REVIEWS

REVIEW
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Global genetic diversity of measles virus (Paramyxoviridae: *Morbillivirus: Morbillivirus hominis*): historical aspects and current state

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Abstract
Monitoring the circulation of the measles virus and studying its genetic diversity is an important component of the measles elimination program. A methodological approach to molecular genetic studies and their interpretation in the measles surveillance was developed in the early 2000s. During its development, clear areas of circulation of each genotype of the virus were identified, therefore, the determination of viruses' genotypes was proposed to monitor circulation and identify transmission pathways. However, in the future, due to a significant decrease in the number of active genotypes, an approach based on sub-genotyping was proposed: determining not only the genotype of the virus, but also its genetic lineage/genetic variant. The Global Measles and Rubella Laboratory Network (GMRLN) systematically monitors the circulation of the measles virus at the sub-genotypic level, depositing the results in a specialized database MeaNS2. It is this database that is the most complete and reliable source of information about the genetic characteristic of measles viruses.
This review presents both historical information and the latest data on the global genetic diversity of the measles virus.

Keywords: *review; measles virus; measles; genotype; genetic line; genetic variant; genotyping*

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НАУЧНЫЙ ОБЗОР
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Глобальное генетическое разнообразие вируса кори (Paramyxoviridae: *Morbillivirus: Morbillivirus hominis*): исторические аспекты и современное состояние

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Резюме
Мониторинг циркуляции вируса кори и изучение его генетического разнообразия является важным компонентом программы элиминации кори. Методический подход к молекулярно-генетическим исследованиям и их интерпретации с целью надзора за корью был разработан в начале 2000-х гг. В период его разработки были установлены четкие ареалы циркуляции каждого генотипа вируса, в связи с чем определение генотипов выделенных вирусов было предложено для мониторинга их циркуляции и выявления путей передачи.

Однако в дальнейшем, по причине значительного снижения количества активных генотипов вируса, был предложен подход, основанный на субгенотипировании: определении не только генотипа вируса, но и его генетической линии/генетического варианта. Глобальная сеть лабораторий по кори и краснухе (GMRLN) проводит систематический мониторинг циркуляции вируса кори на субгенотипическом уровне, депонируя результаты в специализированную базу данных MeaNS2, которая является наиболее полным и достоверным источником сведений о генетической характеристике вирусов кори.
В настоящем обзоре представлены как исторические сведения, так и последняя информация о глобальном генетическом разнообразии вируса кори.

Ключевые слова: *обзор; вирус кори; корь; генотип; генетическая линия; генетический вариант; генотипирование*

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Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.
Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Introduction

Genotyping of measles virus strains, estimation of their circulation timing and their geographic distribution constitute integral components of high-quality epidemiological measles surveillance, which must be implemented in all the countries that have adopted the World Health Organization (WHO) measles control and elimination program [1].

Identification of a measles virus and its assignment to one of the 24 known genotypes as well as identification of the genetic lineage or variants of the isolated virus strains are among the tasks performed by the laboratories participating in the WHO Global Measles and Rubella Laboratory Network (WHO GMRLN). The WHO GMRLN was established in 2000 to provide reliable diagnostic support and to monitor the circulation of pathogens. Its laboratories serve 191 countries and include three global specialized laboratories, 14 regional reference laboratories, 180 national and 506 subnational laboratories [2]. In the Russian Federation, the function of the national laboratory and reference laboratory for CIS countries is assigned to the National and Methodological Center for Measles and Rubella Surveillance of the Gabrichevsky Research Institute of Epidemiology and Microbiology of Rospotrebnadzor.

The WHO GMRLN laboratory consortium provides continuous monitoring of the circulation of the measles virus. Currently, the standard method for genotyping of measles viruses is sequencing of 450 nucleotides (nt) encoding the COOH terminal 150 amino acids of the viral nucleoprotein (the so-called sequencing window) – N-450 [3, 4]. Additionally, the countries where measles has been eliminated or is close to elimination can use extended regions of the virus genome for the analysis, including the full nucleotide sequence of the *H* gene (1854 nt), the 1018-nt-long non-coding region between the *M* and *F* genes (MF-NCR); besides, whole genome sequencing of the virus can be used [5]. While extended sequencing used for genetic monitoring demonstrates good results in studies, it cannot be globally adopted by laboratories due to absence of standardized methods of analysis and interpretation of results [5].

