

Chapter 7

Molecular Epidemiology of Measles Virus

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Contents

Introduction	130
Laboratory Surveillance for Measles	130
Background and Methods	131
Utility of Molecular Epidemiology	131
Standard Methods for Molecular Epidemiology of Measles	132
Data Reporting and Surveillance Guidelines	133
Virus Isolation and Clinical Samples	135
New Molecular Techniques	135
Measles Vaccines and Antigenic Variation	136
SSPE	136
Global Distribution of Measles Genotypes	137
Genotypes in Areas with Endemic Measles or Frequent Outbreaks	138
Measles Elimination	141
Measles Reintroduction	142
Mapping Transmission Pathways	143
Challenges	143
References	144

Abstract Genetic characterization of wild-type measles viruses provides a means to study the transmission pathways of the virus and is an essential component of laboratory-based surveillance. Laboratory-based surveillance for measles and rubella, including genetic characterization of wild-type viruses, is performed throughout the world by the WHO Measles and Rubella Laboratory Network, which serves 166 countries in all WHO regions. In particular, the genetic data can help confirm the sources of virus or suggest a source for unknown-source cases as well as to establish links, or lack thereof, between various cases and outbreaks. Virologic surveillance has helped to document the interruption of transmission of endemic measles in some regions. Thus, molecular characterization of measles viruses has provided a valuable tool for measuring the effectiveness of measles

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control programs, and virologic surveillance needs to be expanded in all areas of the world and conducted during all phases of measles control.

Introduction

The widespread use of live attenuated vaccines for measles has dramatically reduced the worldwide incidence of measles. The disease has been eliminated in the Western hemisphere (Region of the Americas) since 2000 and the European, Eastern Mediterranean, and Western Pacific Regions of the World Health Organization (WHO) have set elimination goals for the near future (Anonymous 2005d). Despite these successes, measles remains endemic in many developing countries. Measles remains a major cause of childhood morbidity and mortality, accounting for an estimated 345,000 deaths in 2005, 87% of which were in the African and South East Asian Regions of WHO (Wolfson et al. 2007). Subsequently the African and Southeast Asian Regions have implemented a strategy of measles mortality reduction. Even counties that have measles vaccination programs experience outbreaks because of the accumulation of susceptible individuals and the constant threat of viral importations from endemic areas. Maintaining measles elimination requires achieving and maintaining very high levels of population immunity and good laboratory-based surveillance to rapidly detect and control periodic outbreaks.

Laboratory Surveillance for Measles

When the incidence of measles is low, surveillance based on clinical presentation of cases has low sensitivity and specificity. Therefore, an essential component of any measles control program is laboratory-based surveillance to provide confirmation of cases and genetic characterization of circulating wild-type viruses. Routine laboratory confirmation of suspected cases is based on detection of measles-specific IgM in a single blood sample taken as soon as possible after rash onset. In some cases, molecular techniques such as RT-PCR to detect viral RNA are used to complement serologic testing. Another important aspect of laboratory surveillance for measles, and the subject of this chapter, is the genetic characterization of circulating wild-type viruses to support molecular epidemiologic studies (World Health Organization 2005a, Anonymous 2005b; Rota and Bellini 2003).

Laboratory-based surveillance for measles and rubella is performed throughout the world by the WHO Measles and Rubella Laboratory Network (LabNet). This network provides for standardized testing and reporting with labs serving 166 countries in all WHO regions. A system for monitoring indicators of laboratory performance, including laboratory accreditation, and proficiency testing has been implemented in all regions (World Health Organization 2005a, Anonymous 2005b). The LabNet also supports genetic characterization of currently circulating strains of measles viruses and LabNet has been responsible for standardization of the nomenclature and

laboratory procedures that are used to describe the genetic characteristics of wild-type measles and rubella viruses (World Health Organization 1998, 2001a, 2001b, 2003, 2005b, 2005c, 2006, 2007a). This standardization has allowed sharing of virologic surveillance data between laboratories and permitted efficient communication of this data throughout the measles control programs (World Health Organization 2007b).

Background and Methods

Measles virus is an RNA virus in the genus *Morbillivirus* within the family *Paramyxoviridae*. Although other members of the genus infect various animal species, measles only infects humans and non-human primates. The negative-sense, single-stranded RNA genome is contained within a helical nucleocapsid in the virion. The genome consists of 15,894 nucleotides, which code for the six structural proteins, the nucleoprotein (N), phosphoprotein (P), matrix (M), fusion (F), hemagglutinin (H), and large protein (L), and two nonstructural proteins, C and V (Griffin 2001). Although measles is a monotypic virus, genetic and antigenic variation has been detected in wild-type viruses (Rota et al. 1992; Tamin et al. 1994; Taylor et al. 1991). The nucleotide sequences of the L, M, and F genes (Bankamp et al. 1999; Rota et al. 1994b) are much less variable than the sequences of the N, P, and H genes, which have 7%–10% variability (Bankamp et al. 2008; Rima et al. 1997; Rota et al. 1992). The N and H gene sequences are most commonly used for genetic characterization of wild-type viruses. In particular, one of the most variable parts of the measles genome is the 450-nucleotide region, which codes for the COOH-terminal 150 amino acids the N protein, where nucleotide variability can approach 12% between wild-type viruses (Xu et al. 1998).

