



Modena, 1 ottobre 2015
Convegno di Medicina Interna e Medicina respiratoria



Breaking News nelle Malattie Infettive

Prof. Adriano Lazzarin
Scuola di Specializzazione
in Malattie Infettive
Università Vita-Salute San Raffaele
Milano

Italy: Patient Zero

Transport with Italian Air Force aircraft KC 767.

Arrival at Pratica di Mare, 24 Nov 2014



LA STAMPA CRONACHE

+ Bossetti: "Prego ogni giorno per Yara"

+ S Eternit, l'impegno di Renzi "Parte civile nel processo bis"

+ S In un block notes i riti della 'ndrangheta

+ S «Non v partisse mai impegno»

Ebola, l'arrivo allo Spallanzani del paziente italiano

(ANSA)



- Physician, 50 yrs old, Emergency
- First mission in Sierra Leone
- Not clear how he became infected
- Experimental treatment with drugs and convalescent plasma
- Discharged 2 Jan 2015

LETTERS

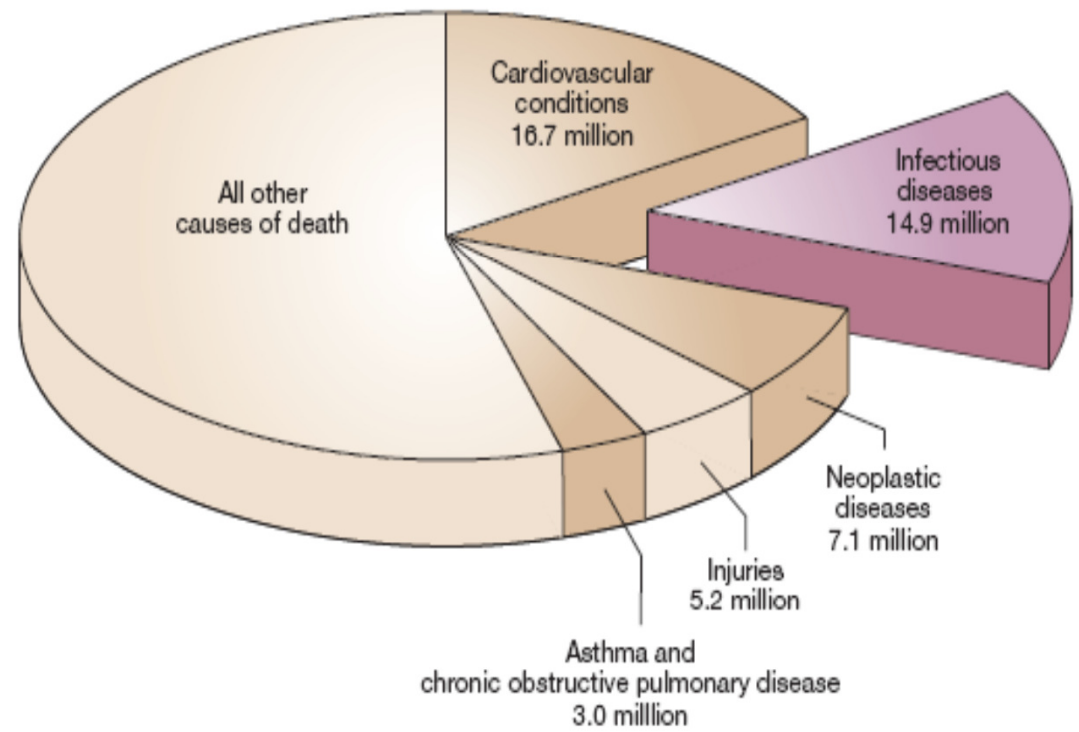
Global trends in emerging infectious diseases

Kate E. Jones¹, Nikkita G. Patel², Marc A. Levy³, Adam Storeygard^{3†}, Deborah Balk^{3†}, John L. Gittleman⁴
& Peter Daszak²

Here we analyse a database of 335 EID ‘events’ (origins of EIDs) between 1940 and 2004, and demonstrate non-random global patterns.



Trattato di medicina interna sistematica



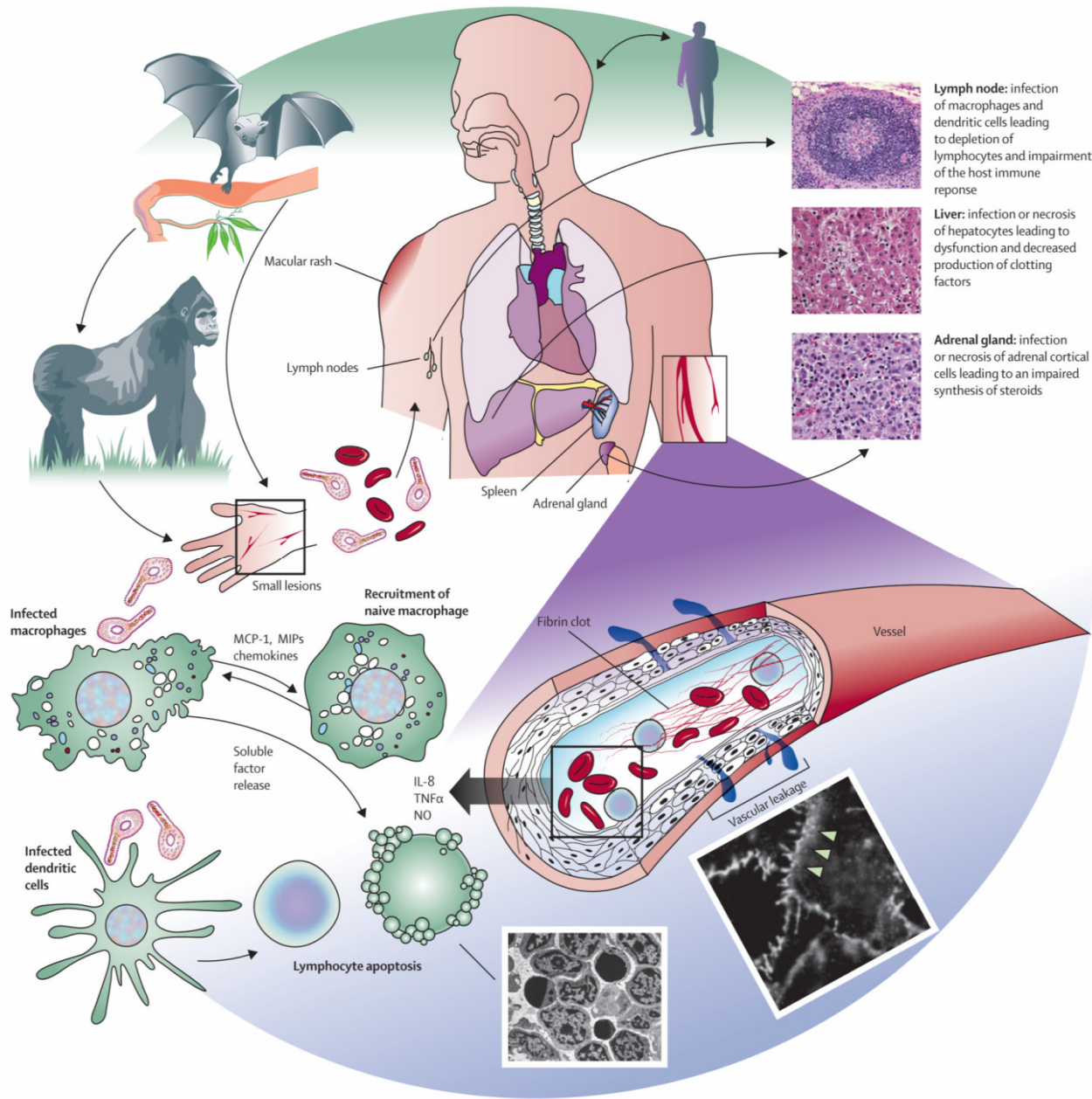
Infectious diseases	Annual deaths (million)
Respiratory infections	3.96
HIV/AIDS	2.77
Diarrhoeal diseases	1.80
Tuberculosis	1.56
Vaccine-preventable childhood diseases	1.12
Malaria	1.27
STDs (other than HIV)	0.18
Meningitis	0.17
Hepatitis B and C	0.16
Tropical parasitic diseases	0.13
Dengue	0.02
Other infectious diseases	1.76

Figure 2 Leading causes of death worldwide. About 15 million (>25%) of 57 million annual deaths worldwide are the direct result of infectious disease. Figures published by the World Health Organization (see <http://www.who.int/whr/en> and ref. 7).

Malattie Infettive: modello didattico per la formazione del giovane medico

- Epidemiologia
- Eziologia
- Patogenesi
- Diagnosi
- Cura





➤ The virus present in the infected secretion enters through the mucosal or percutaneous way.

