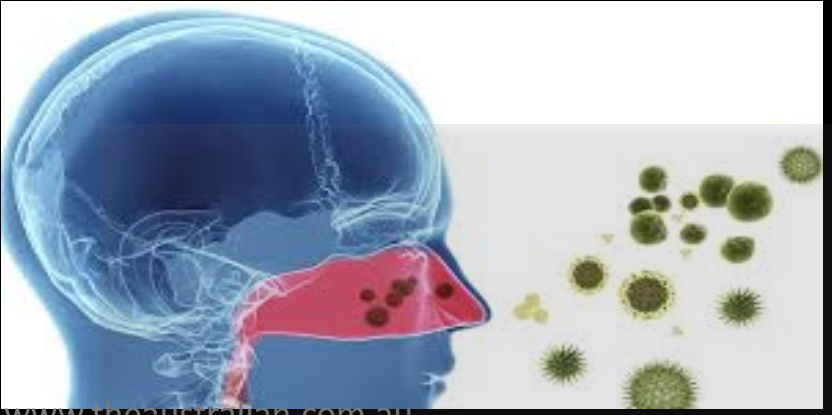
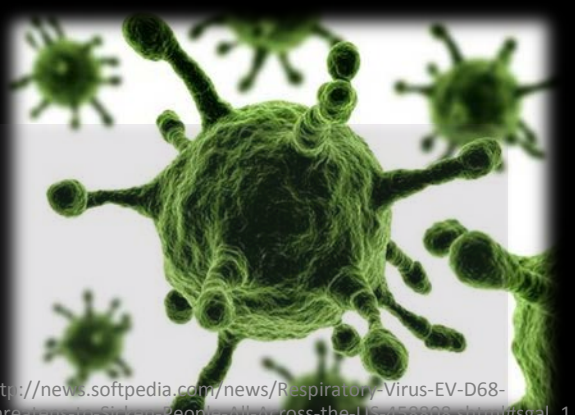
Emergence and resurgence of human enterovirus 68

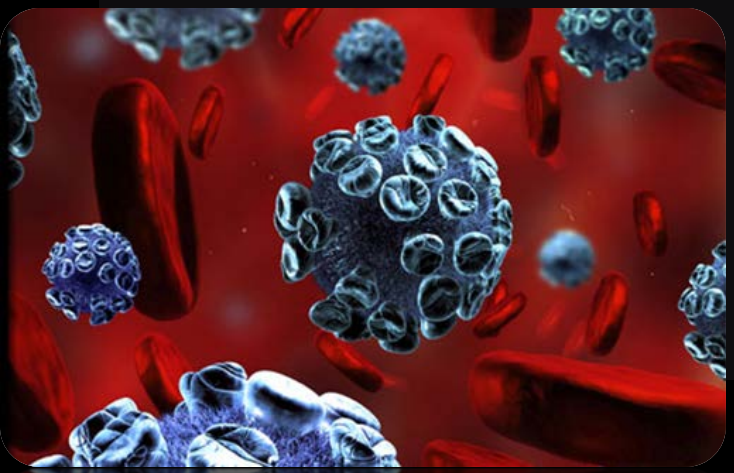


www.theaustralian.com.au



http://news.softpedia.com/news/Respiratory-Virus-EV-D68-Threatens-to-Sicken-People-All-Across-the-US-438806.shtml#sgal_1

Rhinovirus and Enterovirus D68



http://www.webmd.com/children/es/slideshow-enterovirus-68

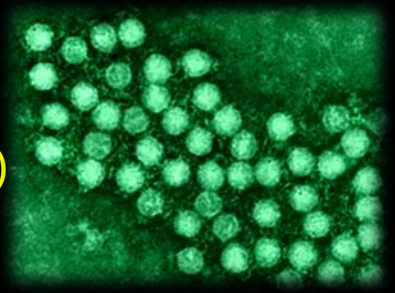
Respiratory virus detected among pediatric patients

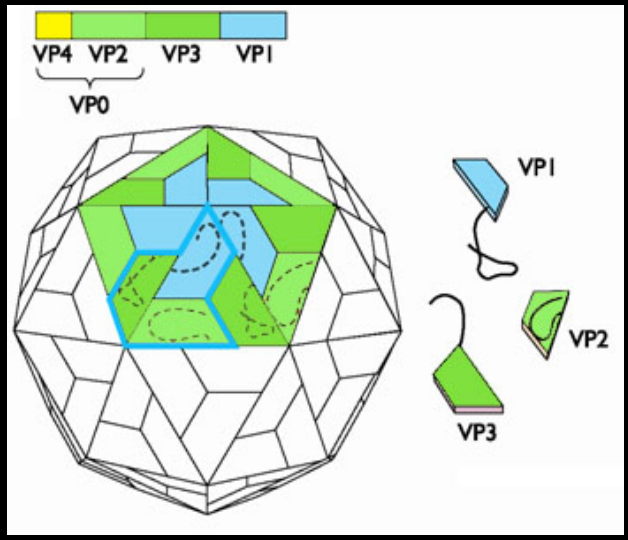
Human Enterovirus

Picornavirus	
Virus classification (ICTV)	
Group: Group IV ((+)ssRNA)	
Family: *Picornaviridae*	
Genera	
Enterovirus	*Aphthovirus*
Hepatovirus	*Parechovirus*
Cardiovirus	*Kobuvirus*
Erbovirus	*Teschovirus*
Sapelovirus	*Tremovirus*
Senecavirus	*Avihepatovirus*

- The most important neurotropic virus identified during infancy and childhood.
- family *Picornaviridae*, genus *Enterovirus*
- replicate both in respiratory and alimentary tract
- transmitted predominantly via oral-fecal route
- a small non-enveloped virus (30 nm)
- incubation period 3-5 days

- Positive ssRNA genome (7.4 kb) icosahedral capsid enclosed





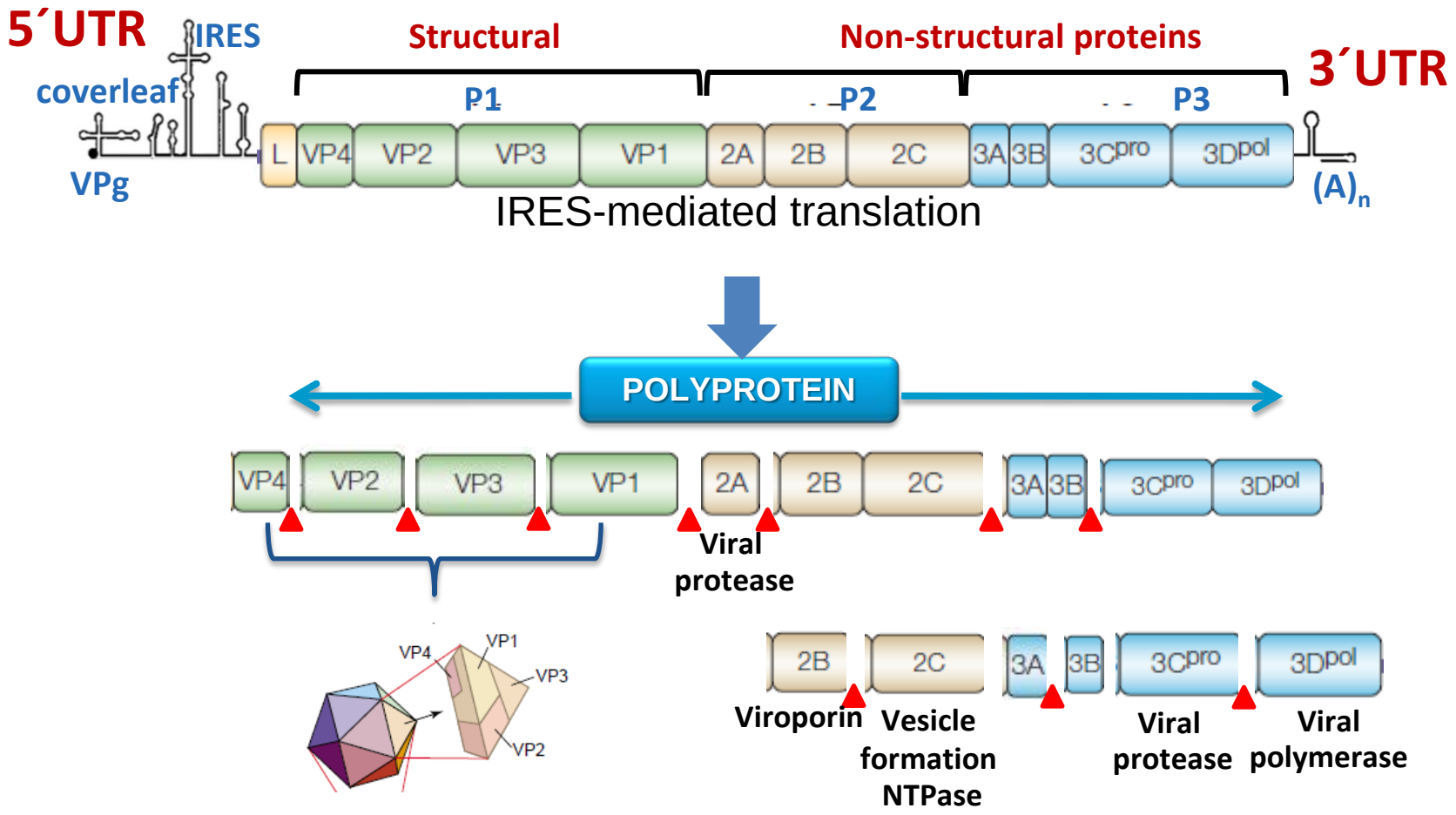
Mackay I. *J of Clin Virol* 2008; 42

Enterovirus

Family:- ***Picornaviridae***
Genus:- ***Enterovirus***

Enterovirus A	**Human** Enterovirus	EV-A71, CV-A16
Enterovirus B		CV-B
Enterovirus C		Poliovirus, Hepatitis A, EV-C105
Enterovirus D		EV-D68
Enterovirus E	**Bovine**	
Enterovirus F		
Enterovirus G	**Porcine**	
Enterovirus H	**Simian**	
Enterovirus J		
Rhinovirus A	**Human** Rhinovirus	
Rhinovirus B		
Rhinovirus C		

