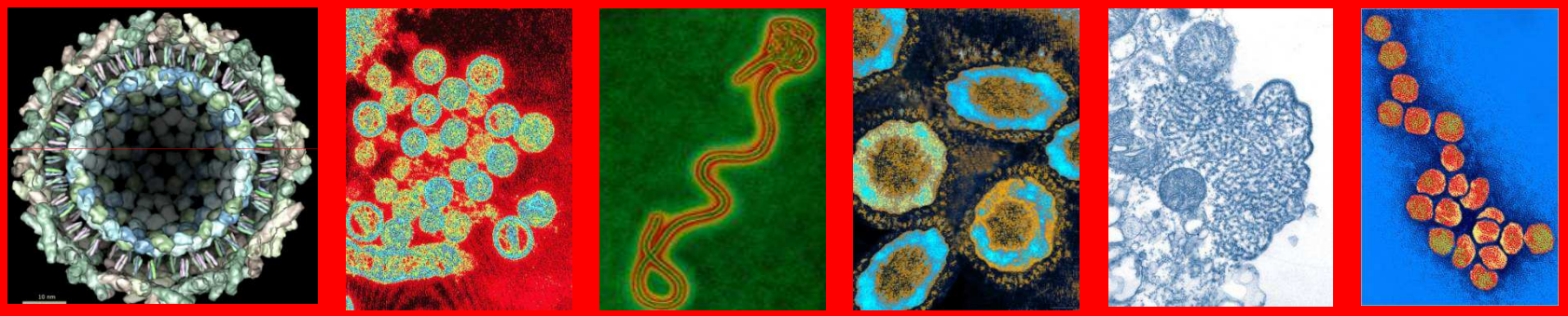
Aspetti virologici e clinici delle antropozoonosi emergenti in Europa



Giustino Parruti

UOC Malattie Infettive, AUSL Pescara

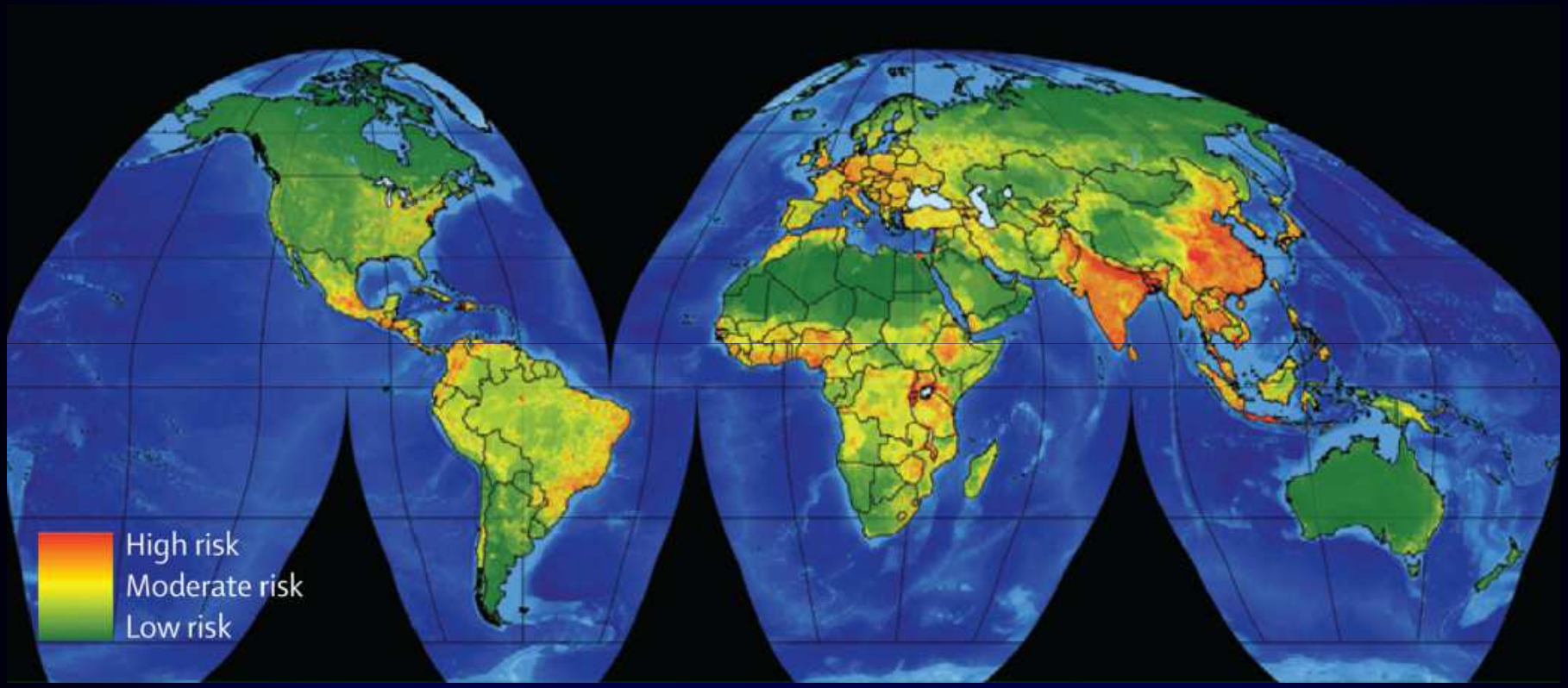
Pescara, 31 gennaio 2015

Definizione di infezione emergente

- 'Nuova' infezione a comparsa improvvisa, causata da un patogeno non precedentemente implicato in infezioni umane
- Aumento 'repentino' di incidenza (e/o virulenza) di un'infezione 'nota'
- Variazioni nella distribuzione geografica di un'infezione 'nota'
- Diffusione epidemica di ceppi resistenti di nuova comparsa

Global hotspots for emerging infectious diseases that originate in wildlife

Aree a rischio di emergenza

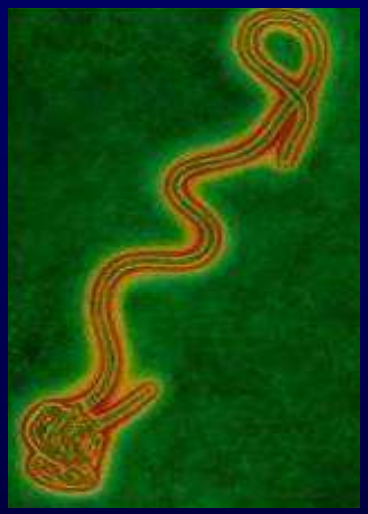


Global hotspots for emerging infectious diseases that originate in wildlife

Ebolavirus

- Il genere Ebolavirus comprende 5 specie distinte:

  - Ebola* virus (EBOV)
  - Sudan virus (SUDV)
  - Reston virus (RESTV)
  - Taï Forest virus (TAFV)
  - Bundibugyo virus (BDBV)



- La differenza interspecie varia tra il 37% e il 41% a livello nucleotidico e dal 34% al 43% a livello aminoacidico

* precedentemente denominato Ebola Zaire

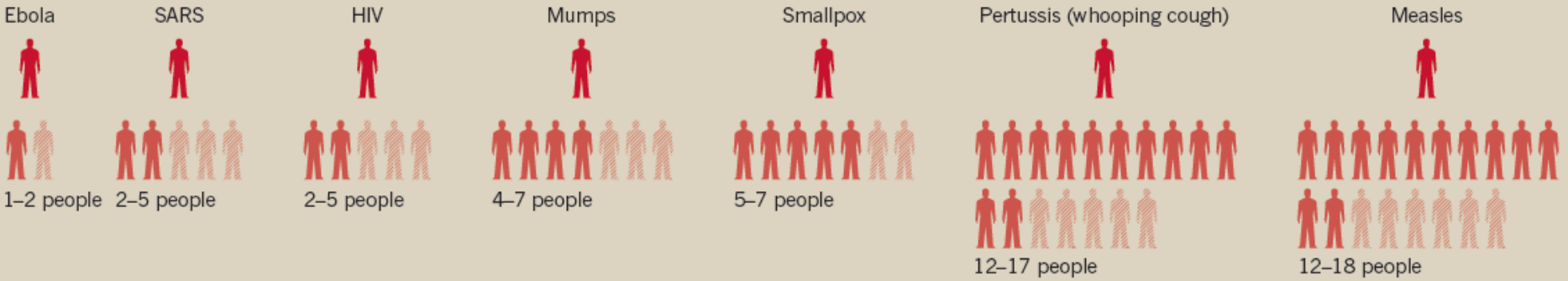
Table. **Cases of Ebola Hemorrhagic Fever in Africa, 1976 to 2014***

Year	Country	Town	Cases, *n*	Deaths, *n*	Species
1976	Democratic Republic of the Congo	Yambuku	318	280	EBOV
1976	South Sudan	Nzara	284	151	SUDV
1977	Democratic Republic of the Congo	Tandala	1	1	EBOV
1979	South Sudan	Nzara	34	22	SUDV
1994	Gabon	Mekouka	52	31	EBOV
1994	Ivory Coast	Tai Forest	1	0	TAFV
1995	Democratic Republic of the Congo	Kikwit	315	250	EBOV
1996	Gabon	Mayibout	37	21	EBOV
1996	Gabon	Booué	60	45	EBOV
1996	South Africa	Johannesburg	2	1	EBOV
2000	Uganda	Gulu	425	224	EBOV
2001	Gabon	Libreville	65	53	EBOV
2001	Republic of the Congo	Not specified	57	43	EBOV
2002	Republic of the Congo	Mbomo	143	128	EBOV
2003	Republic of the Congo	Mbomo	35	29	EBOV
2004	South Sudan	Yambio	17	7	EBOV
2007	Democratic Republic of the Congo	Luebo	264	187	EBOV
2007	Uganda	Bundibugyo	149	37	BDBV
2008	Democratic Republic of the Congo	Luebo	32	15	EBOV
2011	Uganda	Luwero District	1	1	SUDV
2012	Uganda	Kibaale District	11†	4†	SUDV
2012	Democratic Republic of the Congo	Isiro Health Zone	36†	13†	BDBV
2012	Uganda	Luwero District	6†	3†	SUDV

BDBV = Bundibugyo virus; EBOV = Ebola virus; SUDV = Sudan virus; TAFV = Tai Forest virus.
* Adapted from www.cdc.gov/vhf/ebola/resources/distribution-map.html.
† Laboratory-confirmed cases only.

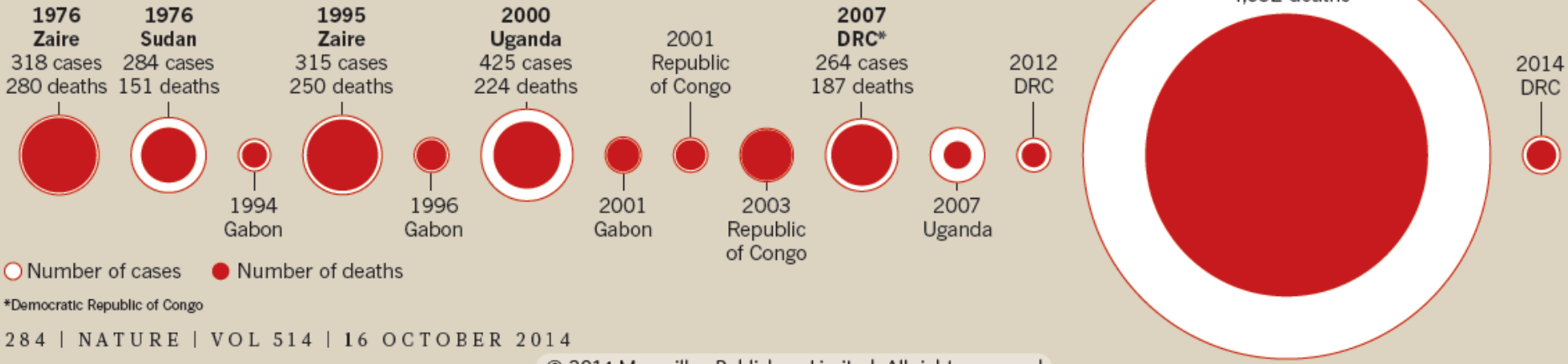
TRANSMITTING DISEASE

Ebola is spread by contact with an infected person's bodily fluids, but is less contagious than many common diseases, such as mumps and measles. In the current outbreak, each person with Ebola will infect 1–2 other people.



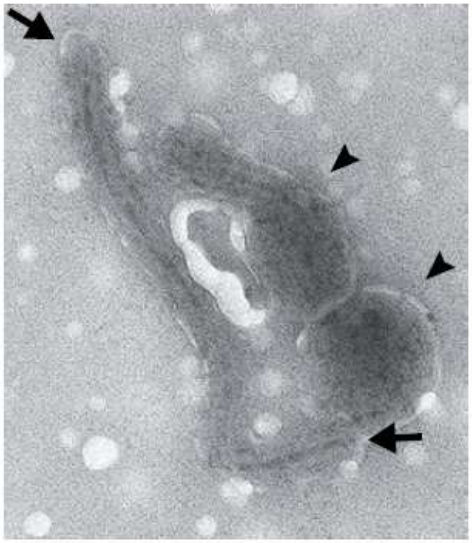
UNPRECEDENTED SIZE

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.



*Democratic Republic of Congo

Perché così tanti casi di EVD?



Meliandou Village, Guéckédou

9 Deaths from Dec. 2, 2013, to Feb. 8, 2014
2 Deaths on March 26, 2014

First recorded cases of the outbreak

(S1) Child, 2 yr of age
Fever, black stool, vomiting
Onset Dec. 2, 2013; died Dec. 6, 2013

(S2) Sister of S1, 3 yr of age
Fever, black diarrhea, vomiting
Onset Dec. 25, 2013; died Dec. 29, 2013

(S3) Mother of S1 and S2
Bleeding
Died Dec. 13, 2013

(S4) Grandmother of S1 and S2
Fever, diarrhea, vomiting
Died Jan. 1, 2014

(S5) Nurse
Fever, diarrhea, vomiting
Onset Jan. 29, 2014; died Feb. 2, 2014

(S6) Village midwife
Fever
Hospitalized in **Guéckédou** Jan. 25, 2014; died Feb. 2, 2014

Dandou Pombo Village, Guéckédou

6 Deaths from Feb. 11 to March 31, 2014

(S13) Family member of S6, took care of S6
Fever, hemorrhage
Onset Feb. 4, 2014; died Feb. 11, 2014

