Standardization of the nomenclature for genetic characteristics of wild-type rubella viruses.

A number of genetically distinct groups of rubella viruses currently circulate in the world. The molecular epidemiology of rubella viruses will be primarily useful in rubella control activities for tracking transmission pathways, for documenting changes in the viruses present in particular regions over time, and for documenting interruption of transmission of rubella viruses. Use of molecular epidemiology in control activities is now more relevant since the WHO European Region and the Region of the Americas have adopted congenital rubella infection prevention and elimination goals respectively, targeted for 2010. However, a systematic nomenclature for wild-type rubella viruses has been lacking, which has limited the usefulness of rubella virus genetic data in supporting rubella control activities.

A meeting was organized at WHO headquarters on 2-3 September, 2004 to discuss standardization of a nomenclature for describing the genetic characteristics of wild-type rubella viruses. This report is a summary of the outcomes of that meeting. The main goals of the meeting were to provide guidelines for describing the major genetic groups of rubella virus and to establish uniform genetic analysis protocols. In addition, development of a uniform virus naming system, rubella virus strain banks and a sequence database were discussed. Standardization of a nomenclature should allow more efficient communication between the various laboratories conducting molecular characterization of wild-type strains and will provide public health officials with a consistent method for describing viruses associated with cases, outbreaks and epidemics.

Epidemiology and logistics

Rubella viral surveillance is an important part of rubella surveillance at each phase of rubella control/elimination; the goal should be to obtain a virus sequence from each chain of transmission during the elimination phase or from representative samples from each outbreak during the control phase. Attempts should be made to obtain specimens for virus isolation and/or sequencing at the same time that serum samples are obtained for serological diagnosis. Epidemiological data should accompany viral surveillance specimens in order to increase the usefulness of the molecular information. These data should include geographic location, date and type of specimen, date of rash onset, clinical presentation (postnatal rubella or congenital rubella syndrome (CRS)), age of patient, vaccine history and vaccination date.

WHO is developing a laboratory manual for measles and rubella which will include detailed instructions for obtaining, processing and analyzing specimens for viral surveillance. It is imperative that appropriate epidemiological data be collected and linked to specimens.

Existing WHO Measles and Rubella Global Specialized Laboratories and measles strain banks at the Centers for Diseases Control and Prevention, Atlanta, United States of America and the Health Protection Agency, London, United Kingdom, will also maintain rubella virus strain banks. The functions of the strain banks will include; identification or validation of new genotype(s), reporting of genotype data, and collection of strains.

Information for candidate genotypes will be submitted directly to a strain bank for identification or validation.

Genotype information will be reported within the framework of the established global laboratory network, including timeliness indicators. Timeliness indicators for reporting rubella genotypes will be the same as those recommended for reporting of measles genotypes (within 3 months of obtaining a sequence(s)). Sequence information will be made available through the WHO strain banks, through websites, and via GenBank[1]. Updates to the recommended nomenclature will be published periodically in the WER. The WHO Global Measles and Rubella Laboratory Network will support efforts to obtain isolates of currently circulating wild-type rubella viruses and will facilitate referral to designated laboratories with the capability of performing genetic analysis.

Sequencing and Sequence Analysis

Isolation of rubella virus from clinical specimens should be attempted with the goal being the identification of representative isolates from each chain of transmission during elimination strategies or each outbreak during endemic transmission. Rubella virus isolation should be performed in Vero cells and should be confirmed by IFA or RT-PCR as cytopathic effect is minimal. Rubella isolation can also be performed using Vero/SLAM cells in laboratories that are attempting to isolate wild-type measles viruses using these cells. Use of RT-PCR to amplify rubella sequences directly from clinical material is highly sensitive and sequence information derived from the products can be used for molecular epidemiological studies. Protocols for isolation, direct RT-PCR, sequencing, and sequence analysis will be available from WHO.

Most of the genetic studies of wild-type rubella viruses have been conducted by sequencing the full length or portions of the coding region of the E1 envelope protein. Sequencing other regions of the rubella virus genome for molecular epidemiology was discussed, but no compelling arguments for changing from the E1 region were identified. At present, different regions (windows) in the E1 coding region are used for genetic characterization. After evaluation of these windows, a window of 739 nucleotides (nts) (nts 8731 to 9469), was recommended for routine molecular epidemiological analysis. This window results from combining two commonly used, overlapping sequence windows, designated 601 and 552 (see below).