Utility of Molecular Epidemiology

The combination of molecular epidemiologic techniques and standard case classification and reporting provides a very sensitive means to describe the transmission pathways of measles. In particular, sequence data can help confirm the sources of virus or suggest a source for unknown-source cases as well as to establish links, or lack thereof, between various cases and outbreaks. Virologic surveillance is especially beneficial when it is possible to observe the change in viral genotypes over time in a particular country or region because this information, when analyzed in conjunction with standard epidemiologic data, has helped to document the interruption of transmission of endemic measles. Thus, molecular characterization of measles viruses has provided a valuable tool for measuring the effectiveness of measles control programs (Mulders et al. 2001; Riddell et al. 2005; Rota et al. 1996, 2002; Rota and Bellini 2003).

Virologic surveillance can also help to classify suspected cases as vaccine reactions. A small proportion of measles vaccine recipients experience rash and fever 10–14 days following vaccination (Griffin 2001). During outbreaks, measles vaccine

is administered to help control the outbreak, and in these situations, vaccine reactions may be mistakenly classified as measles cases. Since serologic methods cannot distinguish between a vaccine-induced antibody response and antibodies derived from natural disease, molecular characterization of viral isolates provides a method to confirm whether vaccine or wild-type measles virus caused the rash and fever. Molecular information is also useful for analyzing unusual or severe cases of measles infection, suspected adverse events following vaccination, and severe sequelae of measles infection such as subacute sclerosing panencephalitis (SSPE) (Bellini et al. 2005). SSPE will be discussed in more detail in Sect. 2.7.

Standard Methods for Molecular Epidemiology of Measles

Before 1998, there was no uniform nomenclature or analysis protocol to describe the genetic characteristics of wild-type measles viruses. In 1998, the WHO made recommendations for a standard nomenclature for naming strains, describing genotypes, and conducting sequence analysis so that genetic data would be directly comparable between laboratories. These recommendations have been updated periodically since 1998 (World Health Organization 1998, 2001a, 2001b, 2003, 2005b, 2005c, 2006, 2007a). WHO recommends that the 450 nucleotides coding for the COOH-terminal 150 amino acids of N are the minimum amount of sequence data required for genotyping a measles virus isolate or clinical specimen. Complete H gene sequences should be obtained from representative strains or if a new genotype is suspected. Phylogenetic analysis of the H gene sequences provides additional support for the genotype assignment while monitoring amino acid substitutions that could affect antigenicity.

For molecular epidemiologic purposes, the genotype designations are considered the operational taxonomic unit, while related genotypes are grouped by clades. WHO currently recognizes eight clades designated A, B, C, D, E, F, G, and H. Within these clades, there are 23 recognized genotypes, designated A, B1, B2, B3, C1, C2, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, E, F, G1, G2, G3, H1, and H2. Some clades contain only one genotype and, in such cases, the genotype designation is the same as the clade name. Other clades contain multiple genotypes and are designated by using the clade letter (in uppercase) and genotype number. Several of the genotypes—B1, E, F, G1, D1—appear to be extinct or inactive since representatives of these genotypes have not been isolated for at least 15 years. However, the sequences of the inactive genotypes are maintained in the set of WHO reference sequences for completeness (World Health Organization 2005b). With the exception of genotype F which is based only on sequences derived from a case of SSPE, all of the genotypes have an assigned reference strain (Table 7.1, Fig. 7.1) chosen to represent the earliest isolation of virus from each genotype. Sequences from recent viral isolates are then compared to the set of WHO reference sequences, which are available from GenBank (World Health Organization 2005b) and the WHO Strain Banks, to determine the genotype. WHO has established guidelines based on both molecular biologic and epidemiologic criteria for the designation of new genotypes (World Health Organization 2001b, 2003, 2005b).

Table 7.1 Reference strains to be used for genetic analysis of wild-type measles viruses: 2008

Genotype	Status ^a	Reference strains (MVi) ^b	H gene accession ^c	N gene accession
A	Active	Edmonston-wt.USA/54	U03669	U01987
B1	Inactive	Yaounde.CAE/12.83 “Y-14”	AF079552	U01998
B2	Active	Libreville.GAB/84 “R-96”	AF079551	U01994
B3	Active	New York.USA/94 Ibadan.NIE/97/1	L46752 AJ239133	L46753 AJ232203
C1	Active	Tokyo.JPN/84/K	AY047365	AY043459
C2	Active	Maryland.USA/77 “JM” Erlangen.DEU/90 “WTF”	M81898 Z80808	M89921 X84872
D1	Inactive	Bristol.UNK/74 (MVP)	Z80805	D01005
D2	Active	Johannesburg.SOA/88/1	AF085198	U64582
D3	Active	Illinois.USA/89/1 “Chicago-1”	M81895	U01977
D4	Active	Montreal.CAN/89	AF079554	U01976
D5	Active	Palau.BLA/93 Bangkok.THA/93/1	L46757 AF009575	L46758 AF079555
D6	Active	New Jersey.USA/94/1	L46749	L46750
D7	Active	Victoria.AUS/16.85 Illinois.USA/50.99	AF247202 AY043461	AF243450 AY037020
D8	Active	Manchester.UNK/30.94	U29285	AF280803
D9	Active	Victoria.AUS/12.99	AY127853	AF481485
D10	Active	Kampala.UGA/51.00/1	AY923213	AY923185
E	Inactive	Goettingen.DEU/71 “Braxator”	Z80797	X84879
F	Inactive	MVs/Madrid.SPA/94 SSPE	Z80830	X84865
G1	Inactive	Berkeley.USA/83	AF079553	U01974
G2	Active	Amsterdam.NET/49.97	AF171231	AF171232
G3	Active	Gresik.INO/17.02	AY184218	AY184217
H1	Active	Hunan.CHN/93/7	AF045201	AF045212
H2	Active	Beijing.CHN/94/1	AF045203	AF045217