The attempts have been made to develop a genotype-specific reverse transcription polymerase chain reaction (RT-PCR) to be further used in WHO GMRLN laboratories [6]. Assumedly, the technique should have become an alternative to sequencing; however, it did not take hold, as it lacks the capacity to detect mutations and track transmission chains of genetic lineages and variants. The genotype-specific real-time RT-PCR is used exclusively for differentiation between vaccine and wild-type strains in recently vaccinated patients [7, 8].

The results of genotyping of all viruses isolated during the monitoring are deposited in the specialized MeaNS2 database (Measles virus nucleotide surveillance; https://who-gmrln.org/means2) created and maintained by the WHO GMRLN. The MeaNS2 database is an improved version of the previous MeaNS database that operated till 2021. For almost 10 years, the monitoring of the measles virus circulation has been based both on genotyping and subgenotyping: identification of a genetic lineage and a genetic variant of isolated strains. Subgenotyping data must also be deposited [3]. Currently, the MeaNS2 database contains 59,176 measles virus nucleotide sequences of the sequencing window, 256 MF-NCR sequences, 169 *H* gene sequences, 167 complete genome sequences of the measles virus; based on the MeaNS2 information, a total of 70 genetic lineages and 5.5 thousand genetic variants have been isolated over the monitoring period [9].

The data on genetic characterization of measles viruses are deposited in MeaNS2; they provide the most complete and reliable information, which is used in monitoring of the pathogen circulation and is regularly expanded by all the laboratories participating in the WHO GMRLN.

The **aim** of this review is to provide up-to-date information on the current nomenclature and global genetic diversity of the measles virus with reference to literature sources and the MeaNS2 database.

Characterization of the measles virus

Based on the classification by the International Committee on Taxonomy of Viruses (ICTV), the measles virus

belongs to the family Paramyxoviridae, the genus *Morbillivirus*, the species *Morbillivirus hominis* [10]. The virus genome is represented by the single-stranded non-segmented negative-sense RNA; it is about 15.8 thousand nt long and encodes 8 proteins. Six non-overlapping structural genes have linear arrangement and encode 6 structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), fusion protein (F), hemagglutinin (H), polymerase (large protein L). The *P* gene encodes two additional non-structural proteins, C and V [11]. From the immunological perspective, the most important role belongs to transmembrane viral proteins – H and F as well as to the N protein that forms the ribonucleoprotein complex participating in RNA transcription and translation. N-protein-specific antibodies are produced early in infection; however, long-lasting immunity depends on transmembrane proteins of the measles virus. It has been found that the H protein mediates attachment of the virus to cellular receptors (CD150, nectin-4); the F protein is responsible for membrane fusion and viral genome entry into the cell. Hemagglutinin induces a strong immune response, being the target of neutralizing antibodies that play a critical role in development of post-infection and post-vaccination immunity [12, 13].

It has been found that the 150-amino-acid C-terminal domain of the N protein is the most variable among morbilliviruses [14]. Immunologically, viruses belonging to different genotypes, genetic lineages, or variants did not demonstrate any differences [15, 16].

Historical insight into genetic diversity of the measles virus

Studies of genetic diversity of the measles virus date back to the 1980s. The cumulative data provided the basis for the standardized measles virus nomenclature that was adopted in 1998 and incorporated genetic and geographic characteristics as well as phylogenetic relationships of the virus. At the meeting on measles elimination program, the WHO Expert Committee introduced a unified protocol for the designation of measles genotypes to integrate molecular and genetic monitoring into epidemiological surveillance practices [4].

In the late 1990s, during development and implementation of universal approaches to global molecular and epidemiological studies of the measles virus, it was found that viruses of different genotypes prevailed in different parts of the world. Based on the data available by 1998-2001, the global genetic diversity of the measles virus was represented by eight clades (each clade is designated by a letter of the Latin alphabet: from A to H) containing 15 subclade-genotypes, 11 of which were classified as active [4, 17]. By the time of establishment of the first unified measles virus nomenclature in 2001, inactive genotypes were represented by genotypes F, D1, E, and G. The term “inactive” (“extinct”) genotype means a genotype that has not been detected worldwide for 10 years and longer during monitoring [4].

