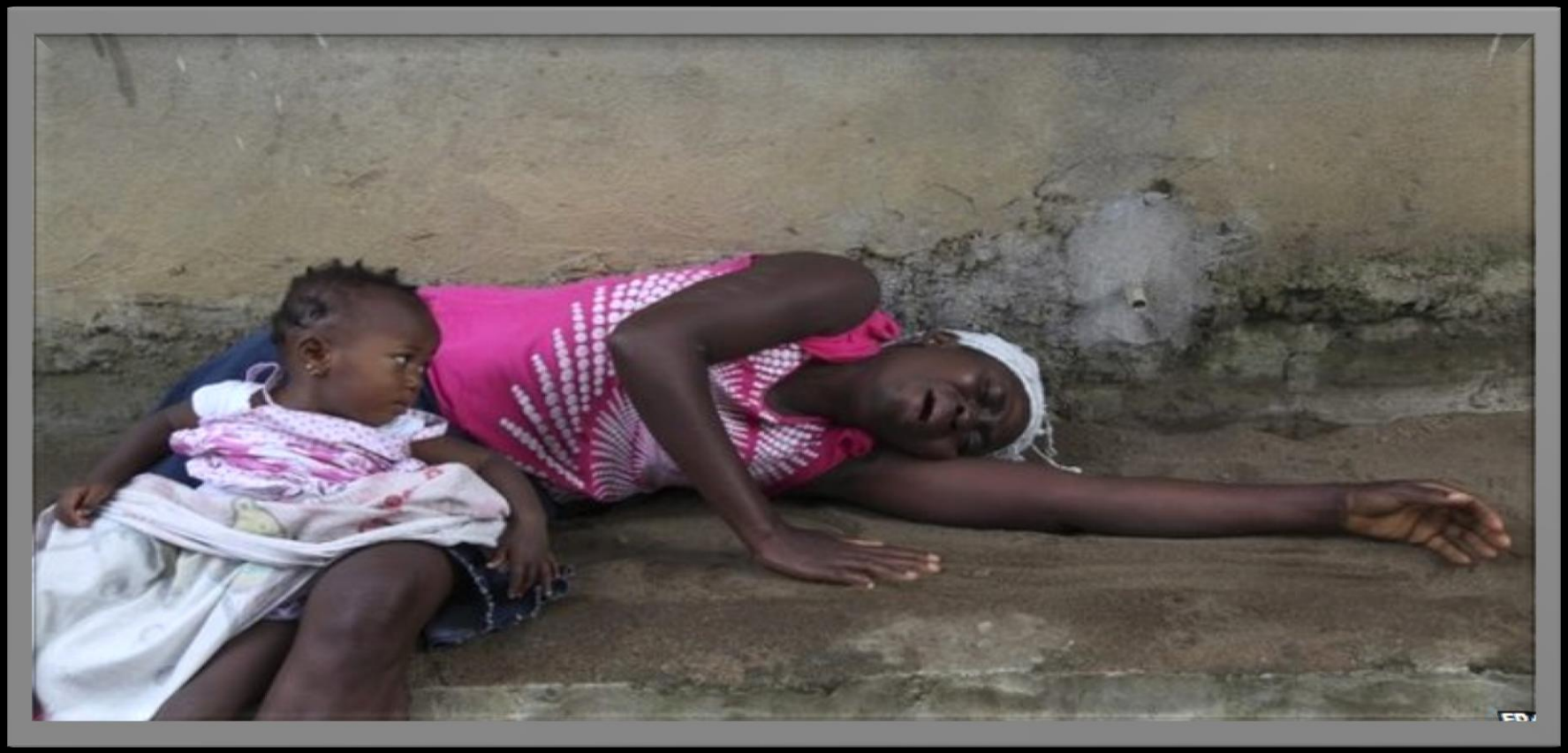


EBOLA

Assist Prof MD. Kaya Süer

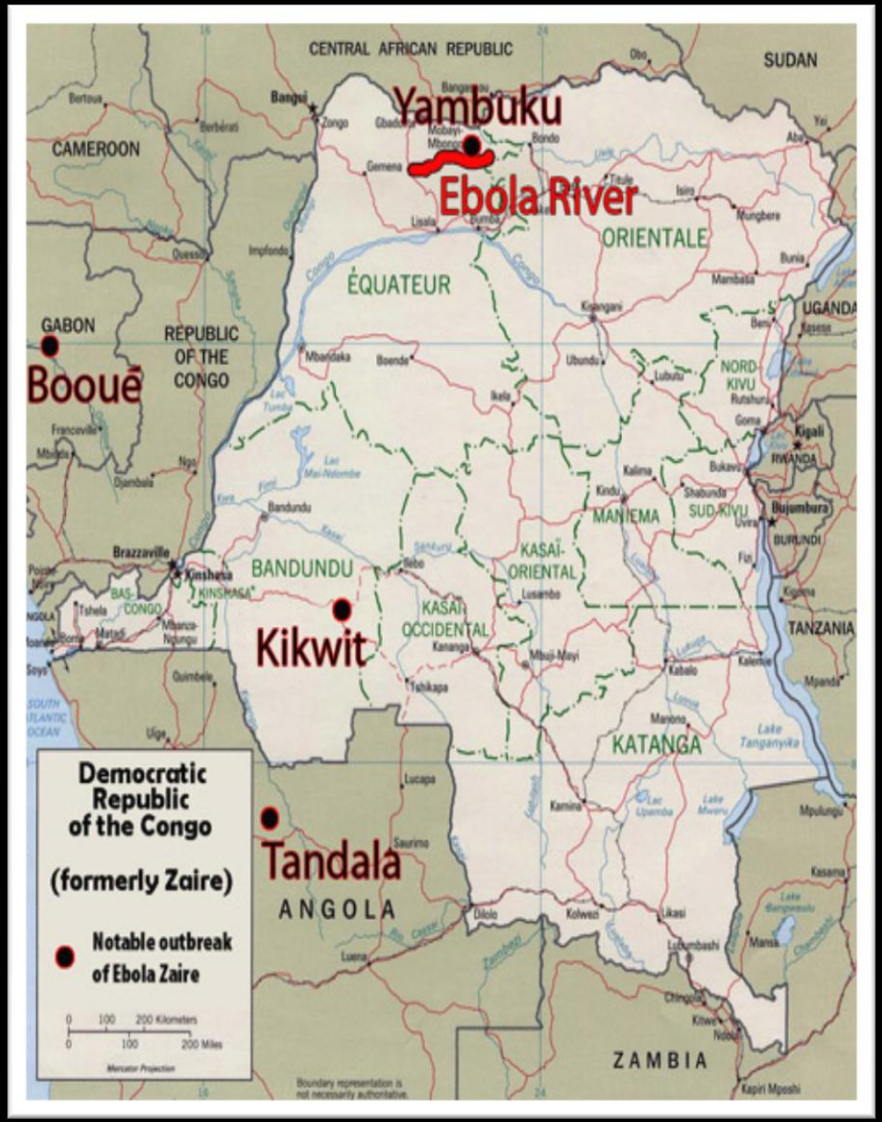
Near East University Faculty of Medicine

Department of Clinical Microbiology and Infectious Diseases

Presentation Plan

- Microorganism
- History
- Epidemiology
- Transmission routes
- Clinical findings
- Treatment
- Control and precautions

- 26 August 1976:
- 44 years old male teacher ➔➔ After the walking around the forest he had high fever
  - Quinine is given
  - 1 week later ,nausea, vomiting, diarea, nasal oral ve rectal bleeding, respiratory distress seen
  - 14. days ex
  - Immediately after ex patient; outbreak is started ➔➔ 318 patient ➔➔280 ex. (%88)


