

# From protection to elimination of measles: what do we learn from molecular epidemiology ?

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WHO Collaborative Center for Measles  
National Avian Influenza Surveillance Lab



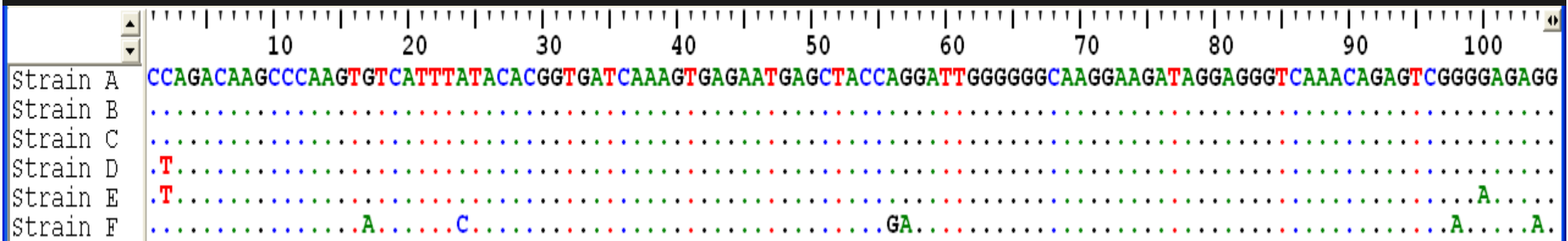
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Luxembourg (claude.muller@LNS.ETAT.LU)

# Activities of WHO RRL Luxembourg

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- Molecular epidemiology of M/R strains
- Retesting of sera from National Labs
- Monthly reporting of M/R surveillance data to WHO
- Training of staff from National labs
- On-site accreditation visits to Sub/National Labs
- Distribution of Proficiency Panels
- Supply to National Labs
  - M/R IgM kits to National Labs
  - M/R clinical sample collection kits to National Labs
  - In-house control sera for measles IgM/IgG
  - Equipment, consumables
- Research activities related to M/R

# Sequence alignment



## Distance Matrix

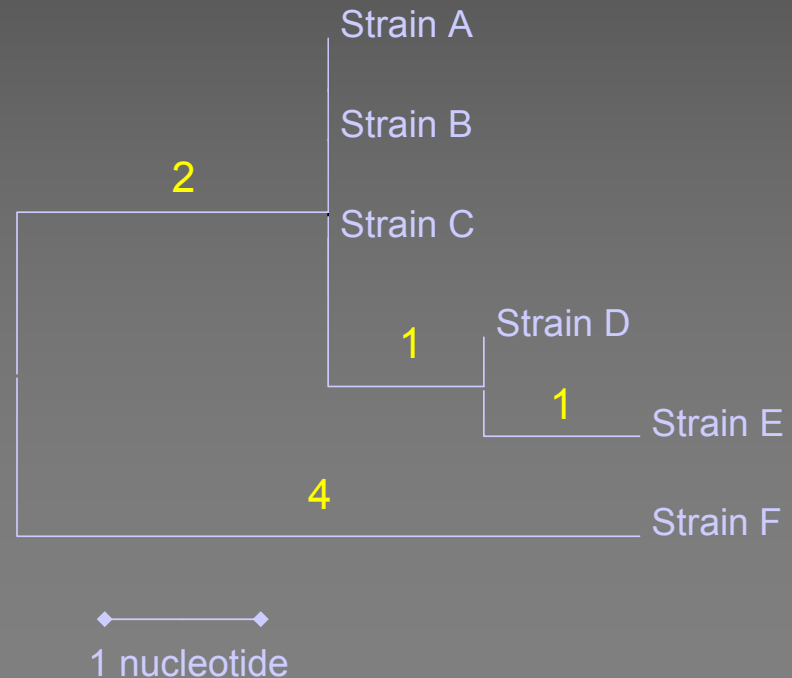
Strain	A	B	C	D	E	F
A	0	0	0	2	2	6
B	0	0	0	2	2	6
C	0	0	0	2	2	6
D	2	2	2	0	1	6
E	2	2	2	1	0	6
F	6	6	6	6	6	0

Numbers of differences

Strain	A	B	C	D	E	F
A	0	0	0	2	1.9	5.7
B	0	0	0	2	1.9	5.7
C	0	0	0	2	1.9	5.7
D	1.9	1.9	1.9	0	1	5.7
E	1.9	1.9	1.9	1	0	5.7
F	5.71	5.7	5.7	6	5.7	0

% difference (Total= 105 nucleotides)

