Emerging encephalitis

Nipah, Enterovirus 71, West Nile, and others …

O. Epaulard

Department of Infectious Diseases
Grenoble University Hospital

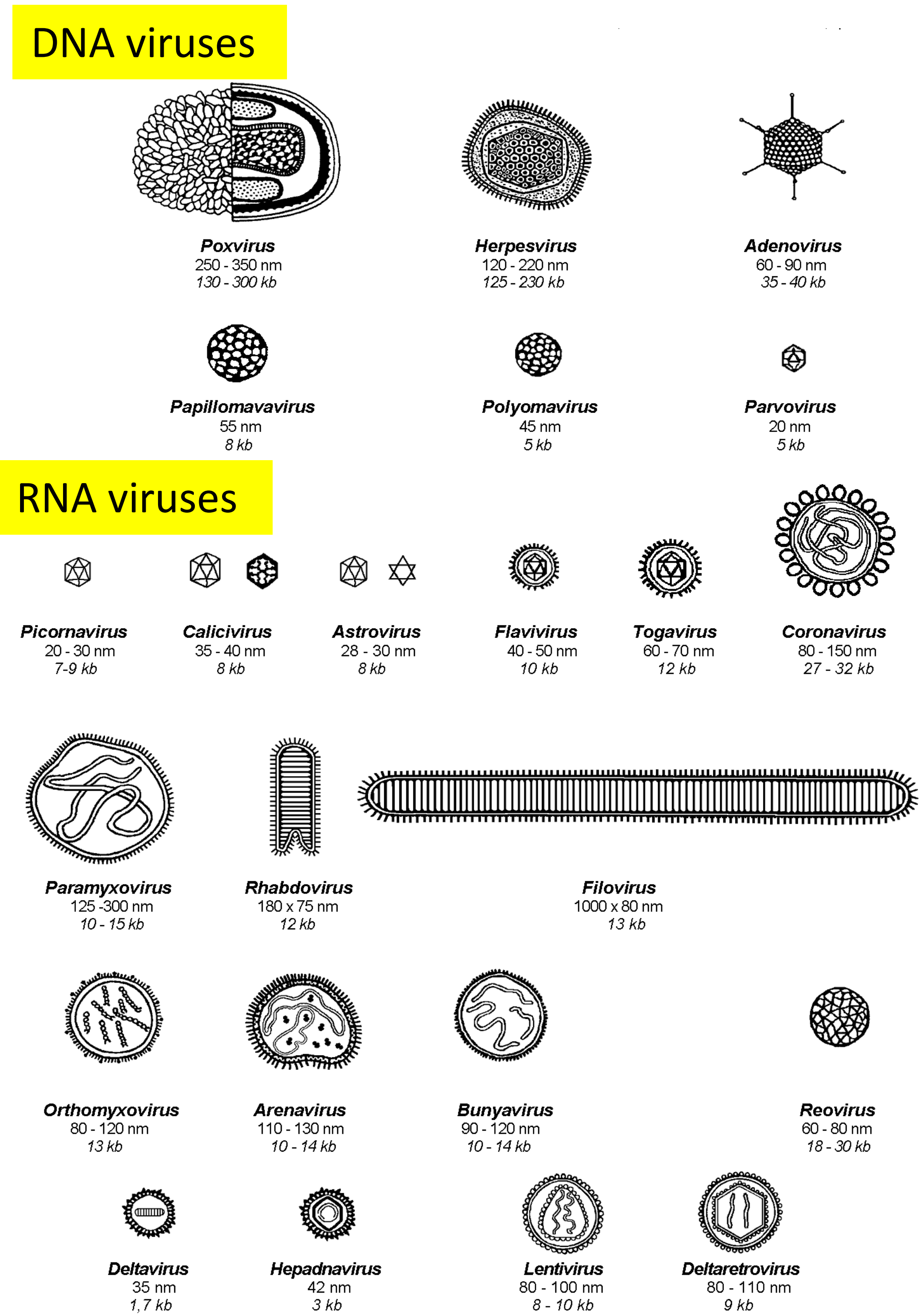
Unit of Virus - host cell interactions
UMI 3265 UJF-EMBL-CNRS

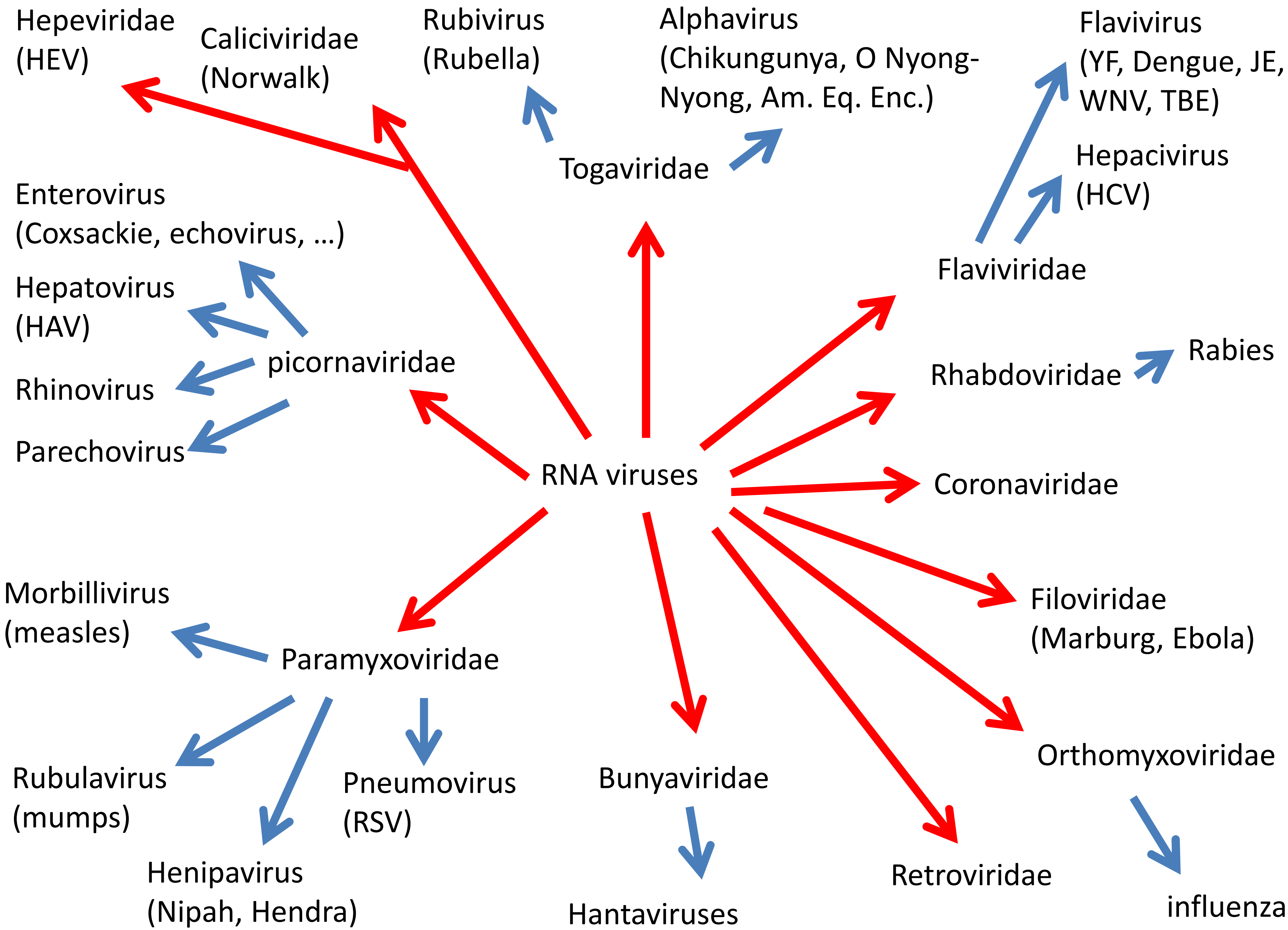
Declaration of interest

- No contradictory interest

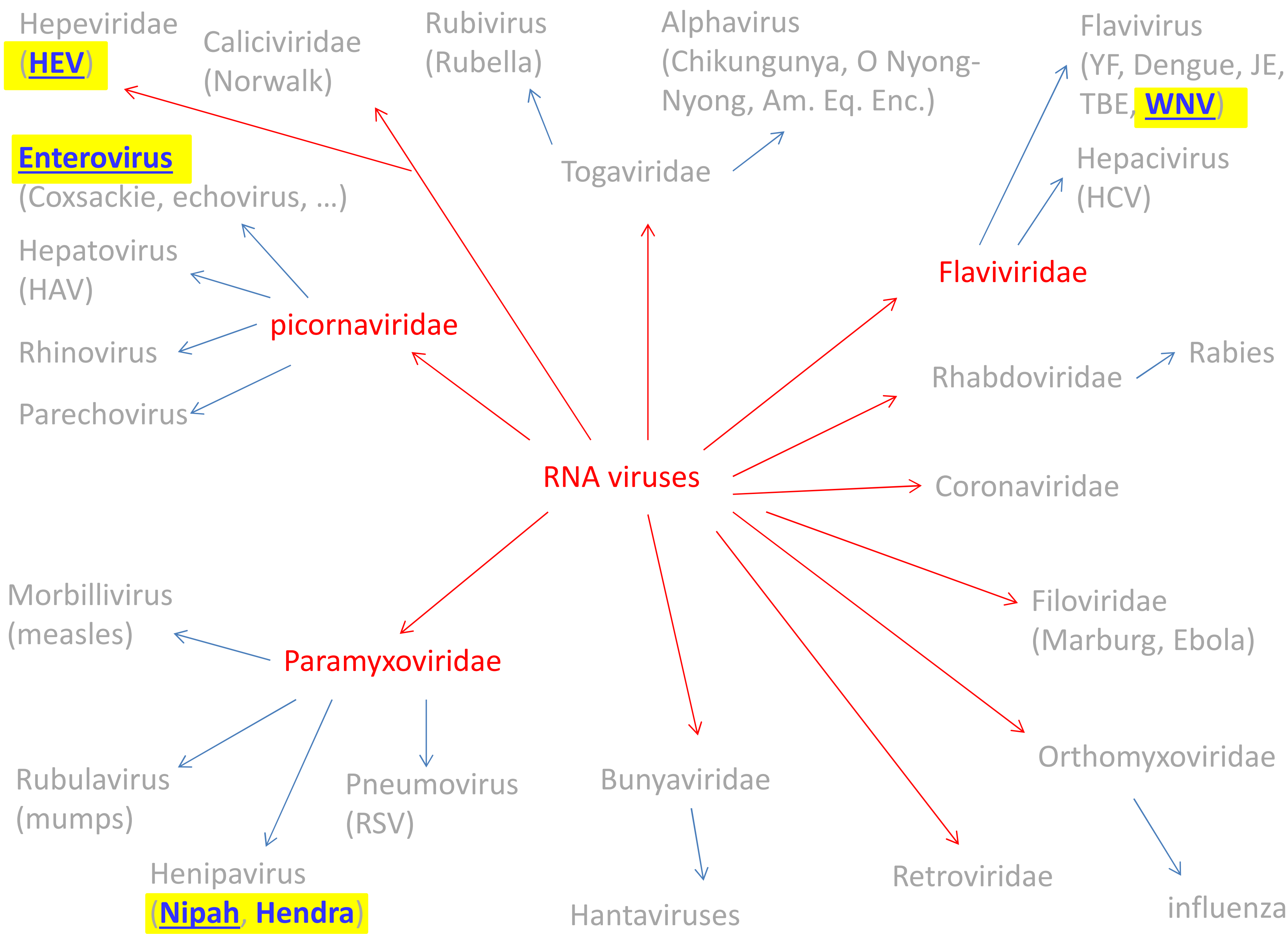
Menu

- General considerations
- Flaviviruses
  - West Nile virus
- Henipaviruses
- Enterovirus 71
- HEV


DNA viruses
Poxvirus
250 - 350 nm
130 - 300 kb
Herpesvirus
120 - 220 nm
125 - 230 kb
Adenovirus
60 - 90 nm
35 - 40 kb
Papillomavavirus
55 nm
8 kb
Polyomavirus
45 nm
5 kb
Parvovirus
20 nm
5 kb
RNA viruses
Picornavirus
20 - 30 nm
7-9 kb
Calicivirus
35 - 40 nm
8 kb
Astrovirus
28 - 30 nm
8 kb
Flavivirus
40 - 50 nm
10 kb
Togavirus
60 - 70 nm
12 kb
Coronavirus
80 - 150 nm
27 - 32 kb
Paramyxovirus
125 -300 nm
10 - 15 kb
Rhabdovirus
180 x 75 nm
12 kb
Filovirus
1000 x 80 nm
13 kb
Orthomyxovirus
80 - 120 nm
13 kb
Arenavirus
110 - 130 nm
10 - 14 kb
Bunyavirus
90 - 120 nm
10 - 14 kb
Reovirus
60 - 80 nm
18 - 30 kb
Deltavirus
35 nm
1,7 kb
Hepadnavirus
42 nm
3 kb
Lentivirus
80 - 100 nm
8 - 10 kb
Deltaretrovirus
80 - 110 nm
9 kb



RNA viruses
Hepeviridae (HEV)
Caliciviridae (Norwalk)
Togaviridae
Rubivirus (Rubella)
Alphavirus (Chikungunya, O Nyong-Nyong, Am. Eq. Enc.)
Flaviviridae
Flavivirus (YF, Dengue, JE, WNV, TBE)
Hepacivirus (HCV)
Rhabdoviridae
Rabies
Coronaviridae
Filoviridae (Marburg, Ebola)
Orthomyxoviridae
influenza
Retroviridae
Bunyaviridae
Hantaviruses
picornaviridae
Enterovirus (Coxsackie, echovirus, …)
Hepatovirus (HAV)
Rhinovirus
Parechovirus
Paramyxoviridae
Morbillivirus (measles)
Rubulavirus (mumps)
Henipavirus (Nipah, Hendra)
Pneumovirus (RSV)


RNA viruses
picornaviridae
Enterovirus
(Coxsackie, echovirus, …)
Hepatovirus
(HAV)
Rhinovirus
Parechovirus
Hepeviridae
(HEV)
Caliciviridae
(Norwalk)
Togaviridae
Rubivirus
(Rubella)
Alphavirus
(Chikungunya, O Nyong-Nyong, Am. Eq. Enc.)
Flaviviridae
Flavivirus
(YF, Dengue, JE, TBE, WNV)
Hepacivirus
(HCV)
Rhabdoviridae
Rabies
Coronaviridae
Filoviridae
(Marburg, Ebola)
Orthomyxoviridae
influenza
Retroviridae
Bunyaviridae
Hantaviruses
Paramyxoviridae
Morbillivirus
(measles)
Rubulavirus
(mumps)
Henipavirus
(Nipah, Hendra)
Pneumovirus
(RSV)

Emerging diseases are mostly …

- Viral
- RNA
- Zoonotic
- No cross-immunity

Why do infectious diseases emerge ?

- Because they always have
- Huge animal reservoir
- Climate evolution
- Air travel
- Urbanization
- Virus mutation
  - Poor fidelity of polymerases of RNA viruses

Did you mention bats ?

- SARS-co
- MERS-co
- Nipah
- Hendra
- Ebola
- Marburg
- Rabies

RNA viruses …

Did you mention bats ?

- SARS-co
- MERS-co
- Nipah
- Hendra
- Ebola
- Marburg
- Rabies

Bats carry pathogenic hepadnaviruses antigenically related to hepatitis B virus and capable of infecting human hepatocytes

Drexler 2013

Amplification of Emerging Viruses in a Bat Colony

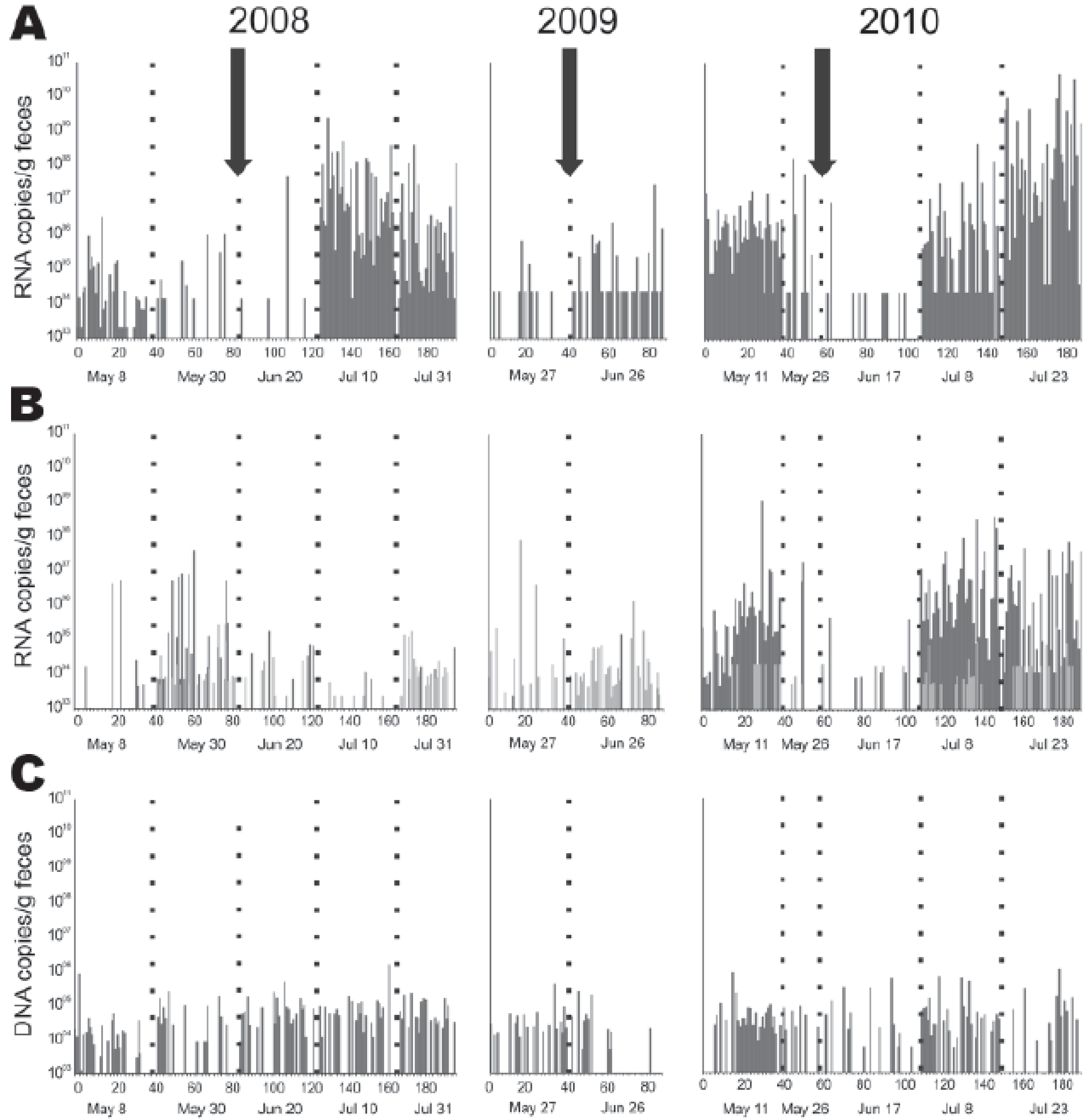
Jan Felix Drexler,[1] Victor Max Corman,[1] Tom Wegner, Adriana Fumie Tateno, Rodrigo Melim Zerbinati, Florian Gloza-Rausch, Antje Seebens, Marcel A. Müller, and Christian Drosten

Drexler 2013

Coronavirus in feces

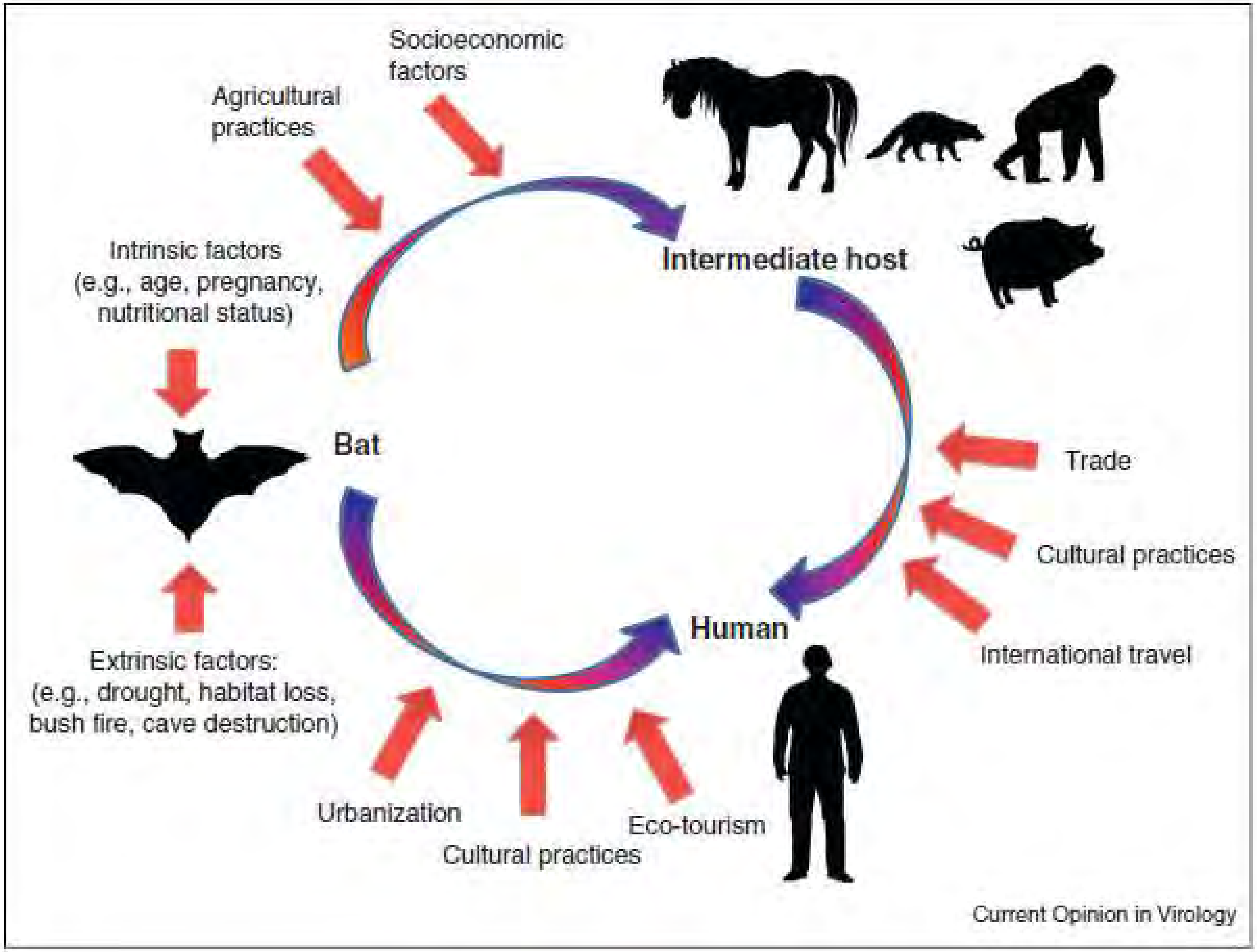
Astrovirus in feces

Adenovirus in feces



Drexler 2013

Did you mention bats ?



Smith 2013

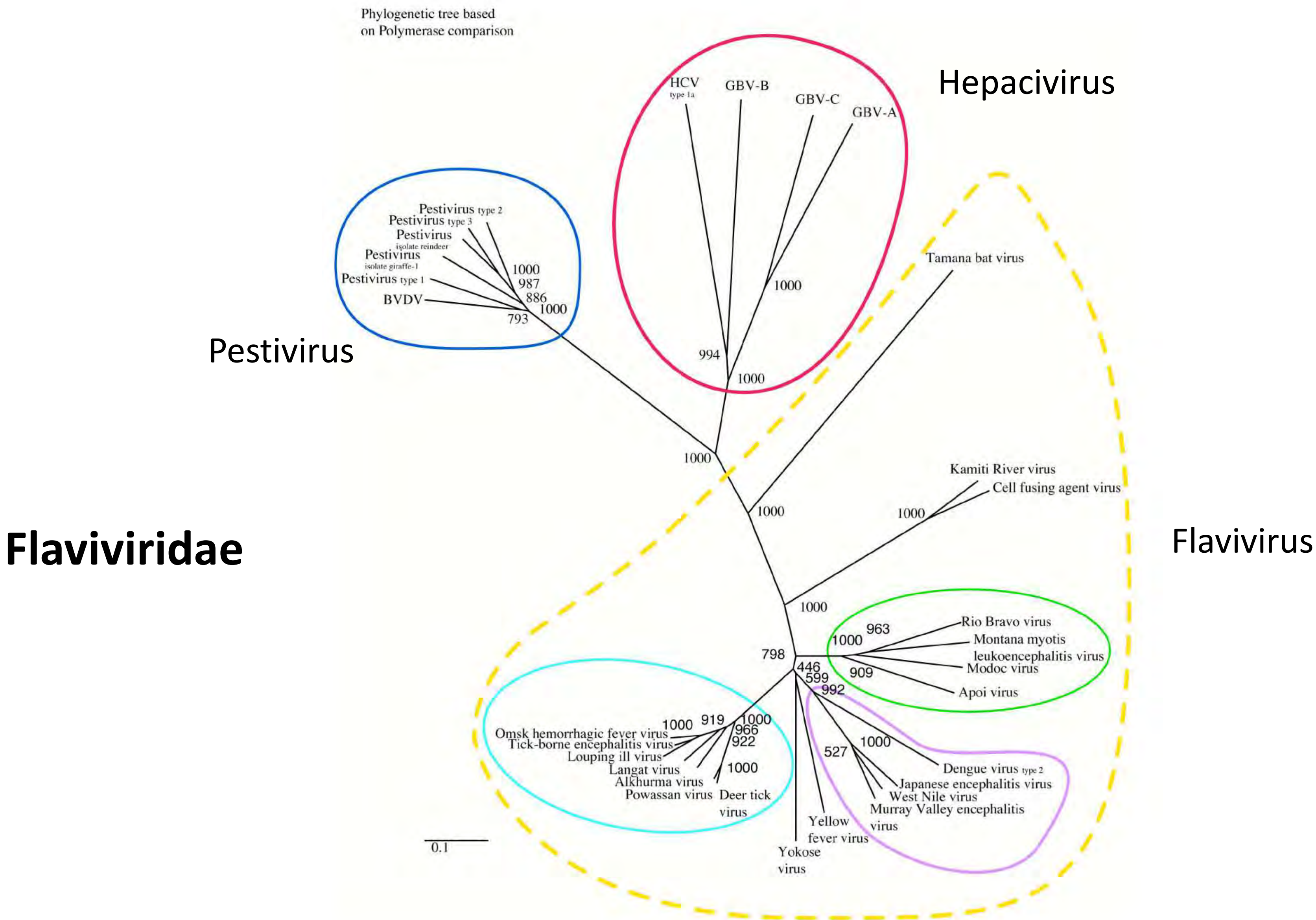
Comparison of drivers and risk factors for selective emerging bat zoonotic viruses

Virus	Drivers	Risk factors/modes of transmission
SARS-CoV	Economic growth Desire for game meat Live wild animal trading in wet markets International travel	Slaughtering Social/cultural practices Farming of wild animals Laboratory acquired infection
Ebola virus	Desire for game meat (Bush meat) Live wild animal trading Burial practices	Slaughtering/hunters Social/cultural Practices Poor health care practices
Marburg virus	Infected monkeys used for research Mining Tourism	Laboratory acquired infection Caves (eco-tourism) Mining
Hendra virus	Population growth/urbanization/ human encroachment/ synanthrophy Climate change Starvation Reproductive stress	Inadequate PPE for veterinarians Intermit contact with horses (cuts, abrasions, respiratory secretions) For example performing necropies
Nipah virus (Bangladesh)	Date palm juice Cultural tradition	Drinking date palm juice Caring for infected patients
Nipah virus (Malaysia)	Agricultural intensification (dual land use) Encroachment into forested areas Movement of pigs to grower piggeries within Malaysia Food processing in Singapore Trade Habitat destruction Stress	Piggery workers (aerosols, husbandry practices) Abbatoir workers (slaughtering)
Reoviruses (Melaka virus and related viruses)	Urbanization Tourism	Close proximity to bats Eco-tourism
Menangle virus	Agricultural practices (transportation of pigs within farm) Movement of pigs to grower piggeries Close proximity to flying fox colony	Piggery workers (husbandry practices – birthing and necropies without PPE)
Lyssaviruses for example Rabies, Australian bat lyssavirus (ABLV), European bat lyssaviruses (EBLV) 1 and 2, Lagos bat virus, Duvenhage virus	Urbanization Deforestation Synanthrophy	Bat carers Cohabitation with bats in houses