^a Active genotypes that have been isolated within the past 15 years^b WHO name; other names that have been used in the literature appear in quotation marks^c Sequences available at GenBank (<http://www.ncbi.nlm.nih.gov>) or from WHO strain banks
Reproduced from World Health Organization 2005b

Data Reporting and Surveillance Guidelines

Through the efforts of LabNet, virologic surveillance has expanded on a global scale. Information on circulating genotypes has been reported from almost every country with endemic or widespread measles. Genbank contains over 1500 partial

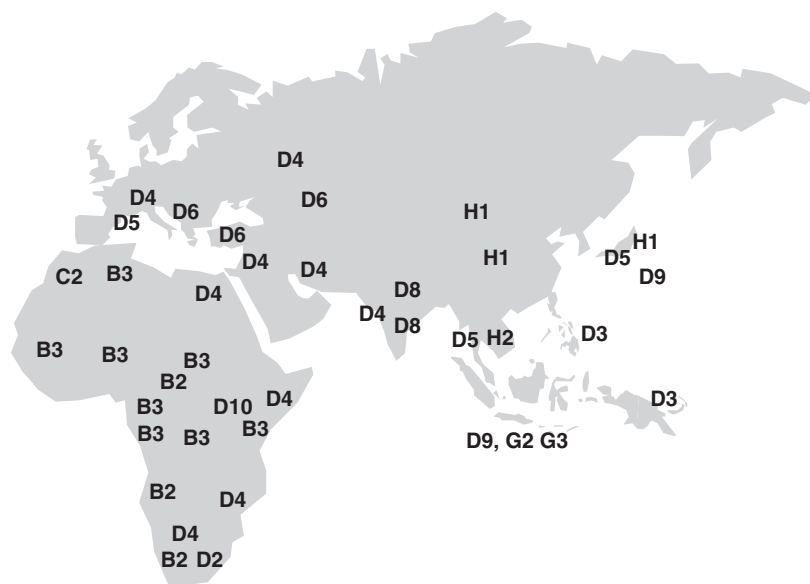


Fig. 7.1 Global distribution of measles genotypes: 1995–2008. Figure shows geographical distribution of measles genotypes for regions that have not yet eliminated measles transmission. Figure is adapted from the Weekly Epidemiologic record of WHO (2006). Figure is based on surveillance conducted between 1995 and 2008. The region of the Americas and Australia are not shown because these countries have eliminated measles and have detected multiple genotypes from imported cases. Because countries in the European Region have a complex pattern, only the genotypes associated with major outbreaks in 2005–2008 are indicated on the map

N gene sequences with over 80% of these sequences reported since 2000 (Rota and Tian, unpublished observations). WHO maintains a database of genotype information that is reported from national and regional laboratories within LabNet. Recently, it has become apparent that comparison of the sequence information is as important as having the genotype designation. Many genotypes contain multiple co-circulating lineages and assignment of a viral sequence to one of these lineages allows for more accurate mapping of transmission pathways. For this reason, rapid exchange of both genotype and sequence information on a global scale is critical. Databases that allow rapid exchange of sequence information are being developed by the Global Specialized Laboratories within LabNet (World Health Organization 2005a).

Surveillance guidelines recommend that countries involved in measles elimination collect appropriate specimens for virus isolation from every chain of transmission, while countries involved in outbreak-control and mortality reduction obtain representative specimens from measles outbreaks (World Health Organization 2007b). It is important to conduct virologic surveillance before accelerated control measures are initiated so that it will be possible to study the pattern of genotypes present both before and after vaccination campaigns. The best samples for virologic surveillance are throat or nasopharyngeal swabs or urine sediments since they can be used for virus isolation as well as direct RT-

PCR. Peripheral blood mononuclear cells are a good source of virus, but this sample requires specialized laboratory techniques and biosafety procedures that are not available throughout the laboratory network. RNA from measles virus can be detected in both oral fluid samples and dried blood spots on filter paper and these samples have been used to expand virologic surveillance when the collection and transportation of the standard samples is not logistically feasible. It is noteworthy that the United Kingdom has used oral fluid for routine measles surveillance for the last decade and greatly expanded their molecular surveillance capabilities. In all cases, it is imperative to obtain the sample for virologic surveillance as soon as possible after onset of rash to maximize chances of isolating virus or detecting RNA (World Health Organization 2007b).

Virus Isolation and Clinical Samples

The Vero/hSLAM cell line is now recommended for routine isolation of measles in the WHO laboratory network. These cells are Vero cells that have been transfected with a plasmid encoding the gene for the human SLAM (signaling lymphocyte-activation molecule) protein (Ono et al. 2001). SLAM has been shown to be a receptor for both wild type and laboratory-adapted strains of measles. The sensitivity of Vero/hSLAM cells for isolation of measles virus is equivalent to that of B95a cells (Kobune et al. 1990) and measles infection of Vero/hSLAM results in the characteristic CPE, syncytium formation. The advantage of the Vero/hSLAM cells compared to B95a cells is that they are not persistently infected with Epstein-Barr virus and therefore are not considered hazardous material. This provides a significant safety advantage for laboratory workers and greatly facilitates international shipments. Vero/hSLAM cells can also be used to isolate rubella viruses from clinical samples with a sensitivity that is similar to that of standard Vero cells.

