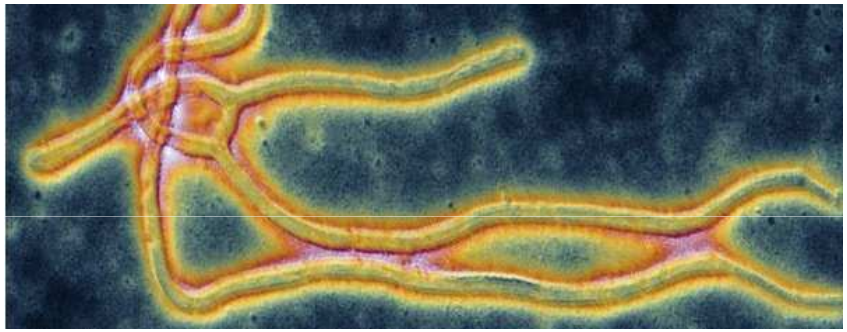
Doença pelo Vírus Ebola

EVD



Dr. Márcio Silveira da Fonseca

UNISUL & Hospital Florianópolis (SES SC / SPDM)

Florianópolis, Brasil, 2014

Resumo

- Situação global atual
- Febres Hemorrágicas Virais
- Doença pelo Vírus Ebola
- Epidemiologia e detecção de surtos
- Fisiopatogenia
- Apresentação clínica
- Diagnóstico
- Tratamento
- Controle de surtos e prevenção

MITOS vs VERDADES???

A próxima epidemia...

Gripe Aviária? (H5N1, H7N9)...

Poliomielite?...

MERS-CoV?...

Chikungunya?...

Cólera?...

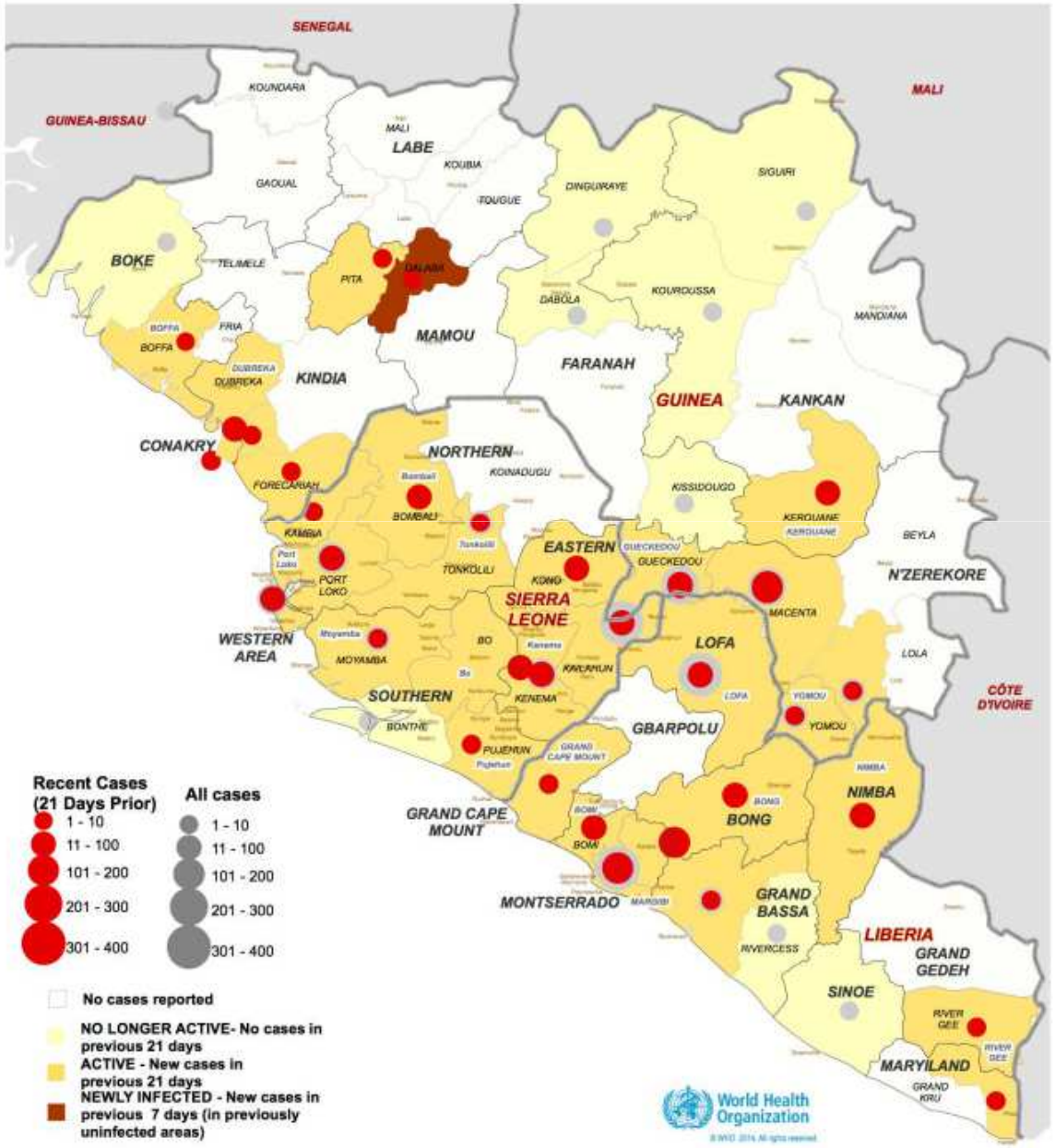
Era Pós Antibiótica?...

TB MDR/XDR/"TDR"?...

Malária Resistente aos derivados Artemisina?...

Quase 2500 mortos (50% letalidade)

Figure 1: Distribution of cases in countries with intense transmission



OMS, 16 Set 2014 – *quase metade de todos casos nas últimas 3 semanas!!!!!*

Table 1: Probable, confirmed and suspected cases of Ebola virus disease in Guinea, Liberia and Sierra Leone

Country	Case definition	Cases			Deaths	
		Total	Past 21 days	Past 21 days/total cases (%)	Total	Deaths/total cases (%)
Guinea	Confirmed	743	276	37	429	58
	Probable	162	21	13	162	100
	Suspected	31	11	35	4	13
	All	**936**	**308**	**33**	**595**	**64**
Liberia	Confirmed	790	546	69	563	71
	Probable	1078	539	50	472	44
	Suspected	539	298	55	261	48
	All	2407	1383	57	1296	54
Sierra Leone	Confirmed	1464	583	40	514	35
	Probable	37	0	0	37	100
	Suspected	119	70	59	11	9
	All	**1620**	**653**	**40**	**562**	**35**
Total		**4963**	**2344**	**47**	**2453**	**49**

Data are based on reported cases up to the end of 13 September 2014 for Guinea and Sierra Leone. Data for Liberia are based on reported cases up to the end of 9 September 2014. Data reported are based on official information reported by Ministries of Health. These numbers are subject to change due to on-going reclassification, retrospective investigation and availability of laboratory results.

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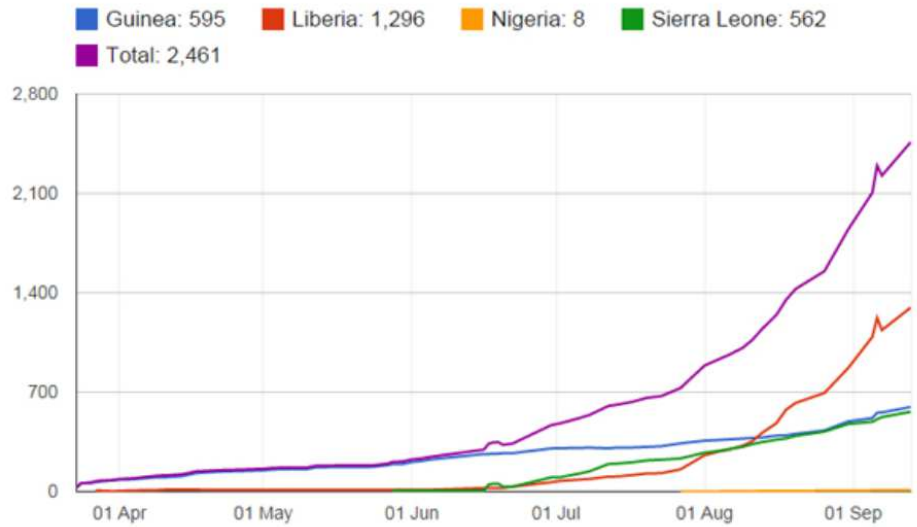
Nigéria & Senegal

Table 2: Probable, confirmed and suspected cases of Ebola virus disease in Nigeria and Senegal as at end of 13 September 2014

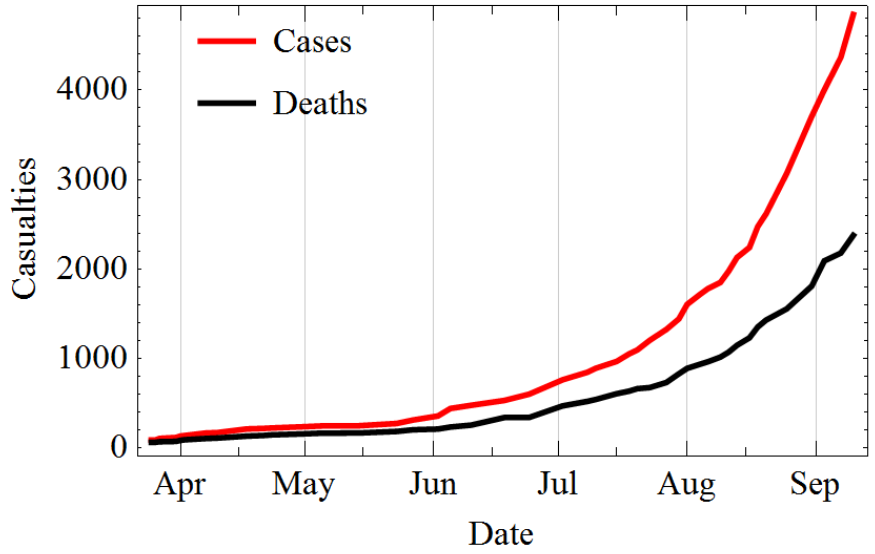
Country	Case definition	Cases			Deaths	
		Total	Past 21 days	Past 21 days/total cases (%)	Total	Deaths/total cases (%)
Nigeria	Confirmed	19	6	32	7	37
	Probable	1	0	0	1	100
	Suspected	1	n.a.	n.a.	0	0
	All	**21**	**6**	**29**	**8**	**38**
Senegal	Confirmed	1	1	100	0	0
	Probable	0	0	0	0	0
	Suspected	0	0	0	0	0
	All	**1**	**1**	**100**	**0**	**0**
Total		**22**	**7**	**32**	**8**	**36**

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.