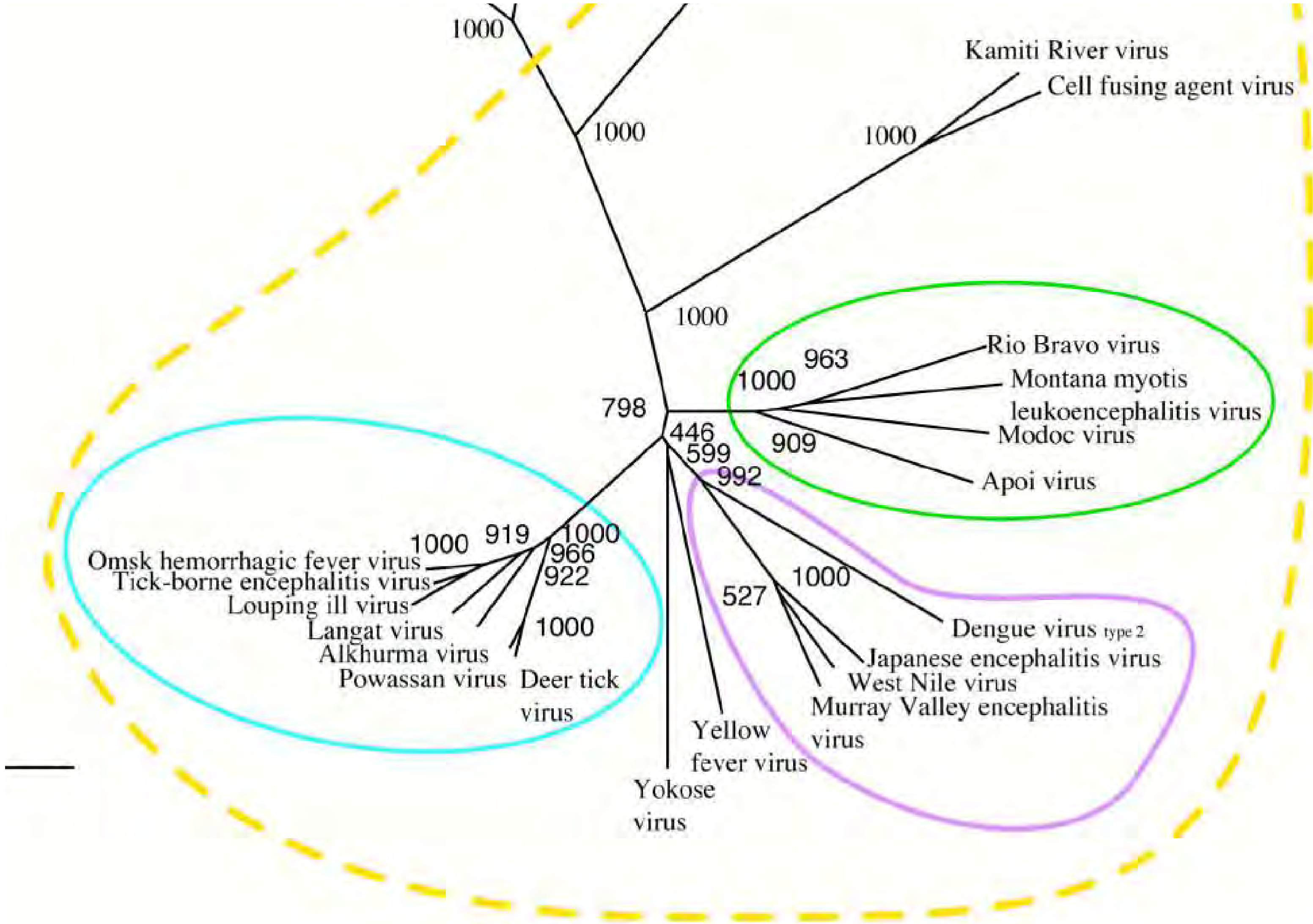
Smith 2013

Flaviviruses

Flaviviruses: highly successful

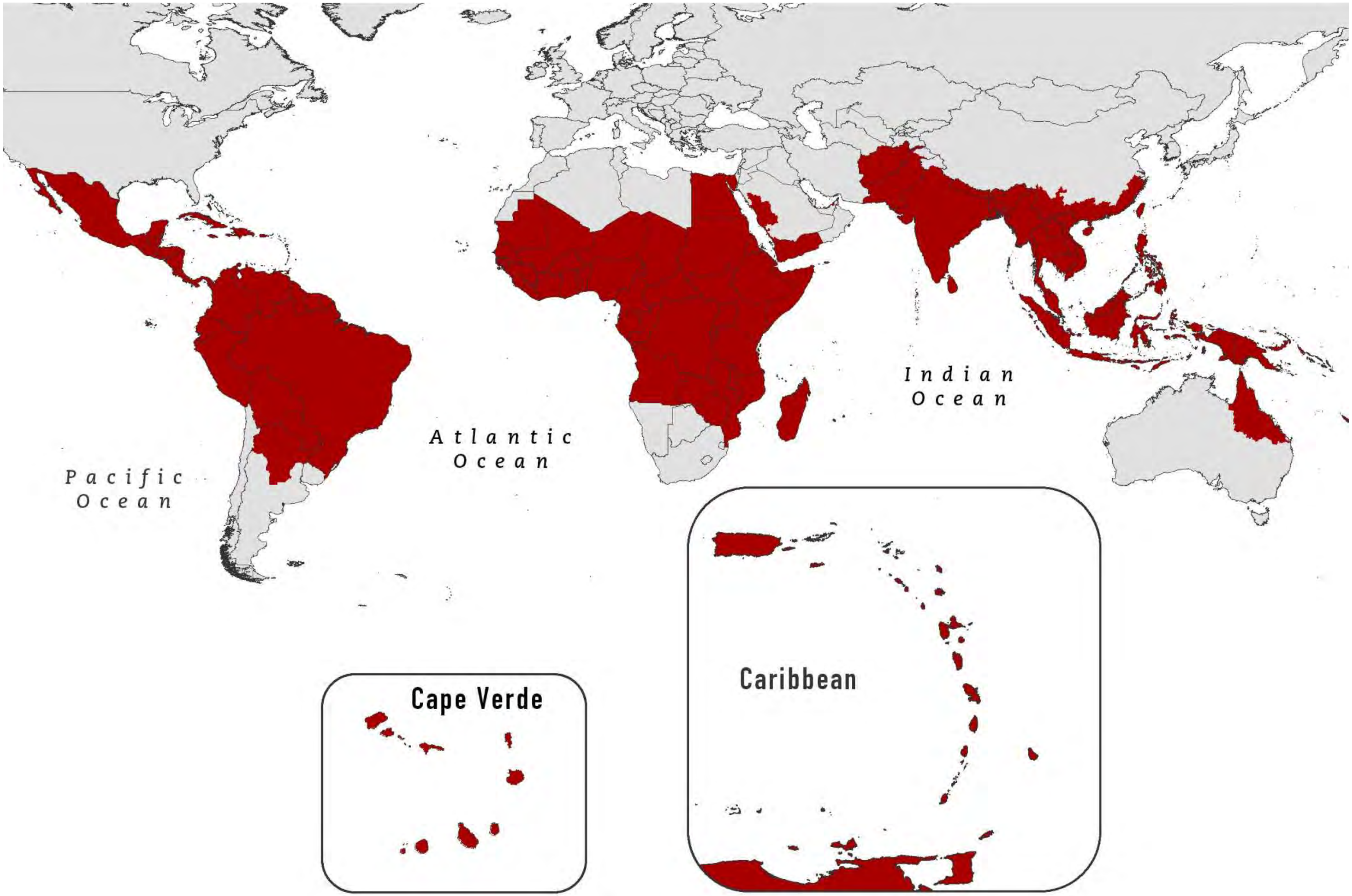


Flaviviruses: highly successful



Dengue

- From 9 to 100 countries concerned
- 2,5 billions of people exposed
- 50 to 100 millions cases a year, increasing
- More explosive outbreaks
- More northern every year
  - Including Europe


Pacific Ocean
Atlantic Ocean
Indian Ocean
Cape Verde
Caribbean

Aedes albopictus in Europe (2012)

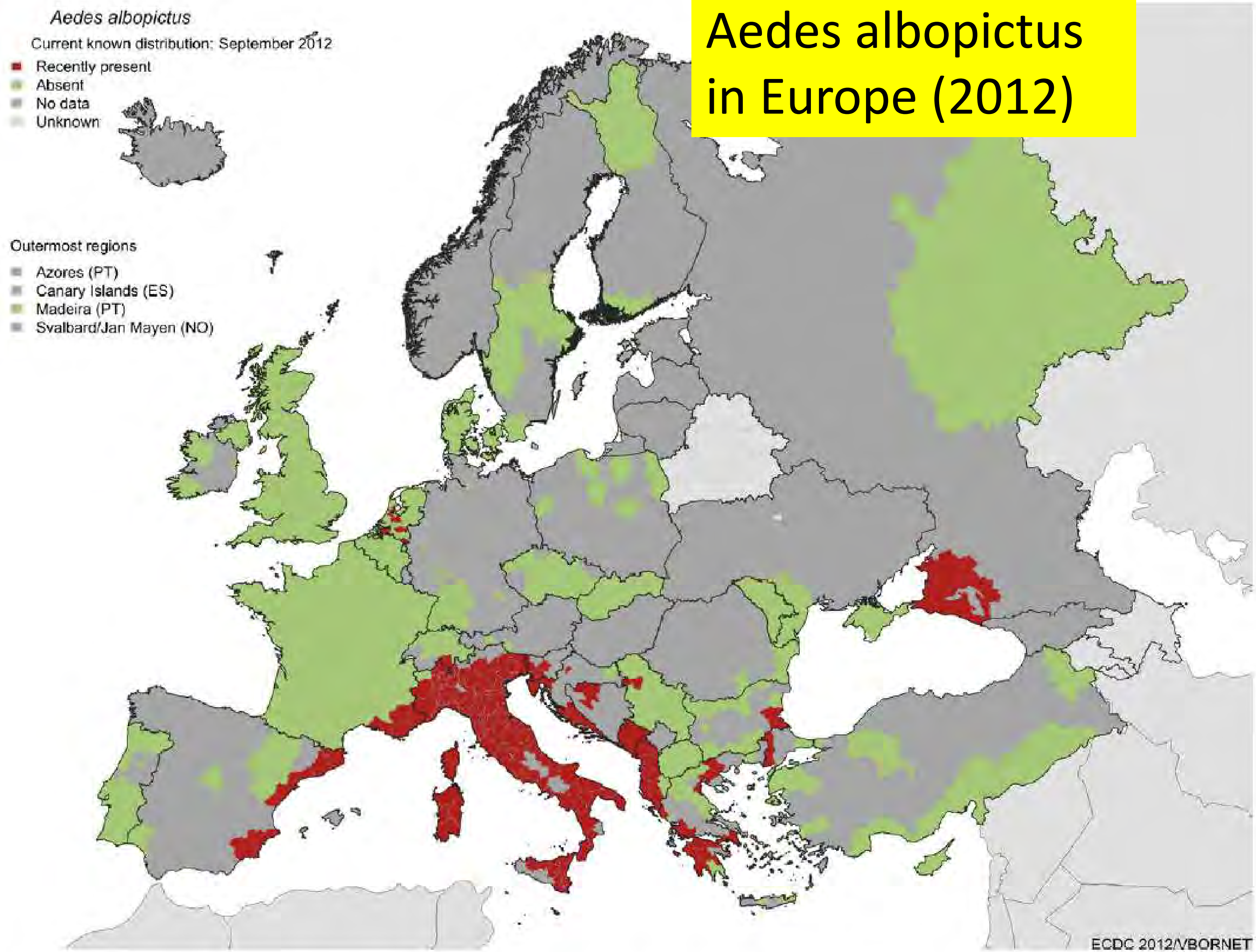


Figure 4 Distribution of *Aedes albopictus* in Europe (Sept 2012), modified from VBORNET.

Dengue Madeira 2012

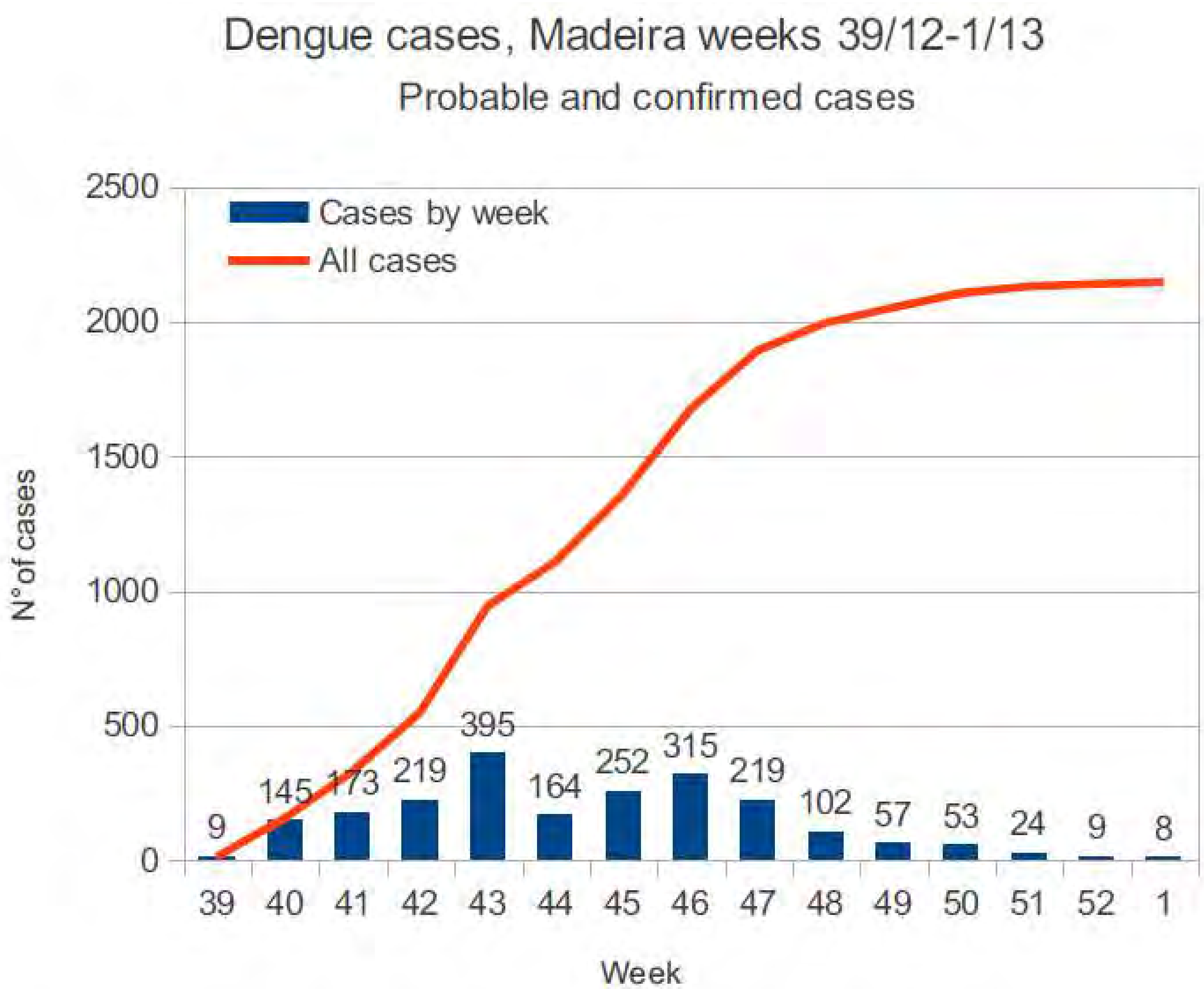


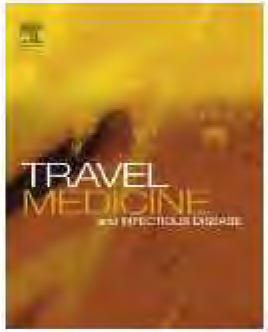
Figure 3 Distribution of cases by week and total of all cases, week 39/12—1/13.

Travel Medicine and Infectious Disease (2013) 11, 274–284

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/tmid



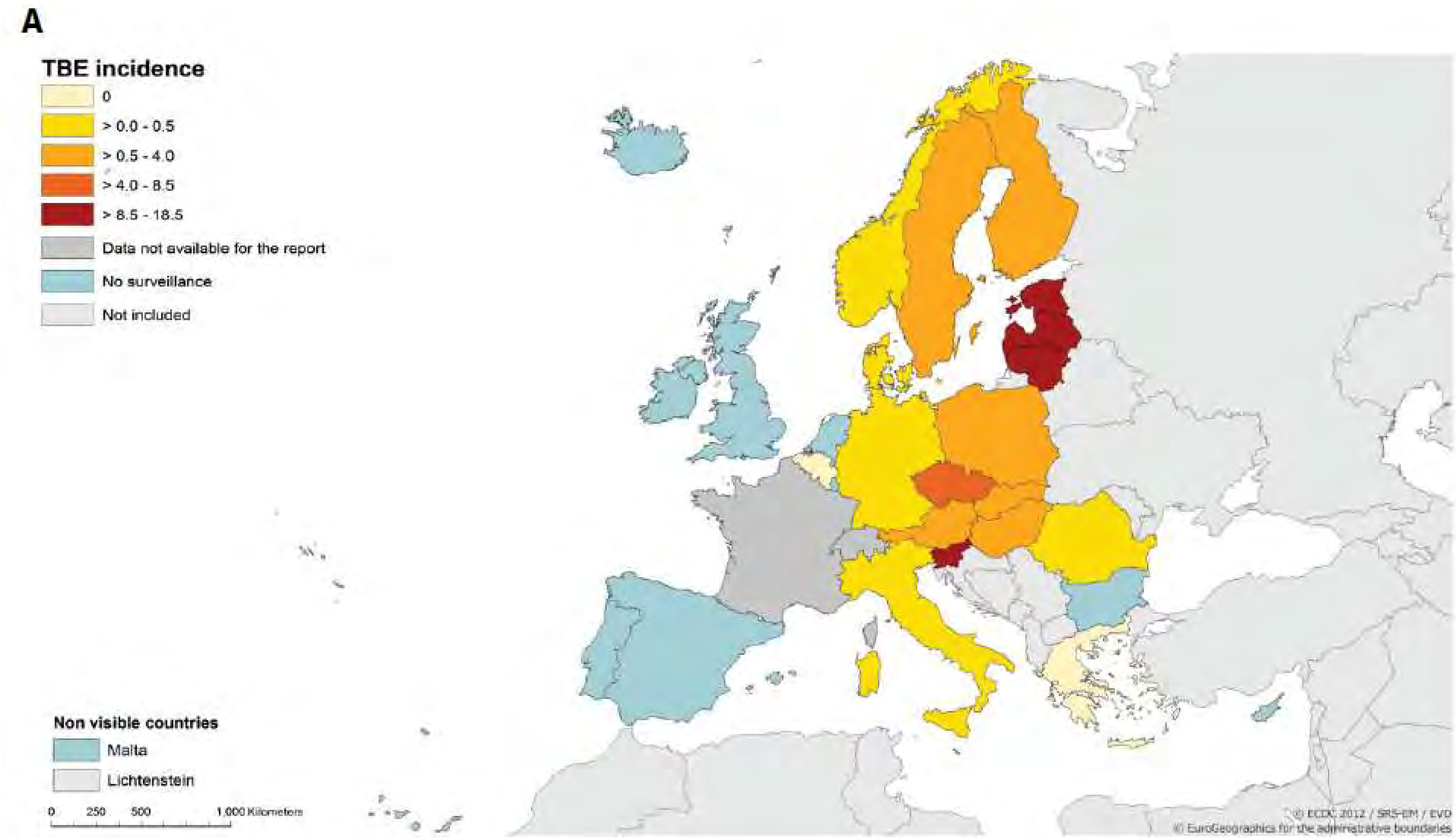
REVIEW

Chikungunya and dengue autochthonous cases in Europe, 2007–2012

Danilo Tomasello*, Patricia Schlagenhauf

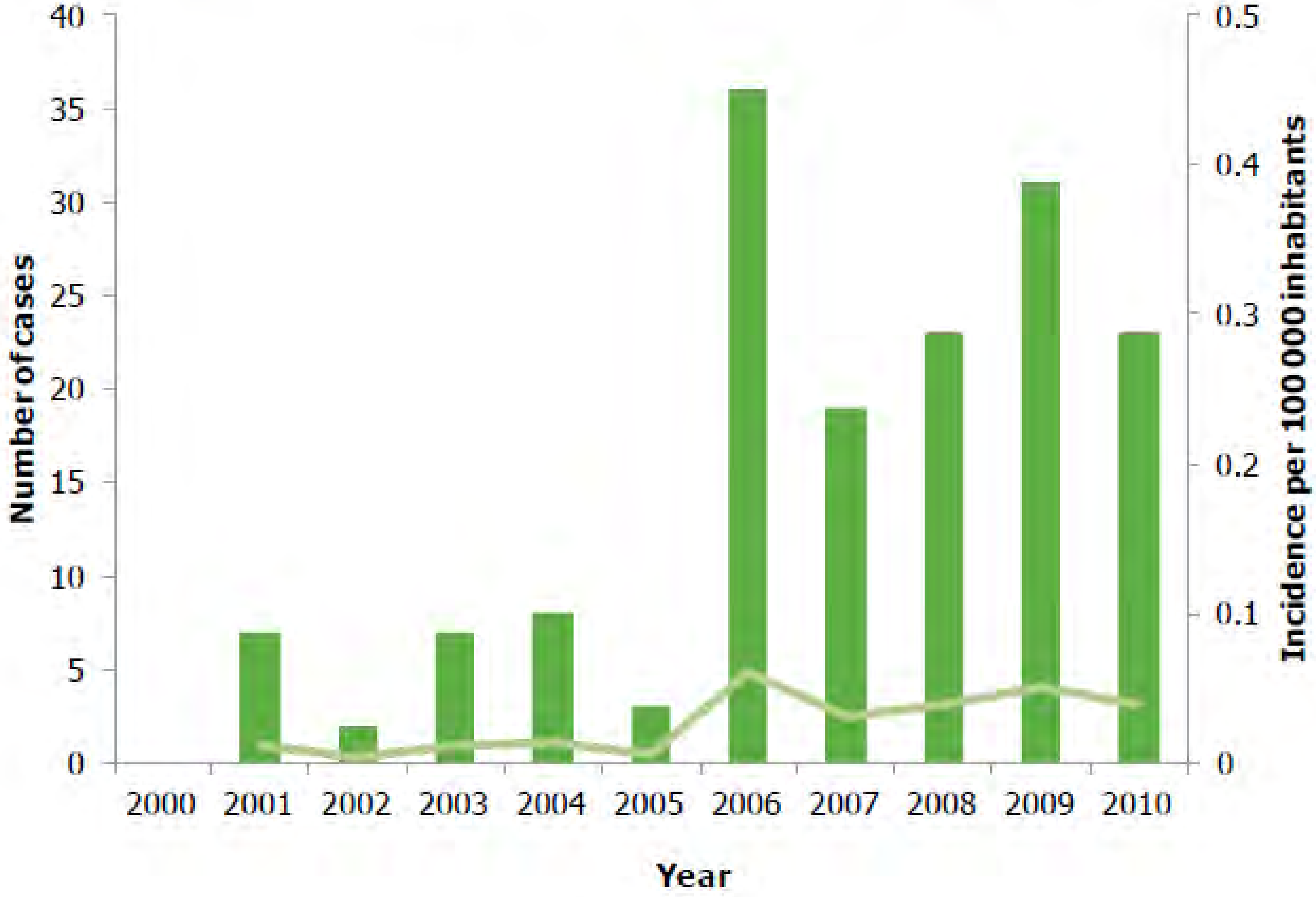
	Frejùs (France), Sept 2010	**2**	–	*0 (0%)*	Frejùs (2 cases)	43°25′N, 6°44′E	*Aedes albopictus*	E1-226A (genotype)
Dengue fever	Nice (France), Sept 2010	**2**	–	*2 (100%)*	Nice (2 cases)	43°42′N, 7°16E	*Aedes albopictus*	DENV-1 (serotype)
	Pelješac (Croatia), Aug–Oct 2010	**17**[c] (1[d])	–	*3 (18%)*	Podobuče (11 cases)	42°56′N, 17°17′E	*Aedes albopictus* Unknown (6 cases)	DENV-1 (serotype)
	Madeira island (Portugal), Oct'12-Jan'13	*Not known*[e]	**2218** (74[f])	*122*[g] *(5.8%)*	Funchal (all cases)	32°39′N, 16°54′E	*Aedes aegypti*	DENV-1 (serotype)

TBE



ECDC datas

Figure 25. Number of TBE cases (bars) and incidence per 100 000 inhabitants (line) by year, Italy (n=159)



ECDC datas

TRANSACTIONS OF THE ROYAL SOCIETY OF
TROPICAL MEDICINE AND HYGIENE.
Vol. 46. No. 5. September, 1952.

COMMUNICATIONS

ZIKA VIRUS

(I). ISOLATIONS AND SEROLOGICAL SPECIFICITY

BY

G. W. A. DICK,

The National Institute for Medical Research, London

S. F. KITCHEN,

Formerly staff member of the Division of Medicine and Public Health, The Rockefeller Foundation, New York, U.S.A.

AND

A. J. HADDOW,

Formerly staff member of International Health Division, The Rockefeller Foundation, New York, U.S.A.

(From the Virus Research Institute, Entebbe, Uganda.)

2009

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Zika Virus Outbreak on Yap Island, Federated States of Micronesia

Mark R. Duffy, D.V.M., M.P.H., Tai-Ho Chen, M.D.,
W. Thane Hancock, M.D., M.P.H., Ann M. Powers, Ph.D.,
Jacob L. Kool, M.D., Ph.D., Robert S. Lanciotti, Ph.D., Moses Pretrick, B.S.,
Maria Marfel, B.S., Stacey Holzbauer, D.V.M., M.P.H.,
Christine Dubray, M.D., M.P.H., Laurent Guillaumot, M.S., Anne Griggs, M.P.H.,
Martin Bel, M.D., Amy J. Lambert, M.S., Janeen Laven, B.S., Olga Kosoy, M.S.,
Amanda Panella, M.P.H., Brad J. Biggerstaff, Ph.D., Marc Fischer, M.D., M.P.H.,
and Edward B. Hayes, M.D.

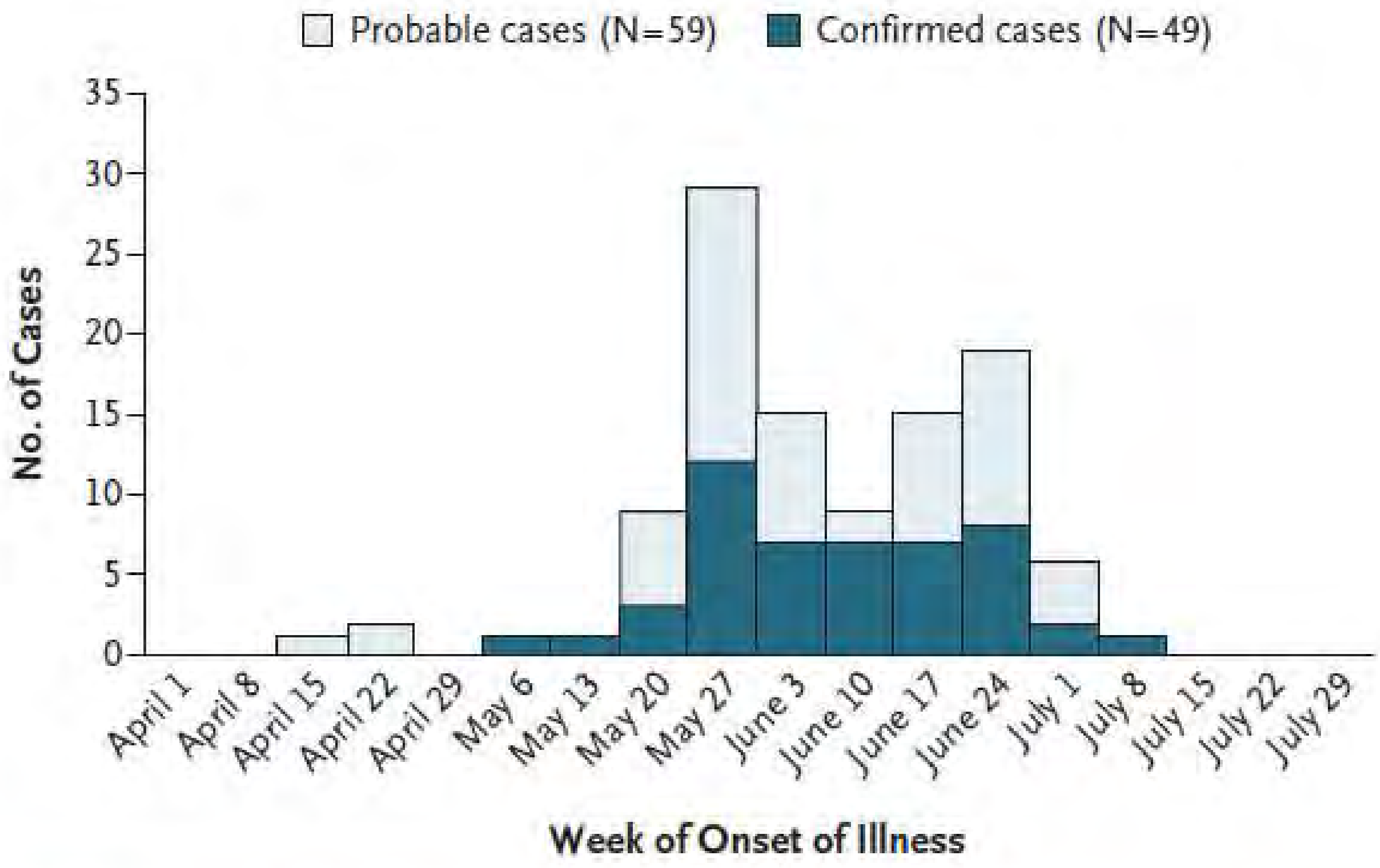
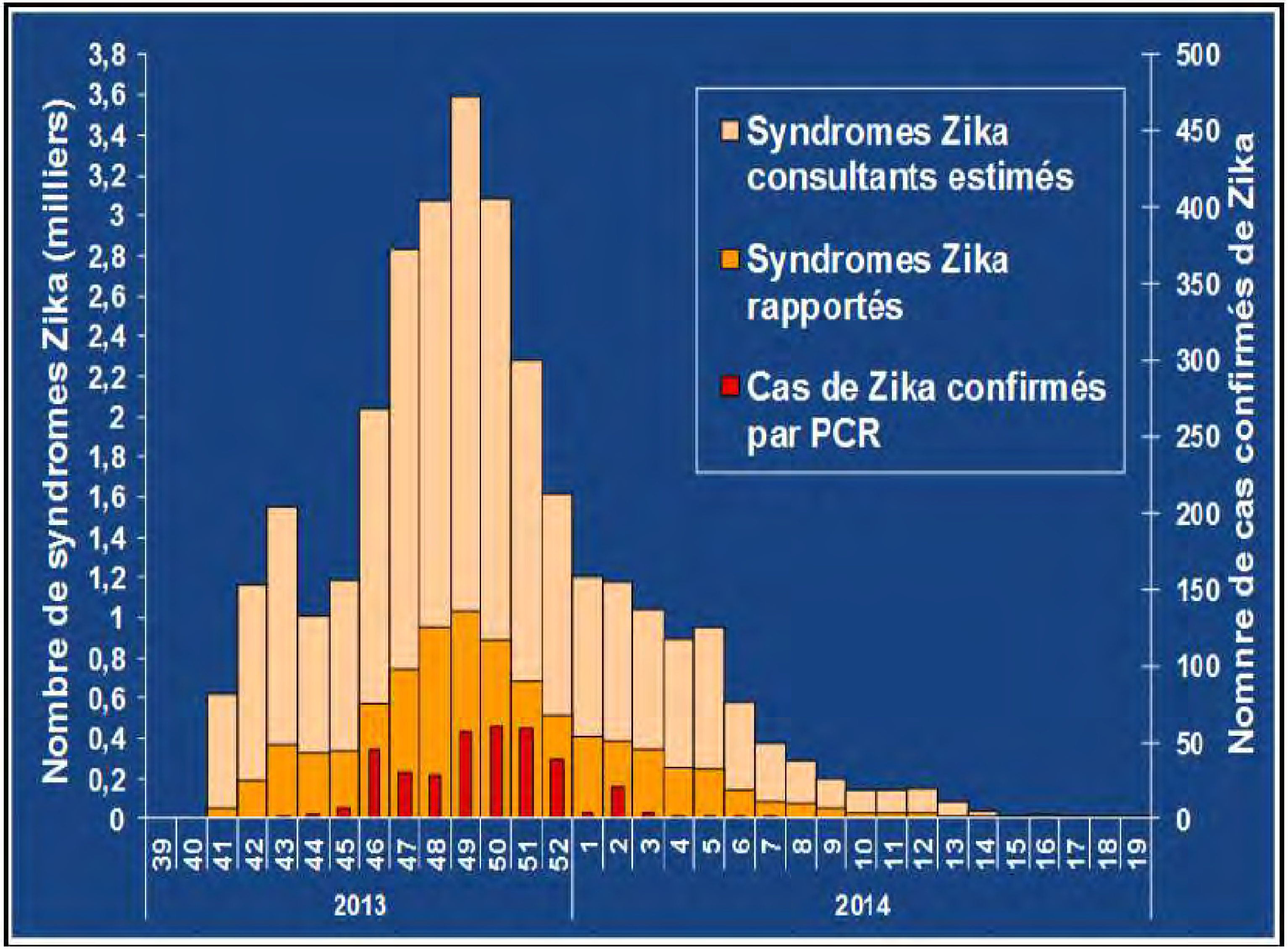
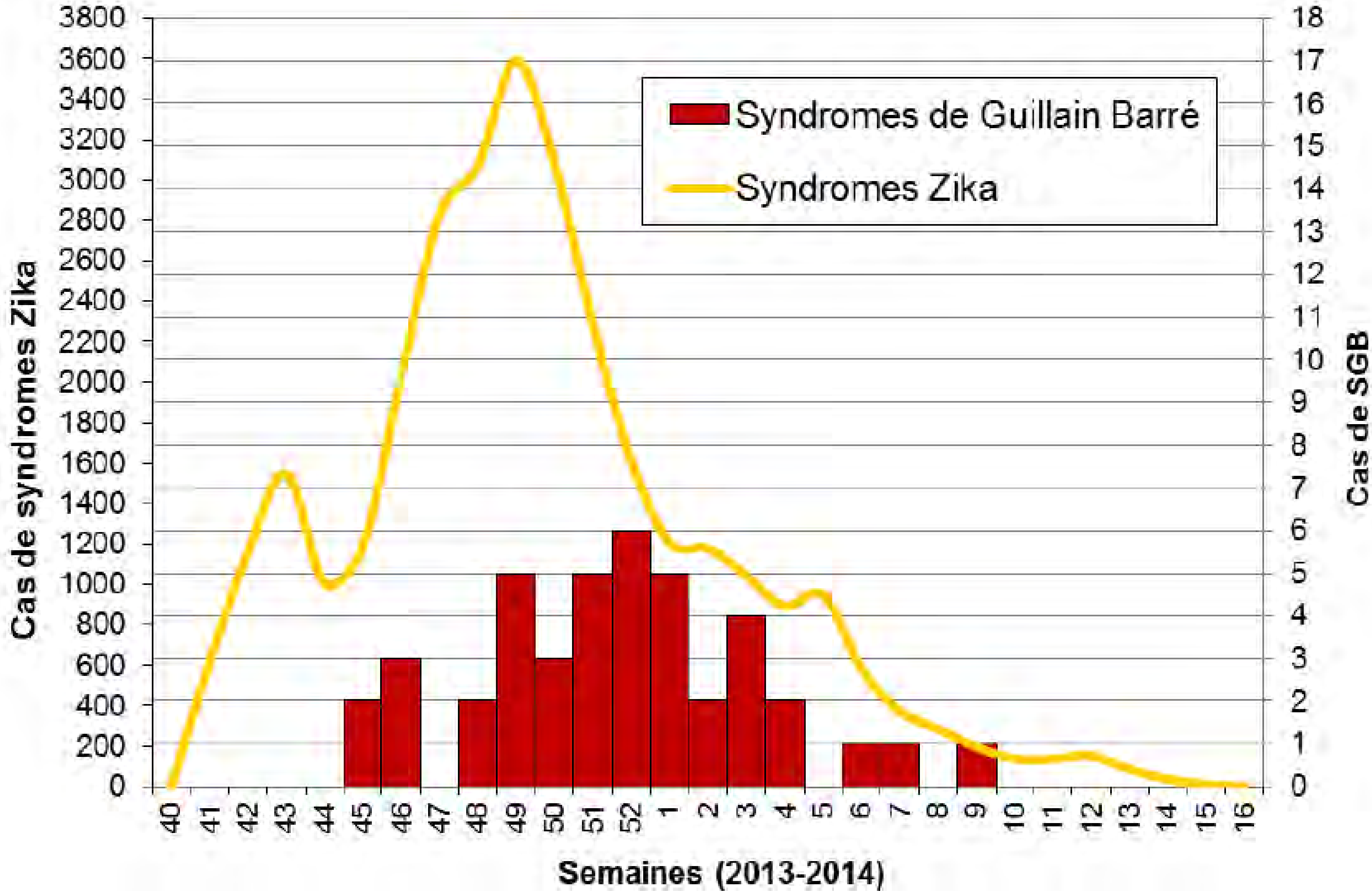