Dawa Village, Guéckédou

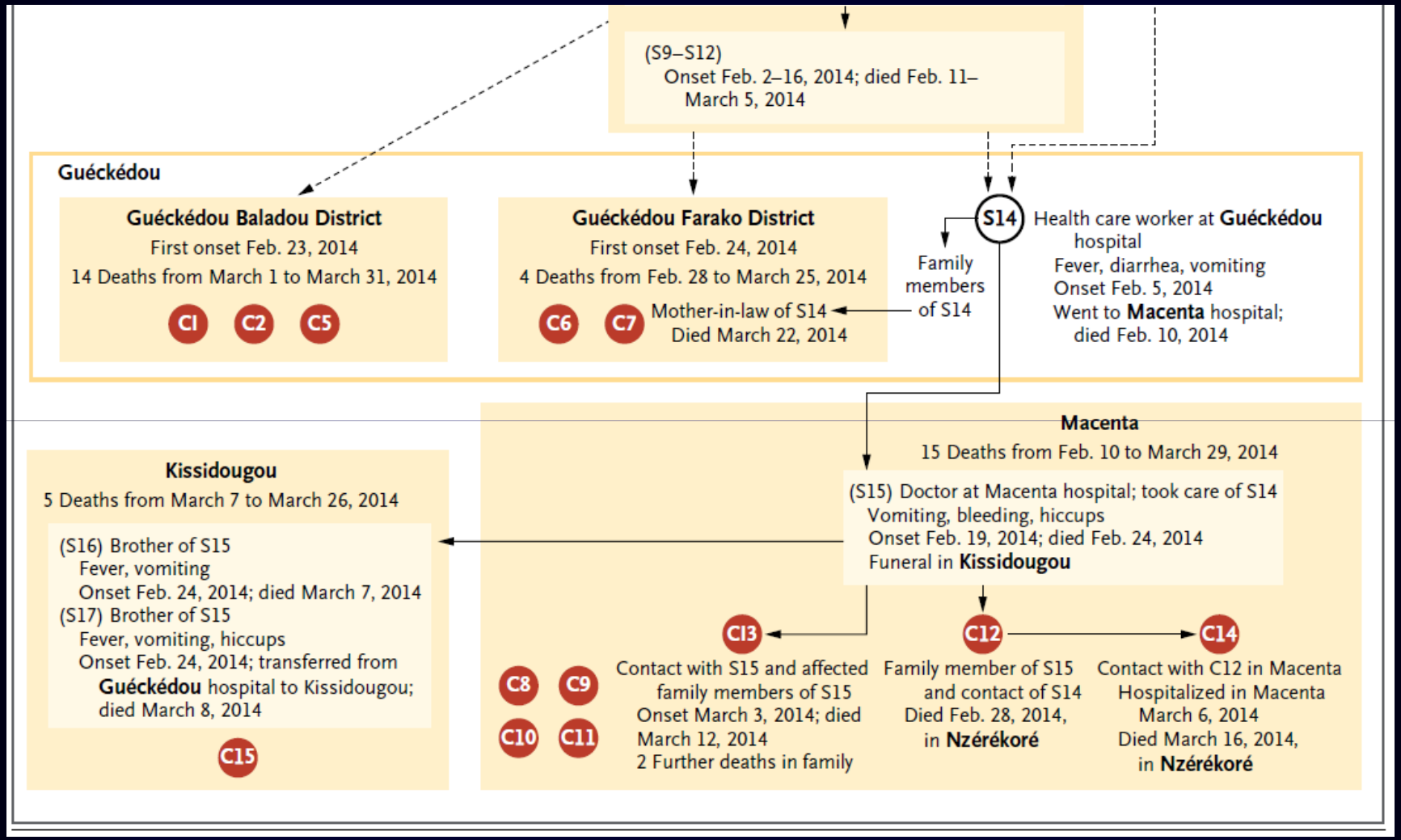
8 Deaths from Jan. 26 to March 27, 2014

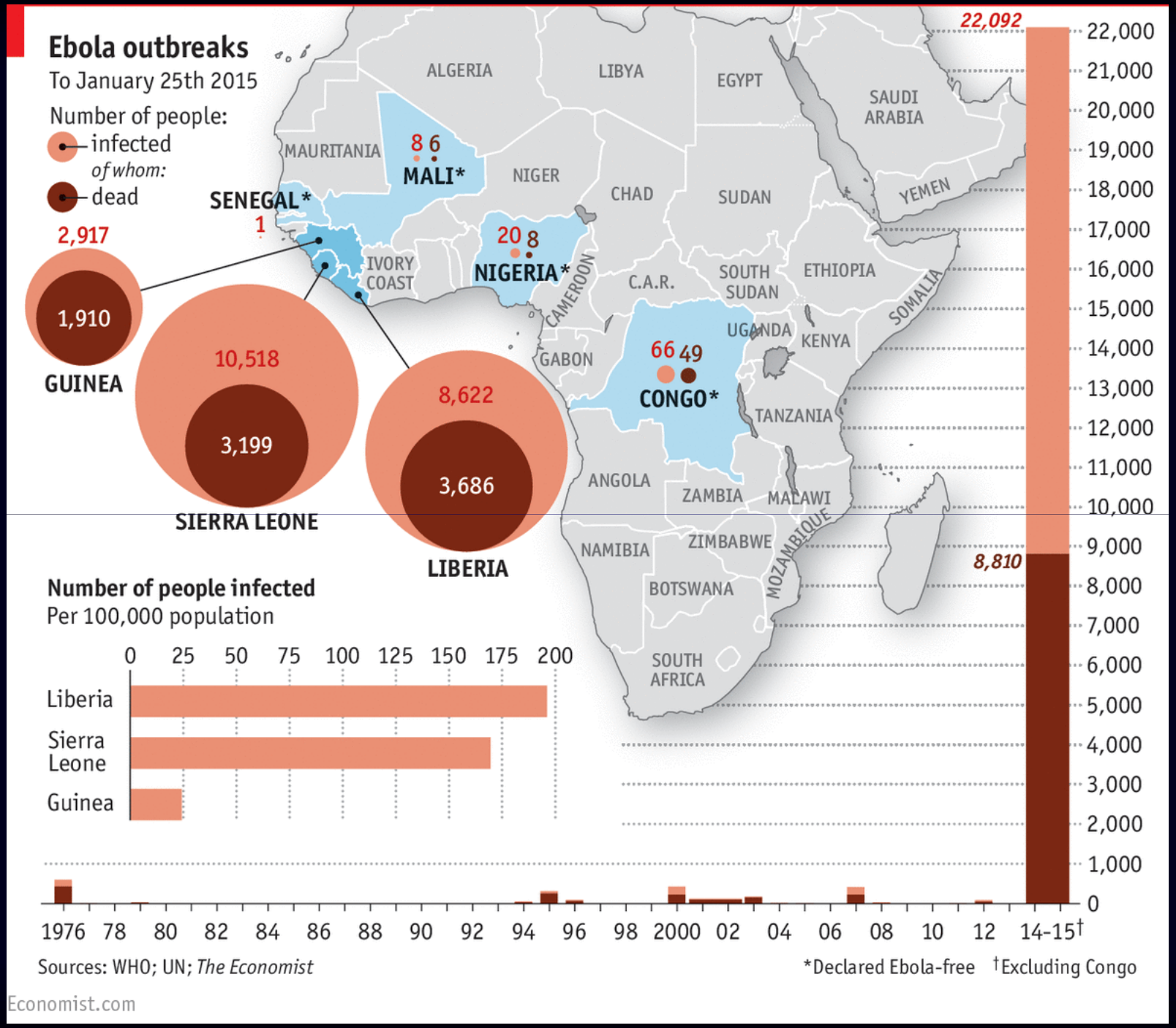
(S7) Sister of S4, attended funeral of S4
Fever, diarrhea, vomiting, hemorrhage
Onset Jan. 20, 2014; died Jan. 26, 2014

(S8) Attended funeral of S4
Fever, bleeding
Onset Jan. 25, 2014; died Jan. 30, 2014

Gbandou Village, Guéckédou

3 Deaths from March 9 to March 12, 2014


(S9–S12)
Onset Feb. 2–16, 2014; died Feb. 11–March 5, 2014
Guéckédou
Guéckédou Baladou District
First onset Feb. 23, 2014
14 Deaths from March 1 to March 31, 2014
C1
C2
C5
Guéckédou Farako District
First onset Feb. 24, 2014
4 Deaths from Feb. 28 to March 25, 2014
C6
C7
Mother-in-law of S14
Died March 22, 2014
S14
Health care worker at Guéckédou hospital
Fever, diarrhea, vomiting
Onset Feb. 5, 2014
Went to Macenta hospital; died Feb. 10, 2014
Family members of S14
Macenta
15 Deaths from Feb. 10 to March 29, 2014
(S15) Doctor at Macenta hospital; took care of S14
Vomiting, bleeding, hiccups
Onset Feb. 19, 2014; died Feb. 24, 2014
Funeral in Kissidougou
Kissidougou
5 Deaths from March 7 to March 26, 2014
(S16) Brother of S15
Fever, vomiting
Onset Feb. 24, 2014; died March 7, 2014
(S17) Brother of S15
Fever, vomiting, hiccups
Onset Feb. 24, 2014; transferred from Guéckédou hospital to Kissidougou; died March 8, 2014
C15
C13
Contact with S15 and affected family members of S15
Onset March 3, 2014; died March 12, 2014
2 Further deaths in family
C8
C9
C10
C11
C12
Family member of S15 and contact of S14
Died Feb. 28, 2014, in Nzérékoré
C14
Contact with C12 in Macenta
Hospitalized in Macenta March 6, 2014
Died March 16, 2014, in Nzérékoré


Ebola outbreaks
To January 25th 2015
Number of people:
infected
of whom:
dead
2,917
1,910
GUINEA
10,518
3,199
SIERRA LEONE
8,622
3,686
LIBERIA
SENEGAL*
1
8 6
MALI*
20 8
NIGERIA*
66 49
CONGO*
ALGERIA
LIBYA
EGYPT
SAUDI ARABIA
MAURITANIA
NIGER
CHAD
SUDAN
YEMEN
IVORY COAST
CAMEROON
C.A.R.
SOUTH SUDAN
ETHIOPIA
SOMALIA
UGANDA
KENYA
GABON
TANZANIA
ANGOLA
ZAMBIA
MALAWI
NAMIBIA
ZIMBABWE
MOZAMBIQUE
BOTSWANA
SOUTH AFRICA
Number of people infected
Per 100,000 population
0 25 50 75 100 125 150 175 200
Liberia
Sierra Leone
Guinea
22,092
8,810
22,000
21,000
20,000
19,000
18,000
17,000
16,000
15,000
14,000
13,000
12,000
11,000
10,000
9,000
8,000
7,000
6,000
5,000
4,000
3,000
2,000
1,000
0
1976 78 80 82 84 86 88 90 92 94 96 98 2000 02 04 06 08 10 12 14-15†
Sources: WHO; UN; The Economist
*Declared Ebola-free †Excluding Congo
Economist.com

The World Health Organization has drawn up a list of 15 countries that are most at risk of an outbreak of Ebola virus disease. The countries have land borders or strong trade and travel routes to the three most affected countries, Guinea, Liberia, and Sierra Leone, and health systems that are not strong enough to cope with a potential outbreak.

The 15 are Mali, Ivory Coast, Senegal, and Guinea-Bissau (the four countries bordering the three affected countries) and Benin, Cameroon, the Central African Republic, the Democratic Republic of Congo, Ghana, South Sudan, Nigeria, Mauritania, Togo, and Burkina Faso.

Perché così tanti casi di EVD?

- I paesi colpiti più popolosi di quelli colpiti in passato
- Il virus ha potuto rapidamente raggiungere le capitali
- Si tratta inoltre di paesi molto poveri, due su tre dei quali sono reduci da spaventose guerre civili
- L'area colpita per prima è stata oggetto di intensiva deforestazione
- Non è stato possibile tracciare fino a tre mesi fa validamente i contatti delle persone colpite
- I dati filogenetici per la prima volta mostrano che le epidemie in Sierra Leone e Liberia derivano da contatti interumani, senza l'interposizione di animali serbatoio o altri animali infetti

Ebola: towards an International Health Systems Fund

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September 4, 2014
http://dx.doi.org/10.1016/
S0140-6736(14)61345-3

See Editorial page 1321
See Comment page 1323

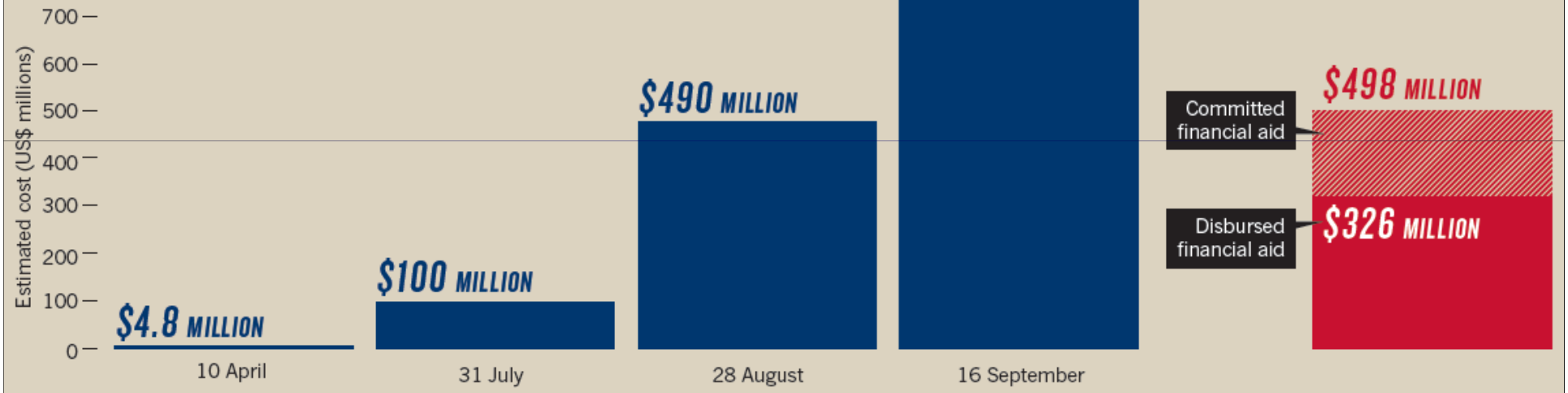
The international response to the current outbreak of Ebola virus in west Africa, which is projected to infect about 20 000 people with a case fatality rate of more than 50%,[1,2] has been fractured and delayed. The index case (a 2-year-old boy from Guinea) died in December, 2013, followed by confirmed Ebola clusters on March 22, 2014, which quickly spread to Liberia and then Sierra Leone. The disease jumped to Nigeria through air travel, and, recently, to Senegal. Yet WHO did not declare a Public Health Emergency of International Concern (PHEIC) until Aug 8, 2014, and only released an Ebola response roadmap on Aug 28—5 months after international spread.[2] WHO must now raise funds to implement the roadmap, which will further delay a robust international response. This tragedy could have been averted and, with more than 20 outbreaks of Ebola since 1976, the need for public health preparedness should have been foreseen.

Hospitals in affected countries have become amplification points for transmission, since they do not have rigorous infection control, personal protective equipment, and safe or sterile isolation facilities. Consequently, fearful patients have avoided hospitals, thus spreading Ebola infection in the community with individuals left untreated for myriad other health hazards, ranging from malaria and chronic disease to childbirth.[9,10] Community health workers similarly fear Ebola, often refusing to examine patients and collect blood and urine samples.

The health infrastructure needed to prevent an initial outbreak from burgeoning out of control—precisely what has happened—remains out of the reach of low-income countries. The affected states do not have adequate community, laboratory, public health, and clinical personnel; infection-control equipment, supplies, and

FINANCIAL AID

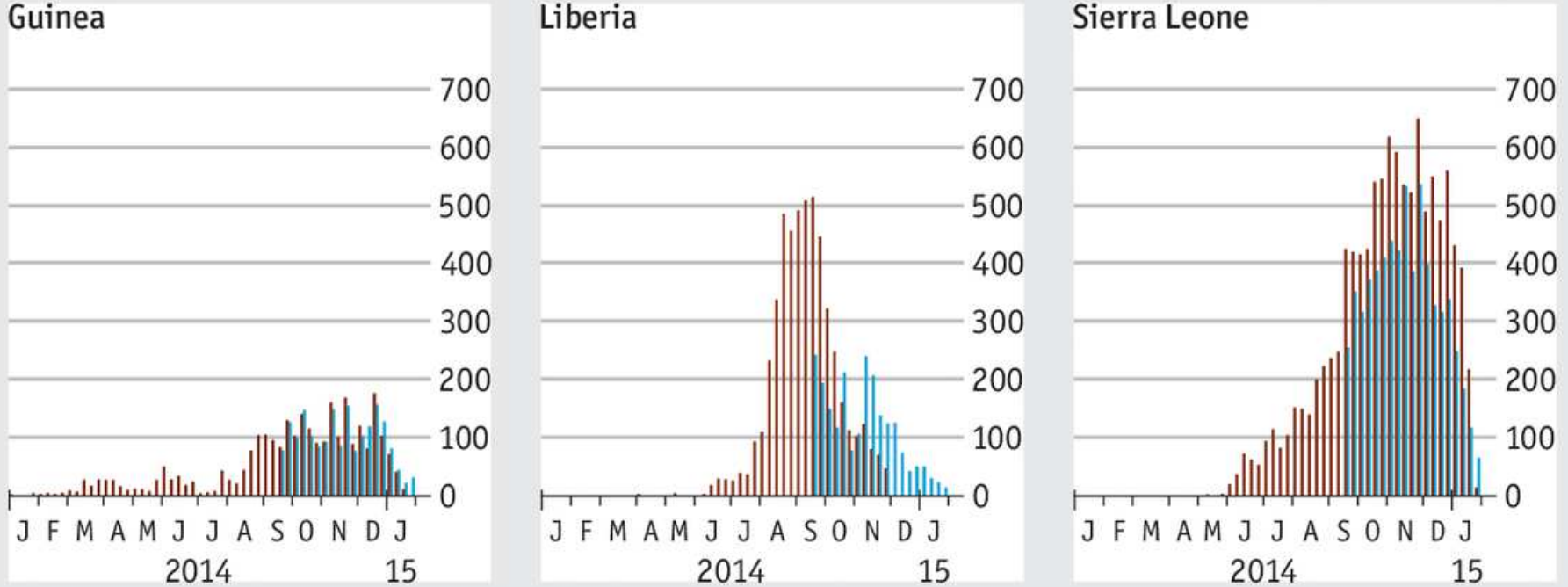
If outbreaks are allowed to grow, they become more difficult and costly to control. In April, the World Health Organization estimated that it would cost US$4.8 million to contain the Ebola outbreak, but by September that figure had ballooned to almost $1 billion. Experts say that the total cost of ending this outbreak is likely to be higher still.



New cases* of Ebola infection per week

To January 25th 2015

Patient database WHO Situation Report



Source: WHO

*Confirmed and probable

Economist.com

EBOLA
BY THE NUMBERS

The Ebola outbreak in West Africa continues to rage, with the number of people infected roughly doubling every 3–4 weeks. More than 8,000 people are thought to have contracted the disease, and almost half of those have died, according to the World Health Organization. Although these estimates are already staggering, the situation on the ground means that not all cases and deaths are being reported, so the true extent is likely to be much greater.

Outside of Africa, a health-care worker in Texas has become infected while treating a patient who was hospitalized in Dallas after travelling from Liberia and who has now died. And a nurse in Madrid has contracted the virus after caring for a missionary who had become infected while caring for patients in West Africa. Health-care workers remain one of the groups at highest risk of exposure: by 8 October, 416 had become infected and 233 had died.

The spread beyond the epicentre of Guinea, Liberia and Sierra Leone remains limited. Apart from the people in Dallas and Spain, only two other exported cases are known: one in Nigeria and one in Senegal. A man who travelled to Lagos from Liberia sparked a further 19 cases in Nigeria, but that outbreak was curtailed by the swift actions of the authorities in tracing and monitoring those who had contact with the infected man. Similar public-health measures stopped further cases in Senegal after an infected man travelled from Guinea to Dakar.

Within the epicentre, authorities have made some progress in slowing transmission — but the disease is resurgent in places where it had seemed under control, such as in Conakry, Guinea's capital.

Meanwhile, the estimated cost of fighting the disease is spiralling upward. UN secretary-general Ban Ki-moon warned on 9 October that "at least a 20-fold surge in assistance" was needed to confront the outbreak. But "things will get worse before they get better", he warned. Just how much worse will depend on the international community — which has been widely criticized for its belated response, and its slow translation of pledges into concrete action.

Seminar

Ebola haemorrhagic fever

Heinz Feldmann, Thomas W Geisbert

Ebola viruses are the causative agents of a severe form of viral haemorrhagic fever in man, designated Ebola haemorrhagic fever, and are endemic in regions of central Africa. The exception is the species Reston Ebola virus, which has not been associated with human disease and is found in the Philippines. Ebola virus constitutes an important local public health threat in Africa, with a worldwide effect through imported infections and through the fear of misuse for biological terrorism. Ebola virus is thought to also have a detrimental effect on the great ape population in Africa. Case-fatality rates of the African species in man are as high as 90%, with no prophylaxis or treatment available. Ebola virus infections are characterised by immune suppression and a systemic inflammatory response that causes impairment of the vascular, coagulation, and immune systems, leading to multiorgan failure and shock, and thus, in some ways, resembling septic shock.

Lancet 2011; 377: 849–62

Published Online November 16, 2010 DOI:10.1016/S0140-6736(10)60667-8

Laboratory of Virology, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Rocky Mountain Laboratories, Hamilton, MT, USA (H Feldmann MD); **Department of Medical Microbiology, University of Manitoba, Winnipeg, MB, Canada** (H Feldmann); **and Department of Microbiology and Immunology, University of Texas Medical Branch and**

Introduction

Ebola virus is regarded as the prototype pathogen of viral haemorrhagic fever, causing severe disease and high case-fatality rates.[1] This high fatality, combined with the absence of treatment and vaccination options, makes Ebola virus an important public health pathogen and biothreat pathogen of category A.[2] development of proper treatment methods and vaccines, although some vaccines have now shown promise in experimental studies.[11] This Seminar reviews the present knowledge about the epidemiology, ecology, disease manifestation, pathogenesis, and case management of Ebola haemorrhagic fever.

