

Introduction

Primary infection with varicella-zoster virus causes varicella (chickenpox) and primarily occurs in children.[1,2] Although varicella infection is usually self-limiting and resolves within a week, infection can be accompanied by severe complications and even death. In recent years, the incidence of varicella in schools has been increasing resulting in a public health emergency.[3–7] Moreover, varicella has become one of the most common infectious diseases and is now responsible for frequent outbreaks. These outbreaks affect both the physical and mental health of students.

In China, the varicella vaccine is not offered free of charge. Children aged 1–12 years only receive a single dose of this vaccine, while those aged over 13 years, adolescents, and adults receive two separate doses at 6–10 week intervals.[8] In recent years, the number of primary school and kindergarten students experiencing a varicella-like rash that developed >42 days post-vaccination has continuously increased.[9] Therefore, Chinese children aged between 1 and 12 years should receive a supplementary dose of the vaccine.[10]

From March to June 2014, a varicella outbreak was reported in a primary school in Dongguan City, Guangdong, China. The outbreak lasted for more than 3 months. In this study, we aimed to describe the course of the varicella outbreak, to identify risk factors for continuous varicella transmission, and to evaluate the protective effect of the varicella vaccine against infection and outbreak.

Methods

Study design

An epidemiological field investigation was performed to assess varicella virus transmission. A retrospective cohort study was conducted to assess the effectiveness of the varicella vaccine. The study was approved by the Medical Ethics Committee of the Dongguan Municipal Center for Disease Control and Prevention (CDC). Outbreak control and investigation are part of the CDC's routine responsibility in Dongguan City. Therefore, requirements for written or verbal informed consent were waived by the Medical Ethics Committee of the Dongguan Municipal CDC on the following grounds: (1) only broad information was available regarding the dates of the outbreaks, the number of cases per day during the outbreak period, and the number of affected individuals, with little possibility of identifying patient information being disseminated; (2) neither medical interventions nor biological samples were involved; and (3) study procedures and results would not affect the clinical management of cases in any way.

Vaccination certificates of 293 students were collected to confirm varicella vaccination history (including date of vaccination).

A questionnaire was developed to collect information on history of infection. All cases diagnosed with varicella in upper second-class or more advanced hospitals in Dongguan City were included. In addition, a grouped case-control study (not 1: 1 matched) including 74 cases and 74 controls was performed to identify potential risk factors for varicella infection including sleeping in dorms, eating in school, transportation, and handwashing habits. Unconditional logistic regression was used to calculate the odds ratio (OR) and its 95% confidence interval (CI) for each risk factor. The variables and their values are defined in Table 1.

Hand washing frequency was rated as follows: 4 points ($\geq$13 times a day), 3 points (10–12 times a day), 2 points (7–9 times a day), or 1 point ($\leq$6 times a day). Proper hand-washing involves cleaning the four main parts of the hand: the purlicue, fingers, back of the hand, and wrist. The following rating scale was used to evaluate whether all or some parts of the hands were washed: 4 points (4 parts), 3 points (3 parts), 2 points (2 parts), and 1 point (1 part). Frequency of hand sanitizer use was rated as follows: 4 points (always, $\geq$10 times per day), 3 points (often, 5–9 times per days), 2 points (sometimes, 1–4 times per day), and 1 point (never). A final score was calculated by summing the points for each indicator, and overall scores were categorized as follows: excellent (11–12 points), good (9–10 points), medium (7–8 points), and poor ($\leq$6 points).

Data collection

In this study, a case of varicella was defined as an acute generalized maculopapular rash without other apparent causes occurring between February 1 and June 27, 2014 in a primary school. Breakthrough varicella was defined as appearance of a varicella-like rash >42 days post-vaccination.[9] Investigators were trained to use a structured questionnaire to collect epidemiological information in the school during the outbreak through face-to-face interviews with school staff. Data on school characteristics, demographic information, medical records, risk/protective factors and vaccination history, and hand washing habits (rated based on frequency and thoroughness of hand-washing as well as whether hand soap was used) were collected. Missing data were obtained by conducting phone interviews with parents. A phone interview was also conducted for students who were absent from school during the field investigation.

