БОЛЕЗНЬ, ВЫЗВАННАЯ ВИРУСОМ ЭБОЛА

Иванова
М.А.

ЛАБОРАТОРНАЯ ДИАГНОСТИКА

- ELISA
- тесты на выявление антигенов
- реакция непрямой гемагглютинации
- полимеразная цепная реакция
- электронная микроскопия
- изоляция вируса в культуре клеток

СПАСИБО ЗА ВНИМАНИЕ

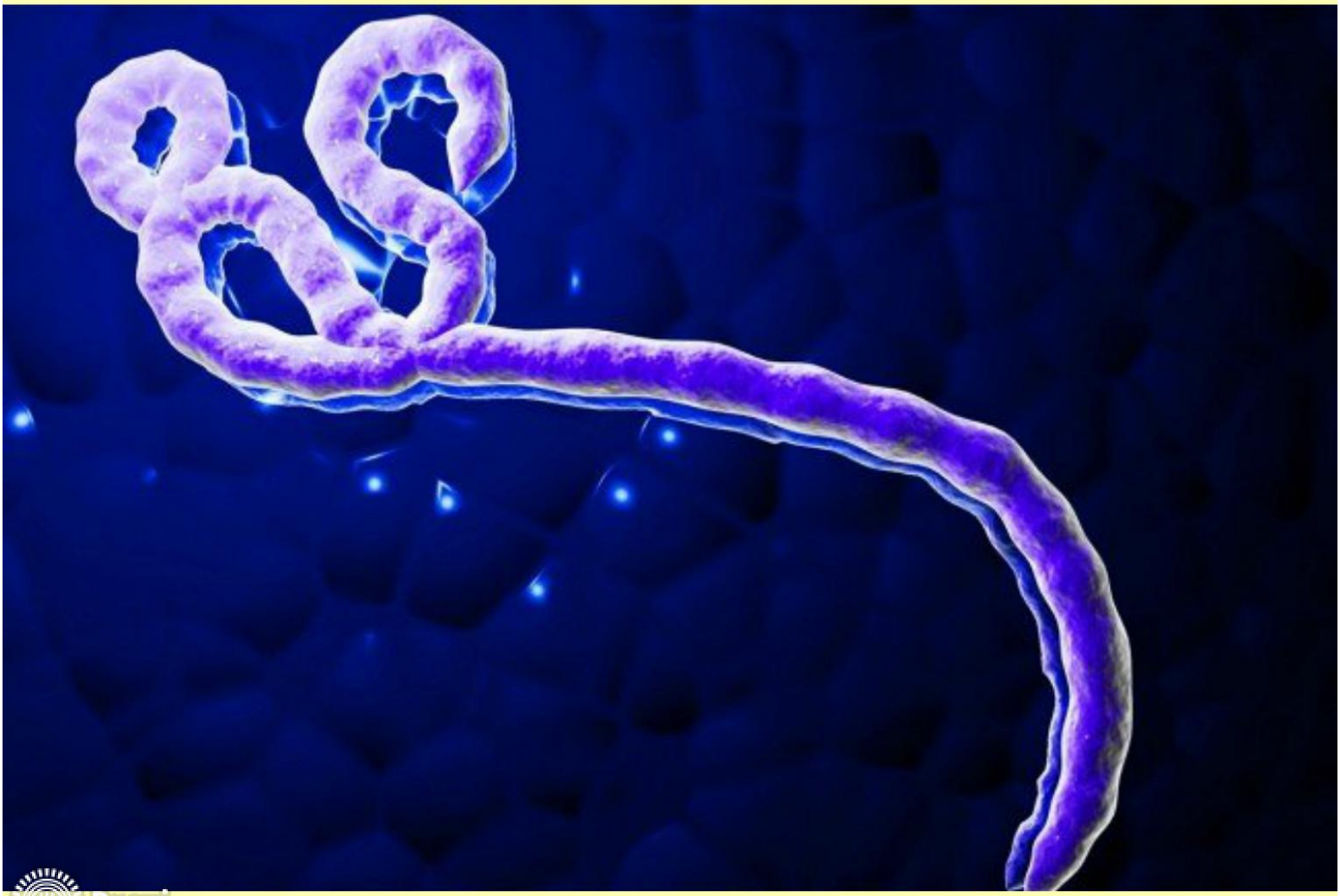
БОЛЕЗНЬ, ВЫЗВАННАЯ ВИРУСОМ ЭБОЛА

Иванова
М.А.