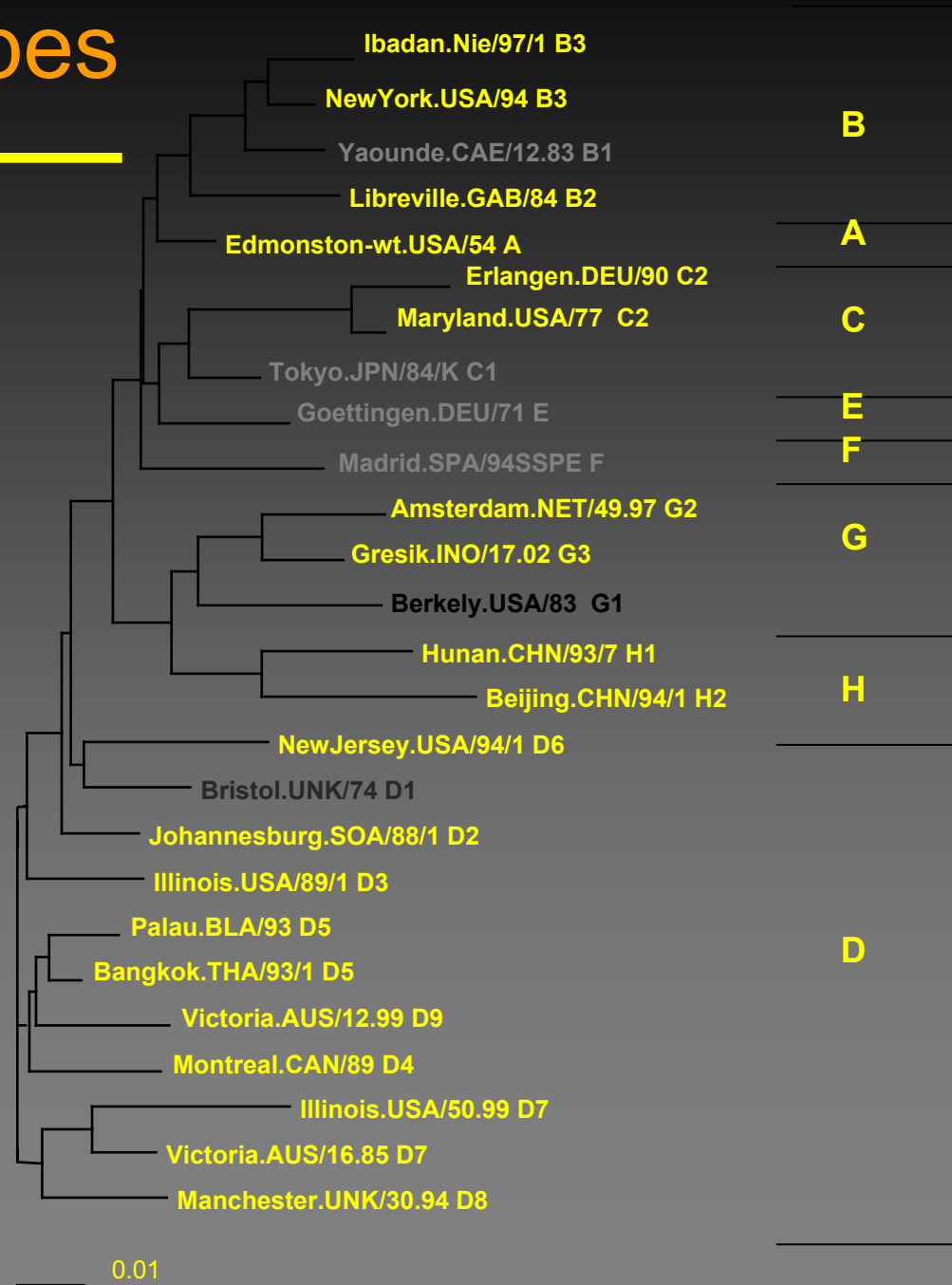
## Phylogenetic tree



# Clades and Genotypes

Classification based on  
H/N:

- 8 clades A-H
- 23 genotypes
  - A
  - B1-3 (B1)
  - C1-2 (C1)
  - D1-10, (D1)
  - (E)
  - (F)
  - G1-3 (G1)
  - H1-2



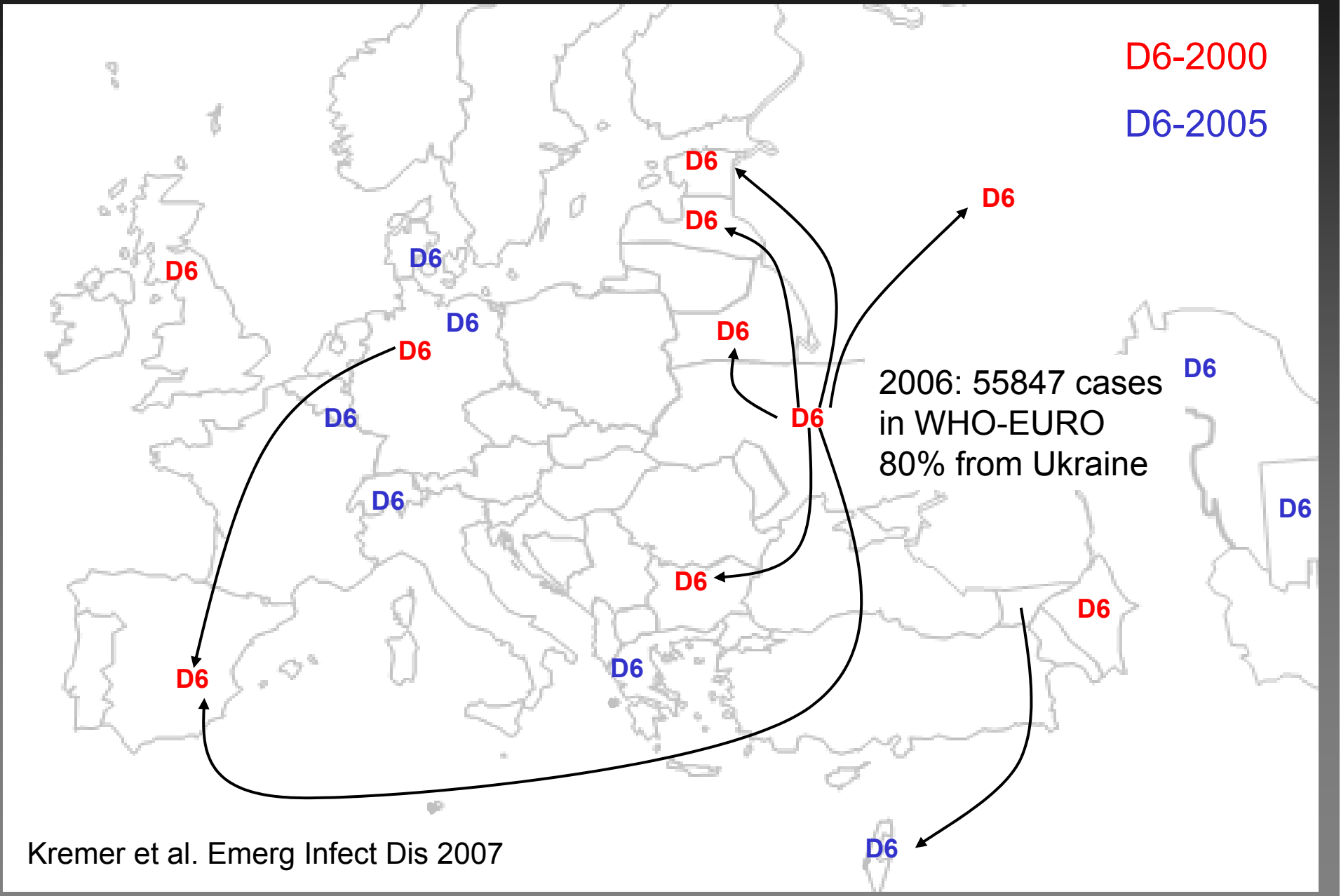
# Genotypes in WHO EURO Region 2005-2006

Countries active genotypes																	Countries active genotypes																		
	A	B2	B3	C2	D2	D3	D4	D5	D6	D7	D8	D9	D10	G2	G3	H1	H2		A	B2	B3	C2	D2	D3	D4	D5	D6	D7	D8	D9	D10	G2	G3	H1	H2
Albania																		Lithuania																	
Andorra																		Luxembourg																	
Armenia																		Macedonia																	
Austria																		Malta																	
Azerbaijan																		Monaco																	
Belarus																		Montenegro																	
Belgium																		Netherlands																	
Bosnia-Herzegovina																		Norway																	
Bulgaria																		Poland																	
Croatia																		Portugal																	
Cyprus																		Republic of Moldova																	
Czech Republic																		Romania																	
Denmark																		Russian Federation																	
Estonia																		San Marino																	
Finland																		Serbia																	
France																		Slovakia																	
Georgia																		Slovenia																	
Germany																		Spain																	
Greece																		Sweden																	
Hungary																		Switzerland																	
Iceland																		Tajikistan																	
Ireland																		Turkey																	
Israel																		Turkmenistan																	
Italy																		Ukraine																	
Kazakhstan																		United Kingdom																	
Kyrgyzstan																		Uzbekistan																	
Latvia																		Total:	0	1	10	0	0	0	14	6	17	0	4	2	0	0	1	5	0