The recommendations published in 2001 not only offered the first-time systematization and description of the measles virus genetic diversity across the world, but also introduced the unified designation for isolated viruses, which is still used in all countries involved in measles surveillance [17, 18].

The standard designation of measles viruses and their nucleotide sequences is in English and includes the following information [17]:

1. The source of the sequence – an isolate in cell culture (MVi) or a biological fluid sample from a patient with measles (MVs).

2. The geographic location where a measles case was reported. The designation of strains isolated in Russia traditionally includes the central city of the region.

3. The three-letter code of the country in the ISO-3166 format.

4. The week and year when the case was reported.

5. The number of the isolate if more than one per week. Special designation for sequences derived from subacute sclerosing panencephalitis (SSPE) cases; the source of importation if required.

Items 1 through 4 are required for identification of the virus. For example, designation MVi/Perm.RUS/12.09 means that the sequence was derived from the virus isolated in Perm in Russia during the 12th week in 2009.

The second revision of measles virus nomenclature was in 2003. The increased amount of data on the genetic identity of viruses isolated in different countries led to more specific designation of genotypes. Within eight clades, the following genotypes were specified: A, B1–B3, C1–C2, D1–D9, E, F, G1–G3, H1–H2. Out of 22 known genotypes, 16 genotypes were recognized as active in 2003; the list of inactive genotypes was extended, adding two more genotypes – B1 and B2 [19].

The next updating took place in 2005–2006; the 22 known genotypes of the measles virus were joined by one more genotype – D10, while genotype B2 recently detected in West Africa was removed from the list of inactive genotypes [20, 21].

Updated information about the genetic diversity of the virus was published in 2012, including the data on genotype D11 – the most recent 24th recognized genotype [3]. The last revision of the measles virus nomenclature was in 2015 **(Table)**. Based on the updated information, only 6 virus genotypes remain globally active: B3, D4, D8, D9, G3, H1. Considering that the virological surveillance and monitoring of the measles virus circulation had become a routine practice in 135 WHO member countries by the time of the last update on the global genetic diversity of the virus, the scientific community must have had reliable information to assign the other genotypes of wild-type viruses to extinct ones [3, 22].

Theoretically, new genotypes may still emerge. As specified in the measles virus nomenclature introduced by WHO in 2012, the requirements for a new genotype include the presence of N-450 and *H* gene sequences supported by the data from different cases, the availability of at least one virus isolate; epidemiological significance of the new genotype; the completed phylogenetic analysis including all the available sequences of the N-450 region and the *H* gene, not being limited to reference sequences; the tentative genotype must not form a cluster with

an internal ancestral node within the existing genotype; the branch belonging to the tentative genotype must have bootstrap support greater than 90% with the same topology of phylogenetic trees based on the N-450 and *H* gene sequences [3, 9, 22].

Subgenotyping of the measles virus for improving surveillance sensitivity

Subgenotyping methods used for identification of a genetic lineage and genetic variant are an integral part of high-quality epidemiological surveillance, having come into practice in 2012. Subgenotyping was initially used for genotypes that were widespread geographically and prevailed in the viral population for a long time. Subgenotyping methods used in epidemiological surveillance were first described for genotypes D4 (countries of Europe, 2007–2011) and B3 (countries of Africa, 2009–2011) [3]. Later, genetic lineages were also identified for other genotypes of the virus; by 2023, the identified lineages included 23 lineages of genotype B3, 10 lineages of genotype D4, 1 lineage of genotype D5, 2 lineages of genotype D6, 26 lineages

***Table*. Genotypes of measles virus, current nomenclature [9, 22]**
***Таблица*. Генотипы вируса кори, действующая номенклатура [9, 22]**