➤ The virus actively replicates in:

- Macrophage/monocytes
- Dendritic cells
- Endothelial cells

and spreads through the blood stream

➤ Main target organs:

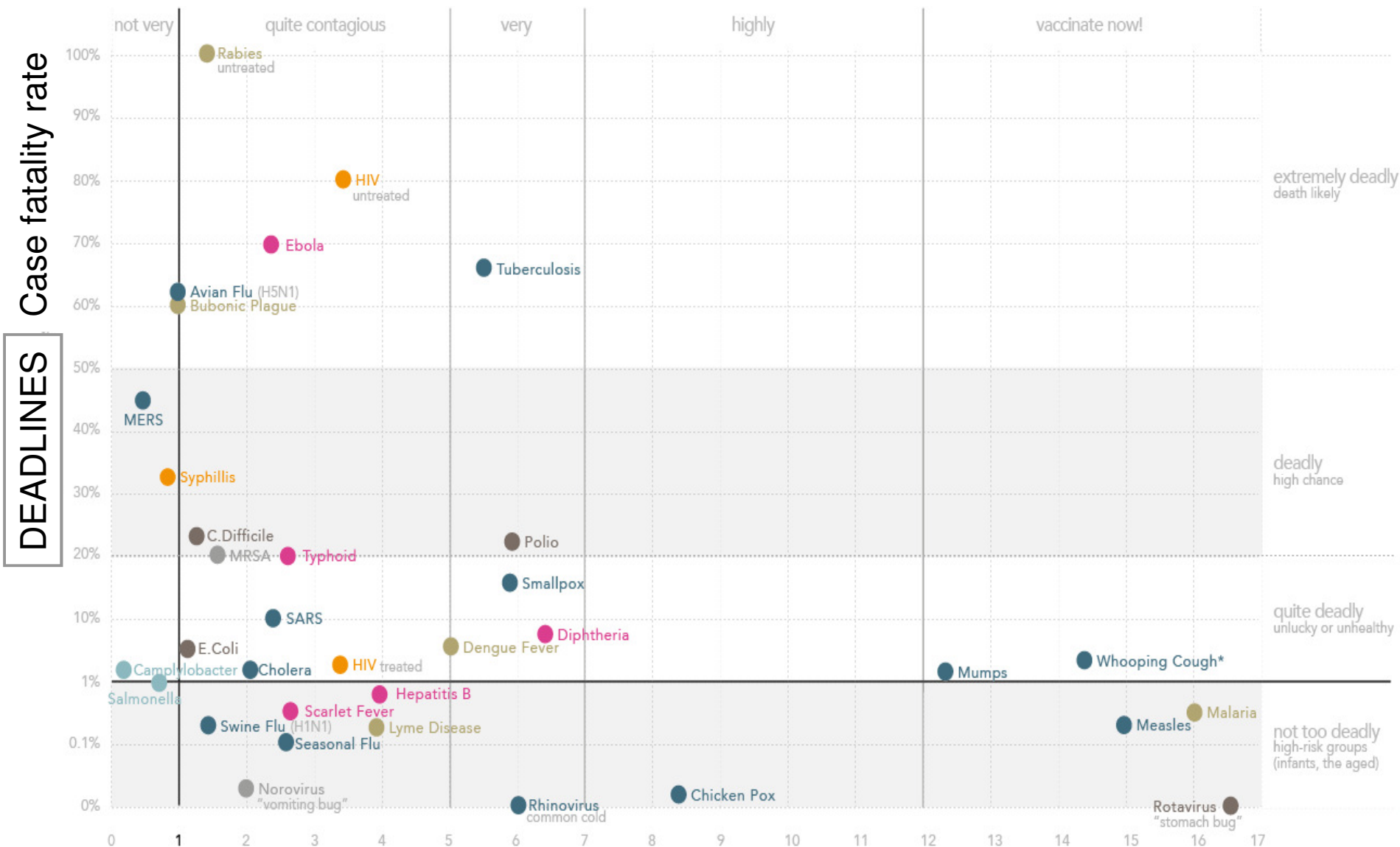
- liver
- kidney
- spleen
- ovary
- testis
- lymphonoid organs



TEMPO

LUOGO SPAZIO

PRIMARY TRANSMISSION METHOD airborne bites body fluids fecal-oral food sexual contact surfaces





Epidemiologia

Eziopatogenesi

Diagnosi e cura

Prevenzione



The Globalisation of Culture means the
Globalisation of Disease

- Luc Montagnier

“No city on the earth is now more than 24 hours away from any other”. Economist 2003

“Annually, the world's airlines carry a staggering total approaching some two billion passengers. At any one moment, about half a million people world-wide are flying in commercial aircraft”.

Select Committee on Science and Technology Fifth Report UK Parliament 2000



insight review articles

The challenge of emerging and re-emerging infectious diseases

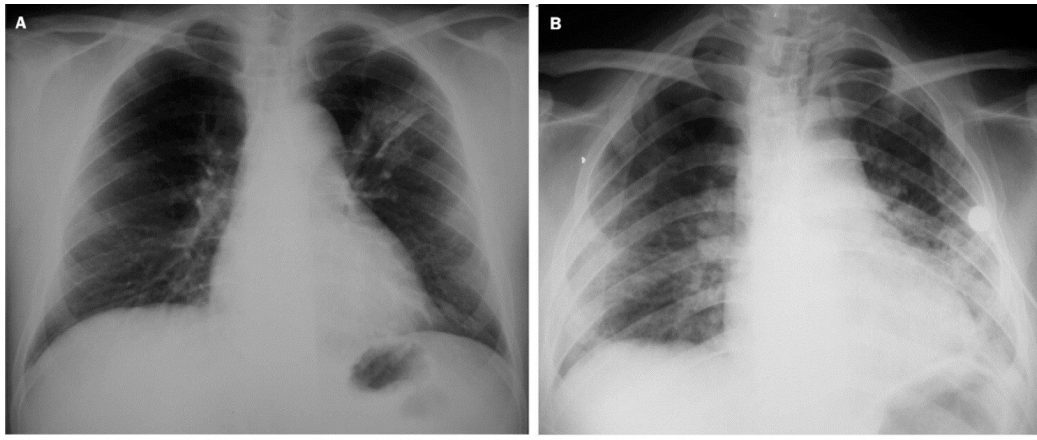
David M. Morens, Gregory K. Folkers & Anthony S. Fauci

National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892-2520, USA (e-mail: afauci@niaid.nih.gov)

Infectious diseases have for centuries ranked with wars and famine as major challenges to human progress and survival. They remain among the leading causes of death and disability worldwide. Against a constant background of established infections, epidemics of new and old infectious diseases periodically emerge, greatly magnifying the global burden of infections. Studies of these emerging infections reveal the evolutionary properties of pathogenic microorganisms and the dynamic relationships between microorganisms, their hosts and the environment.

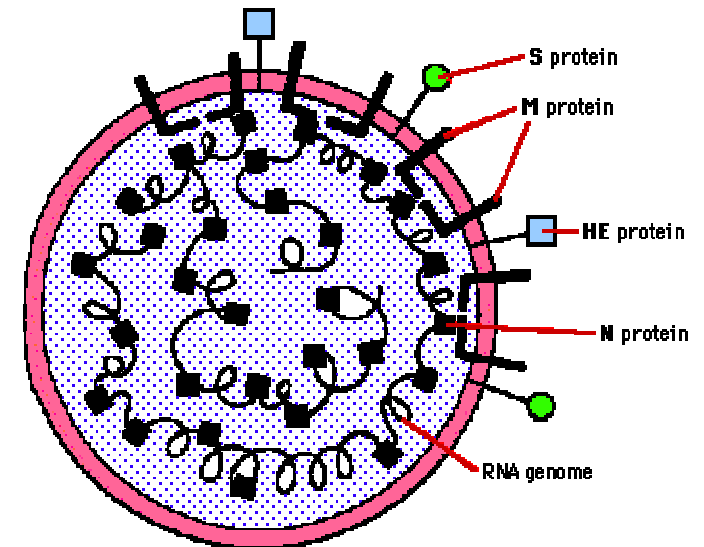
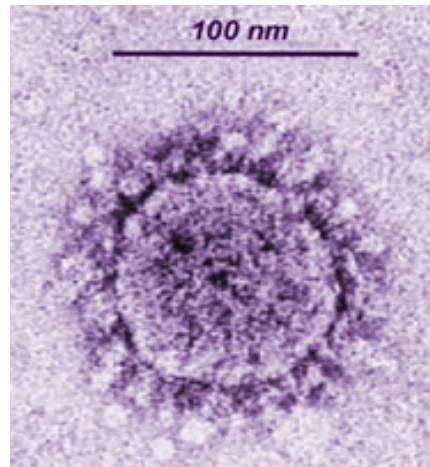
Severe Acute Respiratory Syndrome (SARS)

- Clinical manifestations of SARS:
- 2-10 days: fever, myalgia, malaise and chills
- next 8-12 days: cough, shortness of breath, tachypnea
- 3rd phase: progressive hypoxia and require intubation and mechanical ventilation
- systemic symptom: lymphopenia
- early phase chest radiographs often show peripheral pulmonary infiltrate



.... but within 5 months (Feb-July)

- Virus identified
- Diagnostic tests developed
- Infection control practices established
- International public health response
- Surveillance programs established
- 5 July: WHO removed the last region from the list of areas with recent local transmission



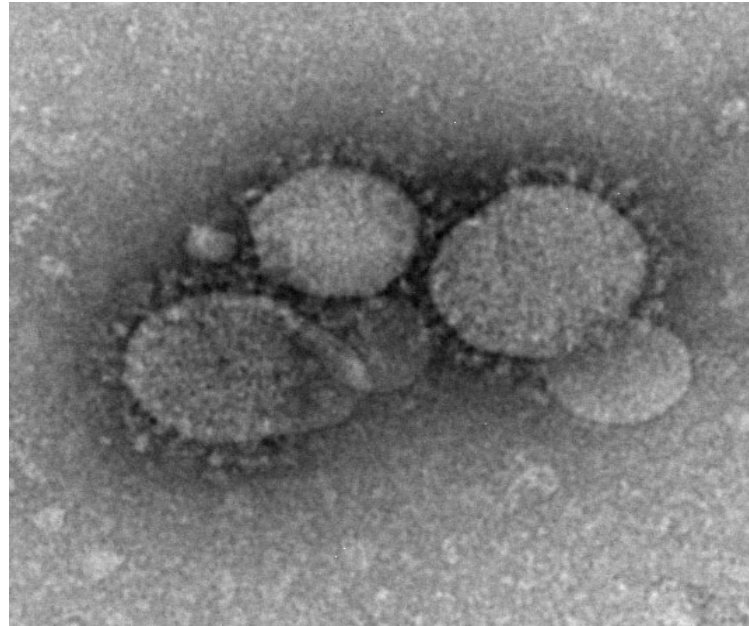
SARS left in its wake.....