CENTRAL AFRICAN REPUBLIC
SUDAN
Yambuku
Ebola River
CAMEROON
ORIENTALE
ÉQUATEUR
GABON
REPUBLIC OF THE CONGO
Booué
UGANDA
NORD-KIVU
RWANDA
MANIEMA
SUD-KIVU
BURUNDI
BANDUNDU
KASAÏ-ORIENTAL
KASAÏ-OCCIDENTAL
Kikwit
TANZANIA
KATANGA
Tandala
ANGOLA
ZAMBIA
Democratic Republic of the Congo
(formerly Zaire)
Notable outbreak of Ebola Zaire

INSIDE THE DEADLY OUTBREAK

Viral Hemorrhagic Fevers

- They are multisystemic viral infections
  - Damage to the vascular endotelium
  - Often presenting with symptoms of hemorrhage
  - Life-threatening diseases

Mandell 2010

Arenaviridae	Bunyaviridae	Filoviridae	Flaviviridae
Junin	Crimean- Congo H.F.	**EBOLA**	Kyasanur Forest Disease
Machupo	HANTAVİRÜS	MARBURG	Omsk H.F.
Sabia	Rift Valley fever		YELLOW FEVER
Guanarito			DENGUE
LASSA			

Mandell 2010

Ebola Virus

- The most mysterious virus group
- Pathogensis is not fully understood
- Endemic in Africa
- RNA virus

Virol J. 2013 Nov 9;10:331 doi: 10.1186/1743-422X-10-331.

Recombinant lentogenic Newcastle disease virus expressing Ebola virus GP infects cells Independently of exogenous trypsin and uses macropinocytosis as the major pathway for cell entry.

Abstract

BACKGROUND: Using reverse genetics, we generated a recombinant low-pathogenic LaSota strain Newcastle disease virus (NDV) expressing the glycoprotein (GP) of Ebola virus (EBOV), designated rLa-EBOVGP, and evaluated its biological characteristic in vivo and in vitro.

RESULTS: The introduction and expression of the EBOV GP gene did not increase the virulence of the NDV vector in poultry or mice. EBOV GP was incorporated into the particle of the vector virus and the recombinant virus rLa-EBOVGP infected cells and spread within them independently of exogenous trypsin. rLa-EBOVGP is more resistant to NDV antiserum than the vector NDV and is moderately sensitive to EBOV GP antiserum. More importantly, infection with rLa-EBOVGP was markedly inhibited by IPA3, indicating that rLa-EBOVGP uses macropinocytosis as the major internalization pathway for cell entry.

CONCLUSIONS: The results demonstrate that EBOV GP in recombinant NDV particles functions independently to mediate the viral infection of the host cells and alters the cell-entry pathway.

PLOS Pathog. 2013;9(10):e1003677.doi:10.1371/journal ppat.1003677.Epub 2013 Oct 17.

Ebola virus RNA editing depends on the primary editing site sequence and an upstream secondary structure.

Mehedi M, Hoenen T, Robertson S, Dolan MA, Taylor T, Falzarano D, Ebihara H, Porcella SF, Feldmann H.

This is achieved RNA editing, during which non-template adenosine residues are incorporated into the EBOV mRNA at an editing site encoding for 7 adenosine residues. However, the mechanism of EBOV RNA editing is currently not understood.

Ebola virus

- 5 different species
  - Bundibugyo (BDBV)
  - Zaire ebolavirus (EBOV)
  - Sudan ebolavirus (SUDV)
  - Reston ebolavirus (RESTV)
  - Tai Forest ebolavirus (TAFV)