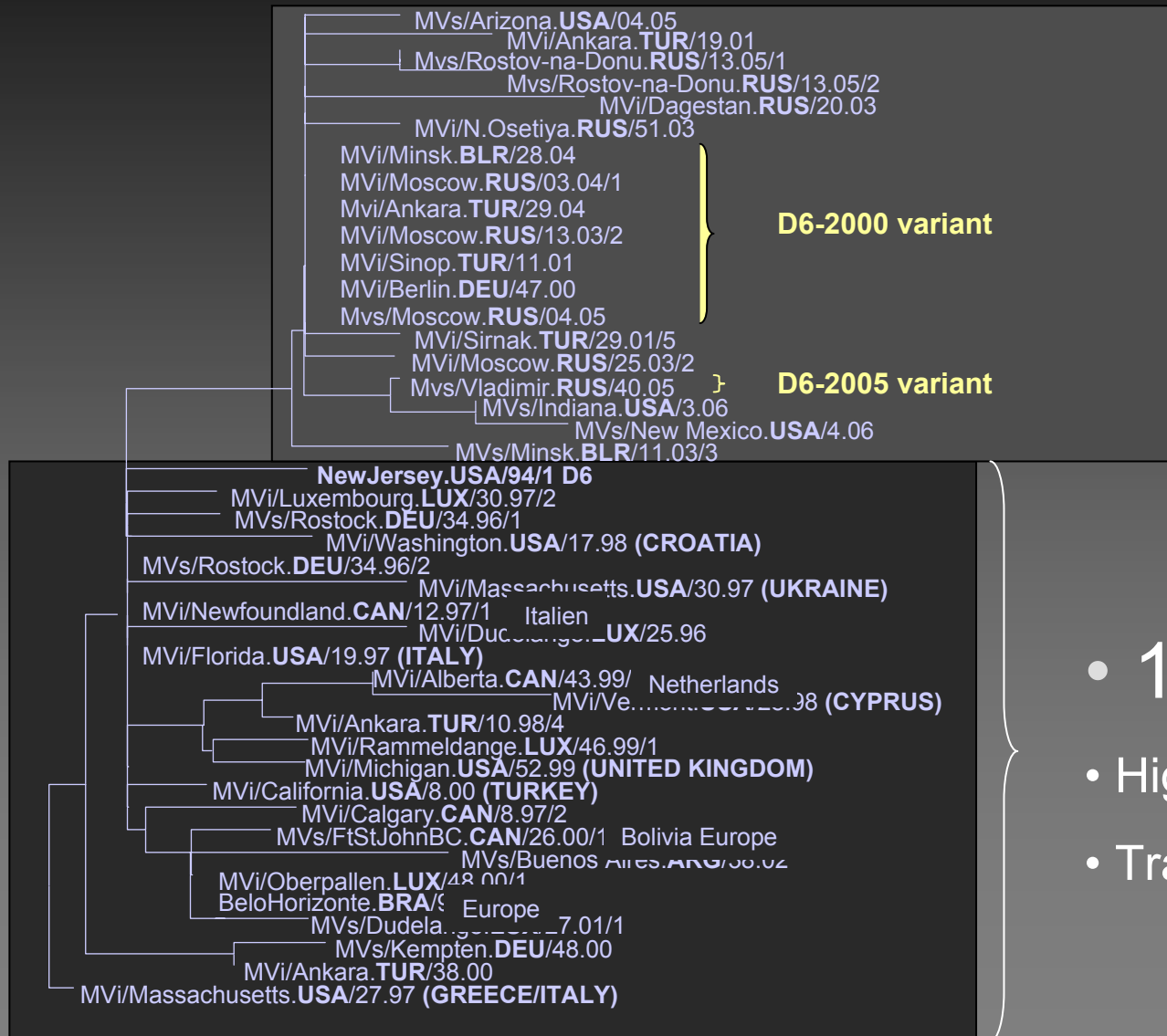
1-100     
  100-1000     
  >1000 reported cases in 2005-2006