Cumulative deaths - up to 13 September



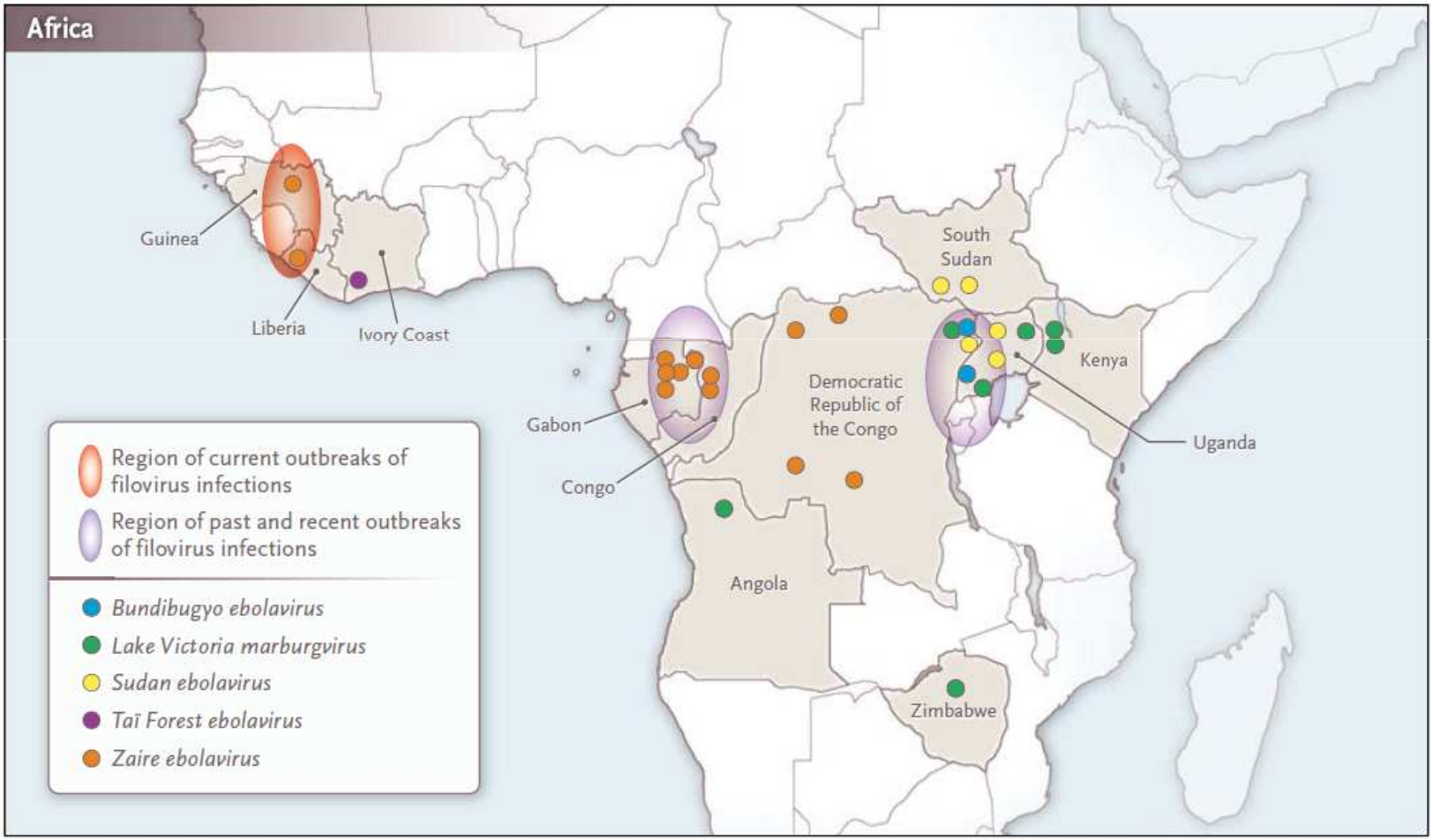
Figures are occasionally revised down as suspect or probable cases are found to be unrelated to Ebola



Surtos anteriores = 1590 mortos

1972	1 non-fatal case (retrospective diagnosis)	Tandala, Congo (not confirmed)
1976	318 cases, 280 deaths	Yambuku, Congo (discovery of the virus)
1976	284 cases, 151 deaths	Nzara, Maridi, Tembura and Juba, Sudan
1977	1 fatal case	Tandala, Congo
1979	34 cases with 22 deaths	Nzara and Yambio, Sudan
1980	1 suspected case	Kenya (not confirmed)
1994	44 cases, 28 deaths	Minkouka, Gabon
1994	1 non-fatal case	Tai Park, Côte d'Ivoire
1995	315 cases, 255 deaths	Kikwit, Congo
1996	1 non-fatal case	Plibo, Liberia (not confirmed)
1996	37 cases with 21 deaths	Mayibout and Makokou, Gabon
1996	60 cases with 45 deaths	Booué, Gabon. One exported case in South Africa with one fatal secondary case.
2000	425 cases with 224 deaths	Gulu, Masindi, Mbarara (Uganda)
2002	43 deaths in Congo, 53 deaths in Gabon	Gabon - Congo
2002	No reliable numbers available	Mbomo, Congo
2003	About 140 cases with about 120 deaths (February-March). Flare-up in November-December, with 35 cases (29 deaths).	Mbomo, Congo
2004	25 cases with 6 deaths	Mbomo and Mbandza, Congo Brazzaville
2005	About 10 cases	Etoumbi, Congo
2007	About 187 cases	Kampungu, Mweka, Luebo, Congo(Western Kasai)
2008	About > 90 cases	Western Uganda
2008-9	New epidemic in Congo, lasting till early 2009. Number of cases unclear	Mweka, Congo
2009	In March 2009, accidental needlestick injury in Hamburg (virologist)	Germany, the first time that vesicular stomatitis virus-based vaccine is used in a human (post-exposure)
2011	Isolated case (May 2011) in Uganda	November 2009, new outbreak in Mweka, Congo.
2012	Number of cases unclear	July 2012, outbreak in Kibaale, Uganda and quasi simultaneous in August 2012 outbreak is Isiro and Viadana, HAut-Uele, Congo

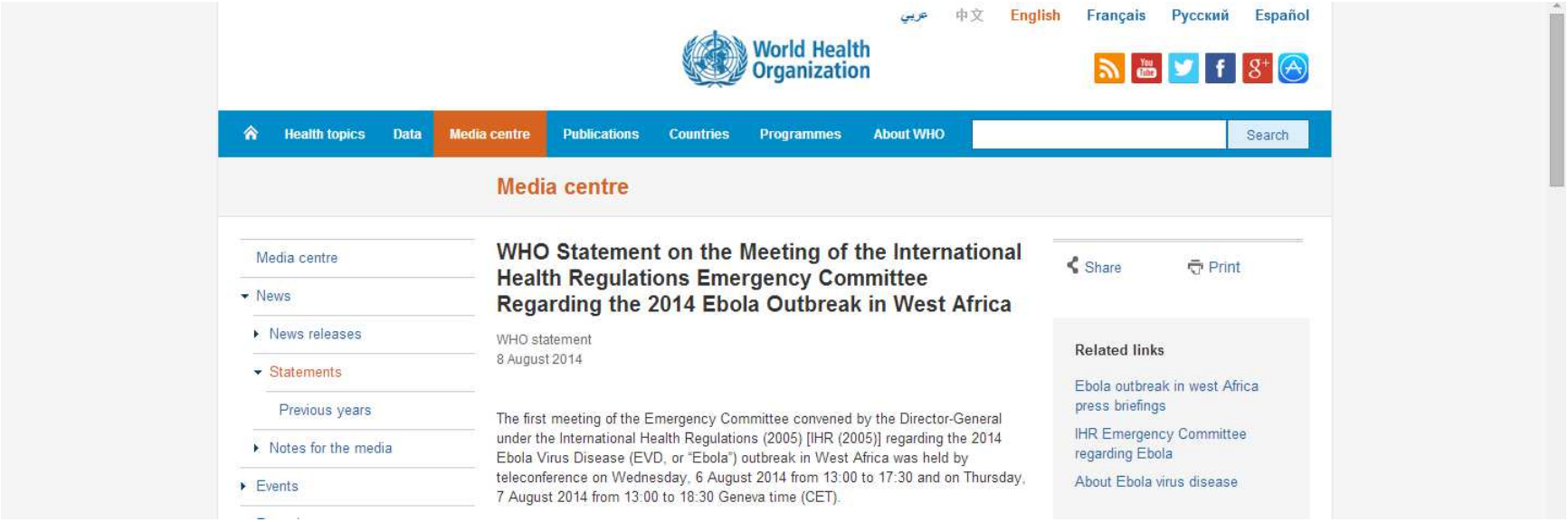
Surtos anteriores (África)



•the Ebola outbreak in West Africa constitutes an **‘extraordinary event’** and a **public health risk to other States**;

•the possible consequences of further international spread are particularly serious in view of the **virulence** of the virus, the **intensive community and health facility transmission** patterns, and the **weak health systems** in the currently affected and most at-risk countries.

•a **coordinated international response is deemed essential to stop and reverse** the international spread of Ebola.



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16 September 2014 Last updated at 21:14 GMT

Share

Obama says Ebola outbreak a 'global security threat'

President Obama: "It's a potential threat to global security"

President Barack Obama has called the West Africa Ebola outbreak "a threat to global security" as he announced a larger US role in fighting the virus.

"The world is looking to the United States," Mr Obama said, but added the outbreak required a "global response".

The measures announced included ordering 3,000 US troops to the region and building new healthcare facilities.

Ebola has killed 2,461 people this year, about half of those infected, the World Health Organization said.

Ebola outbreak

- 'Biological warfare'
- How bad can Ebola get?
- How to avoid Ebola
- Doctor's report

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Global Alert and Response (GAR)

Ebola virus disease

Cuban medical team heading for Sierra Leone

WHO/M. Missioneiro

Cuba is known the world over for its ability to train excellent doctors and nurses who can then go out to help other countries in need. Currently there are more than 50 000 Cuban-trained health workers in 66 countries. And now Dr Roberto Morales Ojeda, Minister of Public Health, has announced that Cuba will send a medical team of 165 people to Sierra Leone to help in the frontline in the Ebola response efforts. The Cuban team consists of 100 nurses, 50 doctors, 3 epidemiologists, 3 intensive care specialists, 3 infection control specialist nurses and 5 social mobilization officers, all overseen by epidemiologist Dr Jorge Juan Delgado Bustillo.

- Read the feature story
- Read the statement
- Read the press conference remarks

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WHO welcomes Chinese contribution of mobile laboratory and health experts for Ebola response in west Africa

Statement
16 September 2014

WHO welcomes the commitment from the Government of the People's Republic of China to dispatch a mobile laboratory team to Sierra Leone to enhance the laboratory testing capacity for Ebola virus disease (EVD) in the country.

GOVERNO DE SANTA CATARINA
Secretaria de Estado da Saúde
Sistema Único de Saúde
Superintendência de Vigilância em Saúde
Diretoria de Vigilância Epidemiológica

Nota de Alerta nº 03
Febre Hemorrágica do Ebola

(Atualizado em 08/08/2014)

- Todo caso suspeito de **Febre Hemorrágica do Ebola** deverá ser notificado, **IMEDIATAMENTE por telefone,** para a Vigilância Epidemiológica do Município e, simultaneamente, para a Gerência Regional de Saúde correspondente e Diretoria de Vigilância Epidemiológica nos telefones:

✓ **(048) 32218472 / (048) 32218454/ (048) 32218412** (de segunda a sexta-feira das 07:00h as 19:00h)
✓ **(048) 91055450** (de segunda a sexta-feira das 19:00h as 07:00h, e finais de semana e feriados durante as 24 horas).

DIVE
DIRETORIA DE VIGILÂNCIA EPIDEMIOLÓGICA

Rua Felipe Schmidt, 774 – Edifício Montreal. Centro – Florianópolis / SC
CEP - 88.010-002 Fone: (48) 3221-8400
E-mail: dive@saude.sc.gov.br

SUV
Superintendência de Vigilância em Saúde

GOVERNO DE SANTA CATARINA
Secretaria de Estado da Saúde

Febres Hemorrágicas Virais

- Infecções virais agudas:
  - Febre e sintomas constitucionais → piora do estado geral e prostração → acometimento circulatório: choque, falência orgânica múltipla, hemorragia (variável, *pode estar ausente*) e morte (em dias a poucas semanas) em proporção varíavel.
- Zoonoses (maioria)
- Transmissão secundária entre humanos, no caso de alguns vírus

Viral Hemorrhagic Fevers

- FILOVIRUSES
  - Ebola
  - Marburg
- BUNYAVIRUSES
  - Rift Valley
  - Hantavirus
  - Crimean Congo
- RHABDOVIRUS
  - Bas-Congo
- ARENAVIRUSES
  - Lassa
  - Junin, Guanarito, Machupo, Sabiá
  - Lujo
- FLAVIVIRUSES
  - Yellow Fever
  - Dengue
  - Kyasanur Forest
  - Alkhurma
  - Omsk

Virus Family	Disease (Virus)	Natural Distribution	Usual Source of Human Infection	Incubation (Days)
Arenaviridae				
Arenavirus	Lassa fever	Africa	Rodent	5-16
	Argentine HF (Junin)	South America	Rodent	7-14
	Bolivian HF (Machupo)	South America	Rodent	9-15
	Brazilian HF (Sabia)	South America	Rodent	7-14
	Venezuelan HF (Guanarito)	South America	Rodent	7-14
Bunyaviridae				
Phlebovirus	Rift Valley fever	Africa	Mosquito	2-5
Nairovirus	Crimean-Congo HF	Europe, Asia, Africa	Tick	3-12
Hantavirus	Hemorrhagic fever with renal syndrome, hantavirus pulmonary syndrome	Asia, Europe, worldwide	Rodent	9-35
Filoviridae				
Filovirus	Marburg and Ebola	Africa	Fruit bat	3-16
Flaviviridae				
Flavivirus	Yellow fever	Tropical Africa, South America	Mosquito	3-6
	Dengue HF	Asia, Americas, Africa	Mosquito	Unknown for dengue HF, 3-5 for dengue