Enterovirion



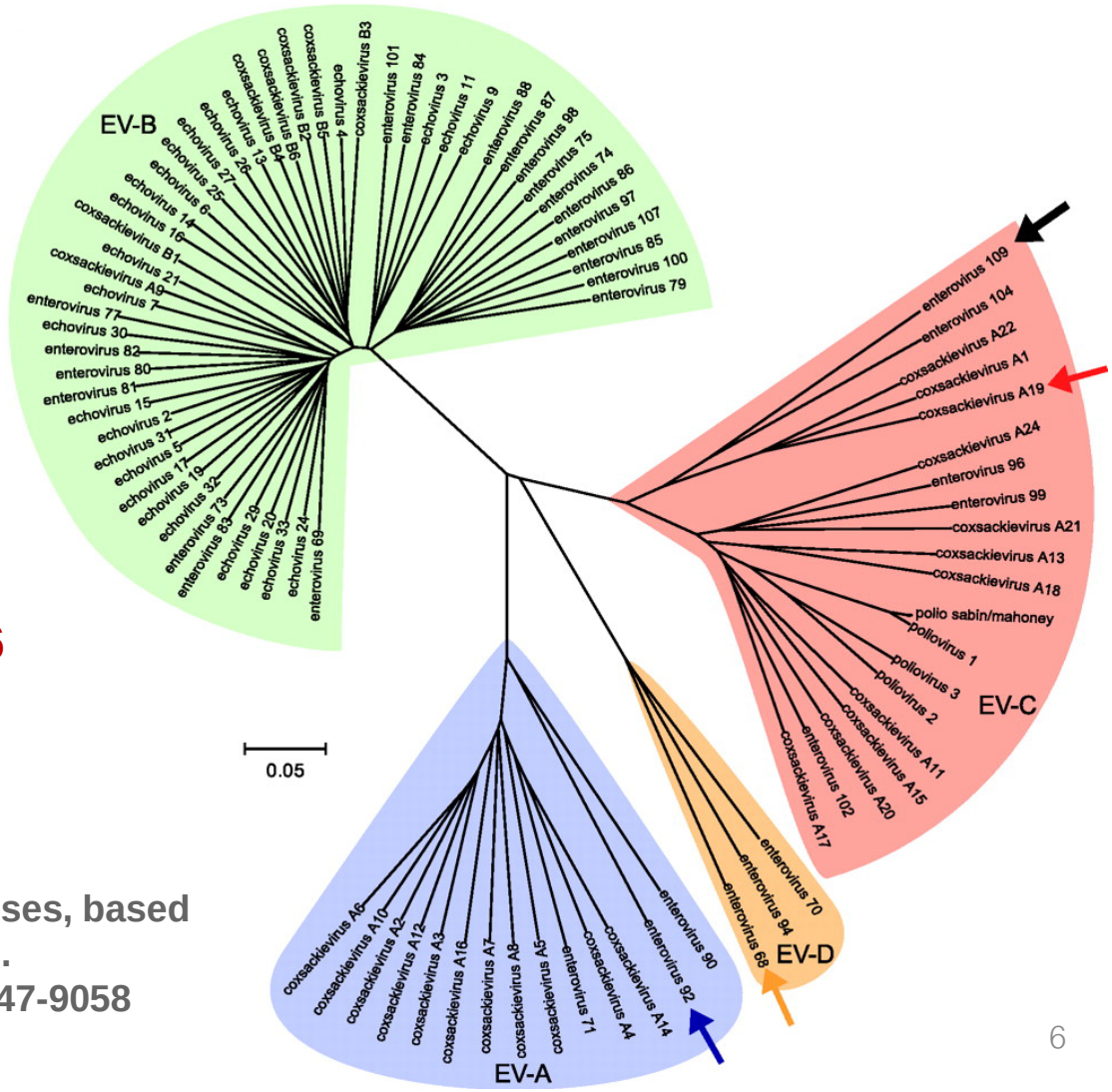
Microbiology, *Nature Reviews* ; 2005

Genetic variability of Human Enterovirus

- 89 serotypes categorized into 4 species

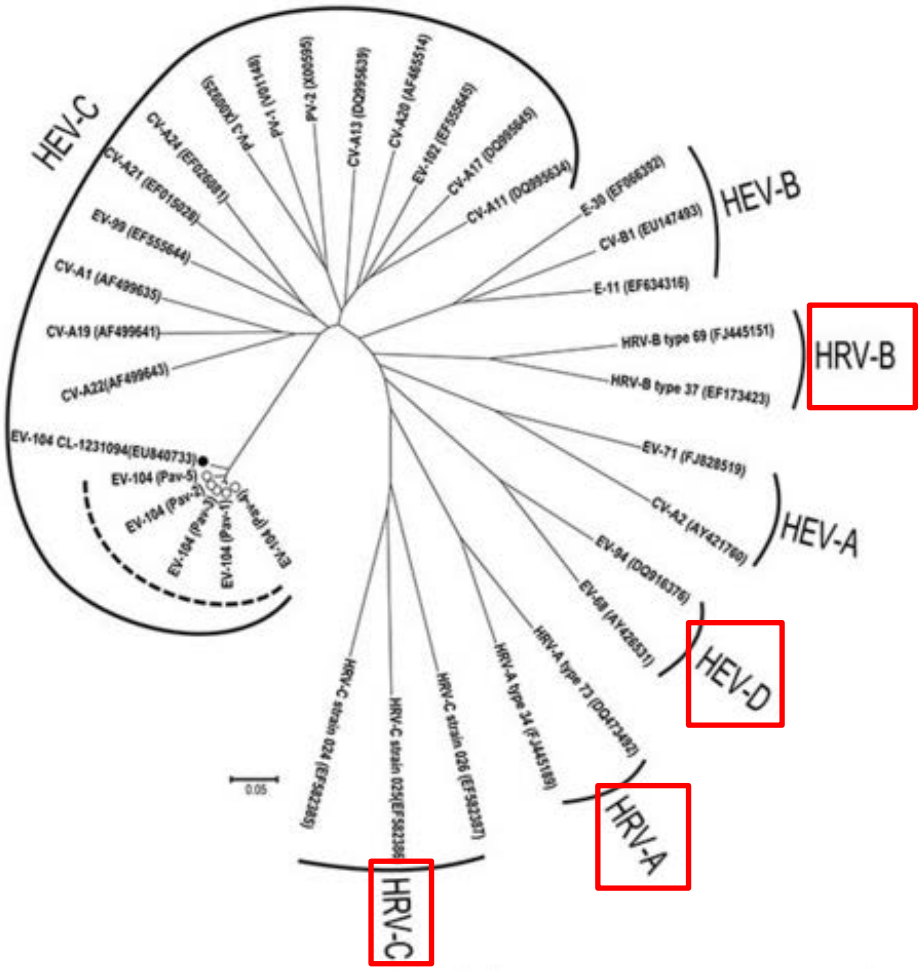
HEV-A	**(14)**
HEV-B	**(52)**
HEV-C	**(20)**
HEV-D	**(3)**

predominantly found in hand foot and mouth disease including EV71, CA16 and CA6



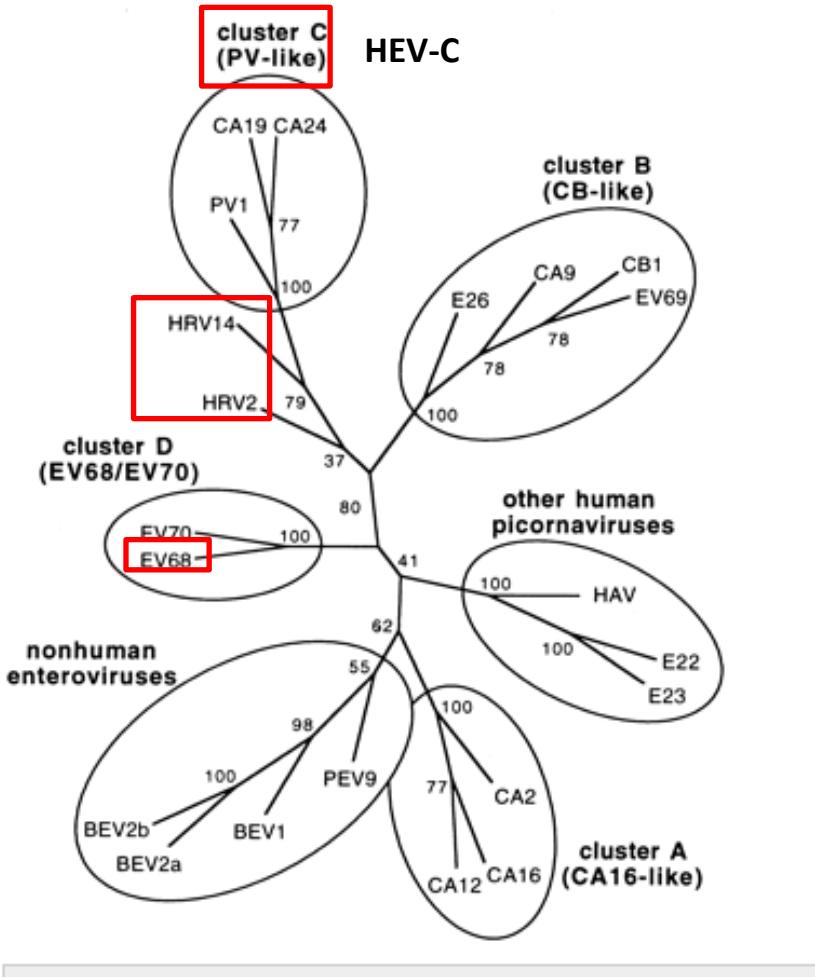
Relationships between known enteroviruses, based on full-length genome analysis.
Yozwiak N L et al. J. Virol. 2010;84:9047-9058

VP4/VP2



Piralla et al., 2010

VP1



Oberste et al., 1999

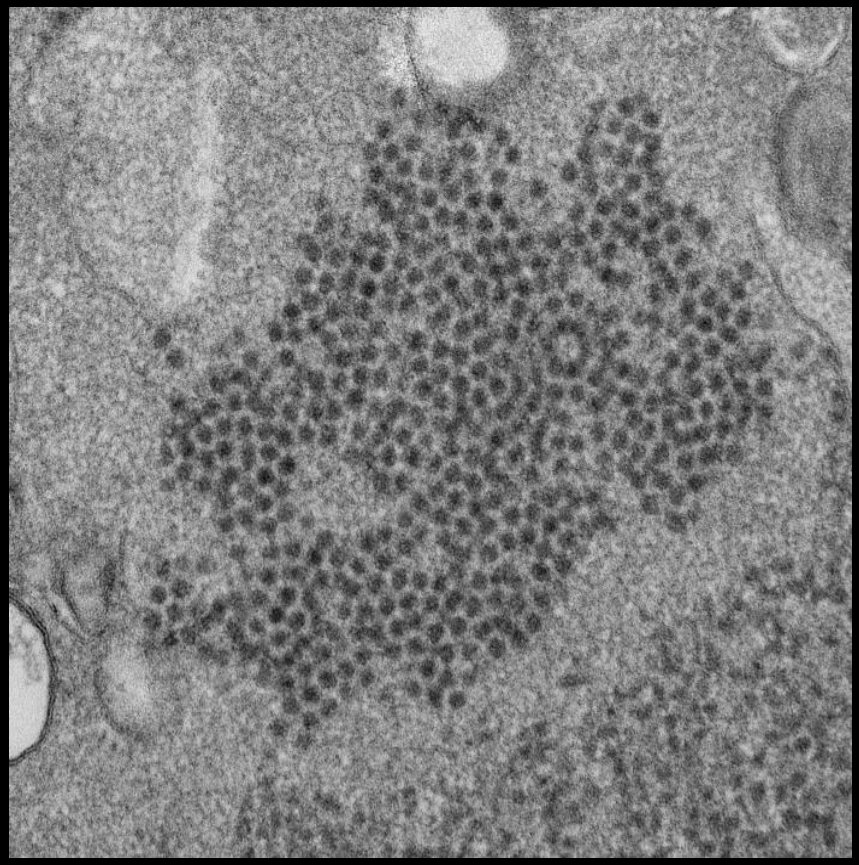


Image source: Cynthia S. Goldsmith and Yiting Zhang, CDC

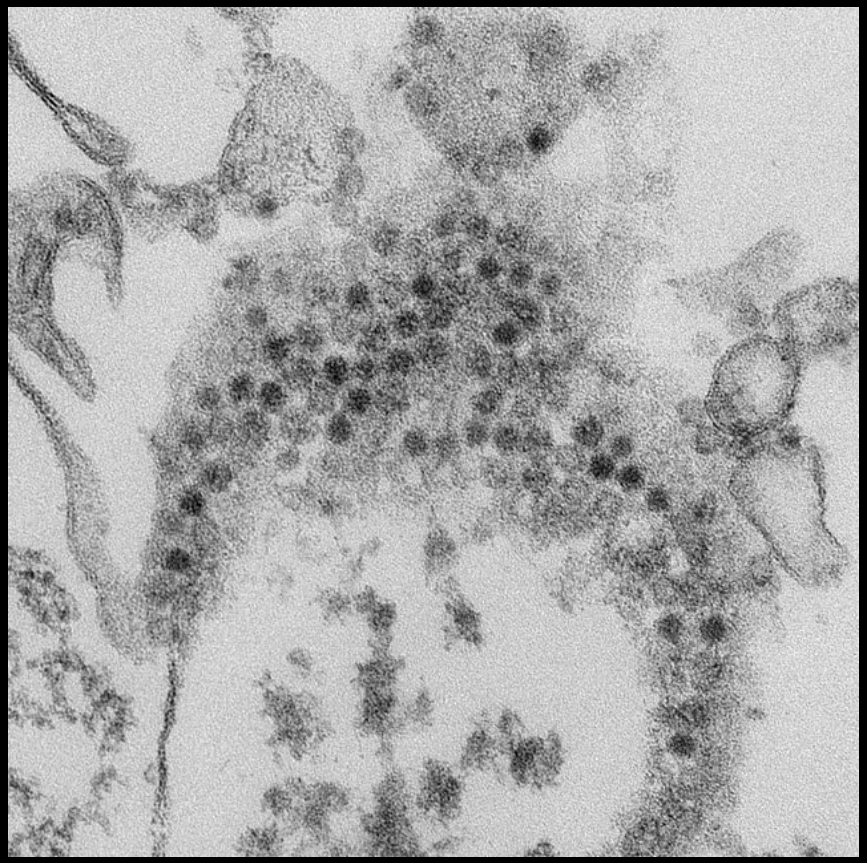
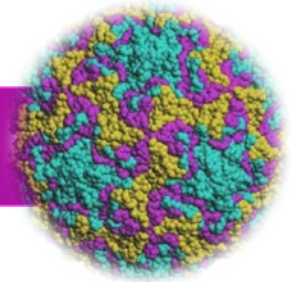
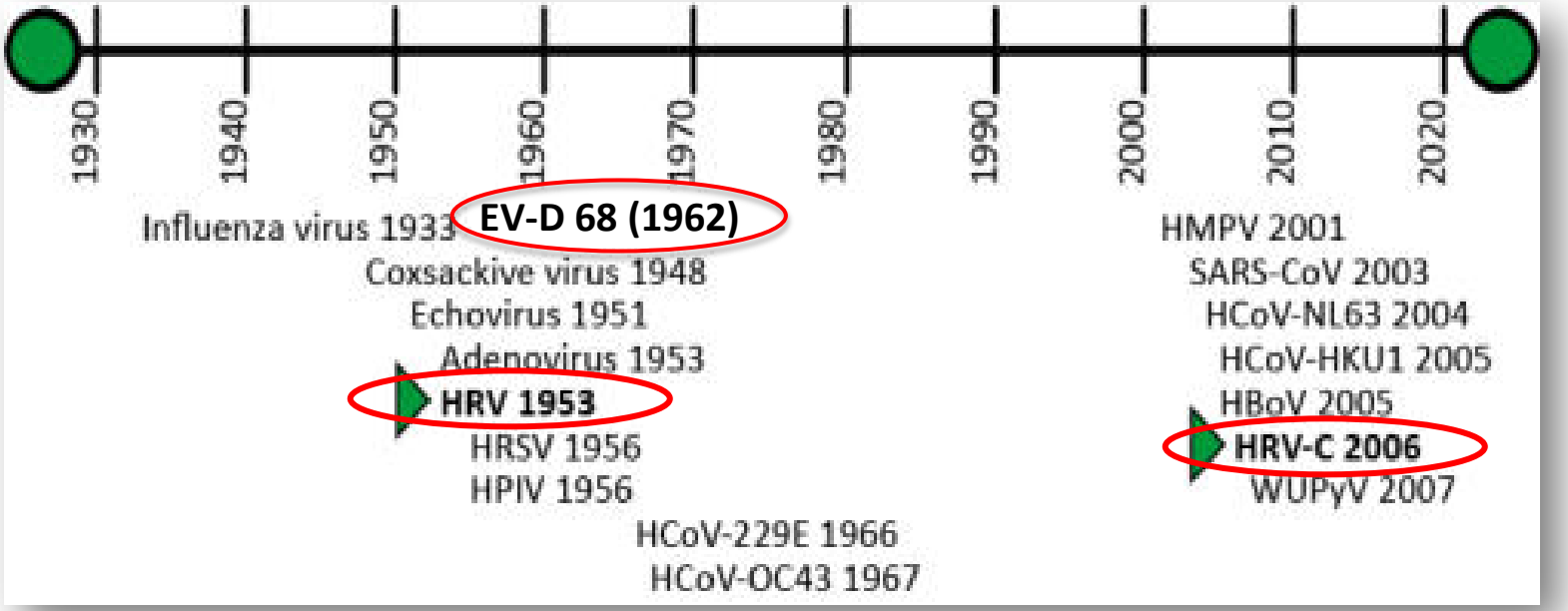


Image source: Cynthia S. Goldsmith and Yiting Zhang, CDC

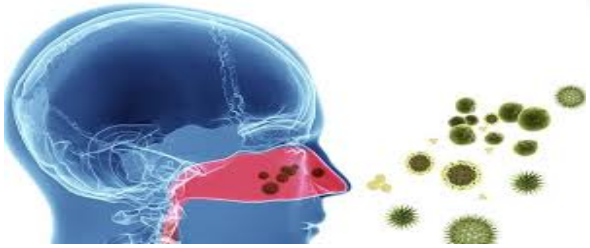
Human RHINOVIRUS (HRV)



