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Original Article

Epidemiological Outbreaks of Measles Virus in Kazakhstan during 2015

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SUMMARY: This study involved epidemiological surveillance of the measles virus (MV) in the territory of the Republic of Kazakhstan during 2015–2016. We detected MV genotype D8 in this season of measles outbreak. A total of 2,341 cases were registered and 19 were identified by genotyping. Sixteen of these samples were attributed to subgroup A of genotype D8, while 3 imported cases were represented by genotypes B3 and H1. Analysis of vaccination coverage showed that a large group of infected people were not vaccinated or did not have a reliable report on their vaccination status. This issue might increase the morbidity rate among the healthy population in outbreak seasons. To prevent the incidence caused by this problem, we have successfully introduced epidemiologic measures for the control of measles.

INTRODUCTION

Measles is a highly contagious infection caused by the measles virus (MV) that occurs primarily in infants and children. Adult infections may cause serious illness and increased mortality (1). Accelerated immunization activities have played a significant role in reducing mortality from measles (2). An estimated 20.3 million deaths were prevented by vaccination between 2000 and 2015. Globally, measles mortality decreased by 74% from 535,300 cases in 2000 to 139,300 in 2010 (3). Despite significant investments in the fight against measles, in the past five years, outbreaks have continued to occur worldwide. In 2015, 30,762 cases of measles were registered in 39 of the 50 countries within the World Health Organization (WHO) European Region. In the same year, 27,086 (88%) of these cases were reported in 4 countries: Kyrgyzstan (17,779, 58%), Bosnia and Herzegovina (4,583, 15%), Germany (2,383, 8%), and Kazakhstan (2,341, 8%) (4). In the Republic of Kazakhstan, vaccination using a live measles vaccine began in 1967 as for all countries of the former Union of Soviet Socialist Republic began (5). Planned vaccination was performed at the age of 1 to 8 years among healthy children. The measles vaccine is currently included in the immunization calendar as part of the trivalent measles-mumps-rubella vaccine administered at the age of 12 months, with revaccination at 6 years.

In 2002, epidemiological surveillance of measles and rubella was introduced in Kazakhstan in accordance with the WHO European Region strategic program for the prevention of measles and congenital rubella infection. At that time, 16 regional laboratories from the Ministry of Health collected samples and sent them to the WHO Europe region National Reference Laboratory for Measles and Rubella in Almaty, which conducted laboratory confirmation of measles cases by enzyme-linked immunosorbent assay (ELISA) and sent samples for polymerase chain reaction (PCR) and genotyping study to the Regional Reference Laboratory in Moscow (G.N. Gabrichevsky Moscow Research Institute of Epidemiology and Microbiology, Russia). In the countries of the former Soviet Union, the laboratory system was created to reduce costs in a difficult economic situation in 1990–2000. To date, the growth of the economies of the post-Soviet countries, the emergence of modern diagnostic methods, the changing epidemic situation for measles, the need for more detailed laboratory data on circulating viruses (subtype, pathogenicity-related mutations, transmission routes, etc.), and the transmission of newly emerging infections has required the availability of a modern, efficient laboratory network at the national level.

Kazakhstan, as a member of the WHO Europe Regional Office, needs to actively promote a common policy for improving laboratory and epidemiological surveillance of measles and rubella by introducing modern molecular-genetic typing methods in the Local National Reference Laboratory. Thus, it is important to achieve the goals of the global measles and rubella elimination plan set by WHO. Prior to the current study, molecular-genetic typing was not carried out in the Republic of Kazakhstan. The aim of this study was to provide epidemiologic data for measles virus circulation in Kazakhstan during 2015–2016 years. In this study, we provide a regional update for epidemiologic surveillance of measles during seasonal outbreaks, in regard to circulating genotypes.

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MATERIALS AND METHODS

Definition of measles cases: Medical personnel diagnosed measles based on the presence of fever, maculopapular rash, cough, rhinitis, and conjunctivitis. Specimens for laboratory testing (blood serum, urine) were collected during a measles outbreak from January 1, 2015, to January 30, 2016. Serum samples were tested by ELISA to detect immunoglobulin M (IgM) using commercial kits manufactured by Vector-Best CJSC (Russia). Blood serum samples were collected from 4 to 28 days after the onset of the rash.