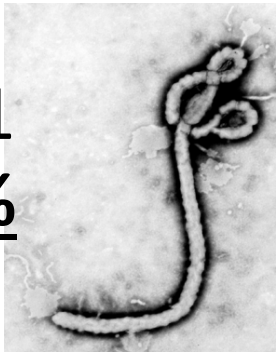
VHF: Direct human-to-human transmission

- None: Yellow fever, Dengue, Rift valley fever, Kyasanur forest disease, Alkhurma hemorrhagic fever, Omsk hemorrhagic fever, hantaviruses (with one exception)
- Low-moderate: Lassa and the South American Hemorrhagic fevers (Arenavirus)
- High: Ebola, Marburg, Crimean-Congo HF

Viral Hemorrhagic Fevers

- FILOVIRUSES
  - ***Ebola*** ***???***
  - Marburg
- BUNYAVIRUSES
  - Rift valley
  - **Hantavirus**
  - Crimean Congo
- RHABDOVIRUS
  - Bas-Congo
- ARENAVIRUSES
  - Lassa
  - Junin, Guanarito, Machupo, **Sabiá**
  - Lujo
- FLAVIVIRUSES
  - **Yellow Fever**
  - **Dengue**
  - Kyasanur
  - Alkhurma
  - Omsk

Filovírus



- Marburg – 1967, Alemanha e Iugoslávia – 31 casos, **mortalidade <25%**; Angola 2005**: 92% (>300 mortes).**

- Ebola – 1976, Zaire (R.D.Congo) e Sudão.
  - Zaire – 70-90% mortalidade
  - Sudan – 50-70% mortalidade
  - Tai Forest (Costa do Marfim) – 1 caso não fatal
  - Reston - não patogênico para humanos (EUA, Itália, Ásia)
  - Bundibugyo – 30-40% mortalidade

- Lluvio virus (Cuevavirus) – morcegos na Espanha, França, Portugal

Surtos e casos - Ebola (global – até 2011)

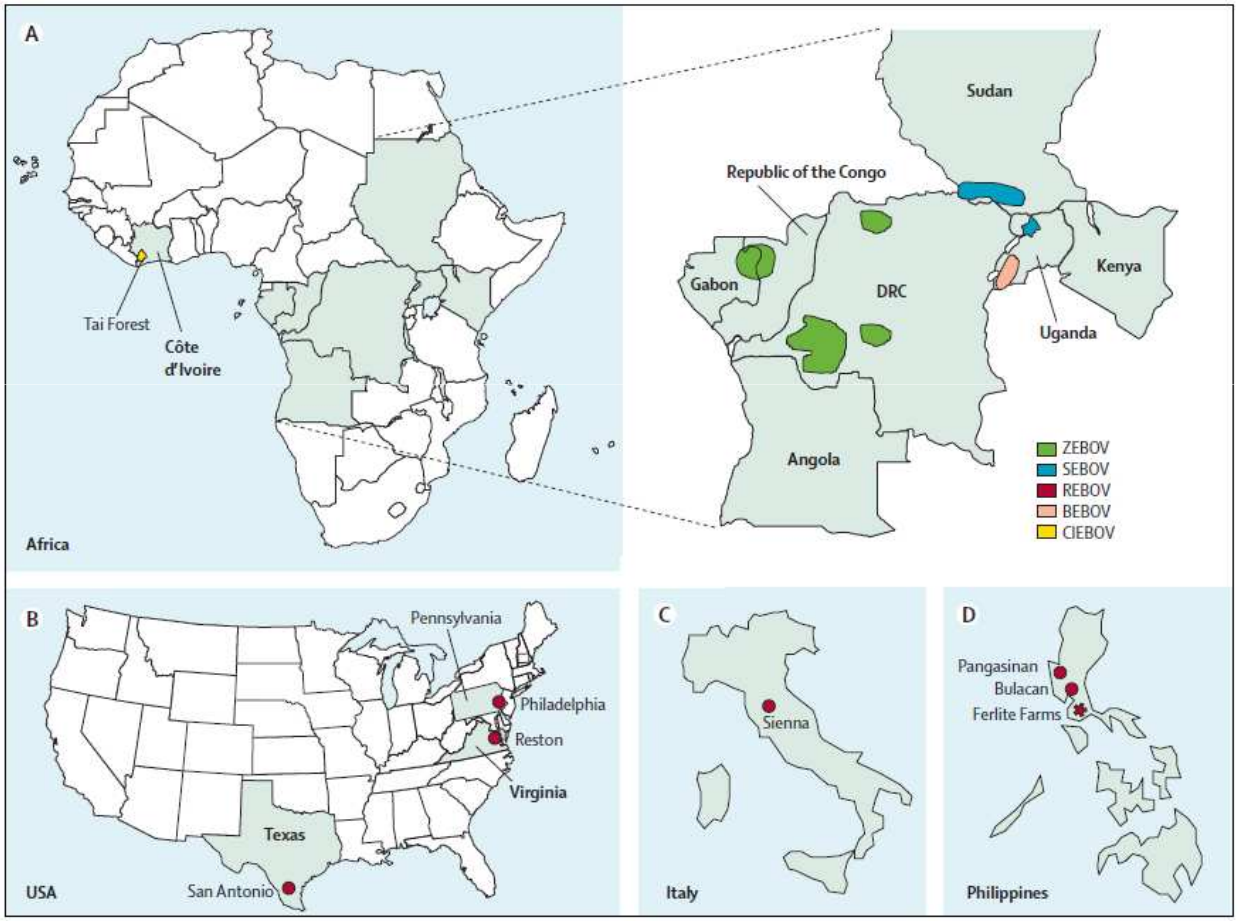


Figure 1: Locations of Ebolavirus infections and outbreaks

Transmissão

- Caso Inicial – contato com primatas mortos (ou porco selvagem, ou antílope); contato com morcegos frutívoros (reservatório provável).
- Casos secundários – transmissão inter-humana: contato (abrasões na pele ou mucosa íntegra) com fluidos corporais (sangue, vômito, saliva, etc), por gotículas e cadáveres.
  - **Não há transmissão durante o Período de Incubação (2-21d)**
  - Viremia aumenta drasticamente com evolução de casos graves – alto contágio
  - Funerais, unidades de saúde, domicílio – **alta transmissão.**

Transmissão inter-humana

- Todos fluidos corporais são considerados potencialmente infectantes.

- Não há evidência de transmissão respiratória por aerossol, apenas gotículas (exceto Vírus Ebola Reston, não causa doença em humanos...); assume-se risco com procedimentos que produzem aerossóis (ex: aspiração traqueal aberta, nebulização, broncoscopia, etc).

Ebola Virus Ecology

Enzootic Cycle

New evidence strongly implicates bats as the reservoir hosts for Ebolavirus, though the means of local enzootic maintainance and transmission of the virus within bat populations remain unknown.

Strains of Ebola:

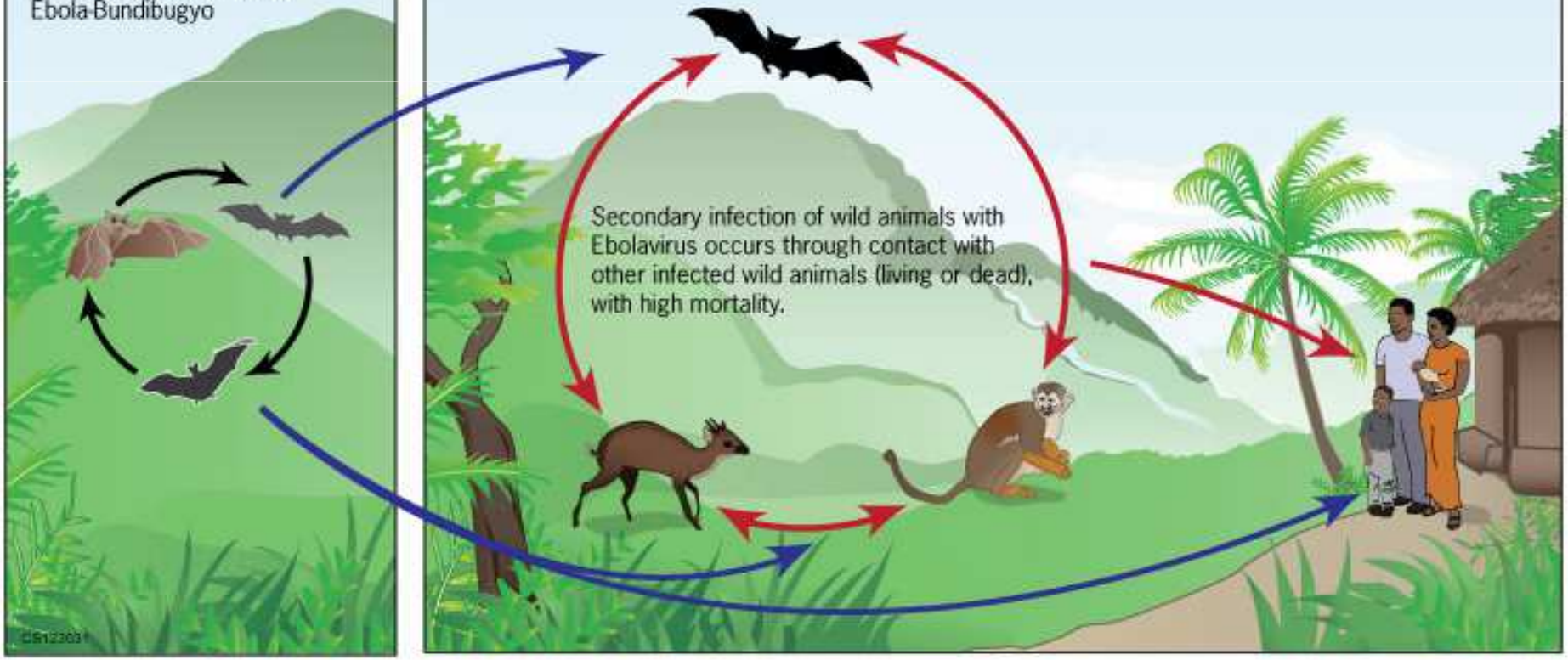
- Ebola-Zaire
- Ebola-Sudan
- Ebola-Ivory Coast
- Ebola-Reston (non-human)
- Ebola-Bundibugyo

Epizootic Cycle

Epizootics of the Zaire strain of Ebolavirus appear sporadically, producing high mortality amongnon-human primates and duikers, and frequently precede human outbreaks.

With the exception of the Reston strain, Ebolavirus in humans produces acute disease with high mortality. Little is known about how the virus first passes to humans to trigger a new outbreak.

Researchers speculate that the first patient may be infected through contact with an infected wild animal (living or dead). Then, human-to-human transmission can occur.