- 8,098 cases, 774 deaths
- Billions lost in airlines, tourism
- World wide economic downturn
- Devastated health care system



A livello globale, da settembre 2012, l'OMS ha notificato **1.542 casi** confermati in laboratorio di infezione da MERS-CoV, tra cui almeno **544 decessi correlati**.

MER-CoV



Data la mancanza di evidenze di trasmissione sostenuta da persona a persona in comunità, l'OMS non raccomanda alcuna restrizione a viaggi o a rotte commerciali. E' buona prassi di sanità pubblica sensibilizzare i viaggiatori da e verso paesi colpiti da MERS-CoV.

- Ebola is a little river in the North of Yambuku (Democratic Republic of Congo, former Zaire)
- The first isolate was obtained from a patient from Yambuku village

THE LANCET, MARCH 12, 1977

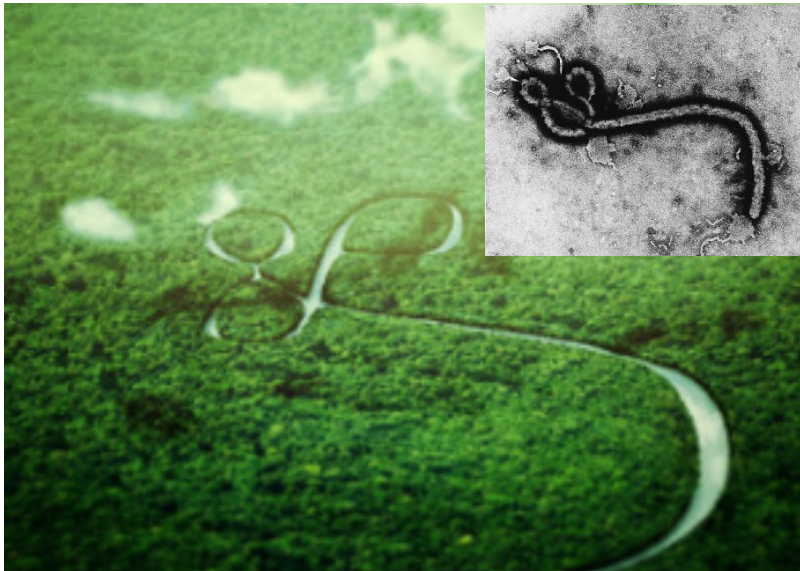
Preliminary Communications

ISOLATION AND PARTIAL CHARACTERISATION OF A NEW VIRUS CAUSING ACUTE HEMORRHAGIC FEVER IN ZAIRE

K. M. JOHNSON
J. V. LANGE

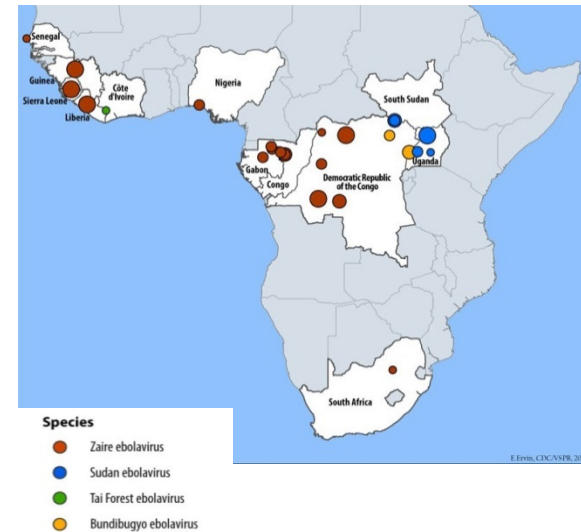
P. A. WEBB
F. A. MURPHY

*Virology Division, Center for Disease Control,
Atlanta, Georgia 30333, U.S.A.*



Ebola Virus

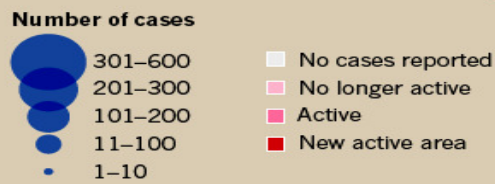
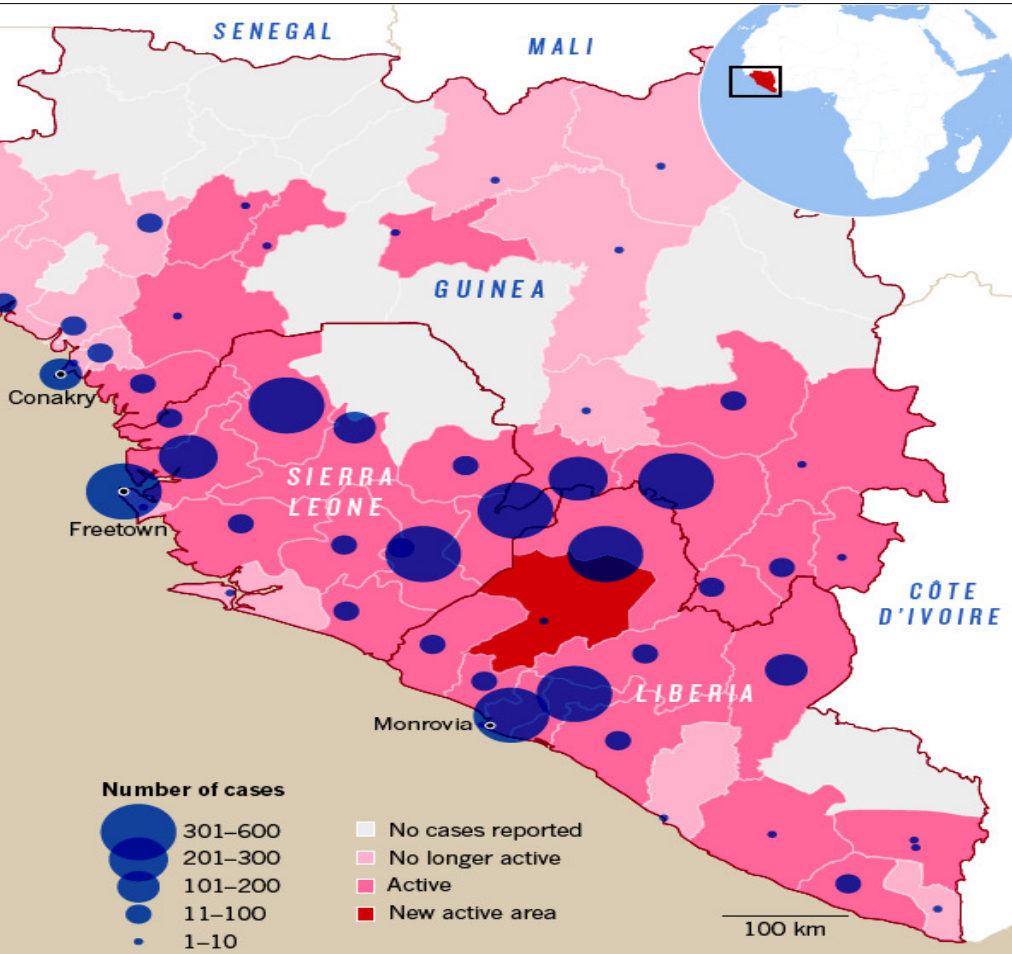
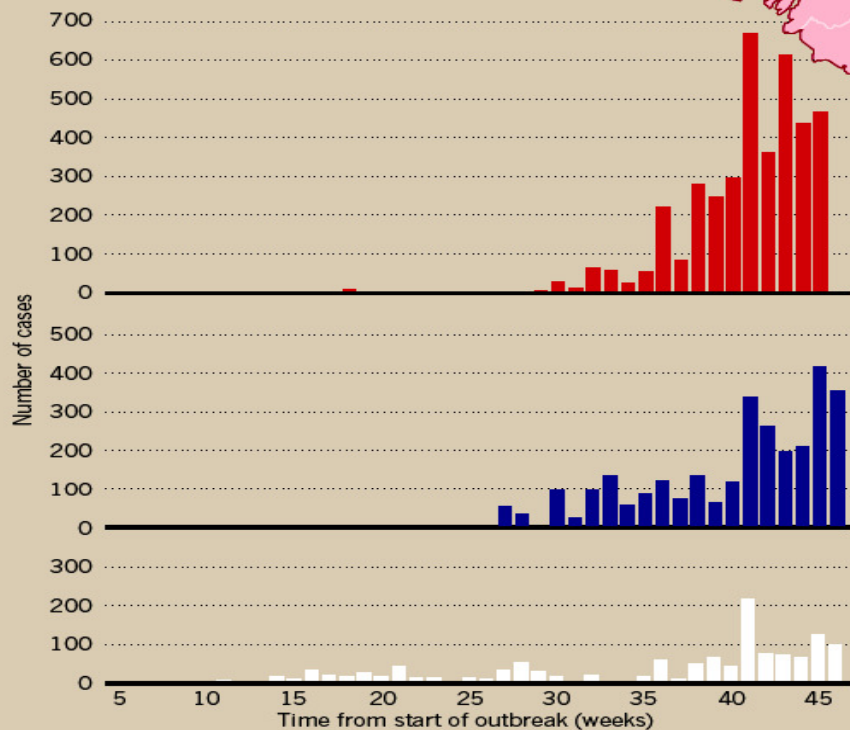
- Prototype Viral Hemorrhagic Fever Pathogen
 - Filovirus: enveloped, non-segmented, negative-stranded RNA virus
 - Severe disease with high case fatality
 - Absence of specific treatment or vaccine
- > 20 previous Ebola and Marburg virus outbreaks
- 2014 West Africa Ebola outbreak caused by *Zaire ebolavirus* species (five known Ebola virus species)



A RISING TOLL

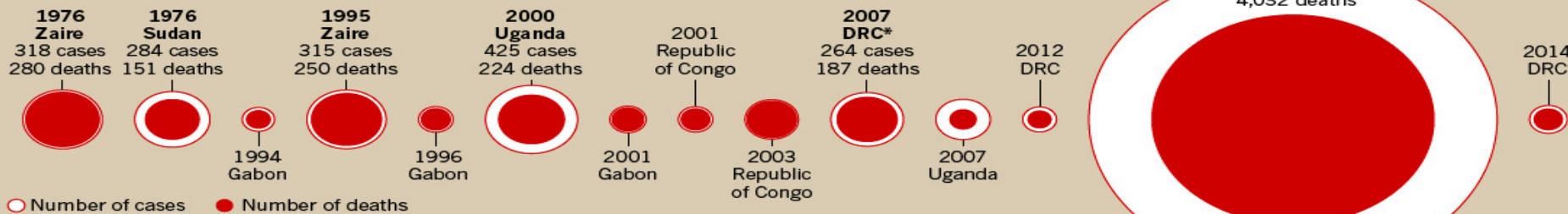
The number of Ebola cases continues to rise because control measures in the outbreak area are insufficient. But it could drop quickly if the international community and affected countries manage to implement an effective response.