Samples confirmed by clinical laboratory testing were transferred to the territorial Departments of the Committee for Public Health of the Ministry of Health. All data were then combined at the Scientific and Practical Center for Sanitary and Epidemiological Expertise by the Public Health Protection Committee of the Ministry of Health of Kazakhstan.

The detection of MV antibodies and RNA, genotyping, and phylogenetic analysis were performed at the National Reference Laboratory for Measles and Rubella of the WHO Europe regional Scientific and Practical Center for Sanitary and Epidemiological Expertise Bureau of the Ministry of Health of the Republic of Kazakhstan in Almaty city.

Genotyping: All urine samples submitted for genotyping were collected in the first 5 days after the rash onset. Isolation and amplification of the viral RNA was performed using a commercial kit according to the manufacturer's instructions (Qiagen cat. No 52906).

Genotyping was carried out based on the C-terminal sequence of a 450-nucleotide fragment of the N gene recommended for MV genotyping (6). Phylogenetic trees were constructed in Mega 7.0 using the maximum likelihood method, Kimura 2-parameter model, gamma distribution, and bootstrap analysis (500 repetitions) (7). The sequences were imported and compared to other MV sequences from the WHO - MeaNS database using the BLAST algorithm (8). Identification of the genotypes was relative to the inventory numbers of the nucleotide sequences with the closest sequence match.

Epidemiological studies: The studies were conducted during the measles outbreak in Kazakhstan from January 1, 2015, to January 30, 2016. We conducted an observational, descriptive, single-stage analysis by determining the prevalence, occurrence, and proportions of measles cases.

The morbidity rates by age groups and regions were calculated for cases in Kazakhstan using 2015–2016 data from official sources.

RESULTS

Epidemiologic surveillance for measles: Measles outbreaks were registered from the beginning of 2015 in all 16 regions of the country. A total of 2,679 suspected cases of measles were detected from January 1, 2015, to January 30, 2016, which included 338 unconfirmed cases, 1,815 laboratory-confirmed cases (including 3 imported cases), and 526 epidemiologically-related cases. Thus, there were 2,341 total established cases of measles.

The majority of cases were reported in Astana city ($n = 396$, 15%), East Kazakhstan region ($n = 333$, 12%), Mangistau region ($n = 292$, 11%), South Kazakhstan region ($n = 269$, 10%), Almaty city ($n = 150$, 6%), and Almaty region ($n = 127$, 5%) (Fig. 1).

In January 2015, the transmission of MV infection increased in 10 regions nationwide. A total of 220 cases were detected, mainly in Astana city ($n = 81$; 36.9%), East Kazakhstan region ($n = 82$; 37%), Mangistau region ($n = 17$; 8%), and South Kazakhstan region ($n = 17$; 8%). In February, the regional centers reported 485 measles cases in 16 regions. In general, the morbidity rate in the country was 13.53 cases per 100,000, peaking in April 2015 with 515 reported cases. After rapidly increasing, the infection rate dropped slowly from August 2015, up