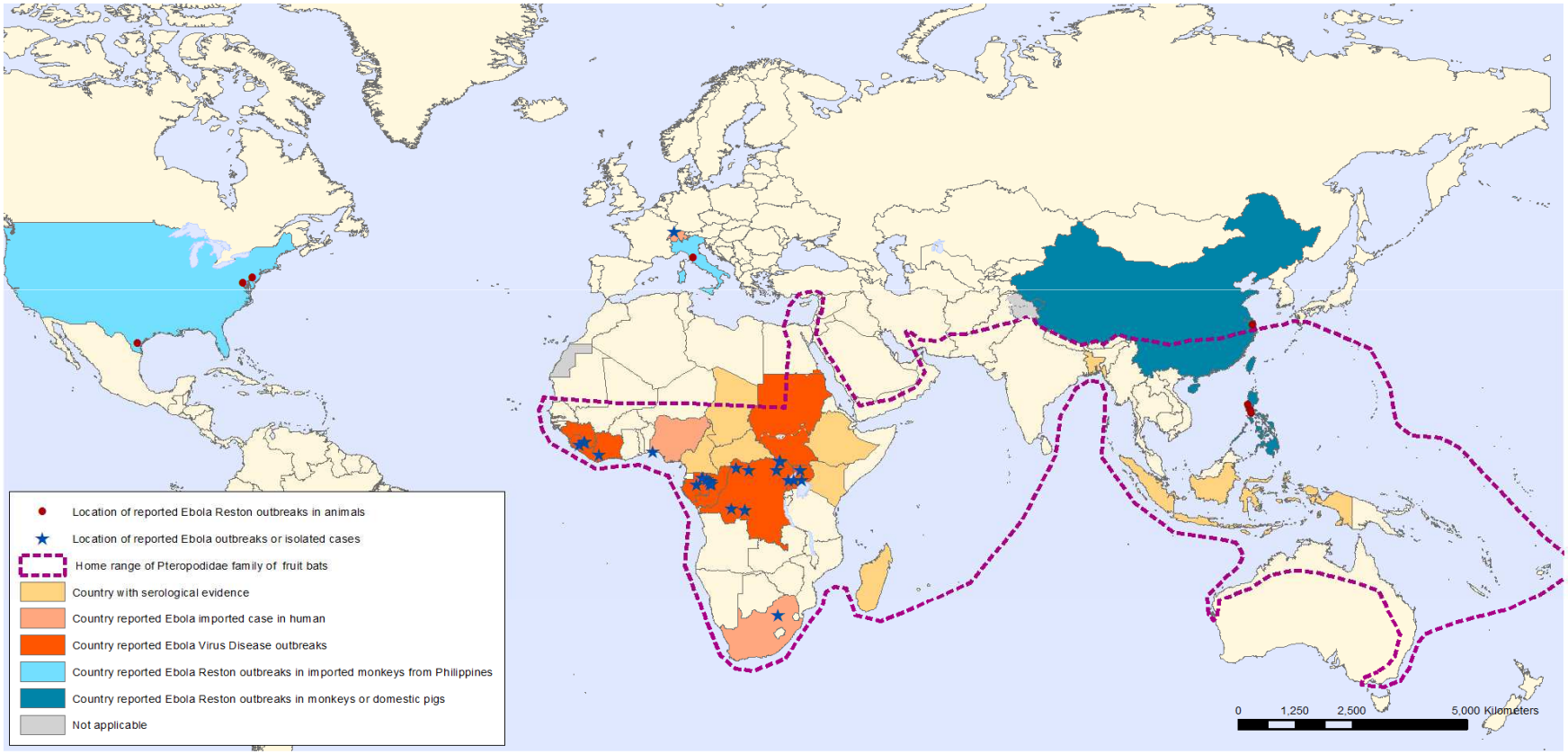
Contaminação ambiental

- Em condições ideais de laboratório: vírus viável por 4 dias em superfície sólida (quantidade decrescente).

- Entretanto, em situação de campo (África!), vírus não detectado em 33 amostras ambientais de enfermaria de isolamento (exceto numa luva suja com sangue).

Surtos e morcegos

Geographic distribution of Ebola virus disease outbreaks in humans and animals



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Health Statistics and Information Systems (HSI)
World Health Organization

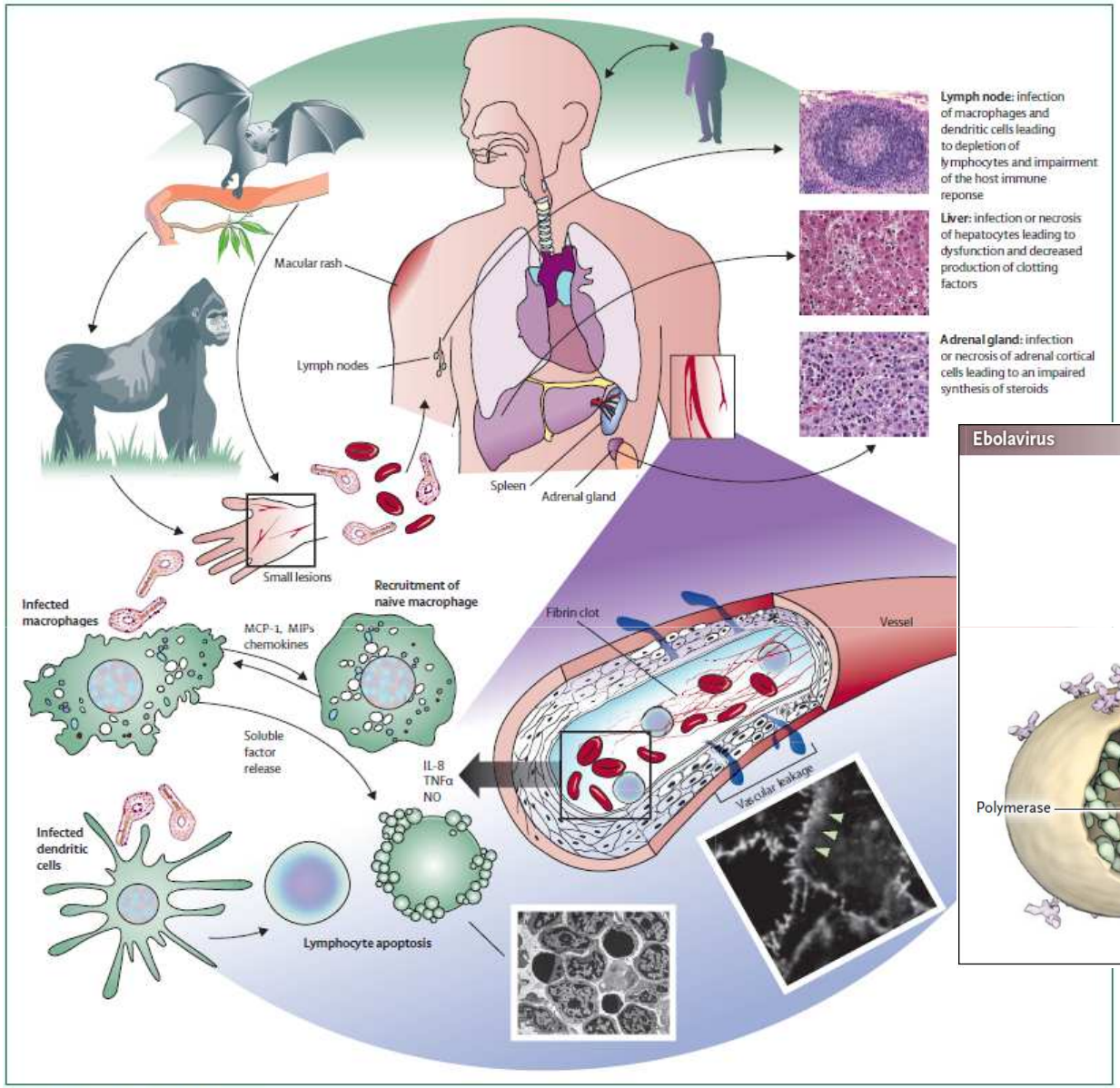
World Health Organization

Suspeição de Surto

- Agregado de óbitos em África rural tropical (esp. em famílias);
- Óbitos relacionados a funerais;
- Mortes entre profissionais de saúde;
- Relatos de febre + manifestações hemorrágicas (não necessariamente!);
- Mortandade entre grandes primatas.

Fisiopatogenia

- Dados limitados!
- Vírus pode infectar várias células: sistema fagocitário – macrófagos, monócitos, células dendríticas; hepatócitos; células endoteliais; adrenal; várias células epiteliais.
- Disfunção endotelial – glicoproteínas virais.
- Disfunção imunológica – depleção de linfócitos (sem infectá-los).
- “Tempestade” de citoquinas (similar à sepse)
- CID
- Infecções bacterianas secundárias



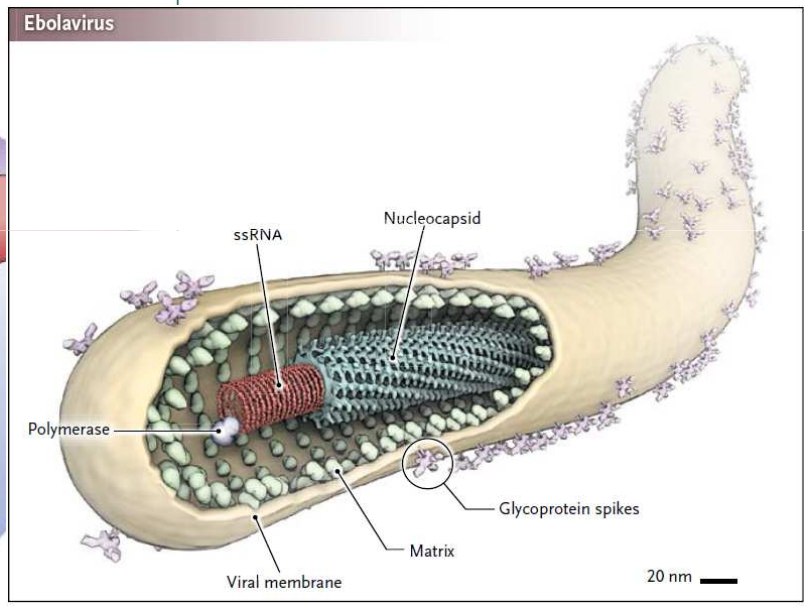


Figure 2: **Model of Ebola virus pathogenesis**

Virus spreads from the initial infection site (small lesions) to regional lymph nodes, liver, and spleen. Although Ebola virus does not infect lymphocytes, their rapid loss by apoptosis is a prominent feature of disease. The direct interaction of lymphocytes with viral proteins cannot be discounted as having a role in their destruction, but the substantial loss of lymphocytes probably results from a combination of factors including infection-mediated impairment of dendritic cells and release of soluble factors from monocytes and macrophages. Soluble factors released from target cells also contribute to the impairment of the vascular system leading to vascular leakage as demonstrated here in cultures of endothelial cells (white arrowheads). The systemic virus spread and replication, the general dysregulation of the host immune response, the coagulation abnormalities, the impairment of the vascular system, and hypotension all together finally result in shock and multiorgan failure. IL=interleukin. MCP-1=monocyte chemoattractant protein-1. MIPs=macrophage inflammatory proteins. NO=nitric oxide. TNFα=tumour necrosis factor α.

Necrópsia (rara em humanos!)

- Necrose hemorrágica focal em vários órgãos, sobretudo fígado, sistema linfocítico-fagocitário; necrose tubular renal.

- Necrose hepatocelular

- Linfonodos e baço – depleção linfocítica.

Manifestações Clínicas

- Registros insuficientes e incompletos – dificuldade em produzir estatísticas representativas.
- Suporte laboratorial nulo na maioria das epidemias.
- Tratamento extremamente limitado.

→ <u>Lacunas no conhecimento da doença.</u>

Quadro Clínico Inicial

- Quadro febril de início abrupto.
- Sinais e sintomas *inespecíficos:*
  - Mialgias;
  - Astenia;
  - Prostração;
  - Cefaléia;
  - Sintomas digestivos (diarréia, vômitos, náusea);
  - Dor de garganta.
  - Eventual linfadenomegalia, hepatomegalia dolorosa (icterícia é rara, <5%), hiperemia conjuntival.

- História epidemiológica (oportunidade de infecção) é ESSENCIAL para suspeição!

DIVE SES SC – CASO SUSPEITO

Para o atual momento epidemiológico considera-se como definição de **caso suspeito da Doença pelo Vírus Ebola:** Indivíduo procedente, nos últimos 21 dias, de país com transmissão atual do Ebola (Libéria, Guiné, Serra Leoa*), que apresente febre de início súbito, podendo ser acompanhada de sinais de hemorragia como: diarreia sanguinolenta, gengivorragia, enterorragia, hemorragias internas, sinais purpúricos e hematúria.

Evolução

- Progressivo agravamento;
- *Rash* cutâneo (não patognomônico) em torno do 5º dia de doença;
- Manifestações hemorrágicas variadas (ausentes em >50%!): petéquias, equimoses, sangramento sítio punção, conjuntival, digestiva, respiratória, hematúria, etc. Frequentemente não volumosa.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© CD-ROM ILLUSTRATED LECTURE NOTES ON TROPICAL MEDICINE

Evolução para óbito

- Instabilidade hemodinâmica, choque;
- Coagulação intravascular disseminada;
- Insuficiência orgânica múltipla;
- SARA?
- Prossível infecção bacteriana secundária;
- Óbito, em geral, na segunda semana de doença (ou término da primeira).