Genotype Генотип	Reference strain Референс-штамм	Last detected, year, country Последняя изоляция, год, страна	Status (active/inactive) Статус (активный/неактивный)
A (VAC)	MVi/Maryland.USA/0.54	2022 / 2022 г.	Active / Активный
B1	MVi/Yaounde.CMR/12.83	2008, France / 2008 г., Франция	Inactive / Неактивный
B2	MVi/Libreville.GAB/0.84	2011, France / 2011 г., Франция	Inactive / Неактивный
B3	MVi/New York.USA/0.94 MVi/Ibadan.NGA/0.97/1	Circulates globally since 2000s / Глобальная циркуляция с середины 2000-х гг.	Active / Активный
C1	MVi/Tokyo.JPN/0.84	Early 1990s / Начало 1990-х гг.	Inactive / Неактивный
C2	MVi/Maryland.USA/0.77 MVi/Erlangen.DEU/0.90	2004, United Kingdom / 2004 г., Великобритания	Inactive / Неактивный
D1	MVi/Bristol.GBR/0.74	1986, Japan / 1986 г., Япония	Inactive / Неактивный
D2	MVi/Johannesburg.ZAF/0.88/1	2005, Democratic Republic of the Congo/ 2005 г., Демократическая Республика Конго	Inactive / Неактивный
D3	MVi/Illinois.USA/0.89/1	2013, USA / 2013 г., США	Inactive / Неактивный
D4	MVi/Montreal.CAN/0.89	2020, India / 2020 г., Индия	Active / Активный
D5	MVi/Palau.PLW/0.93 MVi/Bangkok.THA/12.93/1	2015, China / 2015 г., Китай	Active / Активный
D6	MVi/New Jersey.USA/0.94/1	2007, Kazakhstan / 2007 г., Казахстан	Inactive / Неактивный
D7	MVi/Victoria.AUS/16.85 MVi/Illinois.USA/50.99	2003, United Kingdom / 2003 г., Великобритания	Inactive / Неактивный
D8	MVi/Manchester.GBR/30.94	Circulates globally since 2000s / Глобальная циркуляция с середины 2000-х гг.	Active / Активный
D9	MVi/Victoria.AUS/12.99	2019, Switzerland / 2019 г., Швейцария	Active / Активный
D10	MVi/Kampala.UGA/51.00/1	2005, Democratic Republic of the Congo / 2005 г., Демократическая Республика Конго	Inactive / Неактивный
D11	MVi/Menglian.Yunnan.CHN/47.09	2010, China / 2010 г., Китай	Inactive / Неактивный
E	MVi/Goettingen.DEU/0.71	1987, Germany / 1987 г., Германия	Inactive / Неактивный
F	MVs/Madrid.ESP/0.94 [SSPE]	1994, Spain / 1994 г., Испания	Inactive / Неактивный
G1	MVi/Berkeley.USA/0.83	1984, USA / 1984 г., США	Inactive / Неактивный
G2	MVi/Amsterdam.NLD/49.97	2001, Thailand / 2001 г., Таиланд	Inactive / Неактивный
G3	MVi/Gresik.IDN/18.02	2014, Israel / 2014 г., Израиль	Inactive / Неактивный
H1	MVi/Hunan.CHN/0.93/7	2019, China / 2019 г, Китай	Active / Активный
H2	MVi/Beijing.CHN/0.94/1	2003, Vietnam / 2003 г., Вьетнам	Inactive / Неактивный

of genotype D8, 2 lineages of genotype D9, 6 lineages of genotype H1 [9].

Measles virus lineages and their genetic variants are smaller taxonomic units compared to genotypes. The genetic variant is a sequence that differs at least by 1 nt from the original genotype or genetic lineage. When viruses belonging to the same genetic variant circulate in several countries for more than 2 years, the genetic variant can form an individual lineage. Each genetic lineage has a representative "designated strain", which, as a rule, has the same name as the first globally isolated strain [22].

Subgenotyping methods are designed to increase the sensitivity of virological monitoring during epidemiological surveillance. Subgenotyping of the measles virus provides a retrospective insight into the links in the epidemic chain and helps take adequate measures. There can be situations when several genetic variants of the measles virus co-circulate in the same area; then, the information that the pathogens belong to different genetic variants becomes critically important for differentiating of the transmission chains. Alternatively, the identification of identical genetic variants of the pathogen in isolated cases can provide a basis for their combination into a single outbreak (chain), provided that the chain is limited to an incubation period of maximum length (21 days). The measles incidence is analyzed annually across the country, taking genetic characteristics of isolated virus strains into consideration, constituting a key component in confirmation of successful elimination of measles or continuation of its endemic transmission.

Current data on geographic distribution of measles virus genotypes

Clade A viruses

Clade A includes vaccine strains: These are not only strains derived from the original Edmonston strain isolated in 1954 (Moraten, Schwarz, Edmonston-Zagreb, AIK-C strains), but also strains originating from wild-type viruses (Shanghai-191, Chanchun-47, CAM-70, Leningrad-16) [23–25]. The fact that most of the strains used for vaccines were isolated in the middle of the last century can serve as an indirect proof that genotype A had widespread occurrence in the pre-vaccination era. However, the data on the measles virus genetic characteristics, which were available at the time of development of the unified nomenclature, lead to the conclusion that all the cases of genotype A virus isolation from patients were associated with the recent vaccination, but not with the transmission of wild-type viruses [4, 9, 17].