Figure 2. Confirmed and Probable Cases of Zika Virus Disease on Yap among Persons Seeking Health Care, According to Week of Onset of Illness during the Period from April through July 2007.

Duffy 2009

Zika fever in French Polynesia





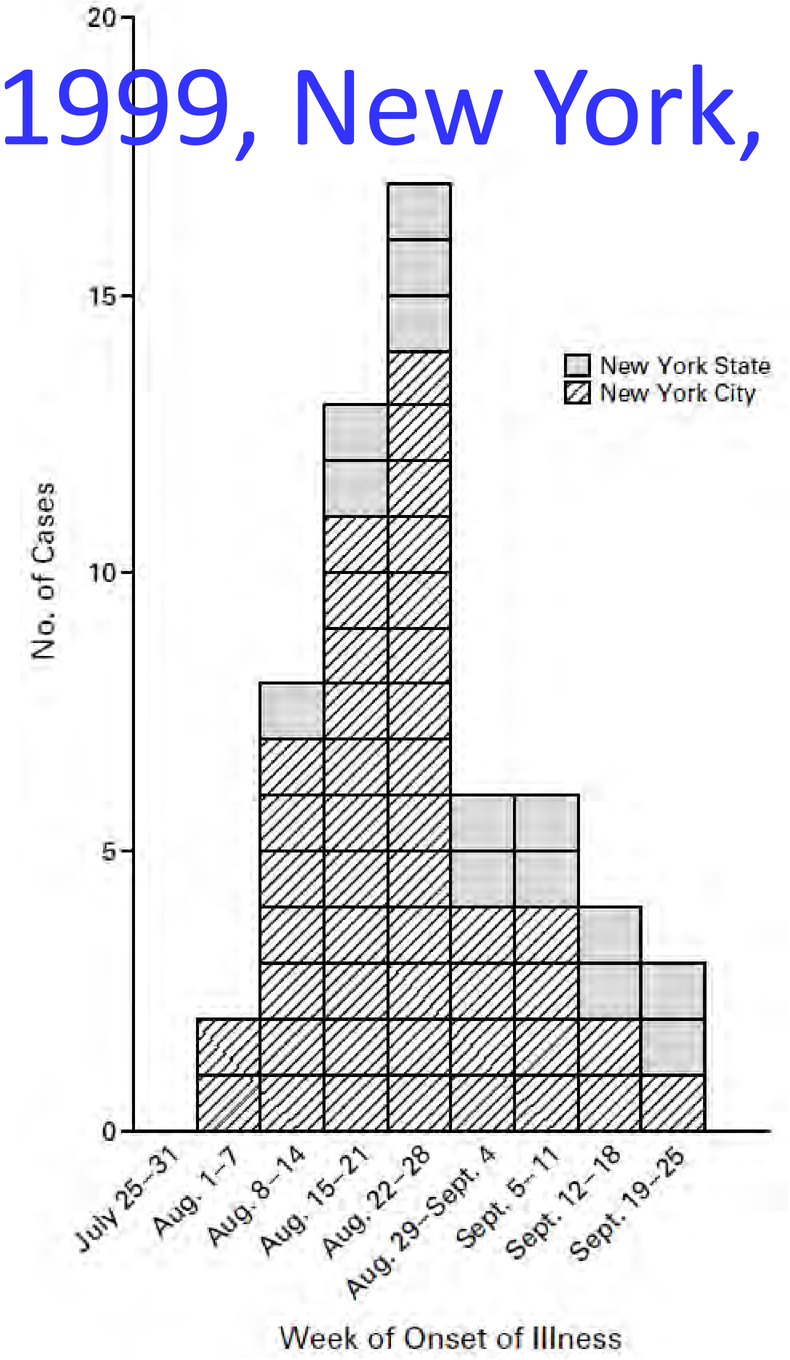
Syndromes de Guillain Barré
Syndromes Zika
Cas de syndromes Zika
Cas de SGB
Semaines (2013-2014)
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
18
17
16
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
0
40 41 42 43 44 45 46 47 48 49 50 51 52 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16

INVS datas

August 1999, New York, New York

- 2 then 8 then finally 59 cases of encephalitis in New York area

August 1999, New York, New York



August 1999, New York, New York

- 2 then 8 then finally 59 cases of encephalitis in New York area
- First hypothesis : St Louis encephalitis
  - Because of outdoor activities of all patients
  - Serologic tests consistent
- Concurrent outbreak in crows
  - Including substantial crow death
  - With encephalitis at necropsy

August 1999, New York, New York

- Final diagnosis of **West Nile virus** infection
  - In local crows
  - In a chilean flamingoe from a local zoo

- Leading to the identification of the same virus in human cases

The New England Journal of Medicine

VOLUME 344 JUNE 14, 2001 NUMBER 24

THE OUTBREAK OF WEST NILE VIRUS INFECTION IN THE NEW YORK CITY AREA IN 1999

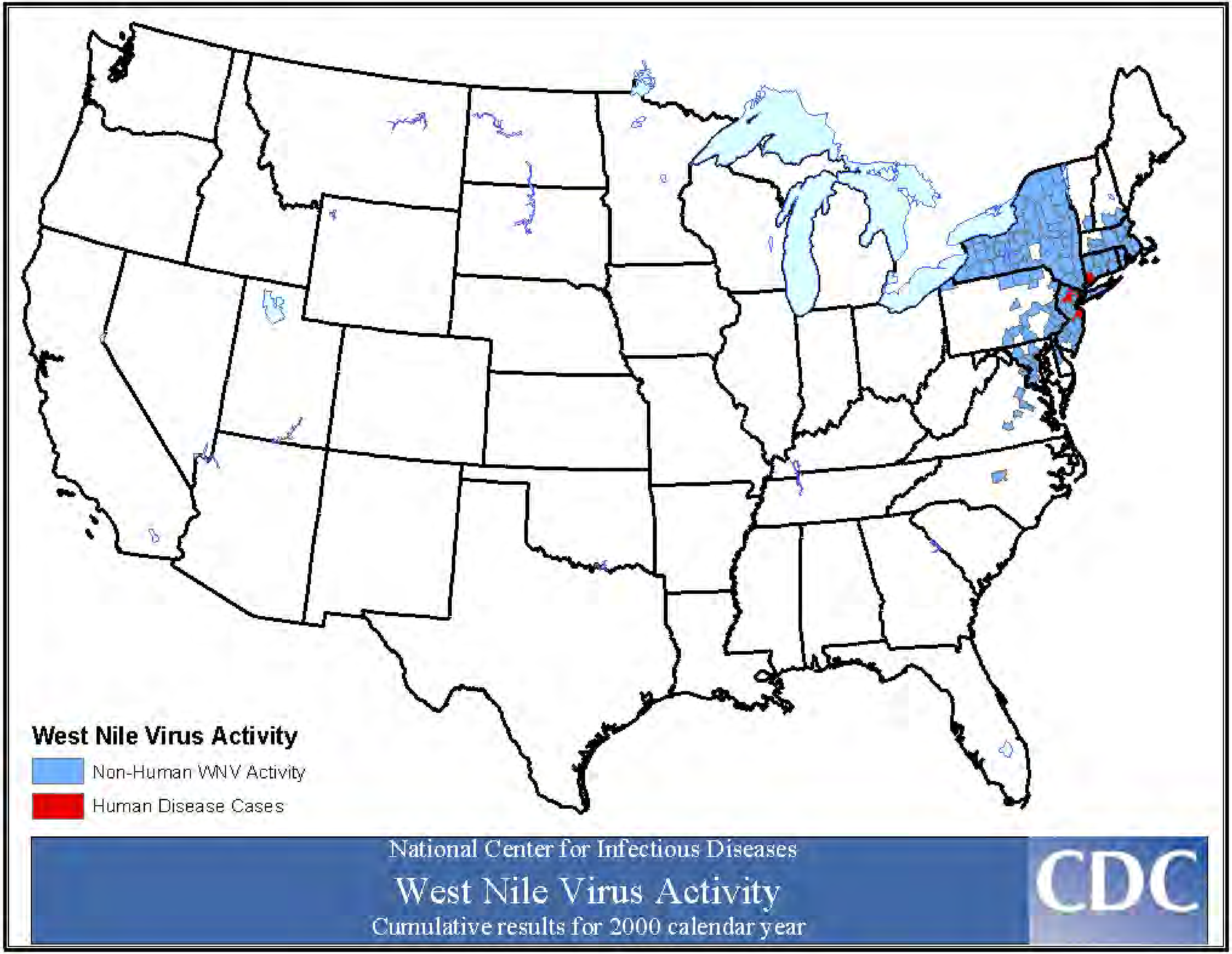
Nash 2001

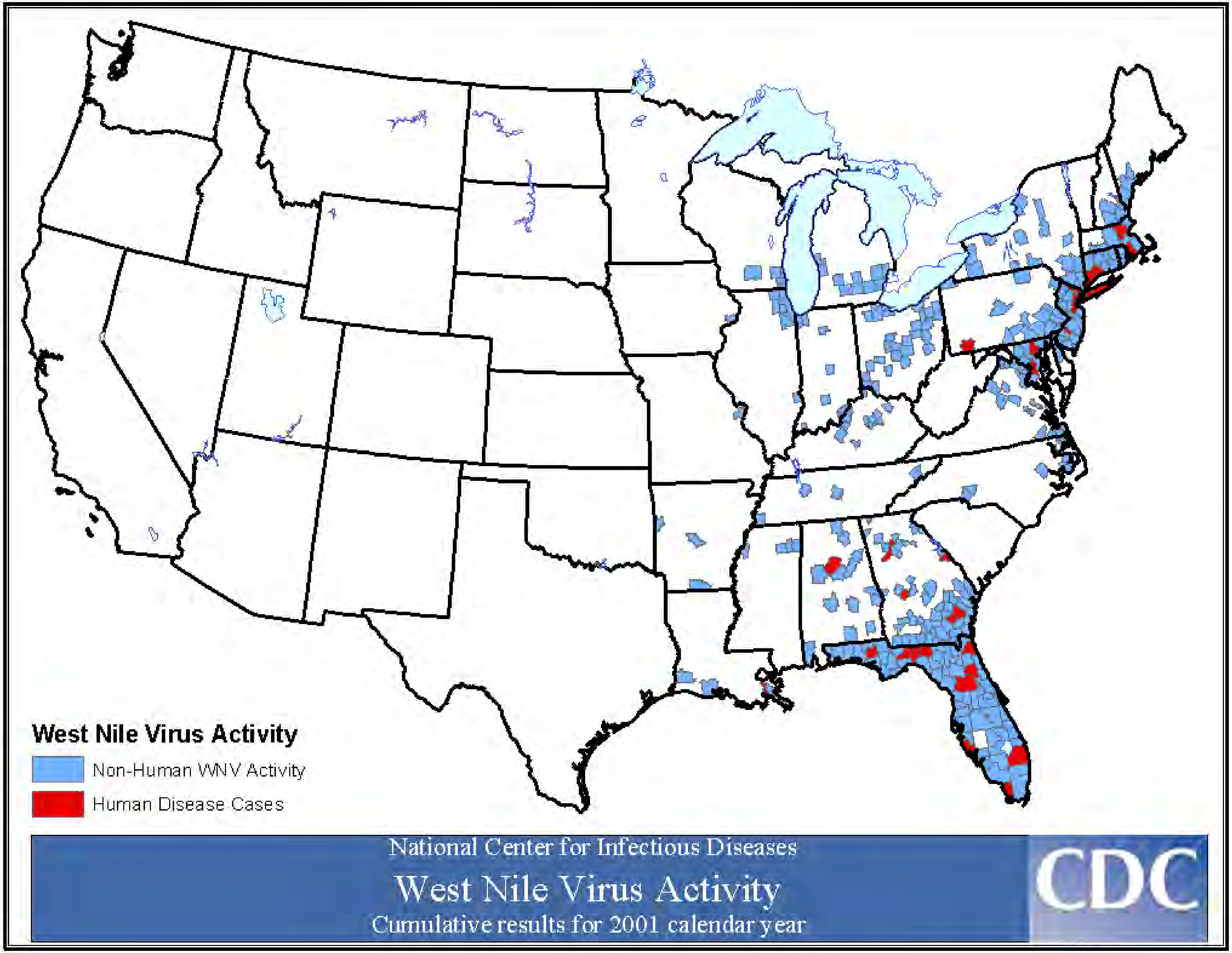
National Center for Infectious Diseases

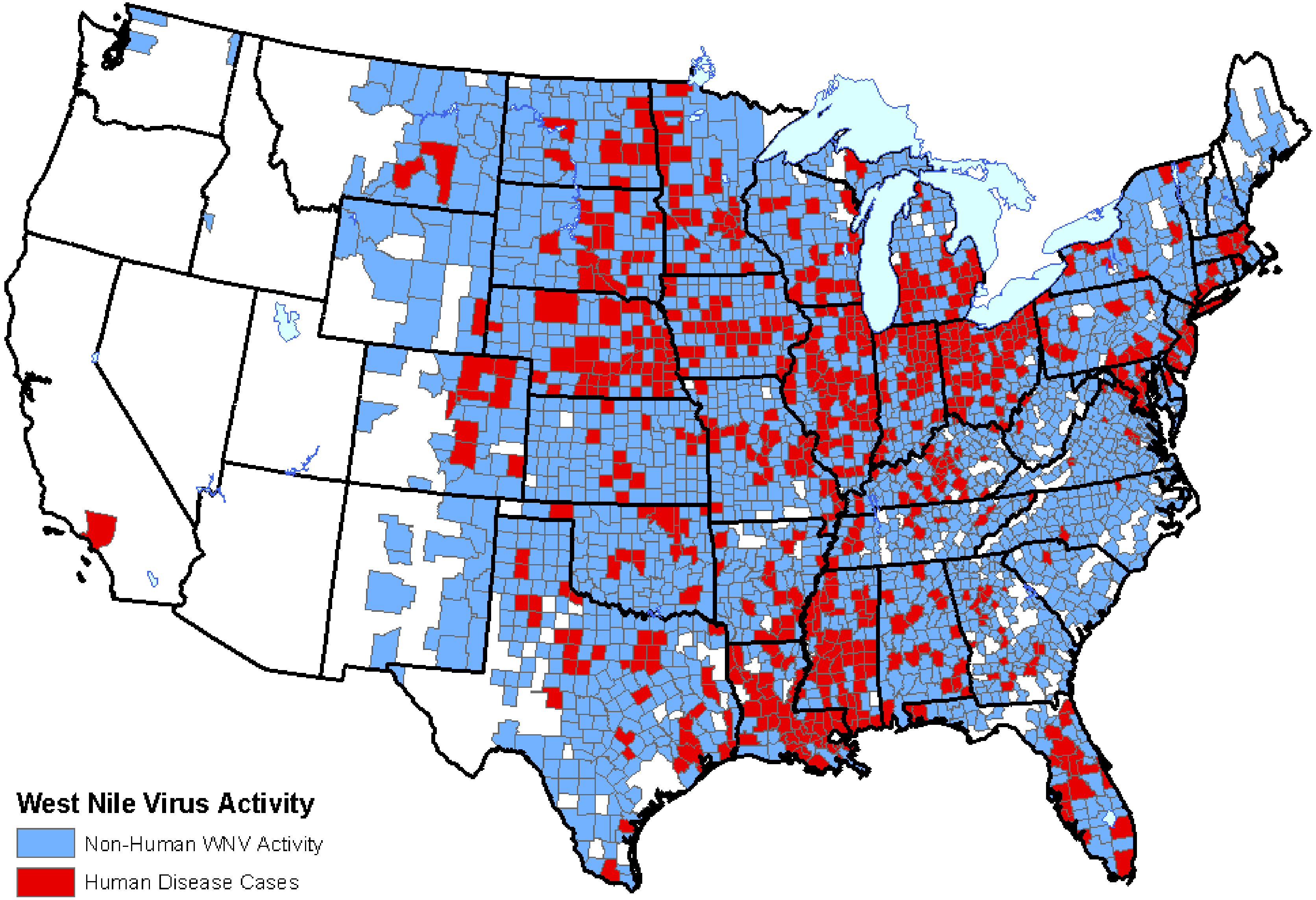
West Nile Virus Activity

Cumulative results for 1999 calendar year

CDC


West Nile Virus Activity
Non-Human WNV Activity
Human Disease Cases
National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2000 calendar year
CDC


West Nile Virus Activity
Non-Human WNV Activity
Human Disease Cases
National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2001 calendar year
CDC



National Center for Infectious Diseases

West Nile Virus Activity

Cumulative results for 2002 calendar year reported as of April 15, 2003

CDC

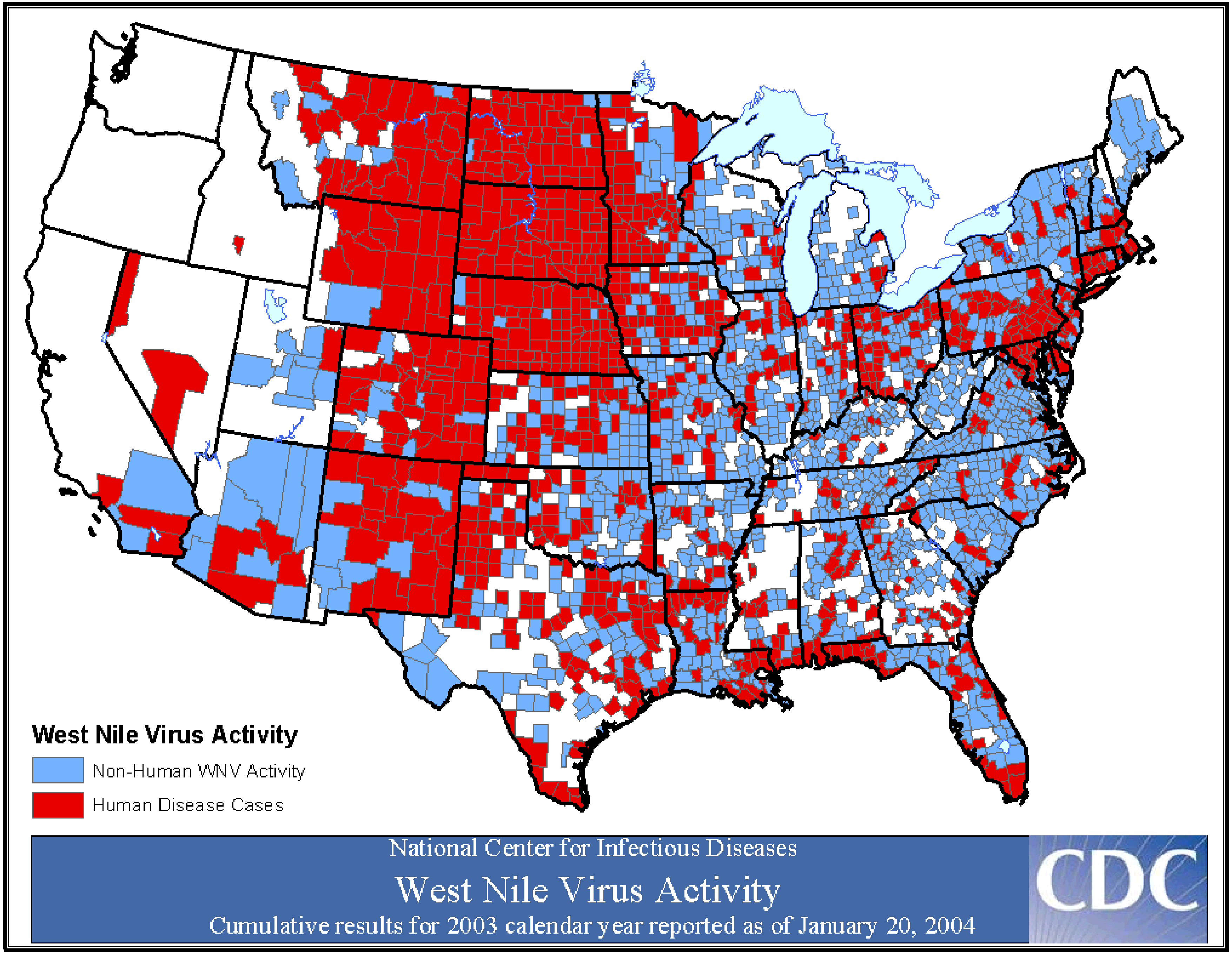
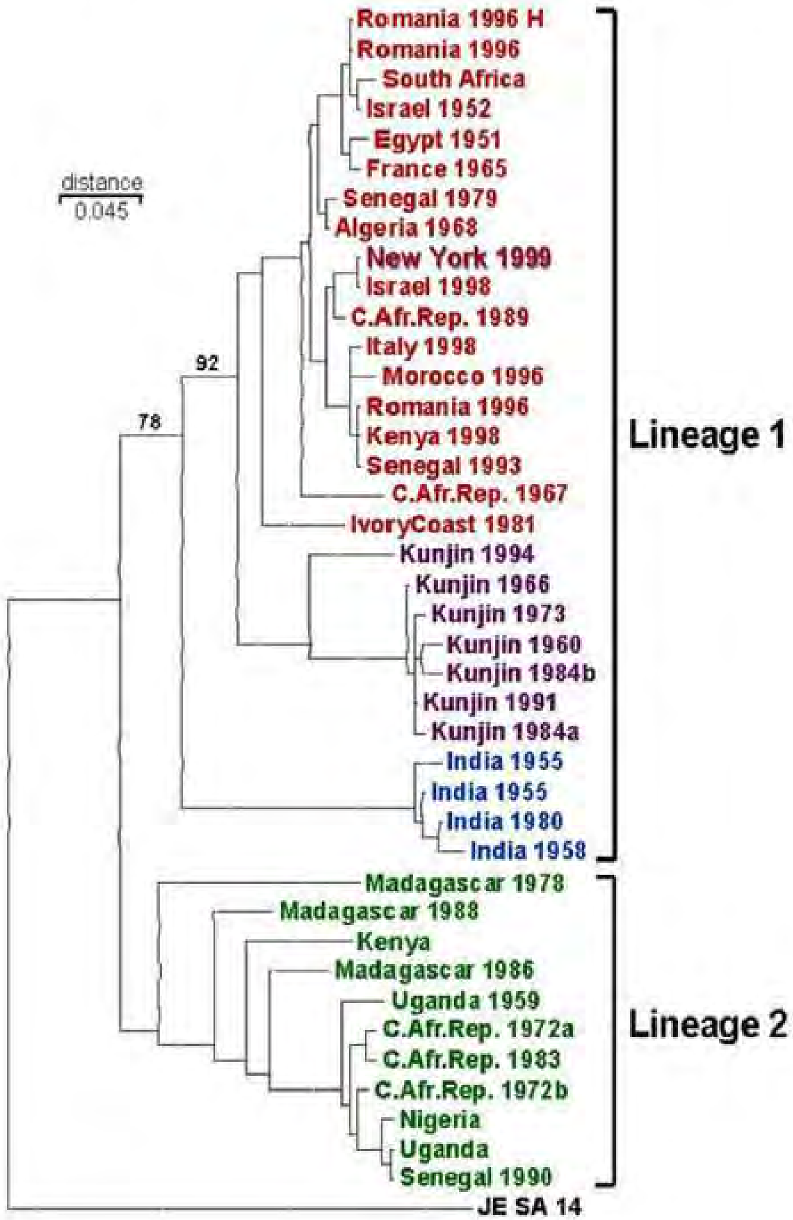

West Nile Virus Activity
Non-Human WNV Activity
Human Disease Cases
National Center for Infectious Diseases
West Nile Virus Activity
Cumulative results for 2003 calendar year reported as of January 20, 2004
CDC

Figure 3. Phylogeny of WNV based on gene sequence of the envelope protein as of 1999 [21]