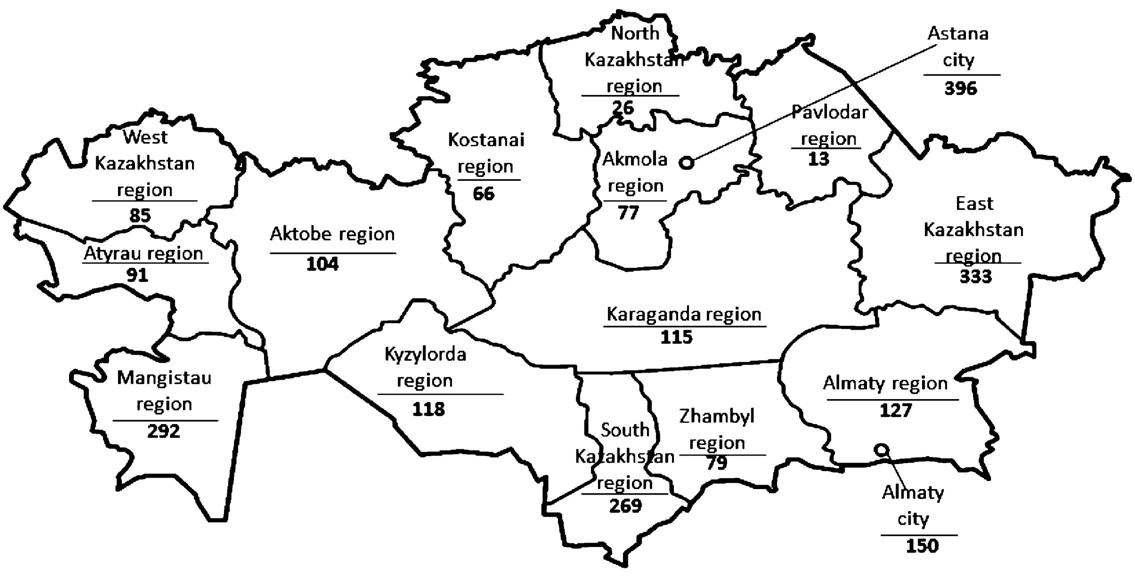

Fig. 1. Number of measles cases by regions of Kazakhstan in 2015.
Bold numbers represent detected measles cases divided by region.

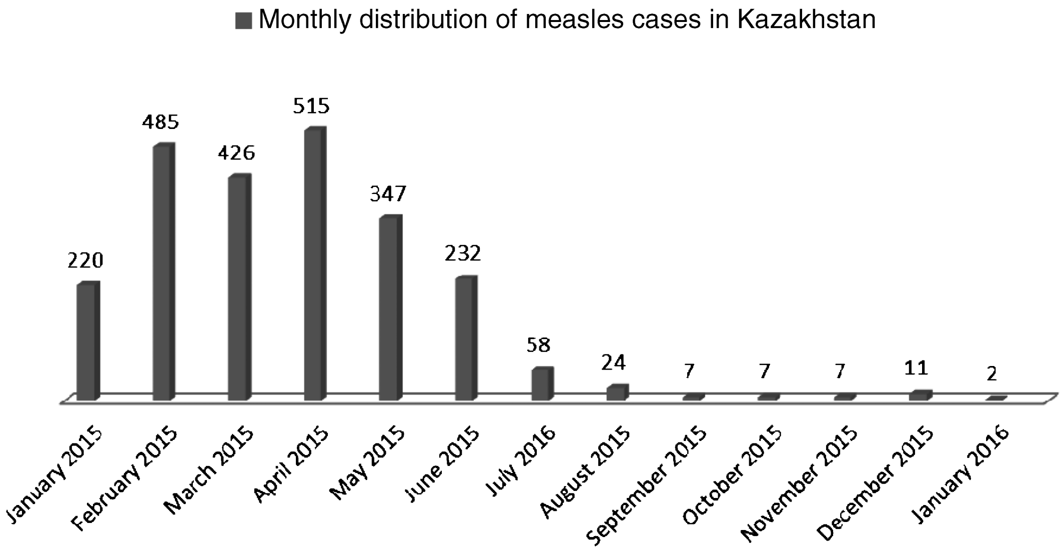

Fig. 2. Number of registered measles cases by month in Kazakhstan, from January 1, 2015 to January 30, 2016 ($n = 2{,}341$).

Table 1. Age and vaccination status of patients with laboratory confirmed, epidemiologically related measles cases (excluding imported cases) from January 1, 2015 to January 30, 2016 ($n = 2{,}341$)

MMR vaccine	Age (yr) group							
	<1 yr	1–4 yr	5–9 yr	10–14 yr	15–19 yr	20–29 yr	30 yr and older	Total
None	560	7	31	10	13	6	1	628
1 dose	12	2	6	3	14	29	27	93
2 or more doses	0	0	15	49	193	237	33	527
No data	4	0	3	5	80	447	554	1,093
Total	576	9	55	67	300	719	615	2,341

MMR, measles, mumps, and rubella.

to 24 cases, and continued until December 2015 (Fig. 2).