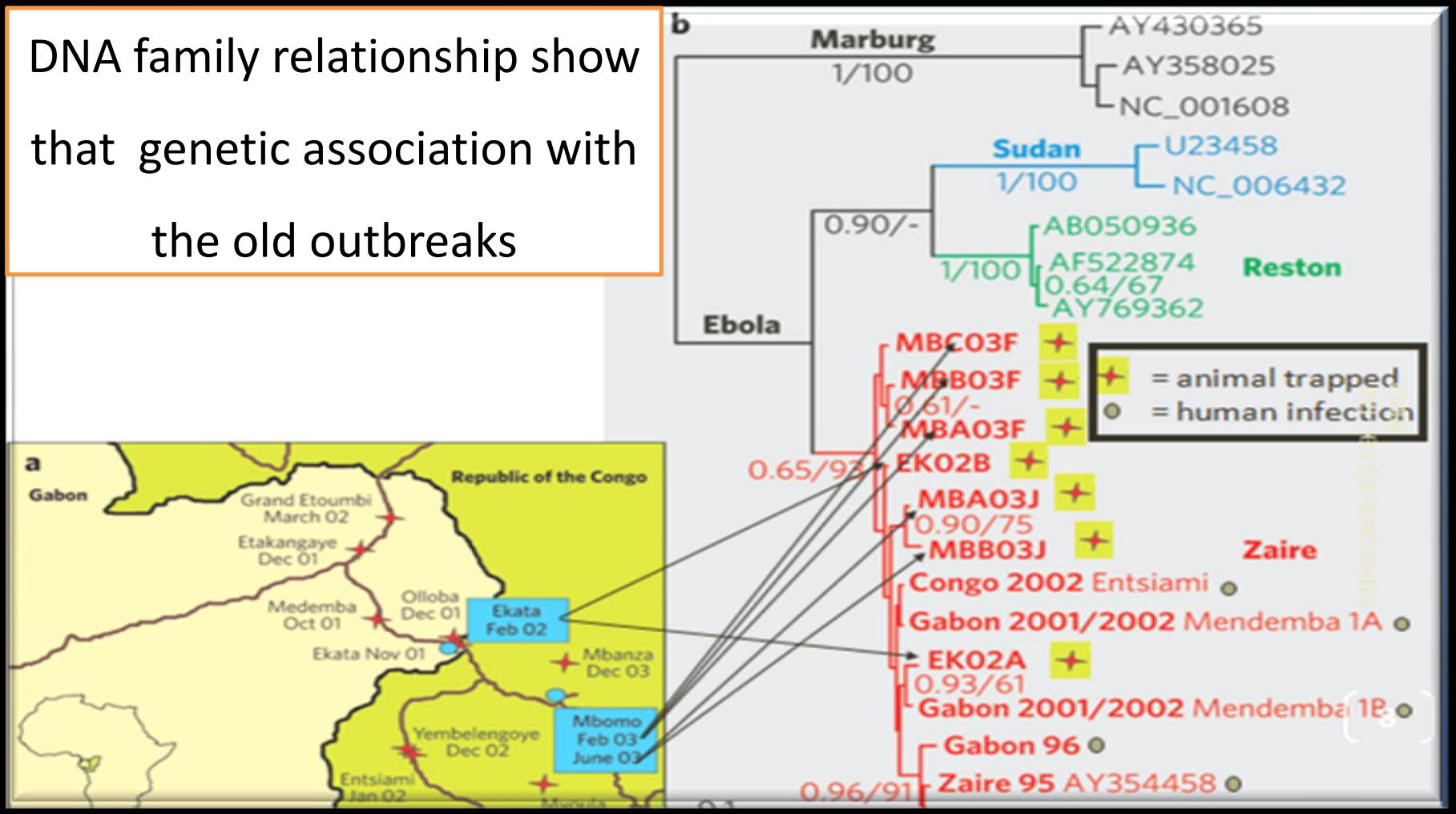
Endemic in Africa

Sporadic in Philippines and China

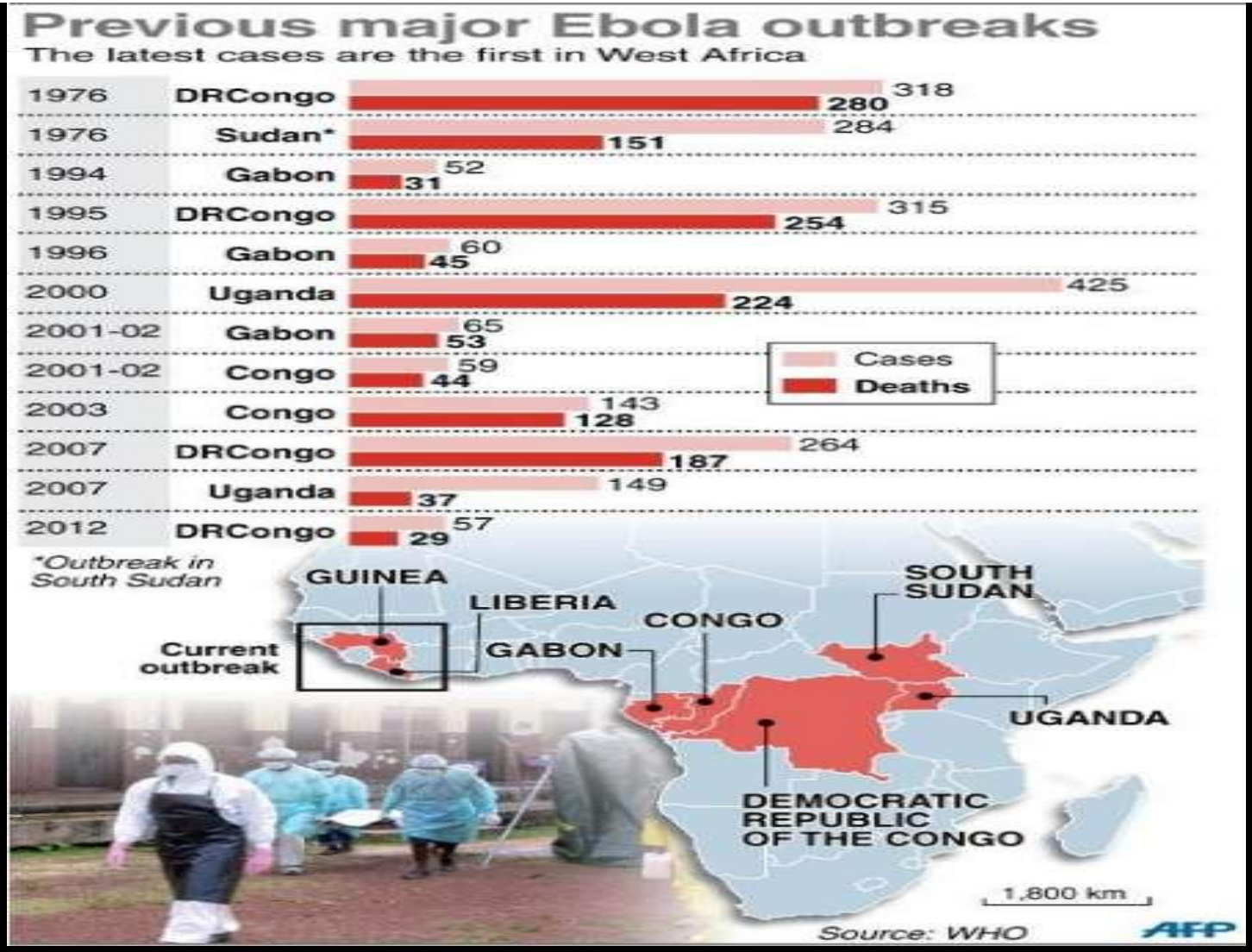
WHO 2014

Ebola virus

DNA family relationship show that genetic association with the old outbreaks



History


Previous major Ebola outbreaks
The latest cases are the first in West Africa
1976 DRCongo 318 280
1976 Sudan* 284 151
1994 Gabon 52 31
1995 DRCongo 315 254
1996 Gabon 60 45
2000 Uganda 425 224
2001-02 Gabon 65 53
2001-02 Congo 59 44
2003 Congo 143 128
2007 DRCongo 264 187
2007 Uganda 149 37
2012 DRCongo 57 29
Cases
Deaths
*Outbreak in South Sudan
GUINEA
LIBERIA
GABON
CONGO
SOUTH SUDAN
UGANDA
DEMOCRATIC REPUBLIC OF THE CONGO
Current outbreak
1,800 km
Source: WHO
AFP