Sobreviventes – manifestações tardias

- Convalescência prolongada

- Uveite
- Hepatite
- Mielite
- Orquite
- Psicose
- Descamação cutânea (rash), alopécia

→ Eliminação viral tardia no sêmen, provavelmente leite materno

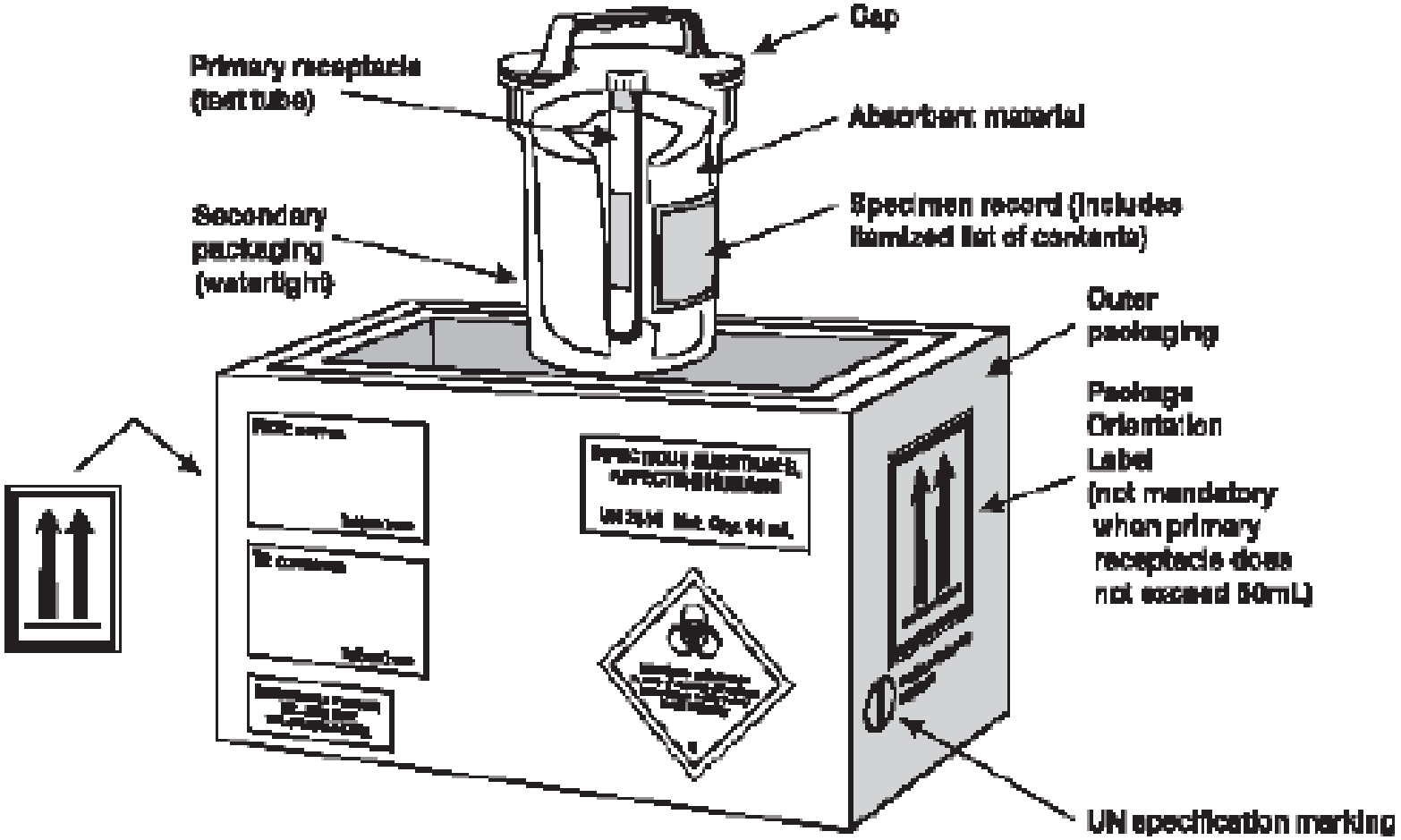
Exames Laboratoriais

- Dados limitadíssimos!
- Leucopenia e linfopenia, depois aumento de linfócitos atípicos; leucocitose e neutrofilia em fase terminal (infecção bacteriana secundária?)
- Plaquetopenia frequente;
- Anemia;
- Aumento de AST e ALT – tipicamente, AST>ALT (mais pronunciado em casos fatais); em geral não atinge níveis elevados como hepatites virais ou febre amarela.
- Aumento de creatinina, hematúria, proteinúria.
- TAP e PTT alargados, CID.
- Eletrólitos RARAMENTE avaliados

Diagnóstico

- Sorologia – pesquisa de anticorpos (ELISA) – pode ser negativa em casos que evoluirão para óbito; pesquisa de antígeno.
- PCR – pode ser negativo nos primeiros 4 dias de doença.
- Isolamento e cultivo viral – apenas em laboratórios nível 4 (inexistente no Brasil).
- Necrópsia (fragmentos) – Imunohistoquímica.

Envio de amostras



Diagnóstico Diferencial

- **Malária**
- Febre Amarela, Febre de Lassa, Febre do Vale do Rift, Febre Hem. Criméia-Congo, Marburg, Arenavírus Sul Americanos
- Leptospirose
- Dengue
- Chikungunya
- Riquetsioses
- Febre Tifóide
- Sepse bacteriana
- Hepatites virais
- Sarampo
- Gastroenterite bacteriana, Cólera
- Influenza
- Peste
- Febre Recorrente

TRATAMENTO???

Outbreaks of Filovirus Hemorrhagic Fever: Time to Refocus on the Patient

Daniel G. Bausch,[1] Heinz Feldmann,[5,6] Thomas W. Geisbert,[2] Mike Bray,[3] A. G. Sprecher,[7] Paul Boumandouki,[8] Pierre E. Rollin,[4] Cathy Roth,[9] and the Winnipeg Filovirus Clinical Working Group

[1]Tulane School of Public Health and Tropical Medicine, New Orleans, Louisiana; [2]United States Army Medical Research Institute for Infectious Diseases, Fort Detrick, and [3]National Institutes of Health, Bethesda, Maryland; [4]Centers for Disease Control and Prevention, Atlanta, Georgia; [5]Special Pathogens Program, National Microbiology Laboratory, Public Health Agency of Canada, and [6]Department of Medical Microbiology, University of Manitoba, Winnipeg, Manitoba, Canada; [7]Medecins Sans Frontières, Brussels, Belgium; [8]Ministry of Health and Population, Republic of the Congo, Brazzaville, Republic of the Congo; [9]World Health Organization, Geneva, Switzerland

In the 40 years since the recognition of filoviruses as agents of lethal human disease, there have been no specific advances in antiviral therapies or vaccines and few clinical studies on the efficacy of supportive care. On 20 September 2006, experts from 14 countries representing 68 institutions integrally involved in the response to outbreaks of filovirus hemorrhagic fever gathered at the National Microbiology Laboratory of the Public Health Agency of Canada in Winnipeg to discuss possible remedies for this grim situation, in a unique ***workshop entitled "Marburg and Ebola Hemorrhagic Fever: Feasibility of Prophylaxis and Therapy***." A summary of the ***opportunities for and challenges to improving treatment of filovirus hemorrhagic fevers*** is presented here.

The Journal of Infectious Diseases 2007; 196:S136–41

FHV & Septic Shock - similarities

EDITORIAL

Ebola Hemorrhagic Fever and Septic Shock

Mike Bray[1] and Siddhartha Mahanty[2]

[1]Biodefense Clinical Research Branch, Office of Clinical Research, Office of the Director, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health (NIH), Bethesda, and [2]Malaria Vaccine Development Unit, NIAID, NIH, Rockville, Maryland

Ebola virus is the cause of sporadic outbreaks of lethal Ebola hemorrhagic fever (EHF) in central Africa. Despite the difficulties of studying this virus, much has been learned over the past decade about the pathogenesis of Ebola virus infection in humans and nonhuman primates. Two articles in this issue of the *Journal of Infectious Diseases* report further progress. The article by Bosio et al. [1] confirms findings that the virus is able to infect dendritic cells (DCs), impairing their innate

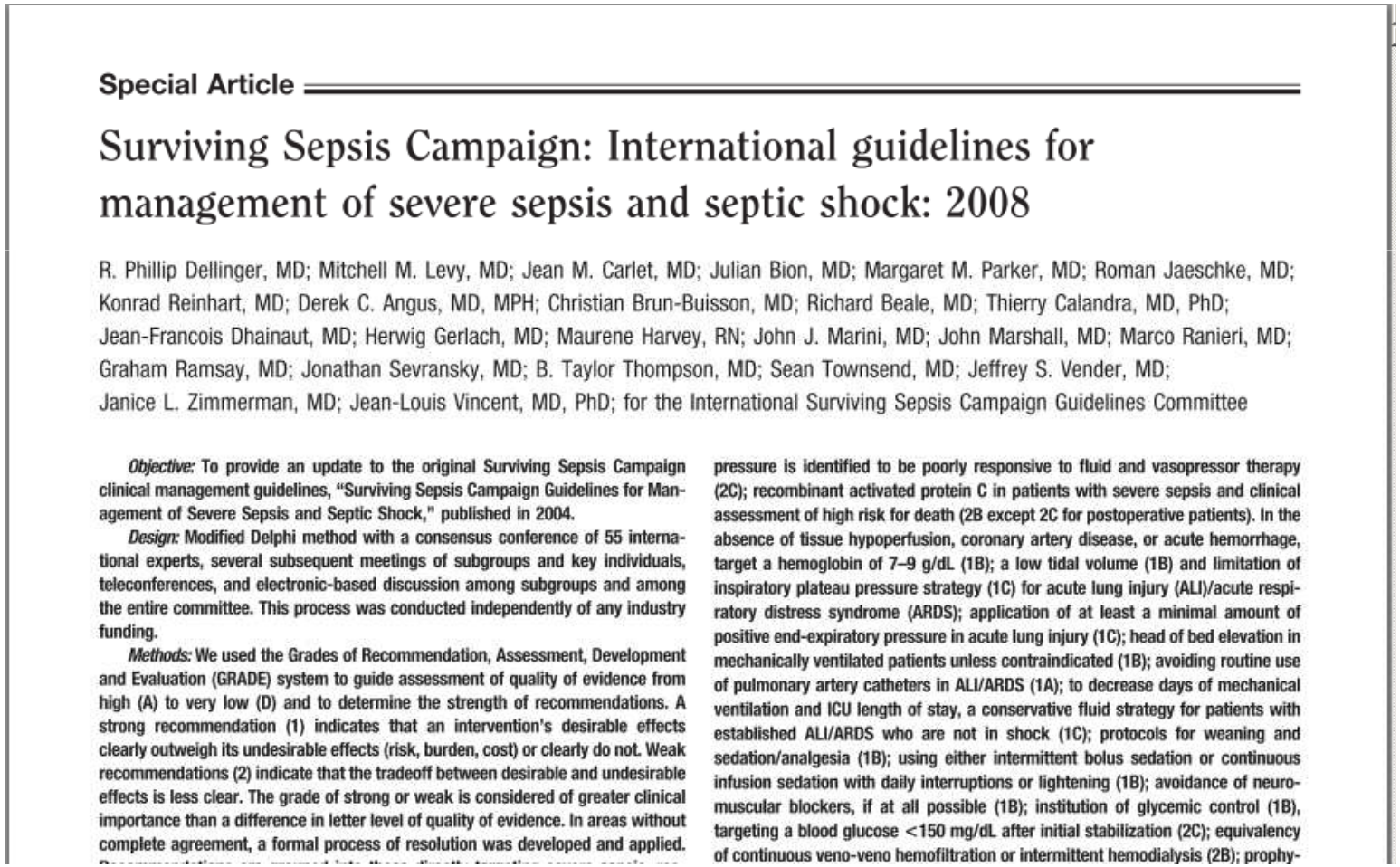
of circulating proinflammatory cytokines and lymphocyte apoptosis, also occur in severe bacterial infections. Other investigators have also noticed these similarities and have suggested that the comparison of EHF with septic shock could lead to insights into pathogenesis and to improvements in therapy [4]. Although viral and bacterial infections obviously differ in fundamental respects, it is now recognized that the interactions of pathogens or their components with pattern-recognition re-

yellow fever, or malaria. Hemorrhagic manifestations tend to be limited to petechiae, ecchymoses, oozing from venipuncture sites, hematuria, and melena. Limited data on immune responses during EHF were obtained during the 1995 Kikwit epidemic, and more-extensive data were obtained during 2 outbreaks in Gabon [8–12]. Analysis of blood samples has shown high levels of proinflammatory cytokines, including tumor necrosis factor (TNF)–α, and evidence of intravascular

JID, 2003

Surviving Sepsis Guidelines (2008)

- Standardizing Sepsis Treatment – early goal-directed therapy



Special Article

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008

R. Phillip Dellinger, MD; Mitchell M. Levy, MD; Jean M. Carlet, MD; Julian Bion, MD; Margaret M. Parker, MD; Roman Jaeschke, MD; Konrad Reinhart, MD; Derek C. Angus, MD, MPH; Christian Brun-Buisson, MD; Richard Beale, MD; Thierry Calandra, MD, PhD; Jean-Francois Dhainaut, MD; Herwig Gerlach, MD; Maurene Harvey, RN; John J. Marini, MD; John Marshall, MD; Marco Ranieri, MD; Graham Ramsay, MD; Jonathan Sevransky, MD; B. Taylor Thompson, MD; Sean Townsend, MD; Jeffrey S. Vender, MD; Janice L. Zimmerman, MD; Jean-Louis Vincent, MD, PhD; for the International Surviving Sepsis Campaign Guidelines Committee

Objective: To provide an update to the original Surviving Sepsis Campaign clinical management guidelines, "Surviving Sepsis Campaign Guidelines for Management of Severe Sepsis and Septic Shock," published in 2004.