Genotype information available from 25/53 countries

# Genotype D6 variants in 2005-2006



# Genotype D6 diversity in Europe 1996-2006

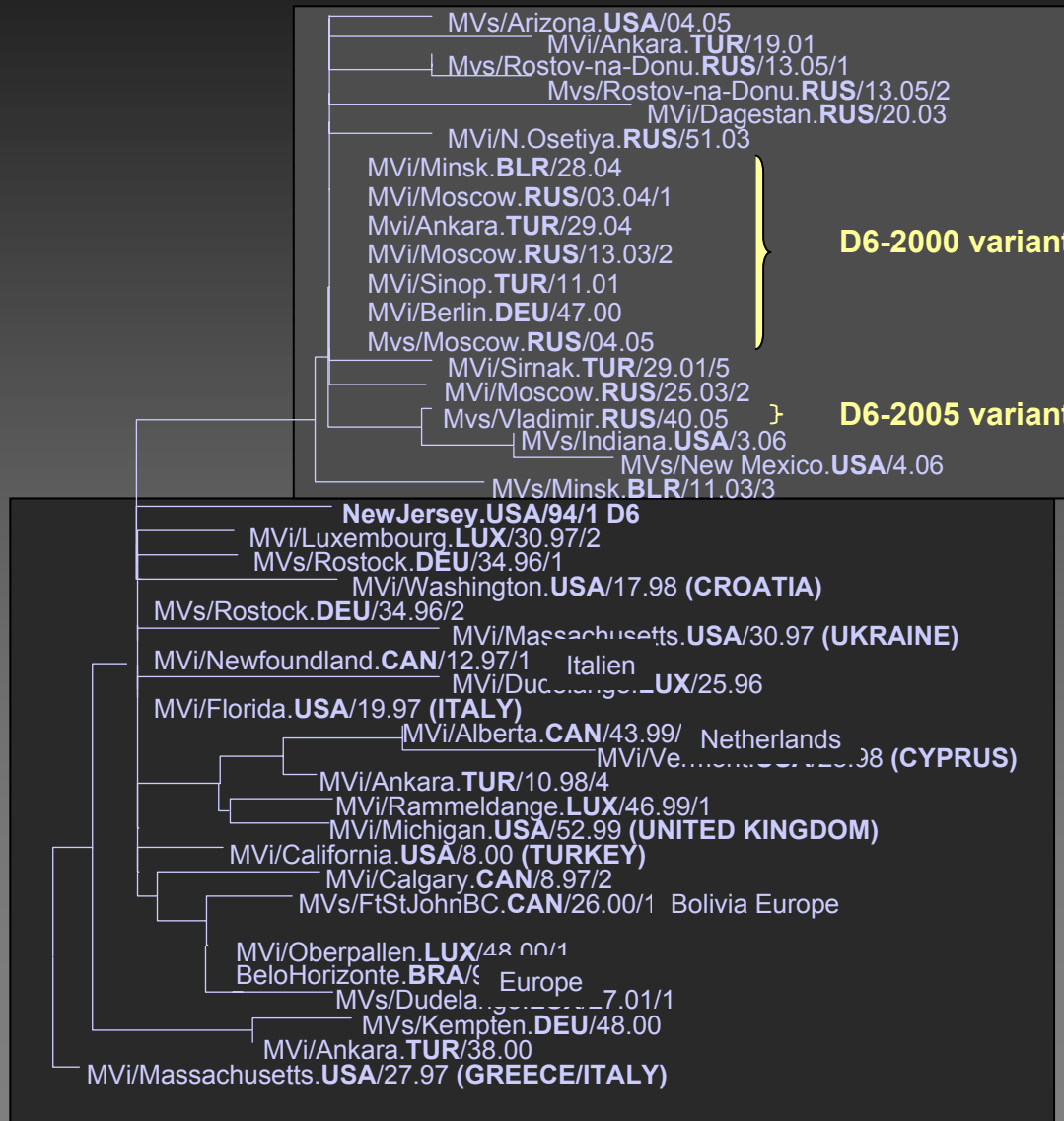


- 2000-2006
- Low genetic diversity
- Continuous endemic circulation

- 1996-2001
- High genetic diversity
- Transmission interrupted

2 nucleotides

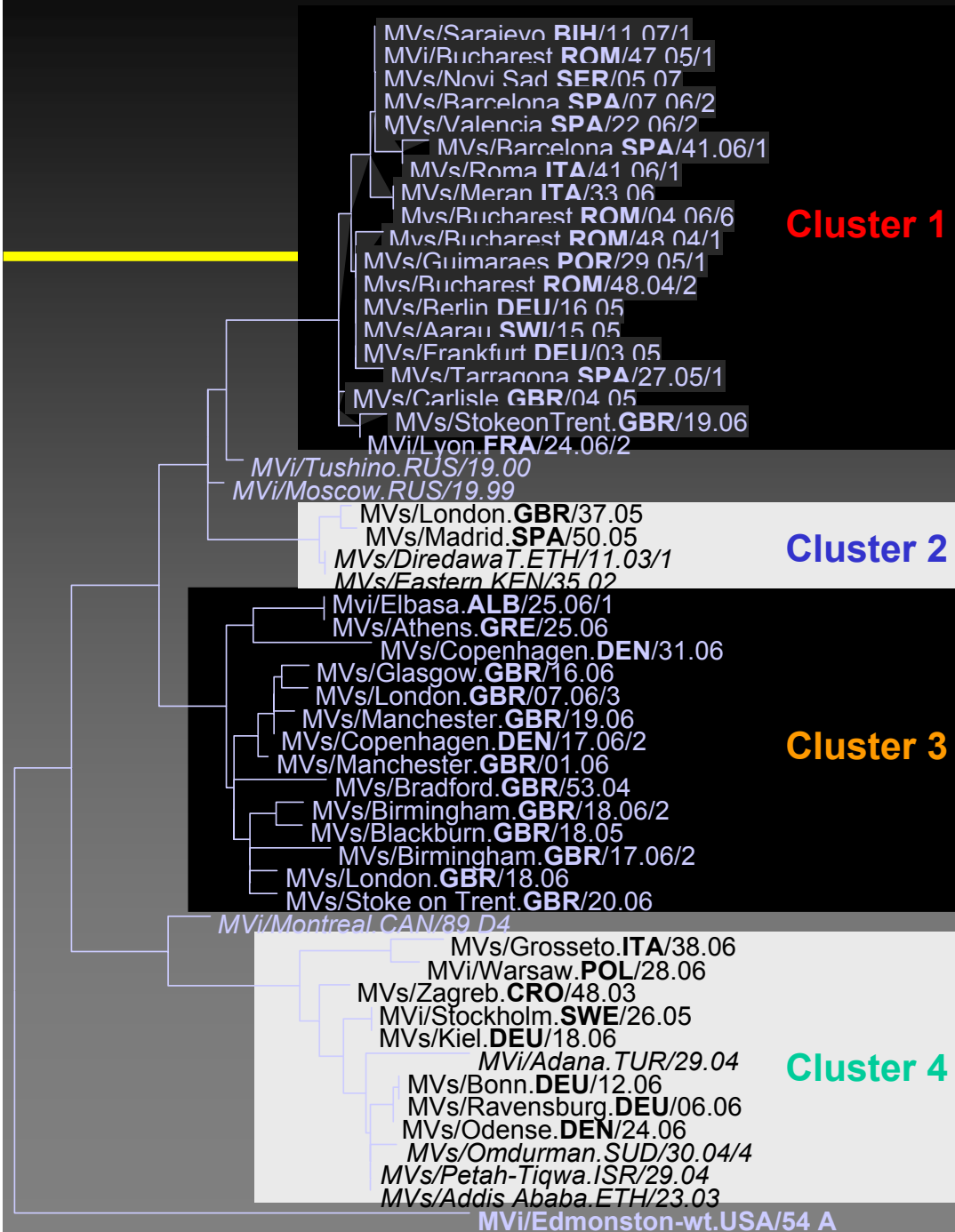
# Genotype D6 diversity in Europe 1996-2006



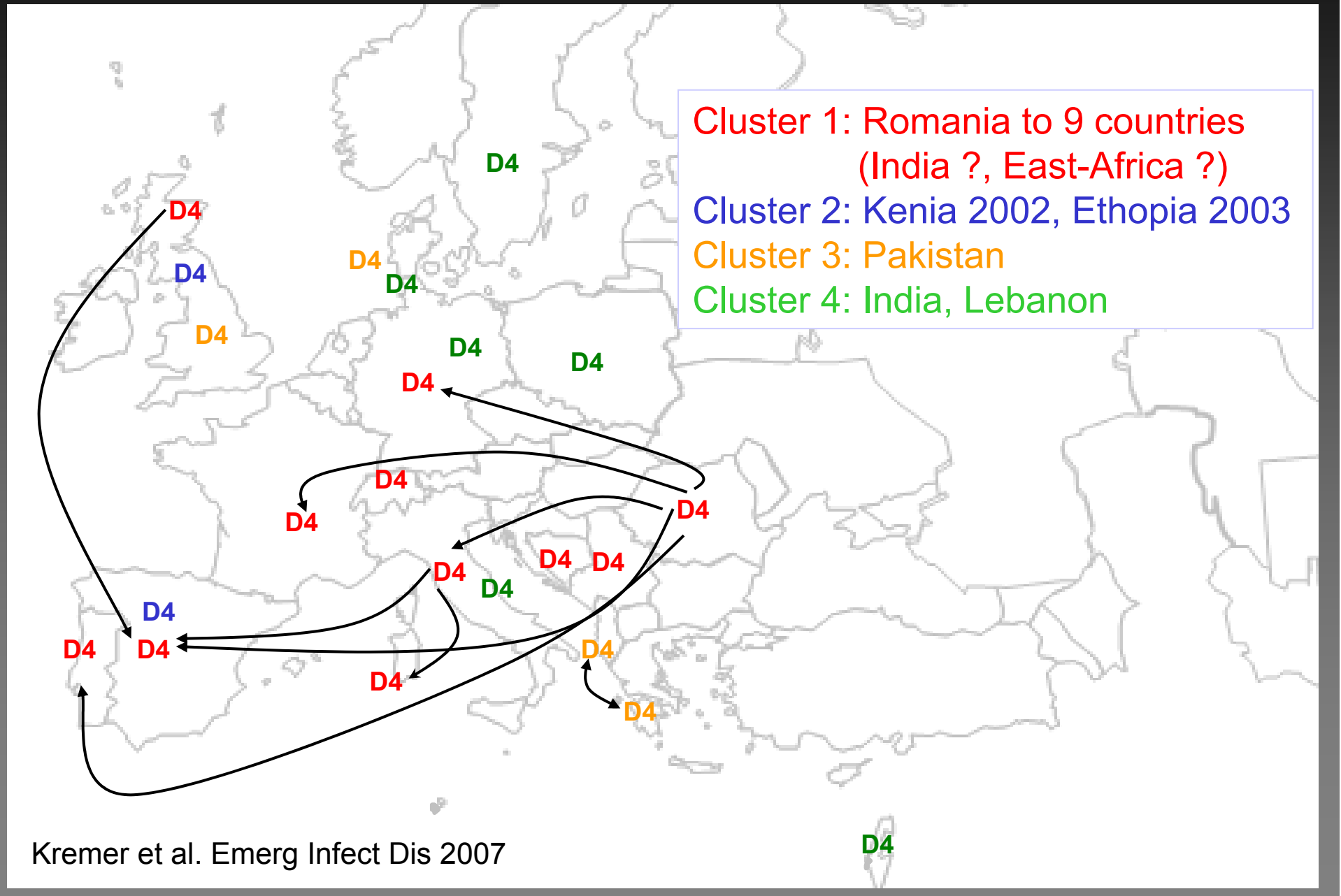
2005 in Germany, Switzerland, Israel, Russia  
2006 in Greece, Kazakhstan, Denmark, Uzbekistan