Varicella vaccination history was verified from vaccination records, which were collected by staff from the Dongguan CDC Dongguan City, Guangdong Province. In addition, a questionnaire was also used to review students' medical records and to retrieve their clinical data from March 3 to

Table 1. Variables and their value definitions.

Variables	Values
Varicella case (Y)	Y = 1, case; Y = 0, not case
Sleeping in dorms (X1)	X1 = 1, sleeping in dorms; X1 = 0, not sleeping in dorms
Eating in school (X2)	X2 = 1, eating in school; X2 = 0, not eating in school
Transportation (X3)	X3 = 1, taking school transportation; X3 = 0, not taking school transportation
Handwashing habits (X4)	X4 = 1, excellent handwashing habits; X4 = 2, good handwashing habits; X4 = 3, medium handwashing habits; X4 = 4, poor handwashing habits

June 3. We met with the staff of the Dongguan CDC and carried out a preparatory investigation, to ensure that the relevant information could be collected accurately and completely during the formal investigation.

All researchers had access to all information that could identify the individual participants during or after data collection. Participant data could only be used for research purposes.

Effectiveness of case isolation

Case isolation should be implemented as soon as possible once suspected cases are reported in accordance with the policies of Guangdong Province.[11] The median time between symptom onset and isolation of cases was 2 days (range: 1–5 days). Classes were stratified into two groups based on the median time between onset and isolation ($\leq$1 day and $>$1 day). The attack rates in both groups were calculated to evaluate the effect of morning examinations.

Individuals with varicella infection were isolated for at least 2 weeks following disease onset.[11] The median time between case isolation and return to school was 12 days (range: 2–33 days). Classes were stratified into two groups based on the median time between case isolation and return to school ($\leq$14 days and $>$14 days). The attack rates for both groups were calculated to evaluate the effect of case isolation.

Effectiveness of vaccination

Due to a shortage of varicella vaccine, no emergency vaccination measures were taken during this outbreak. Thus, we assessed the effectiveness of vaccine doses received prior to the outbreak. An epidemiological curve was used to describe the distribution of varicella during the outbreak. The attack rates in unvaccinated children (ARU) and vaccinated children (ARV) were calculated. Vaccine effectiveness (VE) was calculated as $VE = (ARU\text{-}ARV)/ARU \times 100\% = (1\text{-}RR) \times 100\%$,[12] where RR refers to relative risk. The 95% CIs of the VE were calculated as described previously.[13] Children with a history of varicella prior to the outbreak, who were vaccinated $<$42 days before disease onset, who were vaccinated during the outbreak, or whose vaccination history could not be verified through immunization records were excluded from the analysis. Vaccination coverage was explored in six classes, representing $\geq$5 cases in each class and a total of 328 students.

Statistical analysis

Data were entered in EpiData (EpiData Association, Odense, Denmark). Statistical analyses including rank tests, chi-square tests, and logistic regression were conducted using SPSS (version 17.0, SPSS, Inc., Chicago, IL, USA).

Results

Basic information of the primary school

The primary school was a full-time public school with six grades and 30 classes. The school had a total enrolment of 1,559 students and 104 staff. All of the students were externs, and 52.85% (824) took school public transportation, while 85.76% (1337) ate lunch in the school canteen and slept in the school dormitory. This primary school consisted of three four-floor buildings connected via corridors. Students were allocated to dormitories depending on their classes.

Epidemiological features of the outbreak

In total, 5.53% (92/1,663) of students and staff contracted varicella. None were hospitalized and none died. All cases were students, not staff. The ages of cases ranged from 6.6 years to 11.9 years (median 7.3 years). Among the 92 cases, 59 (64.13%)

had received one dose of varicella vaccine. The outbreak affected 13 classes, accounting for 43.30% (13/30) of all classes. The attack rate varied from 2.33% to 39.62% among all classes reporting varicella cases. The attack rate was similar in boys (5.56%, 53/953) and girls (6.44%, 39/606) ($\chi^2 = 0.510$, $P = 0.475$).

