Ebola Hemorrhagic Fever

Ronald G Nahass, MD, MHCM, FIDSA
President – ID CARE
Clinical Professor of Medicine-Rutgers University
Robert Wood Johnson Medical School

INFECTIOUS DISEASES CARE

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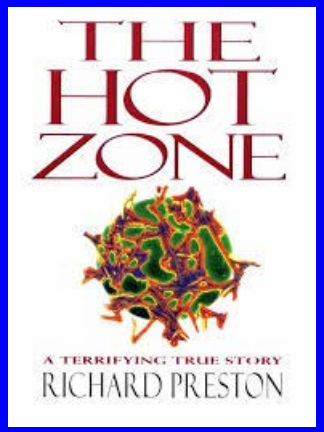
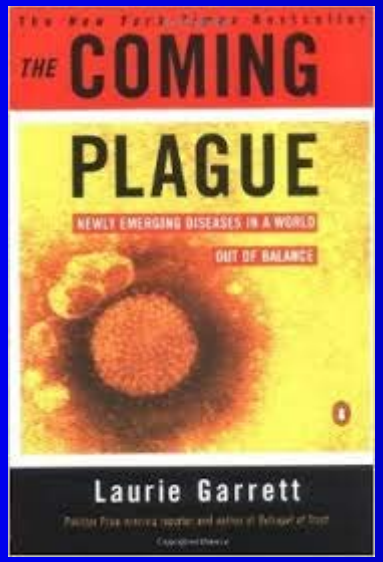
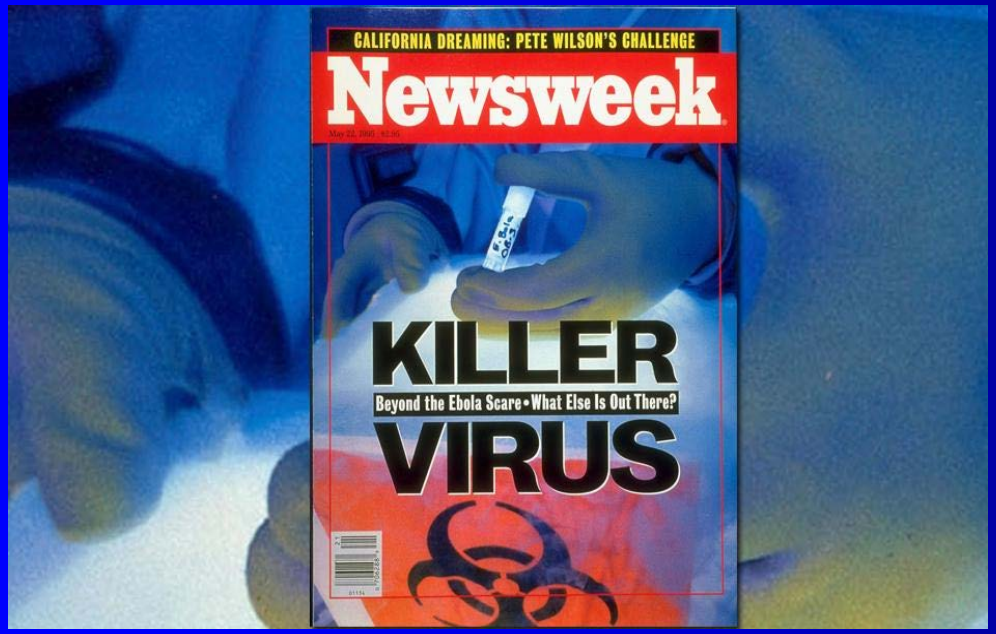
Best Sellers





Media

September 2014



NEWS – September 30, 2014

The Economist

OCTOBER 18TH-24TH 2014

The war on Ebola

GOALS

- Review the history, epidemiology and illness of Ebola Virus Infection
- Discuss Infection Prevention and Preparedness
- Discuss ZMAPP in the treatment of Ebola
- Attempt to answer your questions

History of Ebola – Its Name

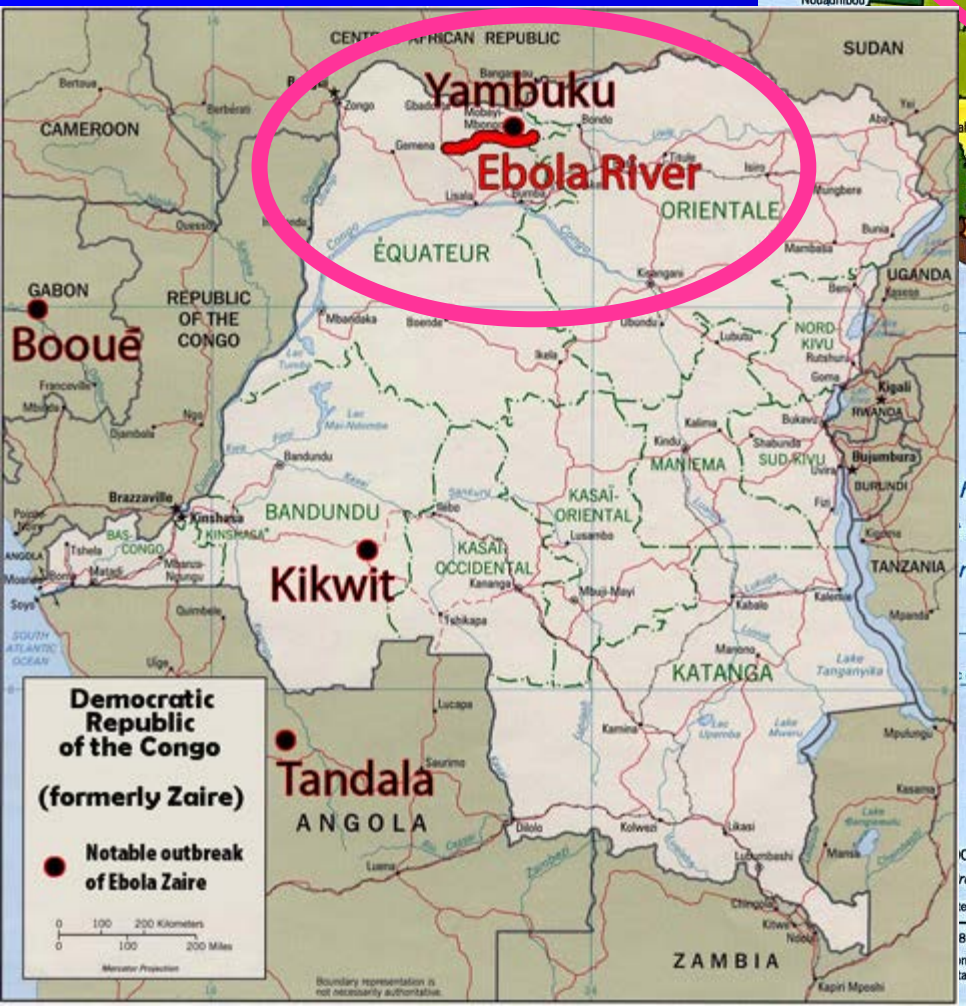
August 26, 1976 in Yambuku, a town in the north of Zaïre. A 44-year-old school teacher returned from a small hike. He went to the doctor and because of his high fever they gave him a quinine shot for malaria

A week later, he had uncontrolled vomiting, bloody diarrhea, trouble breathing and then bleeding from his nose, mouth, and anus.