Roehrig 2013

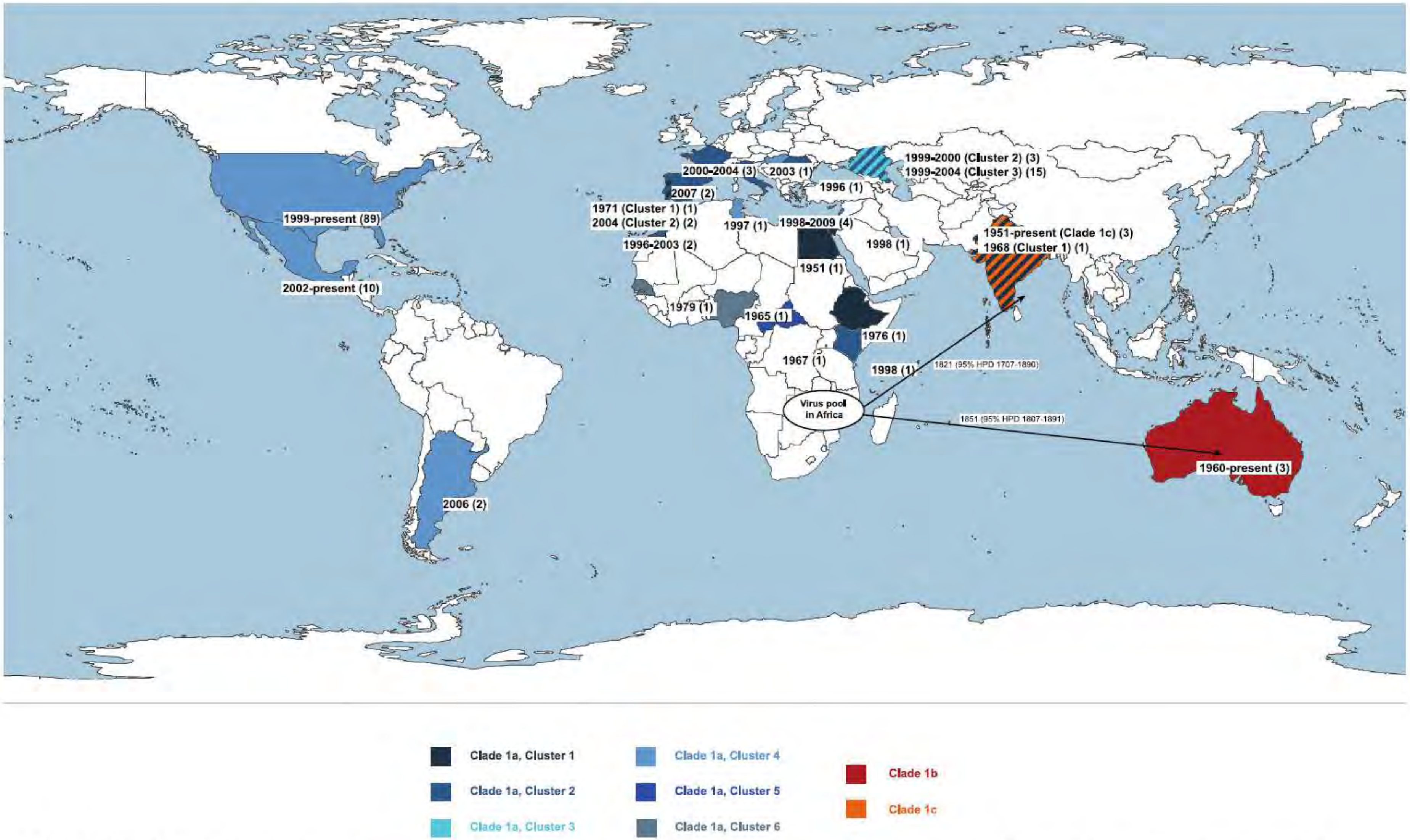
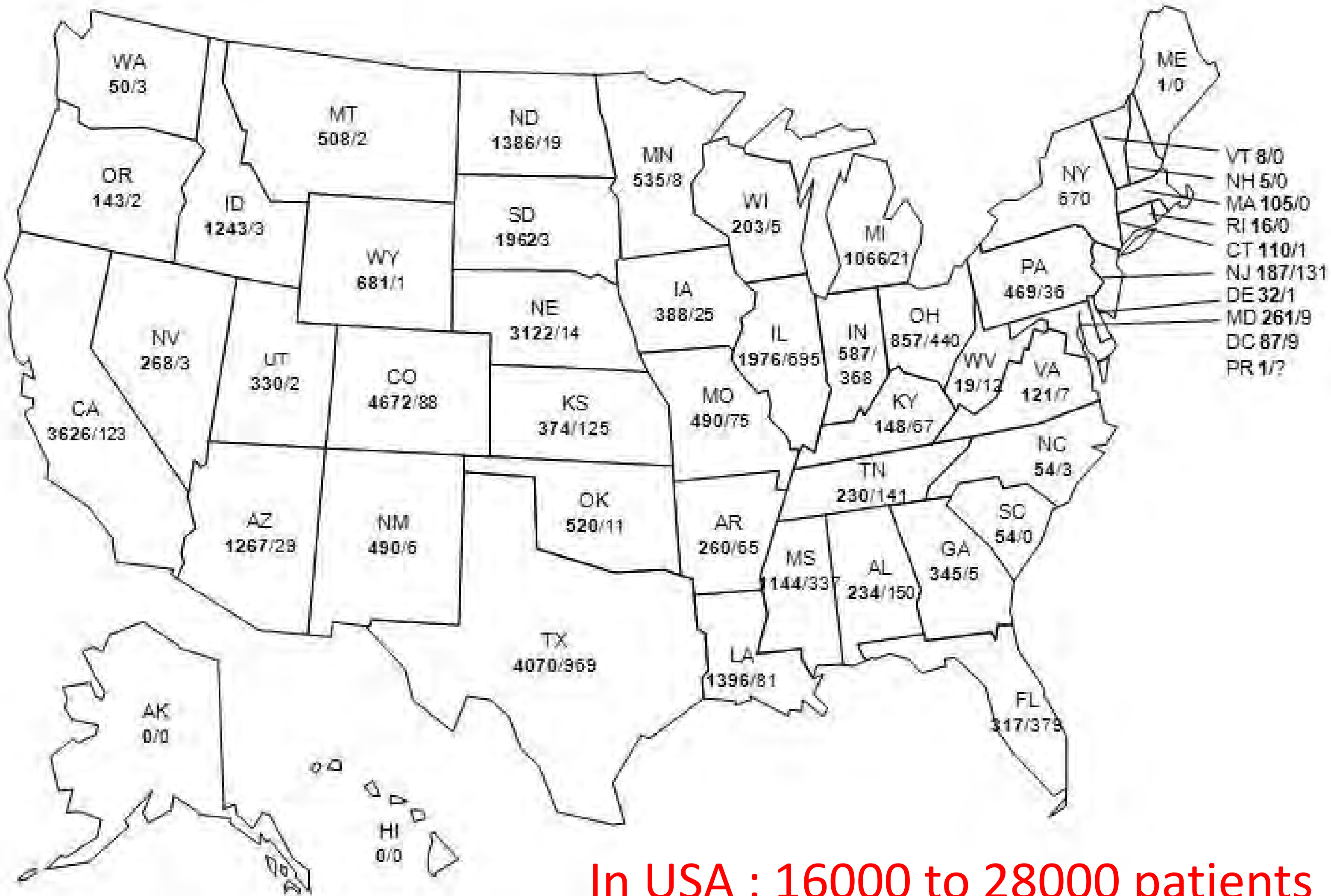


FIG. 1. Worldwide distribution of lineage 1 WNV isolates with known complete genome sequences. The number of isolates from each country is shown in parentheses. Dates of divergence and predicted direction of movement are shown for some isolates.

May 2010

Figure 9. Total WNV and SLEV disease cases by U.S. state (WNV/SLEV). WNV, 1999–2012 (bold) cases reported to ArboNet. SLEV cases from 1964–2000 are listed [1].



In USA : 16000 to 28000 patients

40% (?) neuro-invasive

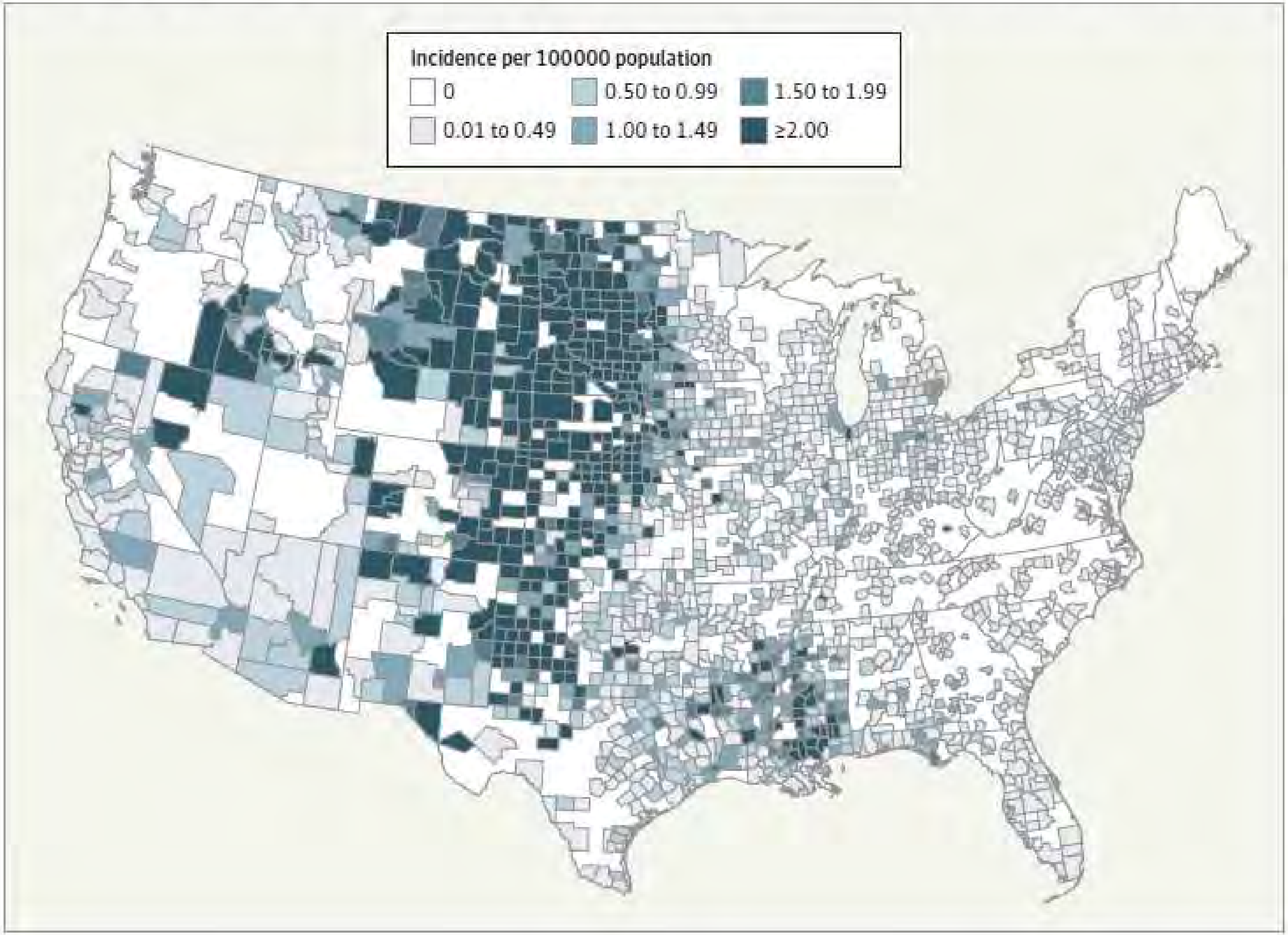
1500 deaths

Roehrig 2013

Figure 10. Total WNV disease cases by province, Canada, 1999–2012. Some cases

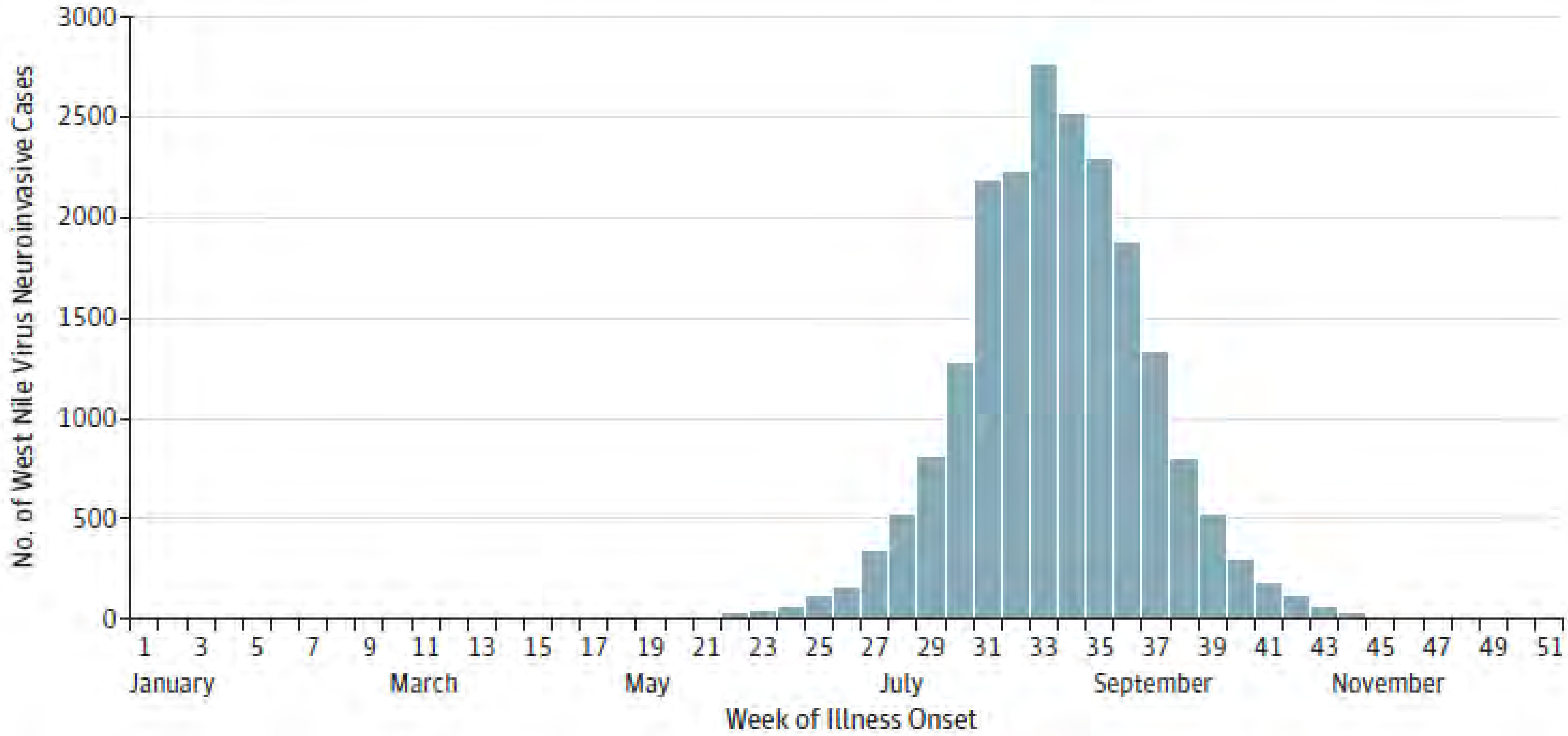
Roehrig 2013

Figure 3. Map of Average Annual Human Neuroinvasive Disease Incidence in the United States, 1999-2012



Petersen 2013

Figure 4. Cumulative Number of Human West Nile Virus Neuroinvasive Disease Cases by Week of Onset, 1999-2012



Petersen 2013

Meanwhile in Europe…

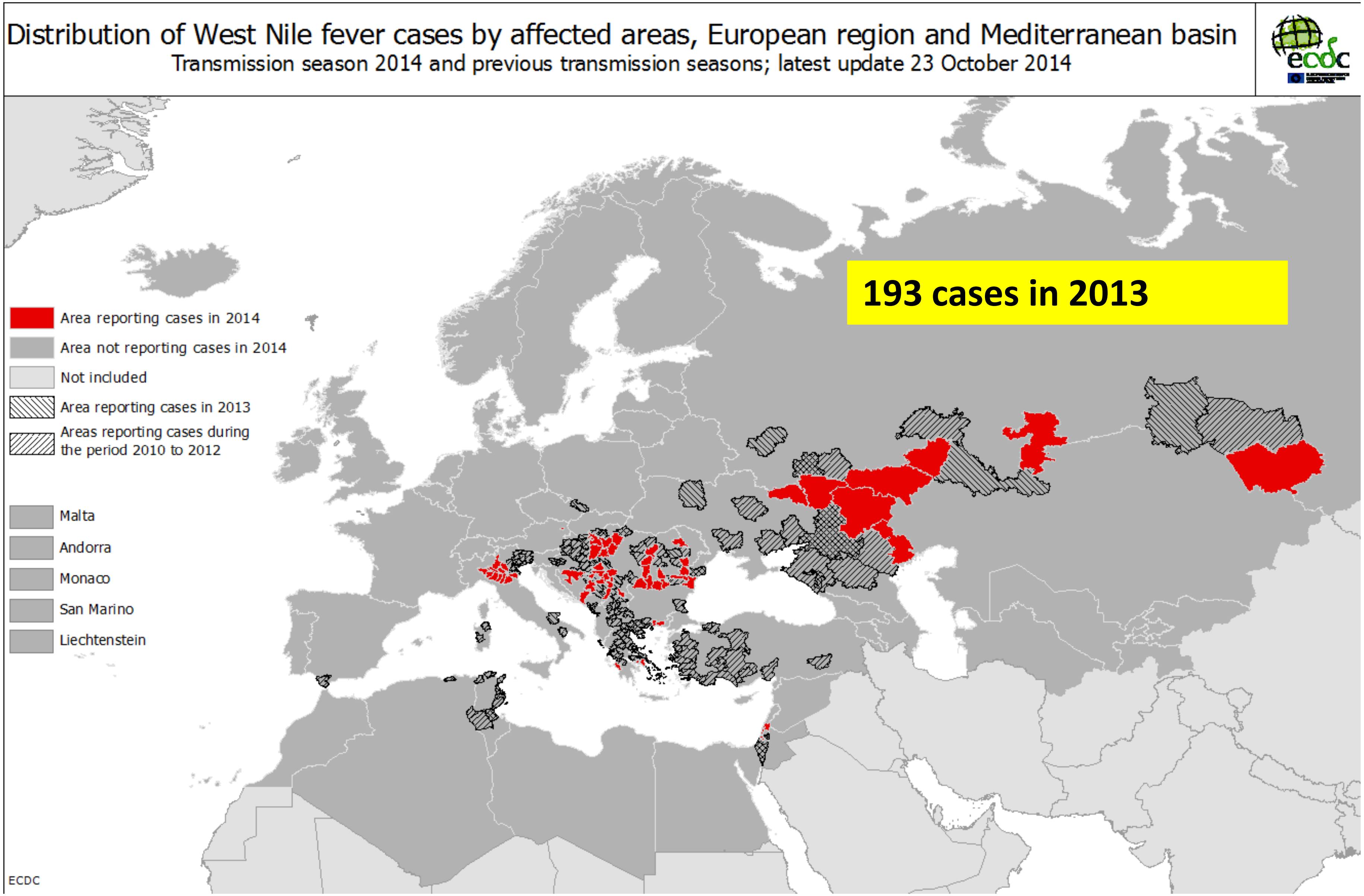
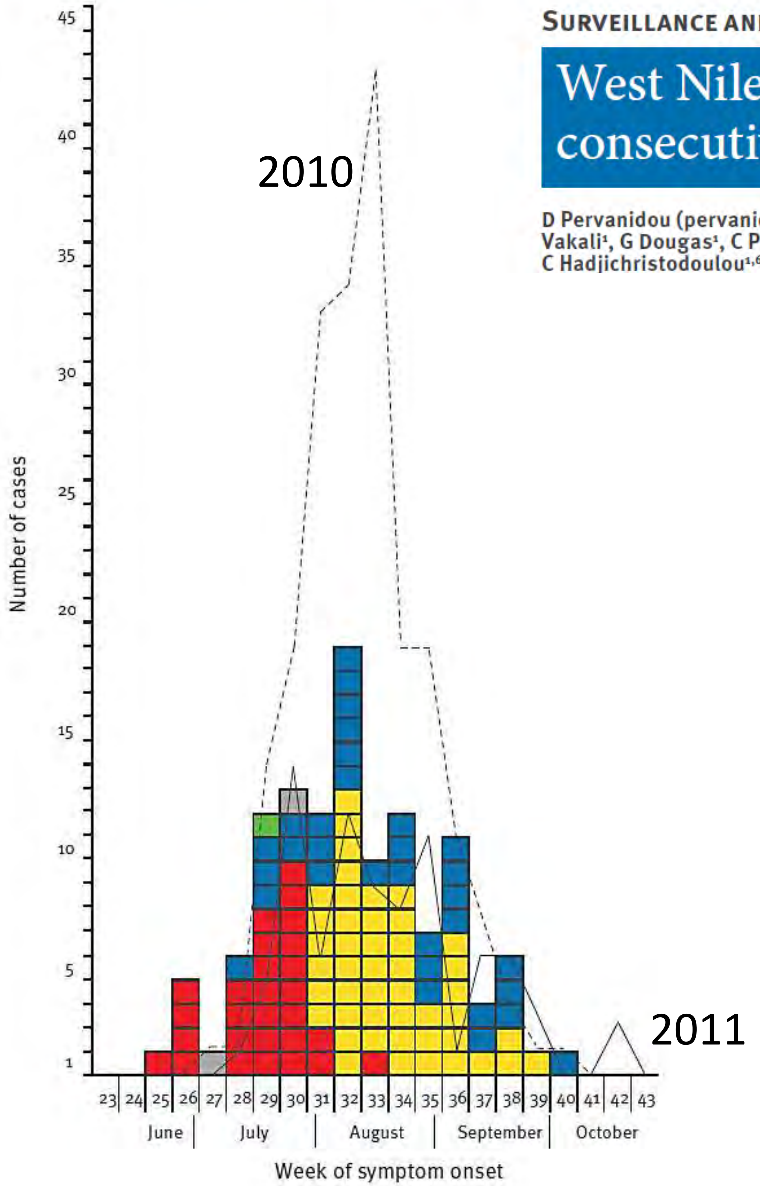


FIGURE 1

Laboratory-diagnosed (confirmed and probable) cases of West Nile neuroinvasive disease by week[a] of symptom onset, Greece, 2010 (n=197), 2011 (n=75), 2012 (n=109)[b]



SURVEILLANCE AND OUTBREAK REPORTS

West Nile virus outbreak in humans, Greece, 2012: third consecutive year of local transmission

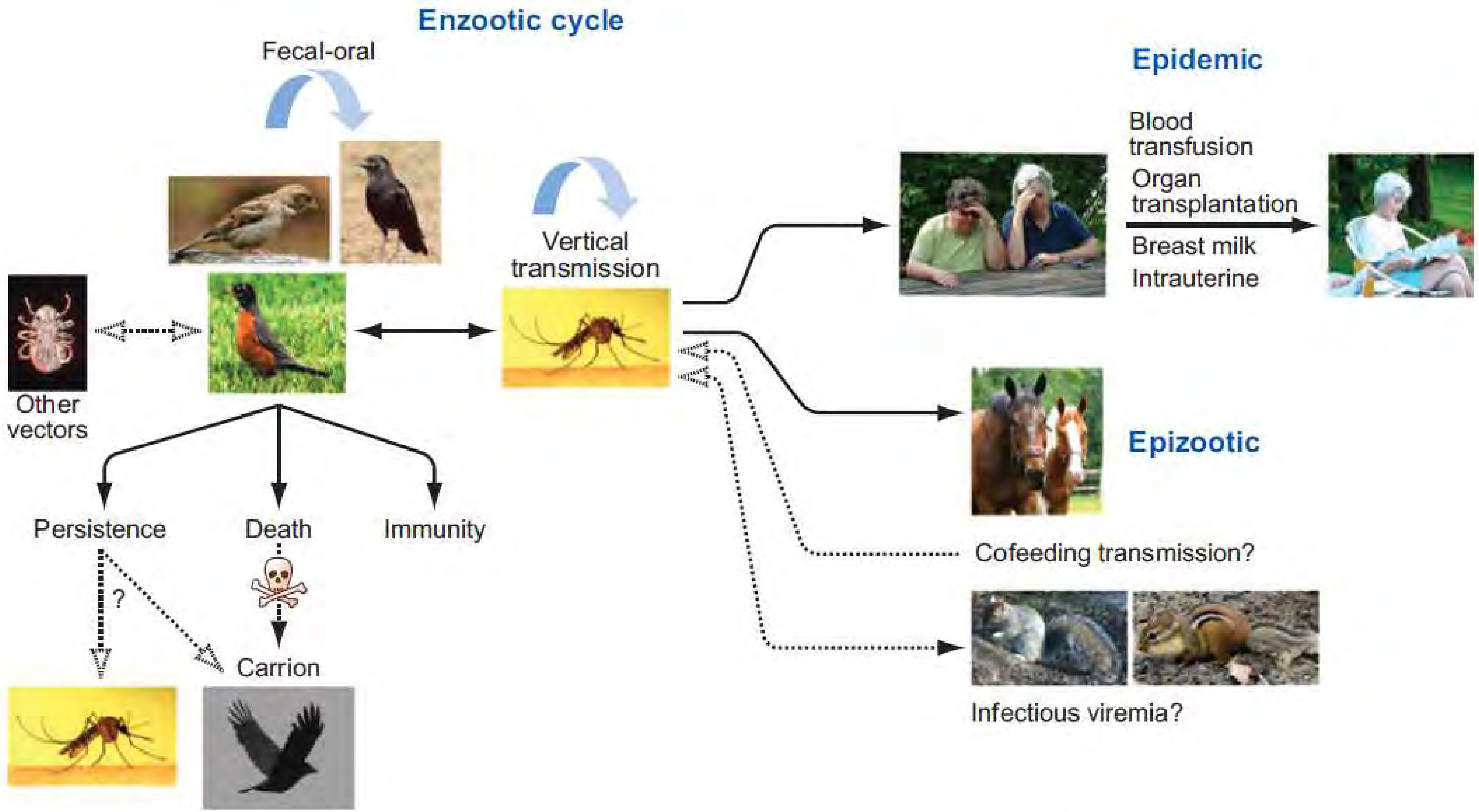
D Pervanidou (pervanidou@gmail.com)[1,2], M Detsis[1], K Danis[1,2], K Mellou[1], E Papanikolaou[1], I Terzaki[1], A Baka[1], L Veneti[1], A Vakali[1], G Dougas[1], C Politis[1], K Stamoulis[3], S Tsiodras[1,4], T Georgakopoulou[1], A Papa[5], A Tsakris[4], J Kremastinou[1], C Hadjichristodoulou[1,6]

163 cases

109 neuroinvasive infections

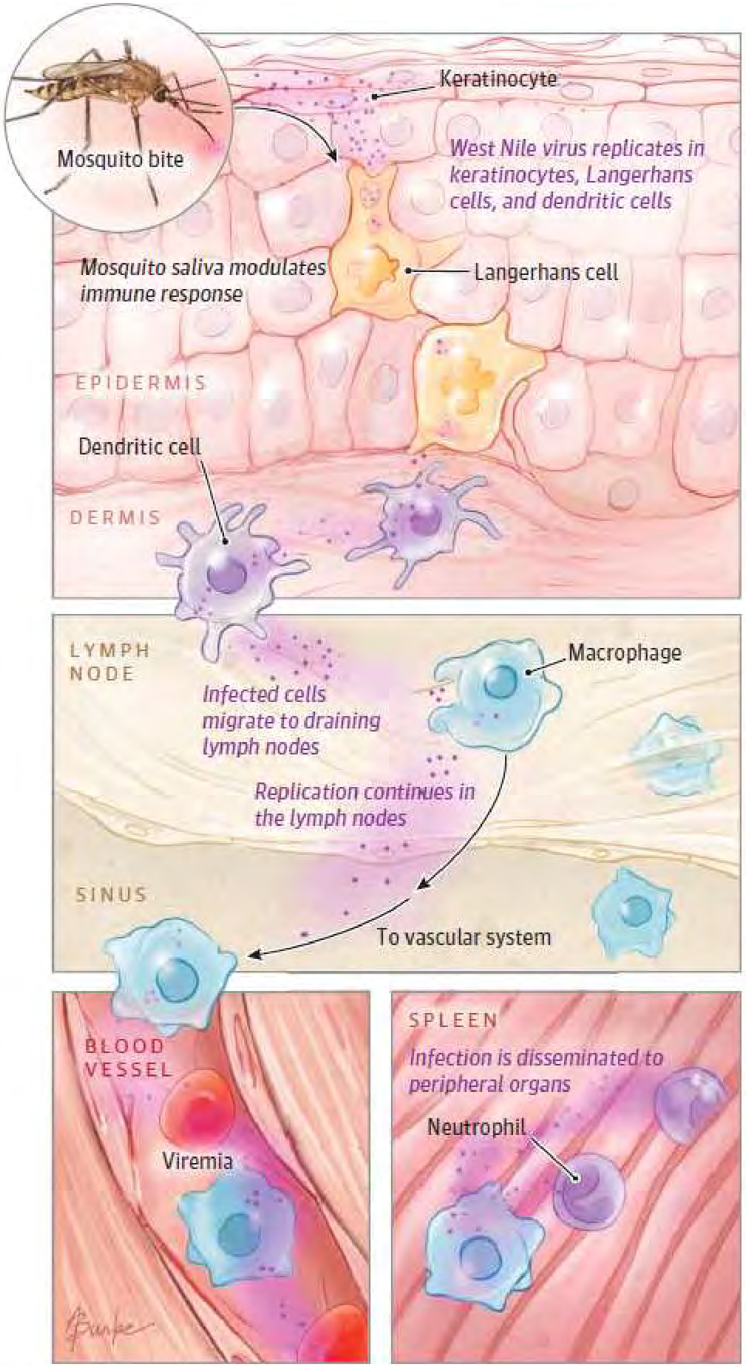
West Nile virus

- First isolated in Uganda, West Nile district, 1937
- Reservoir an amplificating host: birds
  - Mammals (including human) : dead-end
    - Viremia too weak and to short
- Vector: mainly *Culex* mosquitoes

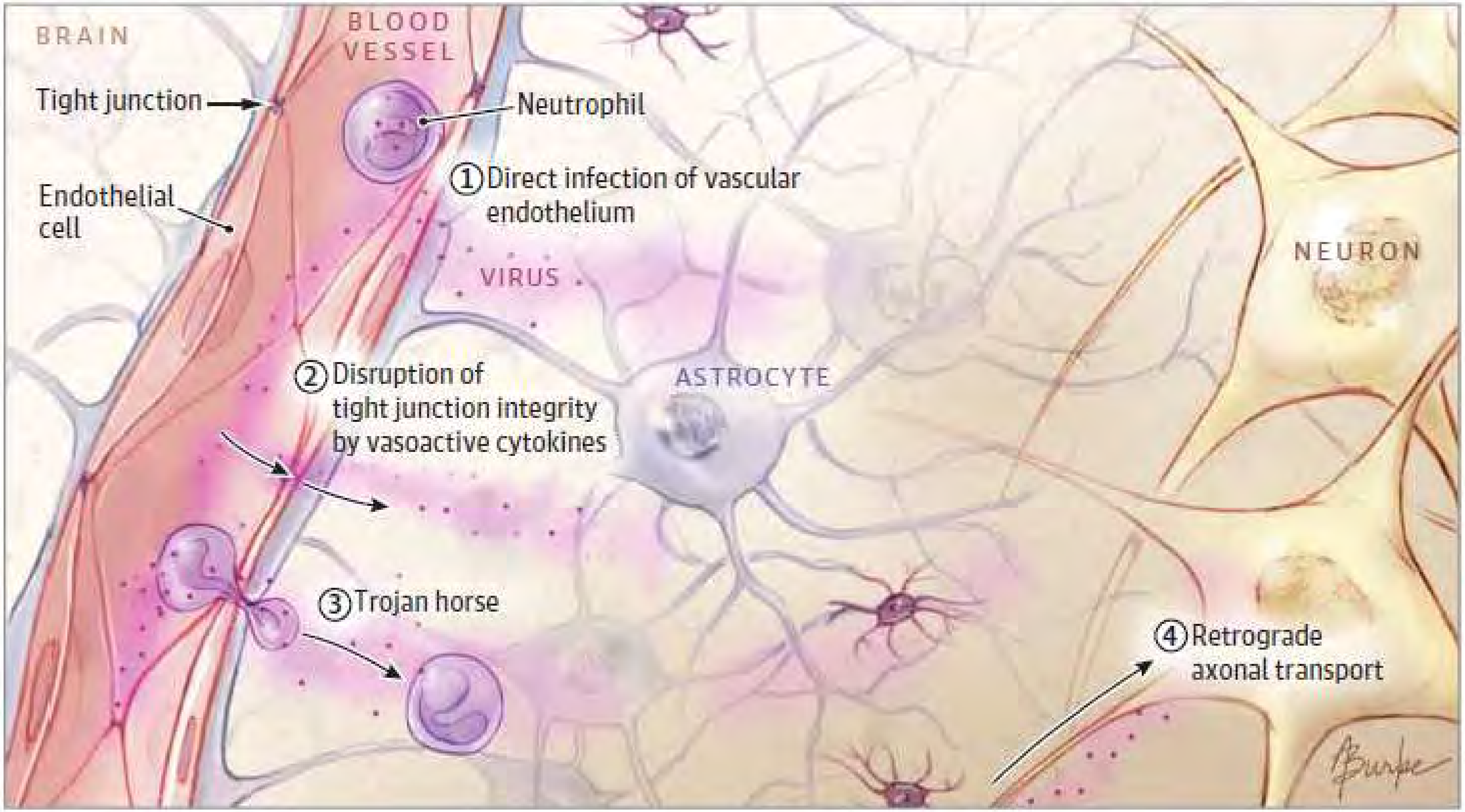


Enzootic cycle
Fecal-oral
Vertical
transmission
Other
vectors
Persistence
Death
Immunity
?
Carrion
Epidemic
Blood
transfusion
Organ
transplantation
Breast milk
Intrauterine
Epizootic
Cofeeding transmission?
Infectious viremia?