The most common symptoms of cases were papules, herpes, and crusts (100%, 92/92), fever (38.04%, 35/92), headache (14.13%, 13/92), and pharyngalgia (9.78%, 9/92). Approximately 26.09% (24/92) of patients developed papules, herpes, and crusts on the head, face, torso, and limbs, and the remaining 68 cases developed papules, herpes, and crusts only the on head, face, or torso. Varicella infection lasted for 2–41 days (median 15 days).

As shown in Figure 1, the varicella outbreak occurred from March 3 to June 3, lasting about 93 days and occurring in six generations. The median duration of varicella infection in each generation was 16 days (range: 14–18 days).

Vaccination history and VE

Vaccination coverage was calculated in six classes (representing a total of 328 students) with ≥5 cases in each class. Of these 328 students, 256 were vaccinated (1 dose, 253 students; 2 doses, 3 students), and 25 had unclear vaccination histories. Vaccination coverage ranged from 78.05% to 85.67% in the six classes. Approximately 20.24% of vaccinated students contracted varicella, while 46.67% of unvaccinated students did. The varicella vaccine was effective in 56.63% the recipients (95% CI: 35.49–70.84%). The association between time of varicella vaccination and VE was evaluated in 293 students for whom data were available (89.33% of the study population). The results showed that the vaccine was effective in 44.88% of students who had been vaccinated 4–6 years previously, much lower than that in other groups (Table 2).

An analysis of 72 students with complete information and verified vaccination history suggested that vaccinated cases had a lower risk of developing fever and had milder rashes than unvaccinated cases (Table 3).

Evaluation of case isolation

A significant difference was observed in the attack rate for cases isolated for ≤1 day and those isolated for >1 day ($Z = -2.75$,

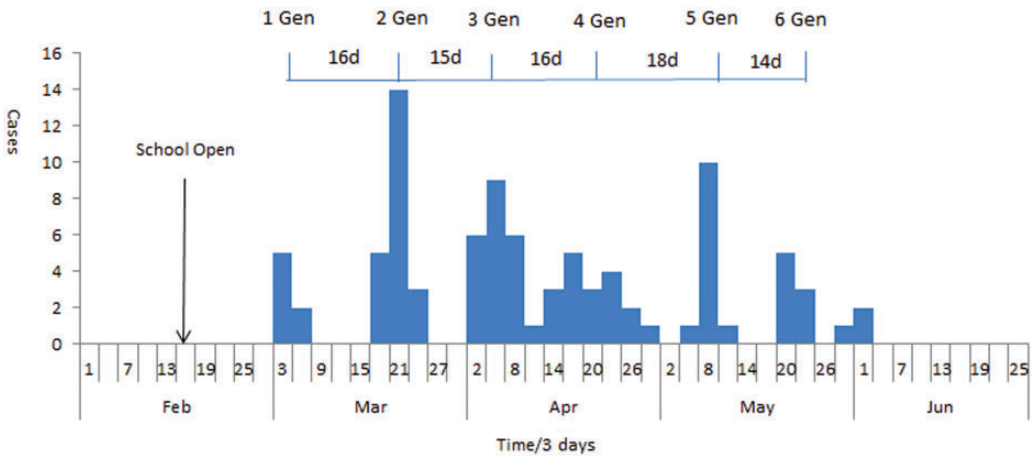

Figure 1. Epidemic curve of a varicella outbreak in a primary school in Dongguan City, 2014.

Table 2. Relationship between vaccine efficacy and length of time since vaccination of cases in a primary school outbreak in Dongguan City, 2014.