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Ebola — Underscoring the Global Disparities in Health Care Resources

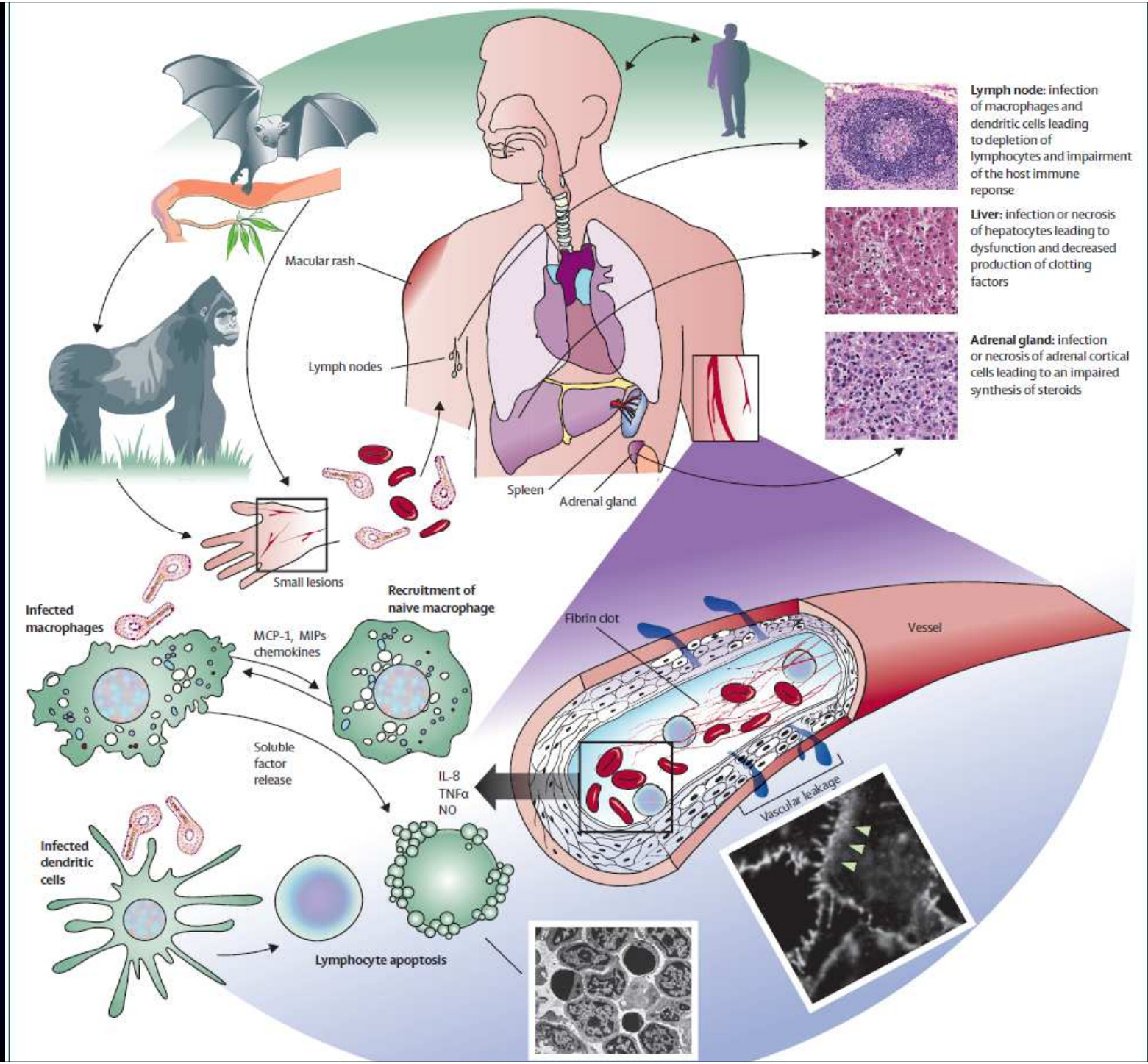
Anthony S. Fauci, M.D.

An outbreak of Ebola virus disease (EVD) has jolted West Africa, claiming more than 1000 lives since the virus emerged in Guinea in early 2014 (see figure). The rapidly increasing numbers of cases in the African countries of Guinea, Liberia, and Sierra Leone have had public health authorities on high alert throughout the spring and summer. More recent events including the spread of EVD to Nigeria (Africa's most populous country) and the recent evacuation to the United States of two American health care workers with EVD have captivated the world's attention and concern. Health professionals and the Democratic Republic of Congo), and Nzara, South Sudan, is caused by an RNA virus in the filovirus family. "Ebola" (named after a river in Zaire) encompasses five separate species — *Zaire ebolavirus*, *Bundibugyo ebolavirus*, *Taï Forest ebolavirus*, *Sudan ebolavirus*, and *Reston ebolavirus*. *Reston ebolavirus* is not known to cause disease in humans, but the fatality rates in outbreaks of the other four species have ranged from 25 although the estimated case fatality rate in the current outbreak is less than 60%.[3]

Outbreaks probably originate from an animal reservoir and possibly involve additional intermediary species. The most likely reservoir appears to be a fruit bat, although that linkage has not been confirmed.[1] Transmission to humans may have occurred through direct contact with tissue or bodily fluids from an infected animal. Notably, Ebola virus is a zoonotic pathogen, and its circulation among humans is uncommon, which explains the intermittent and unpredictable nature of outbreaks. In fact, although the

Frequency of Symptoms Reported in 103 Cases of Ebola Virus Disease in Kikwit, Democratic Republic of Congo, in 1995.*

Symptom	Percent of Patients with Symptom
Fever	≥90
Weakness	80–90
Diarrhea	80–90
Nausea and vomiting	70–80
Abdominal pain	60–70
Headache	50–60
Sore throat, odynophagia, dysphagia	50–60
Arthralgia or myalgia	50–60
Anorexia	40–50
Rash	10–20
Bleeding	
Any type	40–50
Gingival	10–20
Hematemesis	10–20
Melena	0–10
From puncture sites	0–10
Hemoptysis	0–5


Macular rash
Lymph nodes
Spleen
Adrenal gland
Lymph node: infection of macrophages and dendritic cells leading to depletion of lymphocytes and impairment of the host immune reponse
Liver: infection or necrosis of hepatocytes leading to dysfunction and decreased production of clotting factors
Adrenal gland: infection or necrosis of adrenal cortical cells leading to an impaired synthesis of steroids
Small lesions
Infected macrophages
Recruitment of naive macrophage
MCP-1, MIPs chemokines
Soluble factor release
Infected dendritic cells
Lymphocyte apoptosis
Fibrin clot
Vessel
IL-8
TNFα
NO
Vascular leakage

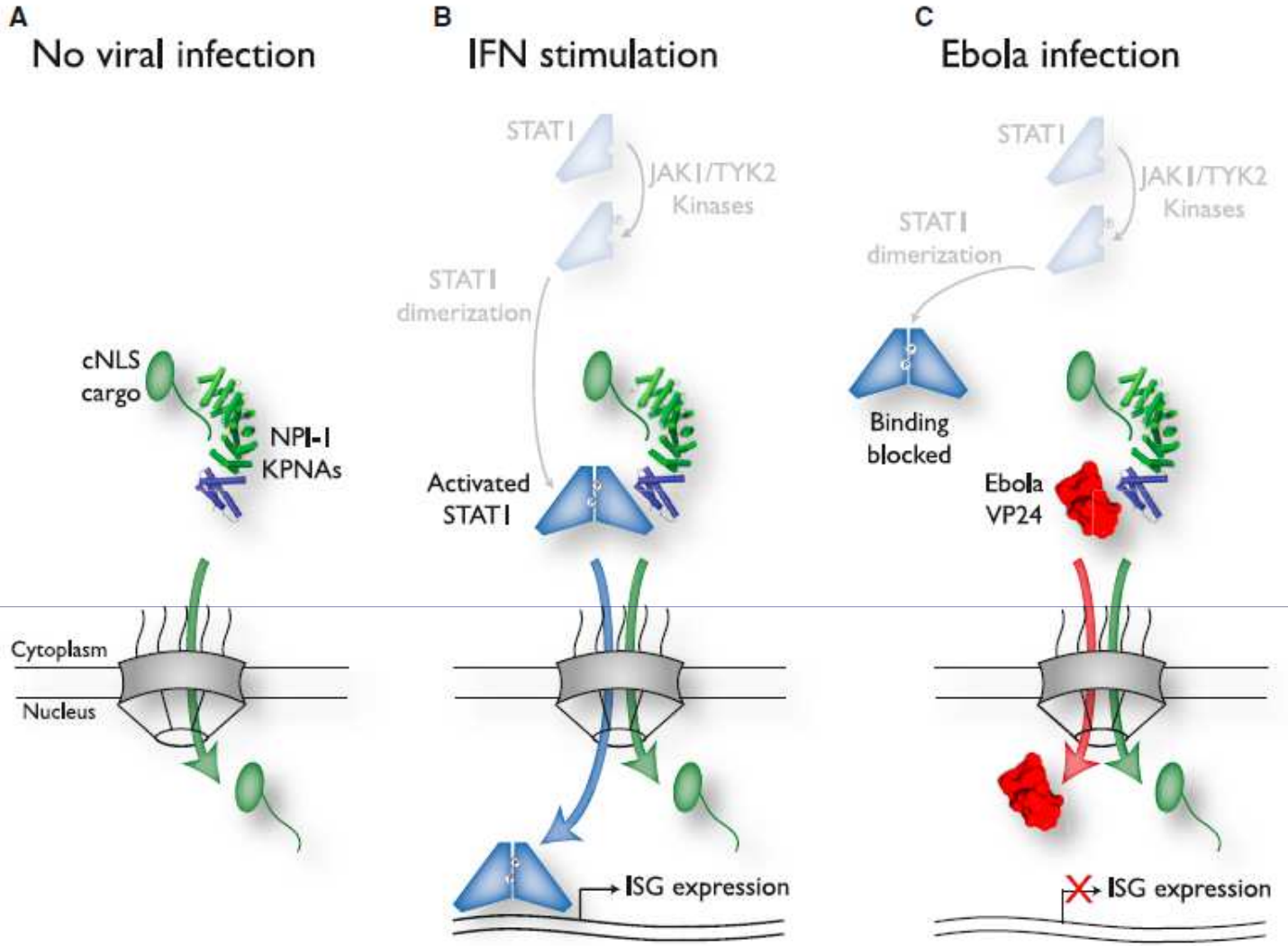


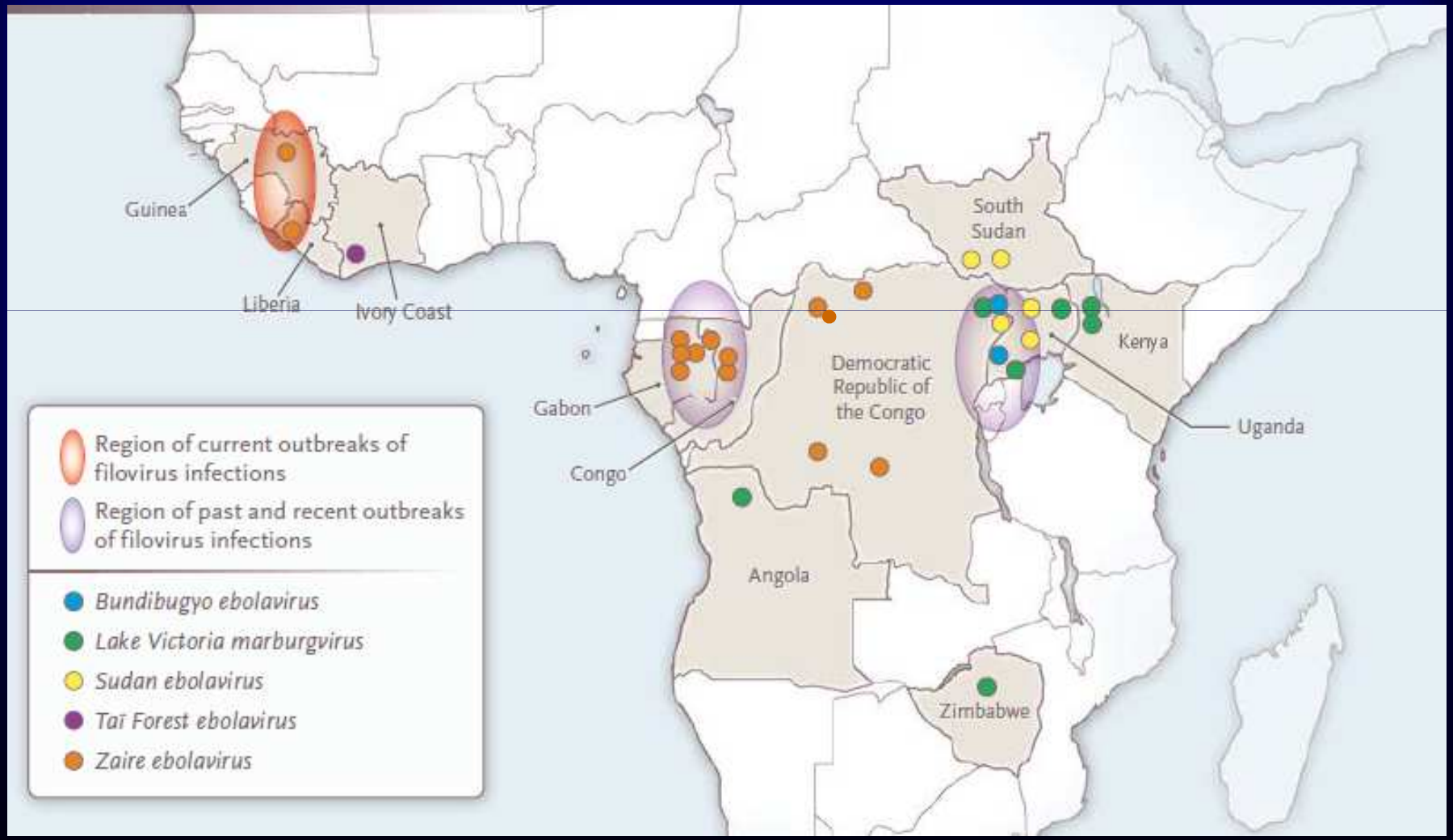
Figure 1. Ebola VP24 Specifically Blocks the Noncanonical Nuclear Import of STAT1

(A) Most cellular proteins rely on a classical nuclear localization signal (cNLS) for their import into the nucleus, via cNLS binding to armadillo (ARM) repeats 2–8 (green) of karyopherin-α (KPNA) proteins, including the NPI-1 subfamily of KPNAs.

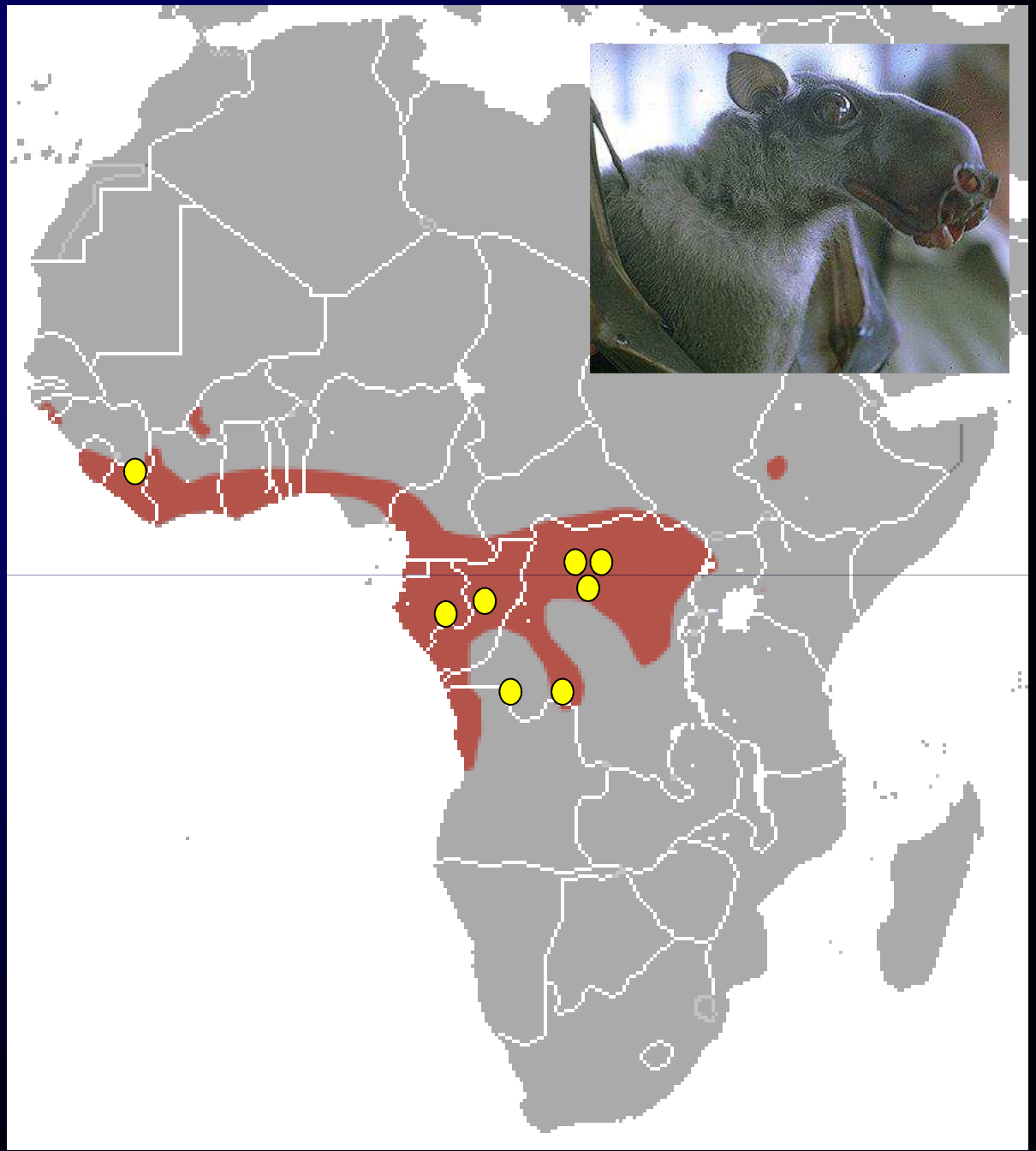
(B) Upon IFN binding to the IFN receptor on a cell surface, Janus kinases (JAK1 and TYK2) become activated and phosphorylate STAT1. Phosphorylated STAT1 dimerizes and then presents a nonclassical NLS (ncNLS), which is recognized by ARMs 8–10 of NPI-1 KPNAs (blue) for nuclear import. STAT1 binding to KPNAs does not interfere with cNLS binding, suggesting that both cargos may be imported simultaneously. Once nuclear, dimeric STAT1 activates expression of several hundred interferon stimulated genes (ISGs), which establish an antiviral state in the cell.

(C) Upon Ebola infection, STAT1 is phosphorylated normally but is unable to bind KPNA due to competition with Ebola VP24 for specific binding to ARMs 8–10. This competitive mechanism of VP24 still allows cNLS-containing cargoes to bind KPNAs, thus specifically blocking only STAT1 import.

