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Phylogenetic and Epidemiological Analysis of Measles Viruses in Shenzhen, China from January 2015 to July 2019

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Background: Measles morbidity and mortality were significantly reduced after the measles vaccine was introduced in China in 1965. However, measles outbreaks easily occur in densely populated areas, especially where there is no universal vaccination. The outbreak that occurred in Shenzhen, the Chinese city with the largest internal immigration, provides a lesson in measles virus mutation and measles prevention. The present study is a phylogenetic analysis of measles viruses and comparison of clinical signs between individuals with and without vaccination.

Material/Methods: We performed phylogenetic analysis of the nucleoprotein (N) genes of measles virus from 129 measles patients in Shenzhen from January 2015 to July 2019. Phylogenetic trees were constructed using the neighbor-joining method.

Results: The phylogenetic analysis showed all viruses were classified into genotype H1. In addition, there is often a seasonal measles outbreak in July each year. The clinical data showed that patients who were unvaccinated were more likely to have coughing, chronic bronchitis, conjunctivitis, catarrh, Koplik spots, and diarrhea. Children of migrant workers and those living in mountainous and rural districts accounted for most measles cases.

Conclusions: Our results showed there was a seasonal measles outbreak in Shenzhen Children's Hospital. All the measles virus from 129 measles patients were H1 viruses. The clinical signs also showed a difference between unvaccinated and vaccinated patients. Moreover, most of the unvaccinated patients came from migrant worker families. We suggest there is a need for increased health promotion and vaccination programs for migrant workers and people living in remote villages.

MeSH Keywords: **Immunization Programs • Measles virus • Transients and Migrants**

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Background

Measles is a highly infectious disease caused by the measles virus, a paramyxovirus, genus Morbillivirus. High vaccination coverage is the most effective strategy to eliminate the transmission of endemic measles. The measles virus is monotypic but has 8 clades and 24 genotypes for sequence differences between wild-type virus [1]. Genotype H1 was identified as the endemic genotype in China, and is divided into 2 clusters – cluster 1 and cluster 2 [2–4].

Since the implementation of mass vaccination programs in 1965, the number of measles infections has declined dramatically in China [5]. The average measles incidence rate has decreased from 1500 per 100 000 population before 1965 to 6.8 per 100 000 population during 2000–2009 [5]. In 2006, China conducted a strategic plan for eliminating measles in 2012, which included mandatory immunization at the time of entry to primary school or kindergarten to ensure that school-age children have been vaccinated against measles [6]. However, the measles elimination goal was not achieved. The annual number of measles cases even increased in the next few years, from 6276 in 2012 to 27 695 in 2013, 52 656 in 2014, and 42 874 in 2015 [7].

The vaccination plan is highly nationwide, but the measles virus is hard to eliminate. The present study focused on Shenzhen, one of the most economically developed cities in China and the city with the largest internal immigration. Moreover, previous studies showed that Shenzhen has a high incidence of measles in Guangdong province [8,9]. In the present study, we combine phylogenetic analyses of viruses from confirmed measles cases in Shenzhen from 2015 to July 2019 with investigations report in order to determine the consequences of measles and the associated potential public health challenges in an attempt to keep China free of endemic transmission of measles virus.

Material and Methods

Ethical consideration

This investigation was approved by the Ethics Committee of Shenzhen Children's Hospital. Informed consent was obtained from the patients or their guardians.

Sample collection

We enrolled 129 measles patients from Shenzhen Children's Hospital from January 2015 to July 2019. All the enrolled cases met the diagnostic criteria of measles. Throat swabs and urine samples were collected from individuals identified as having measles after obtaining informed consent from patients or their parents.

Measles RT-PCR and sequencing

All clinical samples were subjected to measles virus sequencing and genotyping using the standard protocols. Briefly, viral RNA was extracted from 140 µl of throat swab or urine sample according to the manufacturer's instructions (Omega, USA). RNA was reconstituted in 60 µl nuclease-free water and stored at –80°C until tested. Measles virus N gene was amplified using primers;
MeV-F: 5'-GGGAGGCTTGAACTTTGG-3';
MeV-R: 5'-TCCGTGTCTGAGCCTTGT-3'.
Two-step RT-PCR was performed using Takarar PrimeScript RT Master Mix. The PCR program was followed by 98°C for 10 s and 30 cycles of 98°C 1 s, 55 °C for 5 s, 72 °C 10 s, and a final extension step at 72°C for 1 min was completed in a PCR system (Bio-Rad C1000). The PCR products were purified using the Omega Gel Extraction kit.