Ukraine variant: 2006 also in UK, Russia, Belarus, Spain, Latvia, Azerbaidjan, Estonia, Germany, Bulgaria

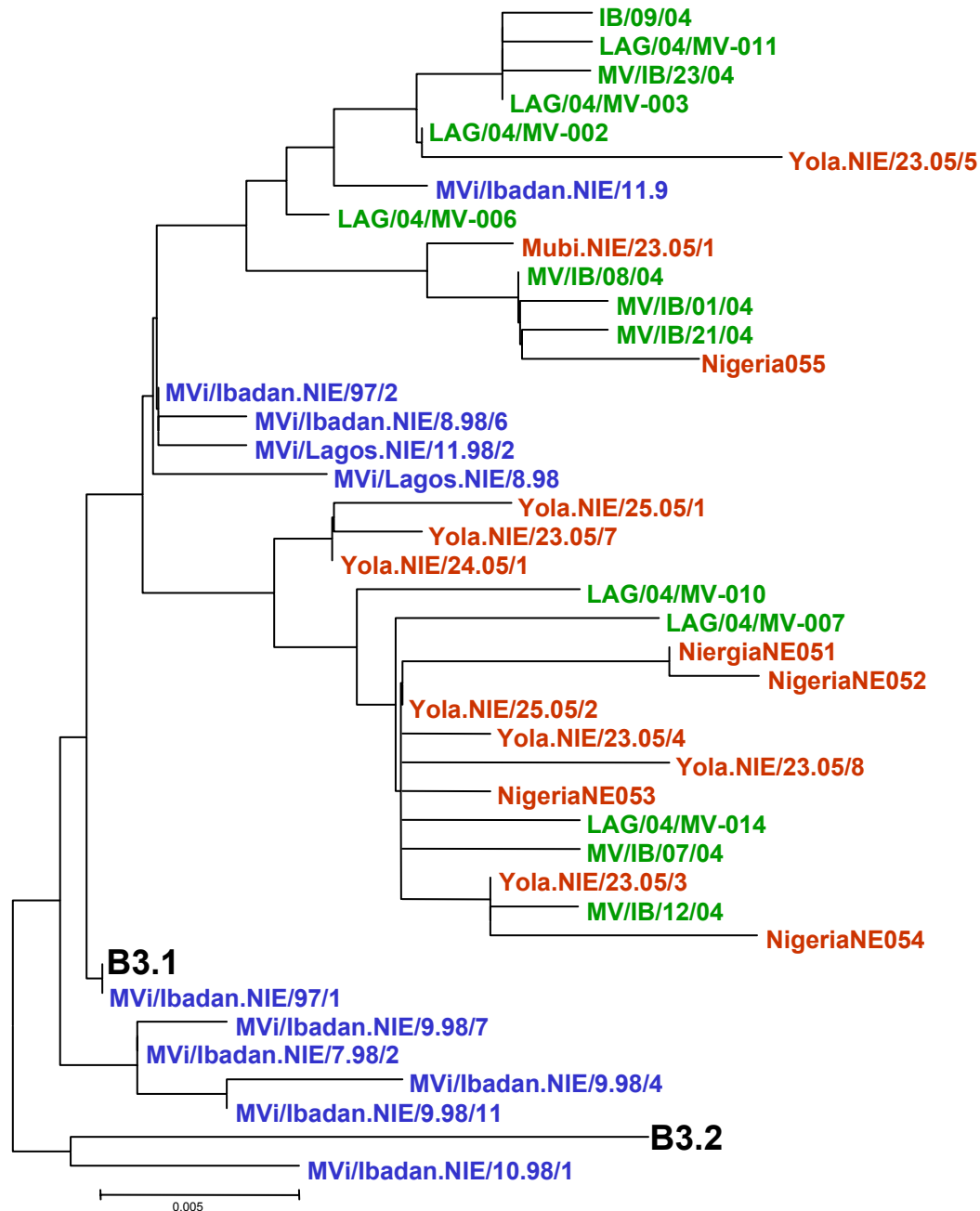
# Genotype D4 in Europe 2005-2006



# Transmission of D4 in 2005-2006



# Diversity of MV in Nigeria 1998-2005



## Ibadan/Lagos 2004

- 15 variants within 29 strains
- genetic distance: 0 to 2 %

## NIE Nigeria 2005

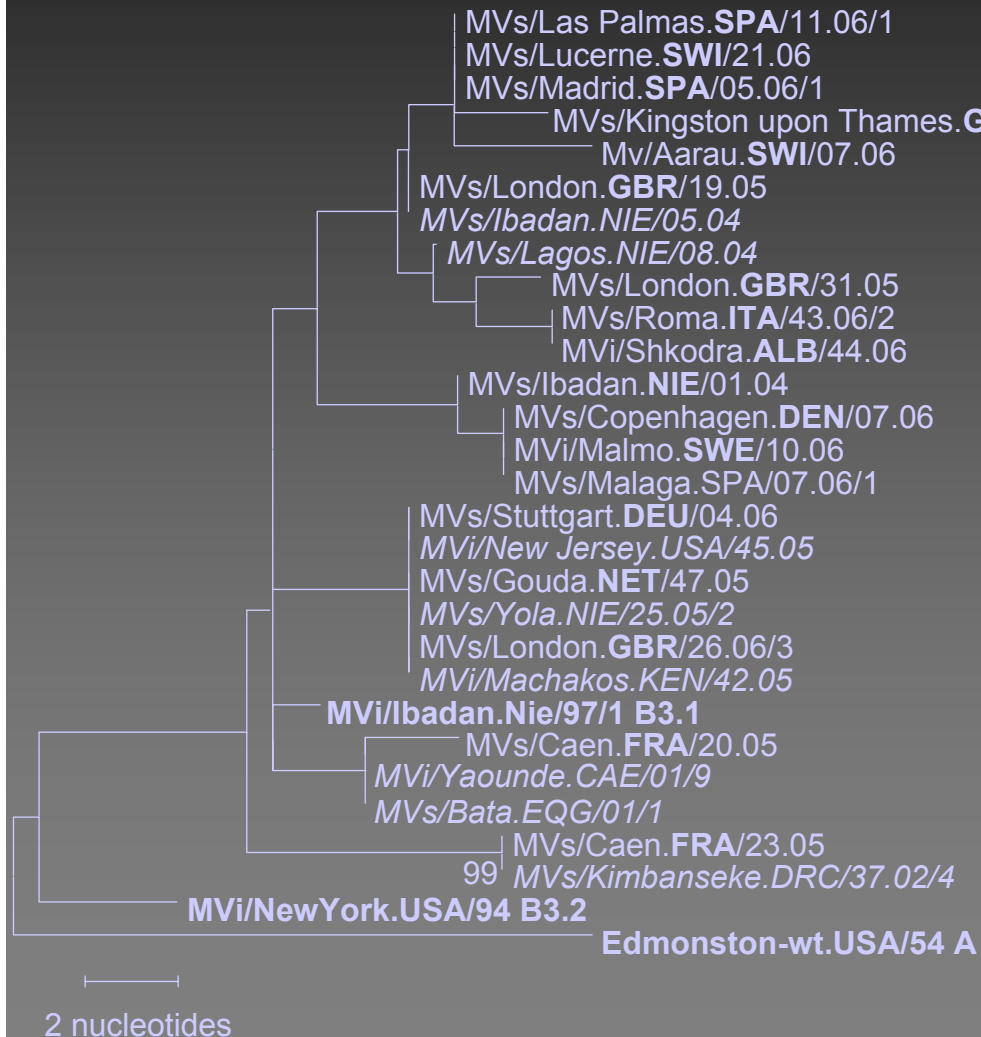
- 14 variants among 37 strains
- genetic distance: 0 to 3.1 %
- 8 variants among 10 strains collected within 2 weeks in Yola