Design: Modified Delphi method with a consensus conference of 55 international experts, several subsequent meetings of subgroups and key individuals, teleconferences, and electronic-based discussion among subgroups and among the entire committee. This process was conducted independently of any industry funding.

Methods: We used the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to guide assessment of quality of evidence from high (A) to very low (D) and to determine the strength of recommendations. A strong recommendation (1) indicates that an intervention's desirable effects clearly outweigh its undesirable effects (risk, burden, cost) or clearly do not. Weak recommendations (2) indicate that the tradeoff between desirable and undesirable effects is less clear. The grade of strong or weak is considered of greater clinical importance than a difference in letter level of quality of evidence. In areas without complete agreement, a formal process of resolution was developed and applied.

pressure is identified to be poorly responsive to fluid and vasopressor therapy (2C); recombinant activated protein C in patients with severe sepsis and clinical assessment of high risk for death (2B except 2C for postoperative patients). In the absence of tissue hypoperfusion, coronary artery disease, or acute hemorrhage, target a hemoglobin of 7–9 g/dL (1B); a low tidal volume (1B) and limitation of inspiratory plateau pressure strategy (1C) for acute lung injury (ALI)/acute respiratory distress syndrome (ARDS); application of at least a minimal amount of positive end-expiratory pressure in acute lung injury (1C); head of bed elevation in mechanically ventilated patients unless contraindicated (1B); avoiding routine use of pulmonary artery catheters in ALI/ARDS (1A); to decrease days of mechanical ventilation and ICU length of stay, a conservative fluid strategy for patients with established ALI/ARDS who are not in shock (1C); protocols for weaning and sedation/analgesia (1B); using either intermittent bolus sedation or continuous infusion sedation with daily interruptions or lightening (1B); avoidance of neuromuscular blockers, if at all possible (1B); institution of glycemic control (1B), targeting a blood glucose <150 mg/dL after initial stabilization (2C); equivalency of continuous veno-veno hemofiltration or intermittent hemodialysis (2B); prophy-

Tratamento

- Suportivo...
- Terapia Intensiva!
  - Reposição volêmia (risco de SARA!!)
  - Diálise
  - Reposição de concentrado de hemáceas, plasma, plaquetas
  - Suporte ventilatório (princ. SARA)
  - Suporte hemodinâmico
  - Tratamento de infecções bacterianas secundárias
- Na ausência de suporte laboratorial – tratamento empírico de malária e infecção bacteriana.

Terapia experimental

- Anticorpos monoclonais humanos recombinantes (ex: **ZMapp**, anti-GP), *small interferring RNA* (*Tekmira*), imunização passiva com soro hiper-imune heterólogo ou humano convalescente (semelhante à Febre hemorrágica Junin), *recombinant nematode anticoagulant protein*...
- Vacinas experimentais
  - Dificuldade em conduzir ensaios clínicos;
  - Necessidade de aplicação precoce;
  - *$$$$$?????*

In the particular circumstances of this outbreak, and provided certain conditions are met, the panel reached **consensus** that **it is ethical to offer unproven interventions with as yet unknown efficacy and adverse effects, as potential treatment or prevention.**

World Health Organization

BACKGROUND DOCUMENT

POTENTIAL EBOLA THERAPIES AND VACCINES

THIS DOCUMENT INCLUDES

PROPOSED ELEMENTS TO CONSIDER DURING THE DELIBERATIONS TO DEVELOP A FRAMEWORK

TO ASSIST DECISION MAKING AT GLOBAL AND NATIONAL LEVEL

1. EBOLA THERAPIES AND VACCINES: WHAT'S IN THE PIPELINE?

The following table lists potential therapies and vaccines for EVD and provides information about how the interventions might work. It also summarises the research, which has been conducted, what is known about safety and availability, and the feasibility of use under current conditions. The list has been produced after a review of studies exploring the effects of potential therapies and vaccines ***in vitro*** and in animal models, and following discussions with clinicians and virologists conducted by WHO and partners from the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) [1].

1.1 Lead experimental therapies

Table1. Overview of scientific information on potential therapies under development (Annex 2)

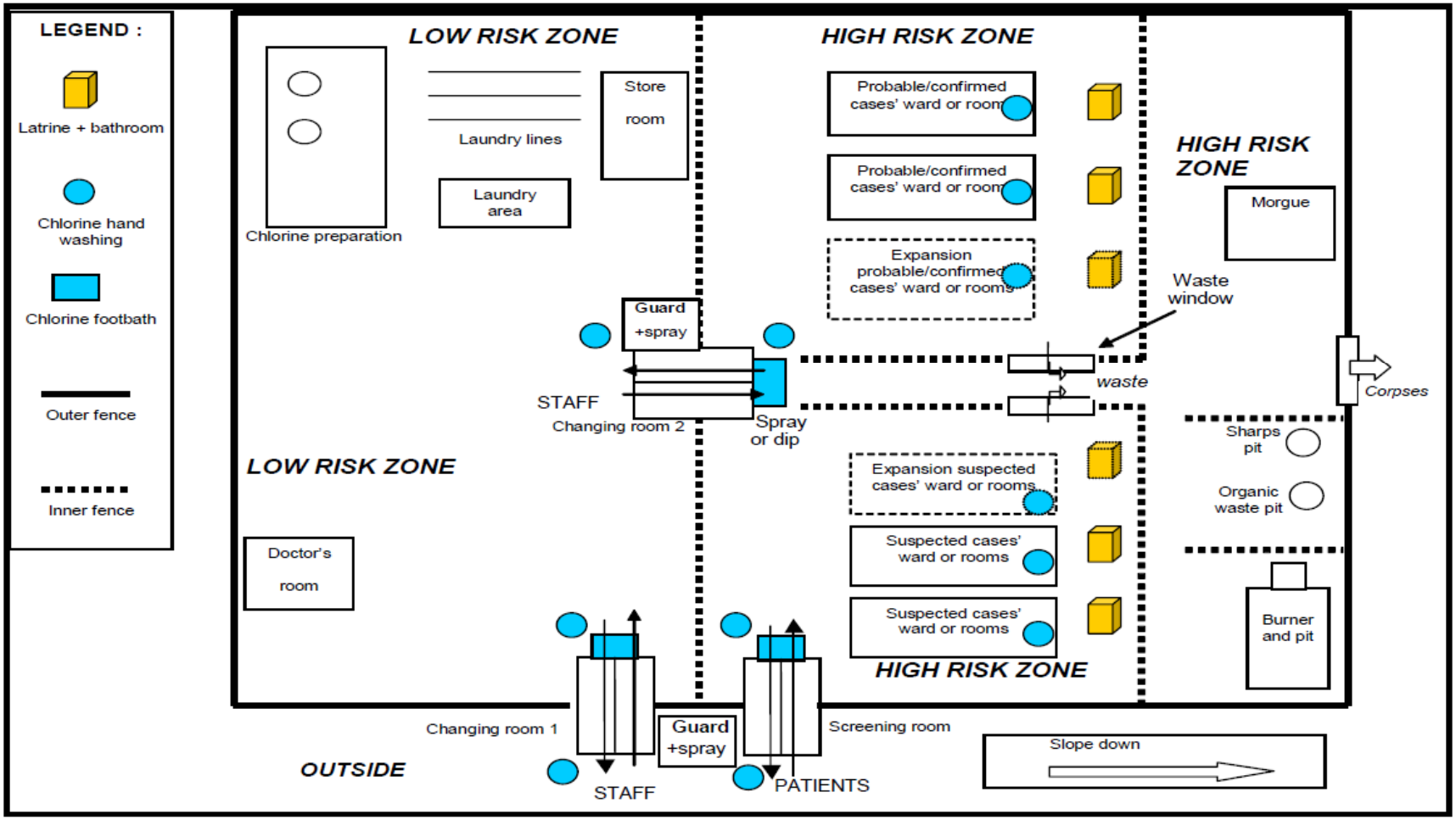
Therapy	What it does?/ State of research	Safety	Availability/feasibility
Convalescent plasma	Studies suggest blood transfusions from EVD survivors might prevent or treat Ebola virus infection in others, but the results of the studies are still difficult to interpret. It is not known whether antibodies in the plasma of survivors are sufficient to treat or prevent the disease. More research is needed.	Safe if provided by well-managed blood banks. Risks are like those associated with the use of any blood products, such as the transmission of blood-borne pathogens that cause disease. There is a theoretical concern about antibody-dependent enhancement of EVD infection, which can increase infectivity in the cells.	Blood transfusion is culturally acceptable in West Africa. Potential donors are Ebola survivors, but the logistics of blood collection are an issue. Options to conduct studies in patients are being explored. The first batches of convalescent plasma might be available by the end of 2014.
ZMapp Cocktail of three chimeric mouse-human monoclonal antibodies (Mapp Biopharmaceutical Inc.)	The three antibodies in this mixture block or neutralize the virus, by binding to or coating a different site on the covering or "envelope" of the virus. Studies in monkeys showed a strong survival up to five days after infection, when virus and/or fever were present.	There have been no formal safety studies in humans. Very small numbers of EVD-infected people have been given ZMapp on a compassionate basis, and no safety issues have been reported to date. Clinical effectiveness is still uncertain.	A very limited supply (fewer than 10 treatment courses) has been deployed to the field. Efforts to scale up production may yield increased supplies of potentially few hundred doses by the end of 2014.
Hyperimmune globulin prepared by purifying and concentrating plasma of immunised animals or previously infected humans with high titres of neutralizing antibody against EVD	Antibodies that can neutralize the different EVD strains have been produced and shown to be protective in monkeys when treatment begins 48 hours after exposure to EVD.	Generally safe. There has been extensive experience with the use of hyperimmune globulin against other infectious agents in humans. Inactivation and purification procedures effectively eliminate blood-borne pathogens that cause disease.	Not currently available. Several months are needed to immunize animals, collect plasma and make the purified product. Work is starting on the production of immune globulin in horses, and of human immune globulin in cattle. Studies in horses could take place within six months, but large-scale batches for use in humans are not expected before mid-2015.
TKM-100802Lipid Nanoparticle Small interfering Ribonucleic acid (siRNA) (Tekmira)	These target two essential viral genes to stop the virus from replicating. Effective in guinea pigs and monkeys. In monkeys 83% survival if administered 48 hours after infection, and 67% survival 72 hours after infection.	A single-dose study in healthy volunteers found side effects including headache, dizziness, chest tightness and raised heart rate at high doses. At lower doses projected to be the dose used for treatment, drug was better tolerated.	The US Food and Drug Administration has authorized emergency use in EVD-infected patients. A limited number of treatment courses are potentially available. There is potential for the production of 900 courses by early 2015.
	In monkey studies, doses of 14 to	Human tolerability has been	The active pharmaceutical

Controle de Surto

- ISOLAMENTO DE CASOS
  - Diagnóstico precoce!!!
  - Segregar casos confirmados; casos prováveis; casos suspeitos.
- Vigilância de contatos (21 dias)
- Funeral supervisionado
- Interrupção de atividades médicas “não essenciais” (cirurgias, laboratório, injeções...)
- Gratuidade de cuidados
- Educação comunitária... (antropologistas!)
- Preservativos na convalescência

Esquema Unidade Isolamento (MSF)

Example 1. A theoretic example to be used to help to design the layout in a real set up.