Sequences of the PCR products were obtained using BigDye terminator chemistry version 3.0 according to the manufacturer's protocol for both sense and antisense strands on an automated ABI PRISM 3100 DNA Sequencer (PerkinElmer, Beijing, China). Sequences were analyzed using Sequencer (Gene Codes Corporation, Ann Arbor, MI, USA) and version 7.0 of BioEdit (*www.mbio.ncsu.edu/BioEdit/BioEdit.html*). Phylogenetic analyses were performed and trees were generated using the Molecular Evolutionary Genetics Analyses (MEGA) software version X. Phylogenetic trees were constructed by comparison with the reference strains defined by the WHO and previously reported measles isolates using the neighbor-joining method. The reliability of the groupings was estimated using bootstrap resampling of 1000 replicates. Nucleotide sequence data from 129 cases and reference sequences were supplied in supplemental data (Supplemenatry Table 1).

Survey data collection

Trained investigators used a standard questionnaire to conduct in-house face-to-face interviews with patient's parents. Variables collected included demographic characteristics, migration status, MCV vaccination history, reasons for non-vaccination (if appropriate), and healthcare service use and access.

Statistical analysis

The χ^2 test was used for categorical data. $P<0.05$ was considered statistically significant in all cases. All statistical analyses were performed using SPSS 13.0.

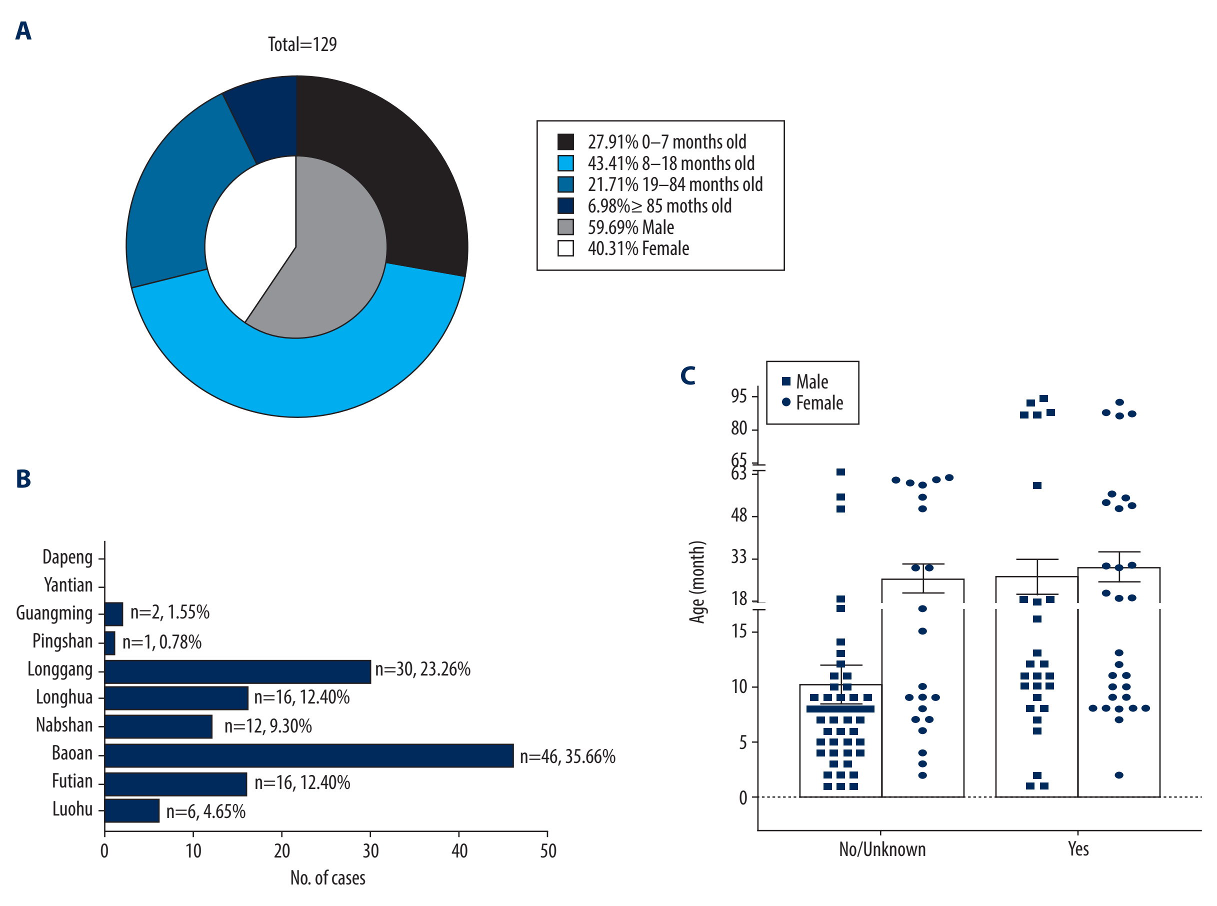

Figure 1. Characteristics of measles cases in Shenzhen Children Hospital, January 2015 to July 2019. (**A**) The age range and sex ratio in measles cases; (**B**) District distribution of measles cases in Shenzhen. (**C**). Scatter plot of age and sex in female and male measles cases.