Use of any one of several widely available computer programs for phylogenetic analysis is acceptable. For example, computer programs based on maximum likelihood, maximum parsimony, or other methods are acceptable, provided the analysis is be done using the set of accepted reference sequences. The use of reference viruses in an analysis will control for ambiguities in the assignment of viruses. Analysis must be performed with at least the recommended, minimum acceptable window (739 nt); the analysis will be considered valid if the accepted set of reference viruses fall into the accepted groups. Analysis of each data set with multiple phylogenetic analysis programs is desirable.

A phylogenetic program called MRBAYES was used to generate the figures in this report. This program provides clade credibility values for the various nodes in phylogenetic trees; clade credibility values are analogous to bootstrap values which can be obtained from maximum parsimony and maximum likelihood analyses.

The major phylogenetic groups of rubella viruses, which differ by 8-10% in nucleotide sequence, are easily separated, and were designated as clades 1 and 2 at the meeting. This is a departure from the terminology previously used, but makes the rubella nomenclature closer to that used to describe the genetic characteristics of wild-type measles viruses. Reference viruses for 7 intraclade groups, called genotypes, were accepted and designated with upper case letters, (1B, 1C, 1D, 1E, 1F, 2A and 2B) (Table 1; Fig 1; Fig. 2.). In addition, 3 provisional genotypes (1a, 1g, 2c) were discussed (Table 1; Fig. 1; Fig. 2).

A provisional genotype will become an established genotype when reference viruses are obtained and phylogenetic relationships between the provisional genotype and other genotypes become clear. Genotype 1a was considered provisional because the phylogeny of this group of viruses was complex and poorly understood. Genotype 1a includes viruses from the 1960s (e.g. early vaccine strains), but this genotype has been found infrequently in recent years, limiting the number of new genotype 1a viruses and thus limiting the opportunities to further characterize the complexity of this group of viruses. However, recently new genotype 1a viruses have been found in Mongolia and Myanmar and this may allow further characterization of this group of viruses. Because of the historical significance of this group, reference sequences were designated for this provisional group (Table 1). Genotype 1g was considered provisional both because reference sequences were not available and because the relationship between genotype 1g and genotype 1B was not clear. The clustering of viruses from genotype 1B and 1g is more sensitive to the sequence window used than genotypes 1C, 1D, 1E, 1F, 2A, 2B, or 2c (Fig. 2). Genotype 2c was considered provisional only because reference viruses were not available; information reported at the meeting indicated that 2c reference sequences will soon be available.

The phylogenetic trees for reference viruses using different windows illustrates why the 739 nt window was recommended (Fig. 2). The SP window includes the entire coding region for the C, E2 and E1 proteins (structural protein open reading frame) and is the standard against which the other windows were evaluated. In the analysis presented, the 601 window did not give the proper groupings for the 1B and 1g viruses and the 552 window did not give high clade credibility values for the 1F genotype. However, the combined window, 739, gave the proper groupings of reference viruses for the 1B genotype and high clade credibility values for viruses from the 1F genotype.

Proposals for new genotypes should be submitted to the strain banks for evaluation. When possible, the earliest isolates should be used as reference viruses.

Criteria for a recognized genotype:

a. Two reference viruses in the genotype are available and submitted to a WHO recognized strain bank.
b. Sequences are available from the entire SP-ORF (coding region for C, E2 and E1 proteins) of the two reference viruses in the genotype.
c. Phylogenetic analyses of the reference viruses in the genotype with the reference viruses from all other genotypes, shows that:
    i. The reference viruses from the genotype cluster together with one another and separately from reference viruses of all other genotypes with high

confidence values (e.g. 80-90% bootstrap values). This clustering should be obtained with at least 2 different analysis methods.

ii. The phylogenetic tree topology obtained with full SP-ORF sequences of the reference viruses of the genotype and other reference viruses should be the same when the coding sequences of C, E2 and E1 are analyzed individually.

iii. The intragenotype and intergenotype distances for the reference viruses in the genotype are consistent with those for the existing genotypes.

iv. The branching pattern obtained in the phylogenetic analysis versus other reference viruses is consistent with a new genotype.

d. Sequence data for reference viruses in the genotype have been submitted to GenBank with the virus name and associated epidemiologic and clinical data (see convention for naming strains, below).

Convention for naming strains

The system of strain naming will include epidemiologic information that is essential for interpretation of the molecular data. Since sequence data may be derived from viruses isolated in cell culture or from RNA extracted directly from clinical materials, strains or sequences will be designated as either:

(1) RVi: rubella virus isolate in cell culture; or
(2) RVs: rubella virus sequence derived from RNA extracted from clinical material.