Clade B viruses

Clade B viruses were originally common in African countries. Viruses of genotypes B1 and B2 had limited areas of circulation: Viruses of genotype B1 were detected only in Cameroon, while viruses of genotype B2 – in Gabon. All the currently available strains representing genotypes B1 and B2 were isolated in the 1980s. Genotype B3 viruses were reported to circulate not only in Central Africa, but also in West Africa (Gambia, Ghana, Nigeria) and East Africa (Kenya, Sudan) [4, 17].

Genotypes B1 and B2 are believed to be extinct. The last globally isolated genotype B1 virus was detected in France in 2008; then, there were no reports about its further transmission [26]. In 2011, also in France, the last strain belonging to the B2 genotype was isolated [27].

Genotype B3 was widespread throughout the African continent till the mid-2000s. It was described as endemic for African countries [20, 28, 29]. Later, genotype B3 viruses spread across the world, and currently actively circulate nearly in all countries; the number of records on nucleotide sequences of viruses of this genotype reaches 15,487. Genotype B3 is the only genotype in clade B, which has genetic lineages. The large number of lineages (23 lineages) can be explained by the long circulation of the genotype in various geographic regions. Based on the MeaNS2 data, genotype B3 genetic lineage MVs/Quetta.PAK/44.20 and genetic variants of other genetic lineages are in circulation in the world in 2023 [9].

Clade C viruses

Clade C measles viruses are represented by two genotypes – C1 and C2. Genotype C1 was endemic in Japan till the early 1990s [30] and in Spain [31]. As there was no consistent monitoring of the measles virus until the mid-2000s, we do not have any information about isolated viruses of this genotype in other regions. Measles viruses belonging to genotype C2 were endemic in Europe till the mid-2000s [9, 17, 31–33]. The last wild-type virus belonging to genotype C2 was isolated in Great Britain in 2004 [34]; it was also reported that measles virus C1 strain was isolated from a patient with SSPE in Germany in 2019 [35]. Currently, clade C is considered inactive.

Clade D viruses

The largest and most genetically diverse clade of measles viruses, clade D, includes 11 genotypes. Seven genotypes of the clade are currently not circulating; their transmission either was not documented and therefore viruses of some genotypes are known only retrospectively (genotype D1) or was interrupted (genotypes D2, D3, D7, D10, D11).

There are no data on infection with genotype D1 viruses during the period of active monitoring of the measles virus transmission. Strains of D1 – the oldest genotype in the clade – were isolated only from SSPE cases; all the patients had measles in 1960-1970, thus supporting the fact that the genotype was active during that period [22, 36]. Viruses belonging to genotype D2 were detected in South Africa where they circulated at least till 2005; their transmission in the African region involved occasional exportation of genotype D2 viruses to countries of Europe [17, 22, 37]. Genotype D3 was considered endemic for East Asia until 2003; viruses of this genotype were detected primarily in Japan and China [17, 30, 38]. Viruses of genotype D7 previously endemic in countries of the European region have not circulated since 2003 [9, 17, 39]. It is known that genotype D10 and D11 measles viruses have not been circulating for quite

a long time. Sporadic cases associated with genotype D10, were reported in Uganda, the Democratic Republic of Congo, and the United Kingdom during 2000–2005 [9, 40]. Genotype D11 caused a measles outbreak in China in 2009–2010 [41].

Measles virus genotypes, representatives of which have not been detected for more than 10 years during global monitoring, can be classified as extinct. However, some genotypes, though have not been detected for a relatively long time, are still considered active, remaining within the 10-year timeframe. For example, endemic in Japan and, possibly, in some other countries of East and Southeast Asia, genotype D5 represented by one genetic lineage MVs/Okinawa.JPN/37.06 was active till 2015; then its global transmission discontinued [9, 30, 42, 43]. Genotype D9 having worldwide occurrence since 2002 is represented by two genetic lineages: MVs/Bristol.GBR/13.05 and MVs/Yamanashi.JPN/51.12. Both lineages circulated primarily in countries of Europe; lineage MVs/Bristol.GBR/13.05 and its genetic variants were active till 2014; viruses belonging to lineage MVs/Yamanashi.JPN/51.12 were in circulation till 2019 [9].