Though virus isolation is encouraged, many laboratories use reverse transcriptase-polymerase chain reaction (RT-PCR) to amplify measles RNA directly from clinical specimens. The use of real-time RT-PCR assays has greatly improved sensitivity (Hubschen et al. 2008; Hummel et al. 2006).

New Molecular Techniques

Though viral genotypes are assigned based on analysis of sequence data, other techniques such as restriction fragment length polymorphism and heteroduplex mobility assays have been proposed (Kreis et al. 1997; Kremer et al. 2007; Mulders et al. 2003). However, it is doubtful that these methods would provide the level of sensitivity required to accurately map transmission pathways. Array-based techniques have been used for genotyping, but these techniques are more costly and technically challenging than standard sequencing assays (Neverov et al. 2006). A potential advantage to the array-based techniques would be the ability to rapidly obtain more sequence information from selected viral isolates or samples.

Measles Vaccines and Antigenic Variation

Sequence analyses have shown that all of the measles vaccine strains are representatives of genotype A (Parks et al. 2001a, 2001b; Rota et al. 1994a). This includes both vaccines derived from the original Edmonston isolate of 1954 (e.g., Moraten, Schwarz, Edmonston-Zagreb, AIK-C) as well as vaccines derived from other wild-type viruses isolated during the 1950s and 1960s in China and Japan (e.g., Shanghai-191, Chanchun-47, CAM-70). While this suggests that genotype A viruses may have had a wide distribution in the pre-vaccine era, it is also possible that genotype A viruses were more frequently detected because they were easier to isolate in the cell culture systems available at the time. There are few samples or viruses from the pre-vaccine era that are available for genetic analysis. However, one study detected viruses with sequences in genotypes C2 and E in samples obtained during the pre-vaccine era in Denmark (Christensen et al. 2002).

Genotype A viruses have been isolated from a few sporadic measles cases in the last 10 years (Wairagkar et al. 2002), but there have been no reports that this genotype has been associated with any large outbreaks. Though it is possible that wild-type genotype A viruses are still circulating, there is a strong likelihood that the more recently detected genotype A viruses are vaccine viruses or laboratory contaminants. Efforts are underway to attempt to identify a set of genetic markers to distinguish wild-type, genotype A viruses from vaccine viruses.

The detection of genetic variation within wild-type measles viruses has led to the suggestion that these viruses have antigenic characteristics that allow them to circulate more efficiently in the presence of vaccine-induced immunity. Although antigenic differences between measles viruses from the various genotypes have been detected by using monoclonal antibodies and polyvalent antiserum (Giraudon et al. 1988; Santibanez et al. 2002, 2005; Tamin et al. 1994), contemporary wild-type viruses are neutralized by polyclonal antiserum to the vaccine virus (Santibanez et al. 2005; Xu et al. 1998). More importantly, measles vaccination programs, when properly administered, have been exceptionally successful in all parts of the world irrespective of the endemic genotype of wild-type virus. Studies are in progress to explore the potential for biologic differences between measles viruses from different lineages.

The publication of the structure of the H protein, the major target of neutralizing antibodies, has allowed fine mapping of the antigenic sites on the molecule (Colf et al. 2007; Hashiguchi et al. 2007). The structural model shows that one of the regions that is accessible to antibody recognition includes the SLAM binding site and conservation of these key residues may account for the monotypic nature of the virus (Hashiguchi et al. 2007). Analysis of the amino acid sequences of the measles H gene show weak, if any, evidence for selective pressure (Woelk et al. 2001).

SSPE

SSPE, also called Dawson's encephalitis, is a persistent measles infection of the central nervous system. SSPE is a progressive, invariably fatal, encephalopathy

characterized by personality changes, mental deterioration, involuntary movements, muscular rigidity, and death. SSPE usually begins 4–10 years after the patient has recovered from naturally acquired measles. Successful isolation of measles virus from brain and lymphoid tissues of SSPE patients (Horta-Barbosa et al. 1969, 1971) clearly established measles virus as the etiologic agent of the disease. However, the introduction of the live-attenuated measles vaccine raised concerns that the vaccine virus might either cause, or in some manner influence the frequency of SSPE, and led to formation of SSPE registries in a number of countries. Epidemiologic studies demonstrated a dramatic decrease in uncomplicated measles as well as the frequency of SSPE (Halsey et al. 1980).

Molecular characterization of measles virus nucleic acid sequences derived from brain biopsy or autopsy has identified wild-type measles sequences with few exceptions, and not those of the vaccine strains (see review by Campbell et al. 2007). Few genotype A virus sequences have been identified (Cattaneo et al. 1989), and it is interesting that those that have been identified were from the first few SSPE isolates ever obtained. Ironically, it was suggested that Halle, the measles isolate believed to provide direct evidence for defining measles involvement in SSPE, was likely a vaccine virus laboratory contaminant. Halle virus grew very well in cell culture, a characteristic unlike any other subsequent SSPE isolate (Rima et al. 1995a). Because genotype A wild-type viruses were widely circulating in the pre-vaccine era, it is difficult to say with certainty that Halle or any other genotype A virus was not the source of infection resulting in SSPE.