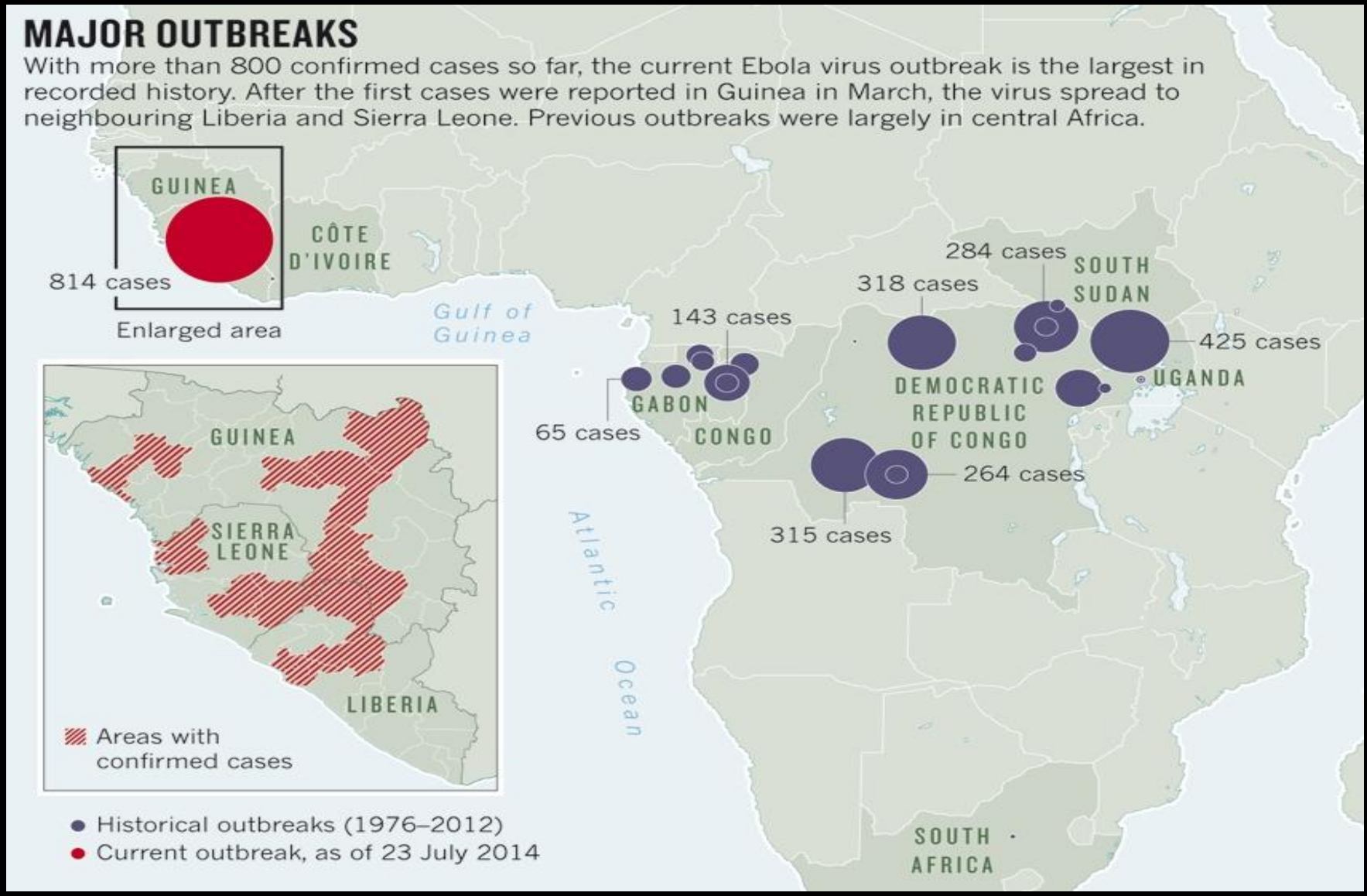
History

Date	Country	Species	Number of patient	Death number	Ratio of death
1976	Zaire	ZEBOV	318	280	88%
1976	Sudan	SEBOV	284	151	53%
1979	Sudan	SEBOV	34	22	65%
1994	Gabon	ZEBOV	52	31	60%
1994	Ivory coast	TAFV	1	0	0%
1995	Zaire	ZEBOV	315	250	79%
1996	Gabon	ZEBOV	37	21	57%
1996–1997	Gabon	ZEBOV	60	45	75%
2000–2001	Uganda	SEBOV	425	224	53%
2001–2002	Gabon Congo	ZEBOV	122	96	79%
2002–2003	DR Congo	ZEBOV	143	128	90%

History

Date	Country	Species	Number of patient	Death number	Ratio of death
2004	Sudan	SEBOV	17	7	41%
2007	DR Congo	ZEBOV	264	187	71%
2007–2008	Uganda	BDBV	149	37	25%
2012 Haziran–Ağu	Uganda	SEBOV	24	17	71%
2013–2014 Aralık–Ağu	Ginea, Liberia Sierra Leone, Nigeria	ZEBOV	1848	1013	64%

History


MAJOR OUTBREAKS
With more than 800 confirmed cases so far, the current Ebola virus outbreak is the largest in recorded history. After the first cases were reported in Guinea in March, the virus spread to neighbouring Liberia and Sierra Leone. Previous outbreaks were largely in central Africa.
GUINEA
CÔTE D'IVOIRE
814 cases
Enlarged area
Gulf of Guinea
143 cases
GABON
CONGO
65 cases
284 cases
318 cases
SOUTH SUDAN
425 cases
UGANDA
DEMOCRATIC REPUBLIC OF CONGO
264 cases
315 cases
Atlantic Ocean
GUINEA
SIERRA LEONE
LIBERIA
Areas with confirmed cases
Historical outbreaks (1976–2012)
Current outbreak, as of 23 July 2014
SOUTH AFRICA

Currently Ebola

- Outbreak began in 2014 in Guineae
- Spread to Sierra Leone and Liberia
- To Nigeria disease moved by a patient

WHO: Ebola Responce Roadmap Situation Report
18 September 2014

Table 1: Probable, confirmed, and suspected cases in Guinea, Liberia, and Sierra Leone as at end 14 September 2014

Country	Case definition	Cases			Deaths
		Total	Last 21 days	Last 21 days/Total (%)	
Guinea	Confirmed	750	266	36%	435
	Probable	162	21	13%	161
	Suspected	30	25	83%	5
	All	**942**	**312**	**33%**	**601**
Liberia	Confirmed	812	462	57%	631
	Probable	1233	596	46%	518
	Suspected	675	398	59%	310
	All	**2710**	**1429**	**52%**	**1459**
Sierra Leone	Confirmed	1513	584	39%	517
	Probable	37	0	0%	34
	Suspected	123	69	56%	11
	All	**1673**	**653**	**39%**	**562**
Total		**5335**	**2394**	**45%**	**2622**

Data are based on official information reported by Ministries of Health. These numbers are subject to change due to ongoing reclassification, retrospective investigation and availability of laboratory results.

- Updated: 31.October.2014
- Total cases: 13567
- Laboratory-confirmed cases: 7728
- Total death: 4960

Epidemiology

Epidemiology

Epidemiology

- Incubation period: 2-21 day
- Not infectious in the incubation period
- Fruit bats are natural hosts
- Primats infected animals

WHO 2014

Epidemiyoloji

Vol 438|1 December 2005 nature

BRIEF COMMUNICATIONS

Fruit bats as reservoirs of Ebola virus

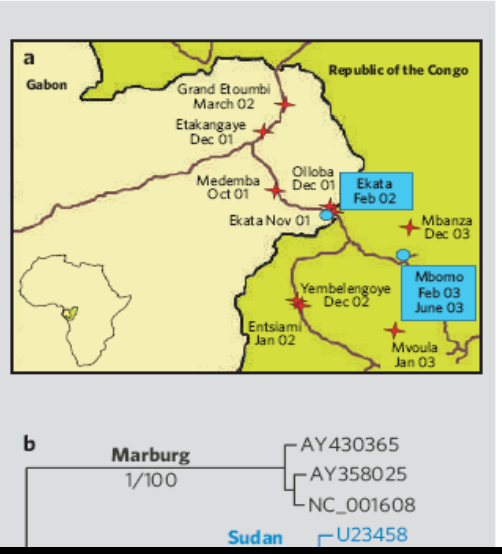
Bat species eaten by people in central Africa show evidence of symptomless Ebola infection.

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.

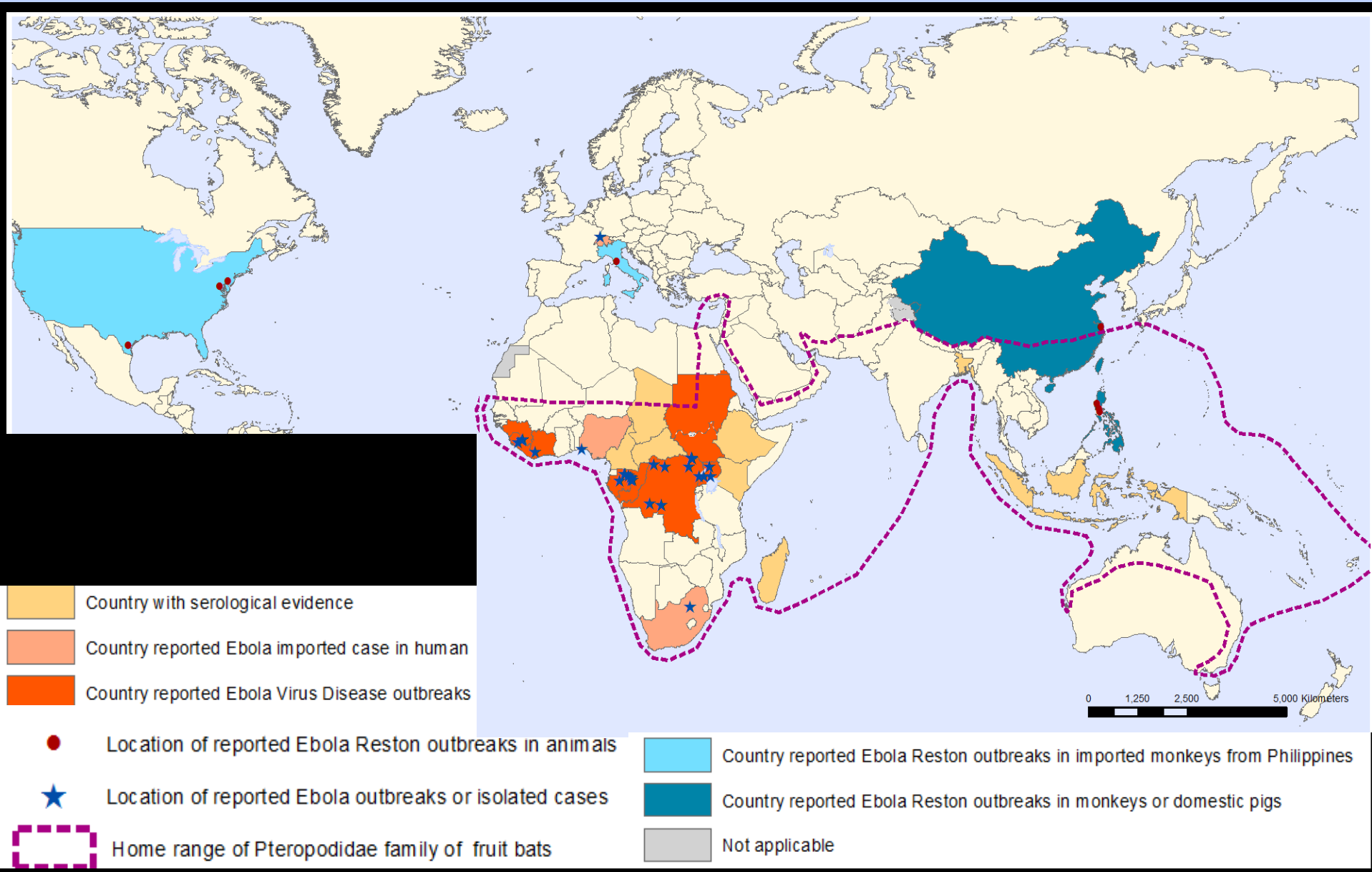
Human Ebola outbreaks that occurred between 2001 and 2005 in Gabon and the Republic of the Congo were linked to concurrent outbreaks that devastated local gorilla and chimpanzee populations[2,3]. To identify the viral reservoir, we undertook three trapping expeditions in areas close to infected gorilla