-first isolated in the 1953



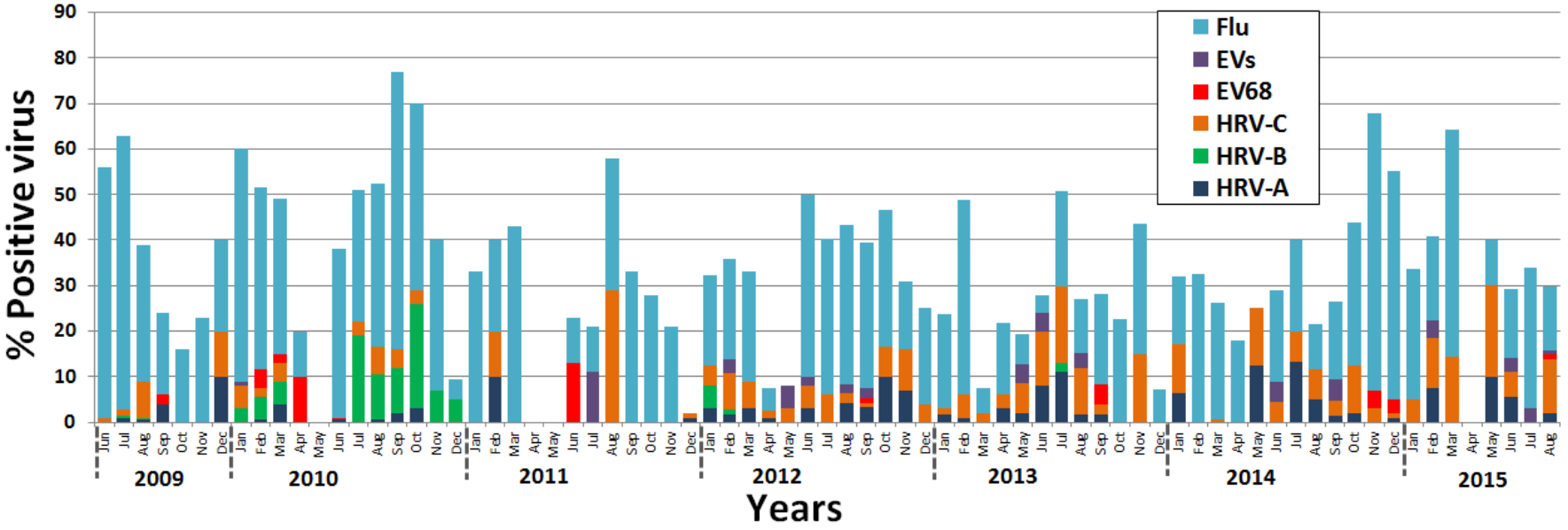
http://www.uq.edu.au/vdu/VDURhinovirus.htm



www.theaustralian.com.au

- **"common cold viruses" - frequent causative agents of mild upper respiratory tractinfections**

Percentage of respiratory virus detection in ILI patients



(Jun09-Aug15)

- HRV = 8.4% (HRV-A = 3.1%, B=1.5%, C=3.8%)
- EV68 = 0.8% other EV = 0.2%

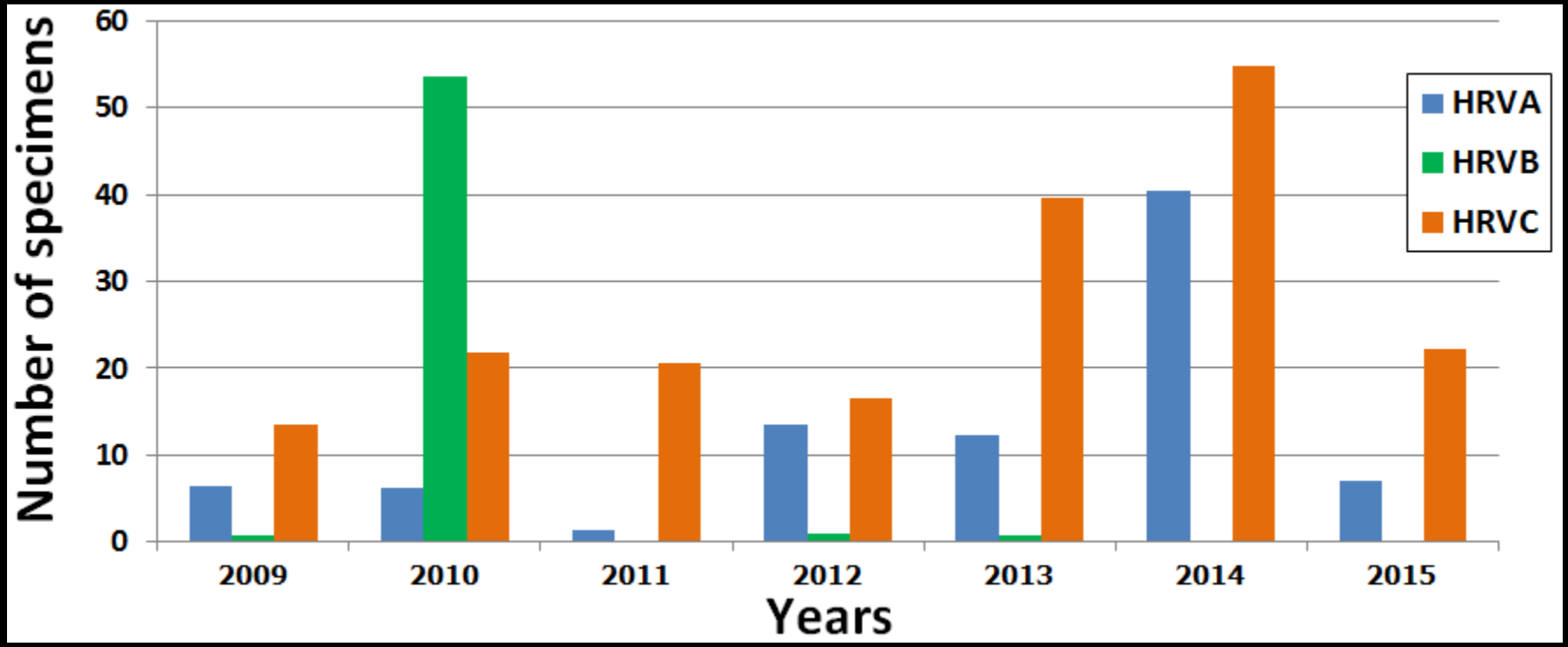
Clinical symptoms

	pH sensitivity	Optimum growth temperature	Site of infection
HRV	acid lability	~ 33°C	respiratory tract

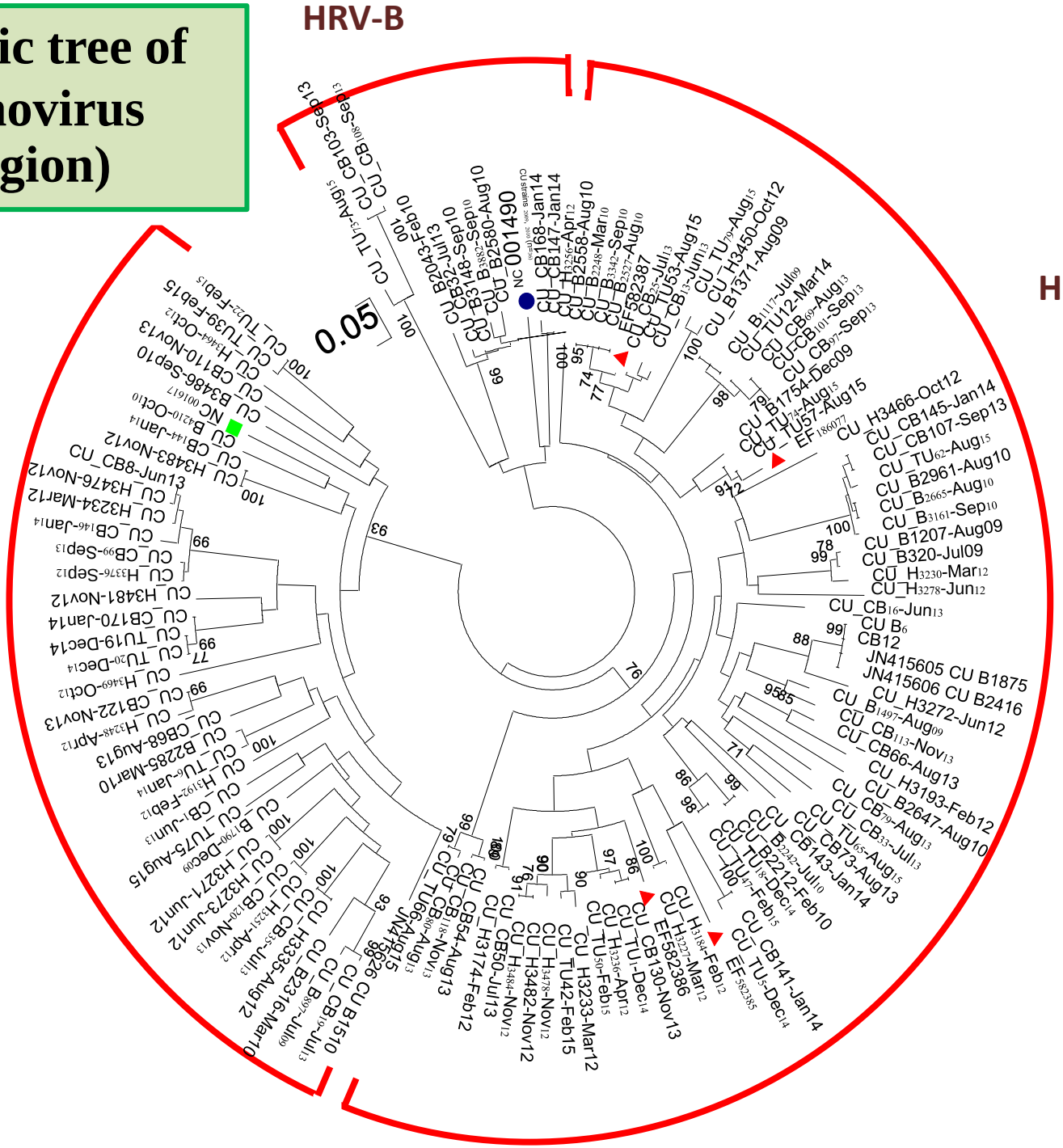
- replicate in the ciliary epithelial cells of the nasal mucosa (lesser extent oral cavity and throat)

- Upper respiratory tract, or common colds
- Lower respiratory tract
  - Pneumonia,
  - wheezing in children,
  - exacerbations of asthma and chronic obstructive pulmonary disease (COPD) in adults
- More severe diseases
  - Acute otitis media in children
  - sinusitis in adults

Prevalence of human rhinovirus in pediatric patients in Thailand, 2009-2015



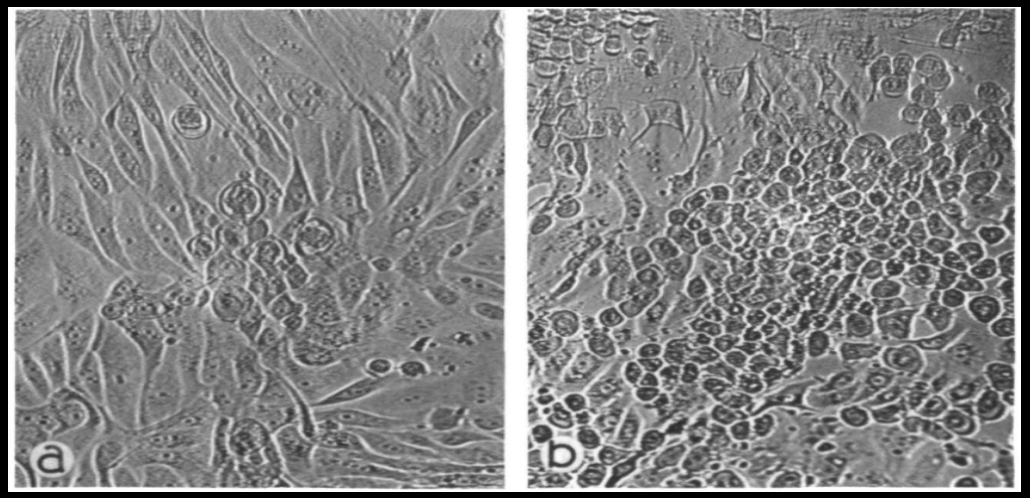
Phylogenetic tree of Thai rhinovirus (VP4 region)



History of EV-D68

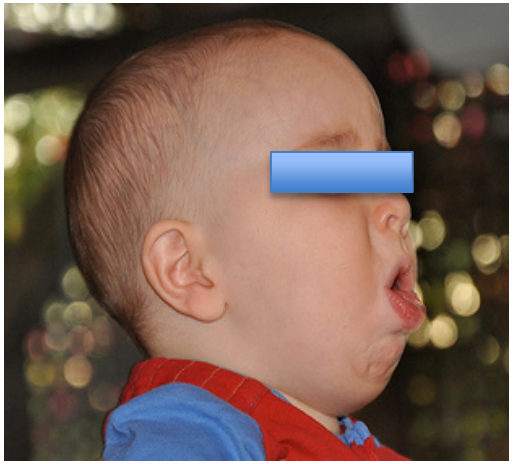
- **Enterovirus D68** (EV-D68) was first identified in **1962** in United State from four pediatric patients with pneumonia and bronchiolitis

Family: ***Picornaviridae***
Genus: ***Enterovirus***
Species: ***Enterovirus D***

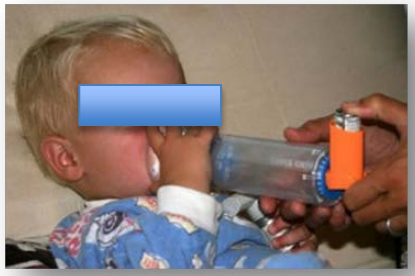


Monkey kidney cells infected with Fermon virus.
(a) shows a single small focus of infected cells. (b) shows an advanced stage of infection; nearly all cells are morphologically altered. (Schieble, Fox et al. 1967)