■ Liberia ■ Sierra Leone ■ Guinea



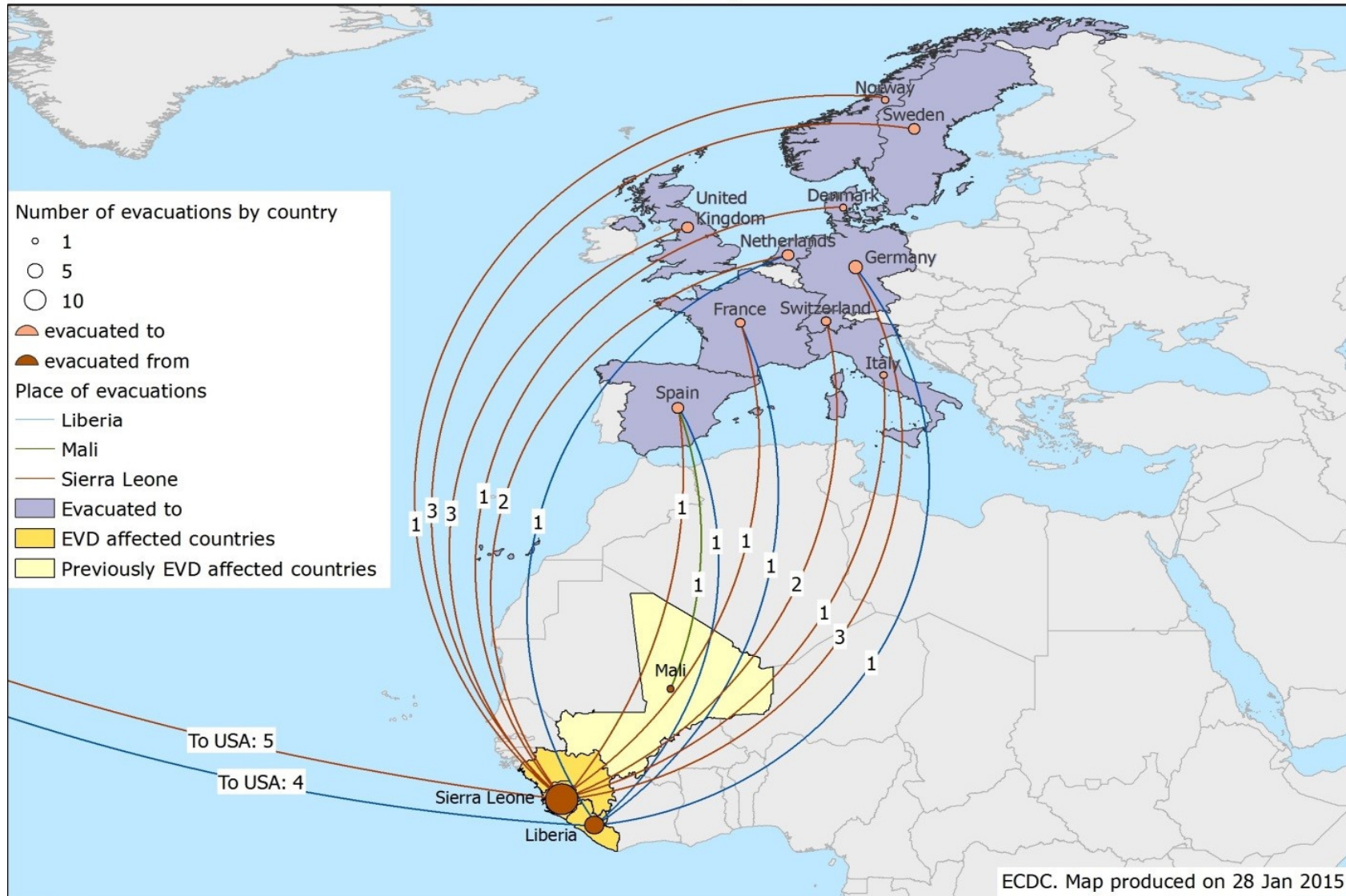
UNPRECEDENTED SIZE

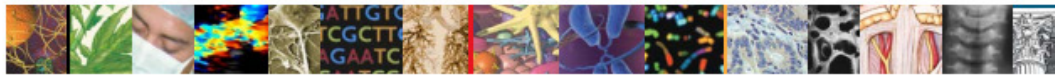
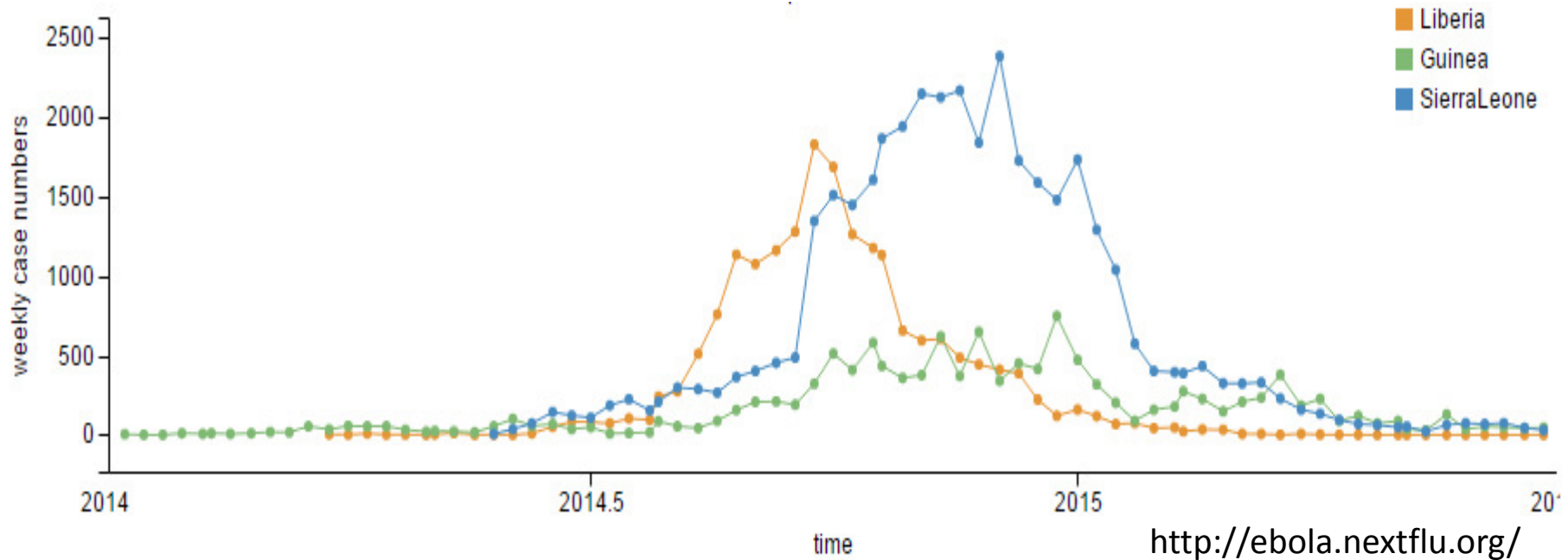
The current outbreak dwarfs the largest historical outbreaks in Africa, which were rural and relatively easy to control. Ebola has now spread to dense urban areas, where control is harder to achieve.



- As of Jan 28, at least 38 cases outside of Africa (Europe and US)
- Mostly repatriated

Medical evacuations and repatriations from EVD-affected and previously affected countries, as of 28 January 2015





The NEW ENGLAND JOURNAL of MEDICINE

Perspective

APRIL 9, 2015

The Next Epidemic — Lessons from Ebola

Bill Gates

Trans R Soc Trop Med Hyg
doi:10.1093/trstmh/trv053



The West African Ebola outbreak: finishing the job, preparing for future

Clare Parsons^{a,*} and Umar Naeem Ahmad^b

COMMENTARY

EVD Summary

- The 2014 Ebola outbreak in West Africa is the largest in history and has affected multiple countries.
- Think Ebola: U.S. healthcare providers should be aware of clinical presentation and risk factors for EVD.
- Human-to-human transmission by direct contact
 - No human-to-human transmission via inhalation (aerosols)
 - No transmission before symptom onset
- Early case identification, isolation, treatment and effective infection control are essential to prevent Ebola transmission.



What next?