## NIE Nigeria 2005

- No identical strains in 1998, 2004 and 2005
- B3.2 strains were only found in 1997/98
- Maximum genetic distance 1998-2005: 4.7 %

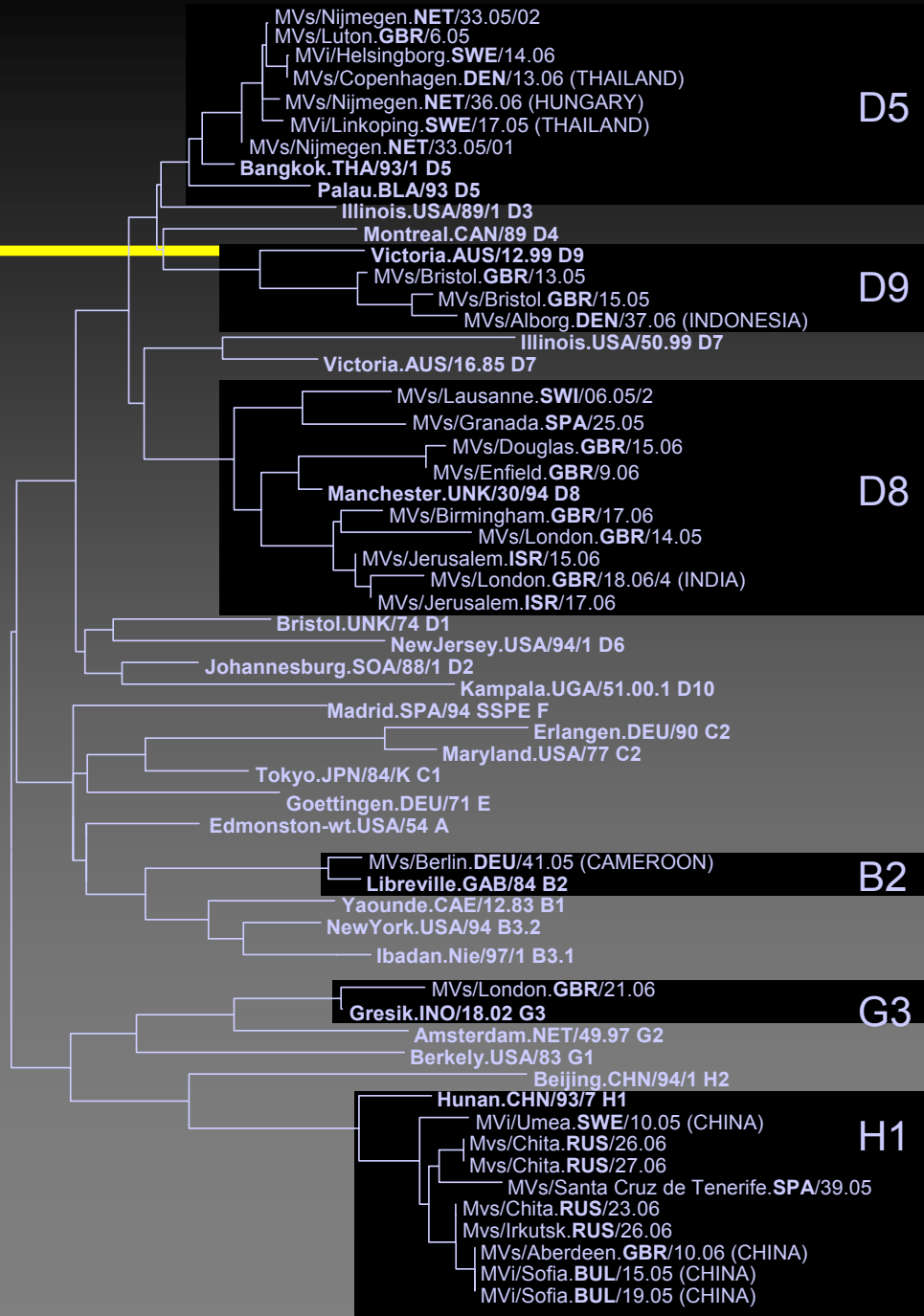
Hanses et al. 1999

# Genotype B3 Europe 2005-2006



- In Spain, Switzerland, UK, Italy, Albania, Germany, Denmark, Sweden, The Netherlands, France
- Multiple variants
- Maximum distance:
  - 13 nucleotides (2.9%)
  - (D4: 24 nucleotides 5.3%)
  - (D6: 7 nucleotides, 1.6%)
- Most likely several independent importations from Africa