ЛАБОРАТОРНАЯ ДИАГНОСТИКА

- ELISA
- тесты на выявление антигенов
- реакция непрямой гемагглютинации
- полимеразная цепная реакция
- электронная микроскопия
- изоляция вируса в культуре клеток

СПАСИБО ЗА ВНИМАНИЕ

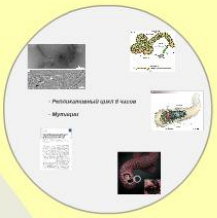


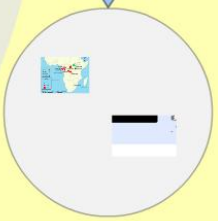
Всемирная организация здравоохранения

Болезнь, вызванная вирусом Эбола, ранее известная как геморрагическая лихорадка Эбола (ГЛЭ), является тяжелой, часто смертельной болезнью людей с летальностью до 90%

Filoviridae

1. Бундибуджио - Bundibugyo ebolavirus (BDBV)
2. Заир - Zaire ebolavirus (EBOV)
3. Судан - Sudan ebolavirus (SUDV)
4. Рестон - Reston ebolavirus (RESTV)
5. Таи Форест - Taï Forest ebolavirus (TAFV)

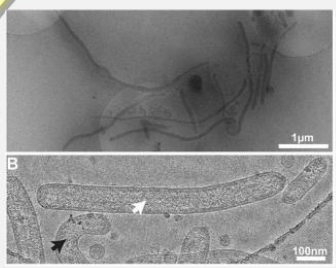


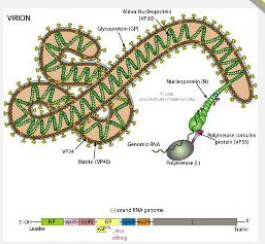


Filoviridae

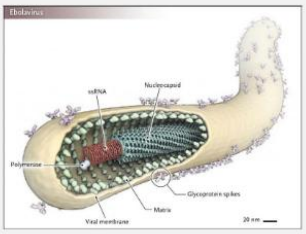
буджио - Bundibu

(BDBV)