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

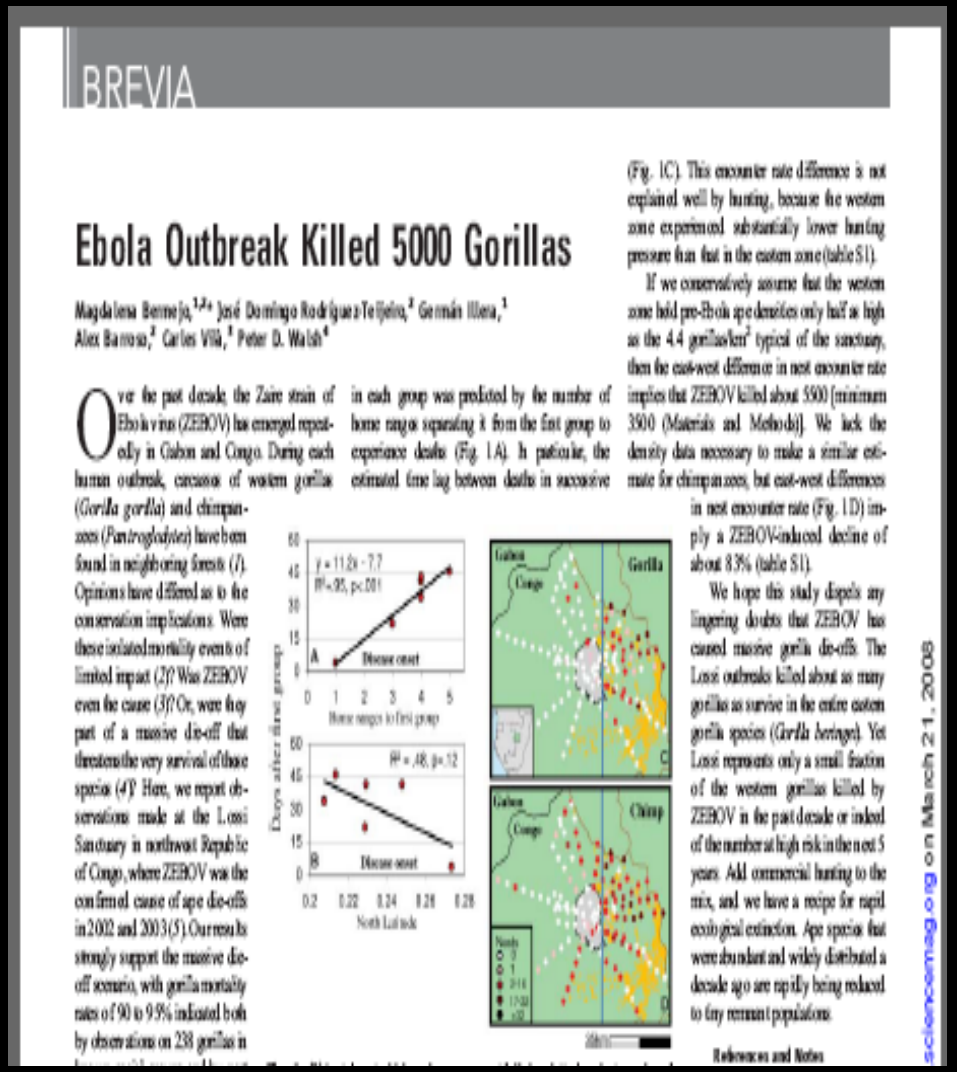


Geographic distribution of Ebola virus disease outbreaks in humans and animals



Epidemiology

- In the world, outbreaks occur in region where the chimpanzees and gorillas live
- Death primats and humans has same viral genetics properties



BREVIA

Ebola Outbreak Killed 5000 Gorillas

Magdalena Bermejo,[1,2]* José Domingo Rodríguez-Teijeiro,[2] Germán Illera,[3] 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 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 (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/km² 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 88% (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.