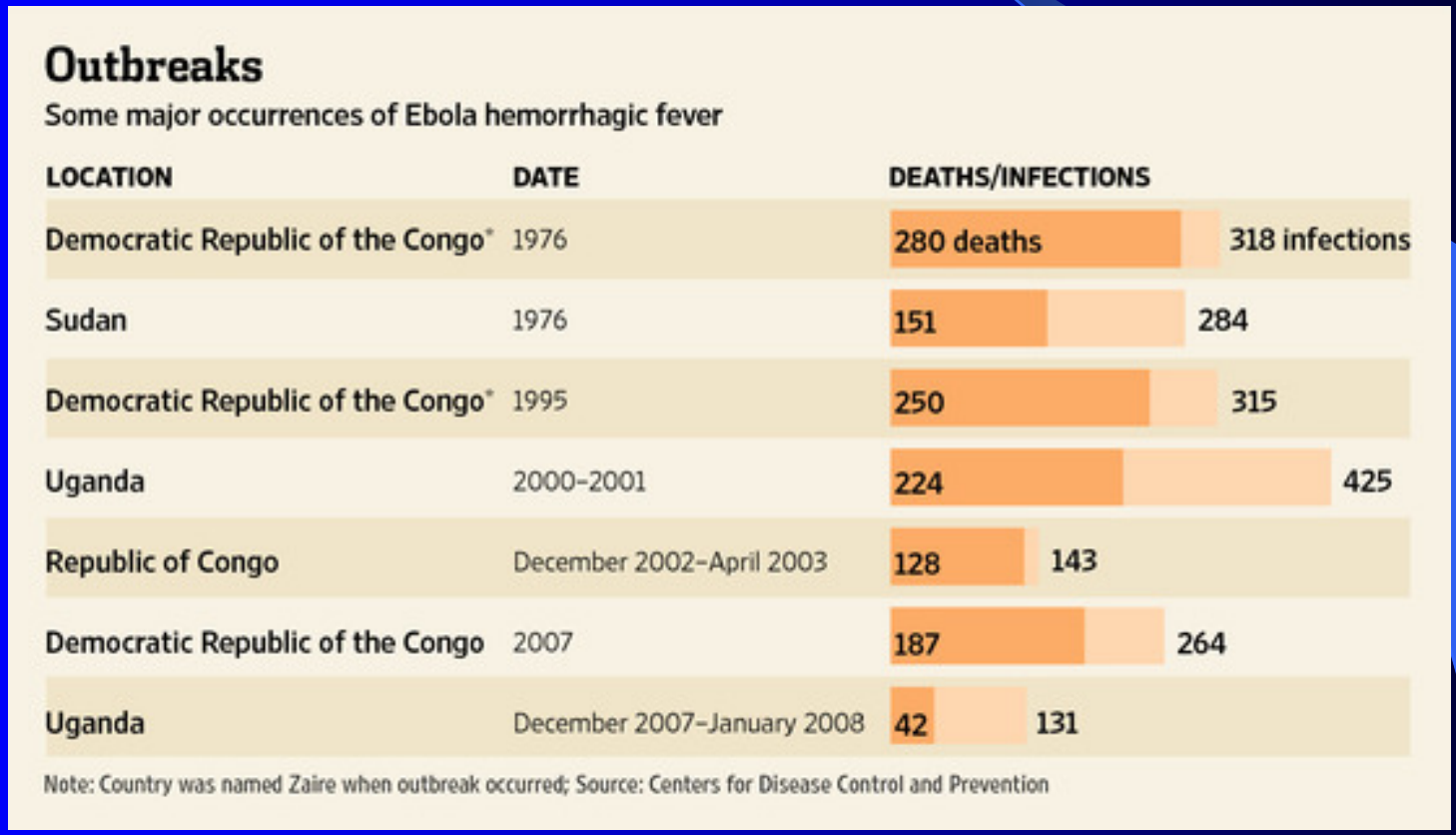
He died ~14 days after the onset of symptoms.

He started an epidemic that killed 280 of the 313 infected persons (88%).

Zaire = Democratic republic of congo



Prior Top Outbreaks



Outbreaks

Some major occurrences of Ebola hemorrhagic fever

LOCATION	DATE	DEATHS/INFECTIONS
Democratic Republic of the Congo*	1976	280 deaths / 318 infections
Sudan	1976	151 / 284
Democratic Republic of the Congo*	1995	250 / 315
Uganda	2000–2001	224 / 425
Republic of Congo	December 2002–April 2003	128 / 143
Democratic Republic of the Congo	2007	187 / 264
Uganda	December 2007–January 2008	42 / 131

Note: Country was named Zaire when outbreak occurred; Source: Centers for Disease Control and Prevention

Geography – Provides Clues to Origin

- The link between human infection by the Ebola virus and their proximity to primates is clear.

  -Outbreaks occurred in countries that house 80 percent of the wild gorilla and chimpanzee populations.

  - The outbreaks coincided with the outbreaks in wild animals.

  - The same viral strains were isolated in animal carcasses and in the bodies of those who handled those carcasses.

  - These outbreaks were preceded by an abnormally large death in wild Gorilla populations.

Ebola - Epidemiology

Since the virus kills gorillas, chimpanzees and other monkeys in such a high percentage – they are not likely to be its natural host.

Ebola Outbreak Killed 5000 Gorillas

Magdalena Bermejo,[1,2]* José Domingo Rodríguez-Teijeiro,[2] Germán Illera,[1] Alex Barroso,[2] Carles Vilà,[3] Peter D. Walsh[4]

Over the past decade, the Zaire strain of Ebola virus (ZEBOV) has emerged repeatedly in Gabon and Congo. During each human outbreak, carcasses of western gorillas (*Gorilla gorilla*) and chimpanzees (*Pan troglodytes*) have been found in neighboring forests (*1*). Opinions have differed as to the conservation implications. Were these isolated mortality events of limited impact (*2*)? Was ZEBOV even the cause (*3*)? Or, were they part of a massive die-off that threatens the very survival of these species (*4*)? Here, we report observations made at the Lossi Sanctuary in northwest Republic of Congo, where ZEBOV was the confirmed cause of ape die-offs in 2002 and 2003 (*5*). Our results strongly support the massive die-off scenario, with gorilla mortality rates of 90 to 95% indicated both by observations on 238 gorillas in known social groups and by nest surveys covering almost 5000 km^2. ZEBOV killed about 5000 gorillas in our study area alone.