Prevenção de transmissão hospitalar

- **EPI – barreira total!!**
  - Luvas, máscara (N95...), óculos ou proteção facial total, botas ou cobertura para calçados; avental impermeável; capote ou macacão, cobertura para cabeça (opcional?).
- Pérfuro-cortantes
- Limpeza/desinfecção de superfícies frequentes

PRECAUÇÕES PADRÃO + CONTATO + GOTÍCULAS

("Reforçadas")

- Quarto individual, evitar produzir aerossol, controle.

Casos “aceitáveis” entre profissionais de saúde? Sacrifício??

Tchernobil – acidente nuclear – “Liquidators”

“Somebody had to do it…” - Alexander Fedotov (liquidator)

Casos “aceitáveis” entre profissionais de saúde? Sacrifício??

Tchernobil – [illegible]idente nuclear – “[illegible]idators”

“Somebody had to do it…” - Alexander Fedotov (liquidator)

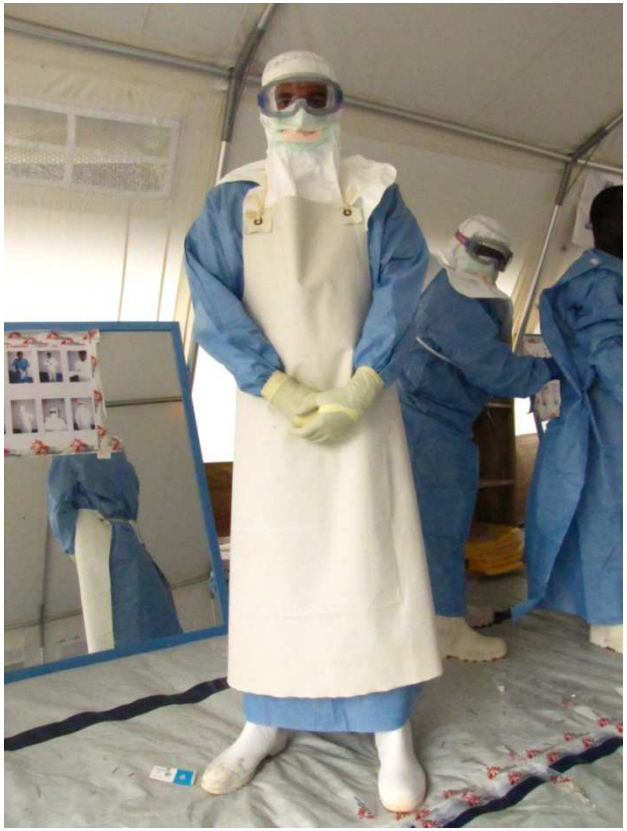
Epidemia atual: +/- **10%** dos casos em profissionais de saúde

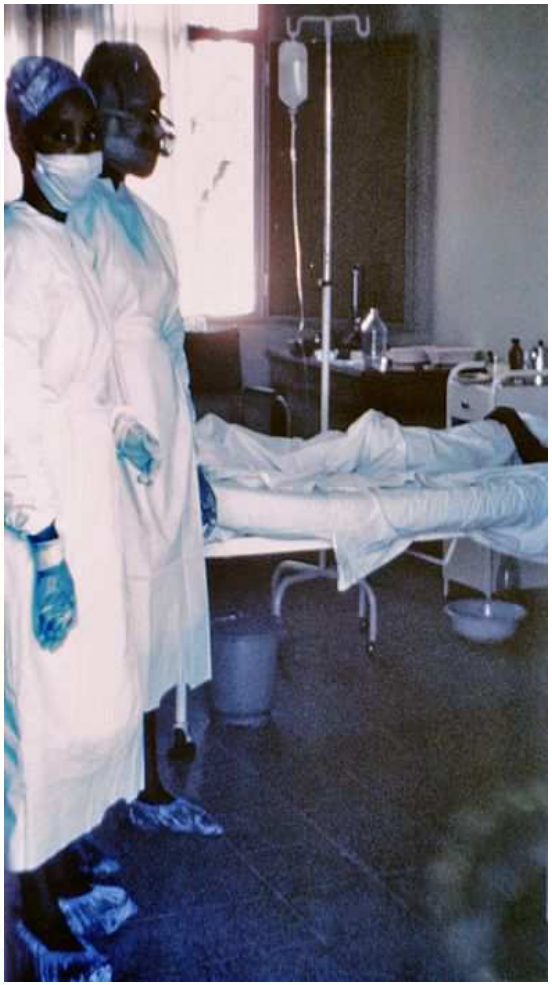
(MSF = 0)

Um outro exemplo: SARS

Table 1 Numbers of Probable Cases of SARS, Deaths, and Healthcare Workers Infected in Selected Countries and Globally

	Cumulative No. of Cases	Deaths No. (%)	Workers Infected No. (%)
Canada	251	41 (17)	108 (43)
China	5,327	349 (7)	1,002 (19)
Hong Kong	1,755	299 (17)	386 (22)
Taiwan	346	37 (11)	68 (20)
Philippines	14	2	4 (29)
Singapore	238	33	97 (41)
Thailand	9	2	1 (11)
Vietnam	63	5	36 (57)
Global	8,098	774	1,707 (21)





Suggested PPE for ***Patient Care***

- ***Recommended***:
  - Gloves (pulled over gown)
  - Gown (covering arms)
  - Apron (covering torso)
  - Mask (covering mouth/nose)
  - Goggles/face shield (covering eyes)
  - Boots
- ***Optional***: No evidence of additional protection for droplet-borne pathogens

  ****Headcover (optional)***

  ****Respirator (optional)***

CDC

Cuidado ao retirar EPI!

Example 1 of Undressing Procedure for Leaving the High-Risk Zone

1. Disinfect the outer pair of gloves.

2. Disinfect the apron and the boots.

3. Remove the apron

4. Remove the outer pair of gloves.

5. Disinfect the gloved hands.

6. Remove the outer gown.

7. Disinfect the gloved hands.

8. Remove the goggles.

9. Remove the head cover.

10. Disinfect the gloved hands

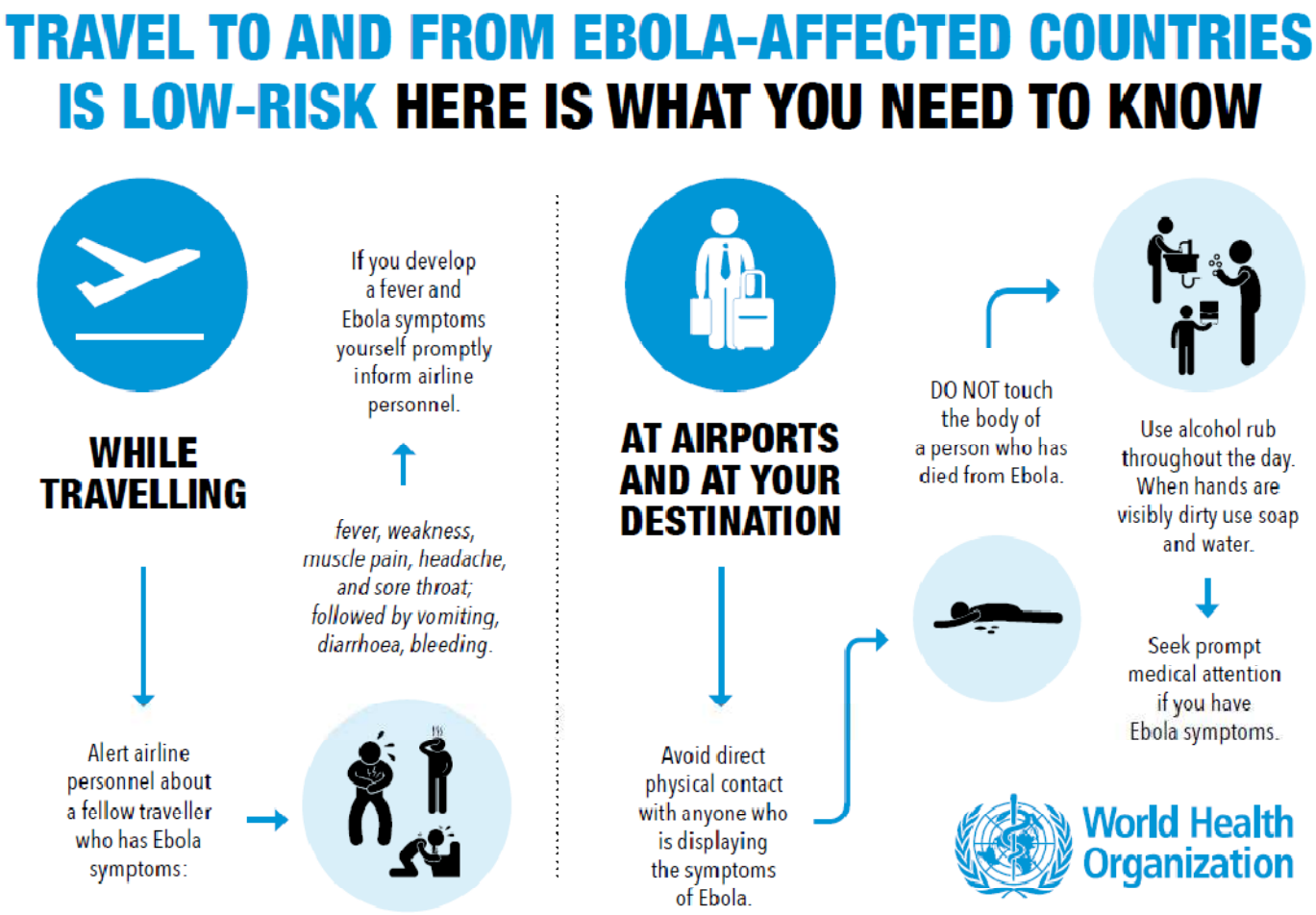
11. Remove the mask.

12. Disinfect the gloved hands.

13. Remove the inner pair of gloves.

14. Wash hands with 0.05% chlorine solution, and put on new gloves.

OMS não recomenda restrições em transporte e comércio...



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22 August 2014 Last updated at 21:36 GMT

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Ebola crisis: Senegal defends Guinea border closure

Airports around the world are screening West African passengers to see if they have a fever

Senegal has defended the closure of its border with Guinea because of the Ebola outbreak, despite warnings that such measures are counterproductive.

The World Health Organization (WHO) says travel bans do not work.

Ebola outbreak

Five top tips

Doctor's report

21 August 2014 Last updated at 21:53 GMT

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Ebola travel: South Africa bans incomers from W Africa

Kenya has not reported any cases of Ebola, but is a common transit point for African travellers

South Africa says non-citizens arriving from Ebola-affected areas of West Africa will not be allowed into the country, with borders closed to people from Guinea, Liberia and Sierra Leone.

Ebola outbreak

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17 September 2014 Last updated at 20:38 GMT

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Ebola could wreck W Africa economies, warns World Bank

Residents of the Liberian capital, Monrovia, watch health workers remove the body of an Ebola victim

The Ebola outbreak could have a catastrophic impact on the economies of Guinea, Liberia and Sierra Leone, the World Bank says.

Ebola outbreak

odated at 16:45 GMT

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Ebola crisis: Ivory Coast closes land borders

Already more people have died in this outbreak of Ebola than in any other

Ivory Coast has become the latest African country to close its land borders to prevent the spread of the deadly Ebola virus on to its territory.

Ebola outbreak

Entretanto...

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20 August 2014 Last updated at 23:03 GMT

Ebola crisis: The economic impact

By Richard Hamilton
BBC News

Military road blocks are preventing the movement of goods and workers

With more than 1,300 reported deaths from Ebola in West Africa, the virus continues to be an urgent health crisis, but it is also having a devastating impact on the economies of Guinea, Liberia and Sierra Leone.

Ebola outbreak

Ebola crisis: Liberia police fire at Monrovia protests

West Point residents say they need to leave the slum to buy food and go to work

Police in Liberia's capital, Monrovia, have fired live rounds and tear gas during protests after a quarantine was imposed to contain the spread of the deadly Ebola virus.