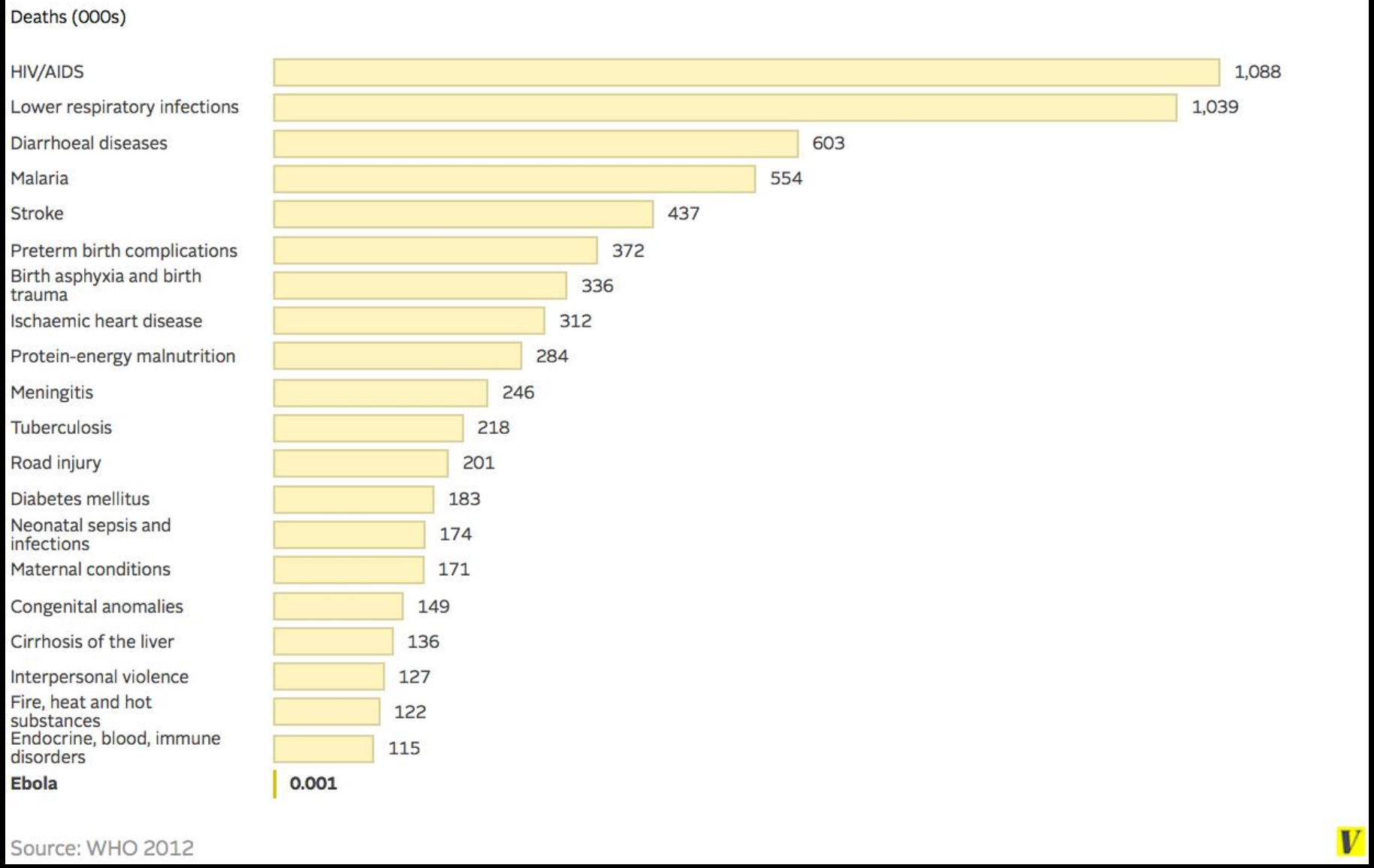
References and Notes

Epidemiology

Country 2014	Population billion	case	EX	Case/100.000	EX /100.000	Ratio of EX	Per capita income USD
Guinea	11.4	*506 *942 *1008	*373 *601 *632	*4 *8.3 *8.8	*3 *5.2 *5.5	*% 73.7 *% 63.8 *% 62.7	491
Liberia	4.19	*599 *2710 *3022	*323 *1459 *1578	*14 *64.7 *72.1	*7 *34.8 *37.6	*% 53.9 *% 53.8 *% 52.2	413
S.Leone	5.9	*730 *1673 *1813	*315 *562 *593	*12 *28.4 *30.7	*5 *9.5 *10	*% 43.1 *% 33.5 *% 32.7	634
Nigeria	168.8	*13 *21 *21	*2 *8 *8	*0.0077 *0.012 *0.012	*0.0012 *0.0047 *0.0047	*%15.3 *% 38 *% 38	775

* 08 August 2014 * 18 september 2014 * 19 september 2014

Leading causes of death in Africa




100
REPUBLIC OF LIBERIA
100
EA3253417
THIS CENTRAL BANK NOTE IS LEGAL TENDER
FOR ONE HUNDRED LIBERIAN DOLLARS
ONE
HUNDRED
MINISTER OF FINANCE
EXECUTIVE GOVERNOR
2003
WILLIAM R. TOLBERT, JR.
EA3253417
100
ONE HUNDRED DOLLARS
100

How do you get the Ebola virus?

- Direct contact with :

① Body fluids of a person who is sick with or has died from (blood,vomit, pee, poop,sweat, semen, urine, other fluids)

② Objects contaminated with the virus(needles, medical equipments)

③ Infected fruit bats and primates

CDC 2014

Case definition

- **Epidemiological criteria: In the 21 days before the onset of symptoms;**
  - Having been an in area with community transmission
  - OR
  - Having had contact with a propable or confirmed EVD case

WHO 2014

Case definition

- High-risk exposure;
  - ANY OF THE FOLLOWİNG
  - Close face to face contact with EVD patient
  - Direct contact with any material of EVD patient
  - Percutaneos injury or mucosal exposure to body fluids of EVD patient
  - Without appropriate personal protective equipment; participation in funeral
  - Direct contact with bats,rodents,primates

Case definition

- **Clinical criteria:**
  - **Fever more than** ≥38.5°C AND any of the following
  - Severe headache
  - Vomiting, diarrhoea, abdominal pain
  - Unexplained haemorrhagic manifestations in various forms
  - Multiorgan failure
  - OR a person who died suddenly or inexplicably

WHO 2014

Case definition

- Laboratory criteria:
  - ANY of the following
  - Detection of EBV nucleic acid in a clinical specimen and confirmation by sequencing
  - Isolation of Ebola virus from a clinical specimen

Case definition

PERSON UNDER INVESTIGATION

- A person meeting clinical and epidemiological criteria
- **OR**
- With high-risk exposure and any of the listed symptoms, including fever of any grade

WHO 2014

Case definition

CONFİRMED CASE;