Kramer 2008



Petersen 2013



Petersen 2013

West Nile virus fever

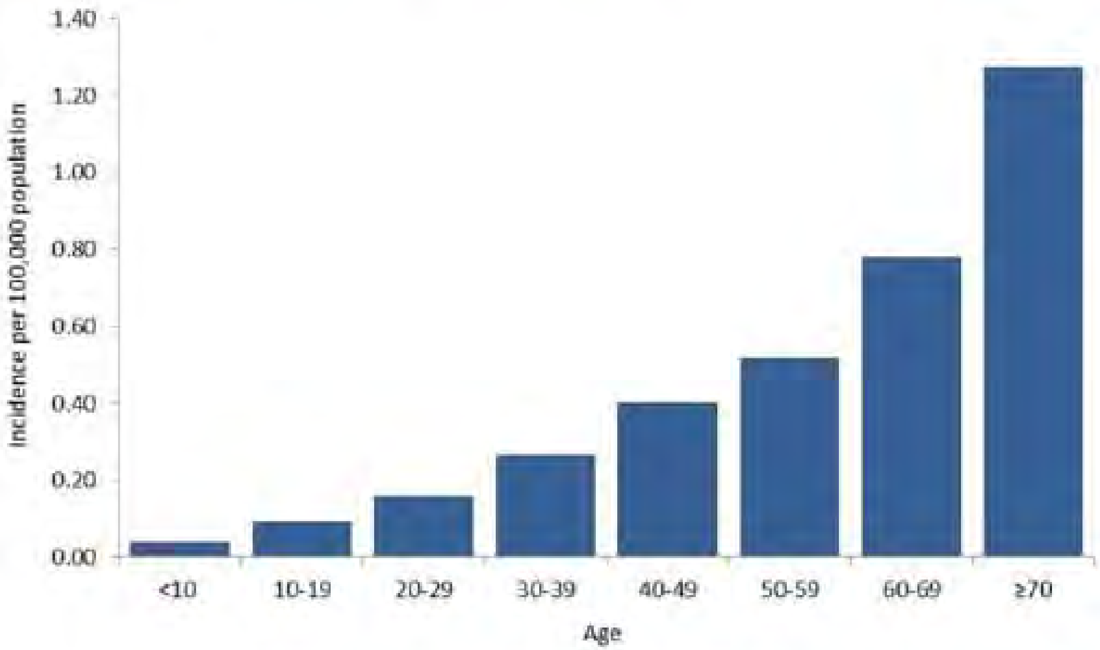
- 25% of infected patient develop symptoms

- In >50% of symptomatic patients :
  - Headache
  - Weakness
  - Rash (morbilliform/maculopapular)
  - Mild fever
  - Myalgia
- Less commonly :
  - Joint pain
  - Eye pain
  - Vomiting/diarrhea
  - lymphadenopathy

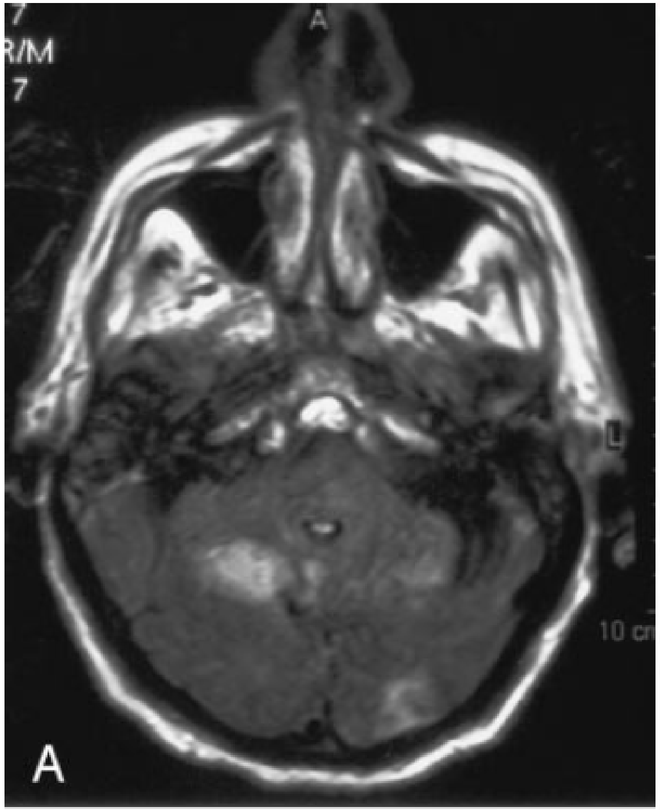
West Nile neuroinvasive diseases

- 1/200 infected patients (1/10 symptomatic)
  - 1/50 in patients >65 yo
  - 1/800 in patients 16-24 yo
  - More frequent if cancer, diabetes, hypertension, alcohol abuse, renal disease
- Abrupt onset
- Different forms
  - Meningitis
  - Encephalitis
  - Acute flaccid paralysis

Figure 6. Average annual incidence of West Nile virus human neuroinvasive disease by age group, 1999–2012, as reported to CDC ArboNet.



Roehrig 2013



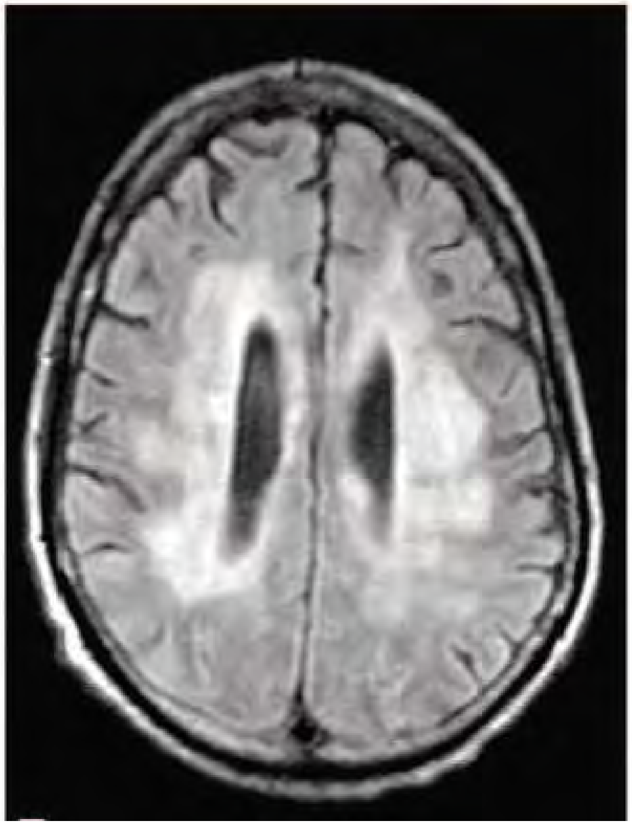
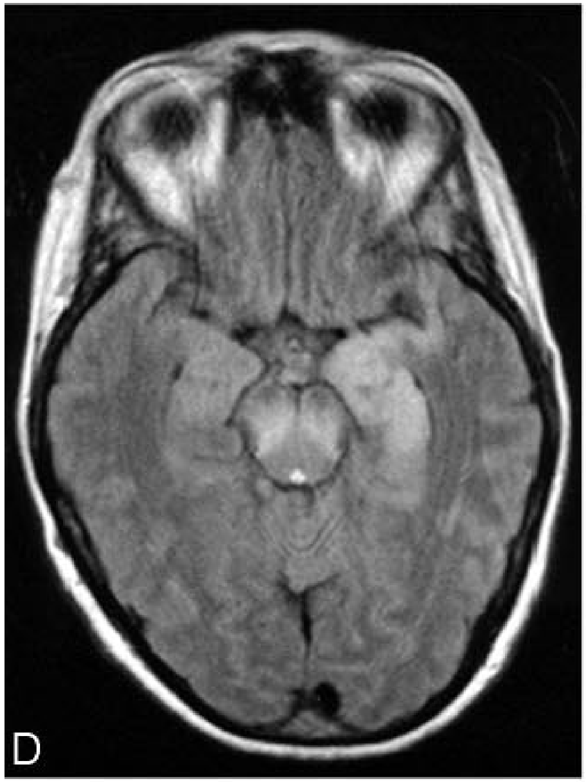



TABLE 1: Clinical outcomes in different MR imaging patterns of WNV infection

Imaging Finding	Mean Age (y)	Mean Hospitalization (d)	Clinical Outcomes
Normal (n = 5)	28.4 (18–43)	6.4 (4–13)	Complete recovery (n = 4), mild residual expressive dysphasia (n = 1)
Isolated restricted diffusion (n = 4)	75.5 (73–80)	6.5 (4–11)	Complete recovery
FLAIR and T2WI hyperintensity (n = 3)	63.7 (46–75)	21.3 (11–27)	Death (n = 2), severe neurologic deficits (n = 1)
Meningeal involvement (n = 2)	60.5 (60–61)	20 (19–21)	Severe neurologic deficits
Intraspinal abnormalities (n = 3)	36.3 (28–46)	26.6 (10–42)	Moderate-to-severe neurologic deficits

Note.—Data in parentheses are ranges.

Petropoulou 2005 - Ali 2005

WNV infection diagnosis

- Plasma serology
- CSF serology
- CSF PCR

West Nile virus infection treatment

- Treatment: only supportive
  - Ribavirin
  - Interferon α-2b
  - Polyclonal γ-globulins
  - Neutralizing specific antibodies
  - Antisens strategies

  No effect

- Preventive vaccines:
  - Phases I and II (derived from equine vaccines)
  - No phase III

Canad. M. A. J.
May 1, 1959, vol. 80

POWASSAN VIRUS: ISOLATION OF VIRUS FROM A FATAL CASE OF ENCEPHALITIS*

D. M. McLEAN, M.D.,
and W. L. DONOHUE, M.D., *Toronto*

- Fatal encephalitis in a 10-y old boy of Powassan, Ontario
- Inoculation to newborn mice: encephalitis in 5d

Powassan virus

- Flavivirus related to TBE complex
- Russia, Canada, USA
  - Imported from Russia ? In 1950s
- Zoonosis transmitted by ticks
  - Dermacentor & Ixodes

2012

Powassan Meningo-encephalitis, New York, New York, USA

Simon Sung,[1] Alysse G. Wurcel,[1] Susan Whittier, Karen Kulas, Laura D. Kramer, Robin Flam, James Kirkland Roberts, and Simon Tsiouris

Powassan cases in the USA, 2001-2012

CDC datas

Usutu virus

Region (year)	Mammals	Birds[a,b]
Italy	human[a,b,c] horse[c]	Common magpie *(Pica pica)* Jay *(Garrulus glandarius)* Common starling *(Sturnus vulgaris)* Blackbird *(Turdus merula)*
Austria (2001)	human[b,c]	Blackbird *(T. merula)* Great grey owl *(Strix nebulosa)* Blue tit *(Parus caeruleus)* Sparrow *(Passer domesticus)* Great tit *(Parus major)* Nut hatch *(Sitta europaea)* Robin *(Erithacus rubecula)* Song thrush *(Turdus philomelos)*
Germany (2011)	human[c]	Black bird *(T. merula)* Common starling *(S. vulgaris)* Domestic canary *(Serinus canaria domestica)* Sparrow *(P. domesticus)* Great grey owl *(S. nebulosa)* Common kingfisher *(Alcedo atthis)*
Switzerland		Sparrow *(P. domesticus)* Black bird *(T. merula)* Blue tit *(P. caeruleus)* Green finch *(Carduelis chloris)* Robin *(Erithacus rubecula)* Boreal owl *(Aegolius funereus)* Great grey owl/Lappland owl *(S. nebulosa lapponica)* Northern hawk owl *(Surnia ulula)* Eurasian pygmy owl *(Glaucidium passerinum)*
Spain		
Hungary		Blackbird *(T. merula)*
Serbia	horse[c,d]	
Czech Republic[e]		antibody[d]
Poland[e]		antibody[d]

Pauli 2014

Usutu virus

- Birds cases

(c)

Beck 2013

Usutu virus

Eurosurveillance

Eurosurveillance, Volume 14, Issue 50, 17 December 2009

Rapid communications

USUTU VIRUS INFECTION IN A PATIENT WHO UNDERWENT ORTHOTROPIC LIVER TRANSPLANTATION, ITALY, AUGUST-SEPTEMBER 2009

F Cavrini[1,2], P Gaibani[1,2], G Longo[3], A M Pierro[1], G Rossini[1], P Bonilauri[4], G E Gerunda[5], F Di Benedetto[5], A Pasetto[6], M Girardis[6], M Dottori[4], M P Landini[1], V Sambri (vittorio.sambri@unibo.it)[1]

1. Clinical Microbiology Unit, Regional Reference Centre for Microbiological Emergencies – CRREM, St. Orsola-Malpighi University Hospital, University of Bologna, Bologna, Italy
2. These Authors contributed equally to this paper and are listed in alphabetical order
3. Oncology and Haematology Unit, Modena University Hospital, Modena, Italy
4. Experimental Institute for Animal Health and Protection of Lombardia and Emilia-Romagna, Brescia, Italy
5. Liver and Multivisceral Transplant Center, University of Modena and Reggio Emilia, Modena, Italy
6. Anaestesiology and Intensive Care Unit 1, Modena University Hospital, Modena, Italy

Other flavivirus encephalitis

Journal of Clinical Virology 55 (2012) 204–208

ELSEVIER

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Toscana meningoencephalitis: A comparison to other viral central nervous system infections

Siraya Jaijakul, Cesar A. Arias, Monir Hossain, Roberto C. Arduino, Susan H. Wootton, Rodrigo Hasbun*

University of Texas Health Science Center at Houston, TX, USA

Characteristic	No. (%) of cases
	Toscana virus infection ($n = 41$)
Symptoms	
Fever	38/39 (97)
Headache	36/36 (100)
Stiff neck	33/38 (87)
Nausea/vomiting	14/18 (78)
Photophobia	6/7 (86)
Malaise	8/13 (62)
Respiratory symptom	0/1 (0)
Focal neurological deficit	6/28 (21)
Seizure	3/25 (12)
Signs	
Altered mental status[a]	14/34 (41)
Nuchal rigidity	33/37 (89)
Rash	4/10 (40)
Focal neurological deficit[b]	6/17 (35)
Encephalitis s/s	16/36 (44)

Journal of General Virology (2009), **90**, 2644–2649 **DOI** 10.1099/vir.0.012336-0

Short Communication

Genetic characterization of Bagaza virus (BAGV) isolated in India and evidence of anti-BAGV antibodies in sera collected from encephalitis patients

Vijay P. Bondre,[1] Gajanan N. Sapkal,[1] Prasanna N. Yergolkar,[2] Pradip V. Fulmali,[1] Vasudha Sankararaman,[1] Vijay M. Ayachit,[1] Akhilesh C. Mishra[1] and Milind M. Gore[1]

[1]National Institute of Virology, Pashan, Pune 411 021, India

[2]National Institute of Virology, Bangalore Field Unit, Bangalore, India

Correspondence
Vijay P. Bondre
vpbondre@yahoo.com *or* bondrevp@icmr.org

- Recently considered to be the same virus that Israel Turkey meningoencephalomyelitis virus

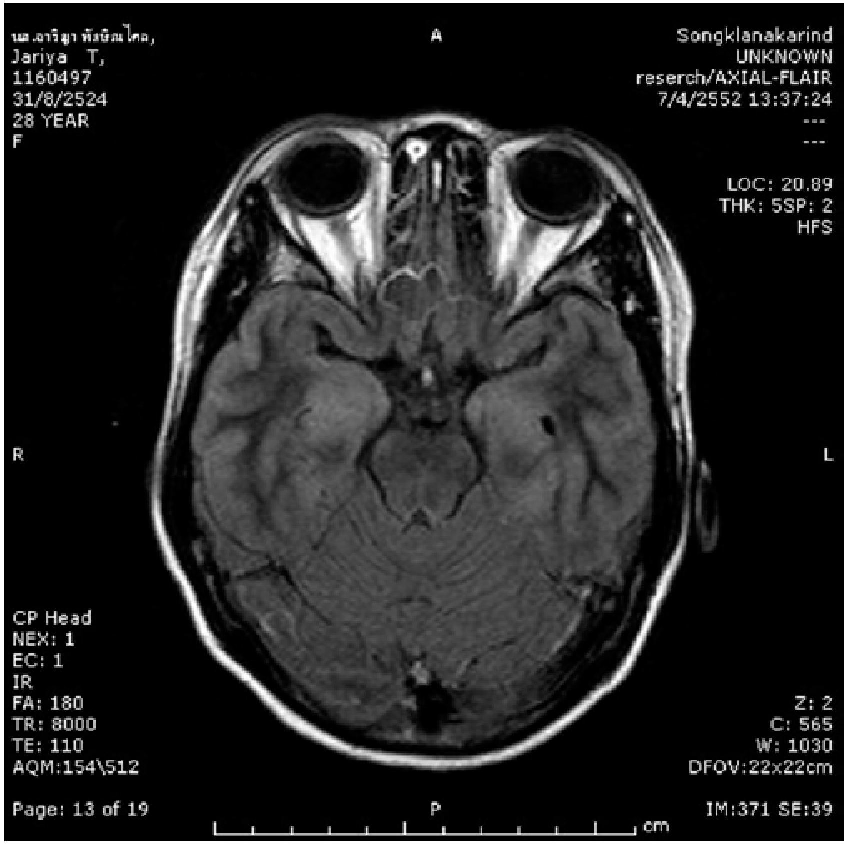
JCM
Journals.ASM.org

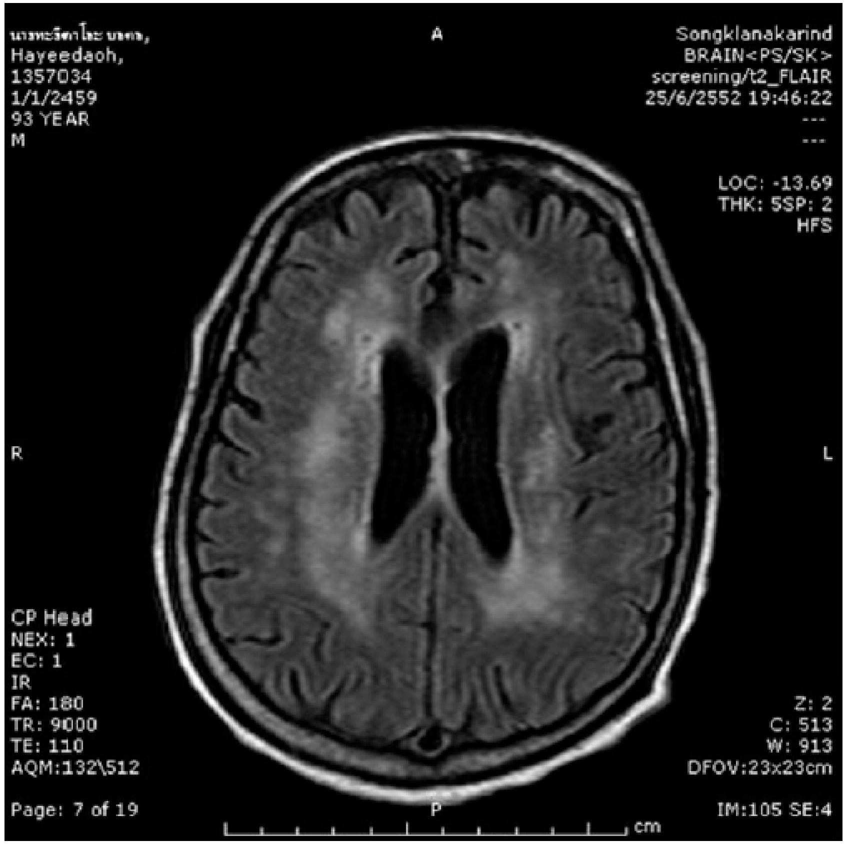
CASE REPORT

Encephalitis Caused by Chikungunya Virus in a Traveler from the Kingdom of Tonga

Joanna Nelson,[a] Jesse J. Waggoner,[a] Malaya K. Sahoo,[b] Philip M. Grant,[a] Benjamin A. Pinsky[a,b]

Depar
Pathol





Am. J. T
doi:10.4
Copyrig

d

Nipah (and Hendra) viruses

Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia

THE LANCET • Vol 354 • October 9, 1999

Kaw Bing Chua, Khean Jin Goh, Kum Thong Wong, Adeeba Kamarulzaman, Patrick Seow Koon Tan, Thomas G Ksiazek, Sherif R Zaki, George Paul, Sai Kit Lam, Chong Tin Tan

- 265 cases / Fatality rate 40%
- First supposed to be Japanese EV - ***but***:
  - More adults than children
  - High attack rate
  - Several cases in the household
- First viral isolate at Kampung Sungai Nipah (march 1999)
- The outbreak was stopped after slaughtering 1.1 M pigs

Fatal encephalitis due to Nipah virus among pig-farmers in Malaysia

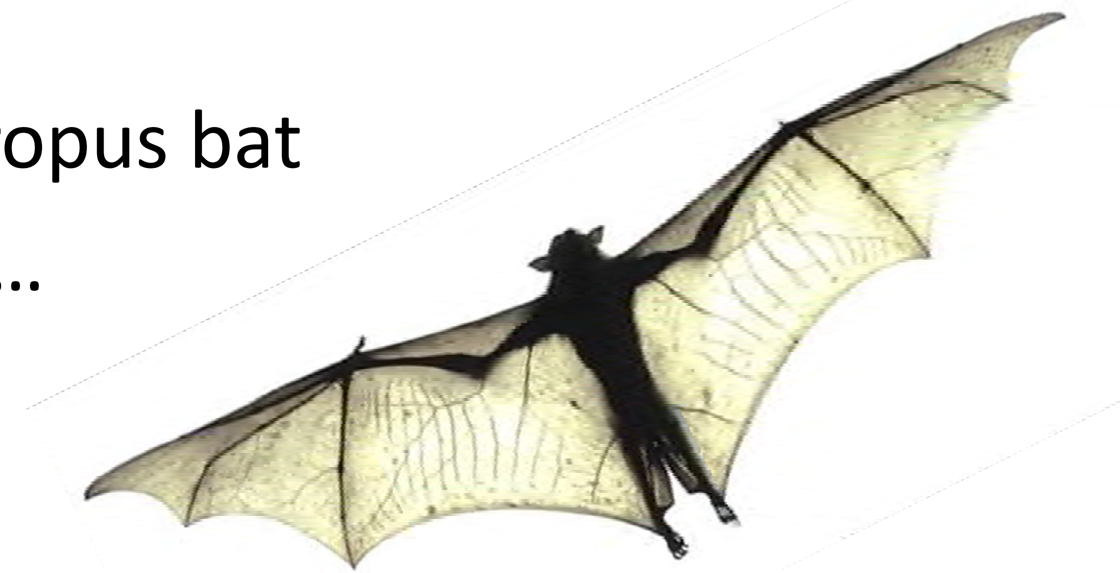
THE LANCET • Vol 354 • October 9, 1999

Kaw Bing Chua, Khean Jin Goh, Kum Thong Wong, Adeeba Kamarulzaman, Patrick Seow Koon Tan, Thomas G Ksiazek, Sherif R Zaki, George Paul, Sai Kit Lam, Chong Tin Tan

- 3 pig farmers
- Clinics:
  - Fever, headache, altered consciousness
  - Dysautonomia / brainstem dysfunction
  - Hypotension and death
- Necropsy:
  - Vasculitis-induced thrombosis
  - Viral inclusions in neurons
  - Cross-reactivity to Hendra Virus

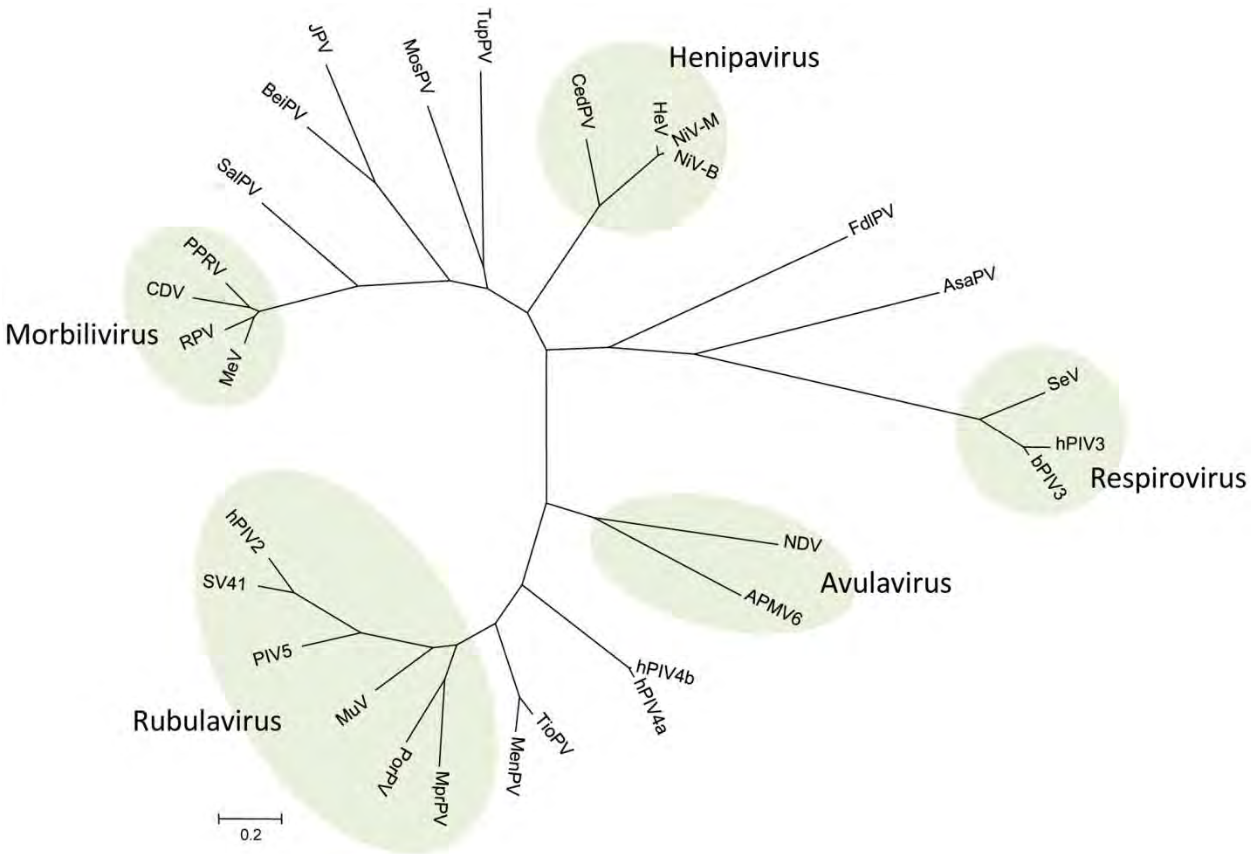
Nipah encephalitis virus

- Natural host: pteropus bat
- Tested positive in…
  - Cambodia
  - Thailand
  - Indonesia
  - India
  - Madagascar
  - Ghana



Nipah encephalitis virus

- Natural host: pteropus bat
- Paramyxoviridae



Nipah encephalitis virus

- Natural host: pteropus bat
- Paramyxoviridae
- First documented cases:
  - Pigs in 1996 (retrospectively)
    - Transmission from bats
    - Due to modification/intensification of pig farming
  - Human in 1998
  - Cats, dogs, goats… : dead-end

Kulkarni 2013

Outbreaks in India & Bangladesh: 292 patients, 221 deaths

Table 1 Morbidity and mortality in humans due to NiV, India–Bangladesh [43, 97]

Year/month	Location	No. cases	No. deaths	Case fatality (%)
Jan–Feb 2001	Siliguri (India)	66	45	68
Apr–May 2001	Meherpur (Bangladesh)	13	9	69
Jan 2003	Naogaon (Bangladesh)	12	8	67
Jan 2004	Rajbari(Bangladesh)	31	23	74
Apr 2004	Faridpur (Bangladesh)	36	27	75
Jan–Mar 2005	Tangail (Bangladesh)	12	11	92
Jan–Feb 2007	Thakurgaon (Bangladesh)	7	3	43
Mar 2007	Kushtia, Pabna, Natore (Bangladesh)	8	5	63
Apr 2007	Naogaon (Bangladesh)	3	1	33
April 2007	Nadia (India)	5	5	101
Feb 2008	Manikgonj (Bangladesh)	4	4	101
Apr 2008	Rajbari and Faridpur (Bangladesh)	7	5	71
Jan 2009	Gaibandha, Rangpur and Nilphamari (Bangladesh)	3	0	0
Jan 2009	Rajbari (Bangladesh)	1	1	101
Feb–Mar 2010	Faridpur, Rajbari,Gopalganj,Madaripur (Bangladesh)	16	14	87.5
Jan–Feb 2011	Lalmohirhat, Dinajpur, Comilla, Nilphamari and Rangpur (Bangladesh)	44	40	91
Feb 2012	Joypurhat, Rajshahi, Natore, Rajbari and Gopalganj (Bangladesh)	12	10	83
Jan–Feb 2013	Gaibandha, Natore, Rajshahi, Naogaon, Rajbari, Pabna, Jhenaidah, Mymensingh (Bangladesh)	12	10	83
Total		292	221	75.7