Young people aged 20–29 years ($n = 719$; 31%), adults aged 30 years and more ($n = 615$; 26%), children under one year ($n = 576$; 25%), and adolescents and young people aged 15–19 years ($n = 300$; 13%) were the most susceptible to the disease. The reported incidence was highest among persons older than 14 years of age ($n = 1634$; 70%).

Analysis of the vaccination status of measles cases in Kazakhstan showed that the vast majority of people were not vaccinated and did not have reliable data regarding vaccination. Of the 2,341 reported measles cases, almost half lacked vaccination data ($n = 1{,}093$). About one-third of patients were not immunized ($n = 628$) and most were infants up to one year of age ($n = 560$) who had not received the vaccine. Among the 620 vaccinated cases, most had received 2 or more doses ($n = 527$). Out of the total number of vaccinated persons, the largest proportions were aged 20–29 ($n = 266$) and 15–19 years ($n = 207$). The distribution of measles cases by age group and the vaccination status are shown in Table 1.

Vaccination coverage: Data analysis over the past four years has shown that the average vaccine coverage for 2 doses of the MMR trivalent vaccine against measles, rubella, and mumps in children aged between 2 and 6 years above 95% (Table 2).

Since 2014, regional monitoring of vaccine waivers has been introduced at the national level in Kazakhstan. There is a tendency toward increasing numbers of vaccination waivers in the country. Between 2013 and 2016, the number of vaccination increased from 500 to more than 10,000.

Table 2. Coverage of routine vaccination in Kazakhstan from 2013 to 2016

Routine vaccination	2013 (%)	2014 (%)	2015 (%)	2016 (%)
MMR vaccine, 1st dose	98	99.2	100	99.4
MMR vaccine, 2nd dose	99.3	99	98.4	99.3

MMR, measles, mumps, and rubella.

MV genotyping: During 2015–2016, blood samples from 2,679 patients were analyzed by ELISA for confirmation of measles; of these, 1,815 samples were positive for anti-measles IgM antibodies. A total of 19 urine samples were examined by reverse transcription (RT)-PCR and MV RNA was detected in all samples. These samples were obtained from patients in North Kazakhstan ($n = 7$), Akmola ($n = 3$), South Kazakhstan region ($n = 7$), Shymkent city ($n = 1$), and Almaty city ($n = 1$). Fragments of the 450-*bp* *N* gene were amplified in all 19 samples for MV genotyping. Of these, 16 of the identified genotypes were endemic and 3 were imported.

The 16 genotyped strains all belonged to genotype D8, subgroup A, which were divided into 5 variants. Among them, 11 strains belonged to variant 1, represented by MVi/Villupuram.Ind/03.07. One strain belonged to variant 2, which is similar to MVs/Frankfurt Main. DEU/17.11, and one strain belonged to variant 3, represented by MVs/Rostov on Don.RUS/47.13/2. Two similar strains were related to variant 4 MVs/Pretoria. ZAF (19.09) and one strain, similar to MVs/Sohar. OMN/23.12, belonged to variant 5 (Fig. 3).

In this period, 3 cases of measles imported from Russia and China were reported. In April 2015, 2 cases of measles in the North-Kazakhstan region were reported