Results

Epidemiological information

From January 2015 to July 2019, 129 measles cases were reported. According to the Shenzhen measles immunization schedule, patients with measles were divided into age groups: 0–7 months old, 8–18 months old, 19–84 months old, and older than 85 months. Of the 129 patients, 59.69% (n=77) were males and 40.31% (n=52) were females (Figure 1A); 43.41% were 8–18 months old, and 27.91% (n=36) were 0–7 months old. In addition, most of the patients were living in Baoan (n=46, 35.66%) and Longgang (n=30, 23.26%) (Figure 1B). There was an obvious seasonal measles outbreak in July each year, after which the incidence rate decreased from December to March each year (Figure 2A). Most cases (n=76, 58.9%) were hospitalized between April and August and the number of hospitalized patients reached a peak (n=23, 17.82%) in July (Figure 2B).

There were differences in whether the patients were vaccinated or not. According to their vaccination cards, 22 female patients and 50 male patients were unvaccinated, while 30 female patients and 27 male patients were vaccinated (Figure 1C). The age group with the greatest difference in vaccination status was 8–18 months old (male: female=23: 6). The clinical data (Table 1) showed that all patients had fever and rash. Cough was more likely to occur in patients who were unvaccinated (n=70, 97.22% in unvaccinated patients), which was also true for the prevalence of chronic bronchitis (n=29, 40.05% in unvaccinated patients), conjunctivitis (n=44, 65.34% in unvaccinated patients), catarrh (n=47, 65.34% in unvaccinated patients), Koplik spots (n=23, 31.62% in unvaccinated patients), and diarrhea (n=33, 46.37% in unvaccinated patients). The median number of white blood cells and AST levels were both high in vaccinated and unvaccinated patients. Febrile convulsions (3.88% of the total) and epilepsy (5.43%) occurred in both groups, while asthma (2.11% in unvaccinated patients) and otitis (4.22% in unvaccinated patients) only occurred in unvaccinated patients, but all of the incidence rates were low.