Clinical Manifestations

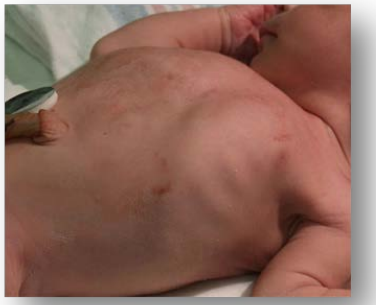


http://www.examiner.com/infant-health-in-national/with-whooping-cough-cases-on-the-rise-cdc-recommends-adult-pertussis-vaccine-for-infant-caregivers



http://www.allergyasthmazone.com/childhood-asthma/wheezing-may-be-a-sign-of-infant-asthma-in-some-little-children-but-not-always/

http://blogs.rrc.ca/wellness/2014/04/watching-paint-dry-what-actually-happening/

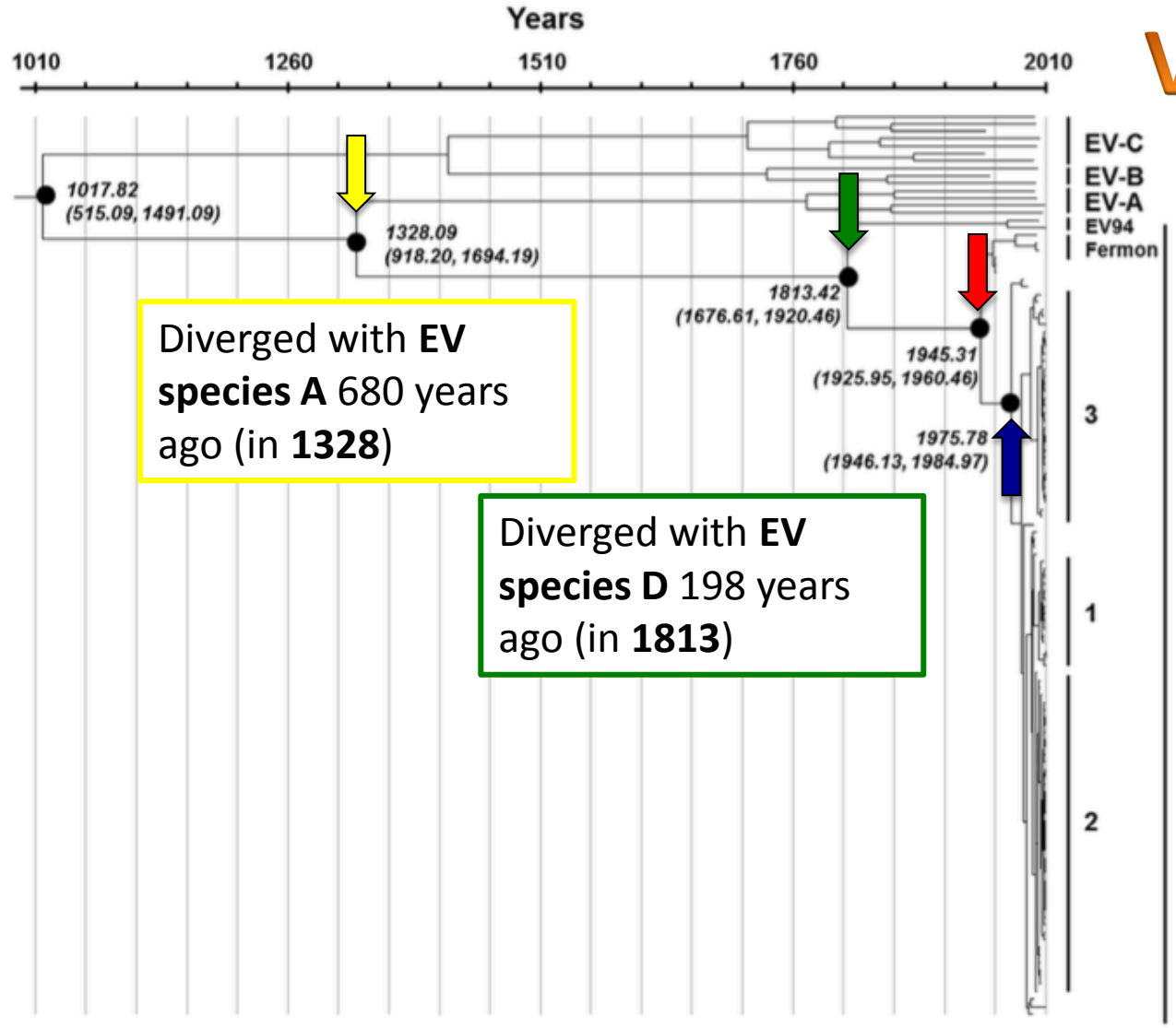


http://drugster.info/ail/pathography/3169/

- **EV-D68** has been reported to cause mild to severe respiratory illness, include upper and lower respiratory manifestations

- **cold-like or influenza-like illness,**
- **atelectasis,**
- **pneumonia,**
- **airway obstruction,**
- **fever,**
- **Rash,**
- **neurologic illness**
  - **aseptic meningitis**
  - **encephalitis**

The evolutionary timescale of EV68-VP1 sequences



Diverged with **EV species A** 680 years ago (in **1328**)

Diverged with **EV species D** 198 years ago (in **1813**)

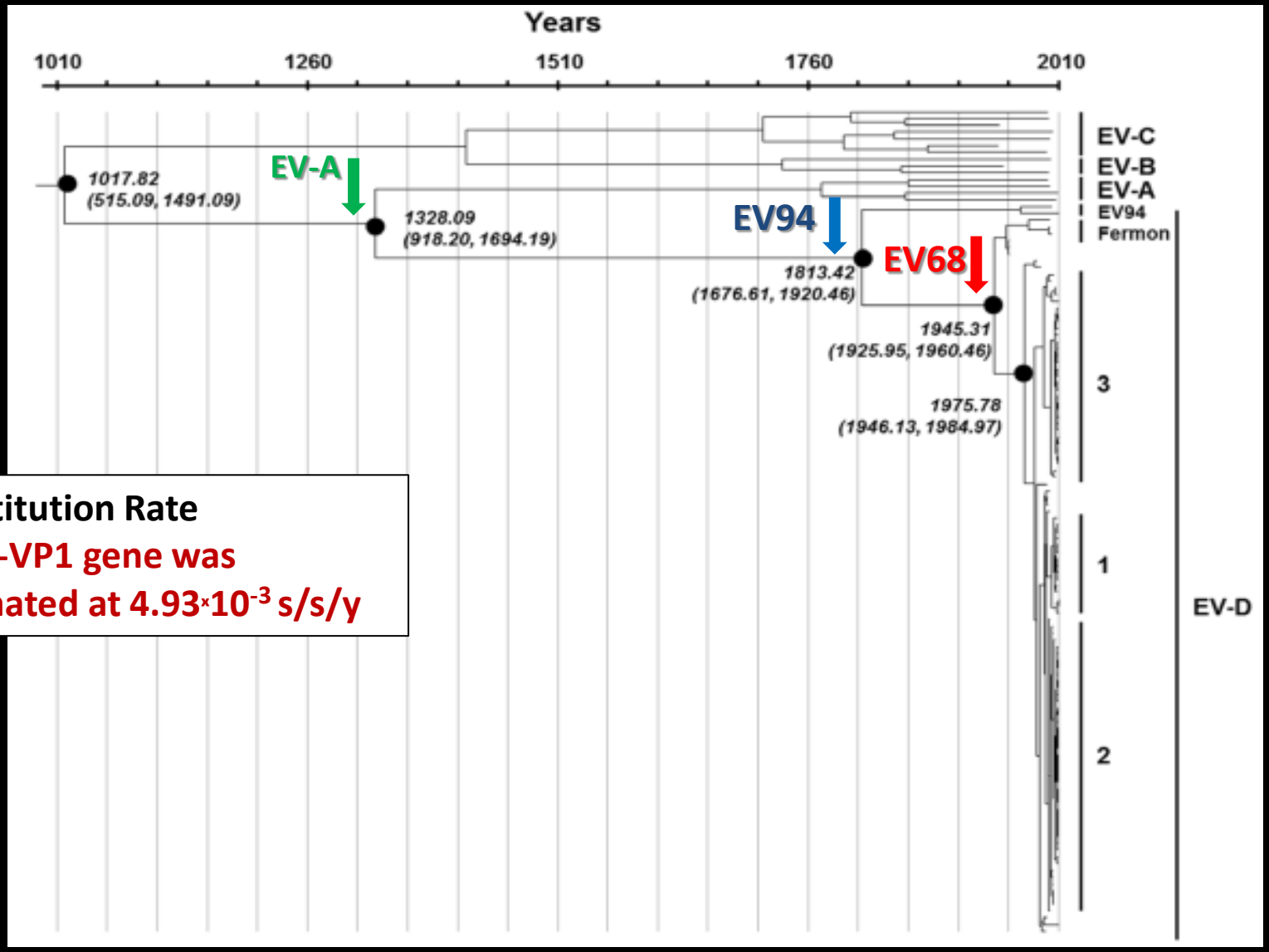
EV68 first isolated prototype (**Fermon strain**) in **1945**

branched off **into 3 clusters** of EV68 in the **1970s**

Figure 3. Bayesian time-scale phylogeny of EV68 and other EVs based on the partial VP1 sequence analysis (dataset 1 containing 122 sequences with 723 nt in length). Maximum clade credibility tree obtained with BEAST with a constant size coalescent prior showing lineage splitting events since the most recent common ancestor to the presently circulating EV68 strains. The divergence times correspond to the mean posterior estimate of their ages. For the TMRCA, the correspondent 95% Bayesian credible intervals are shown. Time axis is shown in years and ranges from the TMRCA to the present year.

CE of Clinical Virology . PLoS One. 2012.

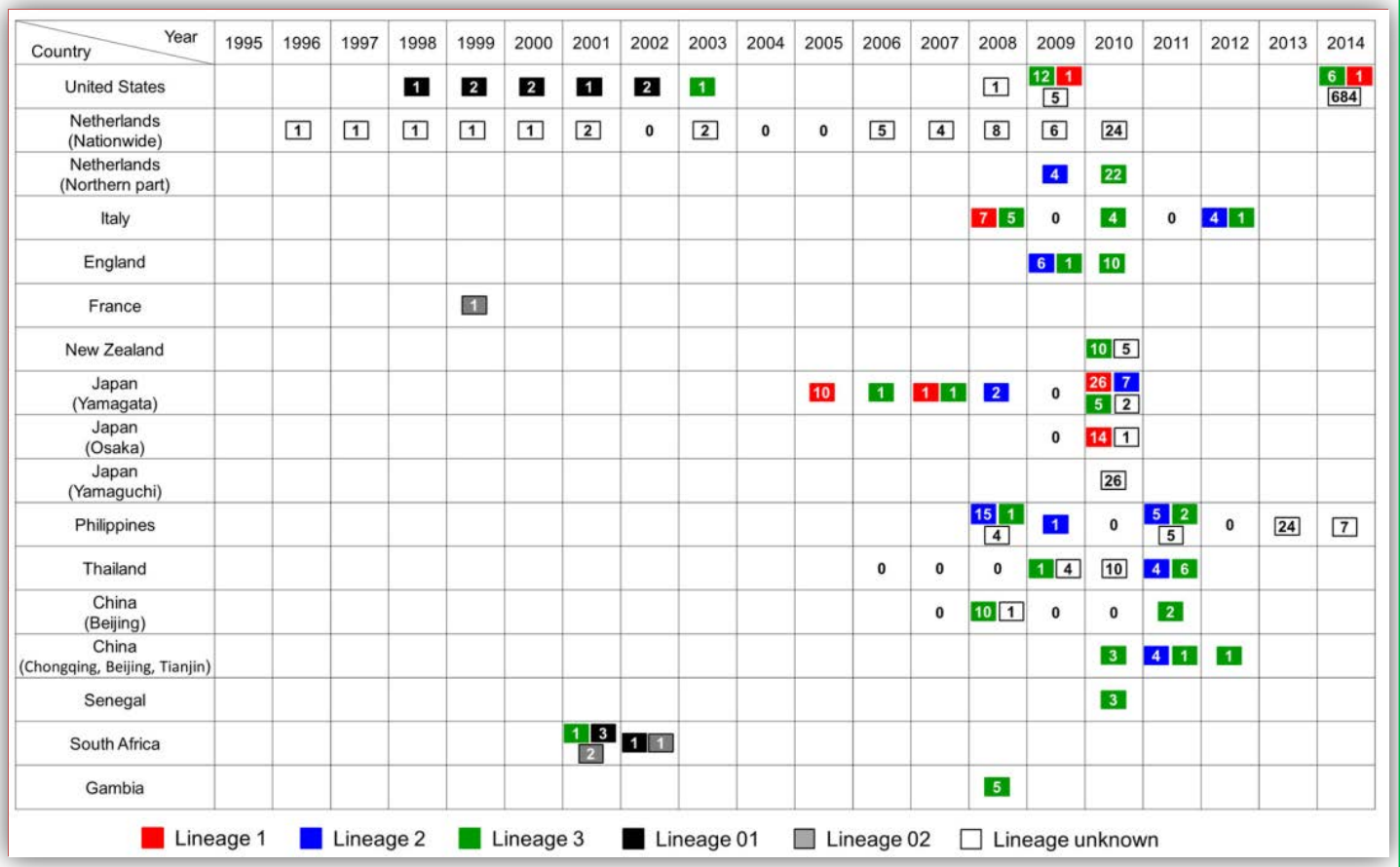
Substitution Rate and Evolutionary Timescale of Circulating EV68 Strains



Substitution Rate

EV68-VP1 gene was estimated at 4.93×10^{-3} s/s/y

Global EV-D68 Epidemiology



- Italy
- France (2009-2010), (2010-2012),
- China (2009-2012),
- New Zealand (2010),
- Great Britain (2009-2010),
- Kenya (2008-2011),
- Japan (2005-2010),
- the Netherlands (2010),
- Thailand (2009-2011)

Our previous studies

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PLoS one

Molecular Epidemiology and Evolution of Human Enterovirus Serotype 68 in Thailand, 2006–2011

Piyada Linsuwanon, Jiratchaya Puenpa, Kamol Suwannakarn, Vittawat Auksornkitti, Preeyaporn Vichiwattana, Sumeth Korkong, Apiradee Theamboonlers, Yong Poovorawan*

Chulalongkorn University, Bangkok, Thailand

Semi-nested PCR : **5′UTR/VP2 region and VP1 gene**

Genome Sequence of Enterovirus D68 and Clinical Disease, Thailand

Sompong Vongpunsawad, Slinporn Prachayangprecha, Jira Chansaenroj, Bart L. Haagmans, Saskia L. Smits, Yong Poovorawan

Nasopharyngeal aspirates obtained from the 3 patients were subjected to **next-generation sequencing and genomic analysis.**

CE of Clinical Virology . PLoS One. 2012.