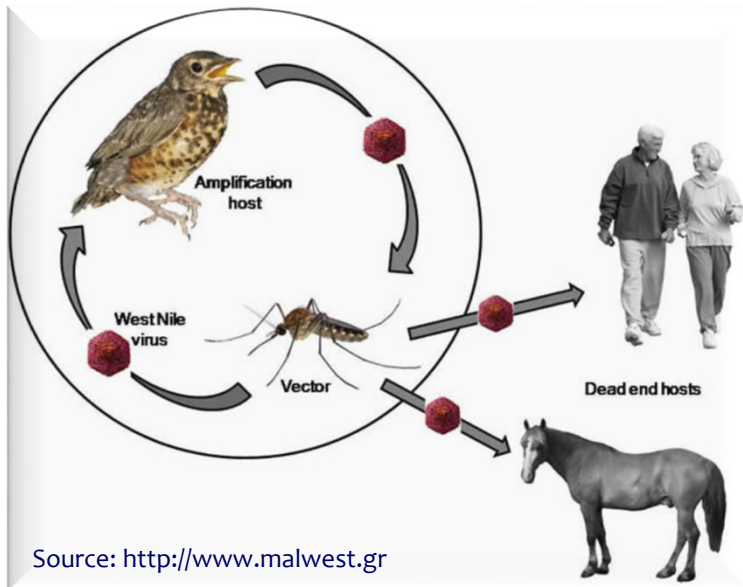
Imagine. Finding disease-causing mutations in samples large enough to be statistically significant. Imagine. A next-generation sequencing workflow that actually flows. Imagine. Taking the restraints off of your research and wielding the full power of sequencing—affordably. With SureSelect Target Enrichment System, you no longer have to imagine what's next.

SureSelect Target Enrichment System

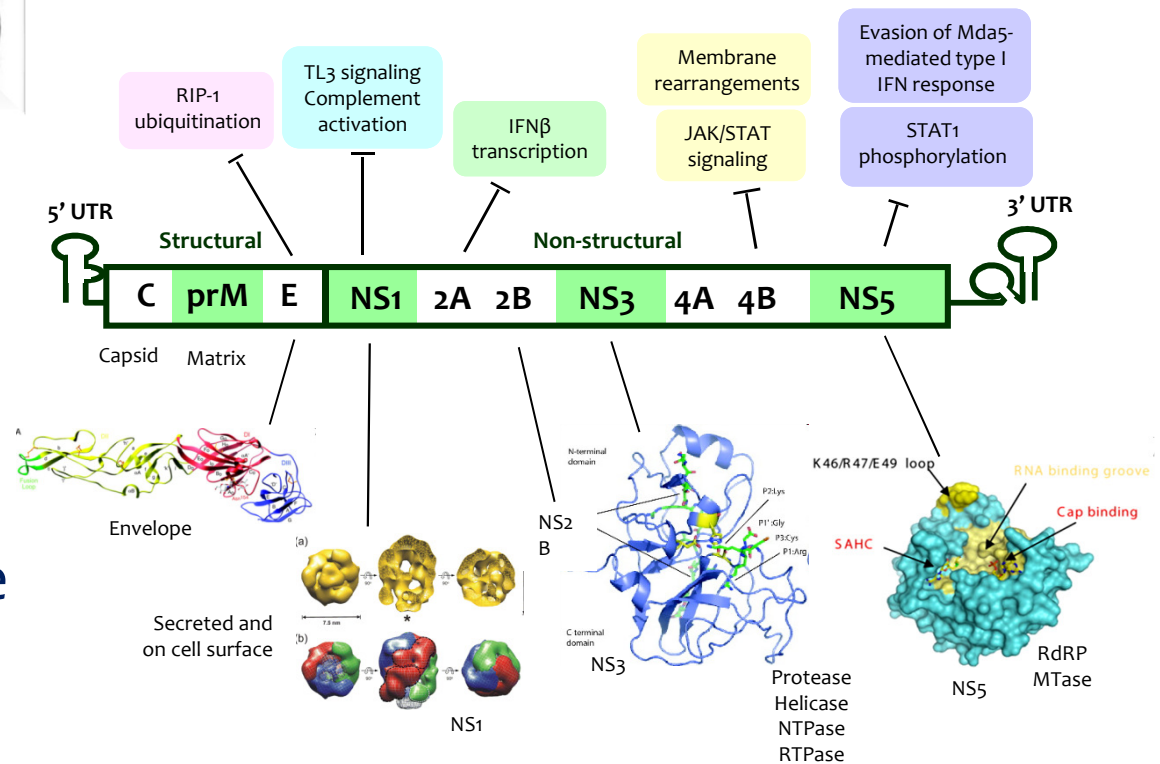
WE MAKE IT. *You make it happen.*

Visit us at opengenomics.com

West Nile virus

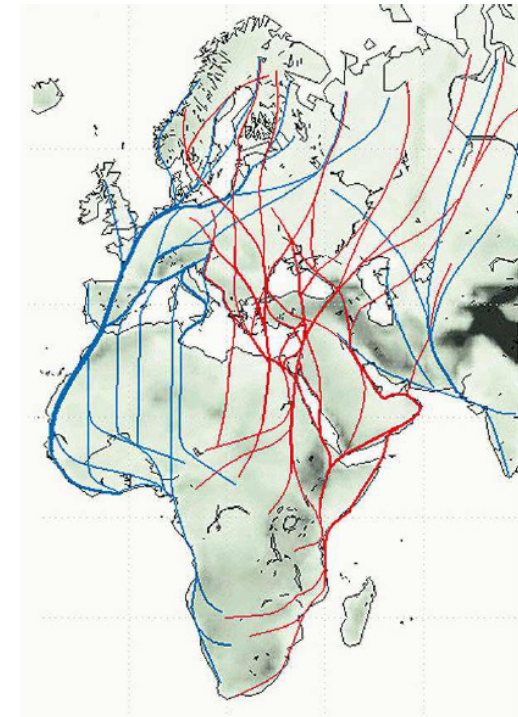
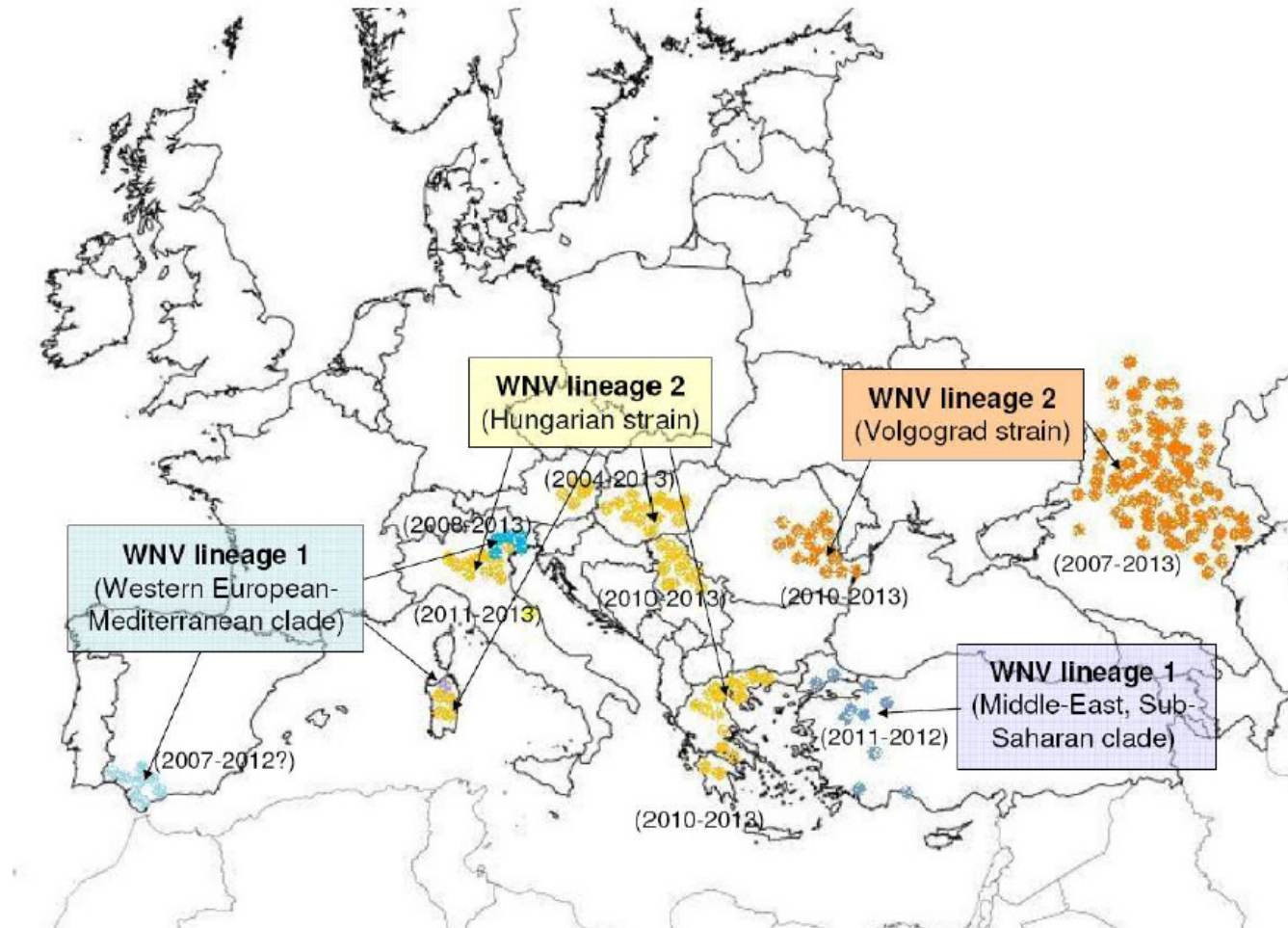