Other information to be included in the strain/sequence name will be:

a. city of isolation, use whole name or abbreviation(required);
b. country, use ISO 3-letter designation(required);
c. date of specimen collection by epidemic week (1-52) and year (required);
d. isolate number if more than 1 per week (optional);
e. genotype (optional initially, required after sequencing the 739 nucleotide window in the E1 coding region);
f. special designation for sequences derived from CRS cases (optional).

The following examples illustrate the proposed naming convention.

- RVi/Tokyo.JPN/03.98/2 [1D]
- RVs/London. GBR/17.97[1B] CRS

Global distribution of rubella genotypes

Although rubella virus surveillance is recognized as being sub-optimal, the current information concerning the global distribution of rubella virus genotypes is shown in figure 3. All genotype information reported at the September 2004 WHO nomenclature meeting and previously published genotype information from the years 1985-2004 is shown.

There are several interesting characteristics observed in the genotype distribution of rubella viruses. Genotype 1a was found most frequently worldwide before 1984 and has almost disappeared, except for Mongolia and Myanmar. The last Genotype 1a identified in the rest of the world was in Canada in 1985. Genotypes 1B, 1C, 1D and 1F have been found to be restricted to certain geographical areas. More precisely, 1B has been found in Europe and on the eastern coast of South America; 1C has been found in Central America and the western coast of South America; 1D has been found in Asian countries and one genotype 1D virus has been found in Ethiopia; 1F has been found in China. Genotype 1C was observed in a single outbreak in Japan and was thought to have been imported from a concurrent outbreak in the Americas, although there is no direct epidemiological data to support this. Genotype 1D was found in the past in Canada and the USA, but was last found in these countries in 1987 in Canada and in 1988 in the USA. Genotype 1E, first identified in 1997, now appears to be a genotype with world wide distribution. Genotype 1g needs more study; nevertheless, countries where this provisional genotype has been found are shown in figure 3.

Viruses in clade 2 have been found only in the eastern hemisphere (Asia, Europe, and Africa). Genotype 2A was isolated only in China in 1979 and 1980 and has not reappeared since then. Genotype 2B is distributed more widely than other genotypes in clade 2. Genotype 2c has been found only in Russia.

Summary

The main goals of the meeting, to provide guidelines for describing the major genetic groups of rubella virus and to establish uniform genetic analysis protocols, were achieved. Guidelines for describing the genotypes as an operational taxonomic group consisted of the designation of reference viruses and reference sequences for 7 genotypes of rubella viruses representing 2 clades, and designation of an additional 3 provisional genotypes. Provisional genotype status was given either because reference viruses were not yet available and/or because there was uncharacterized complexity within the genetic group. Uniform analysis protocols recommended the comparison of unknown viral sequences with the complete set of designated reference viruses, and recommended a minimum acceptable sequence window which produced phylogenetic results with high confidence values. A list of literature references about rubella virus phylogeny and molecular epidemiology is attached. As additional understanding of the genetic characteristics of wild-type rubella viruses is achieved, updates to the recommended nomenclature will be made and published in the WER.

[1] GenBank is the genetic sequence database for all publicly available DNA sequences of the National Institutes of Health, Bethesda, Maryland, United States of America.

Table 1. Reference strains to be used for genetic analysis of wild-type rubella viruses, 2004*

Genotype	Reference Strain**	Current Name***	Accession Number
1a	RVi/BEL/63	Cendehill BEL 63#	AF188704
	RVi/Con.USA/61	HPV77 US 61#	M30776
	RVi/Toyama.JPN/67	TO-336 WT JP 67##	AB047330
1B	RVi/ISR/75[1B]	I-9 IS 75	AY968207
	RVi/ISR/88[1B]	I-34 IS 88	AY968209
	RVi/ISR/79[1B]	I-13 IS 79	AY968208
1C	RVi/Cal.USA/91[1C]	BUR US 91	AY968212
	RVi/SLV/02[1C]	QUI ELS 02	AY968211
	RVi/PAN/99[1C]	P-31 PAN 99	AY968217
1D	RVi/Cal.USA/97[1D]CRS	SAL-CA US 97	AY968206
	RVi/Tokyo.JPN/90[1D]CRS	NC JP 90	AY968214
	RVi/Saitama.JPN/94[1D]	SAI-1 JP 94	AY968216
1E	RVi/Shandong.CHN/02[1E]	T14 CH 02	AY968210
	RVi/MYS/01[1E]	M-1 MAL 01	AY968221
1F	RVi/Shandong.CHN/00[1F]	TS10 CH 00	AY968213
	RVi/Anhui.CHN/00[1F]	TS 38 CH 00	AY968215
2A	RVi/Beijing.CHN/79[2A]	BRD1 CH 79	AY258322
	RVi/Beijing.CHN/80[2A]	BRD2 CH 80#	AY258323
2B	RVi/TelAviv.ISR/68[2B]	I-11 IS 68	AY968219
	RVi/Wash.USA/16.00[2B]	TAN IND 00	AY968220
	RVi/Anhui.CHN/00/2[2B]	TS34 CH 00	AY968218
Vaccine$	RVi/USA/64	RA27/3 US 64#	L78917$$