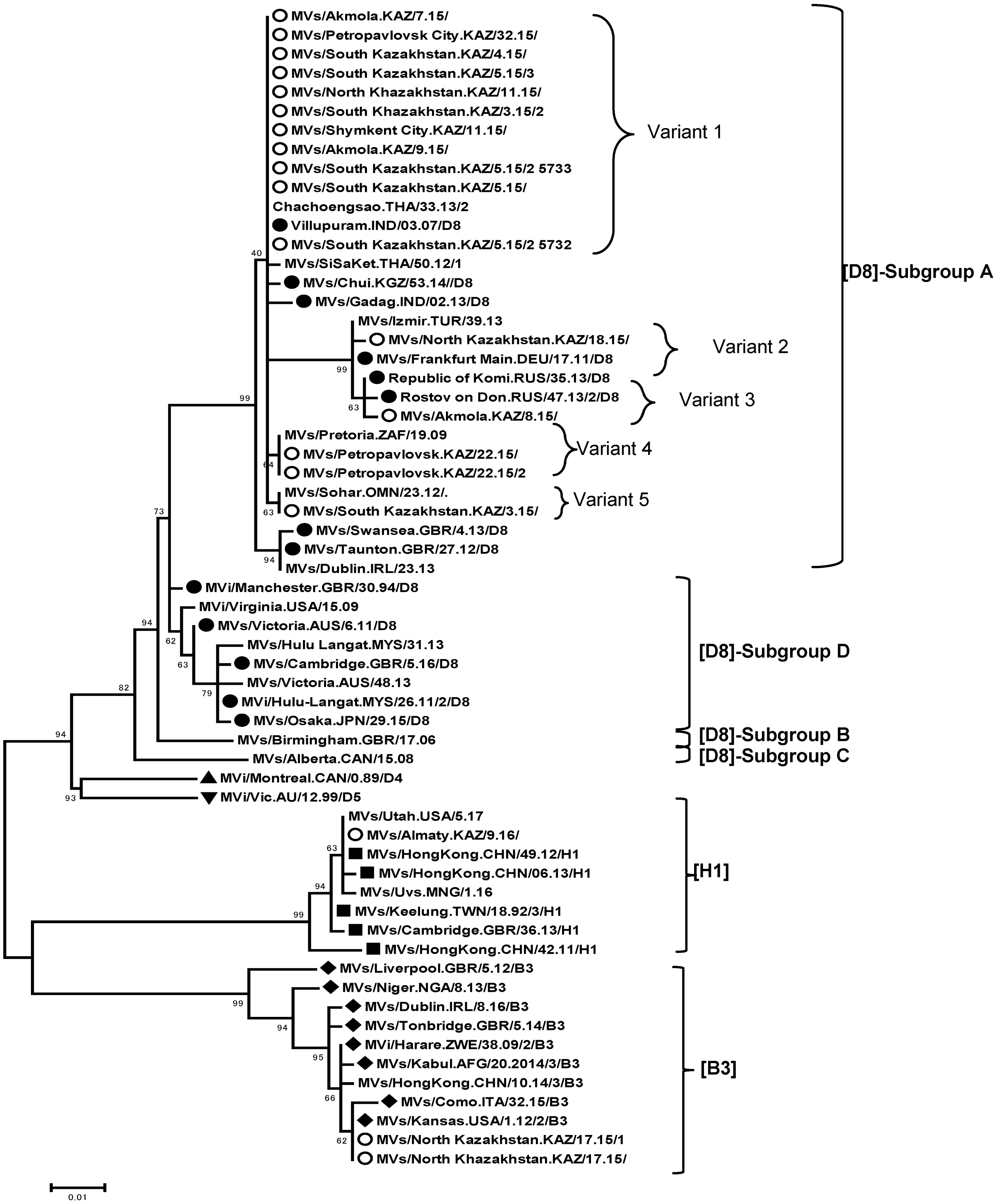

Fig. 3. Phylogenetic tree of MV genotypes identified in Kazakhstan during 2015–2016 years outbreak season. ●,▼,▲, ■, ◆, sequence of MV reference strains; ○, sequences of MV strains isolated in Kazakhstan. Phylogenetic tree of H1 and B3 genotypes of MV, identified in Kazakhstan (2015–2016).

among patients who had visited the Russian Federation. The genotypes of these samples showed that the disease was caused by a virus belonging to the MVs/Kansas. USA/1.12/B3 strain. In January 2016, one case of measles was detected in an individual in Almaty city who reported visiting Mongolia. The genotype of this case matched that of the MVs/Hong Kong.CHN/49.12/H1 (Fig. 3) strain. These strains had not previously been reported to circulate in Kazakhstan.

Epidemiologic surveillance: After assessing the risk of measles disease spread in all regions of the country in 2015 and the constant threat of infection importation, the Ministry of Health of the Republic of Kazakhstan took on additional activities. In October 2015, an additional immunization against measles was carried out, using a monovalent live attenuated measles vaccine administered to adolescents aged 15–19 years (school and university students, soldiers, and others). The campaign for additional immunization was carried out at vaccination points in 16 territorial health organizations (rural medical outpatient clinics, district and central district hospitals, and city hospitals), and educational organizations (schools and universities).