Starting in 1995, we habituated gorillas to our presence, and by 2002 we had identified 10 social groups with 143 individuals (fig. S1). In late 2001 and early 2002, human outbreaks of ZEBOV had flared up along the Gabon-Congo border (*1*). In June 2002, a gorilla carcass was found 15 km west of the sanctuary. By October, gorilla and chimpanzee carcasses began appearing inside the sanctuary. In the next 4 months, we found 32 carcasses. Twelve of the carcasses were assayed for ZEBOV, and 9 tested positive (*5*). From October 2002 to January 2003, 91% (130/143) of the individually known gorillas in our study groups had disappeared.

In June 2003, one fresh carcass appeared south of the sanctuary. In September, we identified seven new social groups with home ranges straddling and to the east of the two rivers and monitored their sleeping nests on a biweekly basis. Then in October carcasses again appeared within the sanctuary. Ten carcasses were found in the following 3 months. From October 2003 to January 2004, Ebola spread sequentially from north to south, killing 91 of the 95 individuals (95.8%) in the newly monitored groups. One remarkable feature of this spread was that the onset of ZEBOV deaths in each group was predicted by the number of home ranges separating it from the first group to experience deaths (Fig. 1A). In particular, the estimated time lag between deaths in successive groups (11.2 days) was very similar to the typical length of the ZEBOV disease cycle of about 12 days (*6*). Assuming deaths were caused by spillover from a north-south reservoir epizootic did not fit the mortality pattern well (Fig. 1B). This implies that recent ape die-offs may not have been caused only by massive spillover from a reservoir host (*1*, *5*). Rather, group-to-group transmission may have also played a role in amplifying outbreaks, as transmission within gorilla groups apparently has (*7*).

The location of carcasses at the end of 2002 suggested a sharp mortality frontier running north to south at about longitude 14.55°E. The late-2003 outbreak reemerged along this frontier, but nest surveys conducted in 2004 and 2005 suggest that it affected only a limited enclave centered on our study site. High gorilla densities still persist in much of the region to the east of the 14.55°E frontier, but to the west a zone covering at least 2700 km^2 was largely emptied of gorillas, with nest encounter rates 96% lower than in the east (Fig. 1C). This encounter rate difference is not explained well by hunting, because the western zone experienced substantially lower hunting pressure than that in the eastern zone (table S1).

If we conservatively assume that the western zone held pre-Ebola ape densities only half as high as the 4.4 gorillas/km^2 typical of the sanctuary, then the east-west difference in nest encounter rate implies that ZEBOV killed about 5500 [minimum 3900 (Materials and Methods)]. We lack the density data necessary to make a similar estimate for chimpanzees, but east-west differences in nest encounter rate (Fig. 1D) imply a ZEBOV-induced decline of about 83% (table S1).

We hope this study dispels any lingering doubts that ZEBOV has caused massive gorilla die-offs. The Lossi outbreaks killed about as many gorillas as survive in the entire eastern gorilla species (*Gorilla beringei*). Yet Lossi represents only a small fraction of the western gorillas killed by ZEBOV in the past decade or indeed of the number at high risk in the next 5 years. Add commercial hunting to the mix, and we have a recipe for rapid ecological extinction. Ape species that were abundant and widely distributed a decade ago are rapidly being reduced to tiny remnant populations.

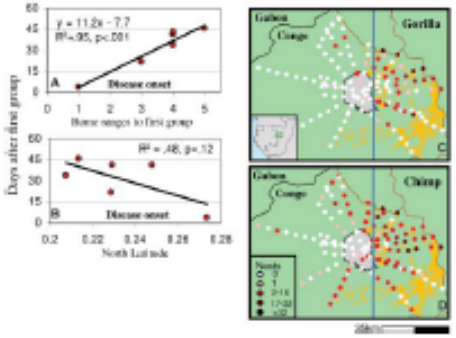


Fig. 1. (**A**) Last day at which each group was at full size plotted against number of home ranges separating that group from the first group to suffer deaths. (**B**) Day of last full group size was not well predicted by latitude, as might be expected with spillover from a north-to-south reservoir epizootic. Assuming other reservoir epizootic trajectories did not improve fit. (**C**) Gorilla nest distribution during 2004 to 2005 surveys (after ZEBOV die-offs). Shading of each dot proportional to number of gorilla nests found on a 5-km survey segment. Blue line at 14.55°E longitude separates eastern from western sampling zone. Lossi Sanctuary in gray, savannas in yellow, and roads in brown. (**D**) Chimpanzee nest distribution in 2004 to 2005 surveys.

References and Notes

1. E. M. Leroy *et al.*, *Science* 303, 387 (2004).
2. J. F. Oates, *Primates* 47, 102 (2006).
3. J. M. Sleeman, *Oryx* 39, 174 (2004).
4. P. D. Walsh *et al.*, *Nature* 422, 611 (2003).
5. P. Rouquet *et al.*, *Emerg. Infect. Dis.* 11, 283 (2005).
6. P. Formenty *et al.*, *J. Infect. Dis.* 179, S120 (1999).
7. D. Gilbert *et al.*, *Ecol. Biol.* 16, 499 (2004).

8. We thank P. Rouquet, X. Fouraté, and E. Leroy for discussions; our field assistants for their personal involvement; the European Union (EU) SCOFAC program, the Congolese Ministry of the Environment, and T. Smith for facilitation; C. Aveling, J. Hallé, and O. Langbein for advice, support, and encouragement; and Sovereign Africa Oil Company, the EU Sphinx-Rivages program, and the University of Barcelona (Becarios Project) for funding.

Supporting Online Material
www.sciencemag.org/cgi/content/full/314/5805/1564/DC1
Materials and Methods
Fig. S1
Table S1
References
Movie S1

27 July 2006; accepted 19 September 2006
10.1126/science.1133105

[1]Ecosystèmes Forestiers d'Afrique Centrale (ECOFAC), Boîte Postale 15115 Libreville, Gabon. [2]Department of Animal Biology, University of Barcelona, 08028 Barcelona, Spain. [3]Department of Evolutionary Biology, Uppsala University, SE-752 36 Uppsala, Sweden. [4]Max Planck Institute for Evolutionary Anthropology, 04103 Leipzig, Germany.

*To whom correspondence should be addressed. E-mail: magda_bermejo@yahoo.es

What is the Natural Host?

Vol 438|1 December 2005 nature

BRIEF COMMUNICATIONS

Fruit bats as reservoirs of Ebola virus

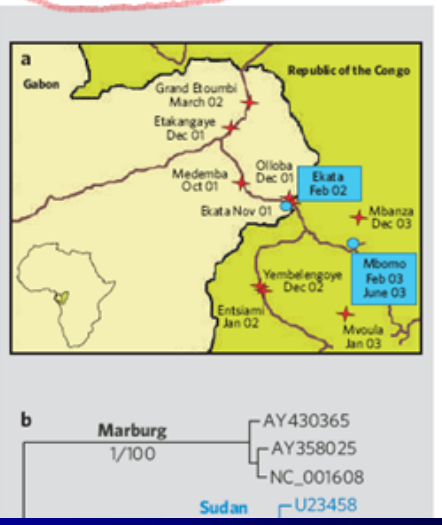
Bat species eaten by people in central Africa show evidence of symptomless Ebola infection.