* Sequence information for the structural protein coding region (C, E2 and E1) is available at CDC.
Reference viruses for provisional genotypes 1g and 2c are not available yet.
** Strains are named using the new convention described in the present report. Missing information for some strains is being obtained or is unavailable.
*** Strains are named using old or previously published identifiers.
# Attenuated vaccine virus for which original wild-type virus has been lost
Progenitor wild-type virus for attenuated vaccine virus TO-336 Vac.
$ Genotype of this virus is considered to be 1a.
$$ CDC SP sequence is at least 2 nucelotides different from this published sequence.
In the CDC sequence nucleotide 9266 is changed from an A to a G and nucleotide 9386 is changed from a C to a G.

Figure 1. Phylogenetic tree of rubella virus reference sequences, listed in table 1, using nts 8731-9469.

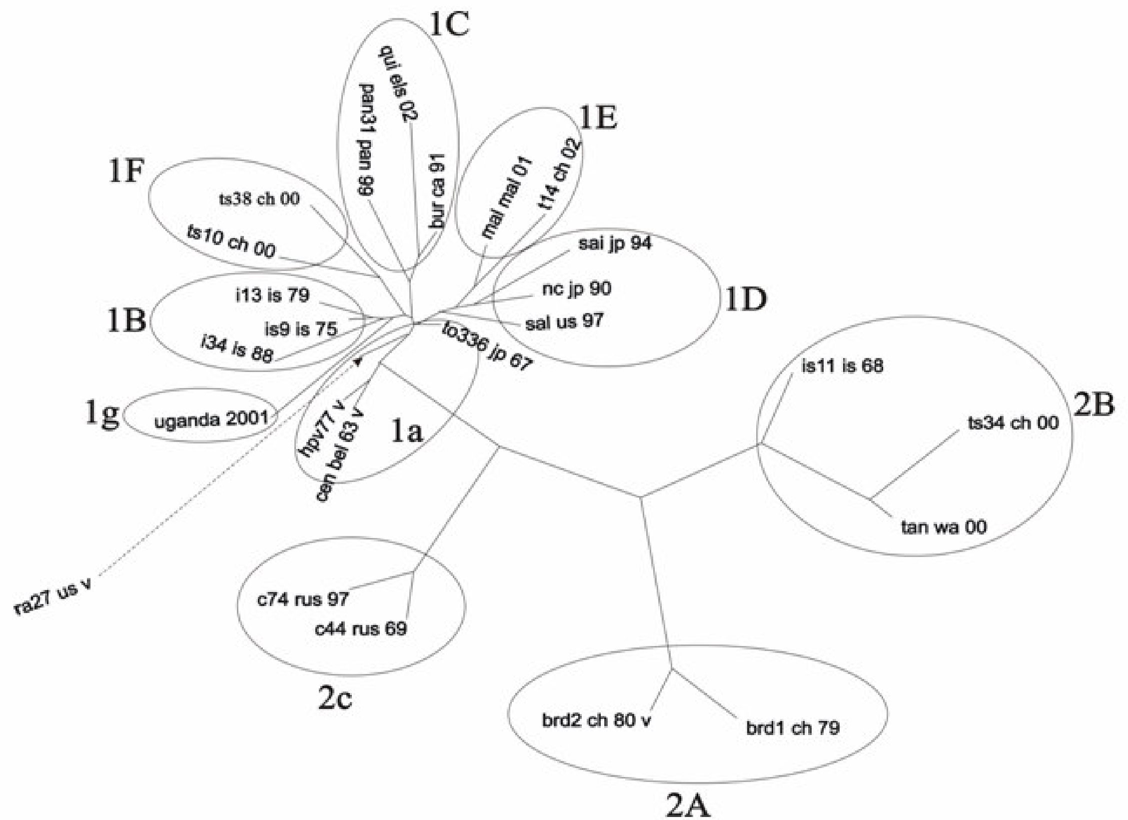

Figure 1. Phylogenetic tree of rubella virus reference sequences, listed in table 1, using nts 8731-9469. The Bayesian inference program, MRBAYES, was used with settings of 200,000 Ngens; Samplefreq, 100; Nchains, 4; Burnin, 10. The position of one sequence (Uganda 2001), which is likely in genotype 1g, is shown to represent this provisional genotype. The positions of 2 genotype 2c viruses are shown using published E1 sequences.

Figure 2. Phylogenetic trees comparing 3 sequence windows within the E1 coding region of rubella virus.