A total of 351,286 (99.4%) children aged one year were vaccinated against measles according to the developed plan and 314,108 (98.3%) children were revaccinated against measles at 6 years of age. Of the total number of individuals within the groups targeted in the additional measles immunization campaign, 99% were vaccinated. The vaccination process was additionally ensured by the organization of 4,120 visiting vaccination teams. The organization and conduct of the anti-epidemic campaigns were designed to prevent the spread of infection.

DISCUSSION

The WHO strategic plan aimed to eliminate measles and rubella at least in 5 regions of the world by the end of 2015. Elimination requires the absence of endemic circulation of measles and rubella viruses in a certain territory for at least 12 months, with an effective system of epidemiological surveillance (9).

Due to increased population immunity following vaccination programs, there has been a pronounced tendency toward a reduced incidence of measles. However, since 2013, the incidence of measles has increased, with outbreaks in most regions of the world. In 2013, 31,520 measles cases were registered in the European Region, compared to the 4,386 cases in 2012 ($n = 27{,}134$) (10). In 2013 and 2014, 73 and 321 suspicious measles cases were reported in Kazakhstan, respectively (data not shown). In our study, we recorded 2,341 measles cases in the 2015–2016 outbreak seasons. The incidence of measles affected all 16 regions of Kazakhstan. The morbidity rate per 100,000 people in our country was 13.53, 7 times higher than that in 2014 (1.88) and 30 times higher than that in 2013 (0.43). The incidence peak occurred in April 2015 and decreased from August to the end of December 2015.

Analysis of vaccination data among measles cases in Kazakhstan showed that the vast majority were vaccinated against measles, most of whom were children under one year of age and those without reliable vaccination data. Therefore, in order to prevent measles outbreaks, large-scale screening of post-vaccination antibodies in vaccinated and non-vaccinated individuals over 14 years of age is necessary since there may be a lack of proper immunization reports and quality control of vaccines in Kazakhstan. Another potential issue is individuals who avoid vaccination. Hence it is necessary to address all problems connected to vaccination risks.

The measles cases identified in Kazakhstan in 2006 belonged to genotype D6 (11). The morbidity changed with the 2010–2013 outbreak with the circulation of genotype D4 from the MVi/Bandarabas.IRN/05.10/2 genetic line. In addition, the global distribution of the /MVi/Villupuram.IND/03.07/ D8 genotype was observed in 2013–2014, including our country (data not shown).

In order to implement the WHO recommendations in 2015, the National Reference Laboratory for Measles and Rubella of the WHO/Europe Region in Almaty introduced molecular genetic methods for the detection and identification of MV. The nucleotide sequences of 19 samples were compared to those of the reference strains in the WHO database (MeanS). The cases that occurred between January 1, 2015, and January 30, 2016, were caused by 5 MV variants from subgroup A of genotype D8. In addition, we detected imported MV strains similar to MVs/Kansas.USA/1.12/ ($n = 2$) of genotype B3 and MVs/Hong Kong.CHN/49.12/ ($n = 1$) of genotype H1, which had not previously been reported to circulate in this country (Fig. 3).

The National Commission ascertained the effectiveness and timeliness of the epidemic activities for additional measles immunization among adolescents aged 15–19 years, with vaccination coverage above 95%. The implementation of these activities resulted in a marked decrease in the incidence of measles in Kazakhstan by more than 19-fold in 2016 ($n = 122$) (data not shown) compared to that in 2015 ($n = 2{,}341$). However, screening studies for the presence of postvaccinal antibodies and "catch-up" vaccinations in at-risk groups (vaccinated and non-vaccinated individuals over 14 years of age) are necessary in order to prevent measles outbreaks.

The results of this study demonstrate the importance and effectiveness of molecular genetic methods for the detection of MV. Epidemiological surveillance of measles is important as many countries continue to move towards the elimination of MV, demonstrating a lack of sustained transmission in the indigenous population. Identification of MV in combination with effective anti-epidemic strategies can limit the further spread of the disease due to endemic circulation and import of infection.

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Conflict of interest None to declare.

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