The first recorded human outbreak of Ebola virus was in 1976, but the wild reservoir of this virus is still unknown[1]. Here we test for Ebola in more than a thousand small vertebrates that were collected during Ebola outbreaks in humans and great apes between 2001 and 2003 in Gabon and the Republic of the Congo. We find evidence of asymptomatic infection by Ebola virus in three species of fruit bat, indicating that these animals may be acting as a reservoir for this deadly virus.

Human Ebola outbreaks that occurred between 2001 and 2005 in Gabon and the Republic of the Congo were linked to concurrent outbreaks that devastated local gorilla and chimpanzee populations[2,3]. To identify the viral reservoir, we undertook three trapping expeditions in areas close to infected gorilla

be because PCR-positive bats were recently infected and were tested before they developed a detectable immune response. Alternatively, it could be that differences in the virulence of Ebola virus strains led to different immunological responsiveness and viral replication patterns. Of the bat species collected at Mbomo in February 2003, 7 of 31 (22.6%) and 0 of 10 (0%) were PCR-positive and IgG-positive, respectively, but five months later the corresponding results were 4 of 184 (2.2%) and 12 of 160 (7.5%). These opposite trends in the PCR and serological results are consistent with the first hypothesis.

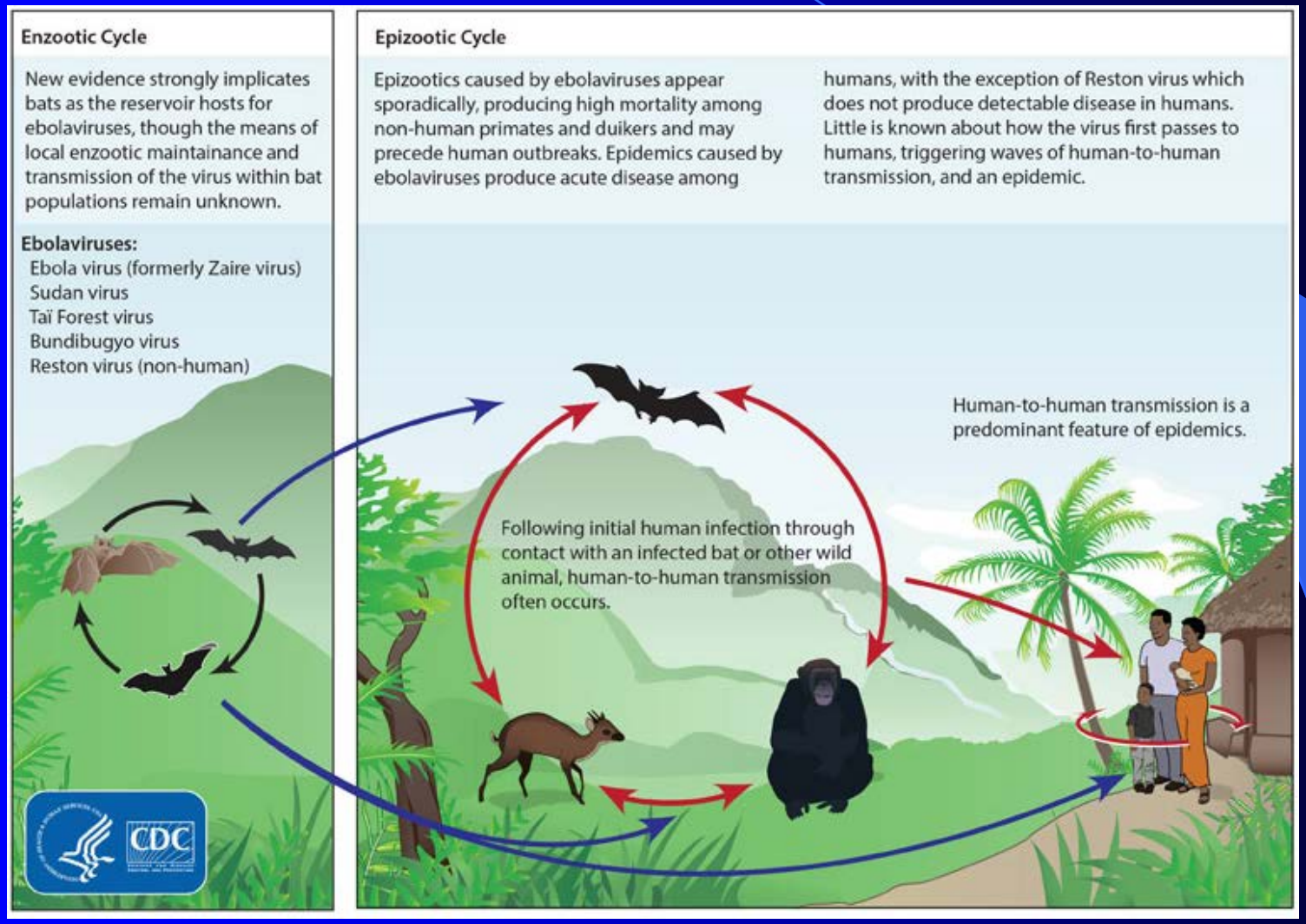
Each of the three bat species has a broad geographical range that includes regions of Africa where human Ebola outbreaks occur[5] (Fig. 1c). Our findings support results of