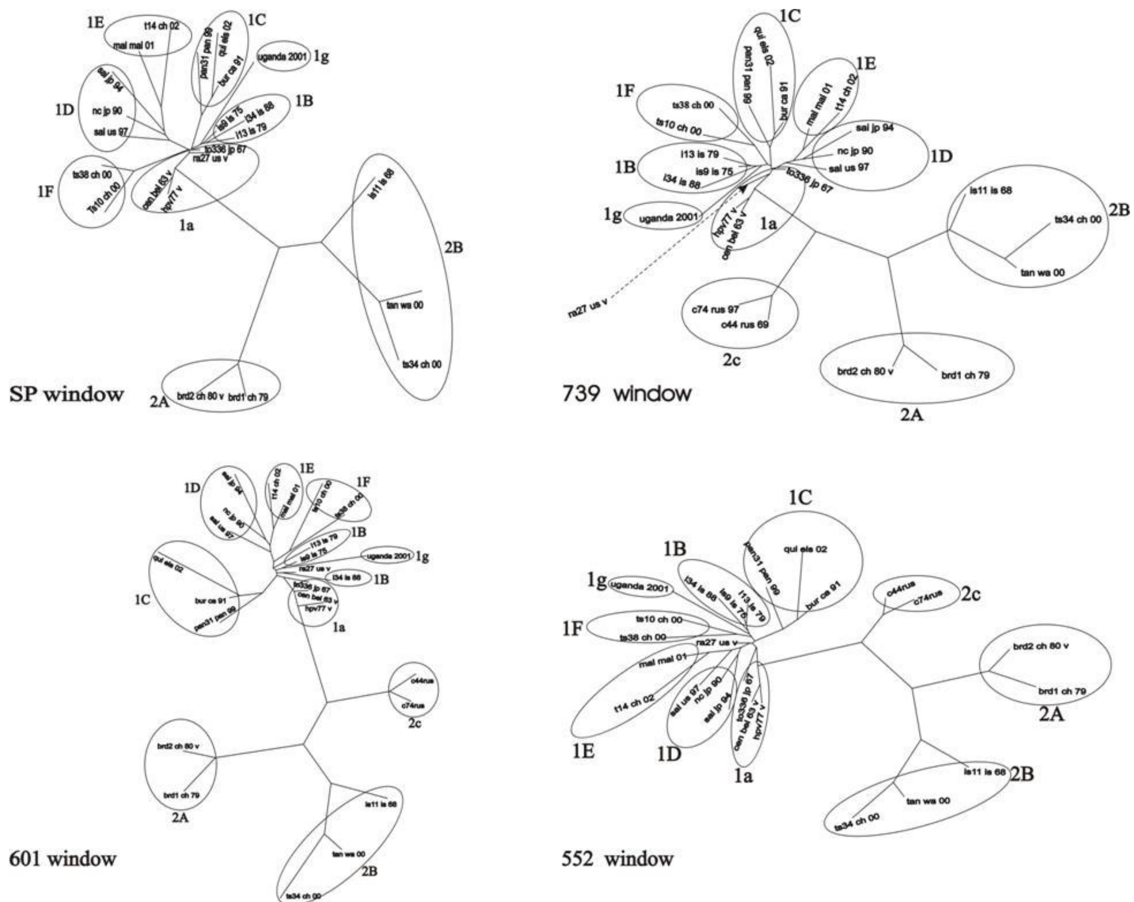

Figure 2. Phylogenetic trees comparing 3 sequence windows within the E1 coding region of rubella virus. Trees using four windows, the entire structural protein coding region (SP), nucleotides 6481-9741, and three windows within the E1 coding region, 739 (nucleotides 8731-9469), 601 (nucleotides 8869-9469), and 552 (nucleotides 8731-9282) are shown. The trees shown were created using the Bayesian inference program, MRBAYES. The settings used for the 739 tree were 200,000 ngens; samplefreq, 100; nchains, 4; burnin, 10. Settings for the other 3 trees were the same except that 100,000 ngens were used. For the 739, 601 and 552 trees 22 reference sequences and 3 sequences from provisional genotypes 1g and 2c were used (uganda 2001, c74 rus 97 and c44 rus 69), while for the SP tree 22 reference sequences and the sequence Uganda 2001 were used. The SP sequences for c74 rus 97 and c44 rus 69 viruses were not available. Clade credibility values for the SP tree are 80 or above for all nodes except the ra27 us v (RA27/3 vaccine virus) node. Clade credibility values for the 739 and 601 trees are 80 or above for 2A, 2B, 2c, 1C, 1D, 1E, 1F, and the Cendehill/HPV nodes. Clade credibility values are 80 and above for 2A, 2B, 2c, 1C, 1D, 1E, and the Cendehill/HPV nodes for the 552 tree.

Table 2. List of strains used for genotype distribution, 1985-2004.*

Country**	Genotype	Strain***	Current name****	Year of isolation#	GenBank accession No.	Contact for sequence##	SP sequence available$
Bahamas	1E	RVi/Freeport.BHS/97[1E]	FRI	97	AY326359		
Bolivia	1C	RVs/BOL/02[1C]	B82	O2		CDC	
Brazil	1B	RVs/Rio de Janeiro.BRA/97[1B]	B32BR97	97	AJ890442		
	1g	RVs/Rio de Janeiro.BRA/99[1g]	BRAZ99	99	AJ890443		
Canada	1a	RVi/Vancouver.CAN/85	ML	85	L16232		
	1D	RVi/Vancouver.CAN/87[1D]	PL	87	AY039114		
	1E	RVi/BC.CAN/97[1E]	DES	97	AY326358		
China	1E	RVi/Shandong.CHN/02[1E]	T14 CH 02	O2	AY968210		Yes
	1F	RVi/Anhui.CHN/99[1F]	AH2	99	AY326350		
	2B	RVi/Anhui.CHN/00[2B]	TS34 CH 00	OO	AY968218		Yes