By the time of the adoption of the first unified measles virus nomenclature, genotype D4 had been characterized by worldwide occurrence. In some countries, including Russia, genotype D4 measles viruses have been circulating for a long time [17, 31, 44–48]. The long-lasting and active global transmission of the genotype resulted in its divergence into 10 genetic lineages. Its latest strains belonging to genetic lineage MVs/Manchester.GBR/10.09 were isolated in India in 2020 during the global monitoring [9].

Currently, genotype D8 is the most active globally circulating genotype of viruses. The first strains of the genotype were isolated in the late 1990s; initially, the genotype was recognized as endemic for Africa and India [17]. However, in the later years, viruses of this genotype spread widely throughout the world, and are currently dominating, together with genotype B3, in the global incidence structure. The active transmission of the genotype led to the development of 26 genetic lineages. Based on the MeaNS2 data, two genetic D8 lineages: MVs/Patan.IND/16.19 and MVs/Victoria.AUS/6.11 and their genetic variants are circulating in 2023. In addition, in some countries, genetic variants from other lineages are of epidemiological significance [9].

Clade E and F viruses

During active global molecular and genetic monitoring of the measles virus, no wild-type viruses belonging to clades E and F were isolated; the identification of the clades was based on the viruses isolated from patients with SSPE [9, 17, 22, 44].

Clade G viruses

Clade G is represented by three genotypes; genotype G1 and G2 viruses have not been circulating since 2001. Previously, genotype G1 viruses were isolated in the United States, while genotype G2 viruses were endemic in Southeast Asia (Indonesia, Malaysia, Thailand) and circulated for a short time in Europe (Germany, the Netherlands) [9, 17, 43, 49].

Genotype G3, which was first isolated from measles cases in Southeast Asia in 2002, circulated at low epidemic levels in countries of the Western Pacific region, the United States, and Western Europe till 2014 [9].

Currently, clade G of measles viruses is not circulating; most likely, it will be classified as extinct.

Clade H viruses

Clade H including two genotypes is recognized as endemic in countries of East Asia, primarily in China [17]. Both genotypes – H1 and H2 – were widespread in China, Vietnam, and South Korea, being actively imported by other countries [9, 17, 46, 50–53]. Genotype H1 is represented by 6 genetic lineages, one of which – lineage MVs/Henan.CHN/9.16/7 – had been active until 2019. There are no data on measles cases associated with clade H genotypes after 2019; since 2020, the incidence in the countries previously endemic for this genotype has been associated with genotypes D8 and B3 [9].

Global subgenotypic characterization of the measles virus

The period of low measles incidence due to restrictive measures aimed at combating the novel coronavirus infection has been followed by a surge in global measles cases. According to the WHO estimates, only 116 cases of measles were reported in Europe in 2021 [54], in 2022 – 903 cases [55], and over 4 months in 2023 – a total of 3,832 cases were reported [56].

For several years, there has been a steady trend towards globalization of the circulation of measles viruses belonging to two genotypes: B3 and D8. In 2021–2023, all the reported cases of measles were caused by viruses of these genotypes [9]. When only two genotypes are represented by circulating viruses, the global genetic diversity cannot be evaluated without subgenotypic characterization of viruses isolated in the world, as molecular and epidemiological studies cannot be based only on the identification of the genotype.

Large-scale measures aimed at infection control and successful measles elimination by many countries led to significant changes in the genetic landscape of the virus. Previously the genetic geography of the virus was understood through the clearly defined areas of circulation of different genotypes; however, over time, the genetic diversity of measles viruses has narrowed down as a natural result of the efforts invested by the global health community in control and elimination of the disease.

The current view of the genetic diversity of measles viruses includes not only genotypes, but also genetic lineages within genotypes as well as genetic variants of these lineages. Lineages and variants of the measles virus are operational taxonomic units used for characterization of the virus circulation during epidemiological surveillance since 2012, having replaced genotypes [3]. Currently, the MeaNS2 database has information about 70 genetic lineages and 5.5 thousand genetic variants of the measles virus. Such approach to the genetic diversity has

been adopted due to the epidemiological surveillance of measles and mandatory laboratory tests required for confirmation of the disease; each genetic variant of the virus must be documented and a unique number – DSid (distinct sequence id) must be assigned in MeaNS2 to each new variant.