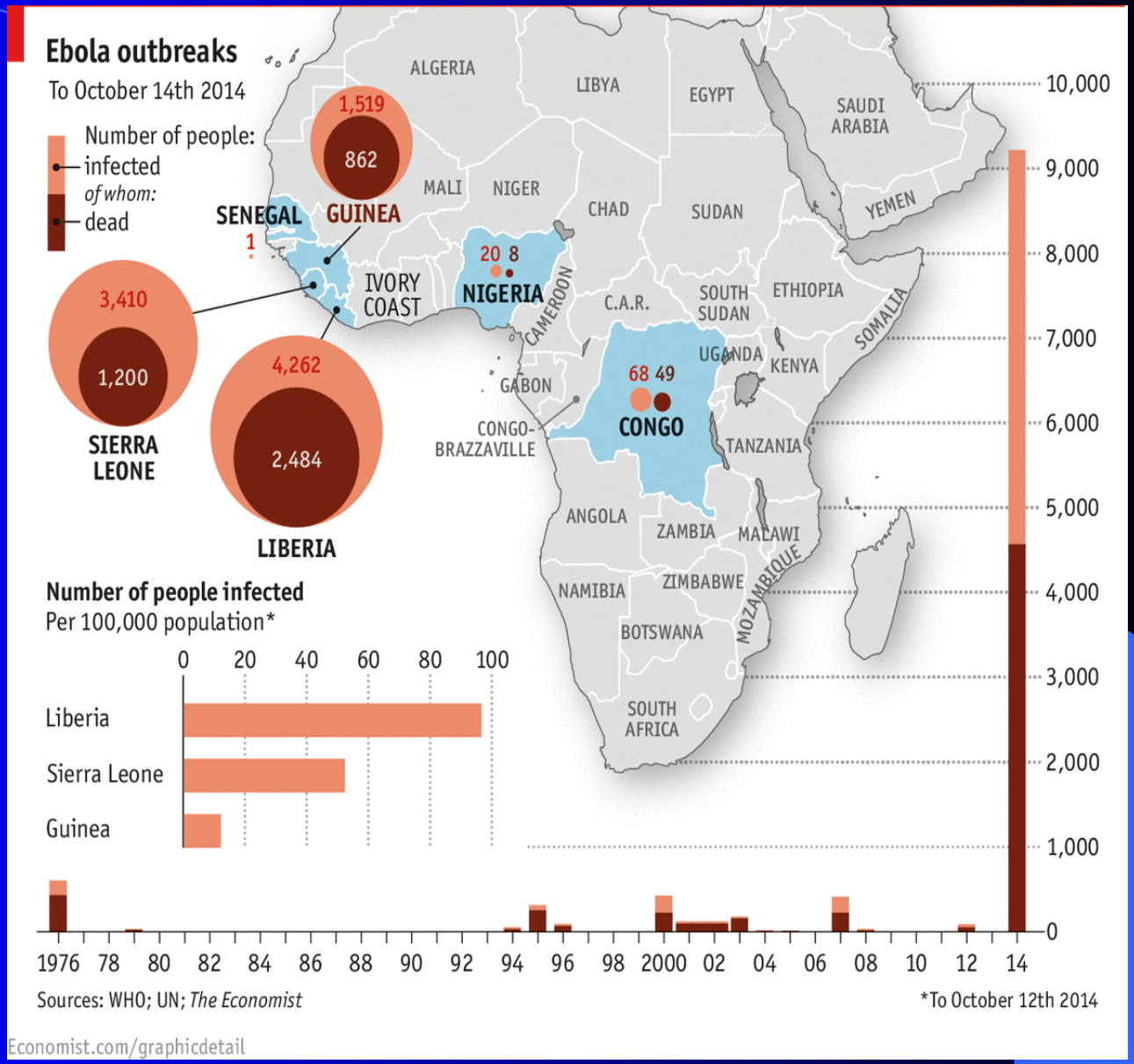
Fruit Bat is the Host

- Antibodies against Ebola
- Ebola Gene sequences in liver and spleen
- Fruit bats do not show any symptoms
- Best candidate to be the reservoir

Transmission



The first reported case was in December 2013, in Guinea near the border with Liberia and Sierra Leone. By late March, Liberia had reported eight suspected cases and Sierra Leone six. By the end of June 759 people had been infected and 467 people had died from the disease, making this the worst ever Ebola outbreak. The numbers are accelerating. As of October 14th, 9,216 cases and 4,555 deaths had been reported worldwide.



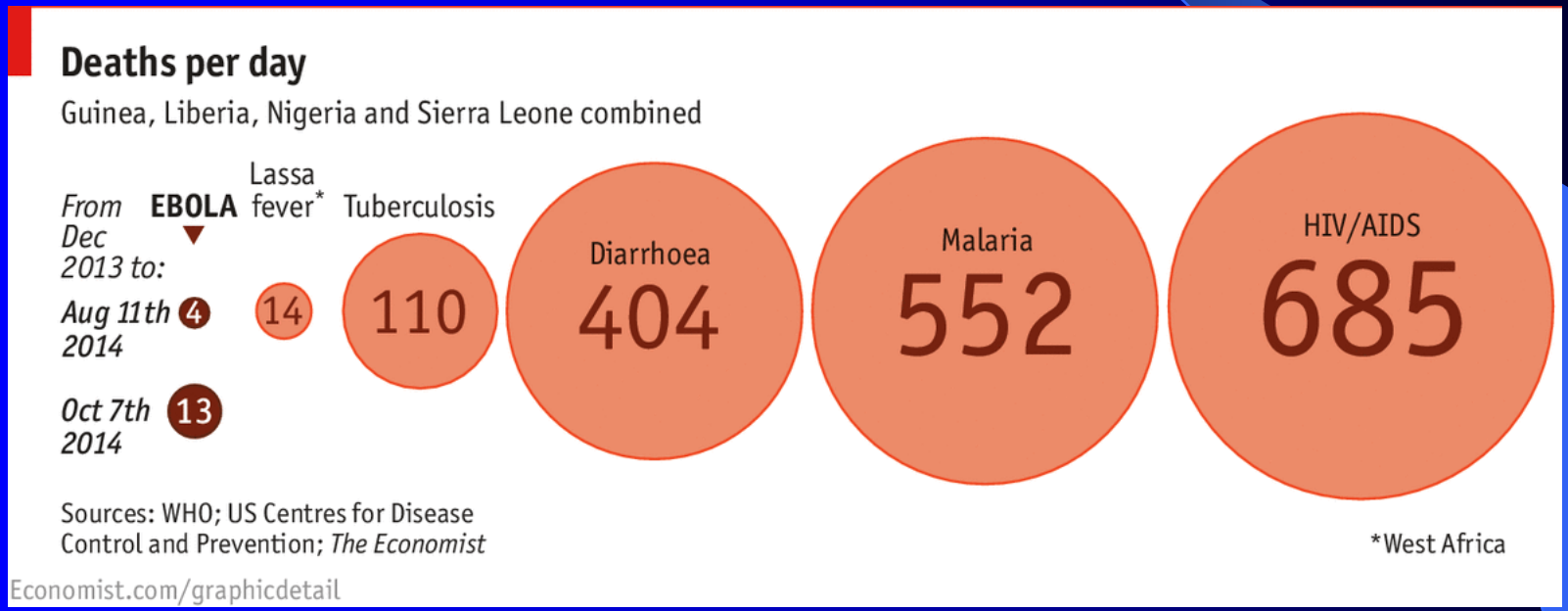
USA Contagious Disease Statistics - 2011

- New tuberculosis cases: 10,528
- New salmonella cases: 51,887
- New Lyme disease cases: 33,090
- New meningococcal disease cases: 759
- Influenza mortality annually of 36,000

World Contagious Disease Statistics

- 200 million cases and 625,000 deaths from Malaria
- 500,000 cases Chikungunya in past 9 months in the Caribbean
- 2.5 Billion with TB, 8.6 Million Sick, 1.3 million died in 2012
- 360 million with chronic Hepatitis B and 600,000 deaths annually