Ecuador	1C	RVi/ECU/99[1C]	CUE	99	AY326357		
El Salvador	1C	RVi/SLV/02[1C]	QUI ELS 02	O2	AY 968211		Yes
Ethiopia	1D	RVs/S.Tigray.ETH/25.04[1D]	ETH04-612	O4		HPA	
	1g	RVs/Guragie1.ETH/15.04[1g]	ETH04-576	O4		HPA	
Germany	1B	RVi/Stuttgart.DEU/95/[1B]CRS	INS	95	AF039133		
	1E	RVi/Stuttgart.DEU/99[1E]	G432	99	AF551761		
Greece	1E	RVs/Thessaloniki.GRC/99[1E]	Thess102GRE99	99		HPA	
Guyana(USA)**	1E	RVi/NY.USA/97/[1E]CRS	NY-97	97		CDC	
Honduras(USA)	1C	Rvi/Washington.USA/00[1C]CRS	WA-00	OO		CDC	
Hong Kong/China	1D	RVi/HongKong.CHN/87/[1D]CRS	C31	87	AB003342		
India	2B	RVi/IND/95/[2B]CRS	BAS	95	AF039134		
Israel	1B	RVi/ISR/88[1B]	I-34 IS 88	88	AY968209		Yes
Italy	1B	RVi/Lodi.ITA/4.91/[1B]CRS	3850PV	91	AY161354		
	1E	RVi/Pavia.ITA/28.97/[1E]CRS	6488	97		CDC/GSU	
	2B	RVi/Milan.ITA/42.94/[2B]CRS	5298MI	94	AY161370		
Japan	1C	RVi/Akita.JPN/90[1C]	JPA5	90	AB003354		
	1D	RVi/Tokyo.JPN/90/[1D]CRS	NC JP 90	90	AY968214		Yes
Malaysia	1E	RVi/MYS/01[1E]	M-1 MAL 01	O1	AY968221		Yes
Mexico	1C	RVi/MEX/97[1C]	ANI	97	AY326352		
Mongolia	1a	RVs/MNG/00	MO29	OO	AB080729		
Morocco	1E	RVs/MAR/04[1E]	386D	O2		CDC	
Myanmar	1a	RVs/MMR/01	MK	O1	AB080199		
	1D	RVs/MMR/01/2[1D]	BTD	O2	AY280706		
New Zealand	1D	RVi/Auckland.NZL/91[1D]	JC2	91	AY326333		
Panama	1C	RVi/PAN/99[1C]	P-31 PAN 99	99	AY968217		Yes
Philippines(USA)	1D	RVi/Cal.USA/97[1D]CRS	SAL-CA US 97	97	AY968206		Yes
Romania(UK)	1E	RVs/Edinburgh.GBR/25.03[1E]	O3-28	O3		HPA	
Russia	2c	RVi/Moscow.RUS/97	C74	97	AY247019		
S Africa	2B	RVs/ZAF/03[2B]	RVS	O3		CDC	
S Korea	1D	RVi/KOR/96[1D]	AN3	96	AY326346		
	2B	RVi/KOR/95[2B]	AN1	95	AY326345		
Suriname	1E	RVi/SUR/98[1E]	633	98		CDC	
Uganda	1g	RVi/UGA/20.01	U588	O1		CDC	Yes
UK	1B	RVi/Wiltshire.GBR/93[1B]	BOW/wilt	93	AF039128		
	1g	RVs/Manchester.GBR/00[1g]CRS	00-128	OO		HPA	
	2B	RVs/Kent.GBR/21.03[2B]CRS	O3-12	O3		HPA	
Ukraina(USA)	1E	RVi/Mass.USA/7.00[1E]	MA-98	98		CDC	
USA	1C	RVi/Cal.USA/91[1C]	BUR US 91	91	AY968212		Yes
	1D	RVi/Cal.USA/88[1D]	NOR-CA	88		CDC	
	1E	RVi/Fla.USA/21.97[1E]	CAS	97	AY326356		
Venezuela(USA)	1B	RVi/NY.USA/15.99/[1B]CRS	BAZ(NY-C)	98		CDC	