Life cycle and transmission

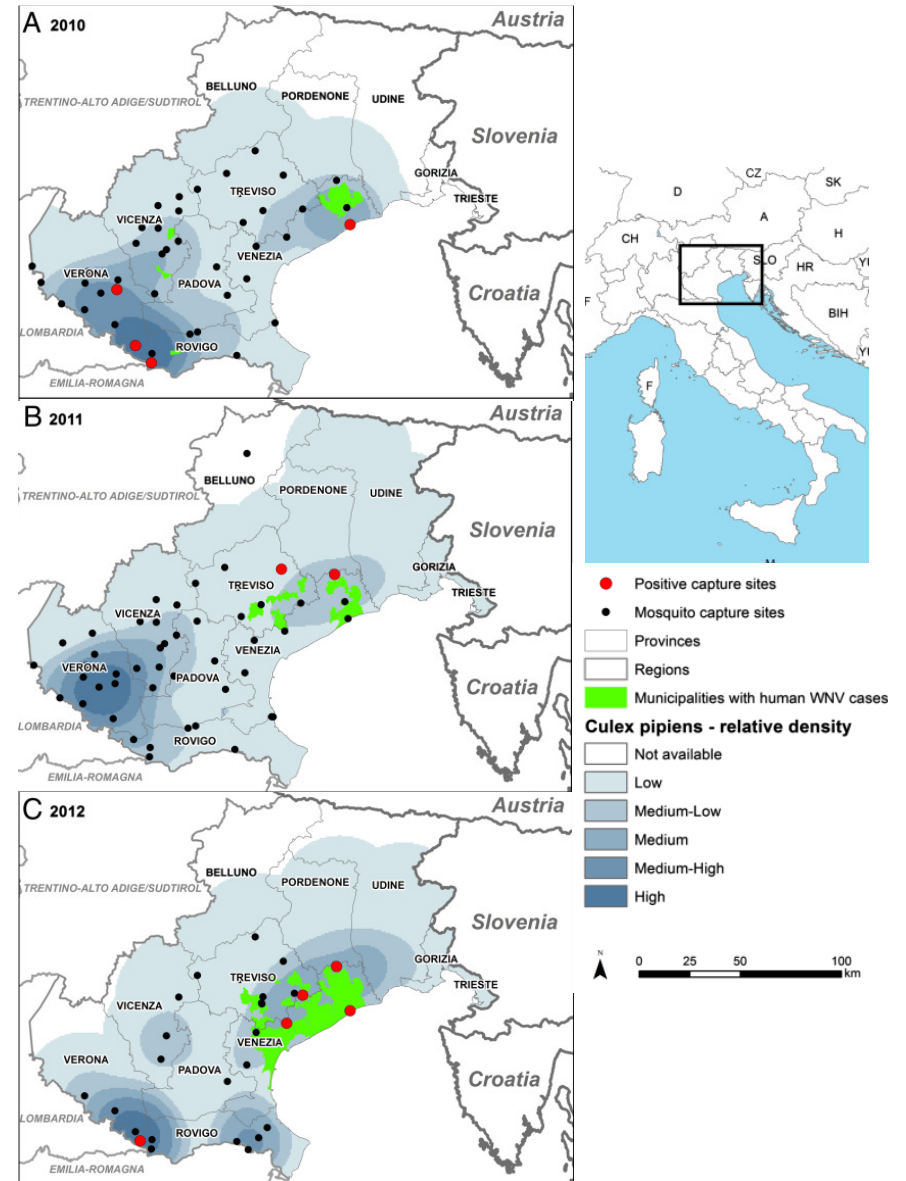
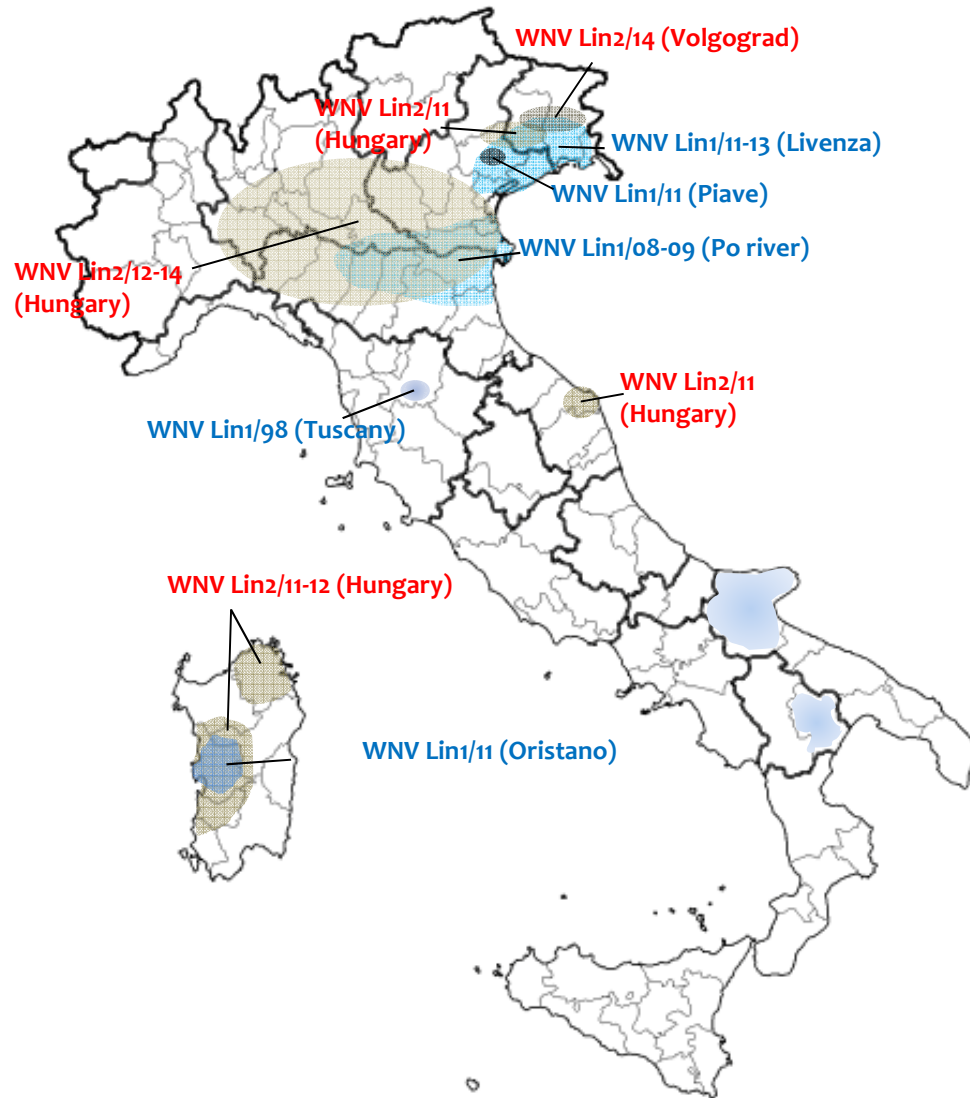


WNV genome

WNV lineage 1 and WNV lineage 2 strains circulating in European and neighboring countries belong to four phylogenetic clusters geographically related to bird migratory routes

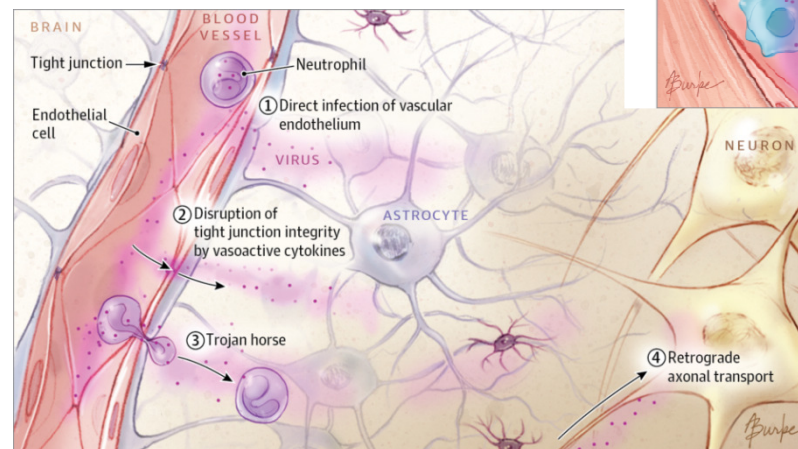
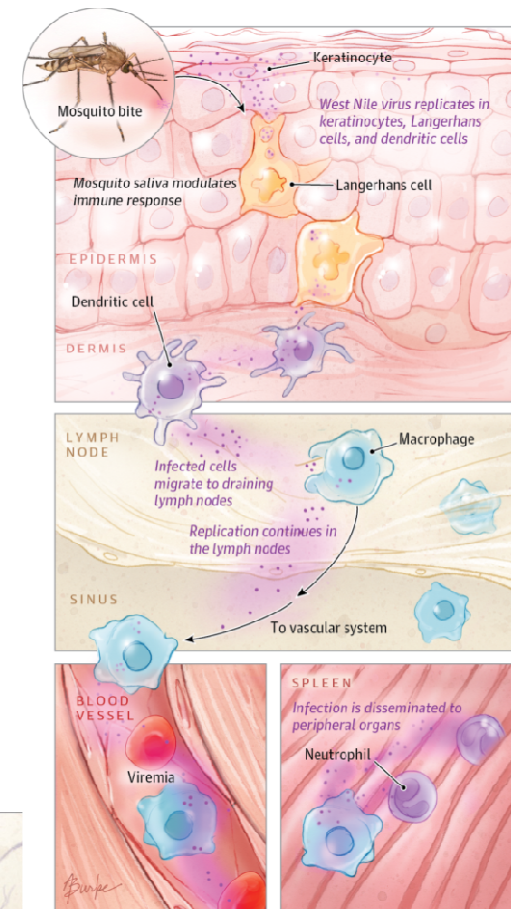


The complex epidemiological scenario of WNV in Italy



Clinical presentation of WNV infection

- **West Nile neuro-invasive disease (<1%)**
 - Encephalitis
 - Aseptic meningitis
 - Acute flaccid paralysis
(Elderly and immunocompromized individuals are the most affected).
- **West Nile fever (~20%)**
 - “benign” influenza-like illness
- **Asymptomatic (~80%)**