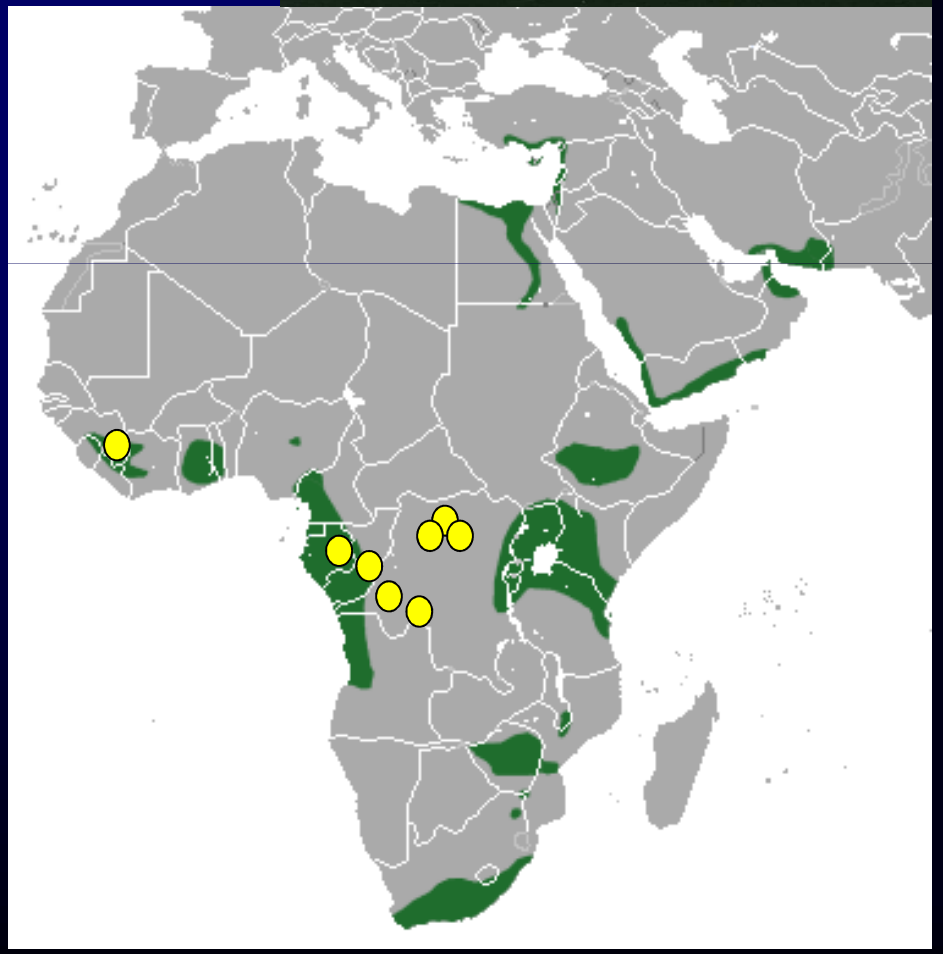
Ebola: aree interessate da epidemie nell'uomo



Areale di distribuzione di *Hypsignathus monstrosus*



Egyptian fruit bat
Rousettus aegyptiacus
Geographic range



L'Ebola è un prezzo inaccettabile per il bushmeat

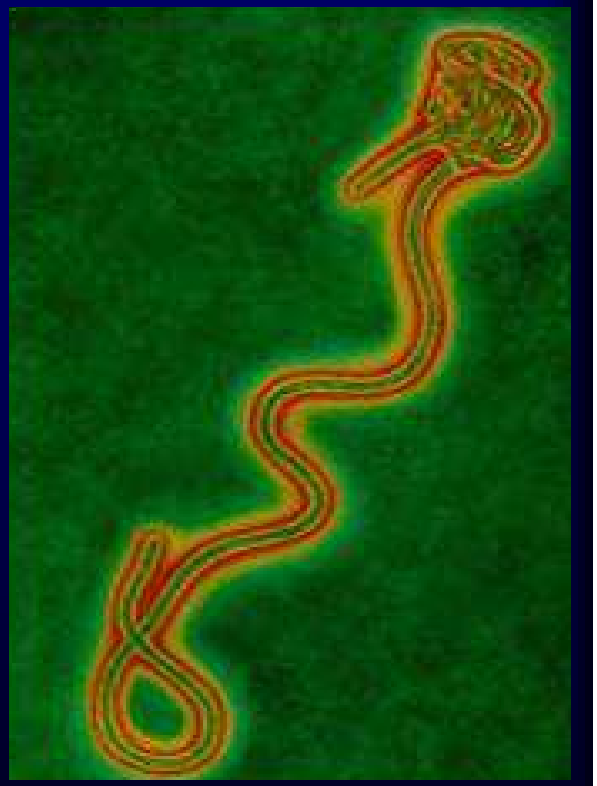
Mercato a Brazzaville, Repubblica del Congo

L'Ebola è un prezzo inaccettabile per il bushmeat

Mercato a Brazzaville, Repubblica del Congo

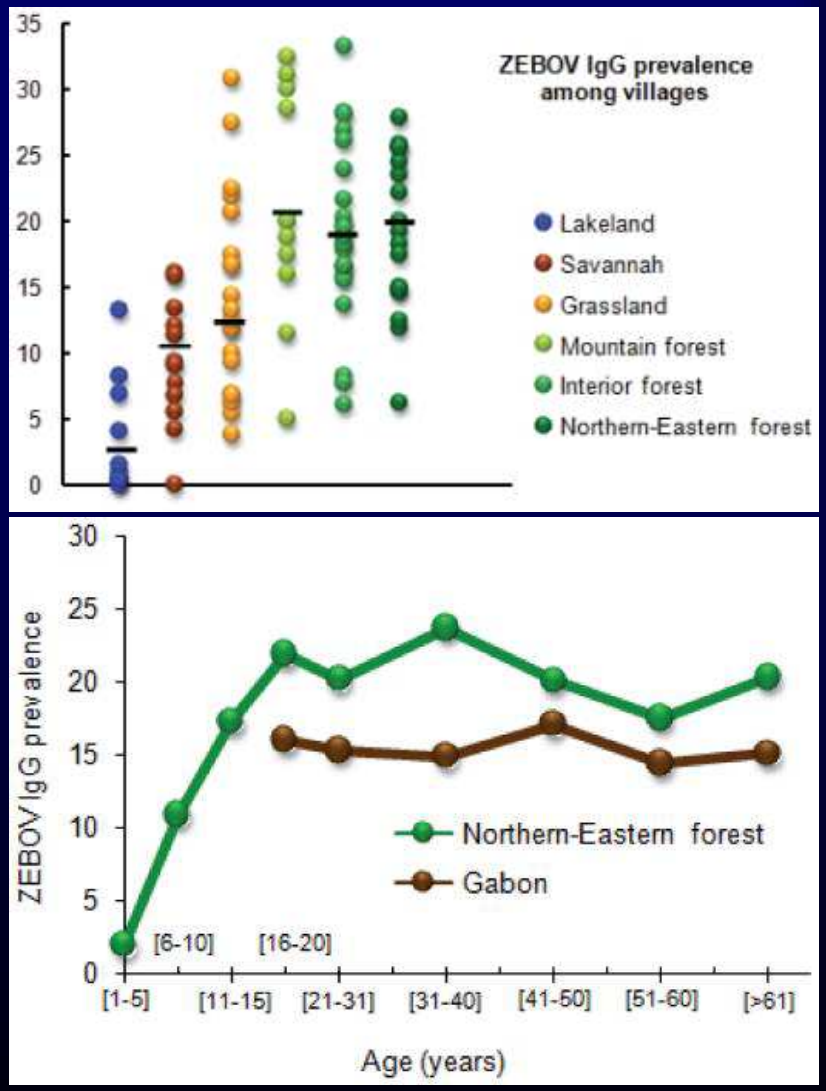
Tutte le epidemie da EBOV sono state causate da ceppi diversi tra loro

- Studi filogenetici su sequenze virali da carcasse di animali e da persone infettate dimostrano che i virus implicati sono diversi tra loro in tempi e in luoghi diversi, mentre sono molto simili le sequenze ottenute da uomini e animali durante la stessa epidemia
- Teoria dello spillover: ogni epidemia è stata generata dall'emergere ex novo dal serbatoio animale di un ceppo diverso dai precedenti
- Fino ad oggi tutte le epidemie si sono esaurite dopo pochi passaggi umani



Si possono trovare anticorpi anti Ebola in persone sane senza precedenti di malattia?

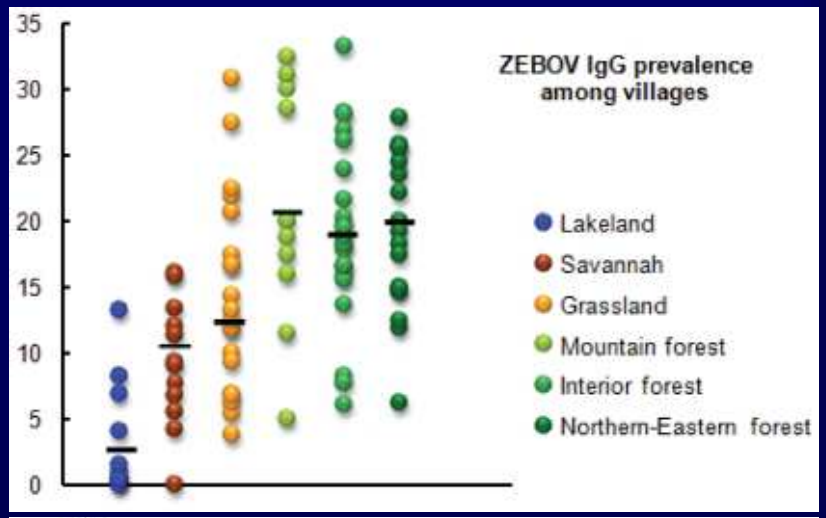
- IgG anti EBOV nel 15,3% dei 4.349 abitanti di 220 villaggi in Gabon
- La prevalenza sale nei villaggi più vicini alla foresta e con l'età, ma non varia dopo i 20 anni
- Non altri fattori di rischio per EBOV, ne evidenza di precedente malattia
- I dati suggeriscono l'esposizione a una fonte d'infezione di accesso facile e generalizzato, come ad esempio la frutta contaminata da saliva di pipistrello

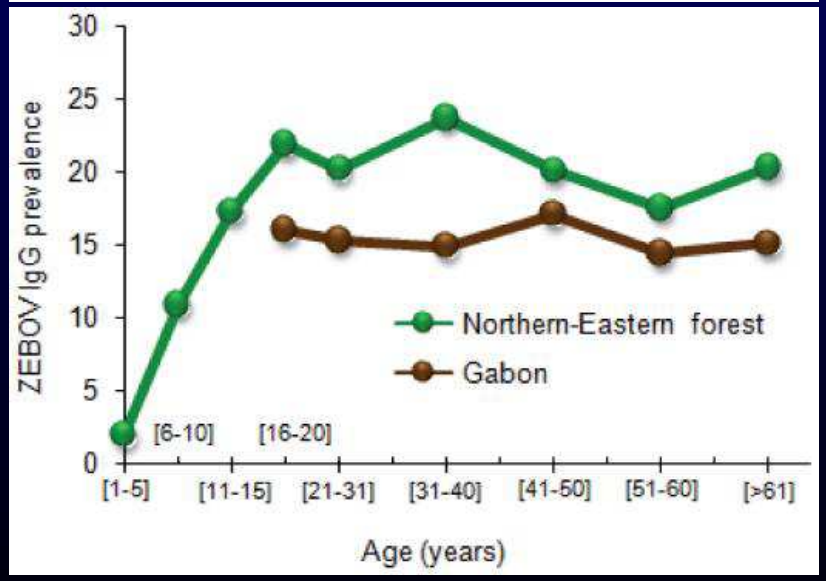


Becquart et al PLoS One 2010,5: e9126

Si possono trovare anticorpi anti Ebola in persone sane senza precedenti di malattia?

- Questi dati sollevano importanti domande riguardo:
  - la patogenicità di EBOV
  - la possibilità di infezioni lievi o paucisintomatiche
  - la possibilità di immunizzazione e di protezione naturale
  - l'esistenza di reazioni crociate con altri filovirus non patogeni





Becquart et al PLoS One 2010,5: e9126

Ebola Reston

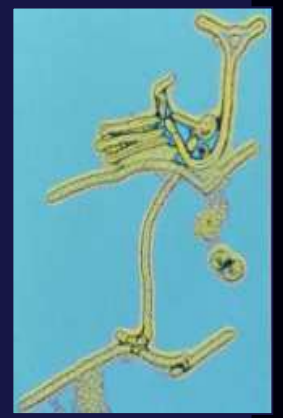
- Ebola Reston viene identificato nel 1989 negli USA in *M. fascicularis* in cattività e successivamente nelle Filippine in esemplari in libertà

- L'infezione ha elevata letalità nelle scimmie, ma non ha avuto effetti di rilievo nei 25 casi umani documentati.

Macaca fascicularis

Ebola Reston

- Del tutto inaspettatamente, a partire dal 2008, sono stati individuati focolai di infezione ad elevata letalità in allevamenti di maiali nelle Filippine
- È possibile che il serbatoio in natura sia rappresentato da *Rousettus amplexicaudatus*



R. amplexicaudatus

Perché il rischio di Ebola in Italia è ed è stato basso?

- Non voli diretti dai paesi colpiti
- I cittadini dei paesi colpiti sono meno di 7000 su oltre 3.5 milioni di stranieri residenti
- I clandestini via mare attraverso il Mediterraneo non costituiscono pericolo:
  - le nazionalità dei paesi colpiti sono virtualmente non rappresentate
  - la lunghezza del viaggio precedente via terra supererebbe comunque il limite massimo di incubazione di EVD di 21 giorni

corruption in the Nepalese health-care system have attracted media attention.[5] In July 2014, doctors at the Bir Hospital, the nation's oldest hospital, serving mainly the underprivileged population, halted all non-emergency services for two weeks, protesting the lack of CT and MRI scanners, and asking for the repair of radiography and radiotherapy equipment.[6] From the perspective of equity in health care, these paradoxical reports call for expenses incurred in medical tourism to be channelled towards ensuring the functionality of facilities at national institutions for the benefit of every citizen. Additionally, the use and strengthening of national institutions and expertise can contribute to motivation of the skilled employees working in the health sector. The wrong precedent set by some leaders in Nepal encourages over-privatisation of the health-care sector, undermining the constitutionally guaranteed provision of universal basic health care, and thereby raising serious questions about social justice.

I declare no competing interests.

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1 Lautier M. International trade of health services: Global trends and local impact. *Health Policy* 2014; published online July 11. DOI:10.1016/j.

Ebola: a call for blood transfusion strategy in sub-Saharan Africa

WHO has stated that convalescent blood or plasma is an option in the treatment of Ebola.[1] In 1999, transfusion of locally collected convalescent blood helped decrease Ebola mortality.[2] WHO recommends collection of convalescent plasma to treat patients in the fight against the Ebola outbreak.[1] As there is an estimated 70% mortality, a randomised clinical evaluation involving 50 patients, receiving convalescent and control normal plasma, would be sufficient to confirm the usefulness of this approach in treatment strategies.

Capacity building for the collection and testing of sufficient convalescent blood or plasma from recovered Ebola patients is crucial. However, paradoxically, the outbreaks are occurring in the countries that have the least capability for blood and plasma collection or viral screening, and which lack infrastructure, equipment, and trained personnel. To ensure collection of safe convalescent plasma, donors must be clinically and virally free of Ebola Virus Disease (EVD) and other relevant viruses. Convalescent plasma is the preferred product, either

strengthening the technical capacity and infrastructure of local transfusion systems, to respond to present and future infectious outbreaks.

The importance of ensuring adequate, accessible, and safe blood—in all countries—is a global priority. Whole blood and labile blood components are now on the WHO's Essential Medicines List (EML),[3] emphasising the crucial role of transfusions in public health. In sub-Saharan Africa, whole blood, when available, is a life-saving product for emergency use[4] that, together with convalescent plasma, might be the only available clinical option in the treatment of Ebola patients at present. National governments should develop sustainable local blood services for an adequate supply of safe blood as a priority. WHO's urgent appeal, supporting the use of convalescent blood products to fight Ebola, is a timely reminder of the many World Health Assembly resolutions supporting such actions, particularly in low resource countries.

We declare no competing interests.

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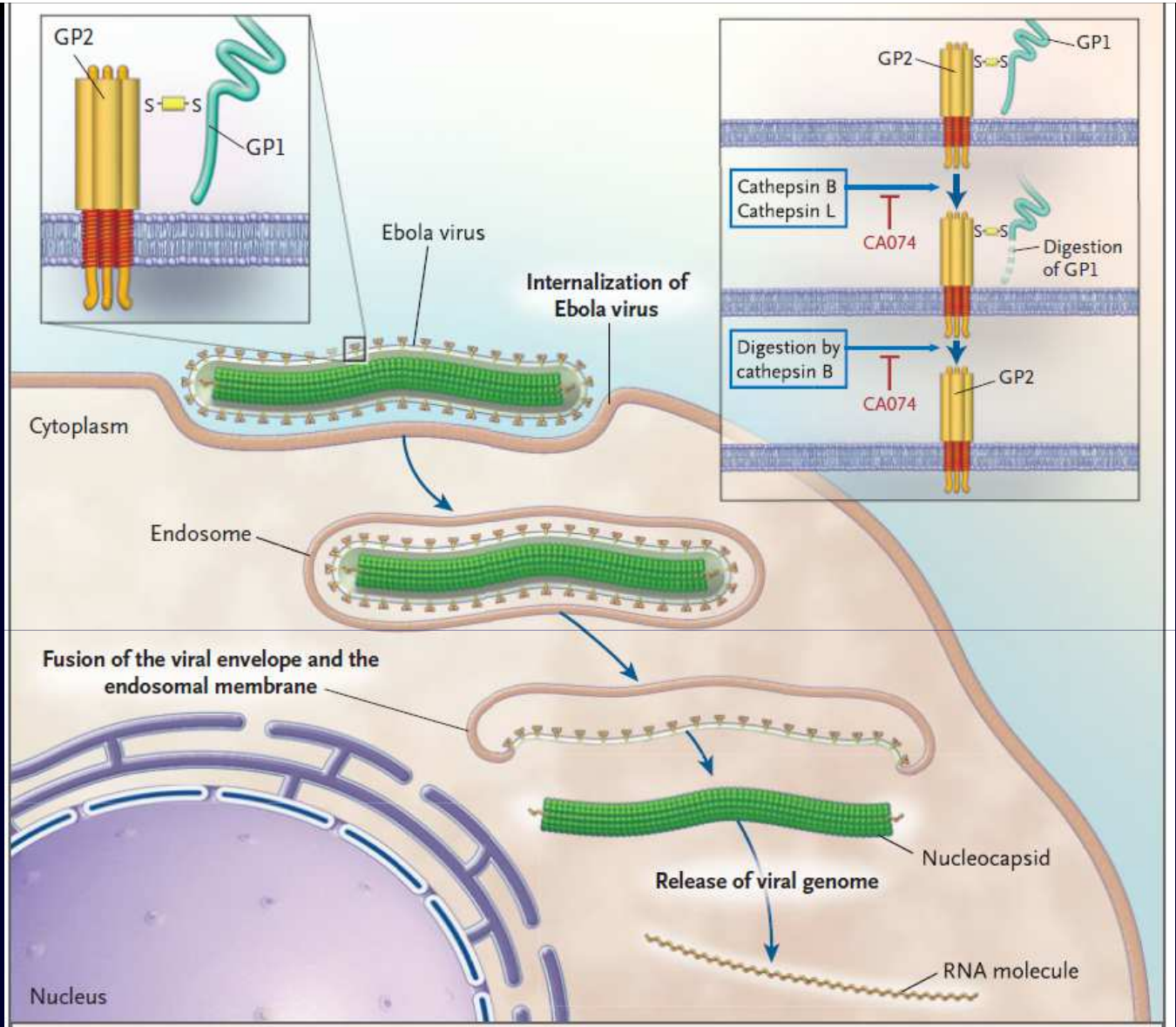

Figure 1. Entry of Ebola Virus into a Cell.

On binding to cell-surface receptors, Ebola virus is internalized and sequestered within an endosome. A recent study by Chandran and colleagues[1] shows that two endosomal proteases, cathepsin B and cathepsin L, then cleave the viral glycoprotein 1 (GP1) to yield a short N-terminal fragment, which is further digested by cathepsin B, leaving only GP2. Presumably, GP2 initiates fusion between the viral envelope and the endosomal membrane, leading to the release of the viral genome into the cytoplasm. A selective inhibitor of cathepsin B, CA074, inhibits the proteolysis of GP1, thereby preventing fusion and thus infection.