*Representative strain from each genotype in each country is listed in the table.
**Virus/Virus genome was detected in the country in parenthesis. However, it was epidemiologically determined that the virus originated in the indicated country.
***Strains named using new convention. Information for some strains is missing or unavailable.
****Strains named using old or previously published identifiers.
#Indicated years are between 1985 and 2004.
##Contact e-mail addresses for sequences without GenBank accesion number; CDC(Centers for Disease Control and Prevention) Emily Abernathy <efa9@cdc.gov>; HPA(Health Protection Agency) Li Jin <li.jin@hpa.org.uk>.
$Sequence information of full length of structure protein coding region (coding for C, E2 and E1 proteins) is available at CDC.

Figure 3 **Genotype Distribution of Rubella Virus 1985-2004**

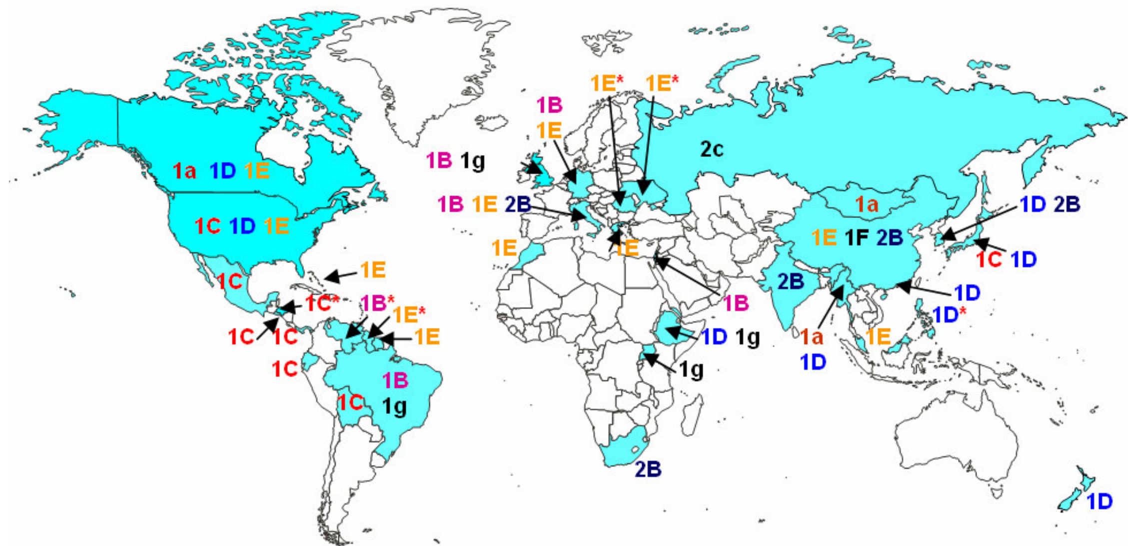

Figure 3. Genotype distribution of rubella viruses 1985-2004.