Time since vaccination (years)	Number of students	Number of cases	Incidence (%)	RR	VE (%)	95%CI (%)
0–3	5	0	0.00	0.00	100.00	–
4–6	171	44	25.73	0.55	44.88	17.44–63.18
7–8	72	6	8.33	0.18	82.12	59.21–92.16
Unvaccinated	45	21	46.67	Ref		

*Length of time since vaccination of cases= date of varicella – date of varicella vaccination.
**Length of time since vaccination of non-cases= date of investigation – date of varicella vaccination.
CI: confidence interval, RR: relative risk, VE: vaccine efficacy.

Table 3. Incidence of fever and rash in vaccinated and unvaccinated students in a primary school in Dongguan City, 2014.

Characteristics	Vaccinated N = 51	Unvaccinated N = 21	OR	95%CI
Fever (°C)				
≥39	5 (9.80%)	8 (38.10%)	0.10	0.02–0.50
37.4–39	9 (17.65%)	7 (33.33%)	0.21	0.05–0.92
≤37.3	37 (72.55%)	6 (28.57%)	Ref	
Rash and place				
Whole body*	6 (11.76%)	9 (42.86%)	0.18	0.04–0.69
Torso/head region**	45 (88.24%)	12 (57.14%)	Ref	

*Whole body refers to the appearance of rash on the head and neck, torso, and limbs.
**Torso/head region refers to the appearance of rash on the head, neck, and torso but mild or no rash on the limbs.
CI: confidence interval, OR: odds ratio.

Table 4. Effect of morning examination and case isolation on attack rate during a varicella outbreak in a primary school in Dongguan City, 2014.

Characteristics	Number of classes	Median attack rate (range)	Mean rank	Z	P
Median time between case onset and isolation					
≤1 day	7	3.70% (2.33–9.09%)	4.43	−2.57	0.01
>1 day	6	28.06% (5.45–39.62%)	10		
Median time between case isolation and return to school					
≤14 day	5	30.19% (9.09–39.62%)	11	−2.93	0.003
>14 day	8	3.81% (2.33–8.93%)	4.5		

$P < 0.01$). The attack rate in classes with median time elapsed between onset and isolation of cases ≤1 day was significantly lower than that in classes with a median time of >1 day ($Z = -2.57$, $P = 0.01$) (Table 4).

A significant difference in the attack rate was observed between the two groups ($Z = -4.80$, $P < 0.01$). The attack rate in classes with median time elapsed between isolation and return to school ≤14 days

was significantly higher than that in classes with a median time of >14 days (Z = -2.39, $P = 0.003$).

Risk factors

No significant differences in the distributions of any risk factors were observed between students who did or did not sleep in the dormitory, eat lunch in the school canteen, or take school transportation. However, students with poor handwashing habits were at higher risk of varicella infection (Table 5).

Discussion

Our study showed that varicella vaccine coverage was high in this primary school. However, more than 60% of cases had been vaccinated 4–6 years previously, and the VE was 45%, which permitted the spread of varicella. The primary reason for this outbreak and persistent spread was failure to isolate cases in a timely manner, resulting in person-to-person transmission. Varicella is an infectious disease that can be transmitted via the respiratory route, either through air or via close contact with an infected person. The former route is difficult to evaluate. However, we found that good hand washing habits was associated with protection against varicella infection. Our findings indicate that close contact with an infected person or individuals with contaminated hands might play a role in the transmission of infection and contribute to an outbreak.

To control varicella outbreaks, pharmacological (vaccination) and non-pharmacological (case isolation, hand hygiene, school closure, and disinfection) interventions can be implemented. In this study, we investigated the effectiveness of vaccination, case isolation, and hand hygiene. Although environmental disinfection was performed in areas experiencing outbreaks, the effectiveness of this intervention was not assessed as it is difficult to quantify this variable. Schools were not closed during the outbreak.

In China the varicella vaccine is not free of charge. Prior to 2017, children under 12 years of age living in Guangdong Province were recommended to receive one dose of the vaccine at age 12 months. Previous studies have shown that vaccine coverage of >85% can effectively prevent outbreaks of infectious diseases.[14] However, some studies[15–17] reported that protection was incomplete even when varicella vaccine coverage reached 88.3–100%. In this investigation, we found that despite varicella vaccine coverage reaching approximately 85%, varicella outbreaks still occurred in schools, probably due to the low effectiveness of

Table 5. Risk factors for varicella infection in a primary school outbreak in Dongguan City.