ENTEROVIRUS 68 AMONG CHILDREN WITH ACUTE RESPIRATORY ILLNESSES IN THAILAND

Pediatric patients with ARTI complications in Bangkok, Thailand between February 14, 2006 and November 8, 2011.

Main characteristics of the study populations and respiratory specimens.

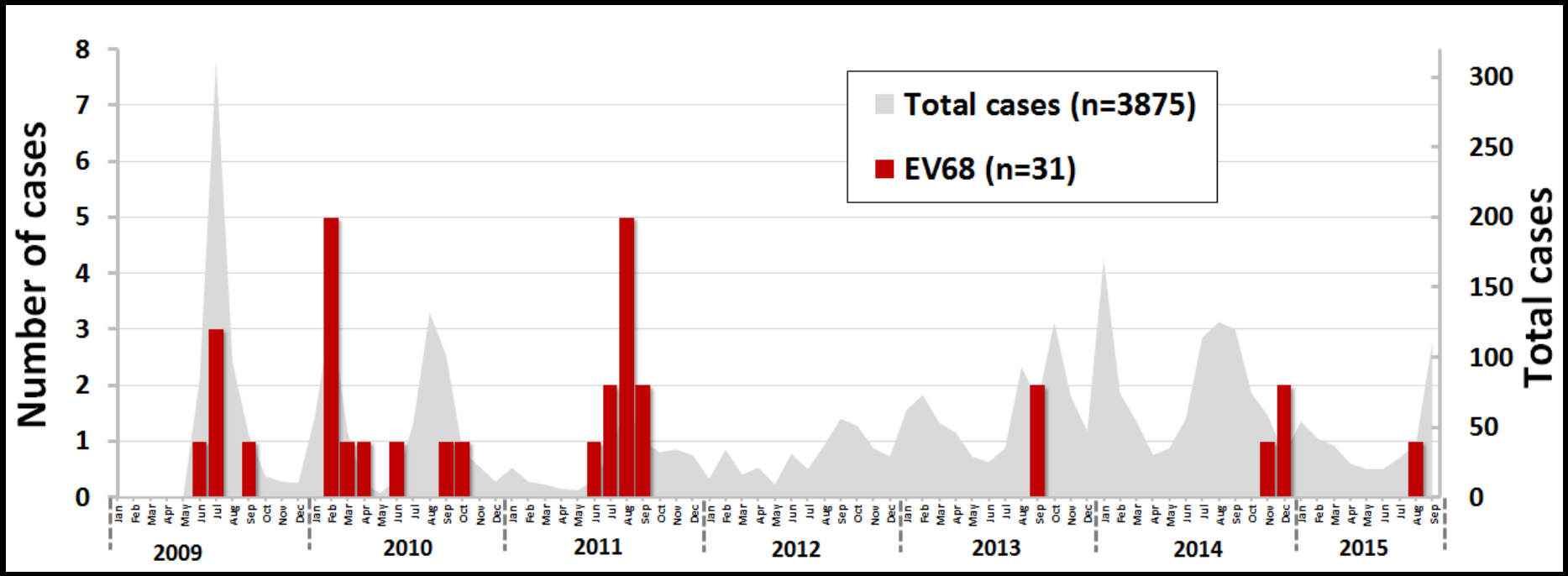
Years of study	Sample	N	Infant	Pre-school	Primary school	Secondary school
Feb 2006–Jul 2008	NP	383	318 (0.9±0.5)	42 (3.5±0.7)	14 (8.9±2.1)	4 (13.5±0.5)
Jun 2009–Sep 2011	NS	1213	238 (1.5±0.6)	352 (4.3±0.8)	442 (8.7±1.9)	167 (14.6±0.9)
Jul 2010–Nov 2011	NP	214	153 (1.1±0.7)	26 (3.7±0.9)	24 (8.5±1.9)	4 (13.3±0.4)
Total		1810	709	420	480	175
Patient age, yrs			1.1±0.6	3.3±0.7	8.7±1.9	14±0.9

NP, Nasopharyngeal aspiration specimens; NS, Posterior oropharyngeal and nasal swab specimens.
Patient age was showed by using mean ± standard deviation.
doi:10.1371/journal.pone.0035190.t001

- Severe cases; 0.9% (n = 16)
- Moderate cases; 32.1% (n = 581)
- Mild cases; 67%; (n = 1213)

CE of Clinical Virology . PLoS One. 2012.

The percentage of pediatric patients with EV68 infection in Thailand, 2009-2015



- EV68 has been found in Thailand since 2009
- The highest number of detected cases were in 2011
- EV68 infection rates were higher during **rainy seasons**

The prevalence of EV-D68 infection in Thailand, 2006 - 2014

Table 1. Enterovirus D68 detection among Thai children with respiratory illnesses from 2006–2014

Years	Specimens Tested No.	EV-D68 detection No. (% of specimens tested)	Strain tested positive (period)	Patient age when tested positive	Sex of EV-D68 detection	Reference
2006		0	-	-	-	
2007	383	0	-	-	-	
2008		0	-	-	-	a
2009	584	5 (0.9)	Jun - Sep	10 years - 15 years	2M, 3F	
2010	611	10 (1.6)	Feb - Oct	6 years - 15 years	5M, 5F	
2011	232	10 (4.3)	Jun - Sep	7 months - 7 years	3M, 7F	a, b
2012	238	0	-	-	-	
2013	232	2 (0.9)	Sep	4 years	2M	
2014	367	3 (0.8)	Nov - Dec	1 years - 3 years	1M, 2F	
Total	**2647**	**30 (1.1)**	**Jun 2009 - Dec 2014**	**7months - 15 years**	**13M, 17F**	

[a] Linsuwanon, Puenpa et al. 2012

[b] Vongpunsawad, Prachayangprecha et al. 2015

4.3% : highest prevalence in 2011

1.1 % of the entired study population

Detection of EV68 in ARTI Patients

Group	Mild ARTI	Moderate ARTI	Severe ARTI	EV68 cases	Average age
Infant (n = 709)	1 (0.1%)	5 (0.9%)	1 (6.3%)	7 (1%)	1.5±0.7
Pre-school (n = 420)	0	2 (0.3%)	0	2 (0.5%)	4
Primary-school (n = 480)	9 (0.7%)	1 (0.2%)	0	10 (2.1%)	8.6±2.0
Secondary-school (n = 175)	6 (0.5%)	0	0	6 (3.4%)	14.2±0.8
Total	16 (1.3%)	8 (1.4%)	1 (6.3%)	25	

Average age = mean ± standard deviation.
doi:10.1371/journal.pone.0035190.t004

25 were confirmed as EV68 infection accounting for 8.7% of RV-EV positive specimens and indicating a prevalence of 1.4% in the entire study population

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Clinical characteristics and demographic data of the 25 cases of EV68 infection.

Strain	Sample	Date	Age	Sex	Co-infection	Diagnosis	5'UTR/VP2	VP1
TH-B190	NS	30/6/2009	13	M	pH1N1/2009	ILI	JQ411799	N/A
TH-B211	NS	1/7/2009	14	F	pH1N1/2009	ILI	JQ411798	N/A
TH-B323	NS	4/7/2009	11	F	pH1N1/2009	ILI	JQ411797	N/A
TH-B521	NS	9/7/2009	10	M	pH1N1/2009	ILI	JQ411796	N/A
TH-B1512	NS	2/9/2009	15	F	–	ILI	JQ411794	JQ411802
TH-B2054	NS	9/2/2010	12	M	pH1N1/2009	ILI	JQ411791	N/A
TH-B2060	NS	10/2/2010	8	F	–	ILI	JQ411792	N/A
TH-B2114	NS	16/2/2010	9	M	–	ILI	JQ411789	N/A
TH-B2192	NS	24/2/2010	9	F	–	ILI	JQ411793	N/A
TH-B2213	NS	26/2/2010	8	F	–	ILI	JQ411790	N/A
TH-B2303	NS	12/3/2010	14	M	–	ILI	JQ411786	N/A
TH-B2340	NS	1/4/2010	6	M	–	ILI	JQ411788	N/A
TH-B2370	NS	2/6/2010	14	M	Flu-B	ILI	JQ411787	N/A
TH-B3611	NS	15/9/2010	15	F	Flu-B	ILI	JQ411781	N/A
TH-B4105	NS	5/10/2010	6	F	Flu-B	ILI	JQ411782	N/A
TH-B4790	NS	27/6/2011	1	F	–	ILI	JQ411785	JQ411809
TH-CU54	NP	8/7/2011	2	F	–	VP	JQ411783	JQ411805
TH-CU70	NP	25/7/2011	1	F	–	VP	JQ411784	JQ411801
TH-CU101	NP	15/8/2011	2	F	–	VP	JQ411776	JQ411804
TH-CU110	NP	18/8/2011	2	F	RSV-A	VP	JQ411777	JQ411810
TH-CU115	NP	22/8/2011	4	F	–	VP	JQ411778	JQ411811
TH-CU124	NP	26/8/2011	7	F	–	VP	JQ411779	JQ411807
TH-CU134	NP	31/8/2011	2	M	–	VP	JQ411775	JQ411803
TH-CU151	NP	12/9/2011	4	M	–	VP	JQ411780	JQ411806
TH-CU171	NP	23/9/2011	7 m	M	–	VP	JQ411795	JQ411808

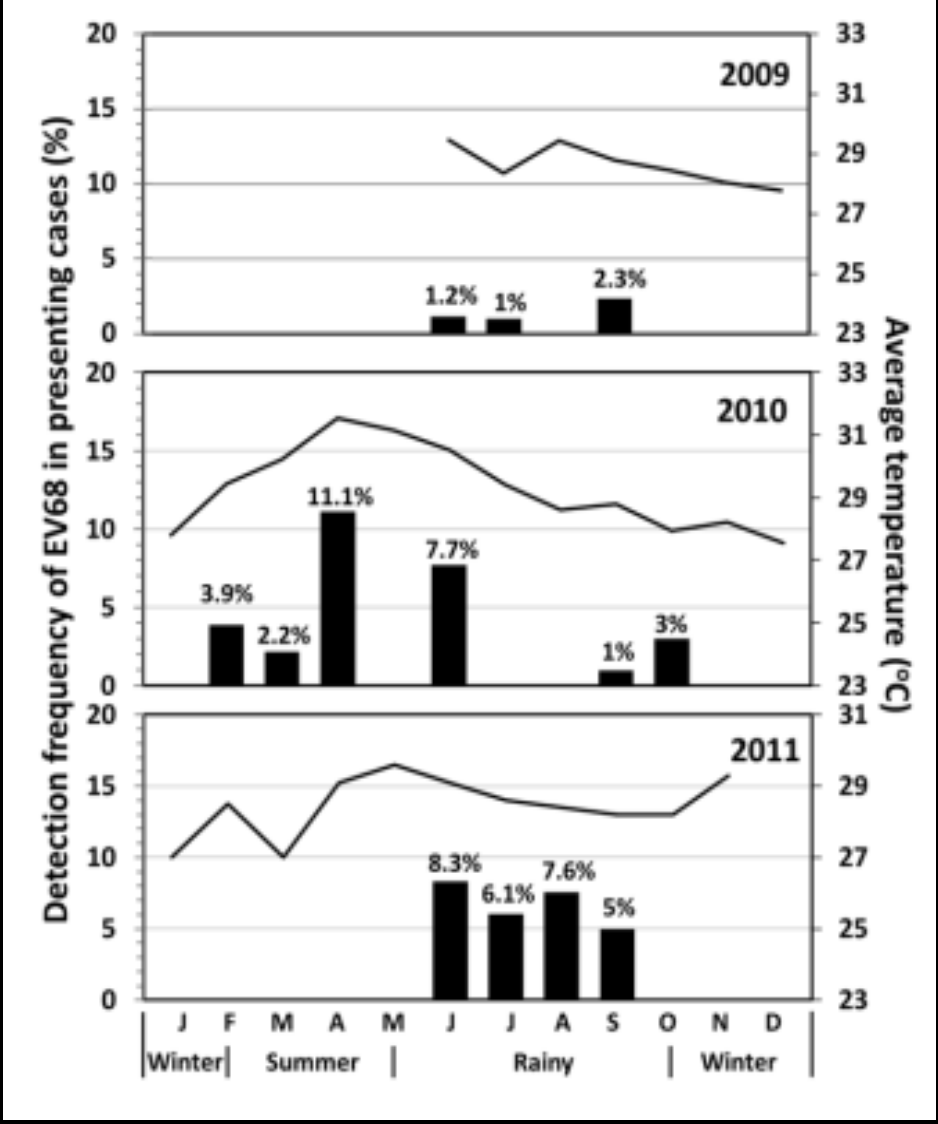
pH1N1/2009, pandemic Influenza A virus subtype H1N1/2009; Flu-B, Influenza B virus; RSV, Respiratory syncytial virus; ILI, Influenza like illness; VP, Viral pneumonia.
doi:10.1371/journal.pone.0035190.t003

Summary of clinical manifestations and diagnoses of the 9 patients hospitalized with EV68 infection

EV68 strain	LT	Underlying	Symptom	O_2 therapy
TH-CU54	5	No	Fever, cough, dyspnea, wheezing	Yes
TH-CU70	3	No	Fever, cough, dyspnea, wheezing	Yes
TH-CU101	5	Autism	Fever, cough, vomiting	Yes
TH-CU110	4	No	Fever, cough, vomiting, diarrhea, dyspnea, wheezing	No
TH-CU115[a]	4	No	Tachypnea, wheezing, runny nose	Yes
TH-CU124[a]	7	No	Fever, cough, dyspnea, wheezing	Yes
TH-CU134	8	GER	Fever, cough, dyspnea, wheezing	Yes
TH-CU151	3	No	Fever, cough, runny nose, dyspnea, wheezing	Yes
TH-CU171[b]	16	CHD	cough, dyspnea, upper airway obstruction	Yes

a = had history of asthma/b = admitted to the intensive care unit.
All of these EV68 infected patients required nebulizer.
LT, Length of hospitalization (days); GRE, Gastro-esophageal reflux; CHD, Congenital heart disease.
doi:10.1371/journal.pone.0035190.t005

Seasonal distribution of EV68 in Bangkok, Thailand combined from 3 years (2009–2011)



Infection rates were higher during the rainy seasons of 2009 and 2011 while no seasonal pattern was apparent in 2010.

CE of Clinical Virology . PLoS One. 2012.