Nipah virus transmission

- Detectable in urine, feces, saliva
- Malaysia, Singapore :
  - pig to human
    - At risk : pig farmers, pig slaughters
- India, Bangladesh :
  - Bats to human
    - Climbing to palm tree
    - Drinking fresh date palm sap
  - Human to human
    - Including to HCW in hospital (Siliguri outbreak)

Siliguri outbreak, India

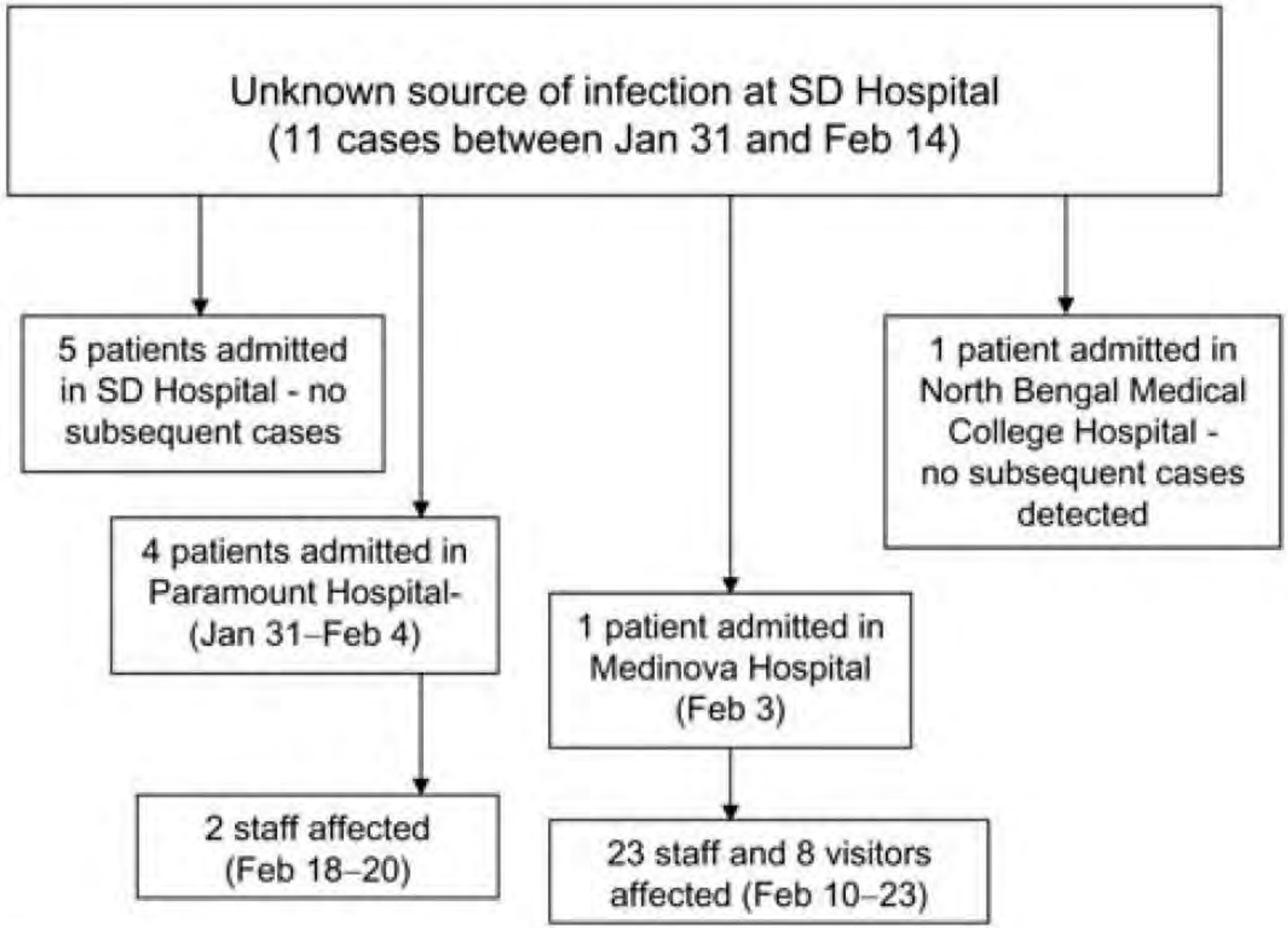
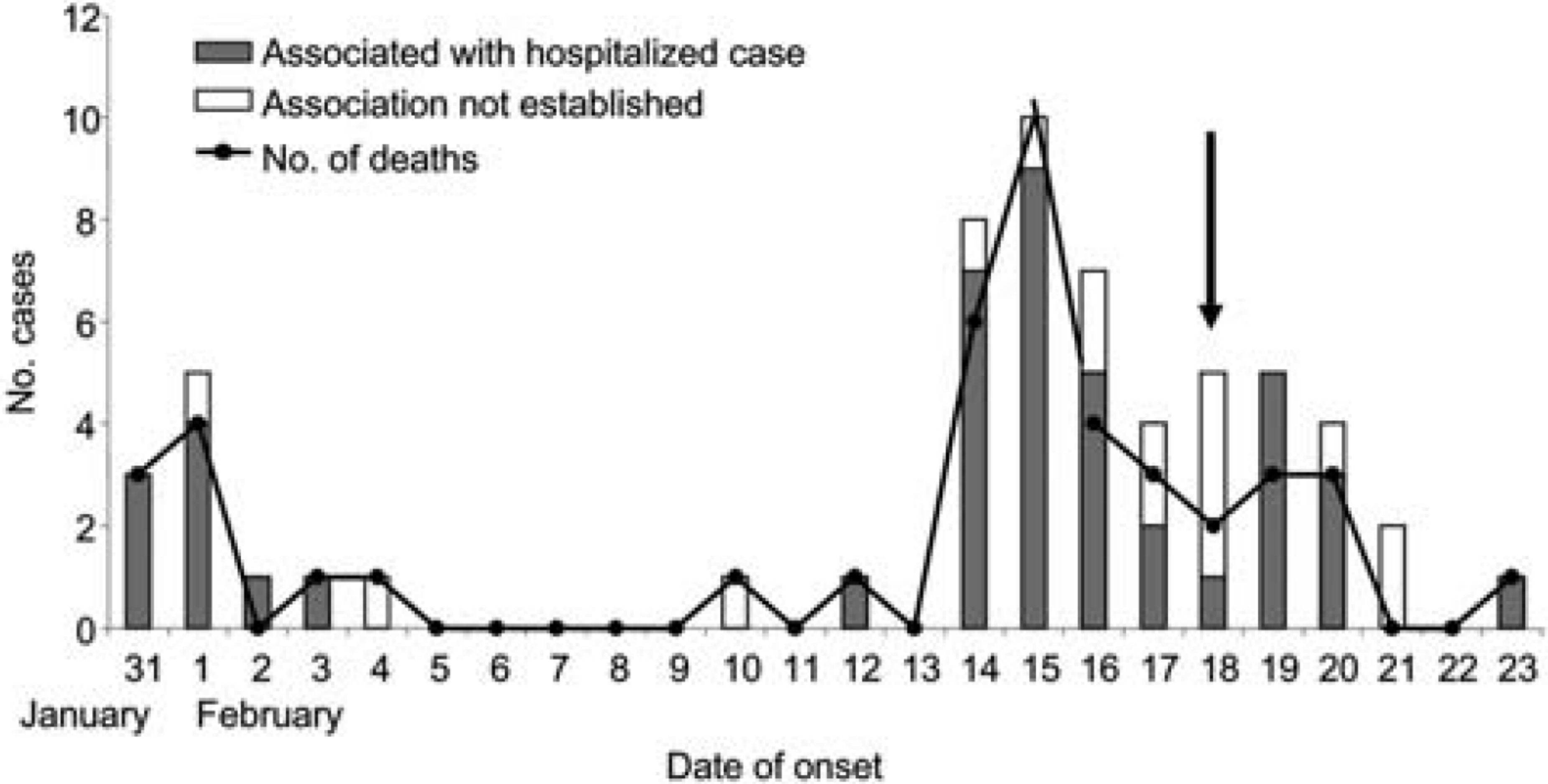


Figure 2. Sequence of events in the Siliguri (SD) outbreak.

Siliguri outbreak, India



Chadah 2006

Nipah encephalitis in human

- Incubation <2 weeks in >90%
  - 4 days to ? 2 months
- Possible subclinical infection (10-50%)

  Chan 2002

The New England
Journal of Medicine

VOLUME 342 APRIL 27, 2000 NUMBER 17

CLINICAL FEATURES OF NIPAH VIRUS ENCEPHALITIS AMONG PIG FARMERS IN MALAYSIA

KHEAN JIN GOH, M.R.C.P., CHONG TIN TAN, F.R.C.P., M.D., NEE KONG CHEW, M.R.C.P., PATRICK SEOW KOON TAN, F.R.C.A., ADEEBA KAMARULZAMAN, F.R.A.C.P., SAZILAH AHMAD SARJI, F.R.C.R., KUM THONG WONG, M.R.C.PATH., BASRI JOHAN JEET ABDULLAH, F.R.C.R., KAW BING CHUA, F.R.C.P., M.D., AND SAI KIT LAM, PH.D., F.R.C.P.

TABLE 1. CLINICAL FEATURES AT PRESENTATION IN PATIENTS WITH NIPAH VIRUS INFECTION.

FEATURE	NO. OF PATIENTS (%) (N=94)
Fever	91 (97)
Headache	61 (65)
Dizziness	34 (36)
Vomiting	25 (27)
Reduced level of consciousness*	20 (21)
Nonproductive cough	13 (14)
Myalgia	11 (12)
Focal neurologic signs	10 (11)
Cerebellar signs	3 (3)
Segmental myoclonus	3 (3)
Cerebellar signs and segmental myoclonus	2 (2)
Rotatory nystagmus	1 (1)
Dysphasia	1 (1)

Nipah: CSF fluid examination

Table 3. Results of Cerebrospinal Fluid Examination in Patients with Nipah Virus Infection.

Examination	No. of Patients	Day of Illness*	White-Cell Count*	Protein*	Glucose*	Pressure*	Patients with Abnormal Results		
							Total	Elevated Protein Levels Only	Elevated White-Cell Counts and Protein Levels
			cells/mm³	g/liter	mmol/liter	cm of water	no./total no. (%)		
First	92	5.2 (2–24)	41.2 (0–842)	0.69 (0.12–2.15)	3.8 (2.0–5.5)	17.4 (3–58)	69/92 (75)	42/69 (61)	27/69 (39)
Second	31	12.1 (4–38)	59.2 (0–720)	0.90 (0.24–5.80)	3.3 (2.0–4.5)	16.1 (8–25)	24/31 (77)	13/24 (54)	11/24 (46)

*Mean values are shown, with the range in parentheses.

- Nipah virus is detectable in CSF by PCR

TABLE 4. FACTORS ASSOCIATED WITH THE PROGNOSIS OF NIPAH VIRUS INFECTION.

FACTOR	DEATH (N=30)	SURVIVAL (N=64)	P VALUE
Mean age — yr	40.9	35.2	0.02
Vomiting — no. (%)	12 (40)	13 (20)	0.04
Mean lowest Glasgow Coma scores	6.8	12.8	0.005
Segmental myoclonus — no. (%)	20 (67)	10 (16)	<0.001
Abnormal doll's-eye reflex — no. (%)	26 (87)	10 (16)	<0.001
Abnormal pupils — no. (%)	29 (97)	20 (31)	<0.001
Hypertension — no. (%)	23 (77)	14 (22)	<0.001
Tachycardia — no. (%)	28 (93)	8 (12)	<0.001
Absent or reduced reflexes — no. (%)	22 (73)	31 (48)	0.02
Seizures — no. (%)	12 (40)	10 (16)	0.01
Mean aspartate aminotransferase level at admission — U/liter	87	34.4	0.001
Mean alanine aminotransferase level at admission — U/liter	94.2	53.6	0.006
Mean platelet count at admission — per mm^3	151,000	197,000	0.005

Treatment of Acute Nipah Encephalitis with Ribavirin

2001

Heng-Thay Chong, MRCP,[1]
Adeeba Kamarulzaman, FRACP,[1] Chong-Tin Tan, FRCP,[1]
Khean-Jin Goh, MRCP,[1] Tarmizi Thayaparan, MRCP,[3]
Sree Raman Kunjapan, MRCP,[3]
Nee-Kong Chew, MRCP,[1] Kaw-Bing Chua, FRCP,[2]
Sai-Kit Lam, PhD[2]

- 140 patients
  - 54 before study, or refused ribavirin
    - Death 54%
  - 86 receiving ribavirin
    - 2g day 1, 3.6g days 2-4, 2.4g days 5-6, 1.2g days 7-10
    - Death 32%

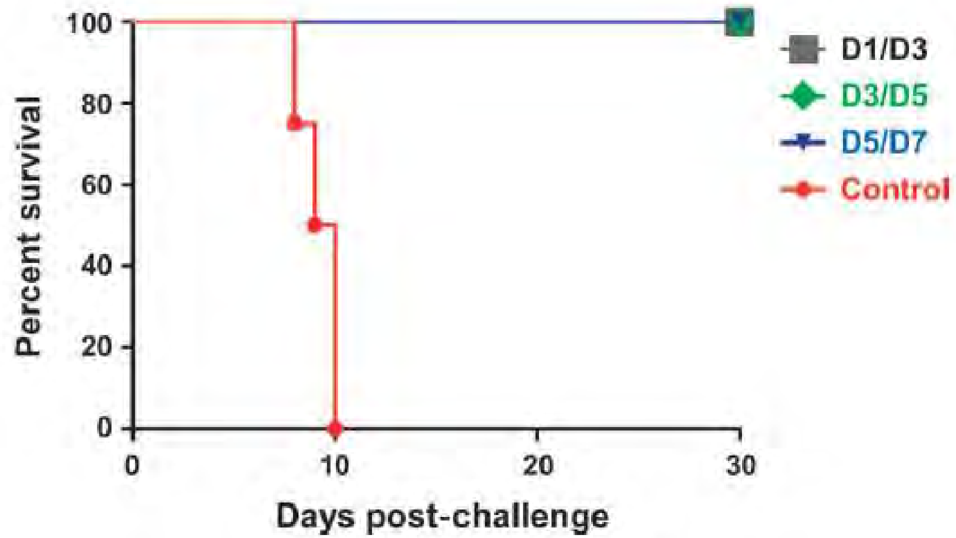
RESEARCH ARTICLE

INFECTIOUS DISEASE

2014

Therapeutic Treatment of Nipah Virus Infection in Nonhuman Primates with a Neutralizing Human Monoclonal Antibody

Thomas W. Geisbert,[1,2*†] Chad E. Mire,[1,2*] Joan B. Geisbert,[1,2] Yee-Peng Chan,[3] Krystle N. Agans,[1,2] Friederike Feldmann,[4] Karla A. Fenton,[1,2] Zhongyu Zhu,[5] Dimiter S. Dimitrov,[5] Dana P. Scott,[4] Katharine N. Bossart,[6] Heinz Feldmann,[7] Christopher C. Broder[3†]



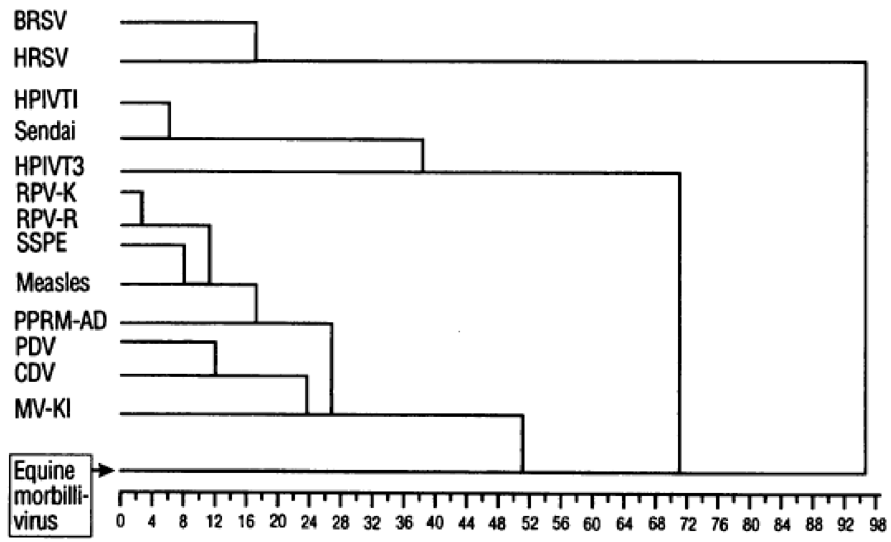
- m102.4
- Phase I study to be initiated in Australia

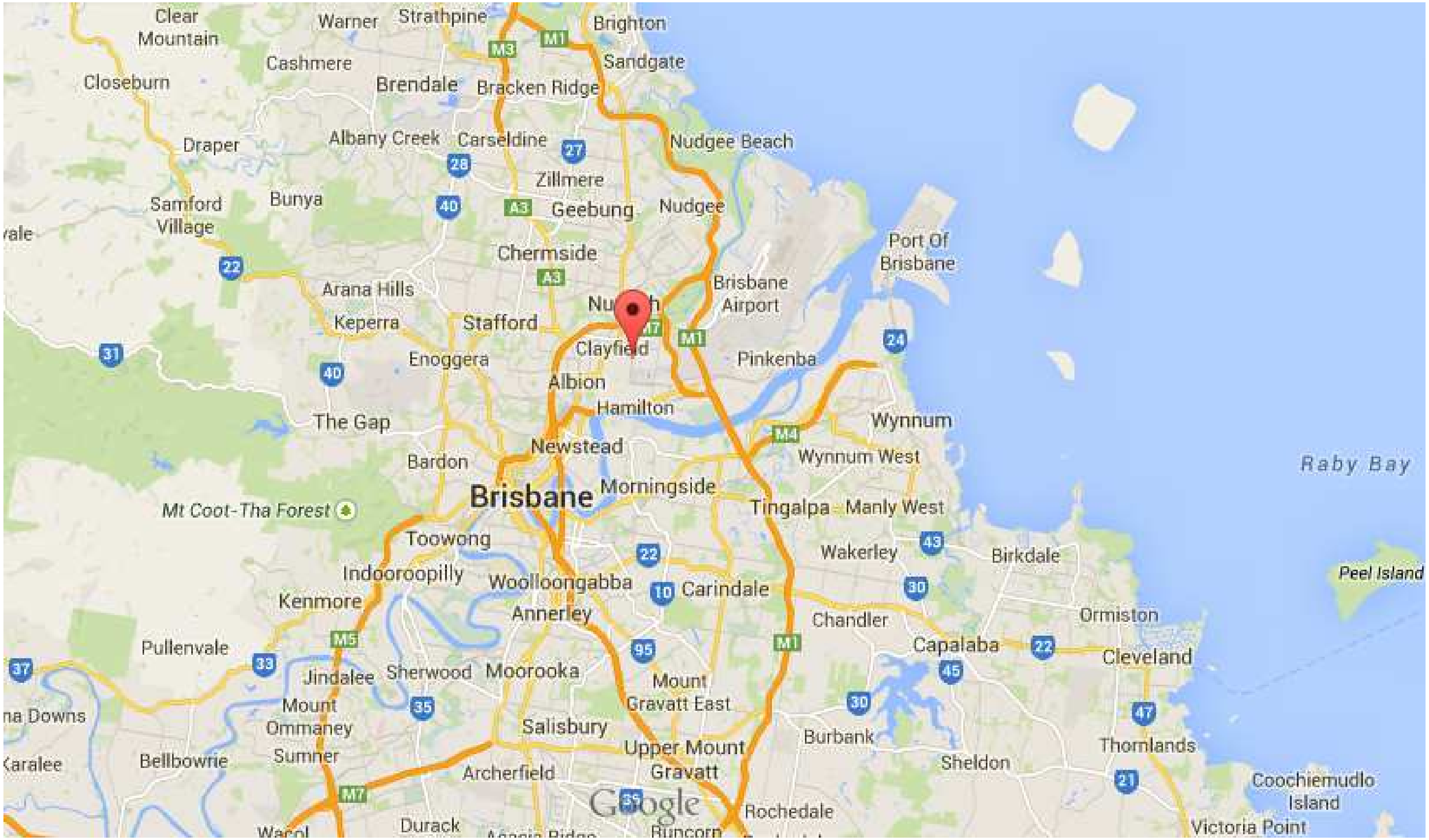
A Morbillivirus That Caused Fatal Disease in Horses and Humans

1995

Keith Murray,* Paul Selleck, Peter Hooper, Alex Hyatt,
Allan Gould, Laurie Gleeson, Harvey Westbury, Lester Hiley,
Linda Selvey, Barry Rodwell, Peter Ketterer

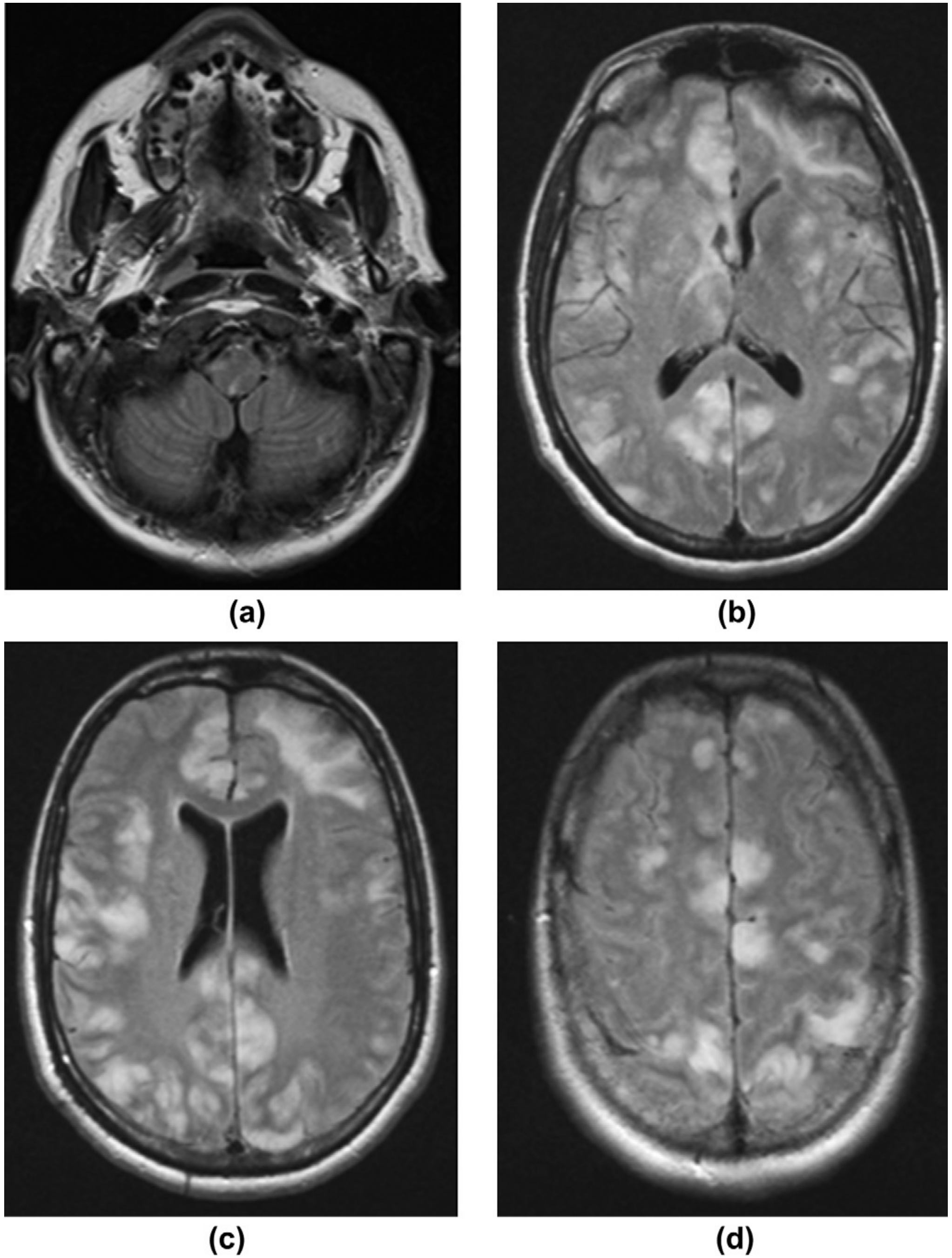
- First described in Australia, 1994
  - Outbreak in 21 horses, 14 deaths
  - 2 cases in humans, all working with horses; one death (pneumonia)
- Mainly respiratory signs




Clear Mountain
Warner
Strathpine
Brighton
Cashmere
Sandgate
Closeburn
Brendale
Bracken Ridge
Albany Creek
Carseldine
Nudgee Beach
Draper
Zillmere
Samford Village
Bunya
Geebung
Nudgee
Chermside
Port Of Brisbane
Brisbane Airport
Arana Hills
Keperra
Stafford
Enoggera
Pinkenba
Albion
Hamilton
The Gap
Wynnum
Newstead
Wynnum West
Raby Bay
Bardon
Morningside
Brisbane
Mt Coot-Tha Forest
Tingalpa
Manly West
Toowong
Wakerley
Birkdale
Indooroopilly
Woolloongabba
Carindale
Peel Island
Kenmore
Annerley
Chandler
Ormiston
Pullenvale
Capalaba
Cleveland
Jindalee
Sherwood
Moorooka
Mount Gravatt East
Mount Ommaney
Salisbury
Burbank
Thornlands
Sumner
Bellbowrie
Upper Mount Gravatt
Sheldon
Archerfield
Rochedale
Coochiemudlo Island
Durack
Victoria Point
Google

Hendra virus

- Outbreaks in horses
  - 48 described, all in Australia
- Rare cases in human : seven described
  - All with close contact with ill horses
  - 4 deaths (1994, 2008, 2009)
  - 1 with pneumonia, 3 with encephalitis



Nakka 2012

Enterovirus 71

Enteroviruses: previous classification

- Coxsackievirus A (23 serotypes)
- Coxsackievirus B (6 serotypes)
- Polioviruses (3 serotypes)
- Echovirus (68 serotypes)
- Others Human EnteroViruses isolated after 1970
  - HEV68

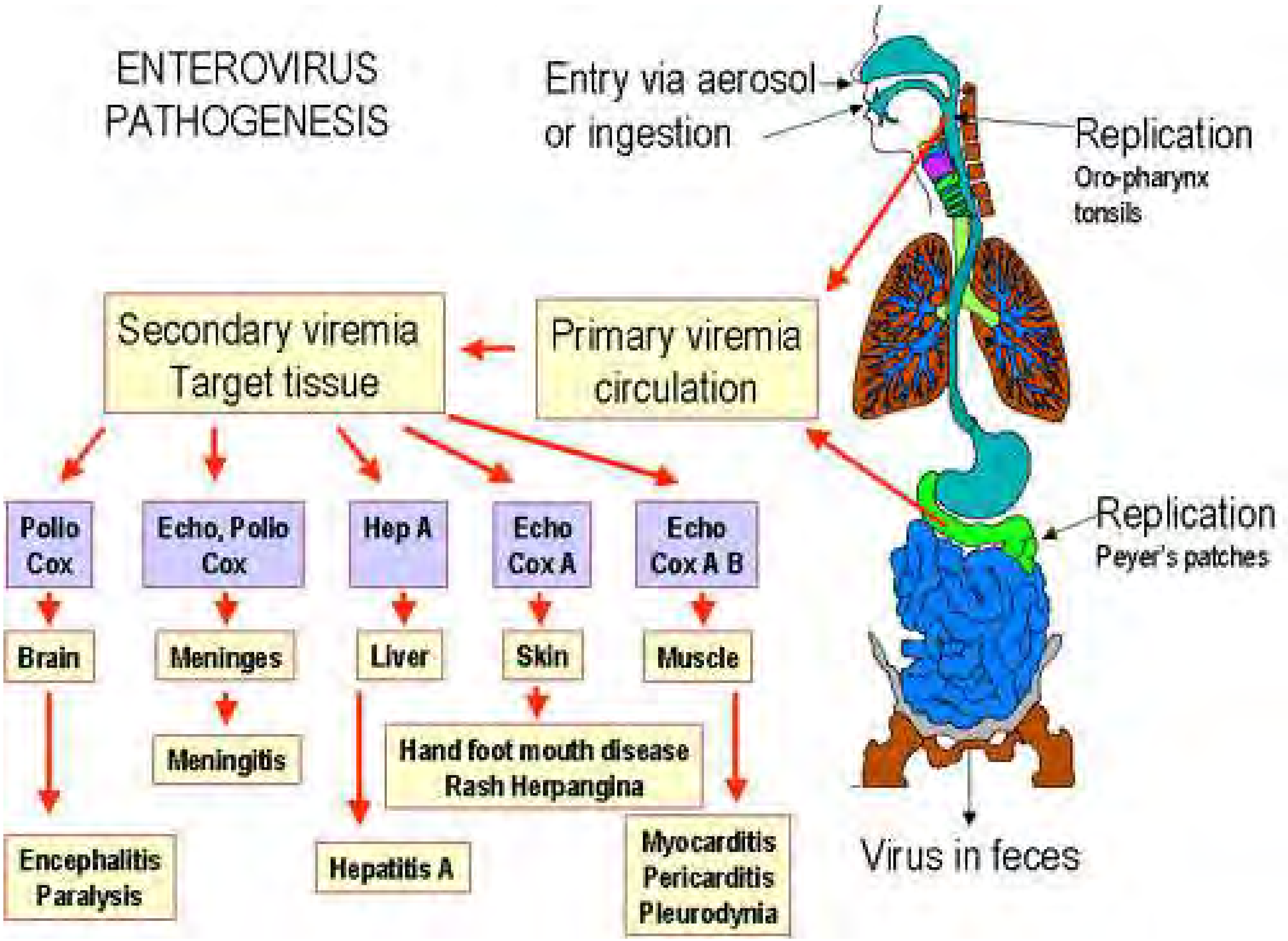
Enterovirus: new classification

	Serotype
A	CV-A2–8, CV-A10, CV-A12, CV-A14, CV-A16, EV71, EV76, EV89–92
B	CV-A9, CV-B1–6, E1–7, E9, E11–21, E24–27, E29–33, EV69, EV73, EV74–75, EV77–88, EV93, EV97, EV98, EV100, EV101, EV106, EV107
C	CV-A1, CV-A11, CV-A13, CV-A17, CV-A19–A22, CV-A24, EV95, EV96, EV99, EV102, EV104, EV105, EV109, PV1–3
D	EV68, EV70, EV94

The Picornaviridae Study Group and the International Committee on Taxonomy of Viruses classified the Enterovirus genus into ten species, which include four human enterovirus species (A–D), three human rhinovirus species (A–C), bovine enterovirus, simian enterovirus A, and porcine enteroviruses (http://www.ncbi.nlm.nih.gov/ICTVdb/ICTVdB/). CV-A=coxsackievirus A. CV-B=coxsackievirus B. EV=enterovirus. E=echovirus. PV=poliovirus.