Measles virus genotypes found in association with SSPE clinical specimens reflect the sequences of those viruses that circulated in the geographic region where the patients acquired natural infection. For example, the measles resurgence occurring from 1989–1992 in the United States was dominated by measles virus belonging to genotype D3. Subsequent characterization of measles sequences associated with SSPE cases over the following 5–12 years identified only genotype D3 sequences. No vaccine sequences were identified from tissues of SSPE patients, regardless of the fact that literally millions of doses of measles containing vaccine were administered over the resurgence period (Bellini et al. 2005). This and other recent studies have clearly demonstrated that measles vaccine virus is not involved in the genesis of SSPE and that the use of measles vaccine not only is beneficial in preventing acute measles, but has all but eliminated SSPE from the United States (Bellini et al. 2005; Jin et al. 2002).

Global Distribution of Measles Genotypes

Virologic surveillance is now well established in all WHO regions. Though surveillance in some areas is still not adequate, a global picture has emerged (World Health Organization 2006). In general, three patterns of measles genotype distribution have been described. In countries that still have endemic transmission of measles, the majority of cases are caused by several endemic genotypes that are distributed geographically (Fig. 7.2). In these cases, multiple co-circulating lineages within the

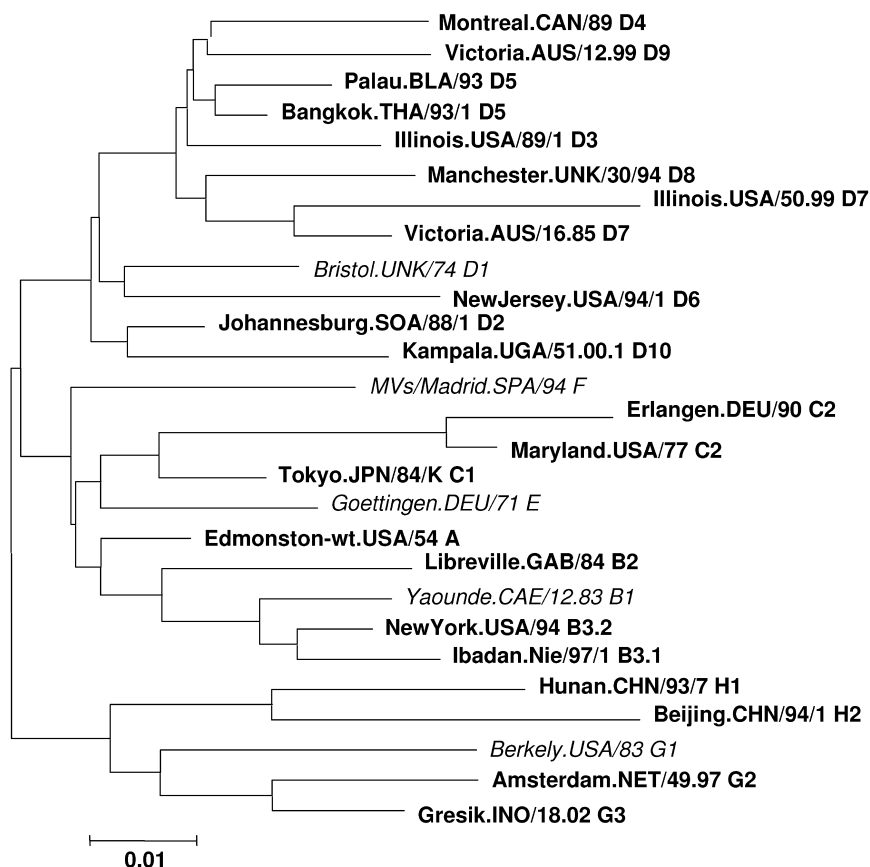


Fig. 7.2 Phylogenetic tree showing the WHO reference strains. Tree is based on the sequences of the N genes

endemic genotype or genotypes are present. In countries that have eliminated measles, the small numbers of cases are caused by a number of different genotypes that reflect various sources of imported virus and suggest the lack of sustained transmission of an endemic genotype or genotypes. The third pattern occurs in countries or regions that have had very good measles control but are experiencing an increase in the numbers of susceptible individuals because of failure to maintain universally high vaccination coverage rates. In this situation, reintroduction of measles usually results in a large outbreak associated with a single genotype of virus with nearly identical sequences.

Genotypes in Areas with Endemic Measles or Frequent Outbreaks

Viral surveillance has improved substantially in recent years and, even though surveillance is still incomplete, at least a few viral isolates have been obtained from most

countries to provide baseline data (World Health Organization 2006). In countries with endemic measles, there is a geographic distribution of genotypes. Some countries have more than one endemic genotype and frequently multiple, co-circulating lineages of virus are present within a genotype, indicative of multiple chains of transmission.

Although the WHO African Region has made substantial progress with reducing measles mortality since 1999 (Wolfson et al. 2007), many African countries have endemic measles and several genotypes have been detected. Clade B viruses are endemic in the central and western parts of sub-Saharan Africa, and analysis of a large number of measles isolates from Nigeria, Ghana, the Gambia, Cameroon, and Sudan has supported the division of clade B into three genotypes: B1, B2, and B3 (World Health Organization 2006; El Mubarak et al. 2002; Hanses et al. 1999; Outlaw et al. 1997; Truong et al. 2001). Genotype B3 has been divided into two clusters. Genotype B3, cluster 1 viruses have been isolated from Cameroon, Ghana, and Nigeria, and as far east as Sudan, Kenya, and Tanzania, suggesting that clade B viruses are widely distributed throughout Africa (El Mubarak et al. 2002). The circulation of genotype B3 cluster 2 viruses appears to be more limited to western Africa (Kouomou et al. 2002). Genotype B2 was considered inactive since, until recently, no representative viruses had been isolated since 1984. However, genotype B2 viruses were detected in southeastern Africa in 2002–2003 primarily in association with cases and importation from Angola and in the Central African Republic (Gouandjika-Vasilache et al. 2006; Smit et al. 2005). This reemergence of what was thought to be an inactive genotype was likely the result of surveillance gaps in some countries in central Africa.