Phylogenetic Analysis – Enterovirus 68

CE of Clinical Virology . PLoS One. 2012.

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Molecular Epidemiology and Evolution of Human Enterovirus Serotype 68 in Thailand, 2006–2011

Piyada Linsuwanon, Jiratchaya Puenpa, Kamol Suwannakarn, Vittawat Auksornkitti, Preeyaporn Vichiwattana, Sumeth Korkong, Apiradee Theamboonlers, Yong Poovorawan*

Chulalongkorn University, Bangkok, Thailand

Abstract

Background: Publications worldwide have reported on the re-occurrence of human enterovirus 68 (EV68), a rarely detected pathogen usually causing respiratory illness. However, epidemiological data regarding this virus in particular on the Asian continent has so far been limited.

Methodology/Findings: We investigated the epidemiology and genetic variability of EV68 infection among Thai children with respiratory illnesses from 2006–2011 (n = 1810). Semi-nested PCR using primer sets for amplification of the 5′-untranslated region through VP2 was performed for rhino-enterovirus detection. Altogether, 25 cases were confirmed as EV68 infection indicating a prevalence of 1.4% in the entire study population. Interestingly, the majority of samples were children aged >5 years (64%). Also, co-infection with other viruses was found in 28%, while pandemic H1N1 influenza/2009 virus was the most common co-infection. Of EV68-positive patients, 36% required hospitalizations with the common clinical presentations of fever, cough, dyspnea, and wheezing. The present study has shown that EV68 was extremely rare until 2009 (0.9%). An increasing annual prevalence was found in 2010 (1.6%) with the highest detection frequency in 2011 (4.3%). Based on analysis of the VP1 gene, the evolutionary rate of EV68 was estimated at 4.93×10^{-3} substitutions/site/year. Major bifurcation of the currently circulating EV68 strains occurred 66 years ago (1945.31 with (1925.95–1960.46)95% HPD). Among the current lineages, 3 clusters of EV68 were categorized based on the different molecular signatures in the BC and DE loops of VP1 combined with high posterior probability values. Each cluster has branched off from their common ancestor at least 36 years ago (1975.78 with (1946.13–1984.97)95% HPD).

Conclusion: Differences in epidemiological characteristic and seasonal profile of EV68 have been found in this study. Results from Bayesian phylogenetic investigations also revealed that EV68 should be recognized as a genetically diverse virus with a substitution rate identical to that of enterovirus 71 genotype B (4.2×10^{-3} s/s/y).

Citation: Linsuwanon P, Puenpa J, Suwannakarn K, Auksornkitti V, Vichiwattana P, et al. (2012) Molecular Epidemiology and Evolution of Human Enterovirus

Japanese Journal *of* Infectious Diseases

National Institute *of* Infectious Diseases, Japanese Journal *of* Infectious Diseases Editorial Committee

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PREVALENCE AND PHYLOGENETIC CHARACTERIZATION OF ENTEROVIRUS D68 IN PEDIATRIC PATIENTS WITH ACUTE RESPIRATORY TRACT INFECTION IN THAILAND

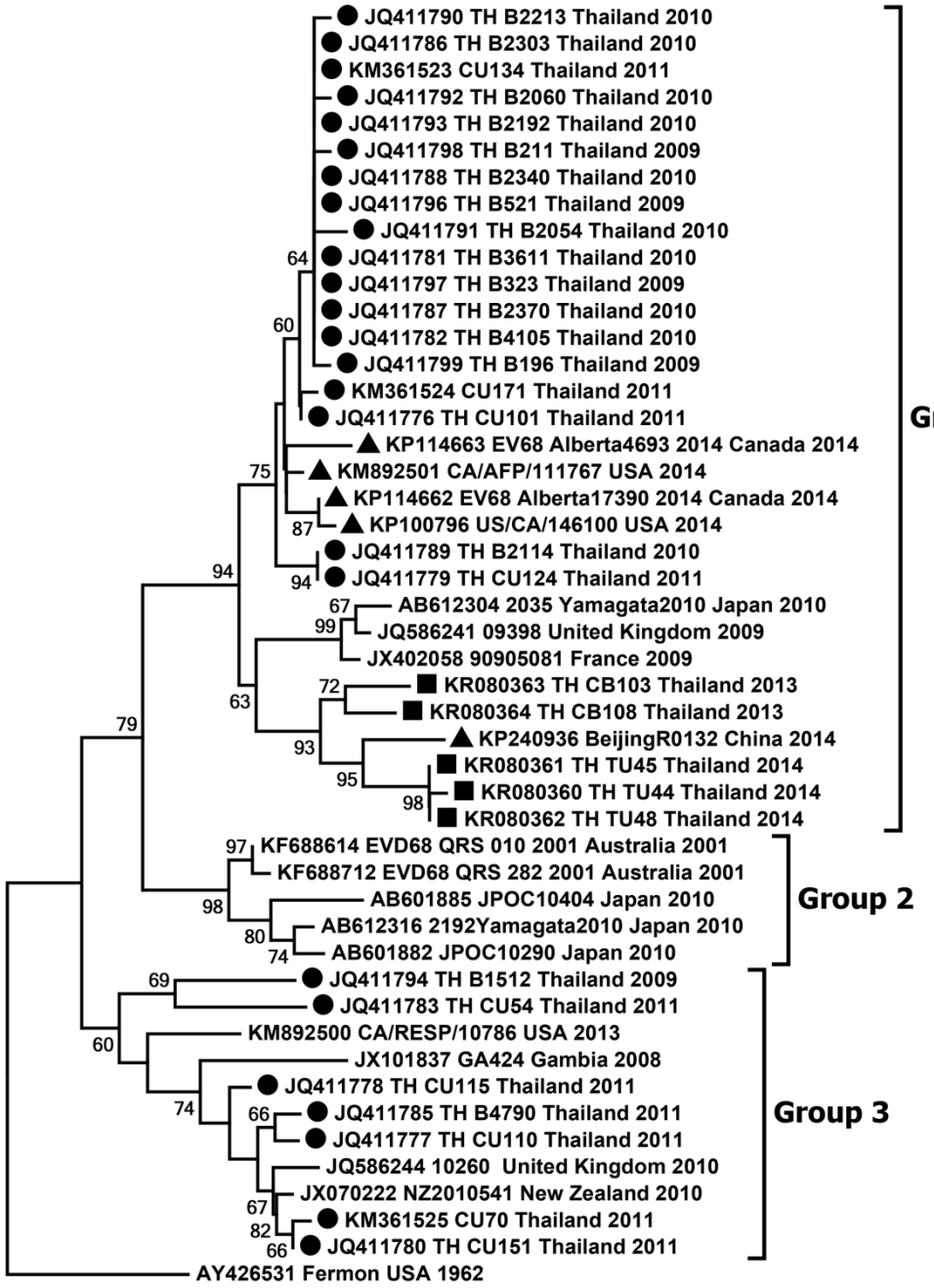
Thongpan I, et al. CE of Clinical Virology Chulalongkorn University, JJID 2016.

Patients were diagnosed with viral pneumonia and all required hospitalization as shown in Table 1.

Table 1. Clinical characteristics of the five cases hospitalized from EV68 infection during 2012-2014 in Thailand.

Patient	Strain	Age	Sex	Sample	Date of Collection	Presenting symptoms	Diagnosis	Severity	Accession number (5'UTR/VP2)
1	TH-CB103	4	M	Tracheal suction	27-Sep-13	Fever, Cough, Runny Nose, Dyspnea, Wheezing, respiratory failure	Viral pneumonia	Required intubation and mechanical ventilation	KR080363
2	TH-CB108	4	M	NP suction	27-Sep-13	Fever, Cough, Runny Nose, Dyspnea, Wheezing	Viral pneumonia	Required hospitalization	KR080364
3	TH-TU44	3	M	NP suction	11-Dec-14	Fever, Cough, Vomiting, Wheezing, Chest Retractions	Viral pneumonia	Required hospitalization	KR080360
4	TH-TU45	2	F	NP suction	13-Nov-14	Cough, Runny nose, Wheezing (third episode)	Viral pneumonia	Required hospitalization	KR080361
5	TH-TU48	1	F	NP suction	13-Dec-14	Low grade fever, Cough, Runny Nose, Vomiting, Wheezing (fourth episode), Dyspnea, Chest Retraction	Viral pneumonia	Required hospitalization	KR080362

Thongpan I, et al. CE of Clinical Virology Chulalongkorn University, JJID 2016.



Phylogenetic tree of VP4/VP2 region

● TH-strains between 2009 and 2011

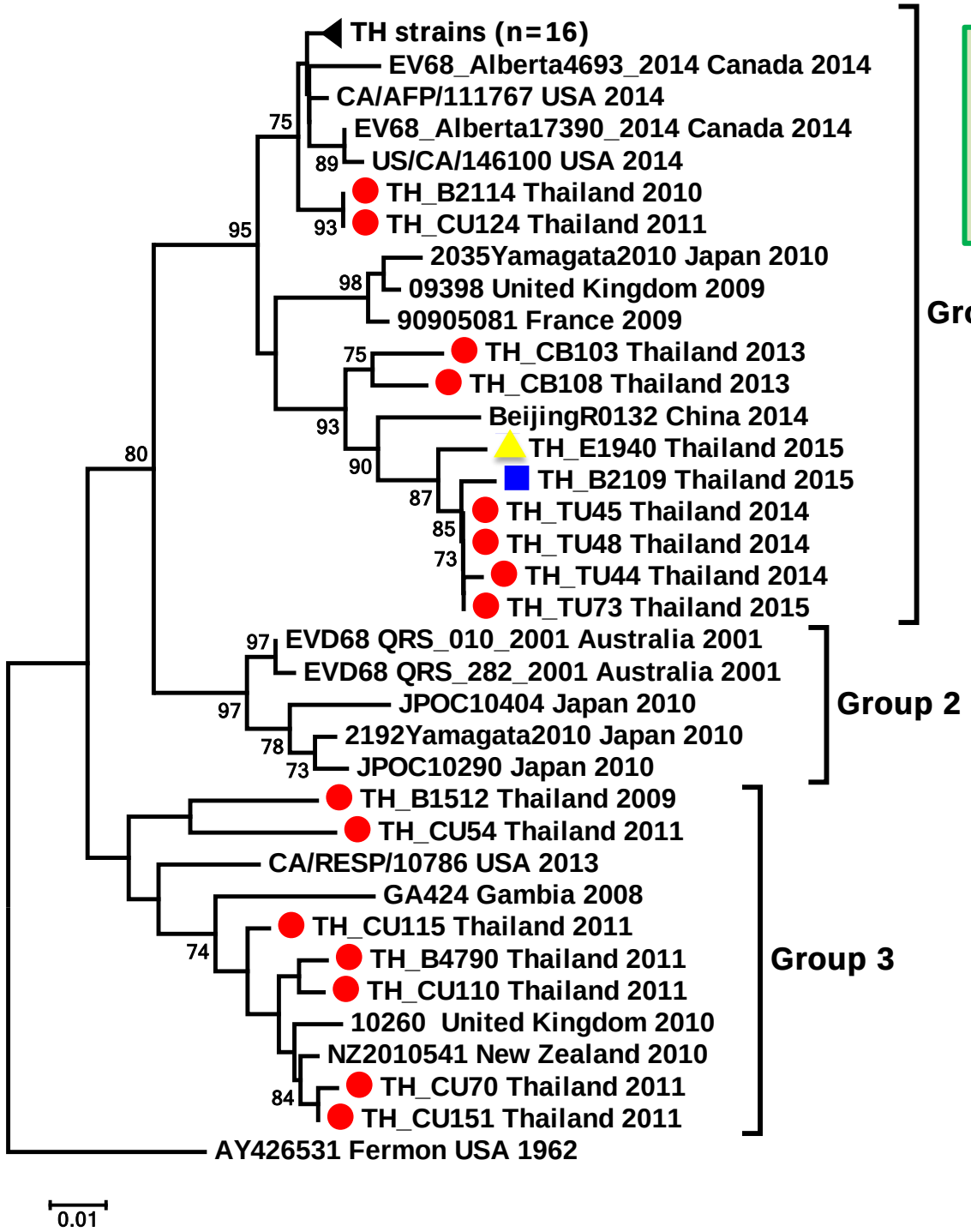
■ TH-strains between 2012 and 2014

▲ Outbreaks strains other reported in 2014

Phylogenetic relationship for EV-D68 detected among Thai pediatric patients during 2012–2014 using Neighbor-joining (NJ) that were constructed from nucleotide alignments of the **VP4/VP2** using MEGA software.

Thongpan I, et al. CE of Clinical Virology Chulalongkorn University, JJID 2016

Phylogenetic tree of Thai EV D68 (VP4/VP2 region)



Influenza-like Illness

Diarrhea

Hand, foot and mouth disease

Phylogenetic relationship for EV-D68 detected among Thai pediatric patients during 2009–2015 using Neighbor-joining (NJ) that were constructed from nucleotide alignments of the **VP4/VP2** using MEGA software.