Table 1: **Human enterovirus serotypes, by species**

Solomon 2010


ENTEROVIRUS
PATHOGENESIS
Entry via aerosol
or ingestion
Replication
Oro-pharynx
tonsils
Secondary viremia
Target tissue
Primary viremia
circulation
Polio
Cox
Echo, Polio
Cox
Hep A
Echo
Cox A
Echo
Cox A B
Replication
Peyer's patches
Brain
Meninges
Liver
Skin
Muscle
Meningitis
Hand foot mouth disease
Rash Herpangina
Encephalitis
Paralysis
Hepatitis A
Myocarditis
Pericarditis
Pleurodynia
Virus in feces

HMFD: skin and mucosa

Ooi 2010

Enterovirus 71

- Isolated in 1969 (1963?)
- HFMD outbreaks (mainly Pacific-Asia area)
- Aseptic meningitis, brainstem encephalitis, acute flaccid paralysis
- Frequently associated with pulmonary oedema and shock

THE JOURNAL OF INFECTIOUS DISEASES • VOL. 129, No. 3 • MARCH 1974

An Apparently New Enterovirus Isolated from Patients with Disease of the Central Nervous System

Nathalie J. Schmidt, Edwin H. Lennette, and Helen H. Ho

From the Viral and Rickettsial Disease Laboratory, California State Department of Health, Berkeley, California

Table 1. Recovery of BrCr virus and related strains from patients with disease of the central nervous system.

Patient	Age	Sex	Date of onset	Clinical diagnosis	Virus isolation		Neutralizing antibody	
					Specimen	Host*	Days after onset	Titer vs. BrCr virus
1. JaFr	9 months	M	9/28/69	Encephalitis	Stool	RhMK	5	128 (100)†
							19	512 (100)
2. ChDa	5 years	M	8/13/70	Encephalitis	Brain‡	RhMK	ND§	
3. BrCr	2 months	M	8/15/70	Aseptic meningitis	Stool	RhMK	3	< 8 (3,200)
						HFDK	13	32 (3,200)
4. JoFa	5 years	M	8/16/70	Meningoencephalitis	Stool	RhMK	2	64 (100)
						HFDK	7	512 (100)
5. CaWi	37 years	F	9/1/70	Encephalitis	Stool	RhMK	2	< 8 (32)
							19	64 (32)
6. HeBo	10 years	M	10/22/70	Meningitis	Stool, throat	RhMK	1	< 8 (32)
							14	256 (32)
7. DaAr	5 years	M	1/20/71	Meningitis	Stool	RhMK	2	1,024 (100)
							20	512 (100)
8. KeMa	5 years	M	4/25/71	Viral meningitis	Stool	RhMK	2	64 (32)
							16	64 (32)
9. LeBr	4 years	M	5/28/71	Meningitis	Stool‖	AGMK	ND	
10. GeGr	46 years	M	6/11/71	Coxsackie B(?) influenza(?) myocarditis	Stool	RhMK	ND	
11. WiTr	2 years	M	7/26/71	Encephalitis	Stool	RhMK	7	128 (32)
12. DoPr	7 years	F	8/11/71	Encephalitis	Stool	RhMK	2	512 (32)
							28	64 (32)
13. MiBr	1 year	M	8/15/71	Encephalitis	Stool	RhMK	2	16 (3,200)
							20	64 (3,200)
14. LuBl	9 months	M	8/22/71	Meningitis	Stool	RhMK	ND	
15. RoLo	14 years	M	8/31/71	Coxsackie-echo?	Stool#	RhMK	3	≥ 1,024 (100)
							16	≥ 1,024 (100)
16. CaMo	11 years	F	11/8/71	Encephalitis	Stool	RhMK	1	< 8 (1,000)
							15	32 (1,000)
17. MaMa	10 years	M	7/18/72	Meningitis	Stool	RhMK	10	256 (32)
							25	128 (32)
18. JeTh	3 years	M	8/22/72	Viral meningitis	Stool	HFDK	7	64 (32)
							27	128 (32)
19. JeWa	3 weeks	M	10/26/72	Meningitis	Stool‖	RhMK	ND	
20. MiHe	2 years	M	11/6/72	Aseptic meningitis	Stool	RhMK	3	64 (100)
							21	128 (100)

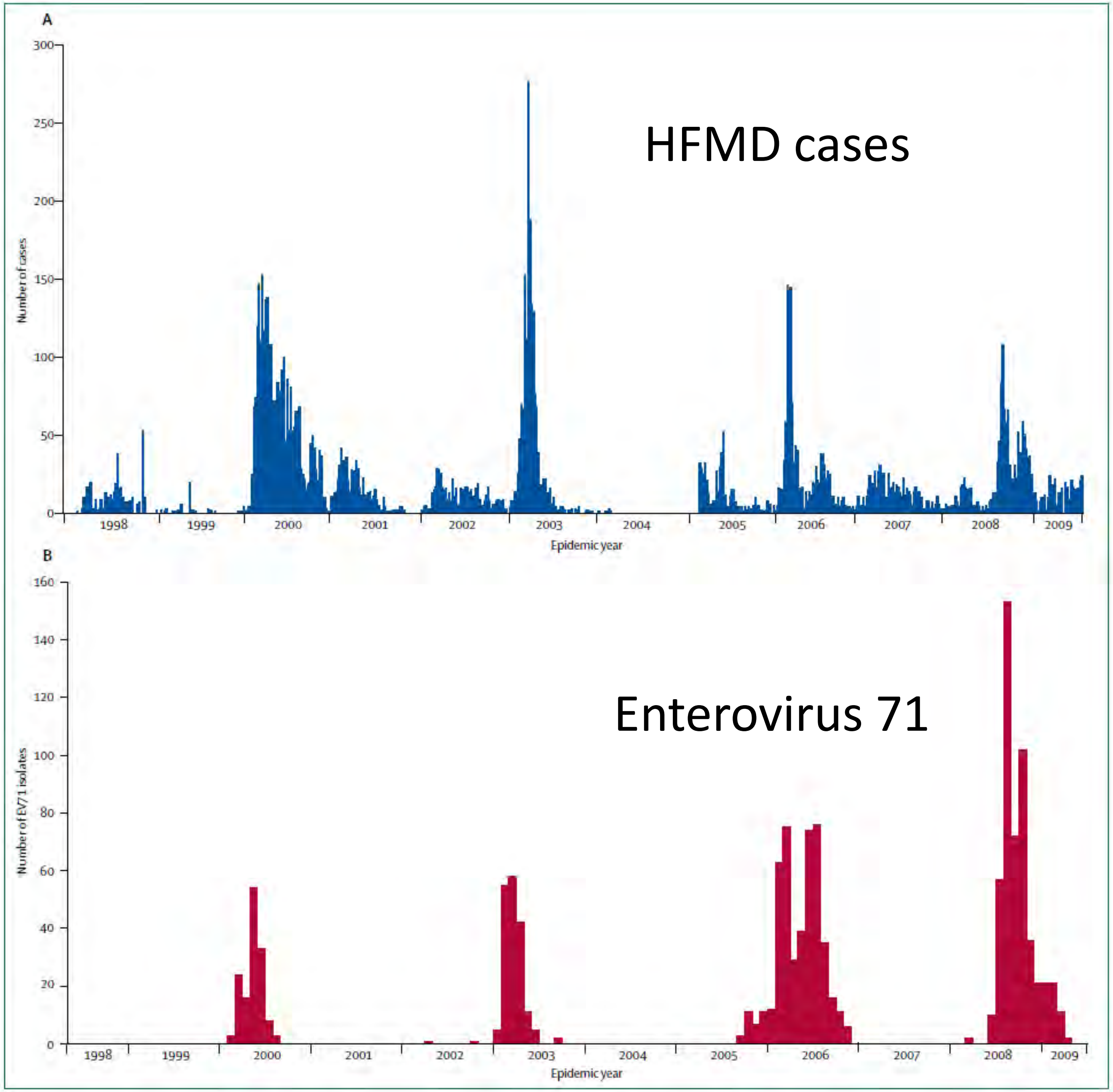
	Number of EV71 cases reported	Number of fatal cases reported	Main clinical presentations
California, USA, 1969–72[2]	20	1	Encephalitis, meningitis, coxsackievirus-like illness
New York, USA, 1972[3]	11	0	Aseptic meningitis, encephalitis, HFMD (only one case)
Sweden, 1973[4]	195	0	Aseptic meningitis, HFMD (some cases)
Bulgaria, 1975[5]	705	44	Aseptic meningitis, paralytic disease, including bulbar encephalitis
Japan, 1973, 1977, 1978[6]	1031	Some deaths, exact number unknown	HFMD (in most patients), cerebellar encephalitis, meningitis, acute flaccid paralysis
New York, USA, 1977[7]	12	0	CNS disease, HFMD, acute respiratory illness, acute gastroenteritis
Hungary, 1978[8]	323 laboratory confirmed	47 (unclear whether all due to EV71)	Meningitis, encephalitis, poliomyelitis, HFMD (only four cases)
Australia, 1986[9]	114	0	HFMD (in most cases), meningitis, encephalitis, encephalomyelopathy
Philadelphia, 1987[10]	5	0	Acute flaccid paralysis
USA, 1977–91[11]	193 laboratory confirmed	Unknown	1985–89: paralysis, meningitis, encephalitis, rash, Guillain-Barré syndrome
Sarawak, Malaysia, 1997[12]	2628	34	HFMD, aseptic meningitis, acute flaccid paralysis, cardiorespiratory dysfunction
Otsu, Japan, 1997[13]	12	0	HFMD, herpangina, meningoencephalitis, encephalitis, meningitis
Taiwan, 1998[14]	129 106	78	Encephalitis, aseptic meningitis, pulmonary oedema or haemorrhage, acute flaccid paralysis, myocarditis
Kenya, 1999[15]	8	0	Dermatitis, mucositis, myositis
Hyogo, Japan, 2000[16]	60	1	HFMD, aseptic meningitis, cerebellar ataxia, acute flaccid paralysis, brainstem encephalitis
Sarawak, Malaysia, 2000[17]	169 laboratory confirmed	2	HFMD, aseptic meningitis, acute flaccid paralysis, brainstem encephalitis
Singapore, 2000[18]	3790	5	HFMD, neurological disease
Korea, 2000[19]	Unknown	0	Aseptic meningitis, HFMD, herpangina, acute flaccid paralysis
Sarawak, Malaysia, 2003[17]	107 laboratory confirmed	1	HFMD, aseptic meningitis, acute flaccid paralysis, brainstem encephalitis
Fukushima, Japan, 1983–2003[20]	Unknown	Unknown	Unknown
Denver, USA, 2003[21]	8	1	Meningitis, acute flaccid paralysis, fever, cardiopulmonary dysfunction
Southern Vietnam, 2005[22]	173 laboratory confirmed	3	HFMD, aseptic meningitis, acute flaccid paralysis, brainstem encephalitis
Sarawak, Malaysia, 2006[23]	291 laboratory confirmed	6	HFMD, aseptic meningitis, brainstem encephalitis
Denver, USA, 2005[21]	8	0	Meningitis, acute flaccid paralysis, fever, encephalitis
Brunei, 2006[24]	1681	3	HFMD, neurological disease
Shandong, China, 2007[25]	1149	3	HFMD, brainstem encephalitis, aseptic meningitis
Anhui, China, 2008[26]	488 955	128	HFMD, neurogenic pulmonary oedema

HFMD=hand, foot, and mouth disease.

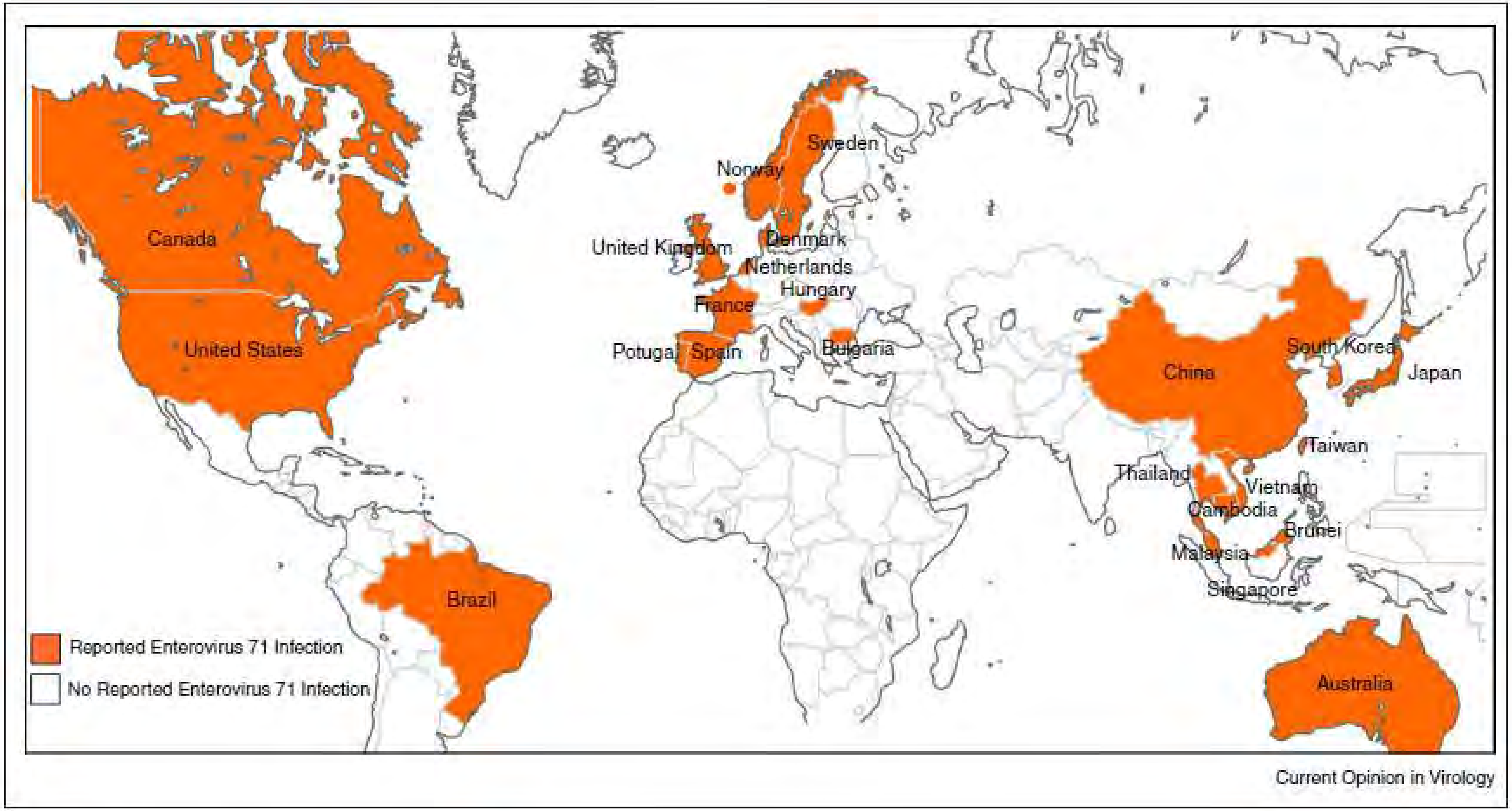
Table 1: **Enterovirus 71 outbreaks worldwide, by country and year**

Ooi 2010

Sarawak, Malaysia



Solomon 2010



Regions with reported human enterovirus 71 infection.

Huang 2014

The New England Journal of Medicine

VOLUME 341 SEPTEMBER 23, 1999 NUMBER 13

AN EPIDEMIC OF ENTEROVIRUS 71 INFECTION IN TAIWAN

MONTO HO, M.D., ENG-RIN CHEN, DR.MED.SCI., KWO-HSIUNG HSU, M.S., SHIING-JER TWU, M.D., PH.D., KOW-TONG CHEN, M.D., PH.D., SU-FEN TSAI, M.P.H., JEN-REN WANG, PH.D., AND SHIN-RU SHIH, PH.D., FOR THE TAIWAN ENTEROVIRUS EPIDEMIC WORKING GROUP*

All cases

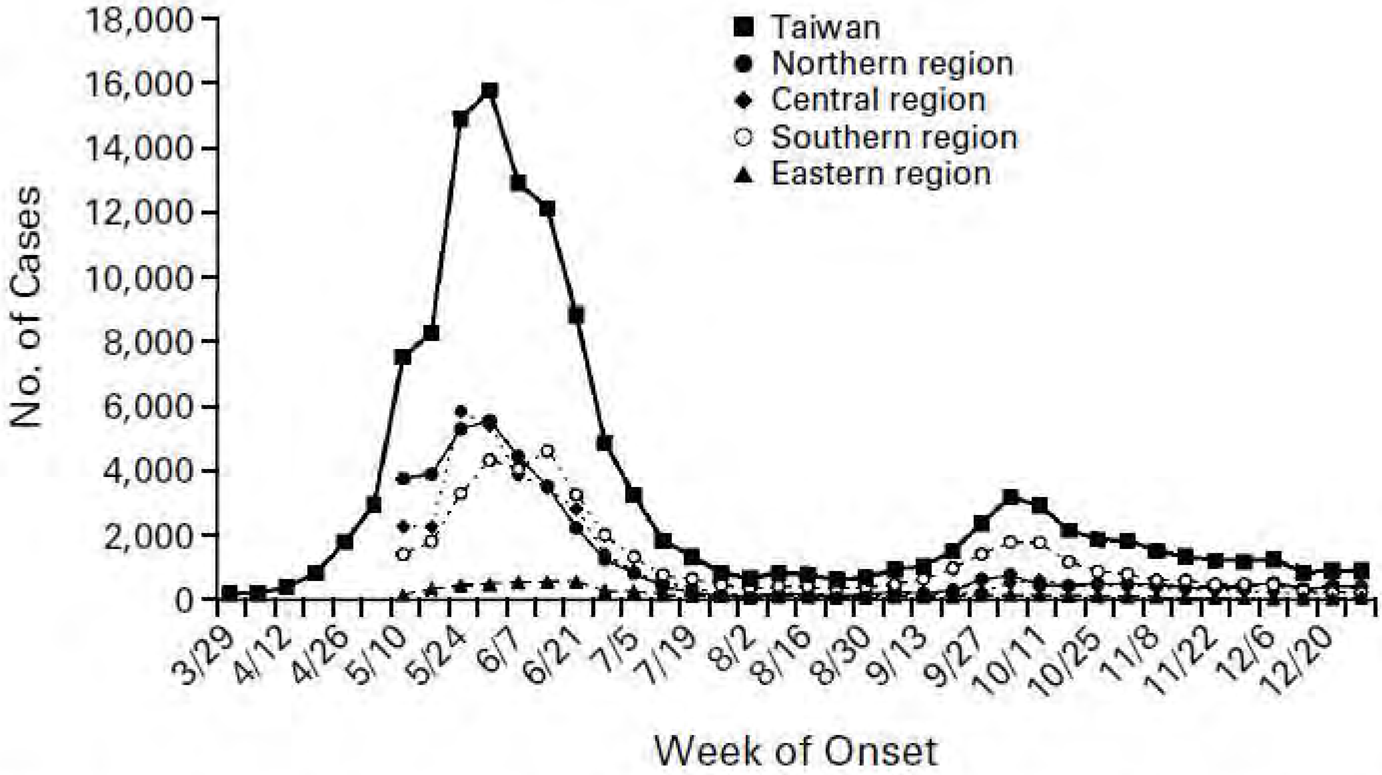


Figure 1. Number of Cases of Hand-Foot-and-Mouth Disease and Herpangina Reported in Taiwan as a Whole and in Each of Its Four Regions by Sentinel Physicians from the Week of March 29, 1998, through the Week of December 27, 1998.

The total number of cases was 129,106.

Ho 1999

Severe cases

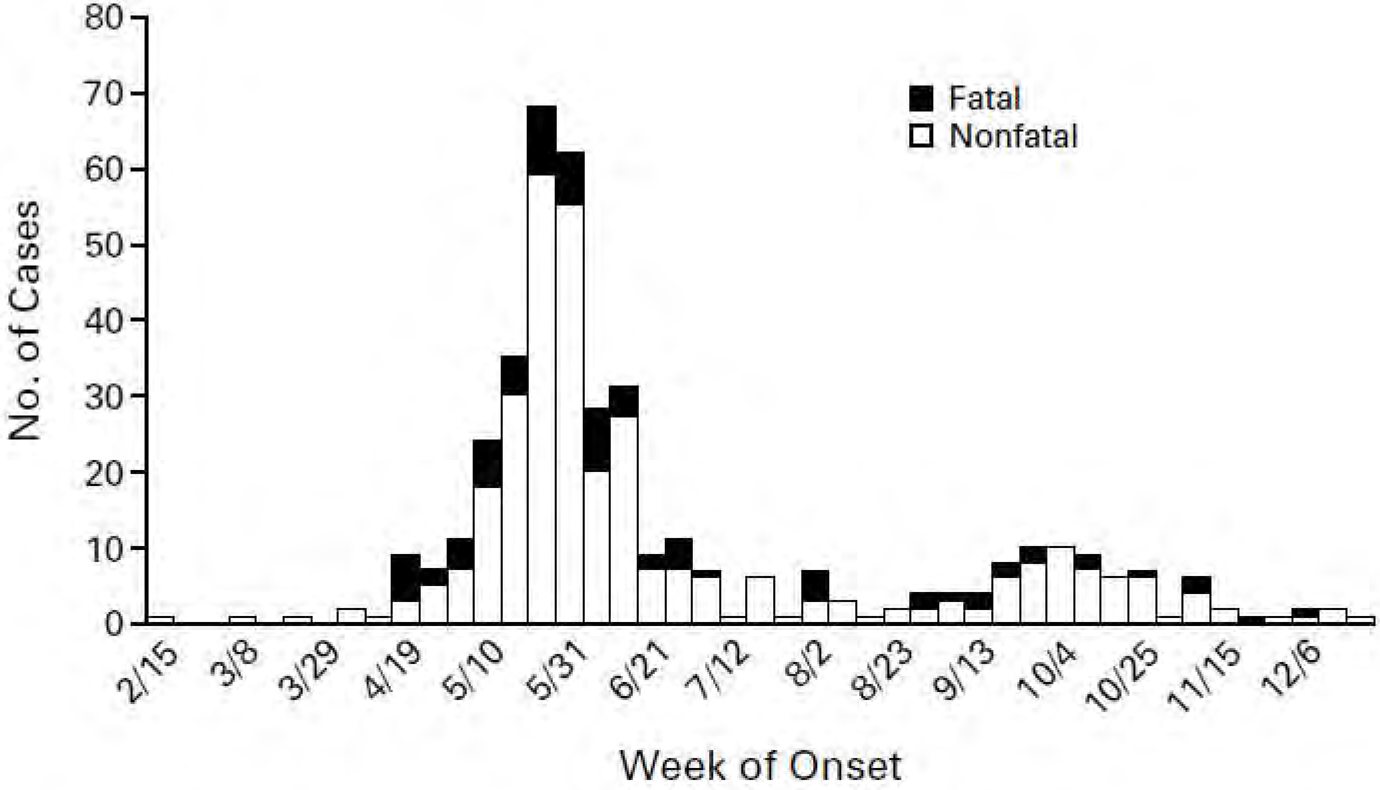


Figure 2. Number of Cases and Outcome of Severe Hand-Foot-and-Mouth Disease and Herpangina in Taiwan from the Week of February 15, 1998, through the Week of December 20, 1998.

A total of 78 patients died, and 327 survived.

Ho 1999

TABLE 3. Clinical Complications in 96 Patients with Severe Enteroviral Infection.

Complications*	No. of Patients (%)	Enterovirus 71 (N=78)	Coxsackievirus A16 or A24, Coxsackievirus B5, or Echovirus 6 or 7 (N=9)	Other Enteroviruses (N=9)
			number of isolates	
Encephalitis	39 (41)	30	5	4
Encephalitis and pulmonary edema or hemorrhage	25 (26)	25	0	0
Aseptic meningitis	11 (11)	5	1	5
Pulmonary edema or hemorrhage	10 (10)	9	1	0
Myocarditis and encephalitis	2 (2)	2	0	0
Myocarditis	1 (1)	1	0	0
Acute flaccid paralysis and encephalitis	1 (1)	1	0	0
Acute flaccid paralysis	1 (1)	1	0	0
Other	6 (6)	4	2	0

*The categories of complications are mutually exclusive.

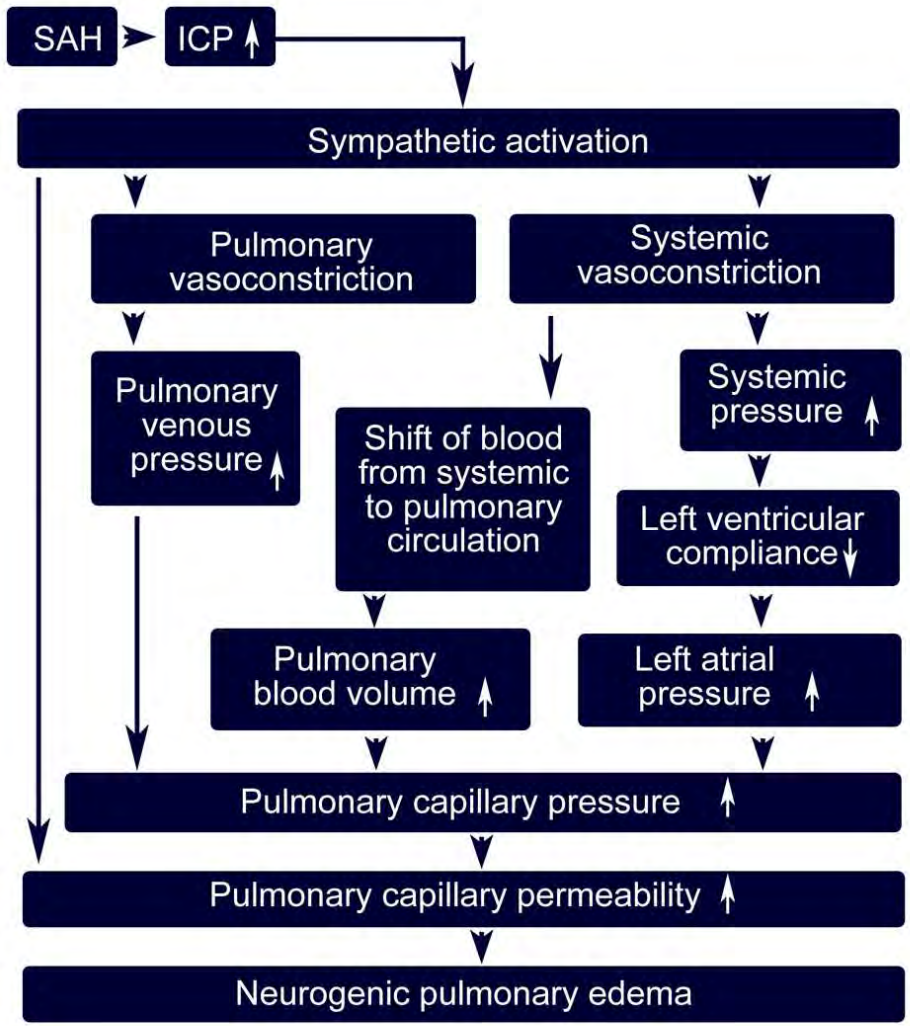
Ho 1999

	Frequency
Purely neurological manifestations	
Encephalitis, especially brainstem	Frequent
Acute flaccid paralysis (anterior myelitis)	Frequent
Encephalomyelitis	Frequent
Aseptic meningitis	Very frequent
Cerebellar ataxia	Infrequent
Transverse myelitis	Rare
Neurological and systemic manifestations	
Brainstem encephalitis with cardiorespiratory failure	Frequent
Manifestations indicative of immune-mediated mechanisms	
Guillain-Barré syndrome	Infrequent
Opsoclonus-myoclonus syndrome	Rare
Benign intracranial hypertension	Rare

Modified from McMinn,[34] with permission of John Wiley and Sons.