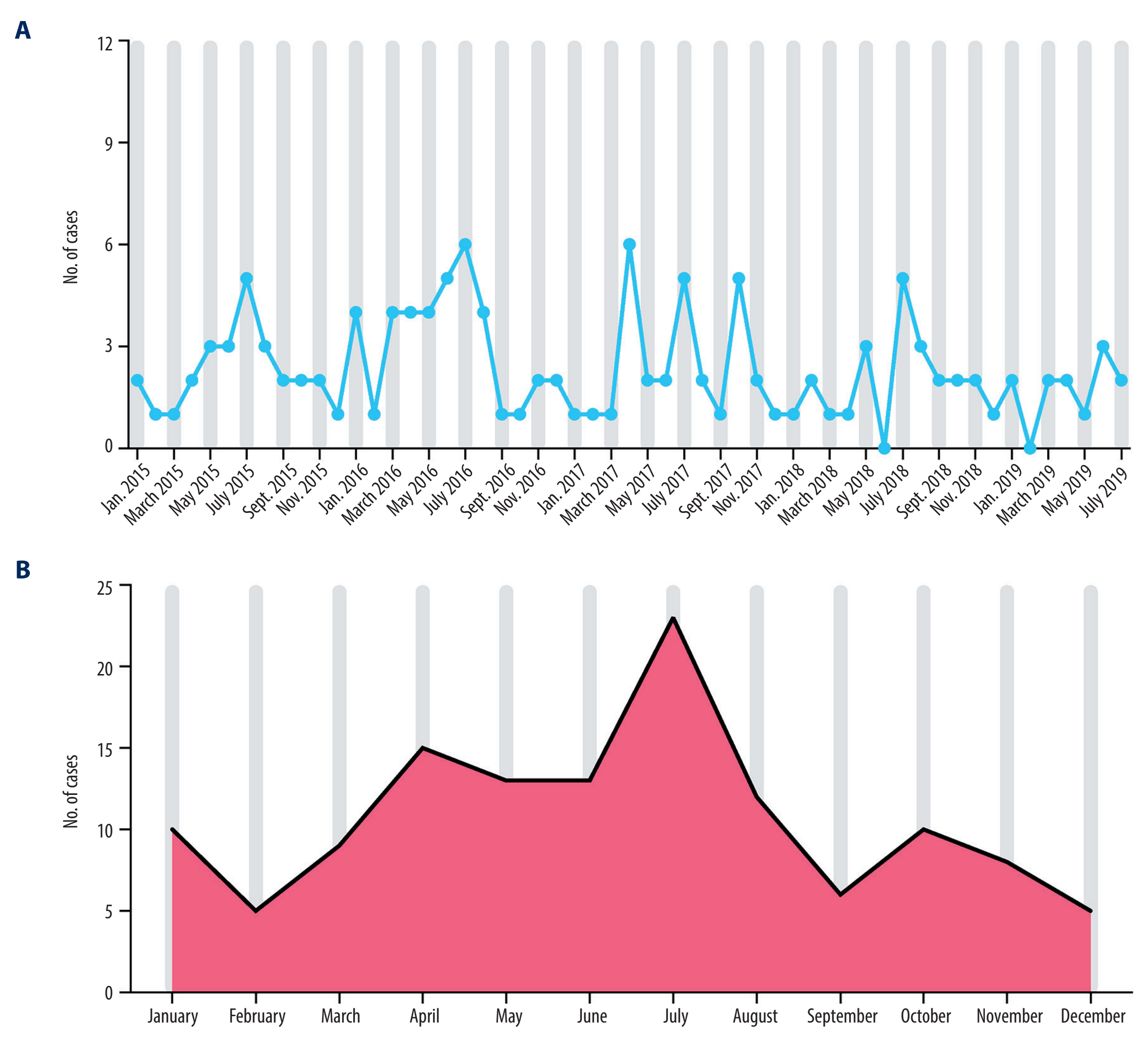

Figure 2. Measles cases over time in Shenzhen Children's Hospital, 2015 to July 2019. (**A**) The number of cases per month January 2015 to July 2019; (**B**) Monthly case count in January 2015 to July 2019.

Children of migrant workers and measles virus transmission

A voluntary survey (Table 2) of pediatric patients' parents showed that a total of 65.12% (n=84) of the children are from migrant worker families, especially in the unvaccinated group (n=52, 72.22% in unvaccinated patients). Overall, most of the vaccinated patients' parents (n=44, 77.19% in vaccinated patients) were also vaccinated themselves, but only 31 parents knew the vaccination program they had received (the 2-dose MMR vaccination program). The median income of the vaccinated group (4500±1739.75) was higher than in the unvaccinated group (3800±1043.66). Many vaccinated patients (n=36, 63.64%) went to school in Shenzhen, but a total of 71 patients were traveling in Shenzhen and live in the rural areas. There was no difference in the average reproductive age between the 2 groups. There was a difference between locals and migrants in unvaccinated patients. The median income of locals (4200±1259.02) was higher than that of migrants (3800±998.89). Nineteen of 20 local parents knew the vaccination program and 13 parents had a vaccination certificate for their children, but few of the migrants knew the program or had a certificate. The primary reason for failure to vaccinate local children was losing track of the recommended vaccination time (see additional remark in the survey). Fewer migrant children were attending school in Shenzhen compared to local children, especially in the unvaccinated group. Furthermore, some of the patients (n=20, 15.5%), especially the migrants (n=18, 13.95%), gave birth at home.

Regarding education level, 35.66% of parents received a middle school education, and 30.23% of parents received a high school education (Figure 3). Only 14.73% of parents had a

Table 1. Clinical data overview of all cases of measles January 2015 to July 2019.

Clinical data	Vaccinated (n=57)		Unvaccinated (n=72)		Total (n=129)	
Febrile convulsions	3	(5.33%)	2	(2.11%)	5	(3.88%)
Koplik spots	8	(13.31%)	23*	(31.62%)	31	(24.03%)
Rash	57	(100%)	72	(100%)	129	(100%)
Fever	57	(100%)	72	(100%)	129	(100%)
Cough	46	(79.88%)	70*	(97.22%)	116	(89.92%)
Diarrhea	12	(21.3%)	33	(46.37%)	45	(34.88%)
Pneumonia	24	(42.6%)	33	(46.37%)	57	(44.19%)
Otitis	0		3	(4.22%)	3	(2.33%)
Laryngitis	2	(3.51%)	9*	(12.65%)	11	(8.53%)
Chronic bronchitis	9	(15.98%)	29*	(40.05%)	38	(29.46%)
Asthma	0		2	(2.11%)	2	(1.55%)
Epilepsy	4	(5.56%)	3	(4.22%)	7	(5.43%)
Abnormal liver function	9	(15.98%	6	(8.43%)	15	(11.63%)
Conjunctivitis	15	(26.63%)	44*	(61.13%)	59	(45.74%)
Catarrh	29	(50.59%)	47*	(65.34%)	76	(58.91%)
Emesis	8	(13.31%)	17*	(23.19%)	25	(19.38%)
Median white blood cells in 10^9/L	12.41	(±6.62)	13.54	(±9.31)	12.53	(±8.25)
Median serum PLT levels in 10^9/L	281.5	(±142.44)	328.10	(±148.19)	297	(±145.97)
Median serum HGB levels in g/L	110	(±12.40)	115.63	(±17.26)	113	(±15.57)
Median serum CRP levels in mg/L	5.7	(±32.52)	4.65	(±13.62)	5.55	(±24.34)
Patients with increased CRP >80	3	(5.26%)	2	(2.78%)	5	(3.88%)
Patients with increased ALT >40 U/L	16	(28.07%)	23	(31.94%)	39	(30.23%)
Patients with ALT 81–200 U/L	6	(10.53%)	8	(11.11%)	14	(10.85%)
Patients with increased (AST) >35 U/L	51	(89.47%)	71	(98.61%)	122	(94.57%)
Patients with AST 71–175 U/L	14	(24.56%)	23	(31.94%)	37	(28.68%)
Patients with AST 176–350 U/L	3	(5.26%)	3	(4.17%)	6	(4.65%)
Patients with increased Leukocytes $\geq 9\times10^9$/L	6	(10.53%)	5	(6.94%)	11	(8.53%)

* $P<0.05$ wa considered statistically significant between vaccinated and unvaccinated group.

bachelor's degree and 25 parents received did not complete primary school (Figure 3).