–A person meeting laboratory criteria

WHO 2014

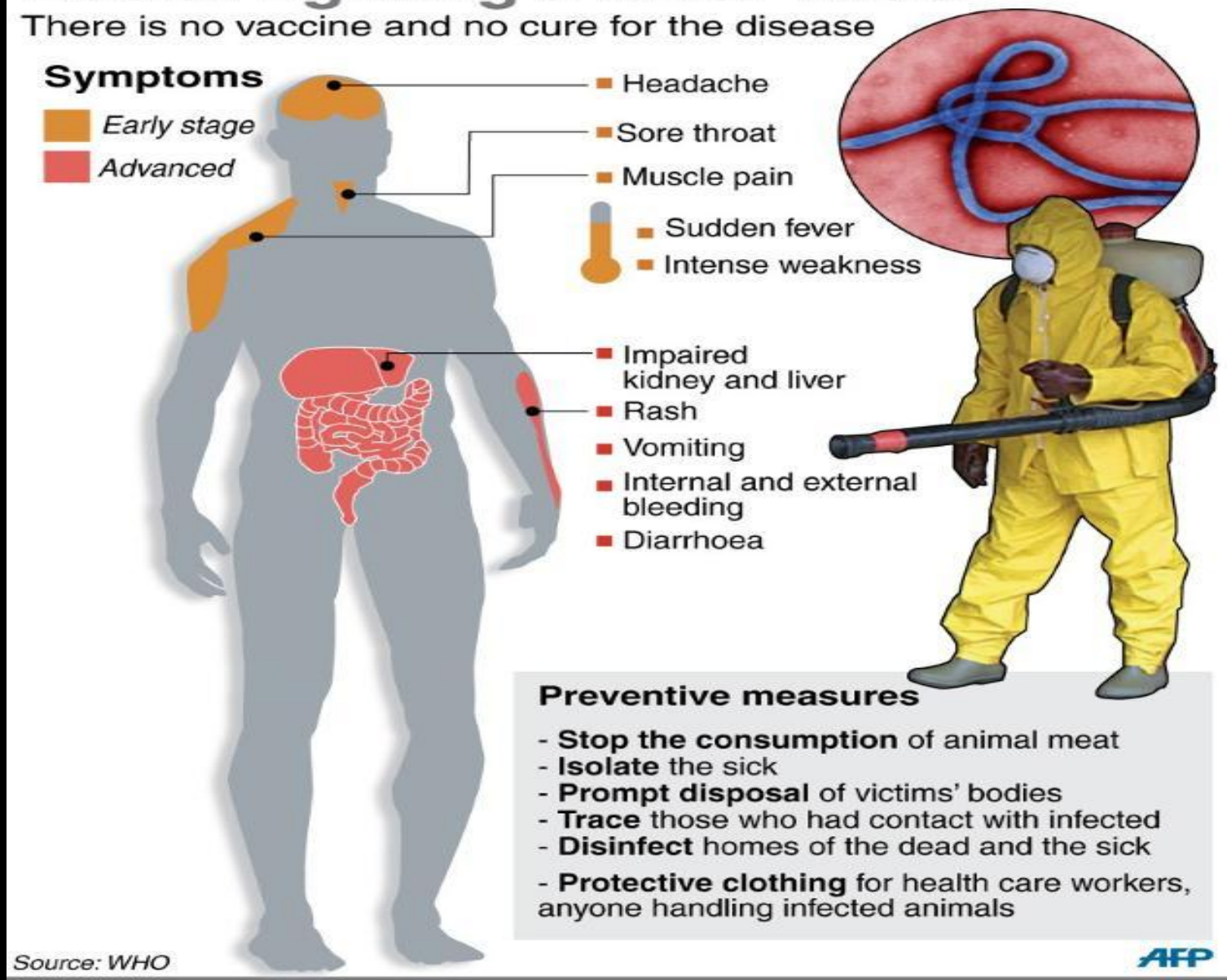
The differential diagnosis

- Malaria
- Shigellosis
- Cholera
- Typhoid fever
- Leptospirosis
- Ricetsiyosis
- Acute hepatitis
- Other viral hemorhagic fevers

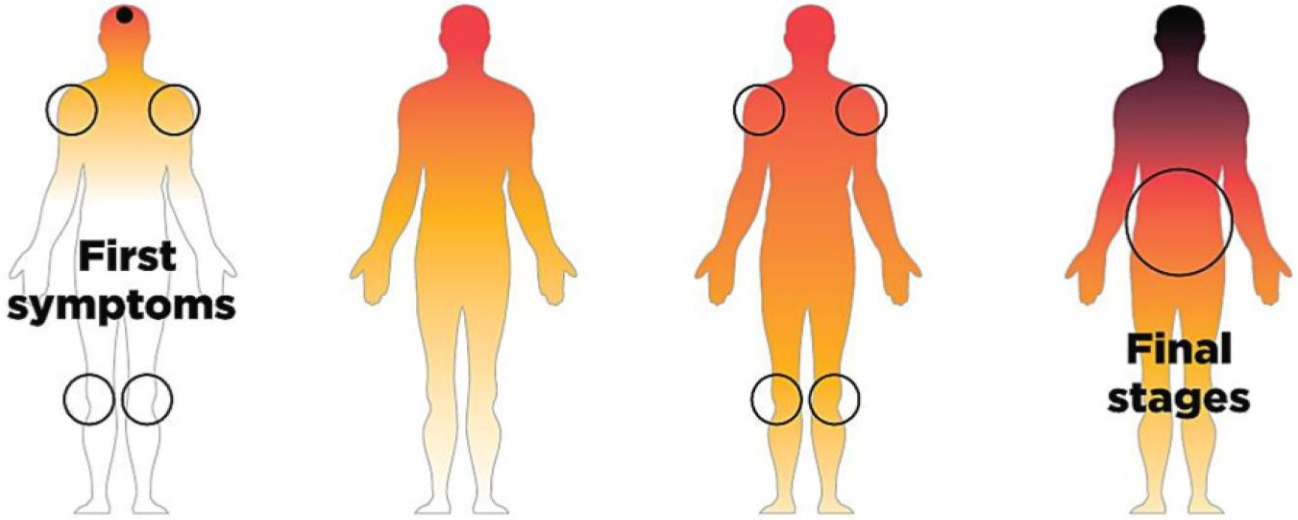
Mandell 2010

Ebola: fighting a killer virus

There is no vaccine and no cure for the disease



Virus's typical path through a human



Day 7-9
Headache, fatigue, fever, muscle soreness

Day 10
Sudden high fever, vomiting blood, passive behavior

Day 11
Bruising, brain damage, bleeding from nose, mouth, eyes, anus

Day 12
Loss of consciousness, seizures, massive internal bleeding, death

NOTE: Symptoms can start as early as two days after infection.

SOURCES: World Health Organization; BBC

Melina Yingling/McClatchy-Tribune

Diagnosis

İnfection time	**Usable diagnosis methods**
First days of the symptoms	ELİSA, PCR, Virus isolation
Late stage of the diseases and improving persons	IgM and IgG Antibody
Retrospective	İmmunohistochemistry, PCR, Virus isolation

Treatment

- Animals on treatment options have proven to be effective
- But not used on humans
- No drugs with FDA licences

AVR 3503
13 September 2014
ARTICLE IN PRESS
No. of Pages 11, Model 5G

Antiviral Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Antiviral Research

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

Meeting Report

Meeting report: 27th International conference on antiviral research

R. Anthony Vere Hodge *

Vere Hodge Antivirals Ltd, Old Denshott, Leigh, Reigate, Surrey, UK

- **BCX4430 e**ffective drug development againts Ebola and Marburg viruses, have attracted much attention

- Rodents and primates
  - Different dosages 30, 20, 3.3 and 1.1 mg
  - Survival %100, %100, %95 and %83

Treatment

- Supportive treatment
  - Fluid replacement
  - Oral or intravenous feeding
  - Analgesic
  - GIS / Anxiety / Agitation

Ideas and Opinions | 21 August 2014

Ebola Vaccination: If Not Now, When? FREE ONLINE FIRST

Alison P. Galvani, PhD; Martial L. Ndeffo-Mbah, PhD; Natasha Wenzel, MPH; and James E. Childs, PhD

[+] Article and Author Information

Ann Intern Med. Published online 21 August 2014 doi:10.7326/M14-1904

- Although no Ebola vaccines are currently licensed, many candidates have been developed in the past decade. A DNA vaccine has been shown to be safe and immunogenic in a phase 1 clinical trial .
- In addition, a therapeutic vaccine based on recombinant vesicular stomatitis viruses (rVSVs) expressing Ebola virus surface glycoprotein was found to confer prophylactic and post exposure protection in nonhuman primates .
- Despite the promise of these and other Ebola vaccine candidates, none have advanced to late-stage human trials and licensure.

Table. **Viable Ebola Vaccine Candidates**

Mechanism	Properties	Vaccination Scenario	Reference
rVSV + ZEBOV-GP	Trials in NHPs elicited immunogenic response against lethal and aerosol challenge. Conveyed protection in Ebola-exposed and immunocompromised NHPs. Potential for oral administration.	Suited for outbreak response, including postexposure prophylaxis. Also appropriate for use in immuno-compromised populations, such as those with a high prevalence of HIV.	3, 7
rRABV + ZEBOV-GP	Trials in NHPs elicited immunogenic response against lethal challenge.	Suited for human and wildlife vaccination. Dual RABV/EBOV vaccine may be more acceptable in endemic areas.	8
DNA + rAd5 + ZEBOV-GP, rAd5 + ZEBOV-GP	Safe and immunogenic in phase 1 clinical trials. Multiple vaccinations may be required. Possible interference with preexisting immunity to Ad5.	Preparedness strategies for health care workers and high-risk populations.	2
Virus-like particles + ZEBOV-GP + ZEBOV-NP + ZEBOV-VP40	Trials in NHPs elicited immunogenic response against lethal challenge. Virus-like particles can be produced in insect cells, making them suitable for large-scale production.	Preparedness strategies for health care workers and high-risk populations.	9
rHPIV3 + ZEBOV-GP	Trials in guinea pigs and NHPs elicited immunogenic response against lethal challenge. Potential for needle-free administration.	Preparedness strategies for health care workers and high-risk populations.	10
rCMV + ZEBOV-NP	Trials in mice elicited immunogenic response against lethal challenge. Highly species-specific.	Suited for great ape vaccination in endemic areas.	6
rEBOV subunit vaccine + TLR agonist	Trials in mice elicited immunogenic response against lethal challenge. Subunit vaccines stable for storage and delivery at ambient temperatures.	Suited for stockpiling and vaccine delivery.	5

GP = glycoprotein; NHP = nonhuman primate; NP = nucleoprotein; rAd5 = recombinant adenovirus serotype 5; rCMV = recombinant cytomegalovirus; rEBOV = recombinant Ebola virus; rHPIV3 = recombinant human parainfluenza virus type 3; rRABV = recombinant rabies virus; rVSV = recombinant vesicular stomatitis virus; TLR = Toll-like receptor; ZEBOV = Zaire ebolavirus.