LETTER

doi:10.1038/nature13027

Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430

Travis K. Warren[1], Jay Wells[1], Rekha G. Panchal[1], Kelly S. Stuthman[1], Nicole L. Garza[1], Sean A. Van Tongeren[1], Lian Dong[1], Cary J. Retterer[1], Brett P. Eaton[1], Gianluca Pegoraro[1], Shelley Honnold[1], Shanta Bantia[2], Pravin Kotian[2], Xilin Chen[2], Brian R. Taubenheim[2]†, Lisa S. Welch[1], Dena M. Minning[3], Yarlagadda S. Babu[2], William P. Sheridan[2] & Sina Bavari[1]

Filoviruses are emerging pathogens and causative agents of viral haemorrhagic fever. Case fatality rates of filovirus disease outbreaks are among the highest reported for any human pathogen, exceeding 90% (ref. 1). Licensed therapeutic or vaccine products are not available to treat filovirus diseases. Candidate therapeutics previously shown to be efficacious in non-human primate disease models are based on virus-specific designs and have limited broad-spectrum antiviral potential. Here we show that BCX4430, a novel synthetic adenosine analogue, inhibits infection of distinct filoviruses in human cells. Biochemical, reporter-based and primer-extension assays indicate that BCX4430 inhibits viral RNA polymerase function, acting as a non-obligate RNA chain terminator. Post-exposure intramuscular administration of BCX4430 protects against Ebola virus and Marburg virus disease in rodent models. Most importantly, BCX4430 completely protects cynomolgus macaques from Marburg virus infection when administered as late as 48 hours after infection. In addition, BCX4430 exhibits broad-spectrum antiviral activity against numerous viruses, including bunyaviruses, arenaviruses, paramyxoviruses, coronaviruses and flaviviruses. This is the first report, to our knowledge, of non-human primate protection from filovirus disease by a synthetic drug-like small molecule. We provide additional pharmacological characterizations supporting the potential development of BCX4430 as a countermeasure against human filovirus diseases and other viral diseases representing major public health threats.

Members of the family *Filoviridae* include Ebola virus (EBOV), Marburg virus (MARV), Ravn virus (RAVV), Sudan virus (SUDV) and Bundibugyo virus (BDBV), all of which cause severe viral haemorrhagic fevers in humans. In nature, filoviruses are transmitted by physical contact between infected individuals, presumably via infected bodily fluids[2]. Initial filovirus disease manifestations include fever, headache, vomiting and diarrhoea[3]. Fatal cases are characterized by viraemia, elevated liver-associated enzyme levels, coagulopathy and haemorrhage. Filovirus disease outbreaks occur sporadically, most frequently in sub-Saharan Africa, with reported case fatality rates exceeding 90% (ref. 1). In 2012, simultaneous outbreaks involved MARV, SUDV and BDBV, an emergent filovirus isolated in 2007[4]. The historical occurrence of independent and simultaneous emergence of distinct filoviruses highlights the need for the identification and development of an efficacious broad-spectrum antiviral product.

Although no licensed antiviral preventative or therapeutic agents are currently available to combat filovirus disease in humans, a number of candidates are being developed and have been evaluated in non-human primate filovirus disease models. These models closely reproduce the known clinical and pathophysiological aspects of fatal human infection. Nucleic-acid-based products, antibody therapies and therapeutic vaccines have successfully protected non-human primates from filovirus disease[5–18], but these approaches rely on virus-specific designs that inherently limit the spectrum of activity and potential utility of individual treatments. The development of a single therapeutic agent active against multiple filoviruses would provide a key, cost-effective component of public-health preparedness plans in outbreak-prone regions.

The broad-spectrum antiviral agent ribavirin, a triazole nucleoside effective against multiple pathogenic RNA viruses, is not active against filoviruses[11]. Other small molecules—including the adenosine analogue 3-deazaneplanocin A (c^3-Npc A) and T-705 (favipiravir), a substituted pyrazine compound—have conferred a high degree of protection against filoviruses in rodents but have not been reported to protect non-human primates[12–18].

BCX4430, a novel nucleoside analogue (Fig. 1a), was synthesized (Supplementary Information) as part of a small-molecule library designed as inhibitors of viral RNA polymerase activity. BCX4430 is designed to inhibit viral RNA polymerase activity indirectly through non-obligate RNA chain termination, a mechanism requiring anabolism of the parent compound to BCX4430-triphosphate (BCX4430-TP). Then, after pyrophosphate cleavage, incorporation of BCX4430-monophosphate (BCX4430-MP) into nascent viral RNA strands would be expected to cause premature termination of transcription and replication of viral RNA. In support of this proposed mechanism, BCX4430 is rapidly phosphorylated to BCX4430-TP in cultured cell lines and primary hepatocytes, similar to the natural adenosine nucleoside (Fig. 1b and Extended Data Fig. 1a). Addition of BCX4430 reduces expression of green fluorescent protein (GFP) in an artificial EBOV minigenome replicon assay (Fig. 1c and Extended Data Fig. 1b), in which virion structural proteins comprising the viral ribonucleoprotein complex mediate transcription and replication of an RNA replicon template containing a GFP-reporter cassette. BCX4430-TP inhibits hepatitis C virus (HCV) RNA polymerase transcriptional activity in a cell-free, isolated enzyme transcription assay (Fig. 1d) (an isolated filovirus RNA polymerase enzyme assay has yet to be reported) and induces premature termination of RNA chain synthesis by HCV RNA polymerase during template-directed primer-extension assays (Fig. 1e and Extended Data Fig. 1c). In virus-infected cells, BCX4430 reduces surface-expressed MARV and EBOV glycoprotein and reduces the production of intracellular and extracellular MARV RNA (Fig. 1f–h and Extended Data Fig. 1d). Additionally, HeLa cells incubated with ≥25 μM BCX4430 produce no detectable infectious MARV virus (concentration providing 90% inhibition (IC_{90}) = 5.4 μM) (Fig. 1h).

Taken together, these assessments strongly support our hypothesis that BCX4430 inhibits viral RNA polymerase function by inducing RNA chain termination. Findings from primer-extension reactions suggest that termination occurs two bases after incorporation of BCX4430-MP, perhaps as a result of inhibitory stereochemical distortions of the nascent RNA chain. We observed no evidence of BCX4430-MP incorporation into human RNA or DNA on exposing human Huh-7 cells to concentrations of BCX4430 exceeding the MARV IC_{50} by more than tenfold (Extended Data Fig. 1f). The basis of the selectivity of BCX4430 for viral polymerases is not yet known.

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OPEN

Sustained protection against Ebola virus infection following treatment of infected nonhuman primates with ZMAb

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SUBJECT AREAS:
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Ebola virus (EBOV) is one of the most lethal filoviruses, with mortality rates of up to 90% in humans. Previously, we demonstrated 100% and 50% survival of EBOV-infected cynomologus macaques with a combination of 3 EBOV-GP-specific monoclonal antibodies (ZMAb) administered at 24 or 48 hours post-exposure, respectively. The survivors demonstrated EBOV-GP–specific humoral and cell-mediated immune responses. In order to evaluate whether the immune response induced in NHPs during the ZMAb treatment and EBOV challenge is sufficient to protect survivors against a subsequent exposure, animals that survived the initial challenge were rechallenged at 10 or 13 weeks after the initial challenge. The animals rechallenged at 10 weeks all survived whereas 4 of 6 animals survived a rechallenge at 13 weeks. The data indicate that a robust immune response was generated during the successful treatment of EBOV-infected NHPs with EBOV, which resulted in sustained protection against a second lethal exposure.

Contents lists available at ScienceDirect

Antiviral Research

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

Short Communication

Successful treatment of advanced Ebola virus infection with T-705 (favipiravir) in a small animal model

Lisa Oestereich [a,b], Anja Lüdtke [a,c], Stephanie Wurr [a,b], Toni Rieger [a,b], César Muñoz-Fontela [a,c], Stephan Günther [a,b,*]

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ABSTRACT

Outbreaks of Ebola hemorrhagic fever in sub-Saharan Africa are associated with case fatality rates of up to 90%. Currently, neither a vaccine nor an effective antiviral treatment is available for use in humans. Here, we evaluated the efficacy of the pyrazinecarboxamide derivative T-705 (favipiravir) against Zaire Ebola virus (EBOV) in vitro and in vivo. T-705 suppressed replication of Zaire EBOV in cell culture by 4 log units with an IC_{90} of 110 1M. Mice lacking the type I interferon receptor ($IFNAR^{-/-}$) were used as in vivo model for Zaire EBOV-induced disease. Initiation of T-705 administration at day 6 post infection induced rapid virus clearance, reduced biochemical parameters of disease severity, and prevented a lethal outcome in 100% of the animals. The findings suggest that T-705 is a candidate for treatment of Ebola hemorrhagic fever.

The clinically approved drugs amiodarone, dronedarone and verapamil inhibit filovirus cell entry

- Amiodarone, a multi-ion channel inhibitor and adrenoceptor antagonist, is a potent inhibitor of filovirus cell entry at concentrations that are routinely reached in human serum during anti-arrhythmic therapy
- A similar effect was observed with the amiodarone-related agent dronedarone and the L-type calcium channel blocker verapamil

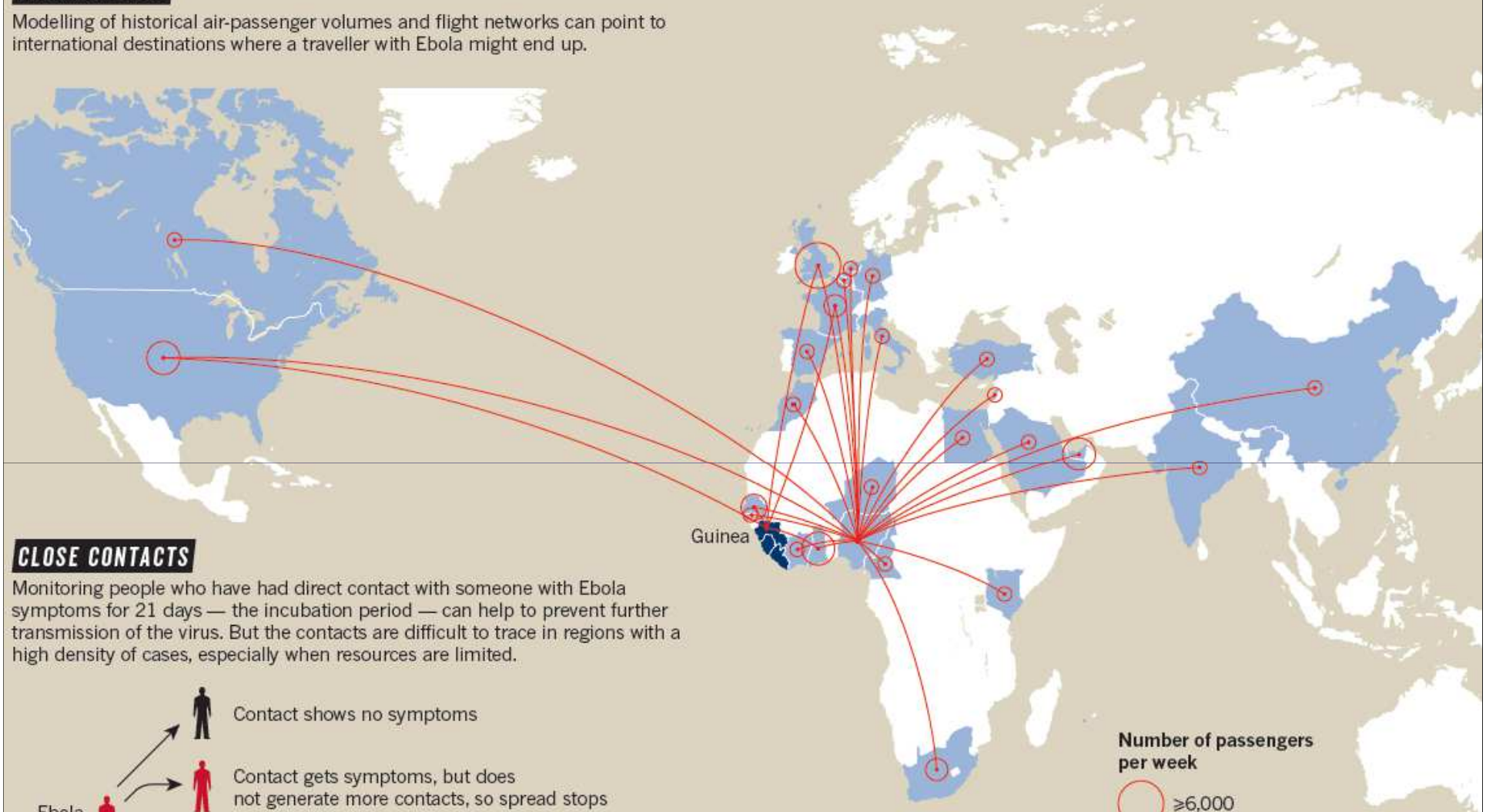
Gehring et al. J Antimicrob Chemother 2014

Ebola vaccines

- Two candidate vaccines have clinical-grade vials available for phase 1 pre-licensure clinical trials
- cAd3-ZEBOV has been developed by GSK in collaboration with the US NIAID. It uses a chimpanzee-derived adenovirus vector with an Ebola virus gene inserted.
- rVSV-ZEBOV was developed by the Public Health Agency of Canada in Winnipeg. The license for commercialization of the Canadian vaccine is held by an American company, the NewLink Genetics company. The vaccine uses an attenuated or weakened vesicular stomatitis virus; one of its genes has been replaced by an Ebola virus gene

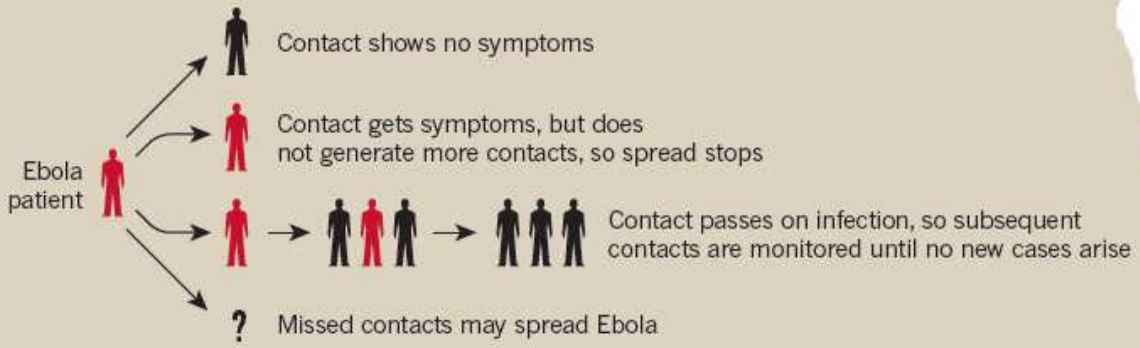
GLOBAL REACH

Modelling of historical air-passenger volumes and flight networks can point to international destinations where a traveller with Ebola might end up.



CLOSE CONTACTS

Monitoring people who have had direct contact with someone with Ebola symptoms for 21 days — the incubation period — can help to prevent further transmission of the virus. But the contacts are difficult to trace in regions with a high density of cases, especially when resources are limited.



Ebola: protection of health workers on the front line

See World Report page 481

For more on the **Ebola outbreak** see http://www.who.int/csr/don/archive/disease/ebola/en/

Although fears were raised about the possible spread of Ebola virus to the UK and USA last week, the real concern remains in west Africa. Unlike previous outbreaks in east Africa that were brought under control fairly swiftly, the west African outbreak has become the worst in history. 1603 people have had suspected or confirmed Ebola virus disease in the four affected countries (Guinea, Sierra Leone, Liberia, and Nigeria) and 887 died between March, 2014, and Aug 1, 2014.

On Aug 1, WHO Director-General Margaret Chan and the presidents of the affected countries launched a new joint US$100 million plan to bring the outbreak under control. The intensified response is much needed. The plan rightly recognises the need for several hundred more personnel, including clinical doctors and nurses, epidemiologists, and social mobilisation experts, to be deployed to the affected countries. Domestic and foreign health workers on the ground dealing with the outbreak have been overstretched. On June 24, Médecins Sans Frontières warned that its teams had reached the limits of what they could do. More than 60 health workers have already died from Ebola while helping others, including doctor Sheik Umar Khan who is credited with treating more than 100 patients with the disease in Sierra Leone.

Health workers on the front line are at increased risk of contracting Ebola by coming into contact with the bodily fluids of infected patients. Use of adequate personal protective clothing and equipment when caring for patients or the deceased, thorough cleaning, and effective waste disposal, can substantially reduce the risk of infection. Worryingly, last week the World Medical Association reported that many of its junior doctor members dealing with the outbreak had not been provided with essential protective equipment.

The situation is disturbing and unacceptable. Governments, WHO, and the international community have a collective responsibility not only to fully staff the effort to bring Ebola under control, but also to provide adequate protective clothing, training, and support for anyone coming into contact with patients. ■ *The Lancet*

thebmj

BMJ 2014;349:g6200 doi: 10.1136/bmj.g6200 (Published 13 October 2014) Page 1 of 2

NEWS

Texas healthcare worker is diagnosed with Ebola

Michael McCarthy

Seattle

Ebola disease has been diagnosed in a health worker in Texas, state health officials said Sunday 12 October. The worker, who press reports say is a nurse, took care of fell ill shortly after arriving in the United of Ebola disease.[1]

Ebola disease is caused by a filovirus first discovered in Africa in 1976. Infection is thought to require direct contact with bodily

In a press briefing Sunday the director of the Centers for Disease Control and Prevention, Tom Frieden, said it was not known how the Texas health worker had become infected, "but at some point there was a breach in protocol and that breach in protocol resulted in this infection." The worker had "extensive contact" with the Liberian patient while he was in the hospital, Frieden said.

Duncan returned, severely ill, on 28 September, and was admitted. Ebola disease was diagnosed 30 September. Despite ventilator support, renal dialysis, and treatment with an experimental antiviral, brincidofovir (an oral nucleotide analog that has been shown to be active against the virus in vitro), he died 8 October. The hospital has no high level bio-containment facilities for isolating patients with highly contagious diseases.

All hospital workers who had had contact with Duncan have been monitoring themselves for symptoms or fever, health officials said, and on the night of Friday 10 October the nurse reported that she had developed low grade fever. She was admitted through the hospital's emergency room and put into isolation within 90 minutes. A blood test conducted in Texas the next day was positive for the Ebola virus. On Sunday the CDC confirmed the diagnosis.