***Table* 2: Neurological syndromes associated with enterovirus 71 infection**

Enterovirus 71 –associated lung failure



BMC Infectious Diseases

BioMed Central

Research article

Open Access

Identification and validation of clinical predictors for the risk of neurological involvement in children with hand, foot, and mouth disease in Sarawak

Mong How Ooi*[1,2,3], See Chang Wong[1], Anand Mohan[1], Yuwana Podin[2], David Perera[2], Daniella Clear[3], Sylvia del Sel[3], Chae Hee Chieng[1], Phaik Hooi Tio[2], Mary Jane Cardosa[2] and Tom Solomon[3]

BMC Infectious Diseases

BioMed C

Research article

Open Acc

Identification and validation of clinical predictors for the risk of neurological involvement in children with hand, foot, and mouth disease in Sarawak

Mong How Ooi*[1,2,3], See Chang Wong[1], Anand Mohan[1], Yuwana Podin[2], David Perera[2], Daniella Clear[3], Sylvia del Sel[3], Chae Hee Chieng[1], Phaik Hooi Tio[2], Mary Jane Cardosa[2] and Tom Solomon[3]

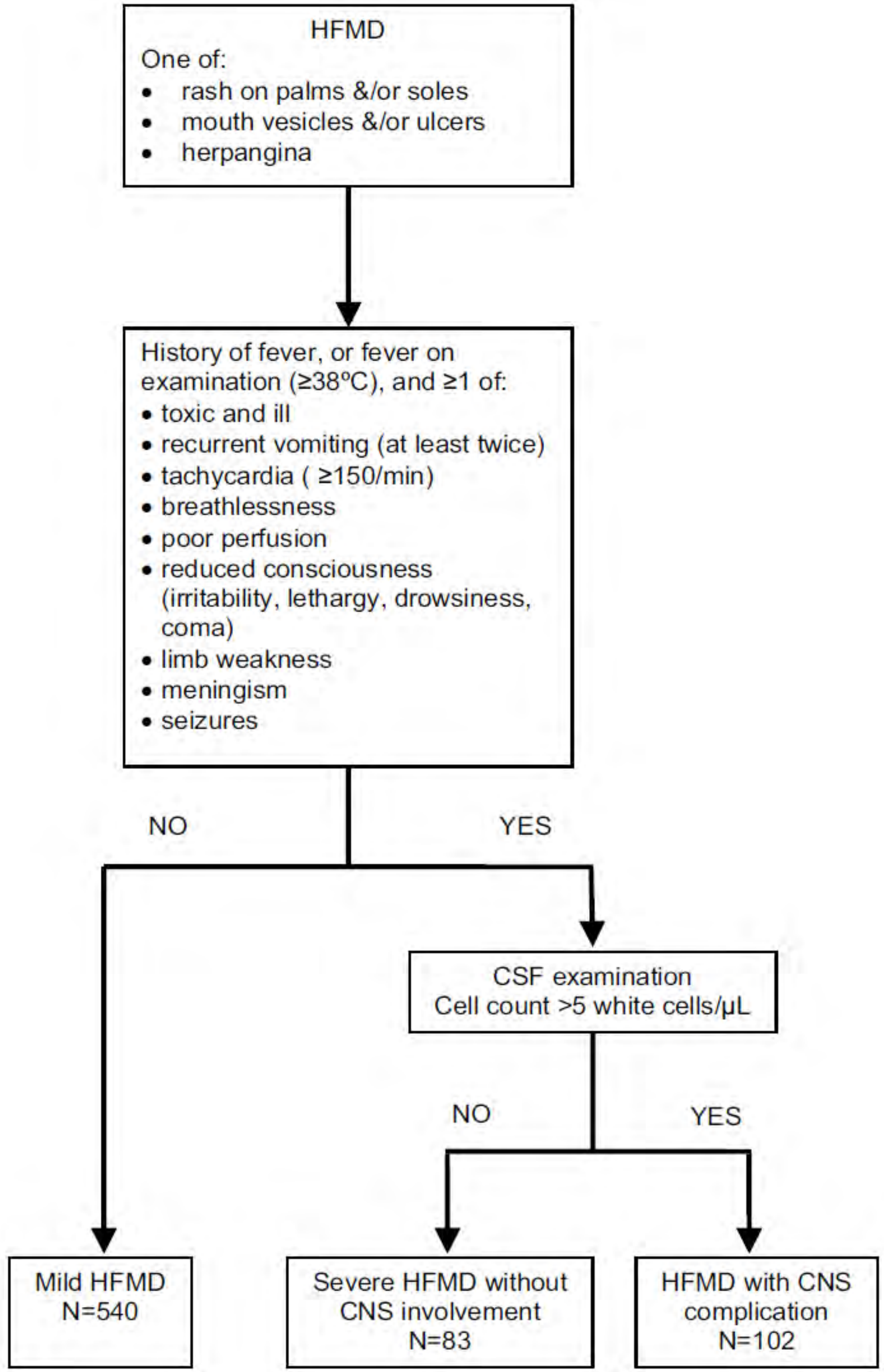


Table 1: Risk factors that were significantly associated with CSF pleocytosis in children with HFMD in the first phase of the study (2000 to 2003).

Risk factors	p value	Odds ratio	95% CI
Total duration of fever ≥ 3 days	< 0.0001	6.52	2.83 – 14.99
Peak temperature ≥ 38.5°C	0.0192	2.27	1.14 – 4.51
History of lethargy	0.001	3.18	1.60 – 6.35

Note: The Hosmer-Lemeshow statistics indicated a non-significance of lack of fit ($\chi^2 = 2.163$, p = 0.904).
CSF: Cerebrospinal fluid
HFMD: Hand, foot, and mouth disease

725 children
Ooi 2009

Neurological Manifestations of Enterovirus 71 Infection in Children during an Outbreak of Hand, Foot, and Mouth Disease in Western Australia

Peter McMinn,[1] Ivan Stratov,[1] Lakshmi Nagarajan,[2] and Stephen Davis[3]

Departments of [1]Microbiology and [2]Neurology, Princess Margaret Hospital for Children, Perth, and [3]Magnetic Resonance Imaging Unit, Sir Charles Gairdner Hospital, Queen Elizabeth II Medical Centre, Nedlands, Australia

---

2001

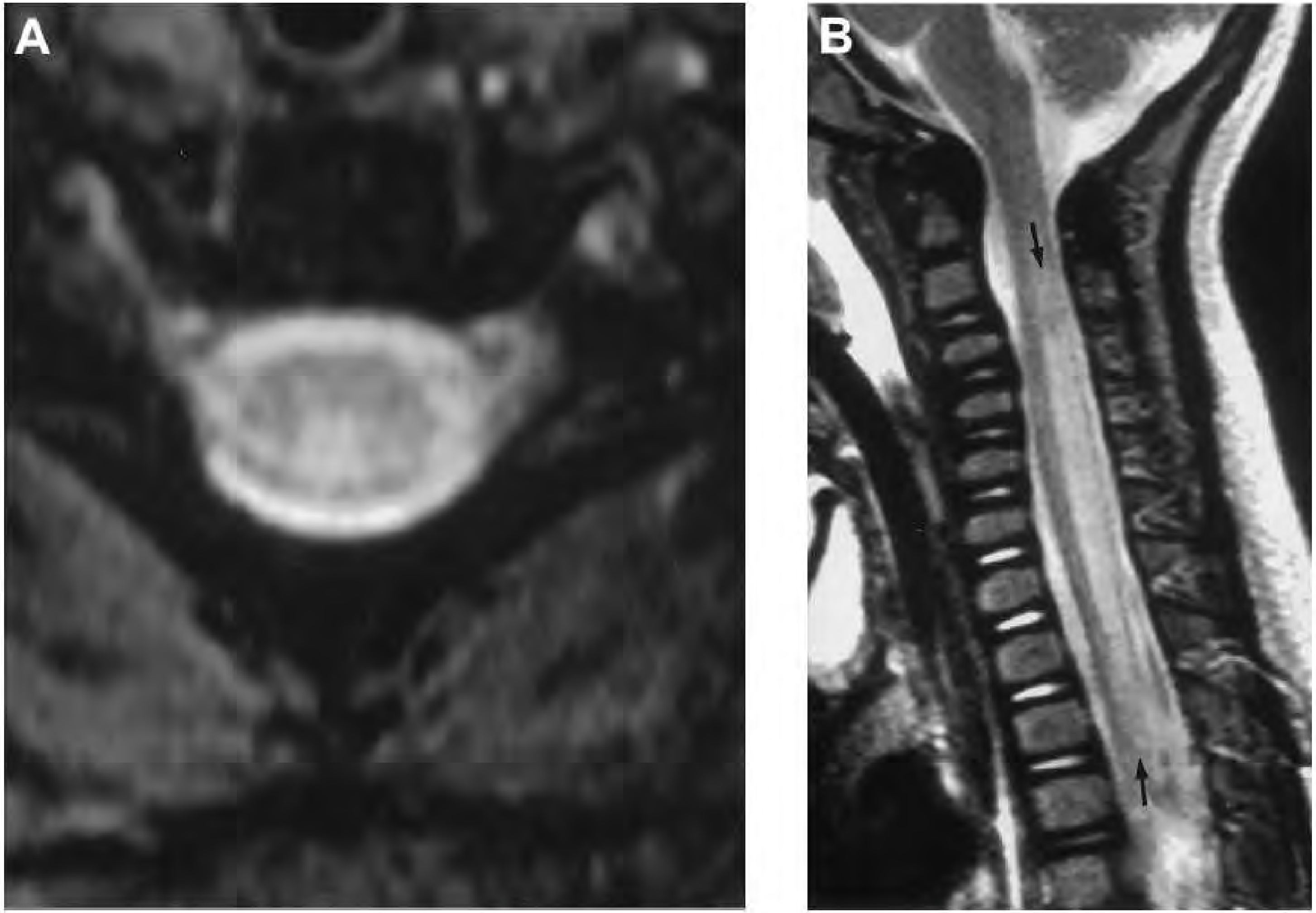
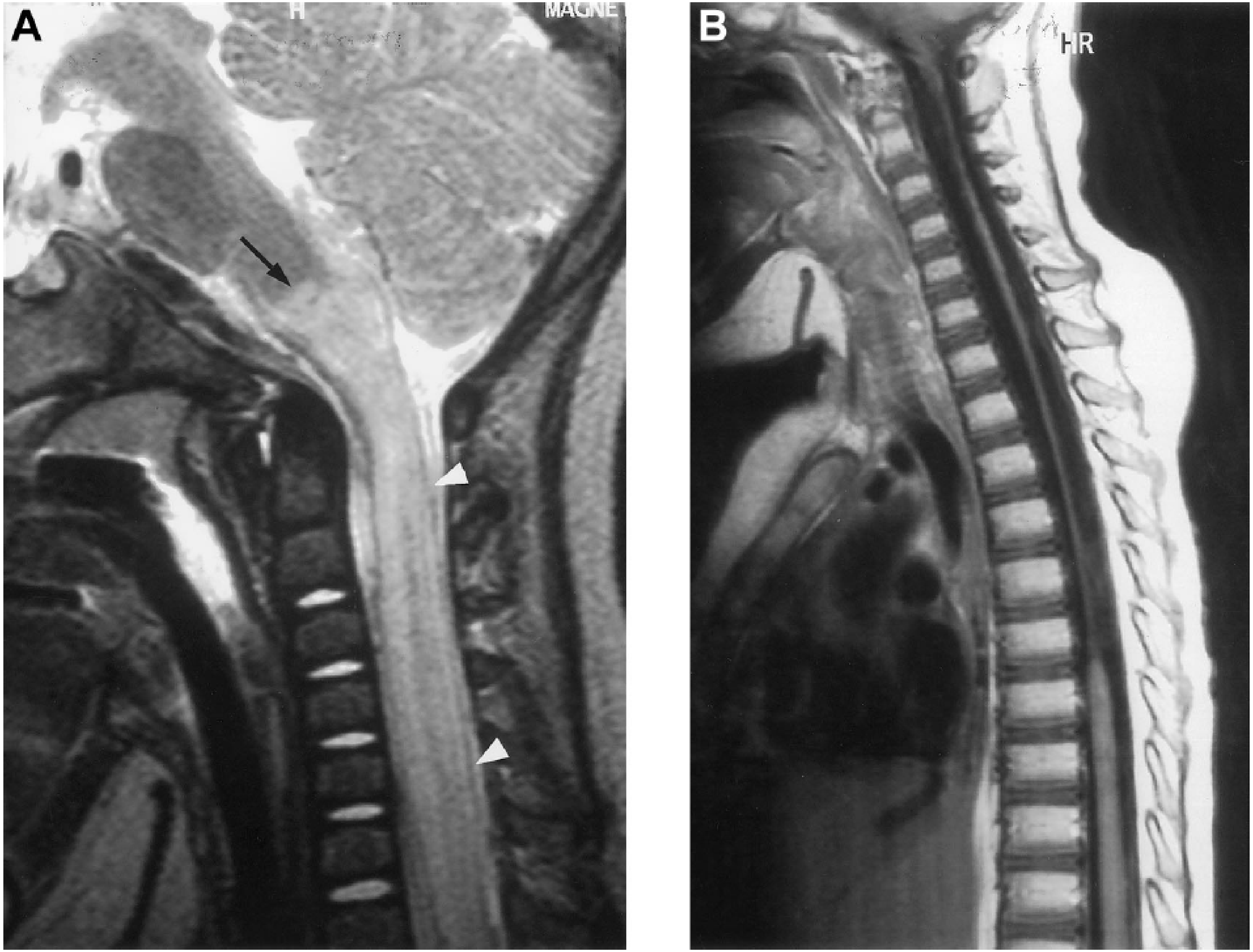
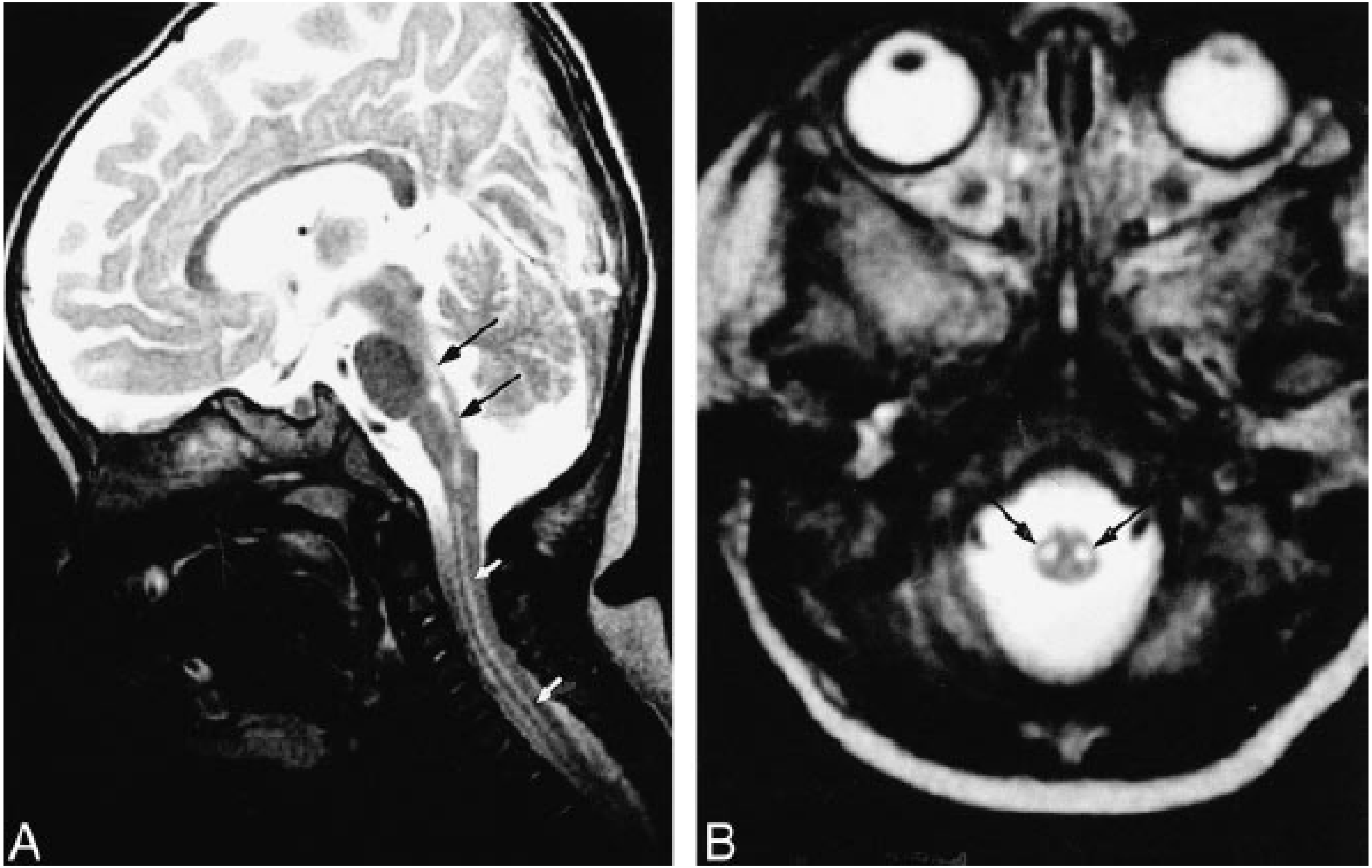


Figure 1. MRI of a 9-month-old male infant (patient 2) with enterovirus 71–associated neurological disease. *A*, Axial gradient-echo T_2-weighted MRI done 3 days after the onset of acute transverse myelitis, showing a high signal lesion centered in the dorsal column white matter of the cervical cord. *B*, Midsagittal turbo spin-echo T_2-weighted MRI scan done during the same examination as in *A*, showing a lesion from C2 to T2 *(arrows)* with mild cord expansion.

McMinn 2001 – 9 month-old



McMinn 2001 – 19 month-old



Chen 1999

CSF parameters

Patient	Age	Time of lumber puncture, no. of days from onset of illness	CSF parameters				CSF PCR result
			WBC count, cells/mm^3	RBC count, cells/mm^3	Glucose level, mg/dL	Protein level, mg/dL	
1	2 years	2	2075	14	56	69	–
2	5 years	4	76	8	126	56	–
3	10 days	1	1	200	68	78	+
4	6 months	2	228	43	71	52	–
5	5 years	10	2	1200	94	40	–
6	2 months	2	15	5100	57	59	+
7	3 months	2	6	1700	58	34	+
8	1 months	2	ND	ND	ND	ND	+
9	9 years	10	5	1110	60	66	–
10	3 months	3	406	0	54	91	–
11	7 months	8	ND	ND	ND	ND	–
12	7 weeks	2	240	250	49	107	–
13	7 weeks	4	205	63	41	65	–
14	3 months	1	6	288	50	49	+
15	2 years	2	55	95	68	39	–
16	2 years	15	11	0	51	44	–

Perez-Velez 2007

Table 2. Enteroviral PCR and culture results for patients with enterovirus type 71 infection.

	Specimen											
	CSF		Blood		Throat		Rectal		Nasal wash		Other	
Patient	PCR result	Culture result	PCR result	Culture result	PCR result	Culture result	PCR result	Culture result	PCR result	Culture result	PCR result	Culture result
1	–	...	...	...	+	...	+	...	...	...	...	...
2	–	...	–	...	...	...	+	...	...	+	+[a]	...
3	+	...	...	...	...	...	...	...	...	...	...	...
4	–	...	Ind	...	+	–[b]	+	+	+	–[b]	+[c]	...
5	–	...	Ind	...	+	–	+	–	...	+	–[c], +[d]	...
6	+	...	...	...	...	...	...	...	...	...	...	...
7	+	...	...	...	...	...	...	...	...	...	...	...
8	+[e]	...	...	...	+	...	+	...	...	–	...	...
9	–	...	...	...	...	+	...	...	...	...	...	...
10	–	...	...	...	...	...	+	+	...	+	+[f]	...
11	–[e]	–	...	...	...	...	...	...	...	...	+[g]	+[g]
12	–	...	...	...	...	...	...	...	...	...	...	+[h]
13	–	...	...	...	...	...	...	...	...	...	+[g]	+[i]
14	+	...	...	...	...	...	...	...	...	...	+[i]	...
15	–	...	...	...	+	–	+	+	...	...	...	...
16	–	...	...	...	+	...	–	...	...	...	...	...
All, no. of patients with positive results/no. of patients with sample tested	5/16	0/1	0/3	0/0	6/6	1/4	7/8	3/4	1/1	3/5		

Perez-Velez 2007

Enterovirus 71 : antiviral therapy

- Anti-polymerase
  - Ribavirine
    - Active on other RNA viruses but not EV
- Capside binders
  - Pleconaril
    - Inhibits the entry and decoating of enteroviruses

      … Not active on EV71
  - Vapendavir (initially developped for rhinovirus)
  - pirodavir
- Protease inhibitor
  - SG85
  - Rupintrivir

Enterovirus 71 : other treatments

- Milrinone
  - Inotropic agent
  - For neurogenic pulmonary edema

TABLE 3. Clinical Course of Children With Enterovirus 71 Brainstem Encephalitis According to Treatment With Milrinone or Standard Management

Variable	Milrinone Treatment ($n = 22$)	Standard Management ($n = 19$)	p
Overall mortality, *n* (%)	4 (18.2)	11 (57.9)	0.01[a]
Enrollment to death (d), median (range)	1.5 (1–4)	1 (0.5–7)	0.43
Mechanical ventilation, *n* (%)	17 (77.3)	18 (94.7)	0.19

Chi 2013

First Case of Severe Enterovirus 71 Infection in Portugal

Venancio 2013

To the Editors:

In December 2011, a 17-month-old boy was admitted to a pediatric intensive care unit in Lisbon, Portugal, because of rapidly progressive acute flaccid paralysis, rhombencephalitis and coma. He had been diagnosed

Journal of Clinical Virology 56 (2013) 348–353

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

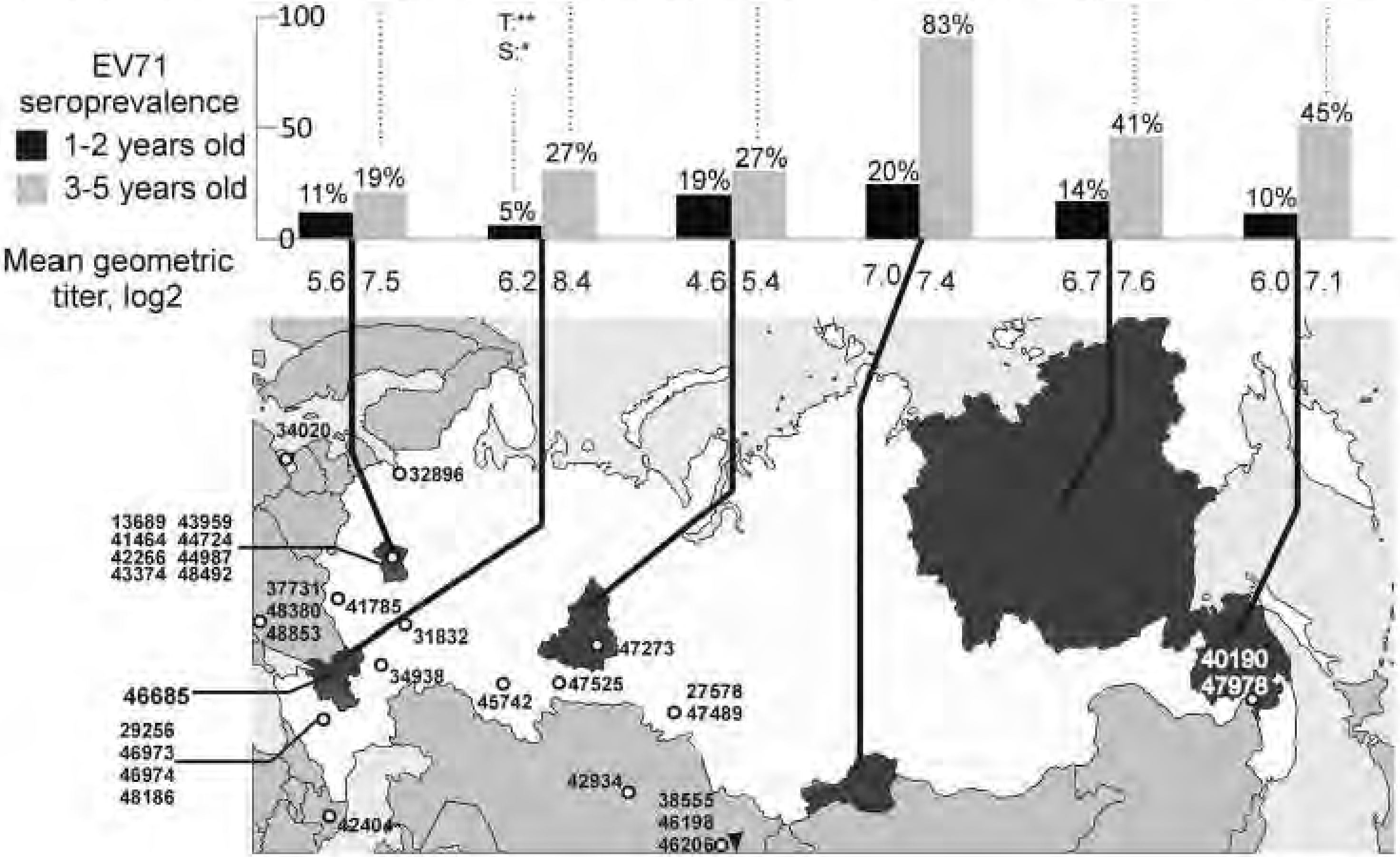
Human enterovirus 71 strains in the background population and in hospital patients in Finland

Hanna Honkanen[a,*], Sami Oikarinen[a], Outi Pakkanen[b], Tanja Ruokoranta[b], Minna M. Pulkki[b], Olli H. Laitinen[b], Sisko Tauriainen[a], Sanna Korpela[a], Maija Lappalainen[c], Tytti Vuorinen[d], Anna-Maija Haapala[e], Riitta Veijola[f], Olli Simell[g], Jorma Ilonen[h,i], Mikael Knip[j,k,l], Heikki Hyöty[a,m]

Seroepidemiology and Molecular Epidemiology of Enterovirus 71 in Russia

Ludmila V. Akhmadishina[1], Tatiana P. Eremeeva[1], Olga E. Trotsenko[2], Olga E. Ivanova[1], Mikhail I. Mikhailov[1], Alexander N. Lukashev[1]*

1 Chumakov Institute of Poliomyelitis and Viral Encephalitides, Moscow, Russia, 2 Khabarovsk Institute of Epidemiology and Microbiology, Khabarovsk, Russia



New Introductions of Enterovirus 71 Subgenogroup C4 Strains, France, 2012

Isabelle Schuffenecker, Cécile Henquell, Audrey Mirand, Marianne Coste-Burel, Stéphanie Marque-Juillet, Delphine Desbois, Gisèle Lagathu, Laure Bornebusch, Jean-Luc Bailly, and Bruno Lina

In France during 2012, human enterovirus 71 (EV-A71) subgenogroup C4 strains were detected in 4 children hospitalized for neonatal fever or meningitis. Phylogenetic analysis showed novel and independent EV-A71 introductions, presumably from China, and suggested circulation of C4 strains throughout France. This observation emphasizes the need for monitoring EV-A71 infections in Europe.

HEV

Hepatitis E virus

- Discovered 1983 in Afghanistan
  - Nude RNA virus of its own genus
- Probably the most common cause of acute hepatitis in the world
  - But chronic form may develop in immunocompromised hosts
- 4 serotypes
  - 1 & 2 : water-borne infection in developing countries
  - 3 & 4 : zoonotic (pig) reservoir

HEV

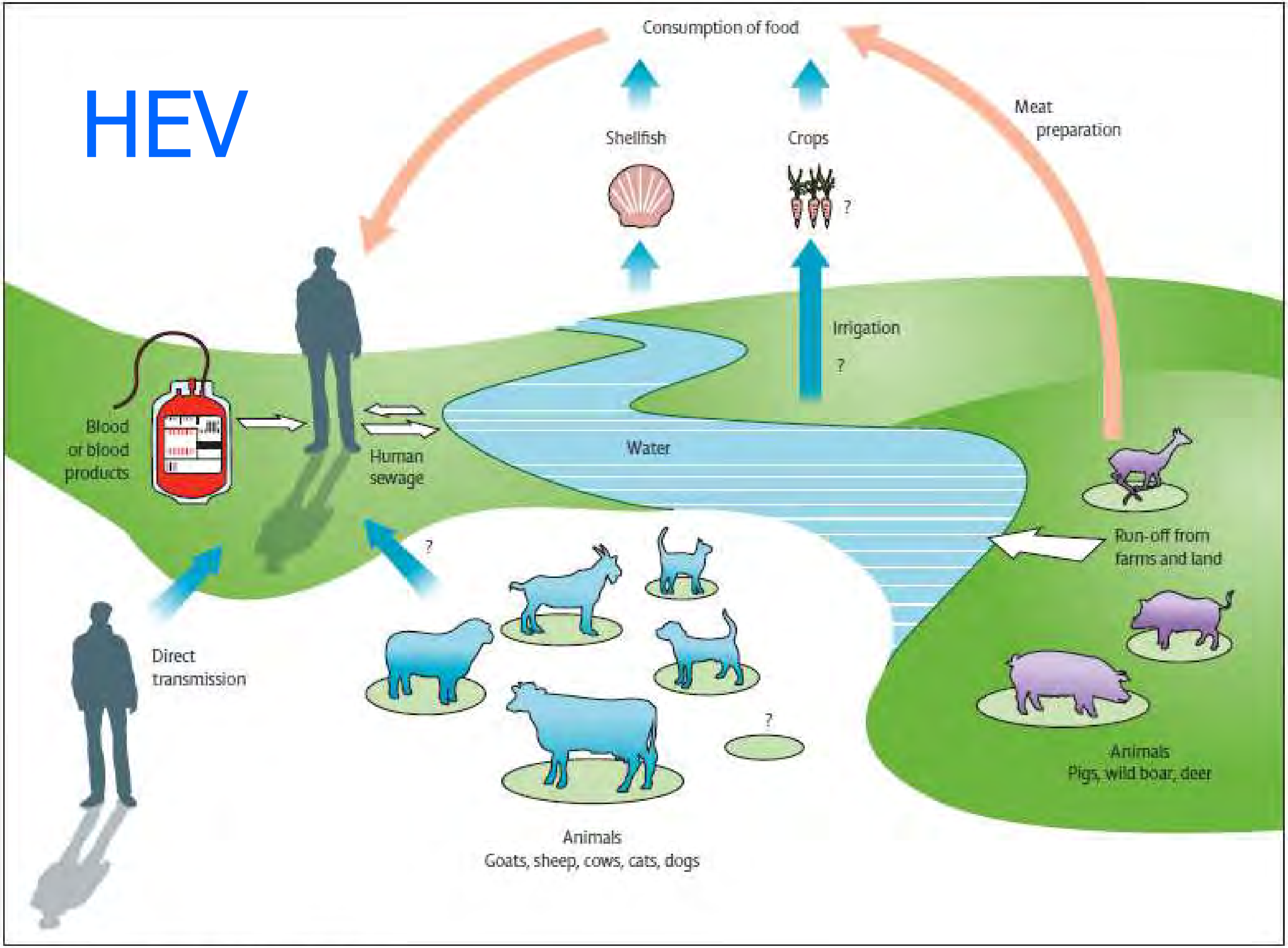


Figure 3: Source and route of HEV1–4 infection

Hepatitis E virus infection with CNS involvment

- Immunocompromised and immunocompetent patients
- Acute (I.competent) or chronic (I.compromised) infection
- Liver enzymes elevated during acute infection
  - Although mild : ALT 300-1000 IU/L

Medical status	HEV infection Phase and genotype	Nervous system lesions	Plasma			CSF		
			HEV IgG/IgM	HEV RNA	ALT, IU/L	HEV RNA	Protein g/L	Leukocytes /mm^3
Not immunocompr.	Acute 3e	PRN	+/+	+	623	Neg	1.27	145
Not immunocompr.	Acute 3e	neuritis	+/+	+	1160	ND	-	
Not immunocompr.	Acute 3f	PRN	+/+	+	384	Neg	2	14
Kidney–pancr. Tx recipient	Chronic 3f	PRN	+/+	+	173	Pos	0.71	1
Kidney Tx Recipient	Chronic 3f	encephalitis	-/+	+	110	Pos	0.8	8
Kidney Tx Recipient	Chronic 3f	PRN	+/+	+	105	Pos	0.76	7
HIV positive	Chronic 3f	Ataxia	+/+	+	150	Pos	0.47	1
Not immunocompr.	Acute 3f	encephalitis	-/+	+	479	Pos	0.56	12
Not immunocompr.	Acute	radiculitis	+/-	NA	1612	NA	0.68	<5

Adapted from Kamar 2011 and Deroux 2014