Ebola outbreak

Five top tips

5. Don't panic

Spreading rumours increases fear. Do not be scared of health workers - they are there to help and a clinic is the best place for a person to recover - they will be rehydrated and receive pain relief.

About half of the people infected in the current outbreak have died. There have been cases of medics being attacked and people being abandoned when they are suspected of having Ebola - even when they are suffering from something else.

A belief in irrational traditional remedies has also exacerbated the spread of the virus.

17 August 2014 Last updated at 21:30 GMT

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Ebola crisis: Confusion as patients vanish in Liberia

This man carried a young girl out of the West Point health facility

There are conflicting reports over the fate of 17 suspected Ebola patients who vanished after a quarantine centre in the Liberian capital was looted.

Ebola outbreak

Five top tips

MINISTRY OF HEALTH

CERTIFICATE OF DISCHARGE

This is to certify that

Kanyonyunzi

Name: *Kanyanzi Maureen*

of

Village: *Kiryabyenja* Parish: --- Sub-county: *Muhoro*

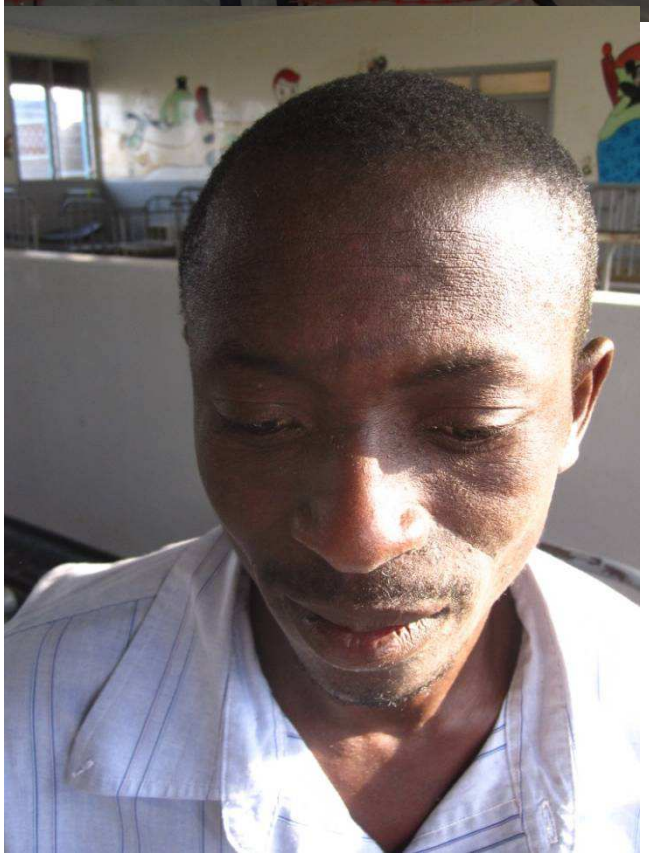
Has been successfully managed at the Ebola treatment facility and is now free of Ebola. He/she does not constitute any risk to the community in any way. He/she has been adequately counselled, is fit to return to his/her home and can resume his/her duty

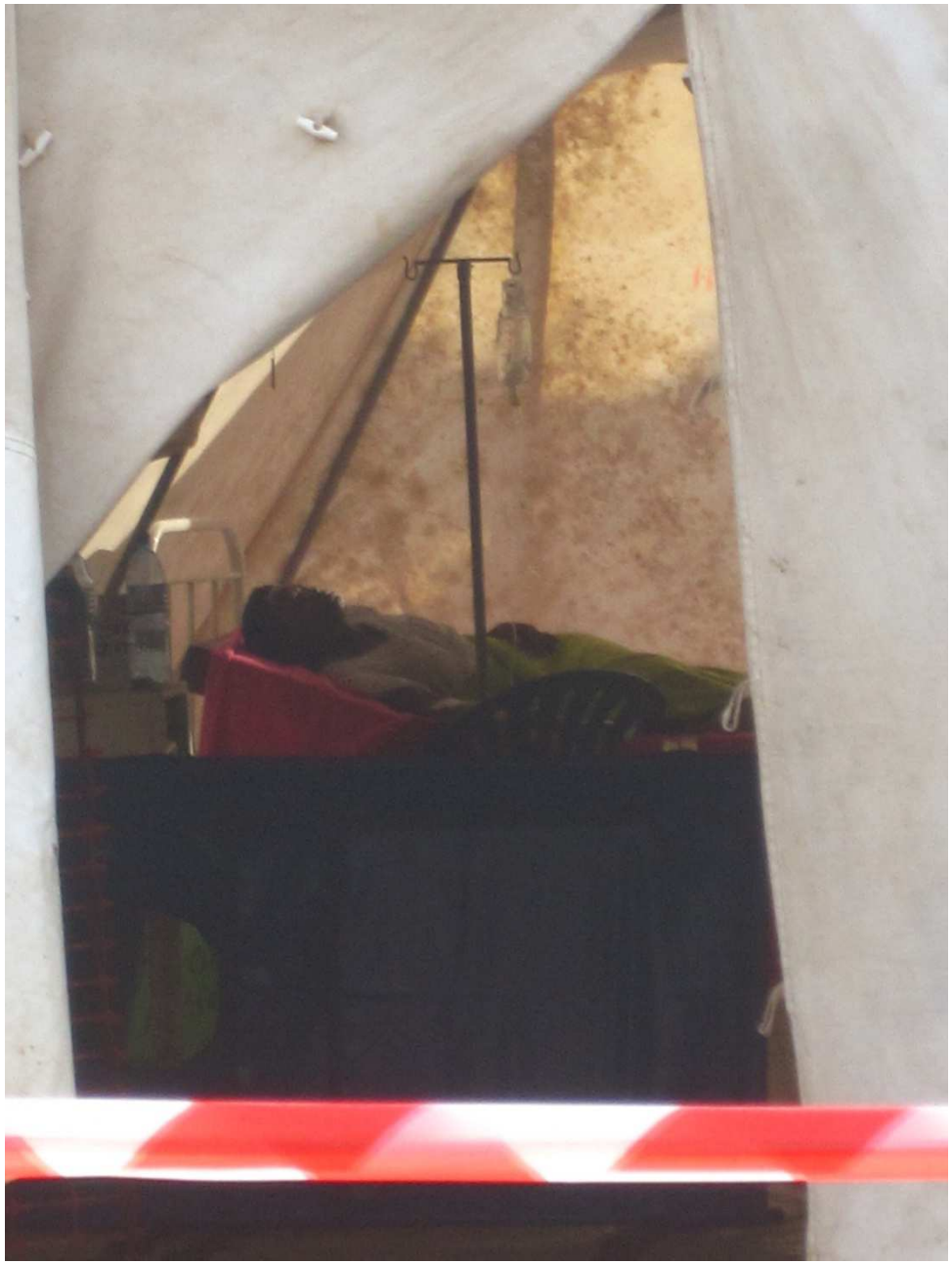
Dr James Olowo
Medical Superintendent, Kagadi Hospital

MEDICAL SUPERINTENDENT KAGADI HOSPITAL

Dr Jackson Amone
National Ebola Coordinator

Date: 8th August 2012





Health probe as Ebola scare woman dies

Suspected Ebola case at KNH (Kenya, MOH) – from local media


AP


AFP


AP

www.bbc.com/news/world-africa-28922290

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25 August 2014 Last updated at 00:29 GMT

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Ebola outbreak confirmed by DR Congo

A health worker gives water to a woman with Ebola in Sierra Leone

The Democratic Republic of Congo has confirmed that an outbreak of haemorrhagic fever in the north of the country has been identified as Ebola.

Health Minister Felix Numbi told the BBC that tests on two people had confirmed the disease in Equateur province, where 13 had already died.

But he said the deaths occurred in an isolated area and the disease seemed a different strain to West Africa's.

Ebola outbreak

Five top tips

Doctor's report

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PT 12:12 27/08/2014

Riscos reais além do casos reais de Ebola...

- Em situação de epidemia ou pânico, outras doenças infecciosas que demandam tratamento específico URGENTE (ex: sepse bacteriana, malária, meningococcemia) podem ser errôneamente diagnosticadas e não serem tratadas a tempo.

Riscos reais além do casos reais de Ebola...

- Morbidade (e quiçá mortalidade) devido a estigma, violência, estupidez humana...

MENU G1 SANTA CATARINA

28/07/2014 23h20 - Atualizado em 28/07/2014 23h20

Reunião em Criciúma debate situação de imigrantes haitianos e africanos

Segundo dados da Cáritas, região Sul tem cerca de 1,4 mil imigrantes. A preocupação é a demora da conclusão do pedido de refúgio deles.

Do G1 SC Tweet

Um encontro entre diversas entidades debateu a situação dos imigrantes que chegaram ao Sul catarinense nos últimos meses. Nesta segunda-feira (28), o 1º Fórum das Imigrações discutiu alternativas referentes à imigração, em **Criciúma**. Segundo dados da Cáritas Diocesana, a região tem cerca de 1,4 mil estrangeiros, entre haitianos, ganeses e senegaleses. Muitos sobrevivem de auxílio da comunidade e das secretarias municipais de Assistência Social dos municípios.

MENU G1 JORNAL NACIONAL

Laudo aponta que uma sequência de erros provocou queda de viaduto

Jornal Nacional mostra, com exclusividade, o resultado do laudo que apura os responsáveis pela queda do viaduto em Belo Horizonte, durante a Copa.

O Jornal Nacional antecipa, com exclusividade, o resultado do laudo que apura os responsáveis pela queda do viaduto em Belo Horizonte, durante a Copa do Mundo. Duas pessoas morreram.

FOLHA DE S.PAULO

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LATEST PHOTO GALLERIES

With Fear of Ebola, Senegalese Lie to Avoid Being Barred at Brazil Border

PATRÍCIA BRITTO
SPECIAL ENVOY TO RIO BRANCO

Faced with the fear of having their entry into Brazil refused due to concerns about the Ebola virus, Senegalese immigrants have identified themselves as Haitians at the border of Acre with Bolivia and Peru, the Senegalese told **Folha**.

The Ebola outbreak has already caused more than 2,000 deaths in West African countries this year, especially in Guinea, Sierra Leone and Liberia. In Senegal, only one case has been confirmed.

But immigrants from the country housed in a shelter in Rio Branco maintained by the Acre government confirmed that Federal Police officers have made it difficult for all Africans to enter Brazil.

The Federal Police was contacted, but did not respond. On Wednesday (10), after a report in "O Globo" claimed Africans were being barred at the border, the institution said in a statement that there is no guideline to restrict access to immigrants from the continent to Brazil.

"We said that we are Haitians. If we say we are from Senegal, everyone would go back," a 29-year-old, who asked not to be identified, told **Folha**.

Senegalese immigrants

New Reply Delete Archive Junk Sweep Move to Categories

PRO/PORT> Ebola - Brasil (03), boatos em redes sociais, crimes digitais, notas de esclarecimento

promed-port@promedmail.org 8/20/2014 Newsletters
To: promed-port-post@promedmail.org

EBOLA - BRASIL (03), BOATOS EM REDES SOCIAIS, CRIMES DIGITAIS, NOTAS DE ESCLARECIMENTO

Uma mensagem / Una mensaje / de ProMED-PORT
<http://www.promedmail.org>
ProMED-mail e um programa da / es un programa de la International Society for Infectious Diseases
<http://www.isid.org>

Data: Terça-feira / Martes, 19 de agosto/agosto de 2014

[1] Ministério da Saúde do Brasil
Fonte: Ministério da Saúde do Brasil [15/08/2014] [editado]
<http://portalsaude.saude.gov.br/index.php/cidadao/principal/agencia-saude/14265-ministerio-desmente-boatos-sobre-casos-de-ebola-no-brasil>

Ministério desmente boatos sobre casos de Ebola no Brasil

Conclusão

- Risco de casos de Ebola chegarem ao Brasil é baixo, mas REAL – é necessária preparação! (sistema de saúde plenamente funcionante é a melhor barreira...)
- Risco de disseminação no Brasil é muito baixo.
- Possibilidade de disseminação na África é alta – EMERGÊNCIA INTERNACIONAL (OMS)
- Possibilidade de danos colaterais...

PERGUNTAS?...

...OBRIGADO!

marciosdafonseca@gmail.com