EV-D 68

- ❑ The prevalence of EV-D68 was quite low, accounting for only 0.6%. Lower than other countries in Europe

  Prior to 2014, the prevalence of EV-D68 in Thailand averaging 1.5%,

  0.45% found in China and 0.87% in Japan

- ❑ EV-D68 infections in Thai children

- Severe lower respiratory tract infection that required hospitalization
- Mostly occurred in rainy seasons

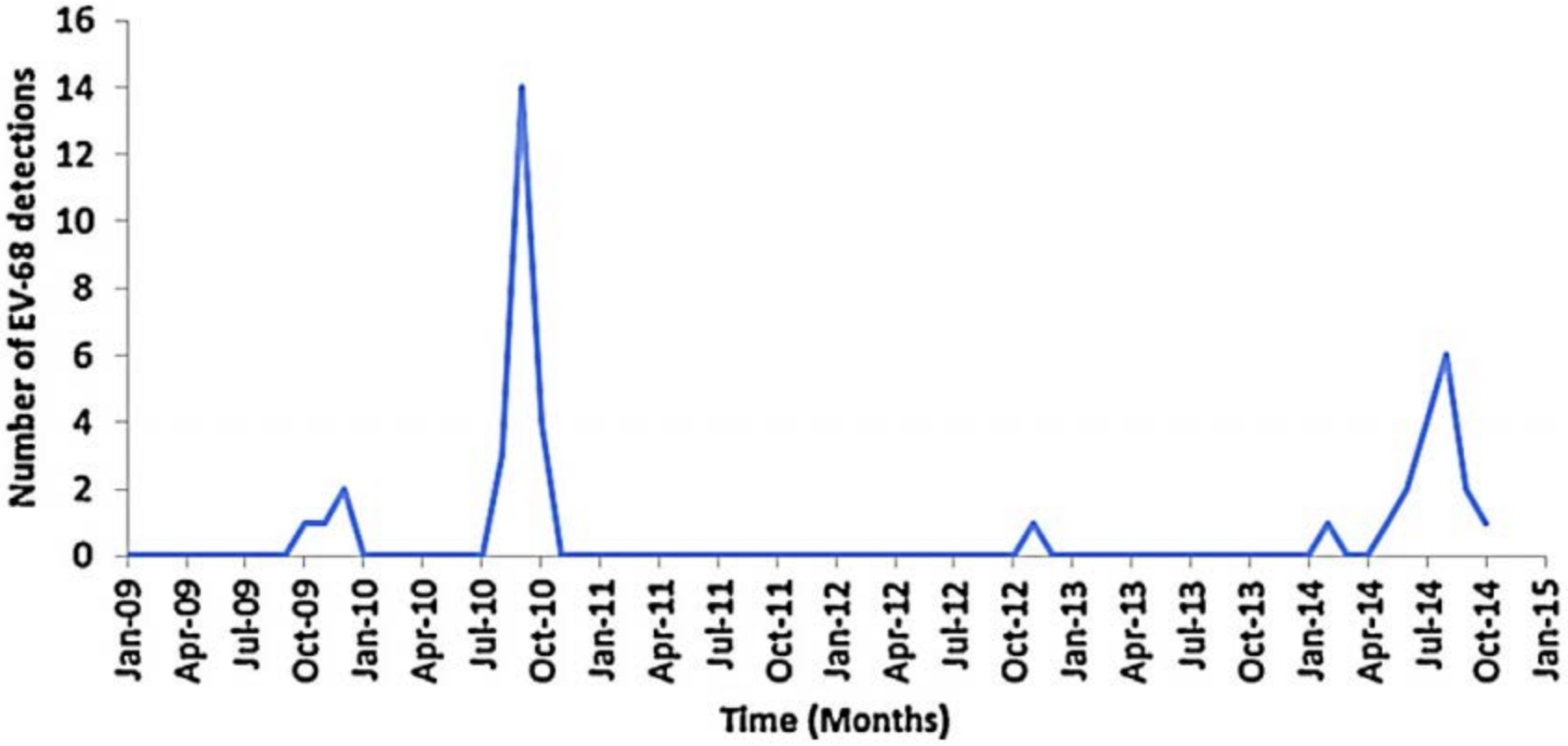
  The circulation pattern was similar to influenza virus

The emergence of enterovirus D68 in a Dutch University Medical Center and the necessity for routinely screening for respiratory viruses

Randy Poelman, Elisabeth H. Schölvinck, Renze Borger, Hubert G.M. Niesters, Coretta van Leer-Buter

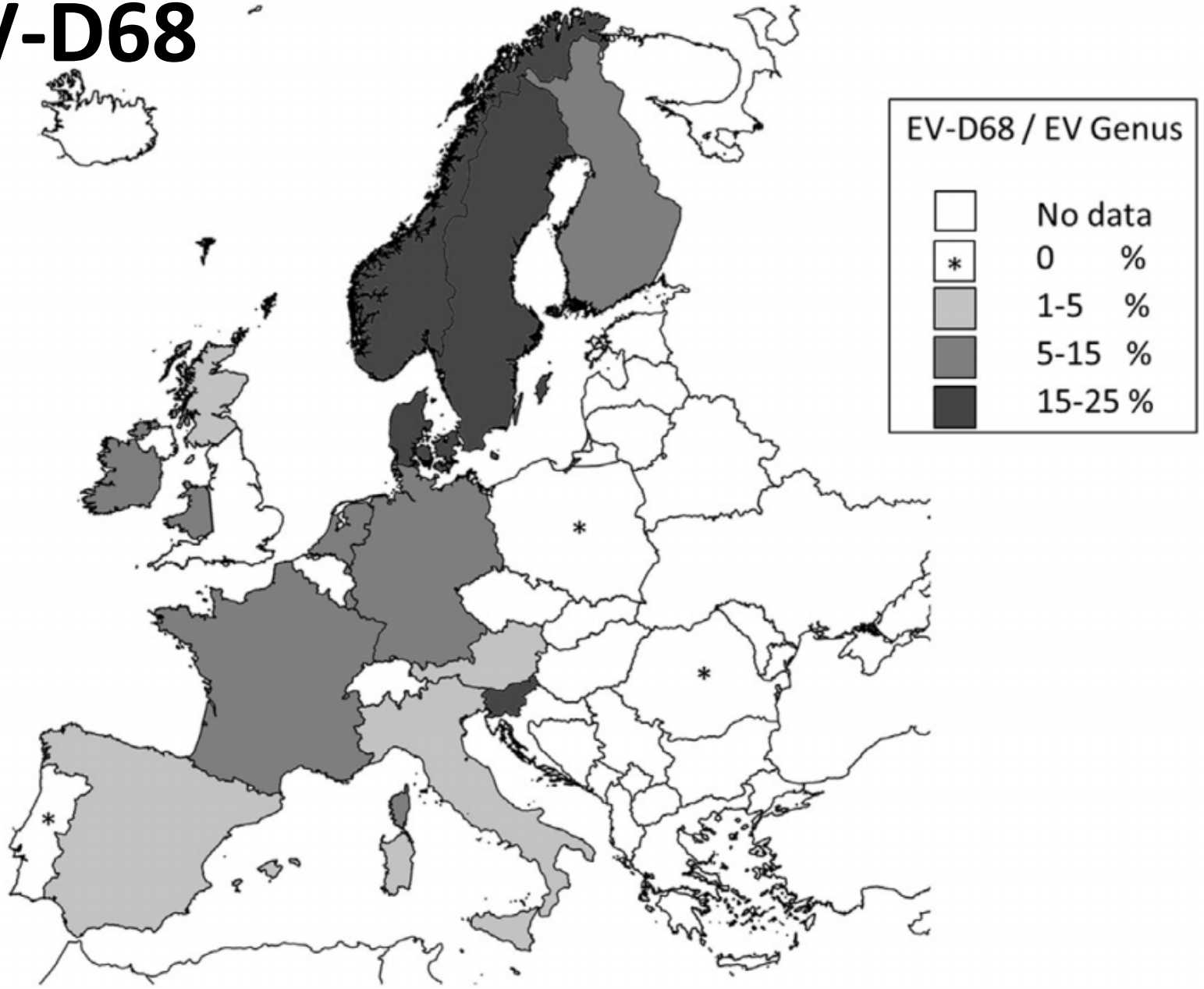
Journal of Clinical Virology
Volume 62, Pages 1-5 (January 2015)
DOI: 10.1016/j.jcv.2014.11.011

EV-D68 occurrence in the Netherland 2009–2014.



R. Poelman et al. / Journal of Clinical Virology 62 (2015) 1–5

EV-D68



R. Poelman et al. / Journal of Clinical Virology 71 (2015) 1–9

Polio like EVD68

A Fatal Central Nervous System Enterovirus 68 Infection

Justin D. Kreuter, MD; Arti Barnes, MD; James E. McCarthy, MD; Joseph D. Schwartzman, MD; M. Steven Oberste, PhD; C. Harker Rhodes, PhD, MD; John F. Modlin, MD; Peter F. Wright, MD

• The anticipated eradication of poliovirus emphasizes the need to identify other enteroviral causes of severe central nervous system disease. Enterovirus 68 has been implicated only in cases of respiratory illness. We therefore report a

diagnostic studies at the Dartmouth-Hitchcock Medical Center (Lebanon, New Hampshire), the New Hampshire Public Health Laboratory (Concord, New Hampshire), and the Centers for Disease Control and Prevention

Arch Pathol Lab Med—Vol 135, June 2011 Enterovirus 68 Infection—Kreuter et al

Acute flaccid paralysis following enterovirus D68 associated pneumonia, France, 2014

M Lang[1], A Mirand (amirand@chu-clermontferrand.fr)[2,3], N Savy[1], C Henquell[2,3], S Maridet[1], R Perignon[4], A Labbé[1], H Peigue-Lafeuille[2,3]

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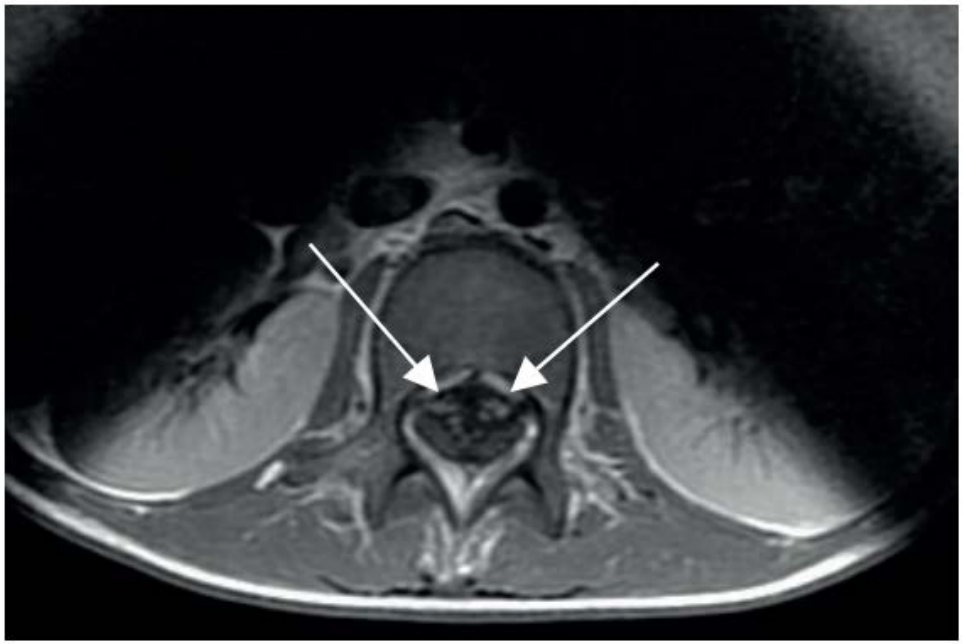
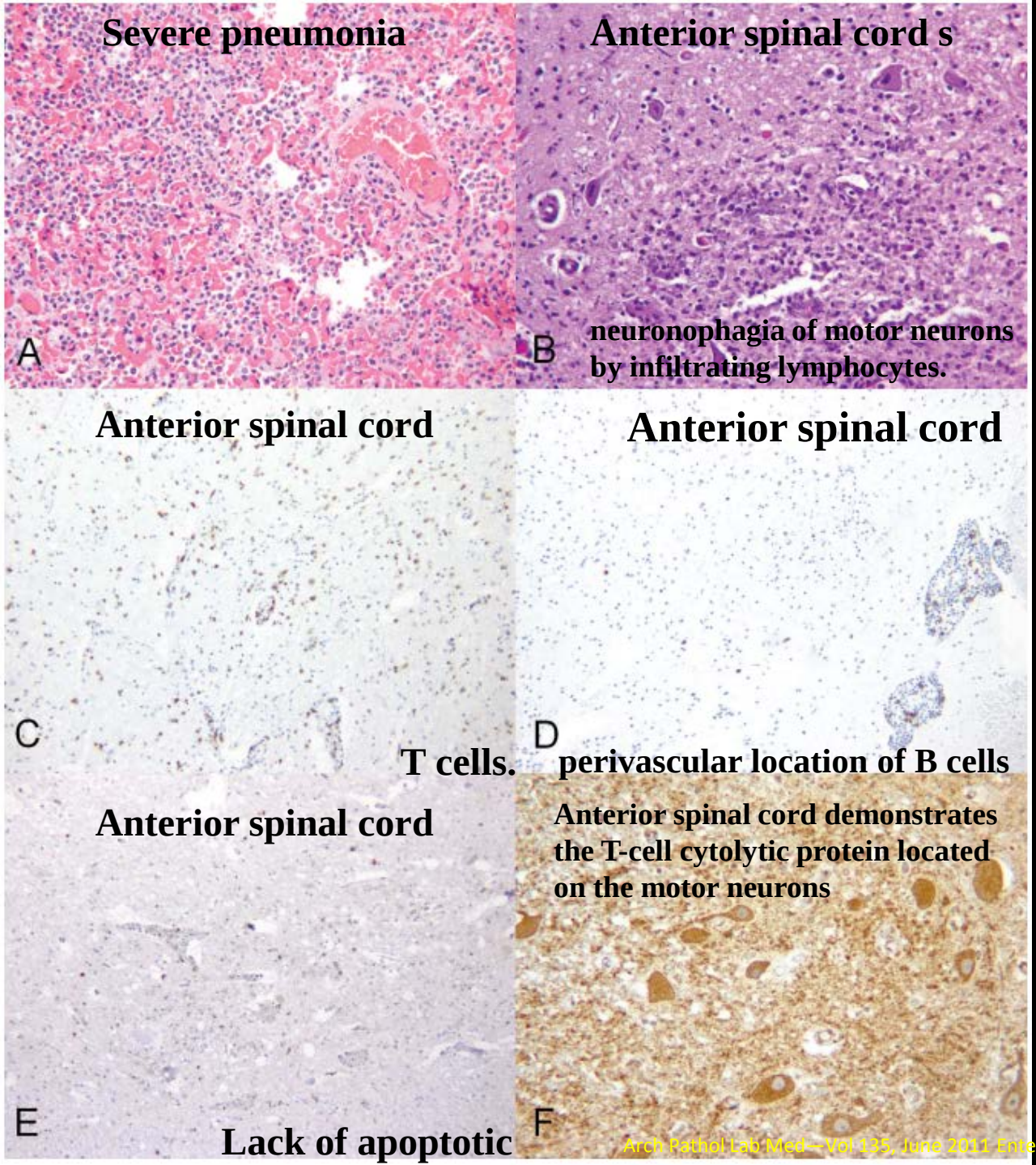
Lang M, Mirand A, Savy N, Henquell C, Maridet S, Perignon R, Labbé A, Peigue-Lafeuille H. Acute flaccid paralysis following enterovirus D68 associated pneumonia, France, 2014. Euro Surveill. 2014;19(44):pii=20952. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20952

Article submitted on 24 October 2014 / published on 06 November 2014

Spinal magnetic resonance image, acute flaccid paralysis case following enterovirus D68 infection, France, 2014