# Other genotypes



D5: The Netherlands, UK, Sweden, Denmark

D8: UK, Spain, Switzerland, Israel

D9: UK, Denmark

B2: Germany

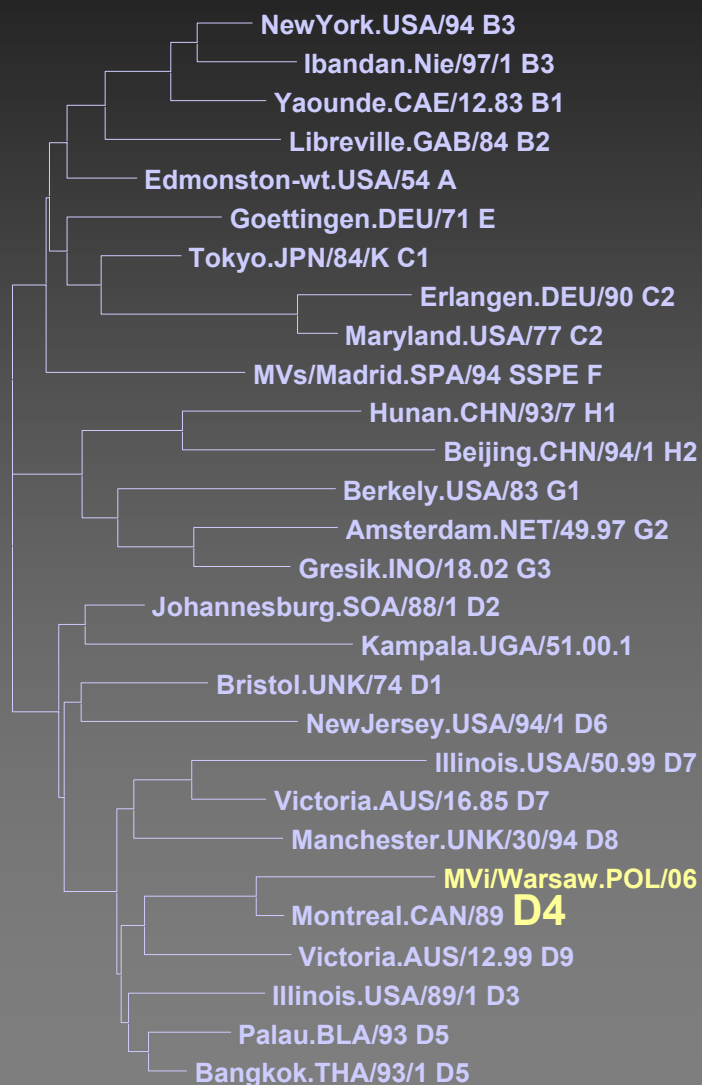
G3: UK

H1: Russia, Spain, UK, Bulgaria, Sweden

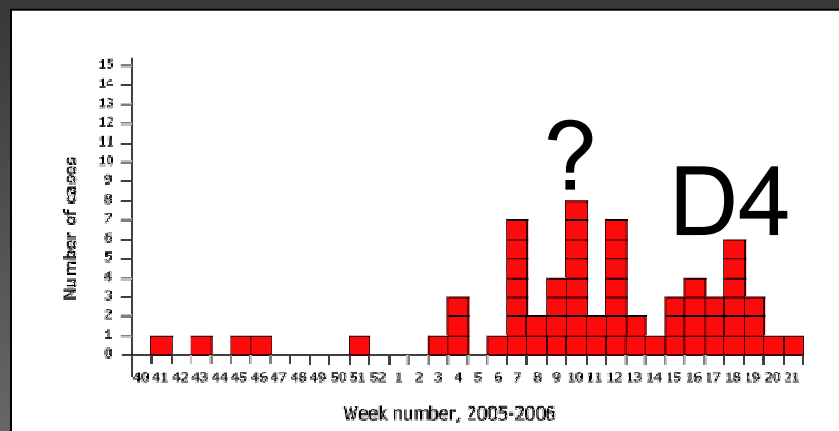
No indigenous C2 and no D7

5 nucleotides

# Poland 2006

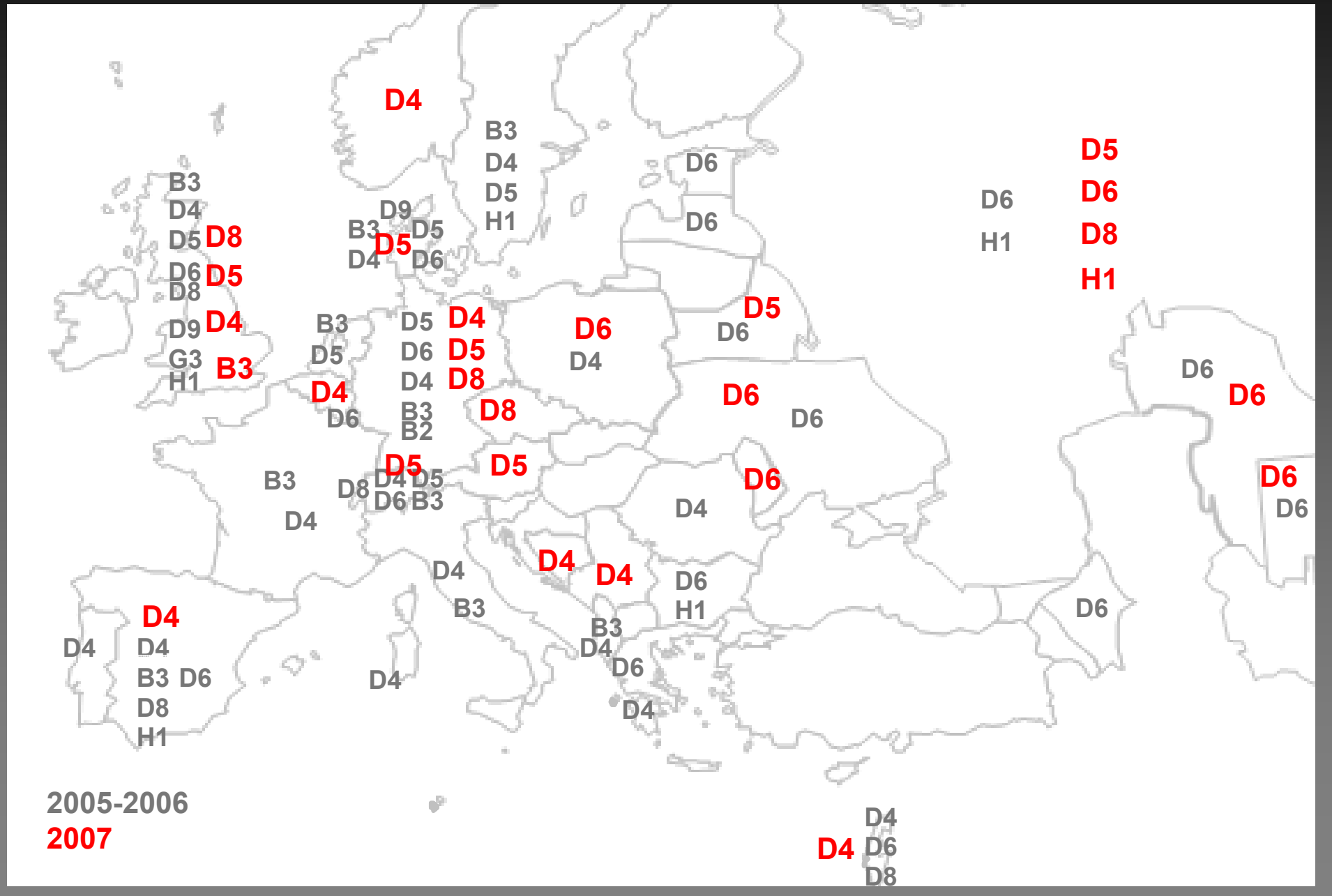


Measles clusters in different regions between Jan-May 2006 – suspected link to the Ukraine