Genotypes D2 and D4 have been the most frequently detected genotypes in the southern part and eastern parts of the African continent (Kreis et al. 1997; Mbugua et al. 2003; Nigatu et al. 2001), though more recent outbreaks in Kenya, Somalia, and Tanzania have been caused by genotype B3 viruses (Rota et al. 2006). A new genotype, D10, was initially detected in Uganda in 2000 and has been detected in mostly central African countries (World Health Organization 2006; Muwonge et al. 2005).

The northern African countries of Tunisia, Libya, and Algeria have detected genotype B3 presumably imported from sub-Saharan countries. Morocco has also reported continued circulation of genotype C2, once one of the prevalent genotypes in Western Europe (Alla et al. 2002, 2006; Waku-Kouomou et al. 2006). Genotype D4, the most prevalent genotype detected in the Middle East and the Arabian Peninsula (Djebbi et al. 2005), has been also reported in Egypt (2006).

Measles is endemic on the Indian subcontinent. Genotype D4 and D8 viruses have been isolated in India and Nepal, and genotype D4 was detected in Pakistan (Anonymous 2001b; Truong et al. 2001; Wairagkar et al. 2002). Genotype D4 and D8 viruses have also been detected in measles cases imported into the United States from both Pakistan and India (Rota et al. 1998, 2002). Recently, genotype D7 was detected in India (Vaidya et al. 2008). This genotype had been one of the most frequently detected genotypes in Europe in the early part of the decade. The recent detection in India suggests that India may have been the original source of genotype D7 in Europe, but expanded virologic surveillance in India is needed to establish the extent of circulation of genotype D7.

Extensive virologic surveillance in Japan demonstrated a succession of genotypes since surveillance activities began there in the early 1990s. Genotypes D3 and

D5 had been co-circulating in Japan for most of the 1990s (Katayama et al. 1997; Kubo et al. 2003; Sakata et al. 1993; Takahashi et al. 2000; Yamaguchi 1997) and genotype D5 viruses had been associated with many measles cases imported from Japan (Rota et al. 1998, 2002). More recently, Japan has experienced large outbreaks associated with genotypes D9 and H1 (Kubo et al. 2002; Nakayama et al. 2003; Zhou et al. 2003). In 2007, genotype D5 was apparently reintroduced in Japan and was associated with large outbreaks (Morita et al. 2007).

Elsewhere in Asia, sequence analysis of wild-type measles viruses isolated in throughout the People's Republic of China show widespread distribution of a single genotype of virus, H1, since 1993 (Xu et al. 1998; Zhang et al. 2007). Sequence analysis of over 300 samples obtained throughout the country has established that genotype H1 is clearly the endemic genotype in China. Viruses that were indistinguishable from the Chinese genotype H1 viruses were isolated during the outbreak of measles in Korea during 2000–2001 (Na et al. 2001, 2003) and were associated with imported cases in a number of countries. However, endemic circulation of genotype H1 appears to be restricted to China. Wild-type measles viruses in Vietnam are also classified as clade H, but they are sufficiently different from the Chinese viruses to be designated as a separate genotype, H2 (Liffick et al. 2001). It is interesting to note that wild-type measles viruses isolated in Thailand and Cambodia are in genotype D5 (Horm et al. 2003; Rota et al. 1998) and more closely related to viruses circulating in Japan than to viruses circulating in other parts of Asia.

Until 1997, the only measles viruses representing clade G had been isolated in 1983, and this clade was considered to be inactive. In 1997, a virus belonging to clade G was isolated from an Indonesian child who was being treated at a Dutch hospital. The H and N sequences of this virus were sufficiently different from the reference strain for it to be considered a new genotype (G2) within clade G (de Swart et al. 2000). Viruses belonging to genotype G2 have recently been isolated in Indonesia and Malaysia (Rota et al. 2000). In addition, viruses from genotypes G2 and G3 have been isolated in Indonesia and East Timor. RT-PCR and sequence analyses of clinical specimens obtained from measles cases imported into Australia confirmed that G3 was present in East Timor. Genotypes G2, G3, and D9 appear to be the endemic genotypes in Indonesia, East Timor, and possibly Malaysia (Chibo et al. 2002).

In some cases, the circulation of a genotype in a particular country has not been verified by virologic surveillance in the source country but was inferred based upon a consistent pattern of importations. For example, although genotype D3 viruses have never been isolated in the Philippines, there have been several instances of genotype D3 being detected in measles cases imported into the United States from the Philippines (Rota et al. 1996, 1998, 2002). In each of these cases, standard case investigation confirmed that the individuals were traveling in the Philippines during the incubation period.