Petersen et al.,
JAMA 2013

Cronaca → nozionismo/
Metodologia clinica → formazione



Non-Neuroinvasive Disease

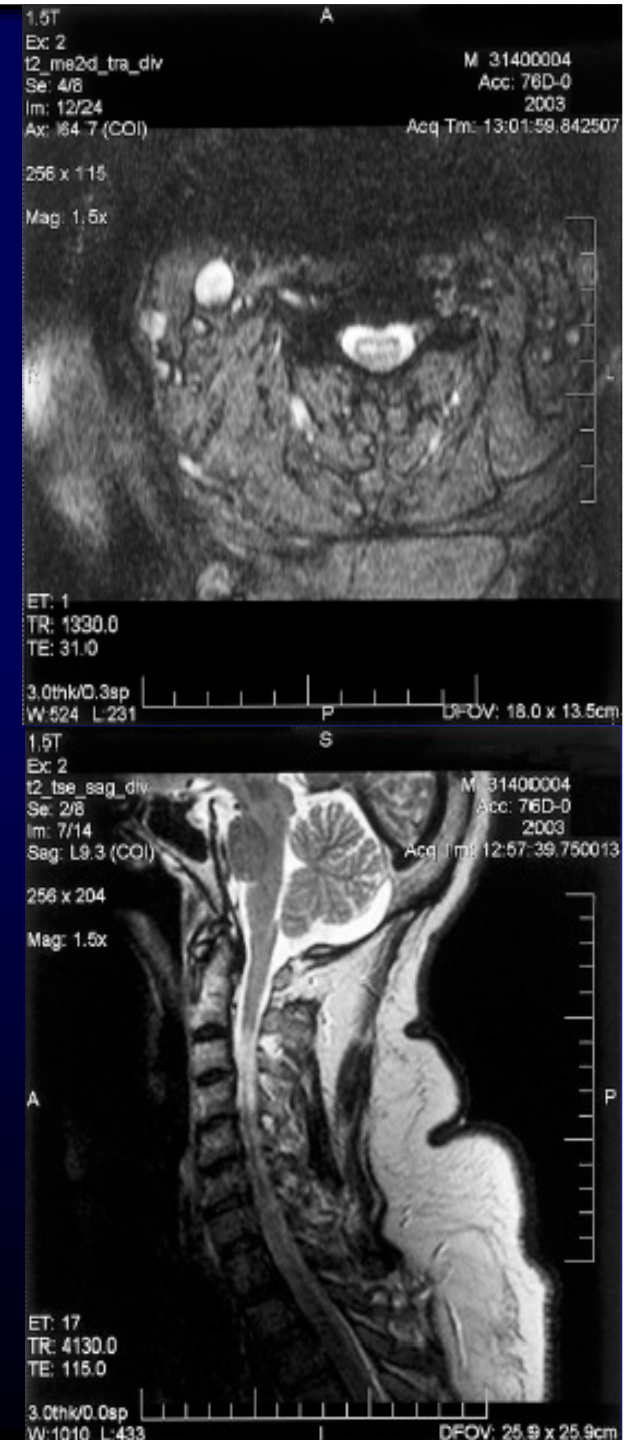
- Mild WNV infection
- Incubation:
2-14 days from mosquito bite
- Febrile illness of sudden onset
- Symptoms - generally last 3-6 days:
 - Malaise/weakness/fatigue
 - Nausea/vomiting/anorexia/diarrhea
 - Eye pain, conjunctivitis
 - Headache, sore throat, myalgia
 - Rash*
 - Lymphadenopathy

*Erythematous maculopapules
(neck, trunk, arms and legs)
19%-57% of cases



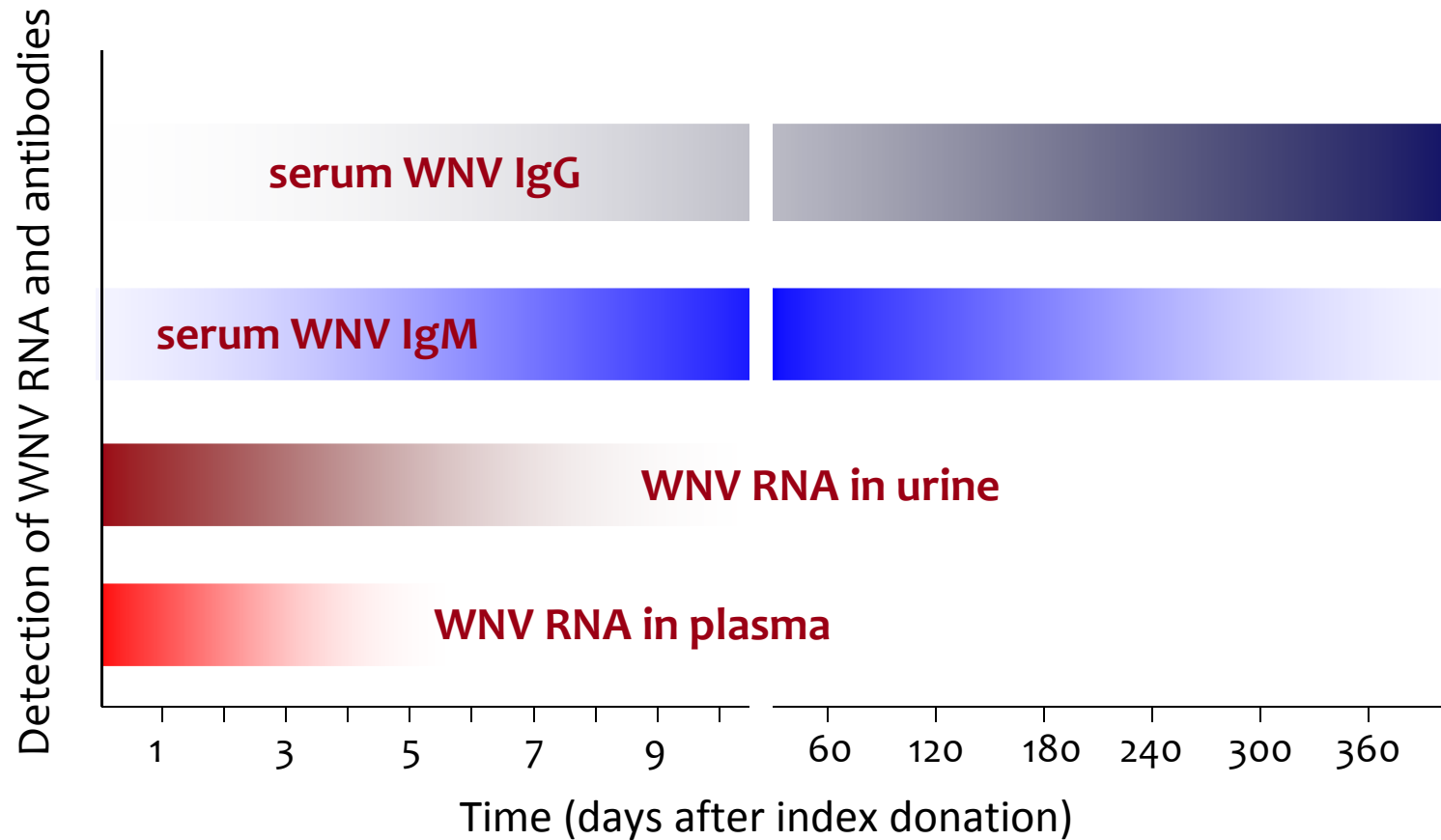
WNV Myelitis

- Acute Flaccid Paralysis (AFP)
- Focal weakness in 50% w/CNS infection
- Progresses to paralysis in \approx 35%
 - Rapidly progressive (2-8 d from onset)
 - LMN pattern
 - Typically proximal musculature
 - Sphincteric dysfunction possible
 - Quadriparesis, paraparesis, or monoplegia
 - Poliovirus \neq encephalopathic
 - GBS \neq fever, CSF pleocytosis, rash, back pain
- Respiratory muscle weakness can require prolonged mechanical ventilation
- EMG:
 - Anterior horn cells process (axonal neuropathy)
 - Not demyelination



Kinetics of WNV RNA and antibody response after primary infection with WNV

WNV RNA and antibody response in viremic blood donors during follow-up



Laboratory diagnosis of WNV infection

Table 2. Results of laboratory tests in patients with West Nile virus infection diagnosed in northeastern Italy during the 2012–2013 seasons.

Test	No. positive/no. tested (% positive)		
	<i>WNND</i> (<i>n</i> = 39)	<i>WNF</i> (<i>n</i> = 35)	<i>Blood donors</i> (<i>n</i> = 21)
Time to test (mean ± SD)	10 ± 9 days	15 ± 7 days	4 ± 2 days
WNV RNA in plasma [†]	11/33 (33.3)	4/31 (12.9)	12/21 (57.1)
WNV RNA in urine [‡]	14/26 (53.8)	13/31 (41.9)	5/21 (23.8)
WNV RNA in CSF [‡]	1/23 (4.3)	0/2 (0)	ND
WNV IgM–/IgG– in serum	0/39 (0)	2/35 (5.7)	4/21 (19.0)
WNV IgM+/IgG– in serum	10/39 (25.6)	5/35 (14.3)	6/21 (28.6)
WNV IgM+/IgG+ in serum	29/39 (74.4)	28/35 (80.0)	11/21 (52.4)
WNV IgM+ in CSF	25/25 (100)	0/2 (0)	ND