- D4 strains during 2<sup>nd</sup> phase!
- Co-circulation of D6 during 1<sup>st</sup> phase?
- Epidemiological link to Ukraine not confirmed

# MV Genotypes 2007: Further reduction of diversity



# Identical D4 sequences in 6 countries



UK: April-December 2007

Outbreak in traveller community and Jewish Orthodox community

Norway: May 2007

Outbreak in traveller community linked to UK

Belgium: August-December 2007

Different clusters in Jewish orthodox community linked to UK and Israel

Germany: August 2007: 2 sporadic cases (UK)

Oct.-Dec. 2007: outbreak in Bavaria with suspected link to UK

Israel: August 2007-?

Outbreak in Jewish orthodox community linked to Belgium and UK

US: November 2007

Sporadic case linked to Israel

United States

D4

D4

# Measles Genotypes in Euro 2005-2007

## Summary and Conclusions

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- D6, D4 and B3 dominated in 2005-2007
- D6 continues to be endemic in Europe but diversity decreases compared to the 1990s
- Multiple importations of D4 and B3 from other continents
- Sporadic importations of other genotypes (D8, G3, B2, H1, D5, D9)

→ Endemic transmission of many variants (genotype C2, D7 and partially D6) has been interrupted in EURO

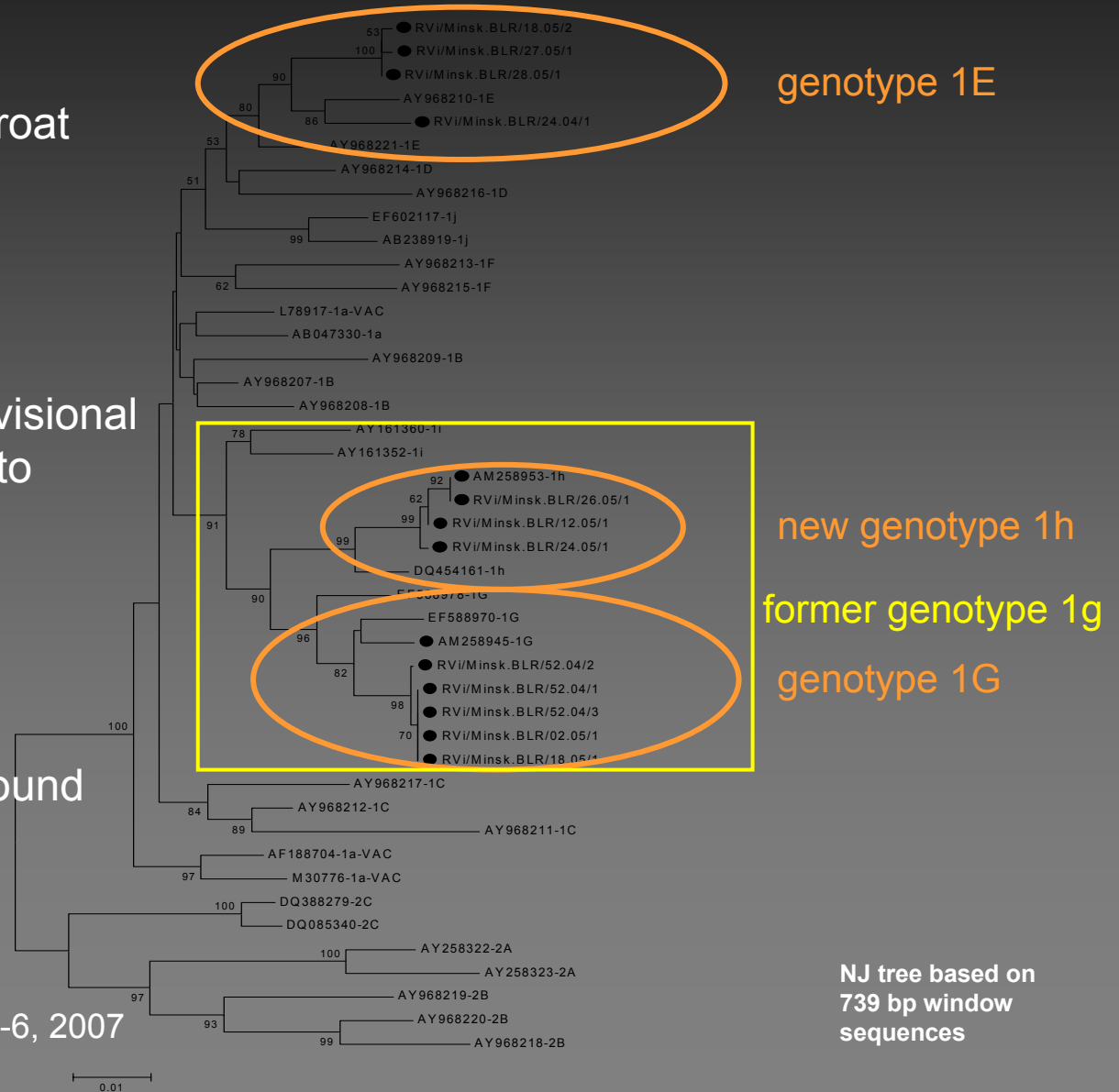
But: Large outbreaks in EURO (2005-2007) were due to continued endemic transmission of MV and the introduction of imported strains into hard-to-reach populations

# Genotyping of RV isolates from Belarus

- First RV strains from Belarus
- 14 isolates from urine and throat swabs
- Lineages
  - 2 lineages of 1E
  - 2 lineages of former provisional genotype 1g separated into
  - new genotype 1h
  - genotype 1G

• New genotypes can still be found (even) in Europe

• Huebschen et al. J Gen Virol 88, 1960-6, 2007



# Molecular epidemiology

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- Monitor transmission of measles virus during and after outbreaks
- Define geographic distribution of MV genotypes
- Detect interruption of indigenous virus circulation
- Differentiate between endemic virus and imported virus
- Monitor efficiency of vaccination strategies
- Estimate the number of co-circulating variants
- Confirm suspected vaccine reactions

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