All genotype information reported at the meeting and previously published information for this period are shown on the map. Genotype information obtained after the meeting is not included. Any genotype with an asterisk indicates that the information was not obtained from the indicated country, but rather from a country into which the virus was imported. Countries from which no genotype information is available are white. Since the time period shown is 20 years, virus circulating in any particular country may currently be different. However, in countries without strong rubella control programs, the indicate genotypes are likely still circulating. See table 2 for detailed information.

References

REVIEWS

Banatvala JE, Brown DWG. Rubella. Lancet **2004**; 363:1127-1137.

Robertson SE, Featherstone DA, Gacic-Doba M, Hersh BS. Rubella and congenital rubella syndrome: global update. Rev Panam Salud Publica **2003**; 14:306-315.

RUBELLA

Bosma TJ, Best JM, Corbett KM, Banatvala JE, Starkey WG. Nucleotide sequence analysis of a major antigenic domain of the E1 glycoprotein of 22 rubella virus isolates. **1996**; J Gen Virol 77: 2523-2530.

Cooray S, Warrener L, Jin L. Improved RT-PCR for diagnosis and epidemiological surveillance of rubella. J Clin Virol **2005**; In Press

Donadio FF, Siqueira MM, Vyse A, Jin L, Oliveira SA. The genomic analysis of rubella virus detected from outbreak and sporadic cases in Rio de Janeiro state, Brazil. J Clin Virol **2003**; 27:205-209.

Frey TK, Abernathy ES, Bosma TJ, Starkey WG, Corbett KM, Best JM, Katow S, Weaver SC. Molecular analysis of rubella virus epidemiology across three continents, North America, Europe and Asia, 1961-1997. J Infect Dis **1998**; 178:642-650.

Hofmann J, Renz M, Meyer S, von Haeseler A, Liebert UG. Phylogenetic analysis of rubella virus including new genotype I isolates. **2003**; Virus Res 96:123-128.

Katow S, Minahara H, Fukushima M, Yamaguchi Y. Molecular epidemiology of rubella by nucleotide sequences of the rubella virus E1 gene in three East Asian Countries. J Infect Dis **1997**; 176:602-616.

Reef SE, Frey TK, Theall K, Abernathy E, Burnett CL, Icenogle J, McCauley MM, Wharton M. The changing epidemiology of rubella in the 1990s: on the verge of elimination and new challenges for control and prevention. **2002**; JAMA 287:464-472.

Vyse AJ, Jin L. An RT-PCR assay using oral fluid samples to detect rubella virus genome for epidemiological surveillance. **2002**; Mol Cell Probes 16:93-97.

Zheng D-P, Frey TK, Icenogle J, Katow S, Abernathy ES, Song K-J, Xu W-B, Yarulin V, Desjatskova RG, Aboudy Y, Enders G, Croxson M. Global distribution of rubella virus genotypes. **2003**; Emerg Infect Dis 9:1523-1530.

Zheng D-P, Zhou YM, Zhao K, Han Y-R, Frey TK. Characterization of genotype II rubella virus strains. Arch Virol **2003**; 148:1835-1850.

Zheng D-P, Zhu H, Revello MG, Gerna G, and Frey TK. Phylogenetic analysis of rubella virus isolated during a period of epidemic transmission in Italy, 1991-1997. J Infect Dis **2003**; 187:1587-1597.

MEASLES

Rota PA, Rota JS, Reed SB, Papania MJ, Bellini WJ. Genetic analysis of measles viruses isolated in the United States between 1989 and 2001: absence of an endemic genotype since 1994. J Infect Dis **2004**; 189 (Suppl 1):S160-164

Rota PA, Bellini WJ. Update on the global distribution of genotypes of wild type measles viruses. J Infect Dis **2003**; 187 (Suppl 1):S270-276.

World Health Organization. Update of the nomenclature for describing the genetic characteristics of wild-type measles viruses: new genotypes and reference strains. Wkly Epidemiol Rec **2003**; 78:229-232.