According to household registration (Figure 4), patients came from 7 provinces – Guangdong (n=34), Sichuan (n=28), Hunan (n=18), Guizhou (n=16), Guangxi (n=13), Hubei (n=11), and Jiangxi (n=9) – and many were from areas near Shenzhen, which is located in Guangdong province. Many patients were from mountainous district and rural districts far from the provincial capital (1 red dot represent 1 case; the marker corresponds to the county level).

Phylogenetic and sequence analysis

In our study, 129 wild-type genotypes were identified as measles virus genotype H1 (Figures 5, 6), which suggested that genotype H1 was the predominant circulating genotype in Shenzhen during 2015–2019. Except for 11 genotypes that were identified as members of cluster 2 genotype H1, most of the cases were identified as members of cluster 1 genotype H1 (n=118, 91.47%).

Table 2. Survey results of patients' parents January 2015 to July 2019.

Survey of children's parents	Vaccinated			Unvaccinated			Total	
	Total	Locals	Migrants	Total	Locals	Migrants	Locals	Migrants
Numbers	57 (100%)	25 (43.86%)	32 (56.14%)	72 (100%)	20 (27.78%)	52 (72.22%)	45 (34.88%)	84 (65.12%)
Median income (CNY)	4500 (±1739.75)	4650 (±1422.26)	4400 (±1659.61)	3800 (±1043.66)	4200 (±1259.02)	3800 (± 998.89)	4200 (±1048.11)	3800 (±1082.08)
Know the vaccination program	31 (54.39%)	18 (31.58%)	13 (22.81%)	30 (41.67%)	19 (26.39%)	11 (15.27%)	37 (28.68%)	24 (18.60%)
Vaccinated oneself	44 (77.19%)	23 (40.35%)	21 (36.84)	25 (34.72%)	15 (20.83%)	10 (13.89%)	38 (29.45%)	31 (24.03%))
Average reproductive age (mother, father)	23.88±3.86, 25.37±3.47	24.12±3.42, 26.44±2.55	23.63±4.24. 24.31±4.41	23.16±4.90, 25.49±4.11	23.34±3.67, 25.87±3.44	22.98±5.14, 25.11±4.78	23.74±3.55, 26.16±3.01	23.31±4.68, 24.71±4.60
Vaccination certificate for children	57 (100%)	25 (43.86%)	32 (56.14%)	18 (25.00%)	13 (18.06%)	5 (6.94%)	38 (29.46%)	37 (28.68%)
School in Shenzhen (Children)	36 (63.15%)	25 (43.86%)	11 (19.30%)	22 (30.56%)	17 (23.61%)	5 (6.94%)	43 (33.33%)	15 (11.63%)
Home birth (Children)	5 (8.77%)	0	5 (8.77%)	15 (20.83%)	2 (2.78%)	13 (18.06%)	2 (1.55%)	18 (13.95%)

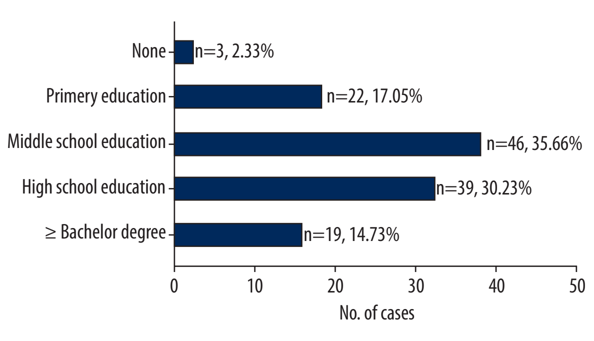

Figure 3. The education level of patients' parents in Shenzhen Children's Hospital, January 2015 to July 2019.

The sequence of 129 isolated wild-type measles virus was compared with the WHO reference strains sequences and other published sequences in GenBank by N gene sequences analysis (Supplementary Table 1). Phylogenetic circles showed that many genotypes of cases in 2016 and 2015 were more similar sequences than the genotypes in 2018 and 2019, which were more isolated and had less similarity to other reported H1 strains in China. There were more subtypes in the 2017 cases, which were similar to the different year's cases genotypes and other reported H1 strains in China, respectively. The sequence of genotypes D9, B3, and D8 were different from the 129 isolated wild-type sequences.