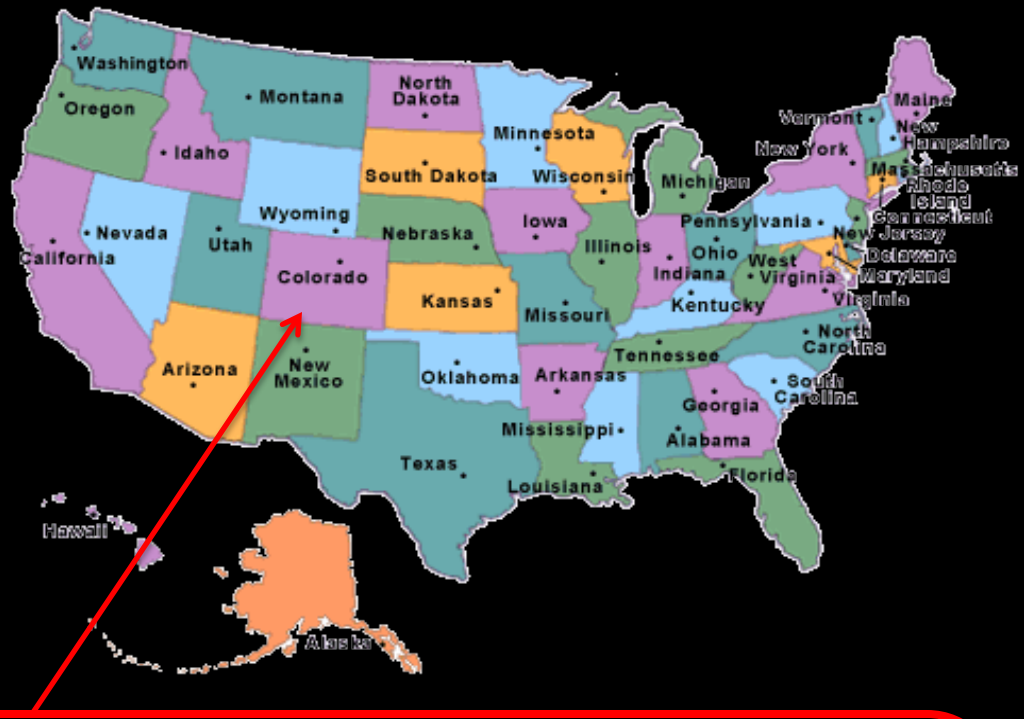
Gadolinium enhancement of the ventral nerve roots of the cauda equina is shown (arrows).


Severe pneumonia
A
Anterior spinal cord s
B
neuronophagia of motor neurons by infiltrating lymphocytes.
Anterior spinal cord
C
T cells.
Anterior spinal cord
D
perivascular location of B cells
Anterior spinal cord
E
Lack of apoptotic
Anterior spinal cord demonstrates the T-cell cytolytic protein located on the motor neurons
F

Acute Flaccid Myelitis Potentially Associated With Enterovirus D68:

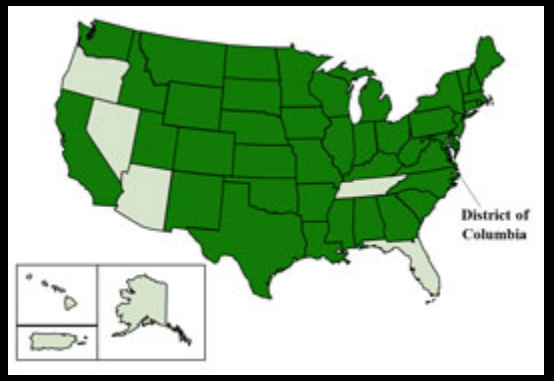
- **Population most affected**: school aged children (median: 7–11 years).
- **Presenting symptoms**: acute febrile respiratory prodrome followed by meningeal signs and acute onset of cranial nerve dysfunction (VI, VII, IX, X) and/or acute flaccid paralysis of limbs.
- **Exam findings**: diplopia (CN VI), facial droop (CN VII), bulbar dysfunction (CN IX, X); limp weakness of the arms/legs associated with hyporeflexia and intact sensation.
- **Cerebrospinal fluid findings**: mild pleocytosis with normal to mildly elevated protein, normal glucose.
- **Brain and spinal cord MRI findings**: focal lesions in the brainstem cranial nerve motor nuclei; longitudinally extensive lesions in the spinal cord gray matter (anterior horn predominant). Lesions non-enhancing with gadolinium; best seen on T2 and FLAIR series.
- **Diagnostic specimens**: respiratory specimen (nasopharyngeal swab or aspirate), oropharyngeal swab, stool/rectal samples, blood and cerebrospinal fluid.
- **Diagnostic testing**: evaluate for infectious (e.g., poliovirus and other non-polio-enteroviruses, West Nile virus and other arboviruses, adenovirus, and herpesviruses), and non-infectious causes of acute flaccid paralysis. EV-D68 specific RT-PCR or sequencing of rhinovirus/enterovirus PCR amplicon necessary to identify EV-D68.
- **Management**: no antivirals approved for treatment. Supportive care, including intubation and feeding support in cases of loss of bulbar function. Physical and rehabilitation therapies for limb weakness.
- **Prognosis**: long-term prognosis unknown. Mild functional improvements noted in some, though most with residual limb weakness after 1 year.

J. Med. Virol. DOI 10.1002/jmv



In August–September 2014, a cluster of 12 children with acute flaccid paralysis and cranial nerve dysfunction was noted at Children's Hospital Colorado

States with lab-confirmed cases of Enterovirus D68



Morbidity and Mortality Weekly Report (*MMWR*)

MMWR

Severe Respiratory Illness Associated with Enterovirus D68 — Missouri and Illinois, 2014

Weekly
September 12, 2014 / 63(36);798-799

On September 8, 2014, this report was posted as an MMWR Early Release on the MMWR website (http://www.cdc.gov/mmwr).

Claire M. Midgley, PhD[1,2], Mary Anne Jackson, MD[3], Rangaraj Selvarangan, PhD[4], George Turabelidze, MD[5], Emily Obringer, MD[6], Daniel Johnson, MD[6], B. Louise Giles, MD[6], Ajanta Patel, MD[6], Fredrick Echols, MD[7], M. Steven Oberste, PhD[2], W. Allan Nix[2], John T. Watson, MD[2], Susan I. Gerber, MD[2] (Author affiliations at end of text)

In 2014, USA. a nationwide outbreak of EV-D68 associated with severe respiratory illness.

From mid-Aug 2014 to Jan 15, 2015,
CDC confirmed a total of 1,153 people in 49 states and the District of Columbia with respiratory illness caused by EV-D68.

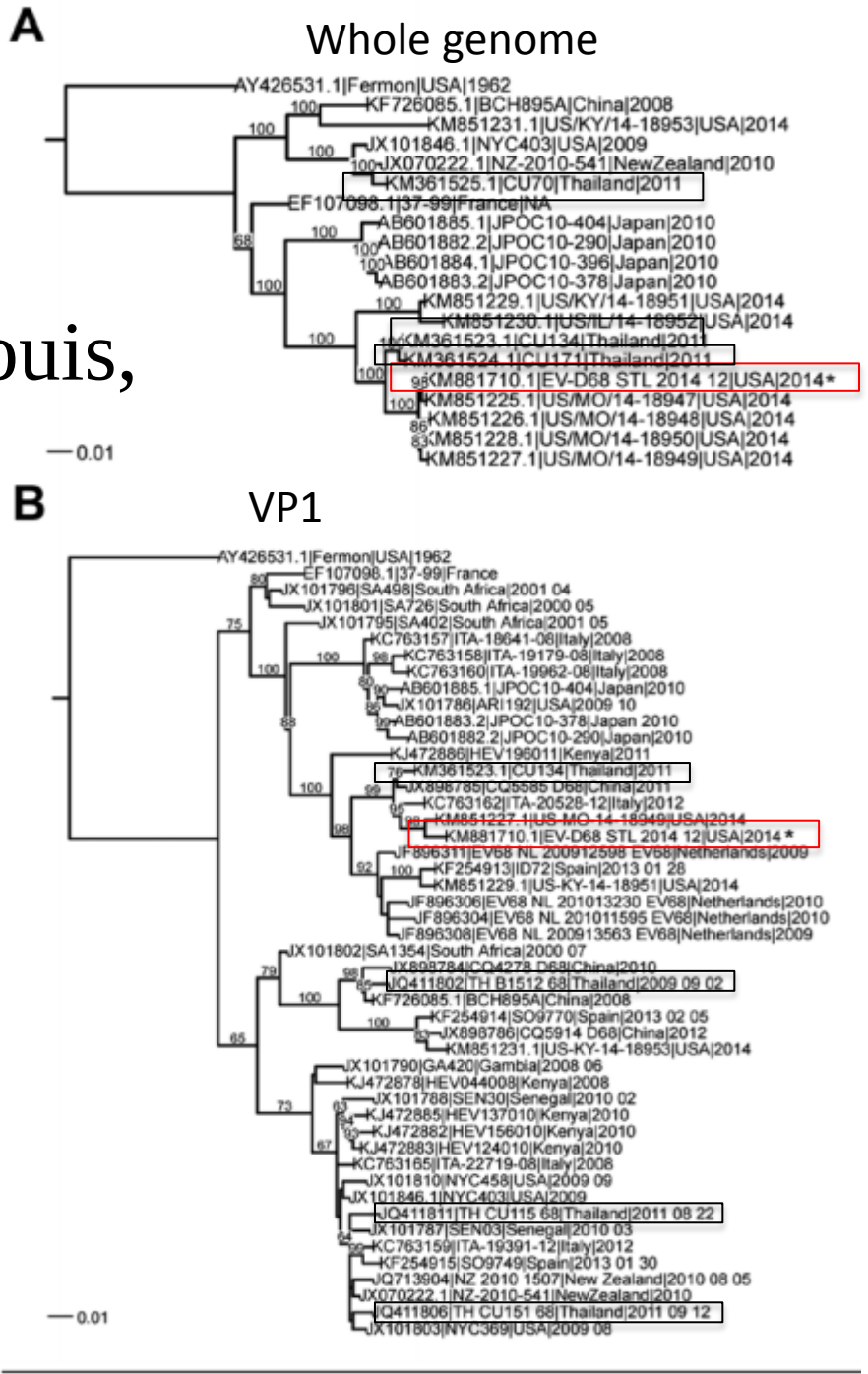
Almost all were among children, many whom had asthma or a history of wheezing.

Additionally, there were likely millions of mild EV-D68 infections for which people did not get tested.

CDC received about 2,600 specimens for enterovirus lab testing during 2014, which is substantially more than usual. About 36% of those tested positive for EV-D68. About 33% tested positive for an enterovirus or rhinovirus other than EV-D68.

EV-D68 was detected in specimens from 14 patients who died.

Genome Sequence of Enterovirus D68 from St. Louis, Missouri, USA



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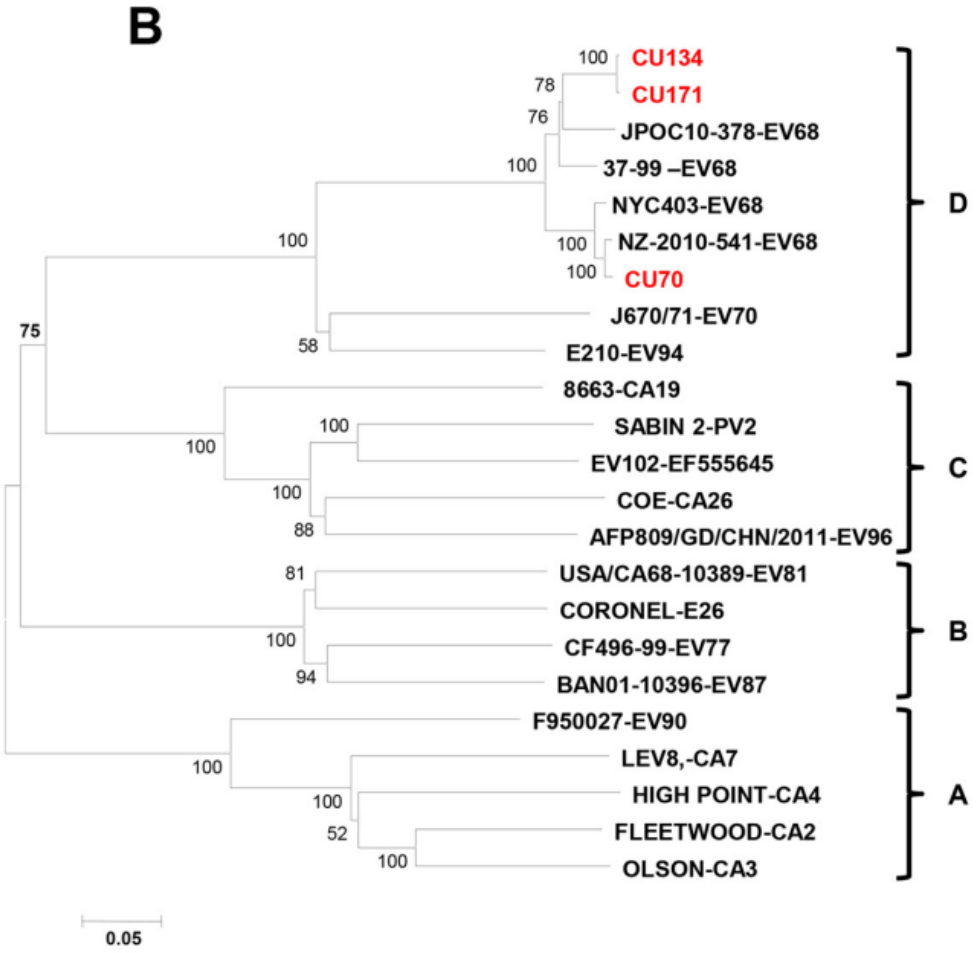
Exploring the Potential of Next-Generation Sequencing in Detection of Respiratory Viruses



Genome Sequence of Enterovirus D68 and Clinical Disease, Thailand

Sompong Vongpunsawad, Slinporn Prachayangprecha, Jira Chansaenroj, Bart L. Haagmans, Saskia L. Smits, Yong Poovorawan

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 21, No. 2, February 2015

EVD68

- is not a novel virus
- can cause respiratory tract infection
- severe in young children with asthma or underlying lung diseases
- may be associated with AFP (acute flaccid paralysis)

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