Because of relatively low vaccination coverage rates in some countries and the constant importation of measles from endemic regions in Asia and Africa, European countries have frequent measles outbreaks. Europe has also experienced rapid change in circulating genotypes. In the early part of this decade, genotypes C2, D6, and D7 were most frequently detected (Hanses et al. 2000; Korukluoglu et al. 2005; Rima

et al. 1995b; Sakata et al. 1993; Santibanez et al. 1999, 2002). Genotype D6 may be endemic in Turkey (Korukluoglu et al. 2005; Korukluoglu and Zarakolu 2006). In 2005–2006, there were major measles epidemics associated with genotypes B3, D6, and D4, and these genotypes were associated with measles cases exported from Europe to other parts of the world (Korukluoglu and Zarakolu 2006; Kremer et al. 2008). Genotype D6 was associated with a larger outbreak in the Ukraine, which fueled spread cases and small outbreaks throughout Europe, while genotype D4 was detected in a large outbreak in Romania. The decreased diversity of the genotype D6 viruses along with the rapid disappearance of the previously circulating C2 and D7 viruses suggest that vaccination programs had successfully interrupted several chains of transmission. However, measles virus was reintroduced by importation and spread via highly mobile, unvaccinated communities (Kremer et al. 2008).

Measles Elimination

Endemic transmission has been eliminated in many areas of the world, including the countries in the Western hemisphere. Both virologic and epidemiologic data collected in the United States between 1989 and 2000 indicated that interruption of transmission of the genotype D3 viruses that were associated with the measles resurgence of the early 1990s was achieved in 1993 and subsequently maintained (Rota et al. 1996, 1998). Analysis of viruses isolated from measles cases and outbreaks in the United States between 1994 and 2007 failed to detect ongoing transmission of an endemic genotype. Rather, the diversity of genotypes detected in the last 15 years is indicative of multiple, imported sources of virus (Rota et al. 1998, 2002). Likewise, the diversity of genotypes detected in Australia and Canada, and the United Kingdom is similar to that observed in the United States, suggesting frequent importation of measles and lack of endemic circulation of virus (Chibo et al. 2000, 2003; Jin et al. 1997; Ramsay et al. 2003; Rota et al. 1998, 2002). However, gaps in the vaccination program may have allowed for re-establishment of endemic transmission of measles in the United Kingdom (Asaria and MacMahon 2006).

Though virologic surveillance has improved recently in South America, there is no record of the endemic genotypes that circulated before PAHO launched its very successful measles elimination efforts in the early 1990s. However, molecular epidemiologic studies have demonstrated interruption of circulation of genotype D6 viruses that were responsible for the large measles outbreak in Sao Paulo in 1997 and subsequent outbreaks in Rio de Janeiro, Argentina, Chile, Bolivia, Haiti, and the Dominican Republic (Barrero et al. 2000; Baumeister et al. 2000; Canepa et al. 2000; Hersh et al. 2000; Oliveira et al. 2002; Siqueira et al. 2001). The record low number of cases and the identification of genotypes other than D6 in association with measles cases imported into South and Central America are consistent with regional elimination (Hersh et al. 2000).

During 2002, indigenous transmission in the Americas was limited to a large outbreak (>2000 cases) that started in Venezuela and spread to Colombia. Viruses isolated in Venezuela were found to be members of what was a previously

unknown genotype, D9 (Anonymous 2002). At the time, genotype D9 was considered to be a previously undetected endemic genotype in the Americas and its discovery cast doubts on the assertion that measles had been eliminated from the region. However, shortly after the outbreaks in Venezuela and Colombia, genotype D9 viruses were found to be circulating in Java, Indonesia and were associated with measles cases imported into Australia (Chibo et al. 2003). Since genotype D9 was found to be circulating in a country with endemic measles, the more likely scenario was that genotype D9 viruses were imported into Venezuela from an unidentified index case (Anonymous 2003).

Measles Reintroduction

Laboratory studies have estimated that the mutation rate of measles virus is similar to those of other RNA viruses (Schrag et al. 1999). However, the high level of genetic stability of measles field isolates was also noted by sequencing viruses from the same genotype that had been isolated several years apart (Rima et al. 1997). In addition, molecular epidemiologic studies of the measles resurgences in Brazil in 1997 (Oliveira et al. 2002) and the United States in 1989–1991 (Rota et al. 1996) suggest that there is very little sequence variation in the N and H genes within a single chain of measles transmission. Nucleotide sequences from the N genes of viruses isolated during the large outbreak in Sao Paulo, Brazil, in 1997 were nearly identical to the sequences obtained from viruses that had spread to other states in Brazil as well as other South American countries during 1997 and 1998 (Oliveira et al. 2002). The genotype D3 viruses that were isolated during the resurgence of measles in the United States during 1989–1991 showed very little sequence variability in both the H and N genes, suggesting that one strain of virus had seeded the entire country (Rota et al. 1996). Even in areas with recent endemic transmission of virus, there appears to be very little sequence variation present in viruses isolated from the same chain of transmission. For example, there was very little sequence heterogeneity in viruses obtained during outbreaks that occurred after a mass vaccination campaign in Burkina Faso, suggesting that a single introduction of virus was responsible for the outbreaks (Mulders et al. 2003). This is in contrast to the pattern observed in measles-endemic areas, which shows much more sequence variation within a genotype because the epidemiologic conditions favor maintenance of multiple chains of transmission.