	Cases (N = 74)		Controls (N = 74)					
Risk factors	Exposed	Unexposed	Exposed	Unexposed	Wald χ^2	*P*	OR	95%CI
Sleeping in dorms	66 (87.84%)	8 (12.16%)	60 (82.43%)	14 (17.57%)	1.879	0.170	1.925	0.755–4.910
Eating in school	62 (83.78%)	12 (16.22%)	59 (79.73%)	15 (20.27%)	0.406	0.524	1.314	0.568–3.038
Transportation	34 (44.59%)	40 (55.41%)	29 (40.54%)	45 (59.46%)	0.690	0.406	1.319	0.686–2.535
Handwashing habits					5.151	0.161		
Poor	8 (10.81%)		3 (4.05%)		3.683	0.055	0.241	0.056–1.031
Medium	16 (21.62%)		11 (14.86%)		2.725	0.099	0.442	0.168–1.165
Good	32 (43.24%)		32 (43.24%)		1.270	0.260	0.643	0.298–1.386
Excellent	18 (24.32%)		28 (37.84%)					Ref

CI: confidence interval, OR: odds ratio.

the vaccine. In this outbreak, breakthrough cases accounted for 60% of all cases and VE was approximately 55%. VE diminished to 45% 4–6 years post-vaccination. The VE during this outbreak was lower than that observed in clinical trials. One explanation might be the length of time elapsed from vaccination to the outbreak. The long time elapsed might lead to decreased levels of protective antibodies. Students aged between 5 and 8 years had the highest varicella incidence. This finding suggests that varicella vaccination could not reduce the risk of varicella infection among high-risk children, and was consistent with the results of several previous studies[3,18–23] including several demonstrating that breakthrough cases were common during varicella outbreaks.[24,25]

The United States was the first country to implement a universal varicella vaccination program. The implementation of a single-dose regimen led to a dramatic decline in varicella infection incidence, near elimination of severe disease, and reduction in the number of cases and the duration of outbreaks.[26] Similar results have also been reported in Canada.[27] In spite of the high VE of the single-dose varicella vaccine, this vaccine does not provide sufficient population immunity to inhibit endemic disease transmission and prevent outbreaks completely. In 2006, the Advisory Committee on Immunization Practices of the United States revised the varicella vaccine guidelines and recommended that children should receive a first dose of varicella vaccine between 12 and 15 months of age and a second dose between 4 and 6 years of age.[28] Since the implementation of the universal two-dose program in the United States, further reductions have been observed in both varicella disease burden[29,30] and the number of outbreaks.[24] Two-dose varicella vaccination schedules were also implemented in the national immunization plans of several countries including Cyprus, Germany, Greece and Luxembourg. Studies from Spain, Germany, the United States, Italy, and Canada all suggested that two-dose varicella vaccination was very effective in preventing varicella.[31–36] Another study conducted in Argentina indicated that both one-dose and two-dose varicella vaccines were safe.[37] Therefore, we advised evaluating the VE of two-dose varicella vaccination and revising the immunization schedule in China. In November 2012, the Beijing CDC adopted the technical guidelines[38,39] and recommended that children should receive one dose of varicella vaccine at age 18 months and a second dose at the age of 4 years. In October 2017, the Guangdong Health and Family Planning Commission also revised the vaccination schedule from one dose to two doses, with the first dose given at age 12–24 months and the second dose given at the age of 4–6 years.[40] However, this schedule was only implemented in some developed areas such as Beijing and Guangdong. We expect the implementation a revised vaccination procedure in China in which safety issues are clearly stated, so we can effectively reduce the number of varicella outbreaks and protect children's physical and mental health. The studies mentioned above clearly showed that two doses of varicella vaccine are helpful in reducing the number of cases and the severity of the disease.