Clima, vettori e malattie

Esempi di infezioni virali emergenti trasmesse da vettori la cui diffusione interessa o potrebbe interessare il territorio italiano

Agente (famiglia)	Vettore principale	Potenziali serbatoi in Italia	Casi umani in Italia
West Nile Virus (WNV) *Flaviviridae*	*Culex pipiens*	*Pica pica* *Corvus coronae* *Columba livia (?)*	Si, in aumento
Chikungunya virus (ChikV) *Togaviridae*	*Aedes albopictus*	-	Si, una singola epidemia
Tick-Borne Encephalitis Virus (TBEV) *Flaviviridae*	*Ixodes ricinus*	*Apodemus flavicollis*	Si
Crimean – Congo Haemorrhagic fever virus (CCHFV) *Bunyaviridae*	*Hyalomma marginatum*	*Lanius senator*	No

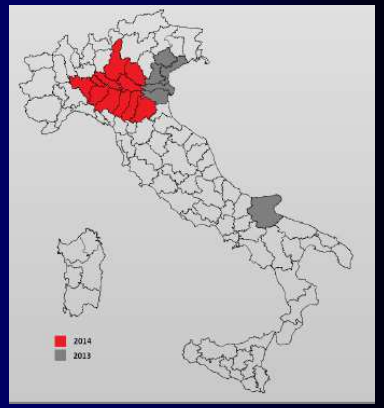
Reported cases of West Nile fever for the EU and neighbouring countries

Transmission season 2013 and previous transmission seasons; latest update: 06/11/2013

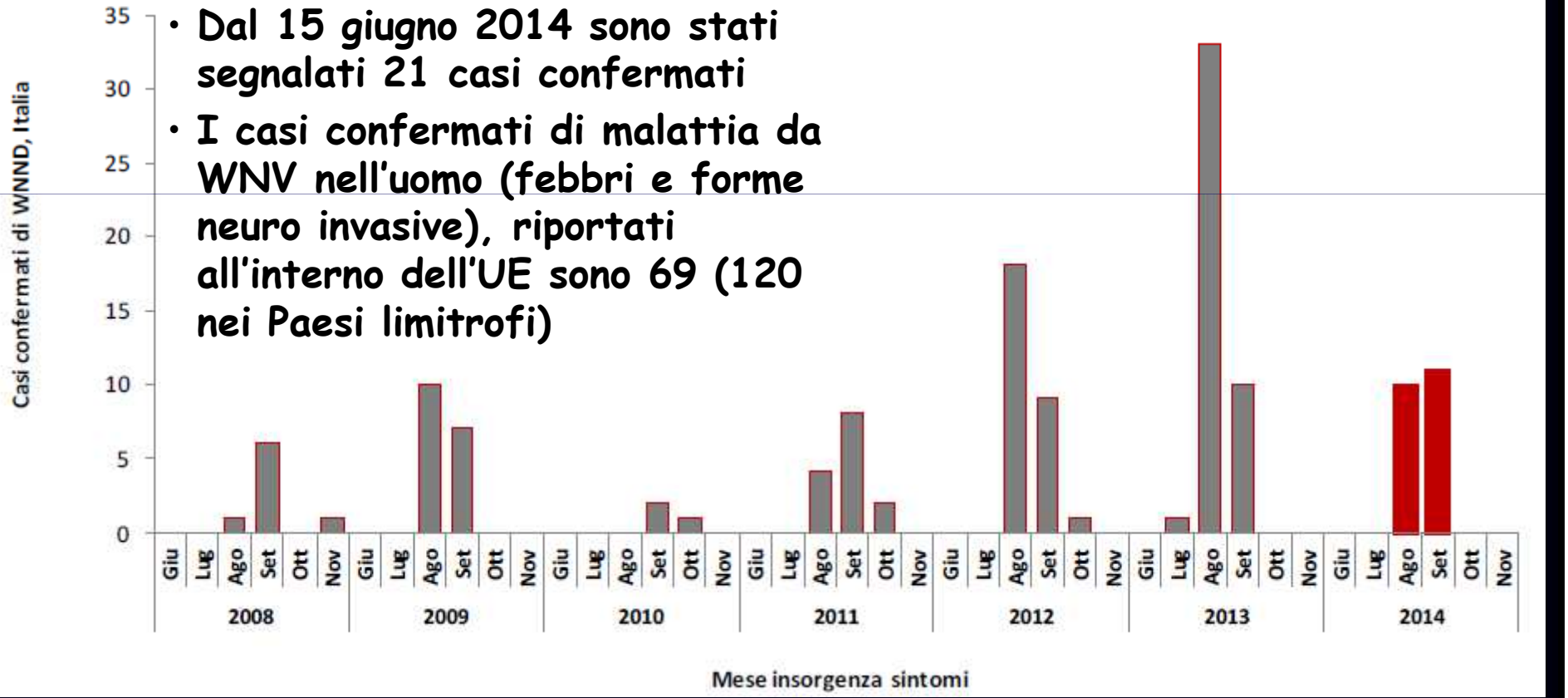
- As of 6 November 2013, 226 human cases of West Nile fever (including 150 neuro-invasive infections) have been reported in the EU; 16 cases in Croatia, 86 in Greece, 31 in Hungary, 69 in Italy and 24 in Romania.
- In neighbouring countries, 557 cases have been declared in Bosnia and Herzegovina, the Former Yugoslav Republic of Macedonia, Montenegro, Serbia, the Russian Federation, Ukraine, Israel and Tunisia.

Area reporting cases in 2013
Area not reporting cases in 2013
Not included
Area reporting cases in 2012
Area reporting cases in 2011 and/or 2010
Malta
Andorra
Monaco
San Marino
Liechtenstein

Sorveglianza dei casi umani di malattia neuro-invasiva da West Nile virus in Italia

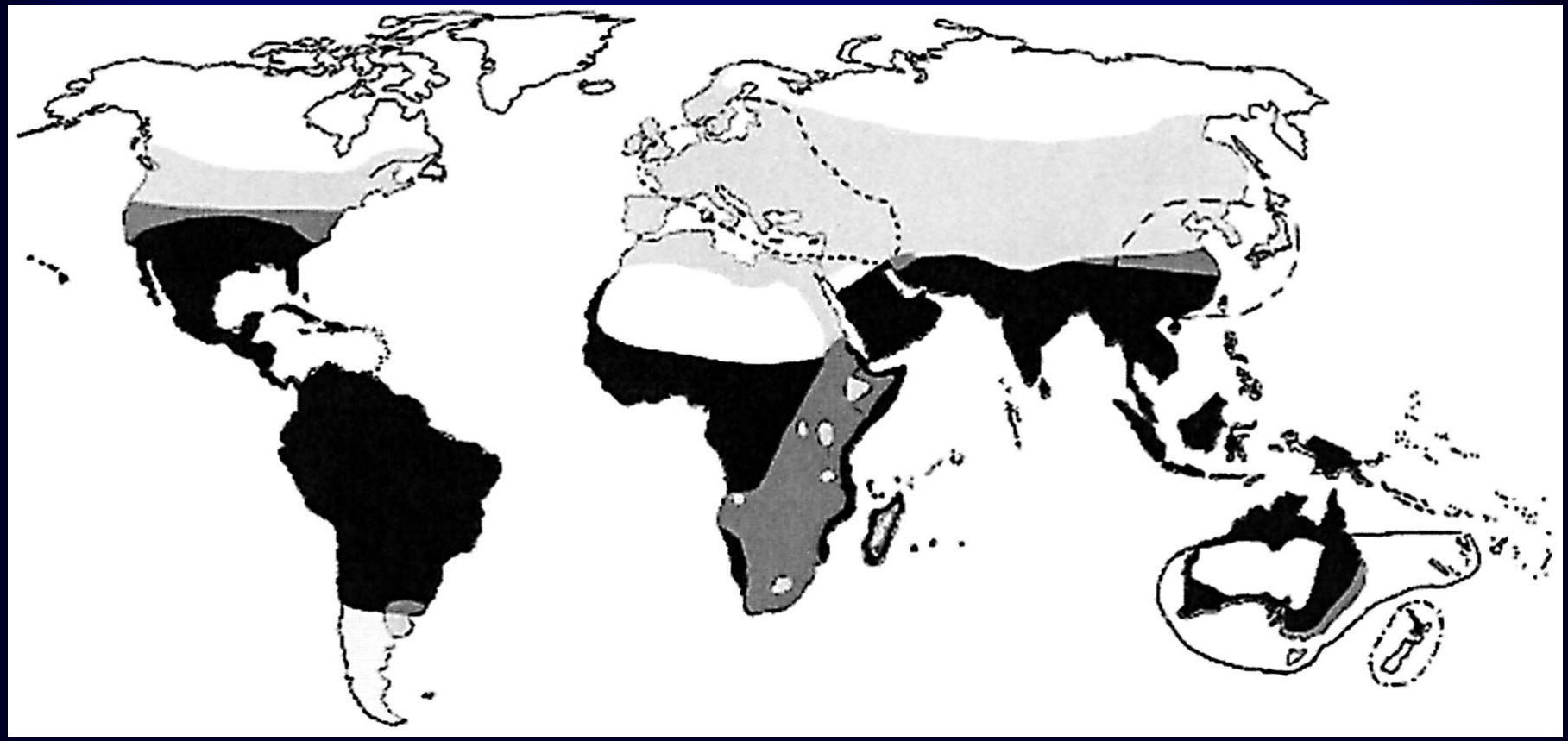


- Dal 15 giugno 2014 sono stati segnalati 21 casi confermati
- I casi confermati di malattia da WNV nell'uomo (febbri e forme neuro invasive), riportati all'interno dell'UE sono 69 (120 nei Paesi limitrofi)



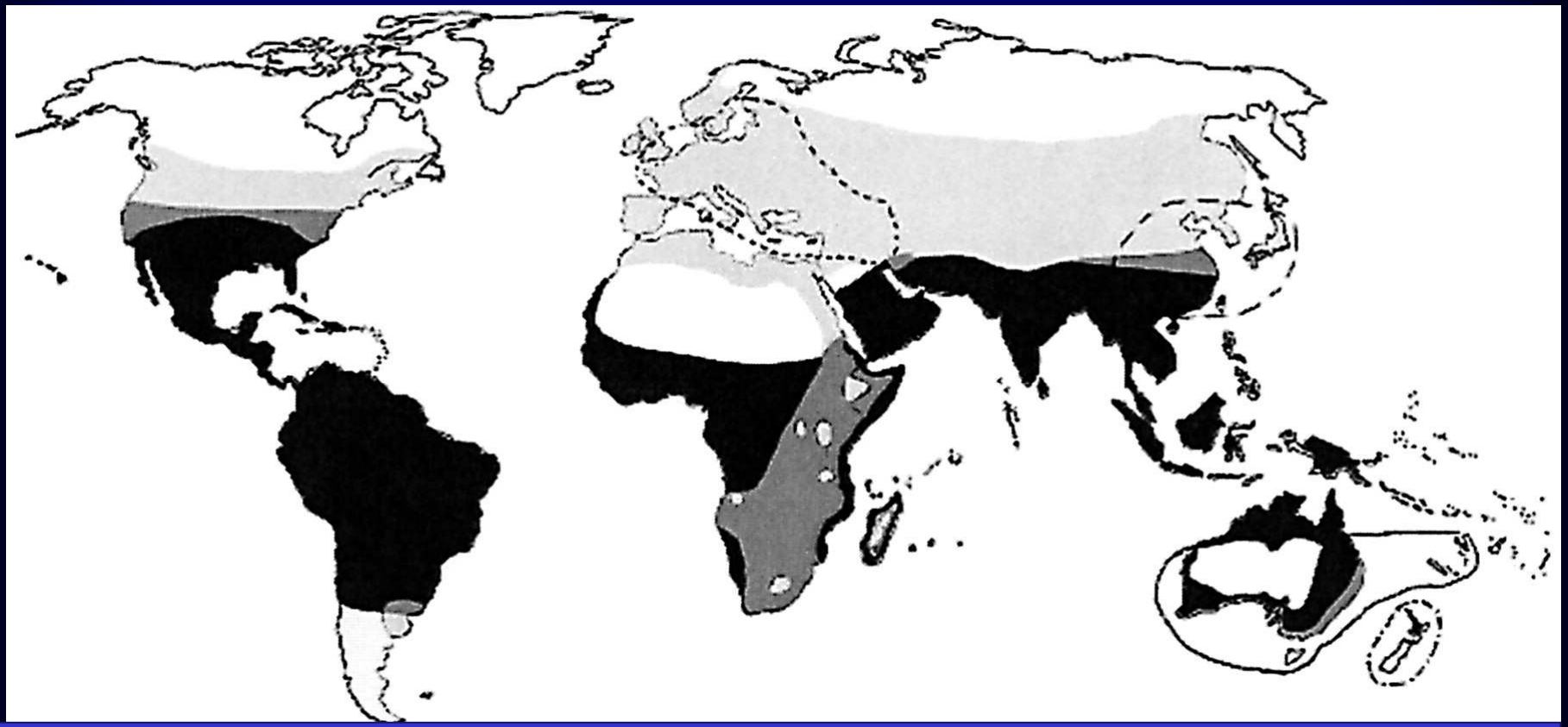
Dati ISS ottobre 2014

Distribuzione dei vettori



Grigio chiaro = *Cx. pipiens*;
Nero= *Cx. quinquefasciatus*;
Grigio scuro = sovrapposizione di *Cx. pipiens* e *Cx. quinquefasciatus*;
Linee tratteggiate = *Cx. torrentium*;
Linee continue = *Cx. australicus*;
Linee punteggiate = *Cx. pipiens pallens*;
Nuova Zelanda = *Cx. pervigilans*.

Distribuzione dei vettori



- Specie diverse di *Culex* sono responsabili della diffusione di WNV in aree geografiche diverse
- La diffusione globale di WNV è stata resa possibile dalla diffusione globale dei vettori.

West Nile Virus: animali serbatoio

- Isolato in vari uccelli selvatici, in specie acquatiche e terrestri
- I *Passeriformes* (>5000 specie!) sviluppano una viremia sufficiente alla trasmissione mediante vettore
- Molti di essi sono resistenti all'infezione (si infettano ma non muoiono)
- In altri (ad esempio in molti corvidi) il virus causa una malattia letale (specie sentinella)

Passer domesticus

Corvus brachyrhynchos

Turdus migratorius

West Nile Virus: animali serbatoio

- Gli uccelli sono gli amplificatori primari dell'infezione
-
- Tra gli ospiti principali:
  - -Negli USA il passero e il merlo americano (*Turdus migratorius*)
  - -In Europa la gazza (*Pica pica*) e la cornacchia (*Corvus coronae*)
- Tra uccelli possibile anche trasmissione diretta (con le feci)

Passer domesticus

Corvus brachyrhynchos

Turdus migratorius

Ciclo di trasmissione di WNV

Ospiti 'accidentali'

Aree palustri

Ospiti serbatoio

Trasmissione verticale

Overwintering

Vettori alternativi

Meccanismi di mantenimento

Possibile perpetuazione del ciclo enzootico attraverso:

- Trasmissione verticale nelle larve di zanzara che consente la sopravvivenza all'inverno (*overwintering*)
- Infezione cronica persistente in alcuni uccelli
- Ruolo dei migratori ?

Ciconia ciconia

Ciclo di trasmissione di WNV

- L'uomo e altri mammiferi sono ospiti terminali in quanto la viremia raggiunta non basta a permettere la trasmissione alle zanzare
- Possibile tuttavia la trasmissione uomo-uomo mediante trasfusione, trapianto, allattamento e in utero.

Possibile perpetuazione
o enzootico
rso:
missione verticale
larve di zanzara
consente la
avvivenza
verno
rwintering)
zione cronica
istente in alcuni
lli
dei migratori ?

Ciconia ciconia

alternativi

NEW MICROBIOLOGICA, 36, 81-83, 2013

Seroprevalence of West Nile virus antibodies in blood donors living in the metropolitan area of Milan, Italy, 2009-2011

Paolo Gaibani[1,2,3], Anna Pierro[1], Giovanna Lunghi[2], Claudio Farina[5], Vincenzo Toschi[6], Caterina Matinato[2], Anna Orlandi[2], Antonella Zoccoli[2], Daniela Almini[4], Maria Paola Landini[1], Erminio Torresani[2], Vittorio Sambri[1]

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0,57%

SUMMARY

A seroprevalence study for anti-West Nile virus-specific antibodies was carried out in healthy blood donors resident in the metropolitan area of Milan in two different years, 2009 and 2011. In 2009 no positive sera were found, whereas 5 positive sera were found in 2011, revealing viral circulation in this naive area. The seroprevalence rate identified in 2011 was 0.57%, suggesting that the area of WNV circulation in Italy is larger than that previously identified.

KEY WORDS: WNV, ELISA, IFA, MNTA, Seroprevalence, Italy.

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Somiglianze e differenze

- La disponibilità di vettori e le condizioni climatiche sono simili in Europa e Nord America
- La rapidità di diffusione di WNV in Nord America ed il numero di casi osservati sono molto maggiori rispetto all'Europa
- In entrambi i continenti sono presenti numerose specie di uccelli suscettibili all'infezione, ma le morie osservate in NA - solo marginalmente in EU - suggeriscono una maggior permissività, con il raggiungimento di viremie più elevate, nelle specie neoartiche
- La possibilità di contatti precedenti con WNV introdotto dall'Africa da migratori, possibile in EU, ma improbabile in NA, potrebbe spiegare la maggior resistenza delle specie paleoartiche

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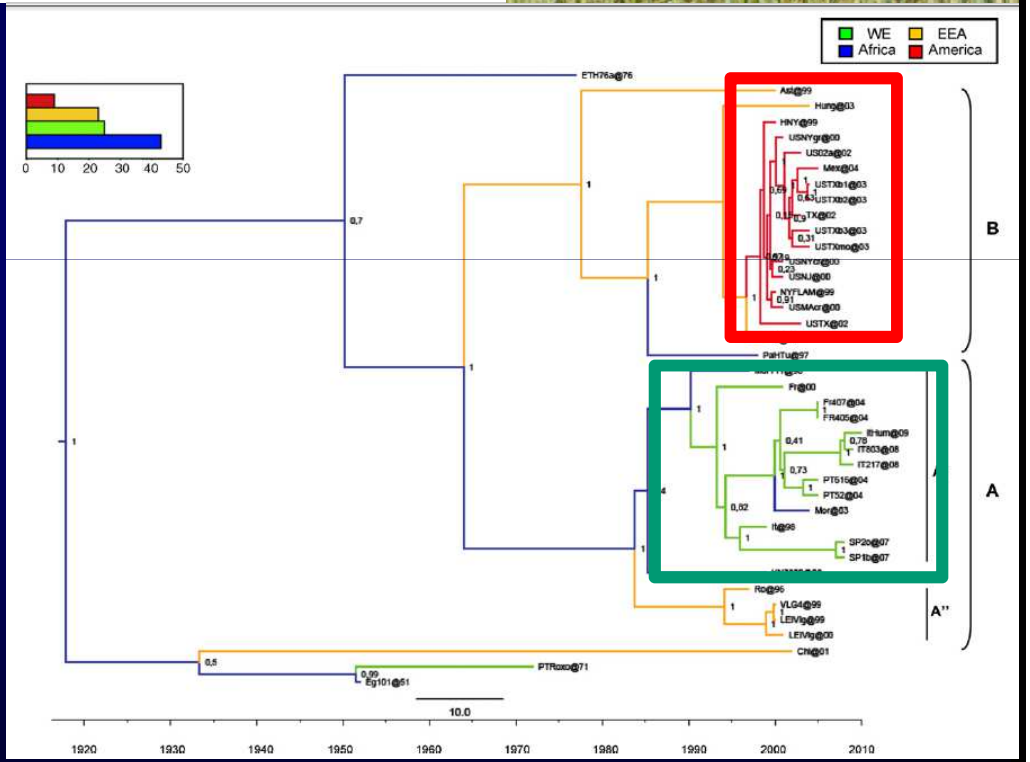
Phylogeography and epidemiological history of West Nile virus genotype 1a in Europe and the Mediterranean basin