Local Perspective



Airborne

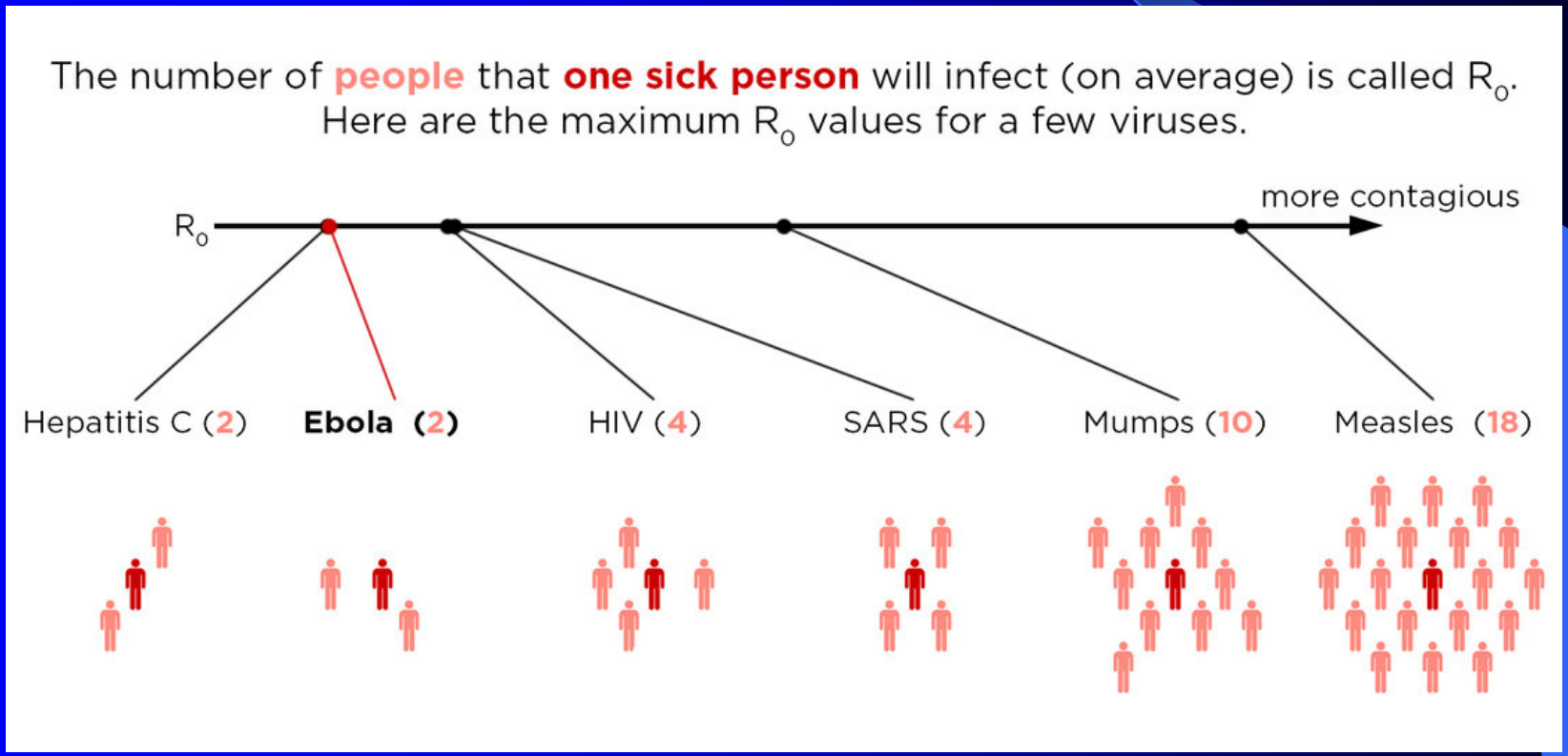
For every 100 infected passengers who board a flight* in Guinea, Liberia or Sierra Leone, number expected to disembark in:

Highest-risk destination countries

*Direct and connecting flights. Before introduction of flight restrictions

Source: Dirk Brockmann, Humboldt University, Berlin

How Contagious Is Ebola?
What is the R0



http://www.npr.org/blogs/health/2014/10/02/352983774/no-seriously-how-contagious-is-ebola

Molecular Structure

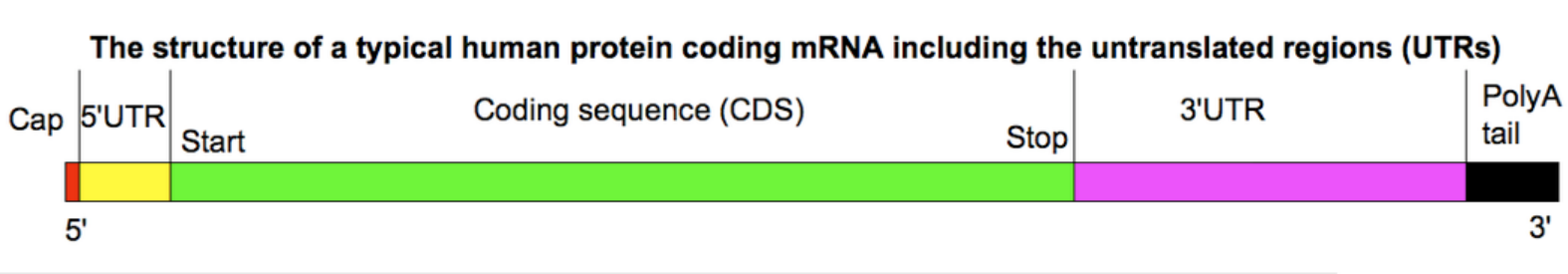
- Characterization of the virus
  - Order: Mononegavirales
  - Family: Filoviridae
  - Genus: Ebolavirus
- Morphology under electron microscope
  - filamentous, enveloped RNA virus
  - approx. 19 kb in length (1 kb = 1000 RNA bases/nucleotides) or 60-80 nm in diameter
  - single-stranded, linear, non-segmented
  - negative-sense RNA (encoded in a 3’ to 5’ direction)
  - appears to have “spikes” due to glycoprotein on outside membrane

Ebola Subtypes

- **Ebola-Zaire** (ZEBOV)
- **Ebola-Sudan** (SEBOV)
- Ebola Ivory-Coast (ICEBOV)
- Ebola-Reston (REBOV)