Discussion

Since 1986, a 2-dose measles vaccination policy was administered at age 8 months, followed by a second at 7 years of age (this was lowered to 18 months in 2005), the annual incidence was markedly decreased [10]. However, measles is still a serious public health problem in some regions of China. Previous studies showed that the periodic reoccurrence of measles is strongly correlated with seasonal factors [11, 12]. Measles epidemics have seasonality in China, with incidence starting to increase in November/December in Winter and peaking in March/April in most regions of China [6,13,14]. Most measles patients are young and unvaccinated children [6]. However, the measles season was delayed in some cities. Guangzhou had a delayed outbreak from 1985 to 2001, in which the incidence began to increase in April and peaked in May [15]. There were 1890 cases reported in Shenzhen, and the disease appeared more frequently between June and July from 2010 to 2016 [9]. In our study, we found a peak season from April to July, which is also consistent with the previous study. Moreover, the measles season might be correlated with patient age. In Mongolia from 2015 to 2016, the measles season among children age 0–11 months occurred from July to October [16]. From 2012 to 2016, the number of confirmed measles patients under age 18 months was highest between May and August in Guangdong province [17]. In our study, 71.32% of patients were under age 18 months, which could be a factor affecting the measles season.

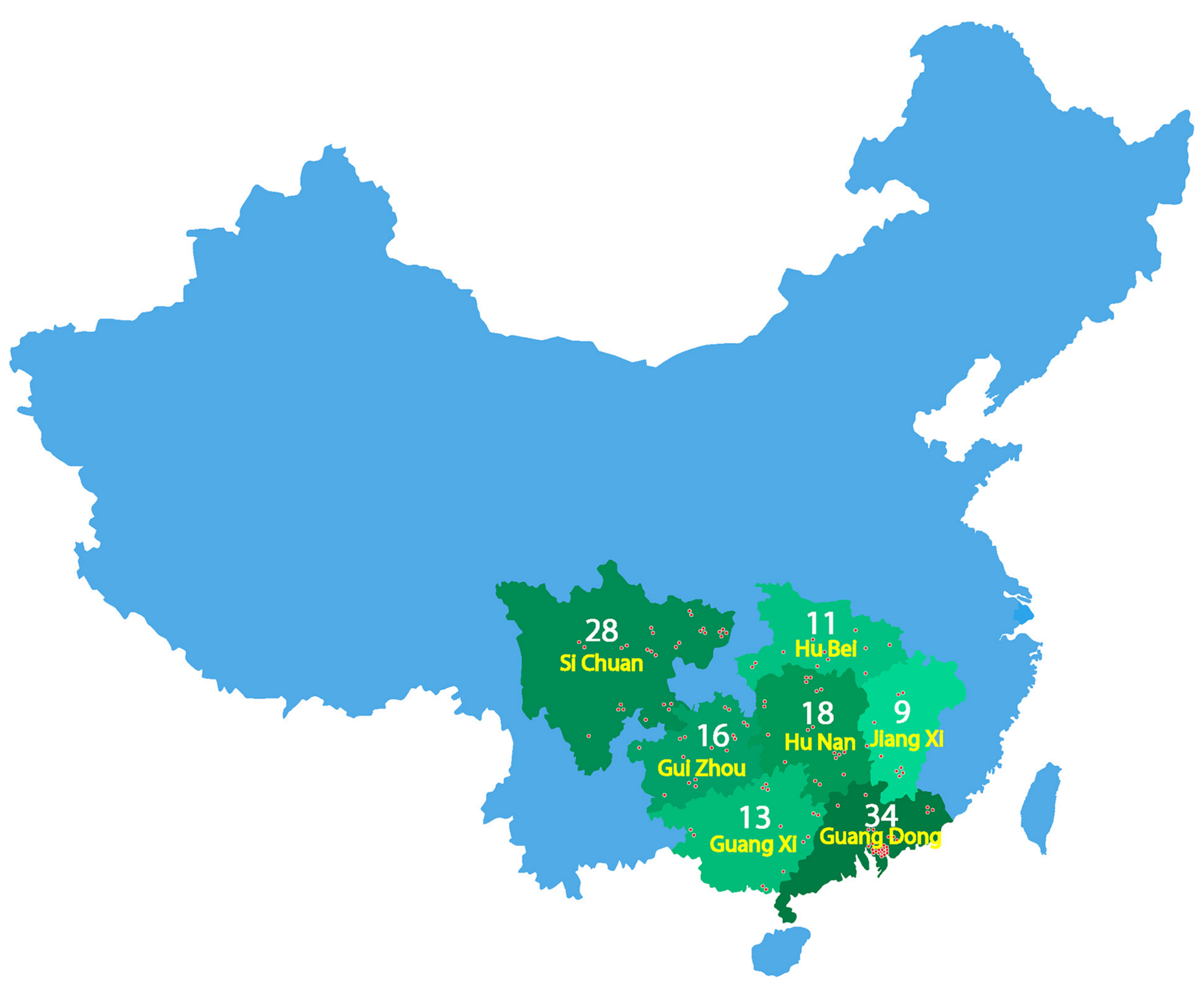

Figure 4. Geographic distribution of patients' household registration in Shenzhen Children's Hospital, January 2015 to July 2019.