Infection control and prevention

- The goal of outbreak control is to
  - interrupt direct human-to-human transmission through the early identification and systematic isolation of cases,
  - timely contact-tracing,
  - proper personal protection,
  - safely conducted burials,
  - improved community awareness about risk factors of viral infection and individual protective measures. Quarantine of infected patients has been shown to effectively stop the spread of the disease in previous outbreaks.

Infection control and prevention

- Quarantine of infected patients has been shown to effectively stop the spread of the disease in previous outbreaks.

Infection control and prevention

- Healthcare workers have frequently been infected while treating patients with suspected or confirmed Ebola infection.
- This occurred through close contact with patients when infection control precautions were not strictly practiced or haemorrhagic viral etiology not recognized.
- The risk for infection can be significantly reduced through the appropriate use of infection control precautions and adequate and strict barrier nursing procedures.

Infection control and prevention

- Implementation of appropriate infection control measures in healthcare settings, including use of personal protective equipment, is effective in minimising the risk for transmission of filoviruses

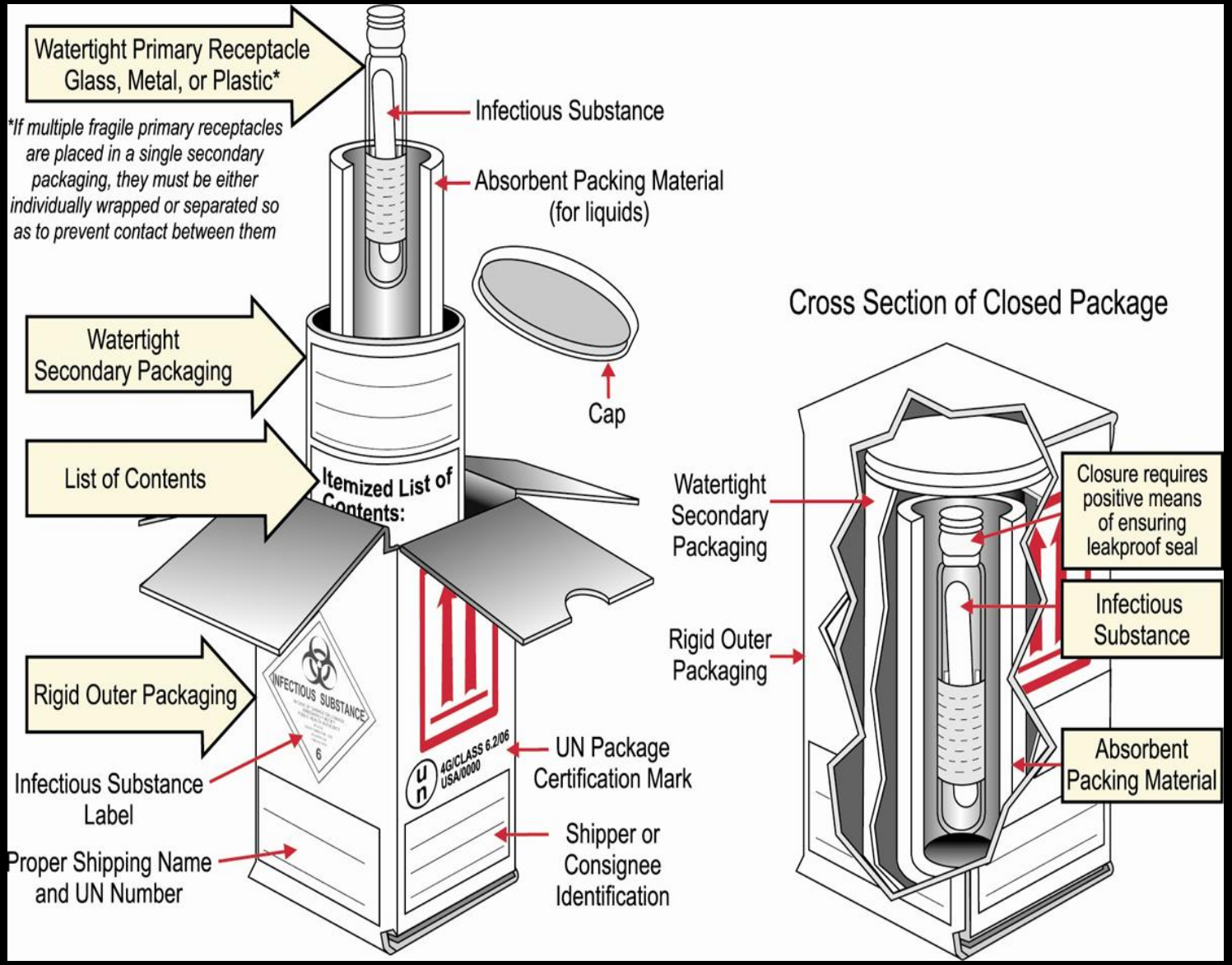

BRITISH AIRWAYS

Infected Healthcare workers

Table 2: Ebola infections in healthcare workers as at end 14 September 2014

Country	Case definition	Cases			Deaths
		Total	Last 21 days	Last 21 days/total cases (%)	
Guinea	Confirmed	52	9	17%	22
	Probable	8	0	0%	8
	Suspected	1	1	100%	0
	All	**61**	**10**	**16%**	**30**
Liberia	Confirmed	66	3	4%	56
	Probable	85	18	21%	26
	Suspected	21	0	0%	3
	All	**172**	**21**	**12%**	**85**
Nigeria	Confirmed	11	2	18%	5
	Probable	0	0	0%	0
	Suspected	0	0	0%	0
	All	**11**	**2**	**18%**	**5**
Sierra Leone	Confirmed	71	1	1%	30
	Probable	1	0	0%	1
	Suspected	2	0	0%	0
	All	**74**	**1**	**1%**	**31**
Total		**318**	**34**	**11%**	151

Data reported are based on official information reported by Ministries of Health. These numbers are subject to change due to ongoing reclassification, retrospective investigation and availability of laboratory results.


Watertight Primary Receptacle
Glass, Metal, or Plastic*
*If multiple fragile primary receptacles are placed in a single secondary packaging, they must be either individually wrapped or separated so as to prevent contact between them
Infectious Substance
Absorbent Packing Material
(for liquids)
Watertight
Secondary Packaging
Cap
List of Contents
Itemized List of Contents:
Rigid Outer Packaging
INFECTIOUS SUBSTANCE
6
UN
4G/CLASS 6.2/06
USA/0000
UN Package
Certification Mark
Infectious Substance
Label
Shipper or
Consignee
Identification
Proper Shipping Name
and UN Number
Cross Section of Closed Package
Watertight
Secondary
Packaging
Rigid Outer
Packaging
Closure requires positive means of ensuring leakproof seal
Infectious
Substance
Absorbent
Packing Material


Thank you