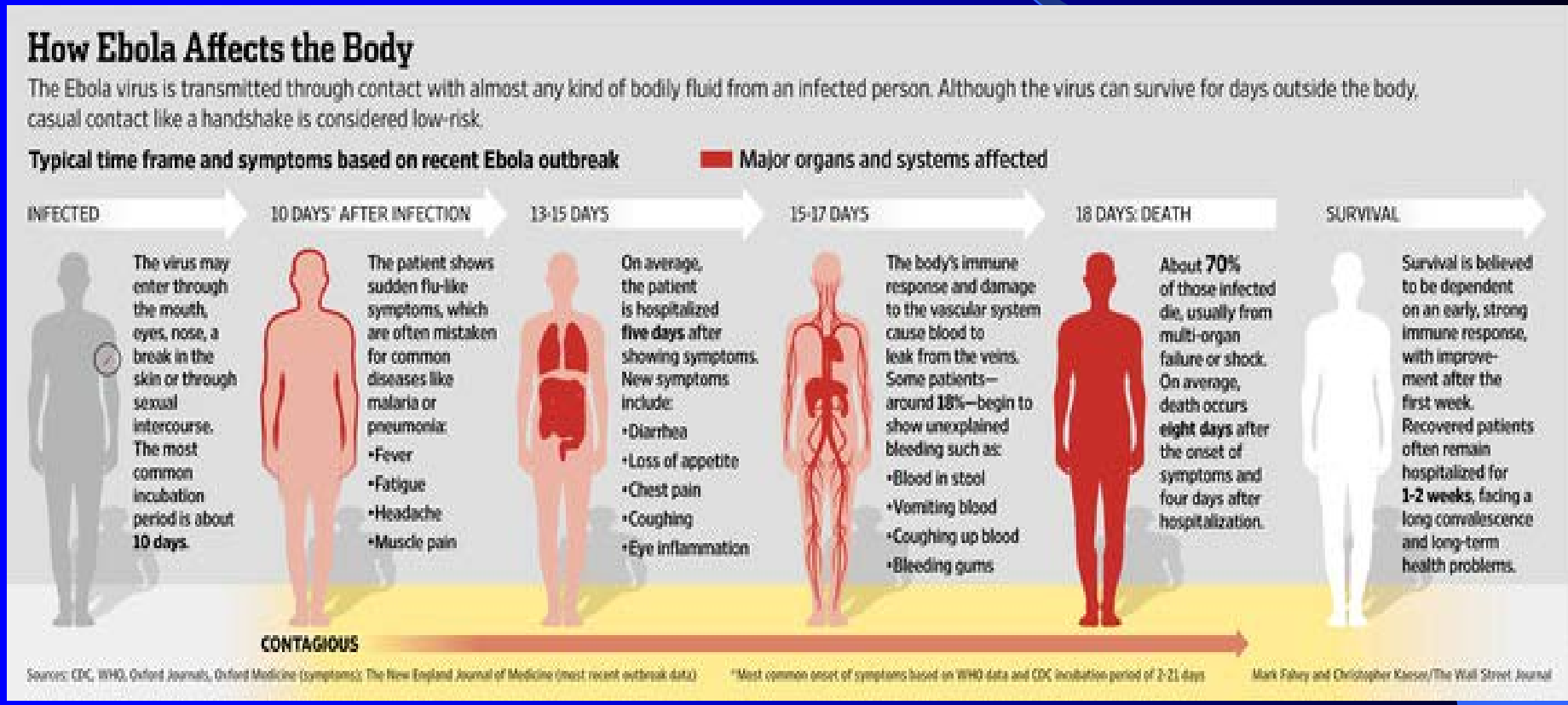
Genome

- Each virion contains one molecule of linear, single-stranded, negative-sense RNA, 18,959 to 18,961 nucleotides in length.
- This is transcribed to mRNA



- Structure of Ebola genome and proteins
  - Translated into 8 sub-genomic mRNA proteins: 7 structural and 1 nonstructural
  - 7 structural proteins:
    - nucleoprotein (NP)
    - 4 viral/virion proteins (VP35, VP40, VP30, VP24)
    - glycoprotein (GP)
    - RNA-dependent RNA polymerase (L protein)
      - NP, VP35, VP30, L protein: required for transcription & replication
      - VP40, GP, VP24: associated with the membrane

Clinical Illness



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

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

* The sample included 84 patients who died and 19 who survived, representing approximately one third of the total cases in the outbreak. Adapted from Bwaka et al.[4]

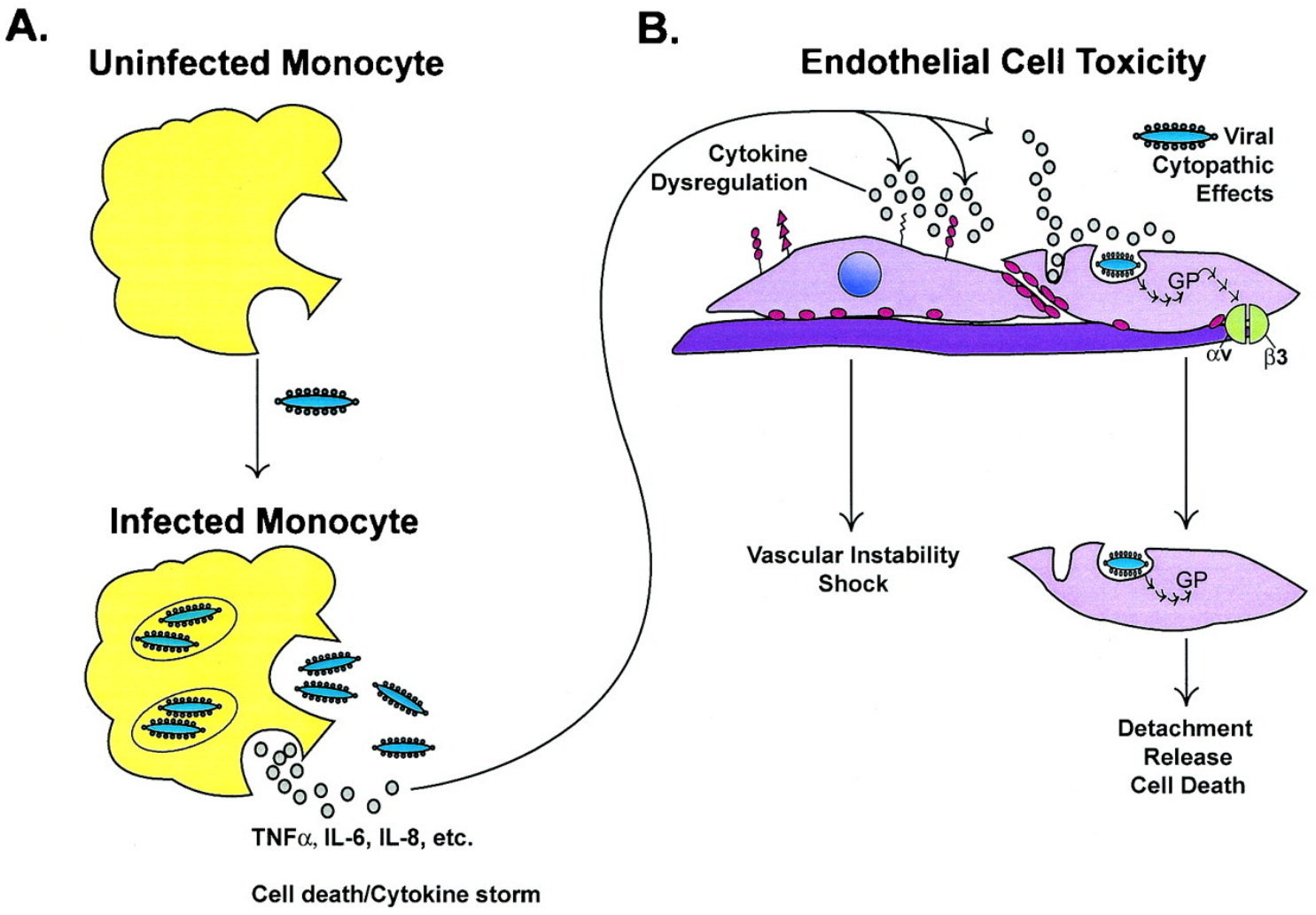
Fauci AS. N Engl J Med 2014;371:1084-1086.