Therefore, measles vaccination programs can reduce the number of co-circulating chains of transmission and eventually interrupt measles transmission. However, viruses are continually being introduced from external sources, and as the number of susceptible individuals increases, sustained transmission of the newly introduced viral genotype is possible. The result of introduction into regions where vaccination programs have failed to maintain a high level of population immunity are apparent rapid changes in the endemic genotype as observed in European countries and/or circulation of viruses with very limited genetic diversity (Kremer et al. 2008; Mulders et al. 2003; Rima et al. 1995b; Santibanez et al. 2002).

Mapping Transmission Pathways

Molecular epidemiologic studies of measles virus have taught us several valuable lessons about transmission of the virus. One of these lessons is that if large measles outbreaks are occurring anywhere in the world, the viruses are soon detected throughout the world. The lineage of genotype B3 viruses that were associated with a large outbreak in Kenya in 2005 were soon detected throughout Europe, the United States, Canada, and Mexico (Fig. 7.3) (Rota et al. 2006). Likewise, there were a number of internationally spread cases and some small outbreaks that could be linked to the large outbreaks in Romania and Ukraine in 2006 (Kremer et al. 2008).

Another lesson is that measles transmission can occur anywhere and that molecular techniques are often the only method for identifying the source of an outbreak or case. Exposures can occur in airports or other areas frequented by international travelers such as amusement parks. In 2005, sequence information was used to link cases that occurred in the Netherlands to an exposure in an airport in the United States (Rota et al. 2006), while in 2007 sequence data were used to link cases that occurred in Texas and Michigan to an imported case at an international youth sporting event in Pennsylvania (Anonymous 2008a). In 2008, measles cases were imported into the United States primarily from large outbreaks associated with genotypes D5 and D4 in Europe (Anonymous 2008b).

Of course, there are limitations to the ability to map transmission pathways. Molecular studies can confirm independent sources of infection if different genotypes or clearly distinct lineages are detected. However, if viruses from the same lineage are detected in nonlinked cases in a particular country, the molecular data alone may not be able to differentiate between continuous circulation of virus and multiple introductions from the same source.

Challenges

Genetic characterization of wild-type measles viruses provides a means to study the transmission pathways of the virus and is an essential component of laboratory-based surveillance. Virologic surveillance needs to be expanded in all areas of the world and conducted during all phases of measles control.

The greatest challenge to expanding virologic surveillance for measles is to collect and transport specimens in a timely and efficient manner. The importance of obtaining samples for viral detection at first contact with the suspected case cannot be understated. In addition, local healthcare workers must have the proper supplies and training needed to obtain, process, and ship samples. This is particularly challenging in developing countries with inadequate infrastructure. The targeted introduction of new sampling techniques such as collection of dried blood on filter paper or oral fluid will help to expand virologic surveillance into remote areas (World Health Organization 2008). The WHO Laboratory Network is expanding the capacity of the national and regional laboratories for virus isolation and viral detection. The Vero/hSLAM cell line has been distributed through the network.

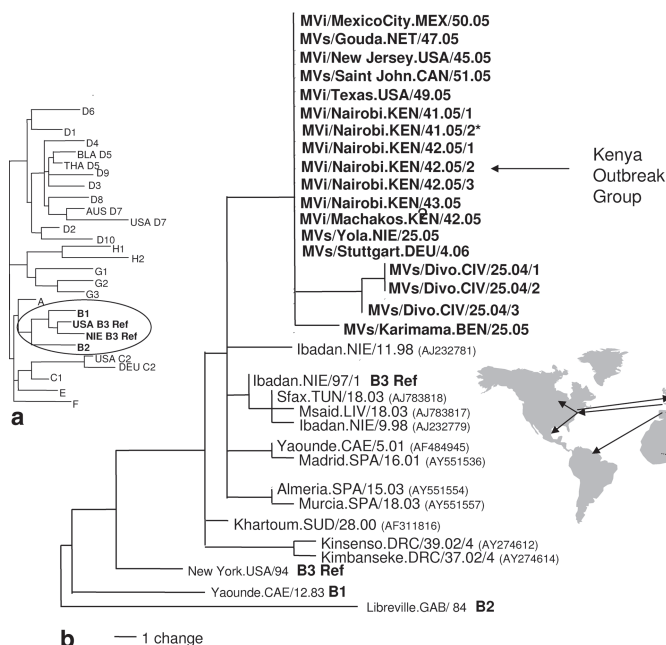


Fig. 7.3 a, b Transmission of measles genotype B3 in 2005 (adapted from Rota et al. 2006). In **A**, the dendrogram shows the relationships among the measles reference strains representing the 23 known measles genotypes. **B** shows the phylogenetic analysis of nucleoprotein genes (450 nucleotides) of measles viruses from cases in the United States, Mexico, the Netherlands, Canada, Germany, and Kenya during 2005–2006. The unrooted tree includes sequences from cases in Ivory Coast in 2004 and Benin and Nigeria in 2005 as well as selected B3 sequences available from GenBank for comparison. *Collected from the Dagoretti area of Nairobi; the other Nairobi sequences were from cases in the Eastleigh area. The insert to the right highlights the transmission pathways. Note that no epidemiologic link was established with western Africa (*dotted line*). A separate importation of genotype B3 with a link to Spain occurred in Venezuela

Another significant challenge is the development of protocols for rapid exchange of sequence information. Timely reporting and dissemination of the genotype information will enhance our ability to track transmission of measles and to evaluate the success of vaccination programs. The planned development of databases and web sites will permit near real-time exchange of genetic information and benefit both laboratorians and public health officials.

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