In 2021–2023, global measles cases were caused by viruses belonging to genotypes D8 and B3. Based on the available data, 1,411 strains belong to genotype D8 and 1,469 strains belong to genotype B3. While in quantitative terms the proportions of cases distributed between genotypes are approximately equal, the divergence level is significantly higher in genotype B3, which was represented by 5 genetic lineages and 319 genetic variants. Genotype D8 is represented by 6 genetic lineages and 136 genetic variants of the virus.

In 2021–2023, lineages D8 MVs/Patan.IND/16.19, MVs/Victoria.AUS/6.11 and MVs/Gir Somnath. IND/42.16 have the greatest epidemiological significance by the time of circulation and the number of isolated strains. Due to active transmission in India, viruses of lineages MVs/Patan.IND/16.19 and MVs/Victoria. AUS/6.11 were repeatedly exported, causing measles outbreaks in many countries that are still affected by them. The transmission of viruses belonging to lineage MVs/Gir Somnath.IND/42.16 discontinued in the middle of 2021; the last large measles outbreak associated with the lineage was reported in Brazil.

Among 228 genetic variants of measles viruses belonging to genotype D8, only 6 contributed significantly to the incidence structure. Long-lasting transmission and wide geographic distribution are generally not typical of genetic variants of the virus, though their possibility exists in the settings of multiple importation. It is known that genetic variant 8248, which is related to lineage MVs/Patan.IND/16.19, was first isolated during the measles outbreak in Tajikistan, which began in 2021. Having been imported from Tajikistan, the genetic variant got to Russia where in 2022–2023 the number of measles cases associated primarily with genetic variant 8248 increased significantly. The circulation of the above variant is maintained in Russia mainly through continued importation of measles from Tajikistan. In addition, sporadic measles cases associated with this variant were reported in Kazakhstan, the Czech Republic, the United Kingdom, and the United States in 2023.

Another genetic variant of lineage D8 MVs/Patan.IND/16.19 – 8348 – circulated in India throughout 2022, and later was also isolated from patients with measles in Sweden and New Zealand. Long-circulating genetic variants related to other lineages were also detected in some countries, mostly in India. Variant 8278 – related to lineage D8 MVi/Hulu Langat.MYS/26.11, variant 8318 – MVi/Delhi.IND/01.14/06, variant 8350 – MVs/London.GBR/21.16/2. Long-lasting local transmission of genetic variants caused their dissemination to other regions, mainly to Western European countries and North America.

Viruses of genetic lineage B3 MVs/Quetta.PAK/44.20, which were first reported in 2020, dominate in the genetic distribution of the genotype and have widespread occurrence mostly in South (Pakistan, Afghanistan) and West Asia (Saudi Arabia, Iran, UAE). The active transmission of lineage MVs/Quetta.PAK/44.20 led to emergence of genetic variants 6382, 6464, 6493 that quickly secured their positions in the population. These virus variants circulated for more than one year in regions where their ancestral lineage was prevalent.

In 2020–2023, genetic variant 5631 originating from lineage B3 MVs/Kansas.USA/1.12 significantly contributed to the incidence of measles in different countries. The variant circulates in Indonesia and Saudi Arabia, though sporadic imported measles cases were reported in Turkey and the Netherlands.

Conclusion

The efforts of the global health community aimed at measles control and elimination have led to a gradual reduction in the genetic diversity of the virus. Since 2021, the global genetic landscape of the pathogen has been represented only by the genotype B3 and D8 viruses; currently, the accurate phylogeographic clustering of measles genotypes is out of the question. Subgenotyping has become an important tool of molecular and epidemiological surveillance in the setting of declining diversity and, consequently, the number of genotypes, on the one hand, and the growing number of genetic variants within circulating genotypes, on the other hand. Identification of N-450 sequences in measles viruses and phylogenetic analysis of the data using the MeaNS2 database are essential components of the WHO GMRLN monitoring of virus circulation and locating of circulation areas of genetic lineages and genetic variants. Identification of new lineages and their genetic variants is of critical importance for epidemiological surveillance and for estimation of the status of measles elimination.

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