One dose of varicella vaccine was able to reduce clinical symptoms.[41] Our study also showed that vaccinated students had a lower incidence of fever and severe rash than unvaccinated students. Therefore, we propose that the immunization schedule in China should be maintained as is prior to its revision.

During this outbreak, the incidence of varicella infection was much higher in classes without strict adherence to morning examination and isolation of non-infectious cases than in classes that strictly

adhered to these measures. Thus, timely detection and effective isolation were critical factors in varicella prevention and control. We also found that some parents did not report their children developing varicella infection due to the long isolation period required (approximately 2 weeks), as this might have adversely affected their children's academic performance. Therefore, we encouraged schools to actively communicate with parents in addition to strengthening morning examination and isolation measures. Enhanced knowledge of the prevention of infectious diseases was also valuable in reducing the exposure of children to infectious diseases and adhering to the school's preventive measures.

In our study, we found that poor hand-washing habits were associated with varicella infection, consistent with the results of previous studies.[42] Hand-washing is the most direct and effective way of preventing droplet and direct transmission of varicella infection.[43] Thus, schools should offer hand-washing equipment and hand sanitizer (or soap), teach students proper hand-washing procedures, and raise their awareness on the importance of hand-washing to reduce the transmission of infectious diseases.

Previous studies reported that sharing school public transportation, having dinner in the same canteen, and sleeping in the same dormitory were primary risk factors for varicella transmission.[44] In this outbreak, none of those factors were significantly associated with varicella transmission, but the effect of daily contact on transmission cannot be ignored. As a result, all schools should decontaminate their transportation vehicles, canteens, and dormitories. In addition, they should provide more public infrastructure for students to reduce the risk of varicella transmission.

This outbreak lasted 92 days, with six generations of cases. However, we were not able to identify the index case. This missing case may have had an asymptomatic infection. Although more than 90% of patients reported in the literature had symptomatic infections, there have also been a few asymptomatic infections.[45,46] Another explanation could be that when we implemented the investigation, the first case had already recovered and returned to school. If this were the reason, this would mean that our school doctors experienced shortcomings in finding and isolating patients. In future work, we should strengthen training in this aspect to improve the ability of school doctors to detect and isolate patients in a timely fashion.

There were several limitations to our study. First, our investigation of this outbreak was not performed in a timely manner. The outbreak occurred in early March but we received reports later and managed it in early April. Therefore, recall bias likely affected data collection. Moreover, misclassification of cases may have occurred as we were unable to collect biological samples from the case and control groups for the diagnosis of varicella infection. Another limitation was that confounding factors might have been ignored, which could affect our results. Finally, we were unable to identify the index case of the outbreak, which might lead to the underestimation of incidence.

Some suggestions for improved public health were proposed during the investigation. Effective morning examination procedures and isolation of cases with fever, rash, and diarrhea should be conducted in schools and other public areas. Patients should be isolated until all sores turn into scabs and fall off to decrease the risk of transmission. Further studies are warranted to evaluate the effectiveness of two-dose varicella vaccination as well as its side effects. If two doses of vaccine are found to be more effective, this vaccination schedule should be implemented as soon as

possible in China. In addition, it is important to raise awareness of good hygiene habits and to educate students regarding proper hand-washing. Disinfection and air circulation measures in public areas should also be promoted.

Author contribution

TC, QZ, and JZ designed the study. JZ, QZ, MZ, ZH, GQ, FR, and ZL collected the data. TC, JZ, MZ, and QZ analyzed the data. JZ and TC wrote the article. The final version was approved by all authors.

Acknowledgements

The authors thank all study participants for providing data and field investigators for collecting data. The authors also thank Jiayao Lei, Department of Public Health Sciences, Karolinska Institutet, for helpful suggestions on the manuscript.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics approval statement

This study was approved by the Medical Ethics Committee of Dongguan Municipal Center for Disease Control and Prevention.

Funding

This work was partly supported by the Open Research Fund of the State Key Laboratory of Molecular Vaccinology and Molecular Diagnostics (SKLVD2018KF001 and SKLVD 2018KF002).

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