There were some differences between vaccinated patients and unvaccinated patients. Most of the patients were under 10 months old, which is under the first vaccination time, which suggests that the maximum susceptibility is among unvaccinated children 8–10 months old. However, there were more male than female unvaccinated patients, even though the mean age of male unvaccinated patients was younger than in females. A study of pediatric measles patients born in Denmark from 1999 to 2010 identified 416 male unvaccinated children and 109 female unvaccinated children; more boys than girls had measles, even among vaccinated children [18]. A study in Tianjin, China found that 57.8% of the measles cases were males [19]. However, many other studies [20,21] found no significant difference in sex ratio in measles cases. Measles can increase susceptibility to opportunistic infections by suppressing the adaptive immune response [22]. Some clinical signs like fever and cough are considered the prodromal phase of measles and appear 7–14 days after the first day of infection [22]. Koplik spots and maculopapular skin rash appear 1–5 days after the prodromal phase, and these are considered the typical clinical signs of measles [22]. Because of measles infection development including immune suppression, bacterial infections, and central nervous system complications, many other clinical signs occur in different tissues, for example, conjunctivitis, chronic bronchitis, diarrhea, laryngitis, pneumonia, emesis, and epilepsy [22,23]. In our study, fever and rash appeared in all of the patients, with no difference between vaccinated and unvaccinated patients. However, 79.88% of vaccinated patients had cough, but 97.22% of unvaccinated patients had cough, and 13.31% of vaccinated patients had Koplik spots *vs.* 31.62% in unvaccinated patients. Previous studies found differences in clinical characteristics of measles cases between vaccinated and unvaccinated patients; more patients in the unvaccinated group had cough, and the same was true for conjunctivitis [24], diarrhea [25], and chronic bronchitis [26]. In our study, the rates of conjunctivitis, diarrhea, and chronic