Gianguglielmo Zehender [a,*], Erika Ebranati [a], Flavia Bernini [a], Alessandra Lo Presti [b], Giovanni Rezza [b], Mauro Delogu [c], Massimo Galli [a], Massimo Ciccozzi [b]

- WNV-1a segrega in 2 clades principali:
  - -Le sequenze recenti del Mediterraneo occidentale formano un gruppo monofiletico all'interno del clade A.
  - -Le sequenze del Mediterraneo orientale e le Americane si collocano nel clade B
- L'analisi filogeografica prospetta un'origine di WNV-1a nell'Africa subsahariana, all'inizio del XX secolo



Zehender et al. Infect Gen Evol. 2011, 11: 246-53

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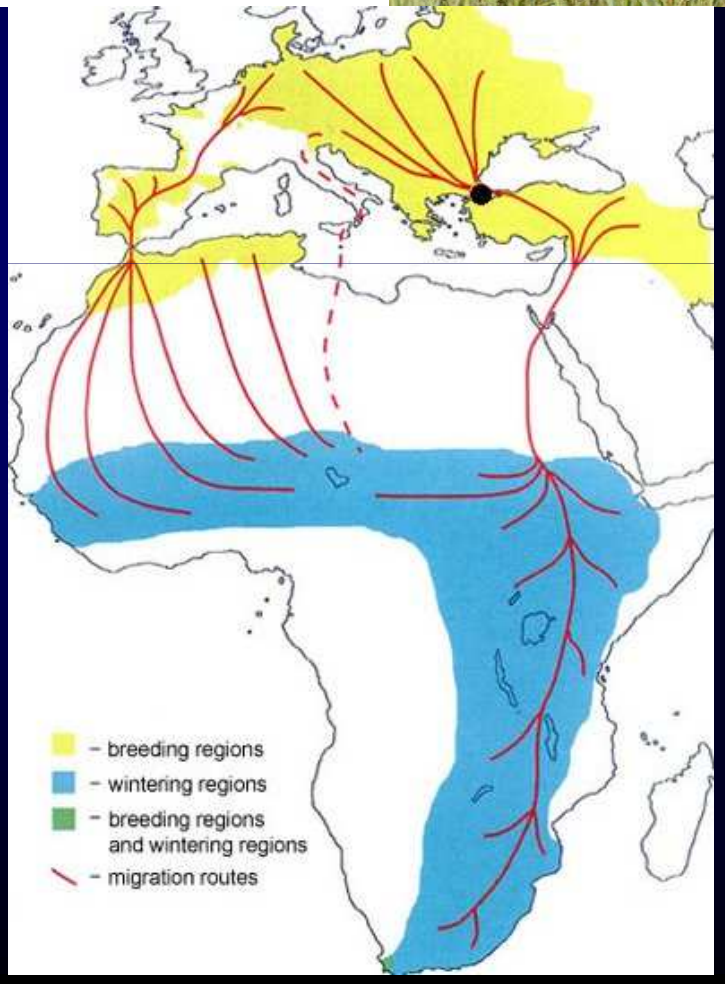
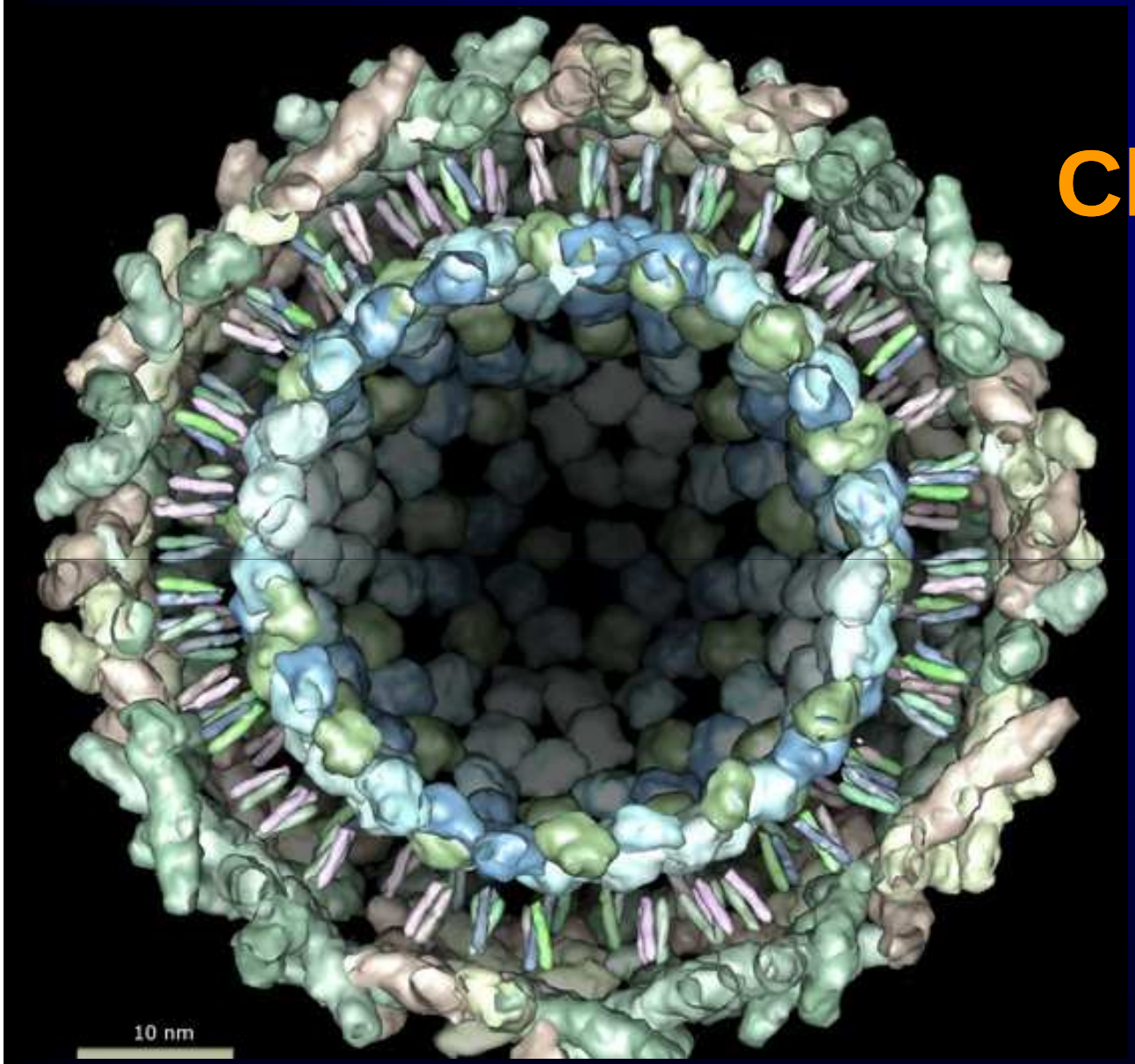
Due vie principali di penetrazione in Europa:

- **da Est (attraverso Israele, Russia e EU centrale) con ripetuti accessi negli anni '70 e '80**
- **da Ovest (dal Marocco e Gibilterra) più recentemente (anni '90)**

Il ceppo Italiano del 2008/2009 deriva dall'occidentale (Francia, Marocco,Portogallo) del 2003/04

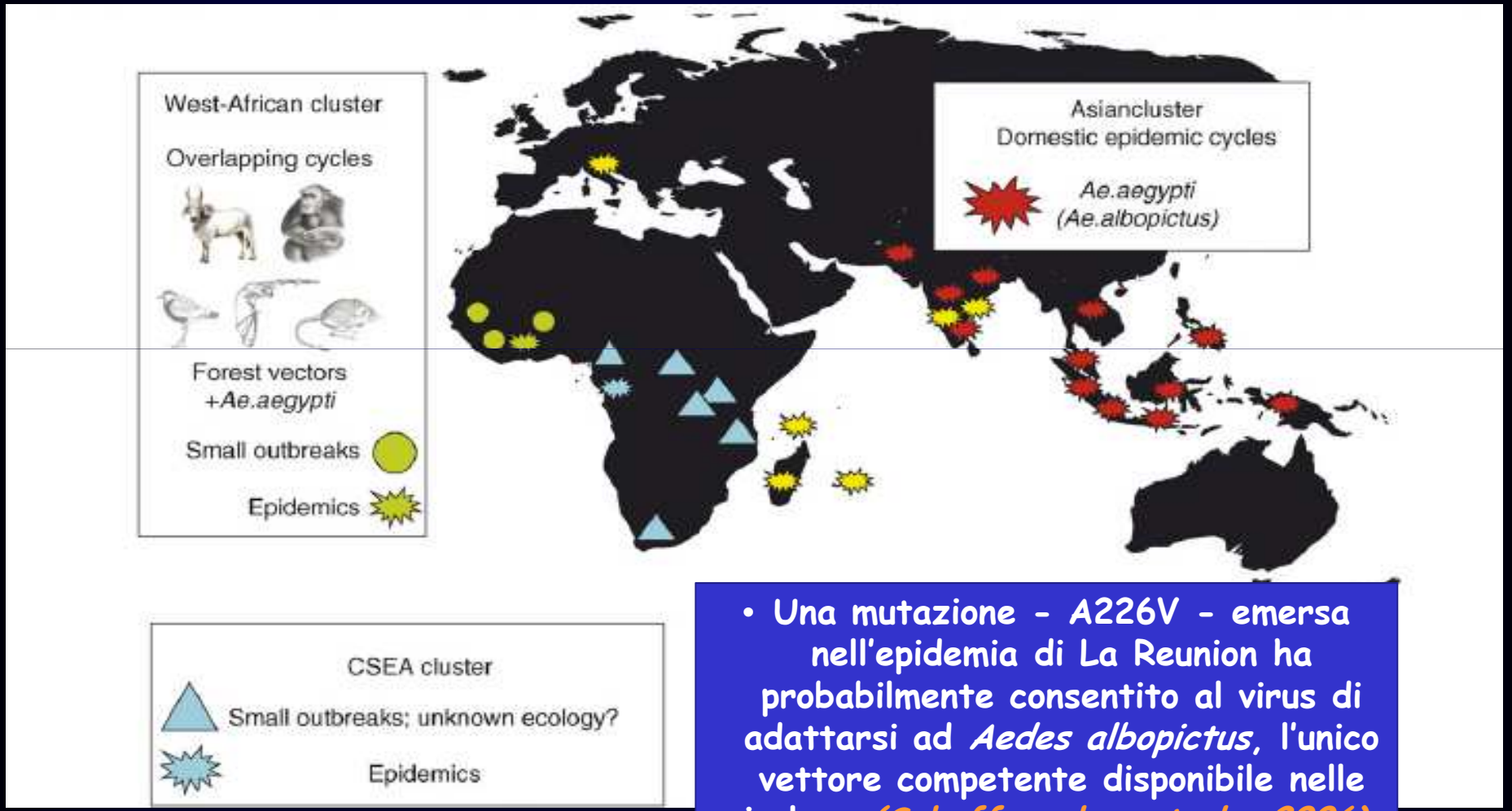


Chikungunya



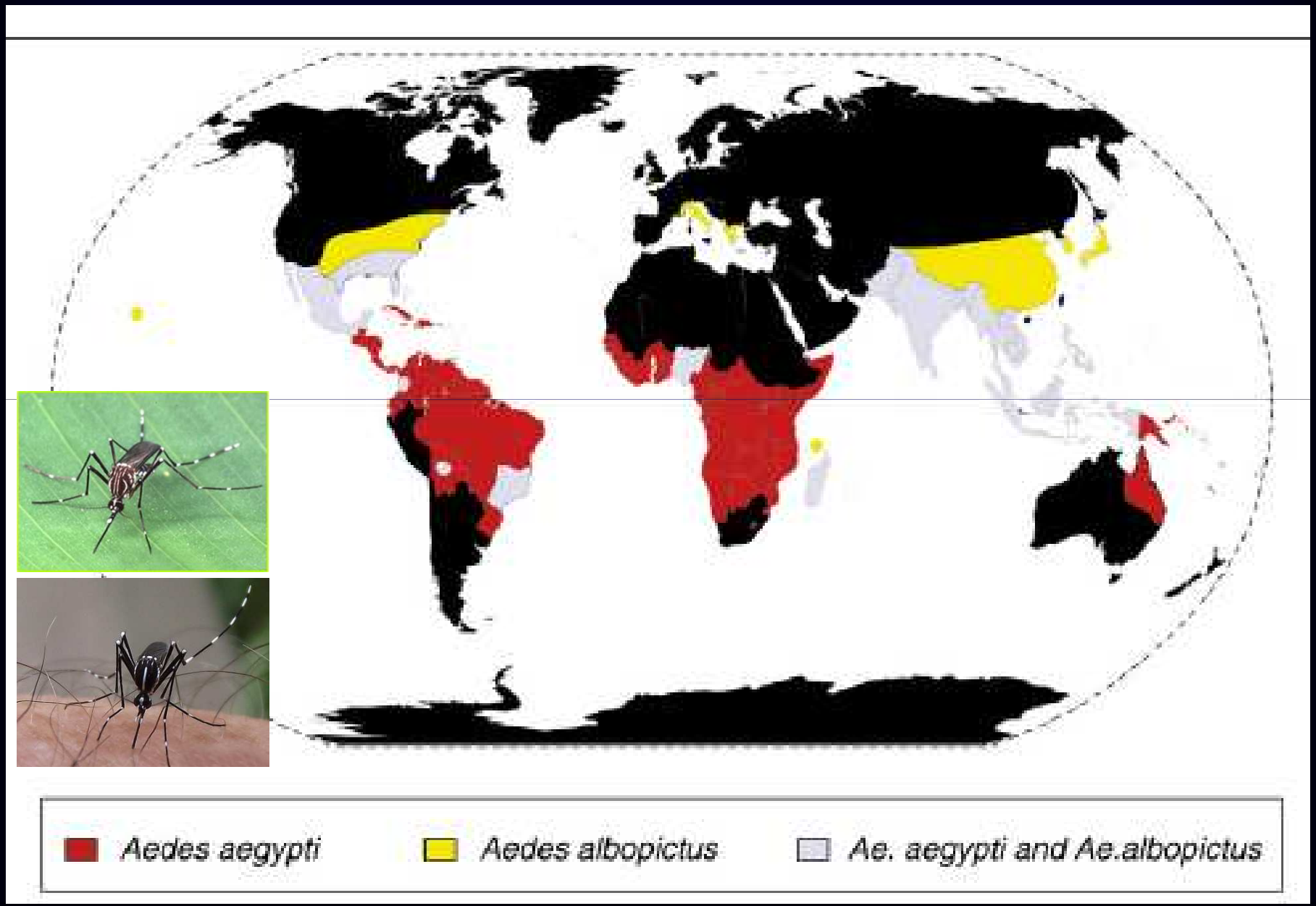
Chikungunya: quattro clusters

Africano Occidentale, Africano Sud-Orientale, Asiatico e 'delle Isole'

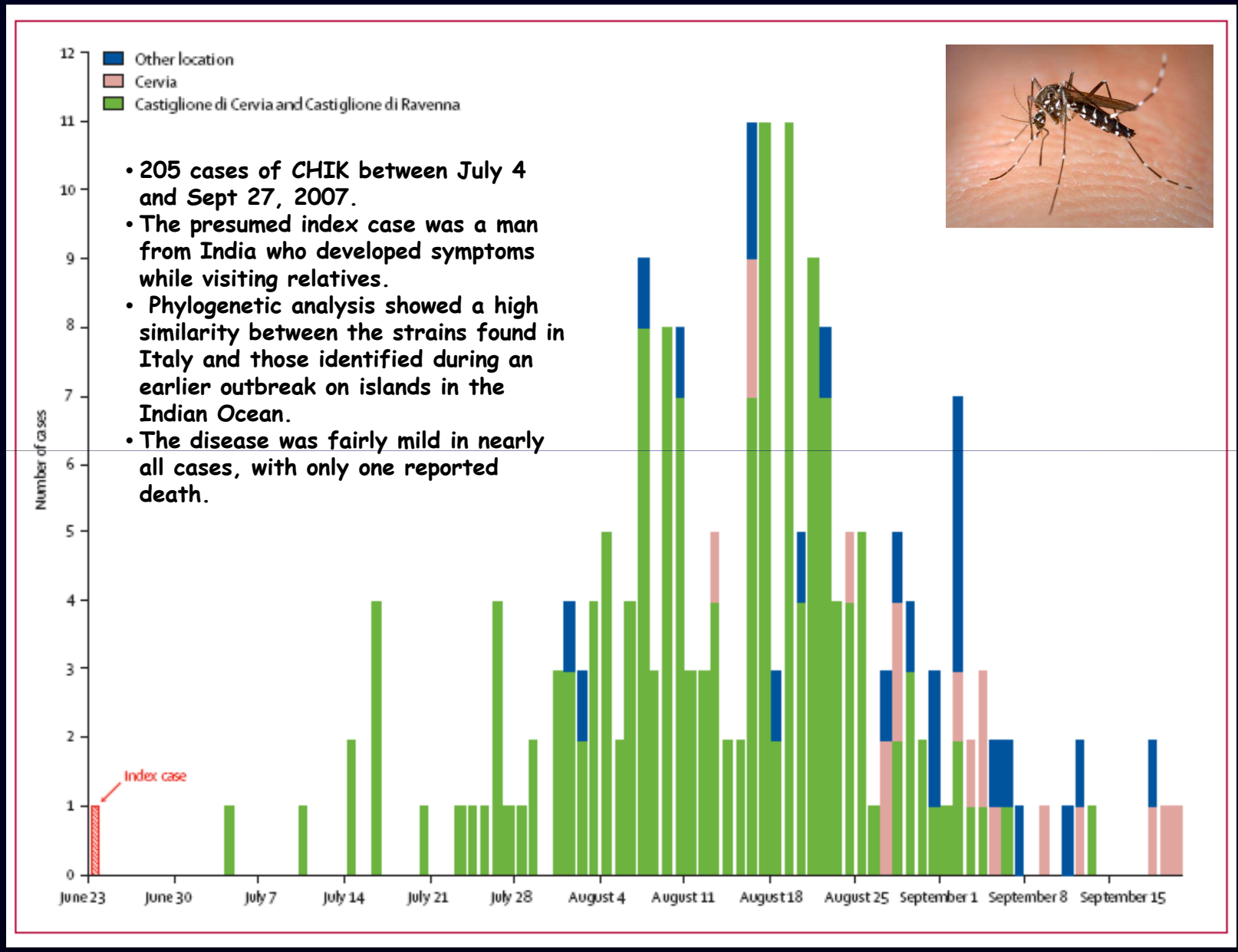


- Una mutazione - A226V - emersa nell'epidemia di La Reunion ha probabilmente consentito al virus di adattarsi ad *Aedes albopictus*, l'unico vettore competente disponibile nelle isole *(Schuffenecker et al., 2006).*