The NEW ENGLAND JOURNAL of MEDICINE

Pathophysiology

- Local invasion leads to infection of local tissues
- Migration to lymph nodes
- Dissemination to liver, spleen and adrenal with rapid necrosis of organs
- Coagulopathy, shock, hemorrhage ensue

Host immune responses to Ebola virus and cell damage due to direct infection of monocytes and macrophages cause the release of cytokines associated with inflammation and fever (A).



Sullivan N et al. J. Virol. 2003;77:9733-9737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A patient bleeding from the mouth as a result of Ebola infection

Diagnosis

- Diagnosis: Ebola is often confused with Malaria, Typhoid fever, dysentery, etc. so Ebola is diagnosed through blood tests

- Differential Diagnosis:
- Must evaluate for
  - Tuberculosis
  - Malaria
  - HIV
  - Influenza

Diagnostic Tests

Timeline of Infection	Diagnostic tests available
Within a few days after symptoms begin	• Antigen-capture enzyme-linked immunosorbent assay (ELISA) testing • IgM ELISA • Polymerase chain reaction (PCR) • Virus isolation
Later in disease course or after recovery	• IgM and IgG antibodies
Retrospectively in deceased patients	• Immunohistochemistry testing • PCR • Virus isolation

Transmission

- **Transmission into humans first occurs from contact with infected animals.**
- **Ebola is then transmitted from human to human through direct contact of the blood and/or bodily secretions of the infected**
- **It is not transmitted by the respiratory route or an insect vector**

Controlling The Spread Of Ebola

- **Identify the patient**
- **Isolate the patient:**
- **Wear appropriate PPE**
- **Restrict visitors:**
- **Avoid aerosol generating procedures**
- **Limit movement of patient**
- **Implement environmental infection control measures**

Isolate The Patient

- Patients should be isolated in a single patient room (containing a private bathroom) with the door closed
- Respiratory isolation and negative pressure not needed although cases will be placed here preferentially

Wear Appropriate PPE

- Gloves, gown (fluid resistant or impermeable), eye protection (goggles or face shield), and a facemask.
- Additional protective equipment might be required in certain situations (e.g., copious amounts of blood, other body fluids, vomit, or feces present in the environment), including but not limited to double gloving, disposable shoe covers, and leg coverings

Wear Appropriate PPE

- Meticulous technique for donning, removing and disposing PPE
- Immediate and through hand hygiene

Patient Care Equipment

- Dedicated medical equipment (preferably disposable, when possible) should be used for the provision of patient care
- All non-dedicated, non-disposable medical equipment used for patient care should be cleaned and disinfected according to manufacturer's instructions and hospital policy

Restrict Visitors

- Avoid entry of visitors into the patient's room.
- Exceptions may be considered on a case by case basis for those who are essential for the patient's wellbeing.
- A logbook should be kept to document all persons entering the patient's room

Avoid Aerosol Generation

- If possible limit
- If necessary
  - incorporate N95 masks,
  - limit number of individuals in room,
  - use additional PPE
  - Immediately clean environmental surfaces after procedure

Implement Environmental IC

- Bleach is primary disinfectant to be used for environmental decontamination
- Management of waste stream
- Survival of virus in dried liquid at room temperature not seen in experimental model*

*Piercy, T.J et al. The survival of filoviruses in liquids, on solid substrates and in a dynamic aerosol. J Appl Microbiol. 2010:109(5): 1531-9

The Challenge

Is Ebola a Bioterror Risk

- Since the September 11 bombings in the United States, the locality of this virus has become less isolated as the threat of bioterrorism looms large.
- The Ebola virus is now on the “A” list for hopeful vaccination development.
- Experiments have even been formed to show how Ebola can be used as a bioterror agent.

Treatment

- Treatment: There is no standard treatment for Ebola, only supportive treatment, which includes balancing patient's fluids & electrolytes, maintaining oxygen & blood pressure, & treating any complications.
- Experimental: Blood transfusions, antiviral drugs, and antibodies

Ebola Vaccine Development

- GSK –
  - Chimpanzee adenovirus vector vaccine into which two Ebola genes have been inserted. This is a non-replicating viral vector, which means the vaccine enters a cell, delivers the gene inserts and does not replicate further. The gene inserts express a protein to which the body makes an immune response. The investigational vaccine has recently shown promise in a primate model
- Crucell Bio Pharm/JANSSEN
  - Multivalent Ebola/Marburg vaccine using recombinant adenovirus vector platforms
- NIAID Intramural Vaccine
  - Based on the established rabies virus vaccine that has demonstrated protection against rabies and Ebola infection in animals

What is Zmapp ?

- Humanized mono-clonal AB (MAB) combination from Zmab and M-003 produced in *Nicotiana benthamiana* a close relative of the tobacco plant
- EBOV glycoprotein epitopes
  - 13C6
  - C2G4
  - C4G7

ZMapp

- Studied in Rhesus monkeys
  - 18 treated – in 3 groups
    - Day 3, 4 and 5 after infection
  - 3 placebo
  - All 18 treated survived
  - All 3 placebo succumbed

Nature. 2014 Aug 29. **doi**: **10.1038/nature13777**

Anti-Viral Medications

- RNA polymerase inhibitors
- Small RNA Nano Particles to Interfere with Protein Synthesis

Conclusions

- Ebola is frightening because of its high mortality rate
- Ebola is not as infectious as many other microbes
- Ebola is an Epizootic infection
- EHFV is relatively easy to contain with the right resources
- The current West African outbreak is a result of the absence of those resources

Conclusions

- Attention to prompt identification of patients and rapid/strict isolation with rigorous use of PPE will prevent dissemination and protect staff and other
- New treatments such as ZMAPP offer promise
- Vaccine development is proceeding

Additional Information

- http://www.mayoclinic.com/health/ebola-virus/DS00996/DSECTION=complications
- http://en.wikipedia.org/wiki/Ebola#Recent_cases
- http://www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/Fact_Sheets/Ebola_Fact_Booklet.pdf
- Pettit J et al. Therapeutic Intervention of Ebola Virus Infection in Rhesus Macaques with the MB-003 Monoclonal Antibody Cocktail. Sci Transl Med 5, 199ra113 (2013);
- http://www.niaid.nih.gov/topics/ebolamarburg/research/pages/default.aspx
- http://www.who.int/csr/disease/ebola/en/
- http://www.cdc.gov/vhf/ebola/
- http://www.cdc.gov/vhf/ebola/hcp/infection-prevention-and-control-recommendations.html