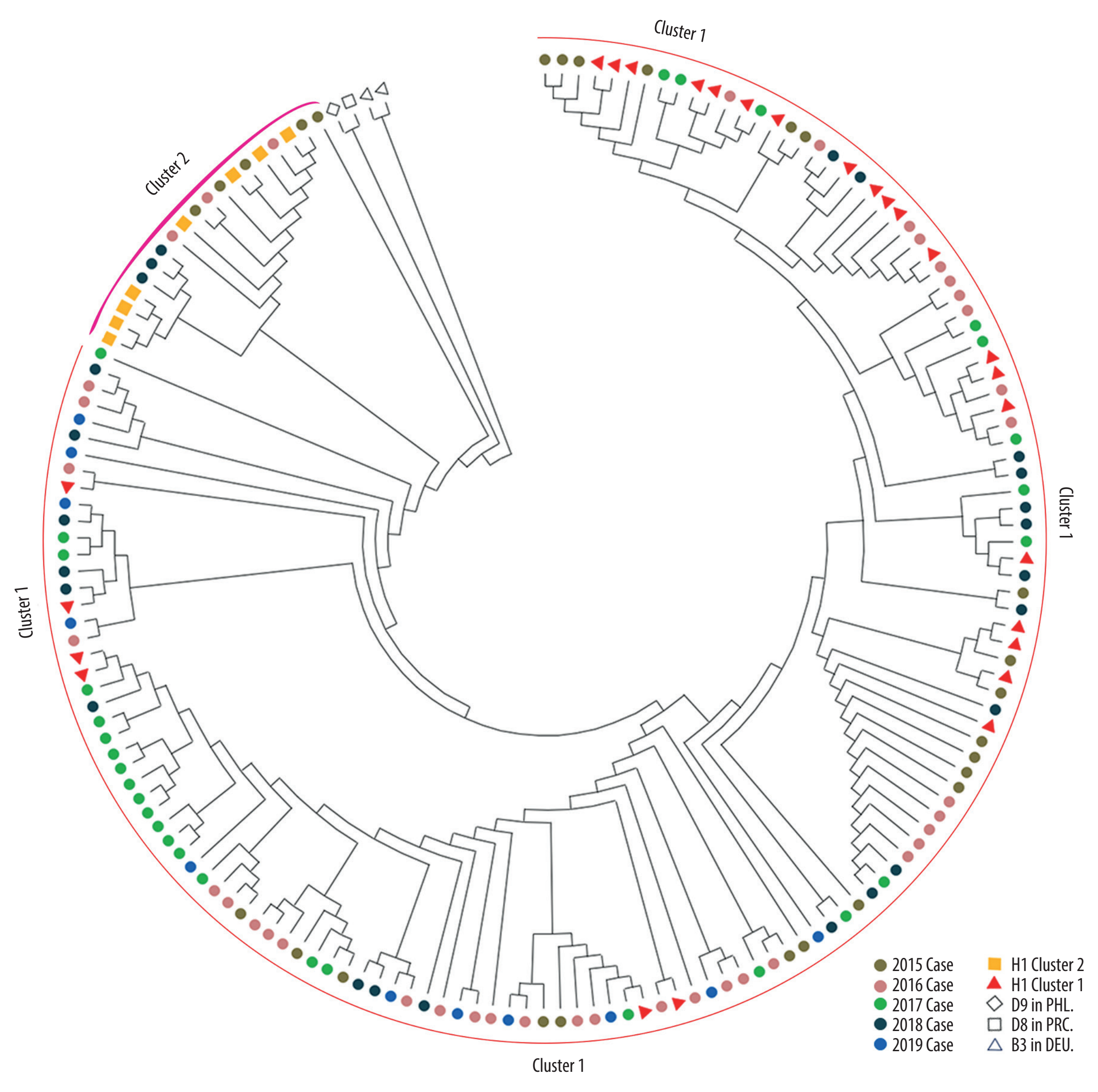

Figure 5. Phylogenetic tree based on the nucleotide protein (N) gene sequences of various strains of the measles virus. The dendrogram was created with MEGAX software and the neighbor-joining method (1000 bootstraps).

bronchitis were also different between vaccinated patients and unvaccinated patients. Moreover, laryngitis and emesis were more frequently found in unvaccinated patients, which may be related to respiratory system disease and central nervous system complications in measles infection. However, the rate of patients with abnormal liver function was higher in the vaccinated group (15.98% in vaccinated *vs.* 8.43% in unvaccinated), and there was no difference in ALT and AST levels between the 2 groups.

Missed opportunities to vaccinate have challenged measles elimination and vaccination programs. The measles outbreak in the USA during 1989–1991 was largely a result of missed opportunities to vaccinate [27]. China has many families migrating with young children for employment opportunities, and it is also challenging for official vaccination clinics in China to be aware of children who are new to an area and who are unvaccinated [28]. In agreement with the present results, previous studies showed that children of migrant workers have lower vaccination coverage [28,29]. Shenzhen has a massive population of migrant workers that are from the rural area of many other provinces. In our study, we found the cases were from 7 provinces, and many were from rural areas and remote villages. Many unvaccinated cases came from migrant worker families, who mostly went to school in their household registration location and were temporally visiting their parents in Shenzhen.

These children's parents had mostly graduated from high school and middle school and did not know the vaccination program requirements and were less likely to have been vaccinated themselves. Although the local people may know the vaccination policy, they may still but forget to get vaccination. In addition, many parents who have a home birth miss the regular official vaccination. China official vaccination programs are well-implemented in most areas, but more health promotion is needed for migrant workers and people from remote villagers.

A vast amount of genetic characterization data showed that genotype H1 is a single endemic measles genotype in mainland China since its initial identification in 1993 [30-32]. In our study, we performed a phylogenetic analysis of the nucleoprotein (N) genes of measles virus from 129 measles patients in Shenzhen Children's Hospital from 2015 to July 2019 and found that H1 viruses were the only genotype. A few cases were closely related to cluster 2 and came from 2015 and 2018, while other cases were closely related to cluster 1. The percentage of clusters was consistent with previous studies [33–35]. The ranges of nucleotide sequence homologies among the 129 cases of wild-type and 34 identified H1 isolates were 92.3–99.8%. Although the cases were from 7 provinces, there were no other genotypes. The phylogenetic tree also showed that the variation of the measles virus varies year-to-year. Measles viruses from 2015, 2016, and 2017 were closely related, while viruses from 2018 and 2019 were less similar. Moreover, many wild-type viruses had less affinity with identified H1 isolates, which suggested that an unreported variation of the measles virus appeared in Shenzhen. Thus, the increased genetic diversity of genotype H1 possibly reflects the infection risk in measles due to unvaccinated populations, especially among migrant workers' children.

We recognize several limitations in our study. First, there were only 129 measles cases from a single hospital in Shenzhen, and we lacked city-level data. Second, the survey data did not differentiate between one-dose *vs.* two-dose vaccination. Third, we only compared wild-type sequences with 34 identified H1 isolates, and the comparison did not include A, D11, H2, and D4, which were also reported in China.

Conclusions

In conclusion, our results showed there was a seasonal measles outbreak between April and August in Shenzhen Children's Hospital from 2015 to 2019. All the measles virus from 129 measles patients were H1 viruses. The phylogenetic tree also showed that measles viruses from 2015, 2016, and 2017 were closely related, while there was less similarity in 2018 and 2019. The clinical signs also showed a difference between unvaccinated patients and vaccinated patients. Moreover, most of unvaccinated patients came from migrant worker families; these children's parents were mostly high school and middle school graduates who were unaware of the vaccination programs and were less likely to get vaccinated themselves. Thus, we suggest there is a need for more health promotion about the vaccination programs for migrant workers and for people from rural areas and remote villagers.

Supplementary Data

Supplementary Table 1. Nucleotide sequence data from 129 cases and reference sequences.

Supplementary/raw data available from the corresponding author on request.

Conflicts of interest

None.

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