Areali di distribuzione di *aegipti* e *albopictus*



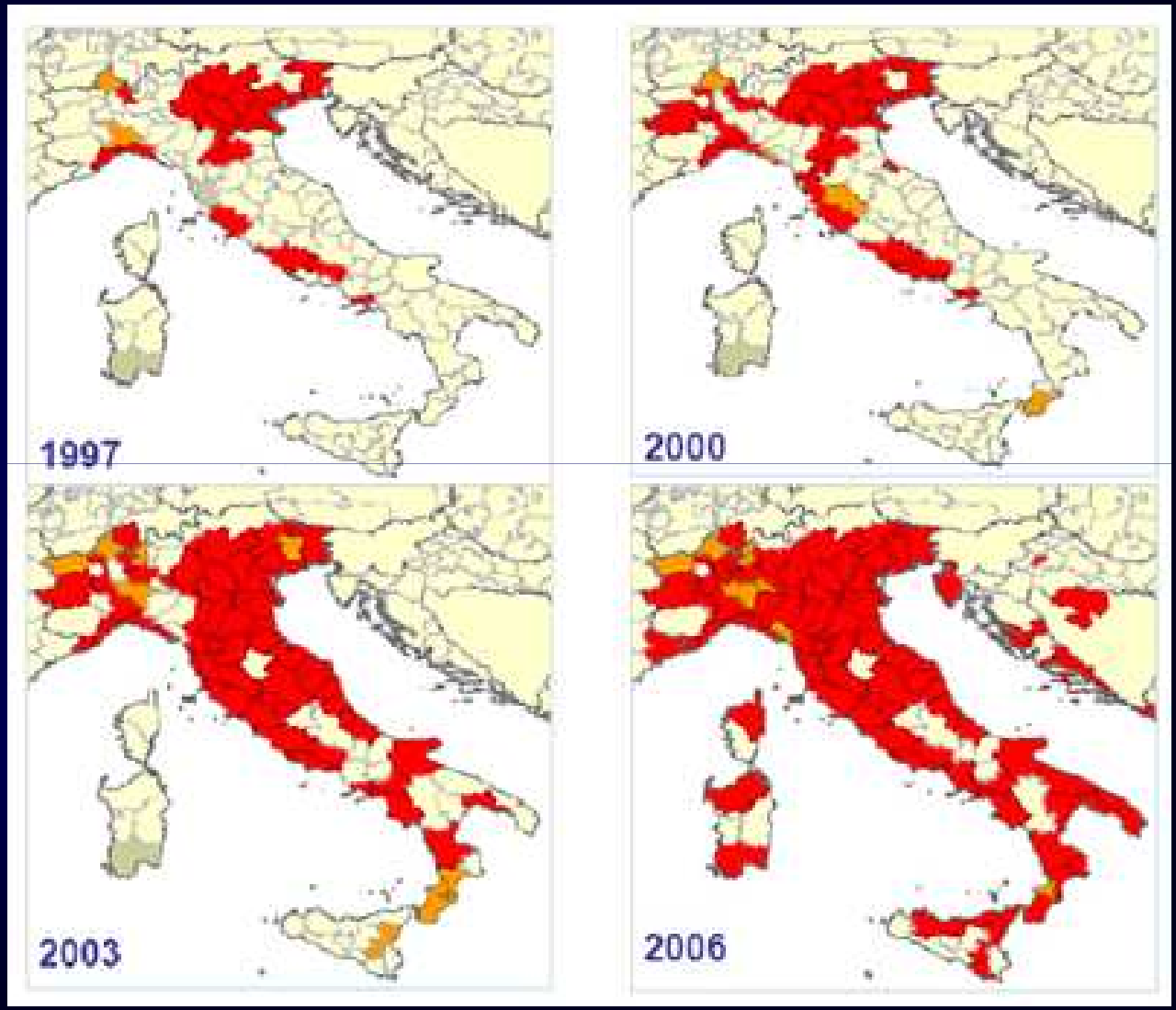
Chikungunya a Cervia, luglio-agosto 2007



- 205 cases of CHIK between July 4 and Sept 27, 2007.
- The presumed index case was a man from India who developed symptoms while visiting relatives.
- Phylogenetic analysis showed a high similarity between the strains found in Italy and those identified during an earlier outbreak on islands in the Indian Ocean.
- The disease was fairly mild in nearly all cases, with only one reported death.

Rezza et al Lancet 2007,370:1840-46

Areali di distribuzione di *aegipty* e *albopictus*



Countries and territories in the Americas where chikungunya cases have been reported *(as of October 14, 2014)*

- Al 14/10/2014 la trasmissione di Chik è stata accertata in **34** paesi dell'area Caraibica
- Un totale di **748,403** casi, di cui 13,186 confermati in laboratorio, sono stati riportati in quest'area in pochi mesi.

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PLOS ONE

High Efficiency of Temperate *Aedes albopictus* to Transmit Chikungunya and Dengue Viruses in the Southeast of France

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Abstract

Background: Since 2005, cases of chikungunya (CHIK) were caused by an unusual vector, *Aedes albopictus*. This mosquito, present in Europe since 1979, has gained importance since its involvement in the first CHIK outbreak in Italy in 2007. The species is capable of transmitting experimentally 26 arboviruses. However, the vectorial status of its temperate populations has remained little investigated. In 2010, autochthonous cases of CHIK and dengue (DEN) were reported in southeastern France. We evaluated the potential of a French population of *Ae. albopictus* in the transmission of both viruses.

Methodology and Principal Findings: We used two strains of each virus, CHIK and DEN: one strain was isolated from an imported case, and one from an autochthonous case. We used as controls *Aedes aegypti* from India and Martinique, the source of the imported cases of CHIK and DEN, respectively. We showed that *Ae. albopictus* from Cagnes-sur-Mer (AL-CSM) was as efficient as the typical tropical vector *Ae. aegypti* from India to experimentally transmit both CHIK strains isolated from patients in Fréjus, with around 35–67% of mosquitoes delivering up to 14 viral particles at day 3 post-infection (pi). The unexpected finding came from the high efficiency of AL-CSM to transmit both strains of DENV-1 isolated from patients in Nice. Almost 67% of *Ae. albopictus* AL-CSM which have ensured viral dissemination were able to transmit at day 9 pi when less than 21% of the typical DEN vector *Ae. aegypti* from Martinique could achieve transmission.

Conclusions/Significance: Temperate *Ae. albopictus* behaves differently compared to its counterpart from tropical regions, where recurrent epidemic outbreaks occur. Its potential responsibility for outbreaks in Europe should not be minimized.

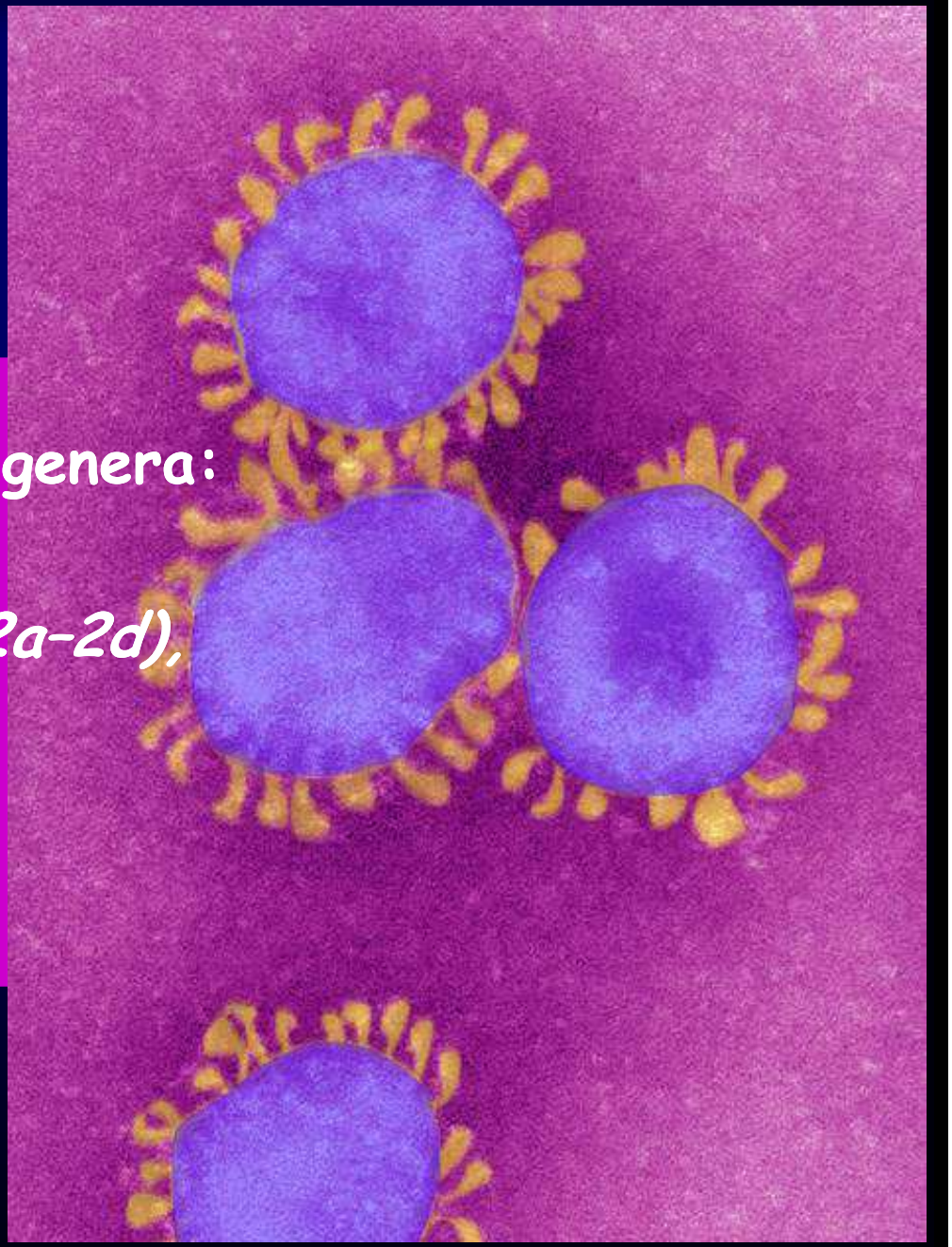
Citation: Vega-Rua A, Zouache K, Caro V, Diancourt L, Delaunay P, et al. (2013) High Efficiency of Temperate *Aedes albopictus* to Transmit Chikungunya and Dengue Viruses in the Southeast of France. PLoS ONE 8(3): e59716. doi:10.1371/journal.pone.0059716

- *Ae.albopictus* from Cagnes-sur-Mer (AL-CSM) was as efficient as the typical tropical vector *Ae.aegypti* from India to experimentally transmit both CHIK strains from Fréjus, with 35–67% of AL-CSM delivering up to 14 viral particles at day 3 post-infection (pi).
- AL-CSM were also highly efficient in transmitting both strains of DENV-1 isolated from patients in Nice (67% vs 21% of the typical DEN vector *Ae. aegypti* from Martinique at day 9 pi).

WHO 23/10/2014: Four cases of chikungunya infection occurred within the same family, with symptoms onset between 20 September and 12 October. The cases live in Montpellier in the vicinity of a chikungunya case imported from Cameroon

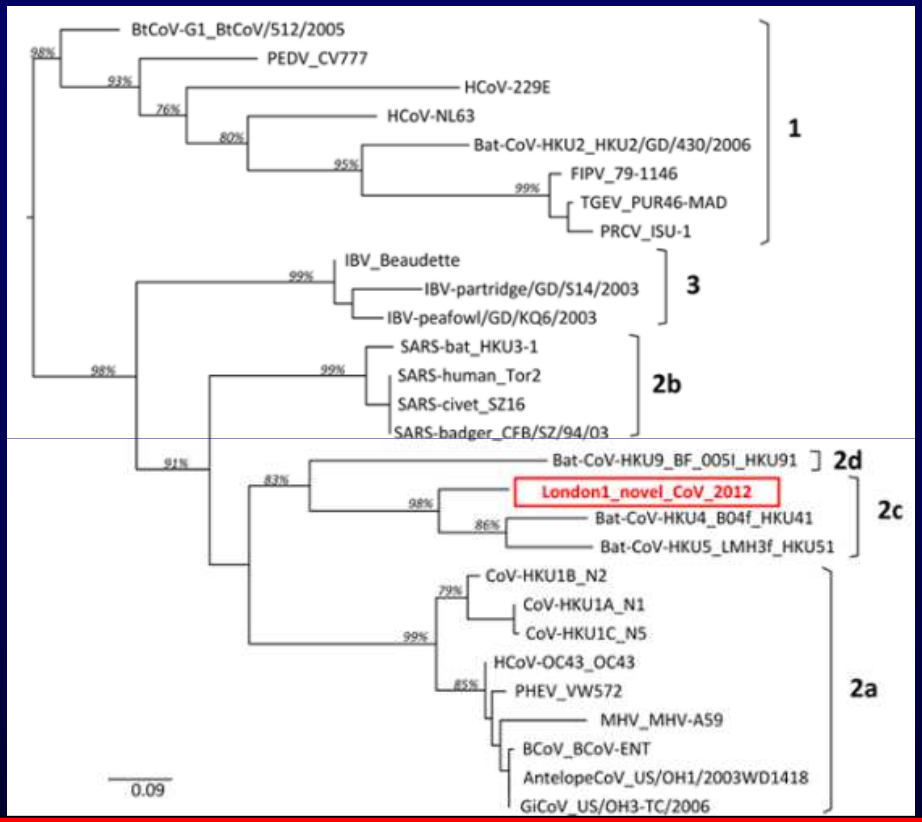
Coronaviridae

- CoVs are classified into 4 genera:
  - *Alphacoronavirus,*
  - *Betacoronavirus (clades 2a–2d),*
  - *Gammacoronavirus,*
  - *Deltacoronavirus.*



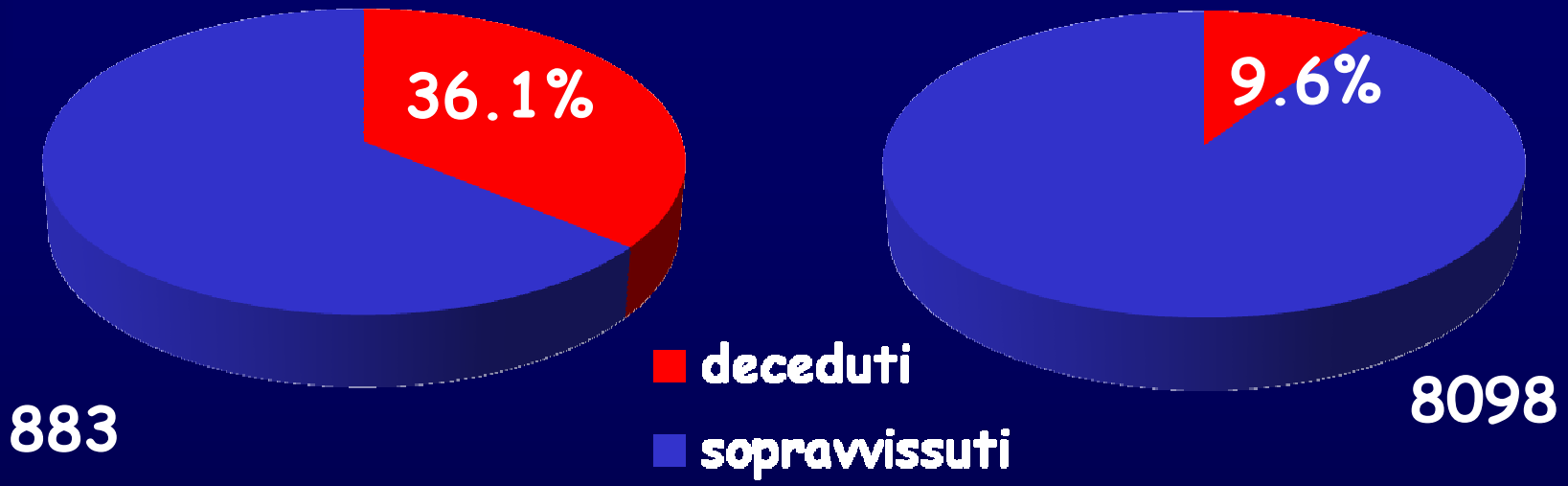
MERS: emergence of a novel human coronavirus

- A novel coronavirus (CoV) that causes a severe lower respiratory tract infection in humans, emerged in the Middle East region in 2012.
- This virus, named Middle East respiratory syndrome (MERS)-CoV, is phylogenetically related to bat CoVs



- Globally, 883 laboratory-confirmed cases of infection with MERS-CoV including at least 319 related deaths have been reported to WHO (24/10/2014)

MERS vs SARS



- La SARS è stata fermata in pochi mesi nel corso del 2003, nonostante avesse interessato più continenti e causato un elevato numero di casi, tra cui 1707 (21.1%) in HCW
- La MERS è in circolazione da più di due anni e colpisce prevalentemente persone con comorbilità, il che spiega la più elevata letalità. Deve essere ancora chiarito se la malattia sia mantenuta da successive immissioni dal reservoir animale o dalla trasmissione inter-umana

Il pipistrello delle tombe egizie

- Isolata una sequenza parziale di MERS CoV in un campione fecale di 1/29 esemplari catturati in Egitto (tasso di infezione 3.5%; 95%CI 0-20, molto inferiore rispetto a quello di SARS CoV - 10-12.5% - osservato nei rinolofidi in Cina) *Memish et al. EID 2013; 19: 1819-23*

Il ruolo del dromedario

- MERS CoV circolerebbe nei dromedari in Arabia Saudita almeno dal 1992 *Alagaili et al.mBio 2014; 5: e00884-14.*
- Dimostrata la trasmissione diretta dal dromedario al proprietario *Azhar et al. NEJM 2014; 370: 2499-2505*
- Non chiarito invece un possibile ruolo di animali serbatoio di pecore, capre, bovini, roditori

?

Virus Genes (2014) 48:366–371
DOI 10.1007/s11262-013-1008-x

Alpha and lineage C betaCoV infections in Italian bats

Paola De Benedictis · Sabrina Marciano · Dino Scaravelli · Pamela Priori · Barbara Zecchin · Ilaria Capua · Isabella Monne · Giovanni Cattoli

Virus molto simili a MERS CoV sono stati ritrovati anche in:

- *Nycteris spp* in Ghana
- *Pipistrellus spp* in Europe
- *Neoromicia cf zuluensis* in Sud Africa

Annan et al. EID 2013; 19: 456-59
Ithete et al EID 2013; 19: 1697-99

Virus Genes (2014) 48:366–371
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Alpha and lineage C betaCoV infections in Italian bats

Paola De Benedictis · Sabrina Marciano · Dino Scaravelli · Pamela Priori · Barbara Zecchin · Ilaria Capua · Isabella Monne · Giovanni Cattoli

- Almeno due altri coronavirus di probabile derivazione da pipistrelli, HCoV-NL63, un αCoV e HCoV-HKU1, un βCoV, si sono dimostrati in grado di causare infezioni nell'uomo