Barzon et al., *Expert Rev Anti Infect Ther* 2015

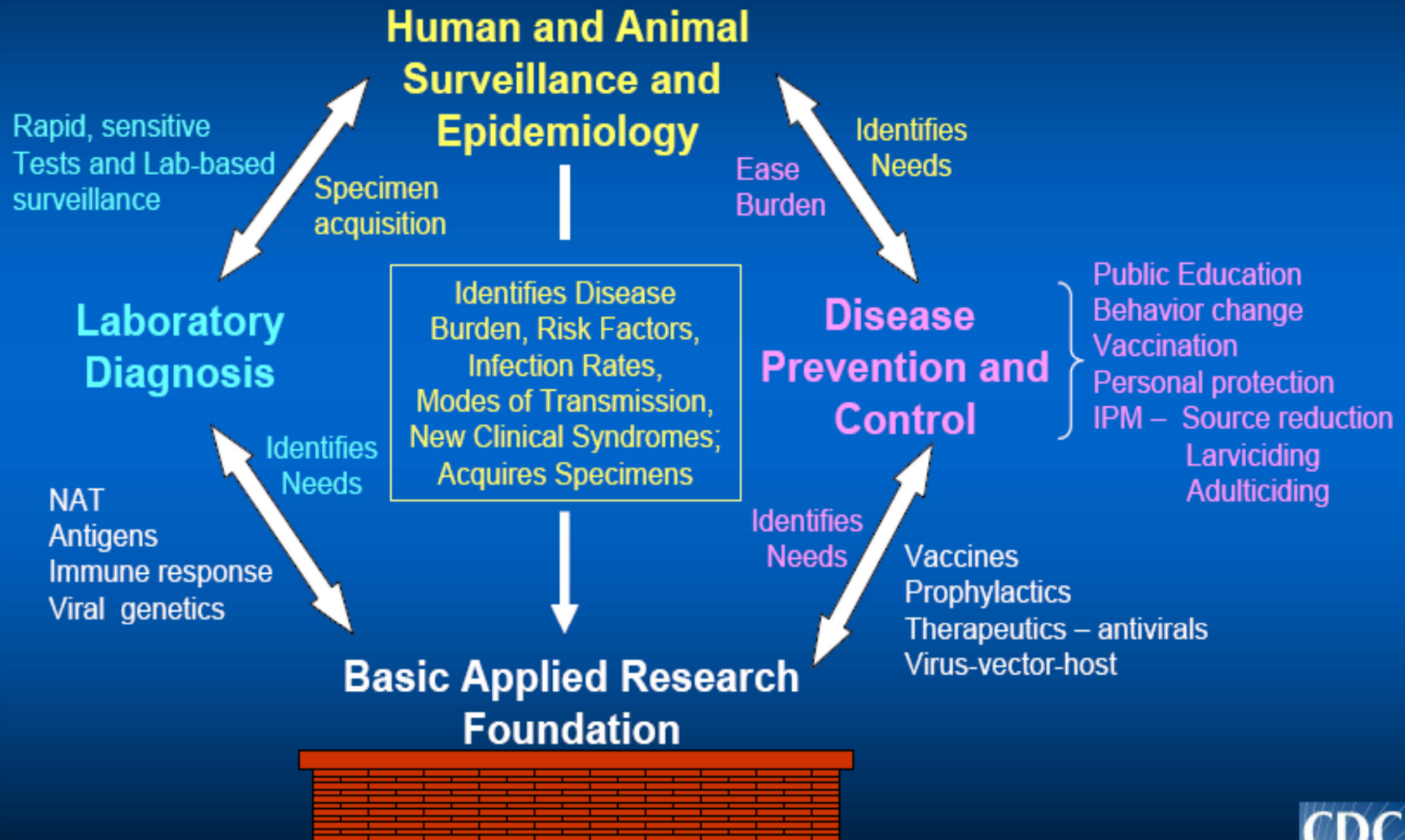
Recommendations on the use of laboratory tests for the diagnosis of WNV infection

Test	Serum	Plasma or whole blood	Urine	CSF	Notes
IgM EIA/IFA	+			+	If IgM+/IgG–, repeat testing in a serum sample collected after 2 weeks to demonstrate seroconversion
IgG EIA/IFA	+				If IgM+/IgG+, repeat testing in a serum sample collected after 2 weeks to demonstrate a fourfold increase of antibody titer
Real-time RT-PCR		+	+	+	If positive, the case is confirmed. However, confirmation by another test is recommended to exclude false-positive results
Pan-flavivirus RT-PCR		+	+	+	Recommended in WNV IgM+ and real-time RT-PCR negative
WNV isolation in cell culture	+		+		Recommended if WNV RNA is detected in plasma or urine (note that WNV antibodies in serum neutralize virus infectivity)
Neutralization test	+				Required to confirm IgM- and IgG-positive results
IgG avidity	+				Suggested if IgM+/IgG+ to identify recent infections in areas where WNV is endemic

RT-PCR: Reverse transcription-polymerase chain reaction; WNV: West Nile virus.

Barzon et al., Expert Rev Anti Infect Ther 2015

Vector-borne Viral Disease - An Integrated Approach



Are physicians ready to hit the EID?

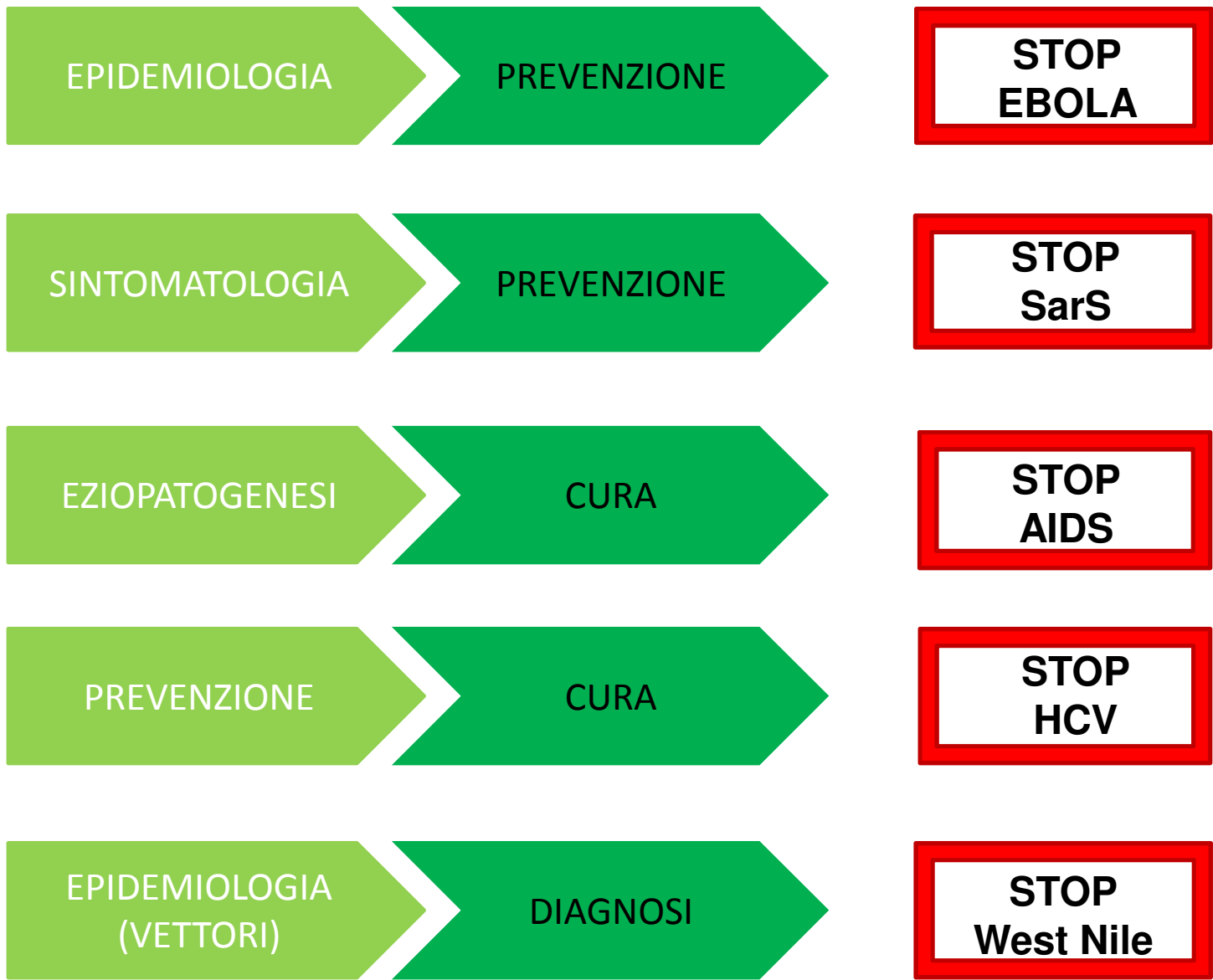
Some features that should be carefully kept in mind:

- Clinical presentation of emerging diseases (key-symptoms)
 - Geographical provenience of patient
 - Outbreak currently occurring worldwide
-

AIDS - a new disease fought with an integrated approach: main concerns

- extensive spread before noticed
 - good outbreak investigation
 - multiple methods of spread
 - quickly discovered how to prevent
 - quickly discovered good diagnostic test
 - no vaccine
 - short wait of specific drugs
-

but AIDS is still a global disaster



Conclusioni (1)

- La comparsa di nuove infezioni o il cambiamento della ricettività dell'ospite, nel corso degli anni, può cambiare notevolmente la priorità da dare all'apprendimento di una singola malattia infettiva.
- Ciò che, quasi sempre, accomuna le diverse infezioni è il metodo con il quale va affrontato l'algoritmo della diagnosi e cura di ciascuna.

Conclusioni (2)

- La particolare importanza dell'anamnesi (tempo, luogo e modalità di esposizione all'agente eziologico e ai suoi vettori), la relativa facilità di conoscerne la causa a differenza di altre malattie d'organo, le caratteristiche della risposta immune individuale, la peculiarità di alcune manifestazioni cliniche (malattie esantematiche) e la possibilità di arrivare nella maggioranza dei casi a una rapida guarigione, con o senza l'aiuto di antimicrobici, fanno della malattia infettiva un modello didattico lineare di metodologia clinica.



[Ospedale San Raffaele - Dipartimento di Malattie Infettive](#)



Modena, 1 ottobre 2015
Convegno di Medicina Interna e Medicina respiratoria



Breaking News nelle Malattie Infettive

Prof. Adriano Lazzarin
Scuola di Specializzazione
in Malattie Infettive
Università Vita-Salute San Raffaele
Milano