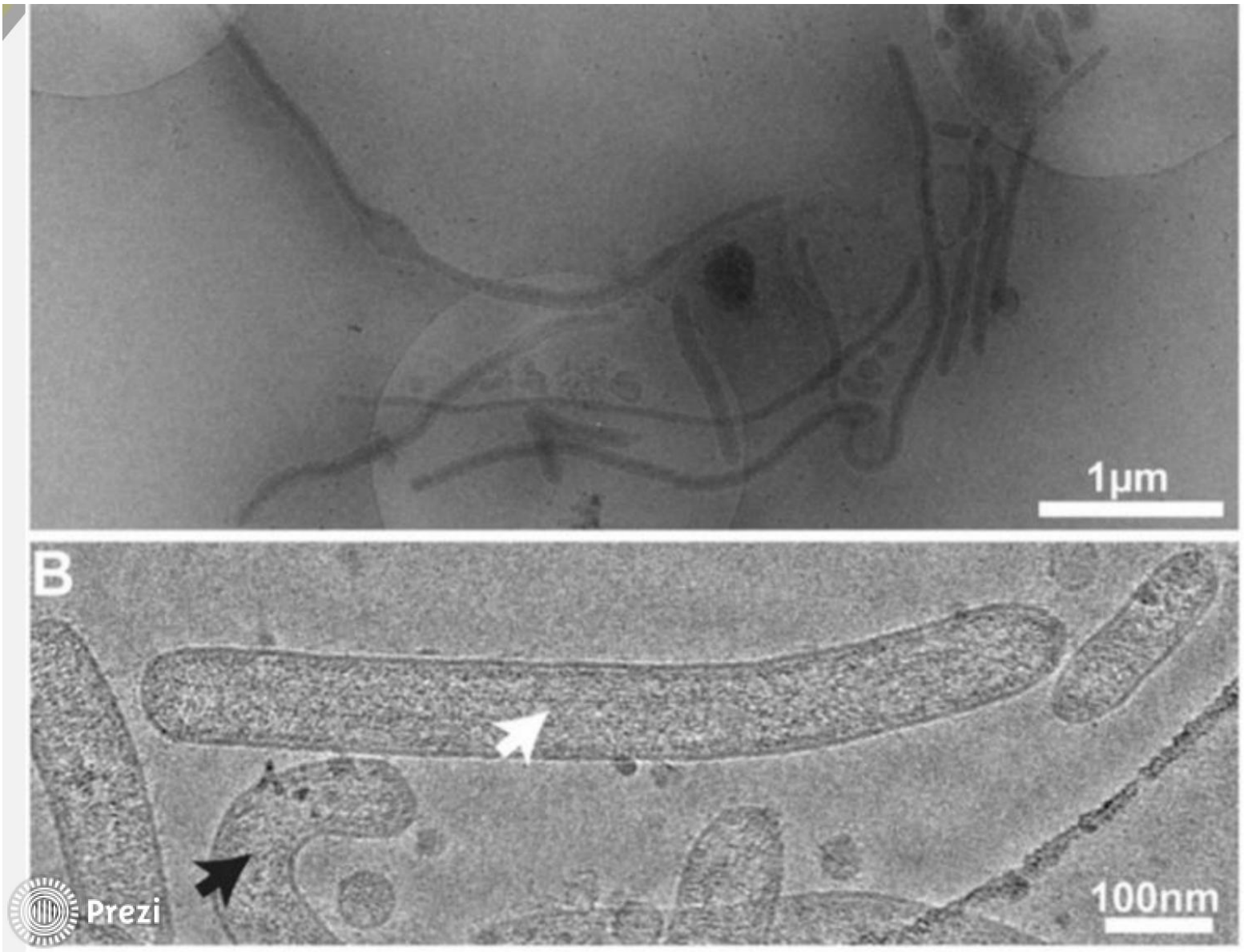


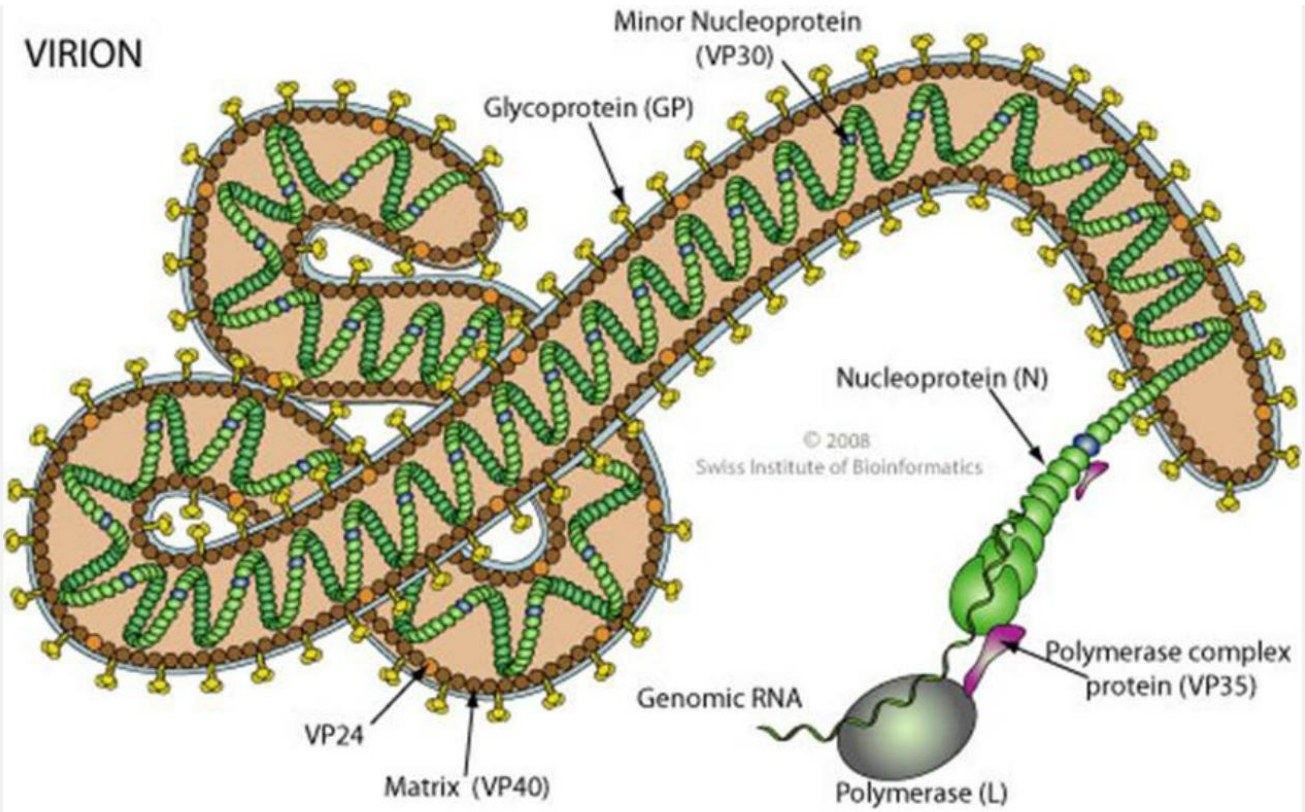
- ***Репликативный цикл 8 часов***
- ***Мутации***

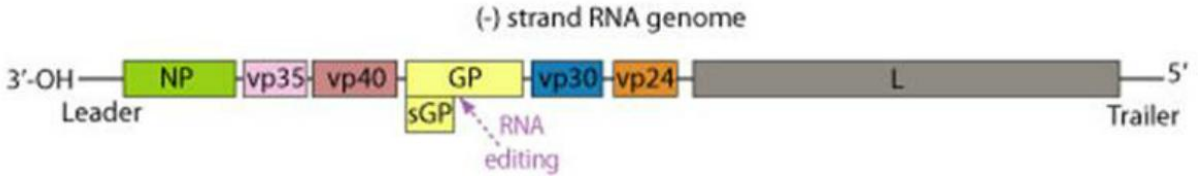


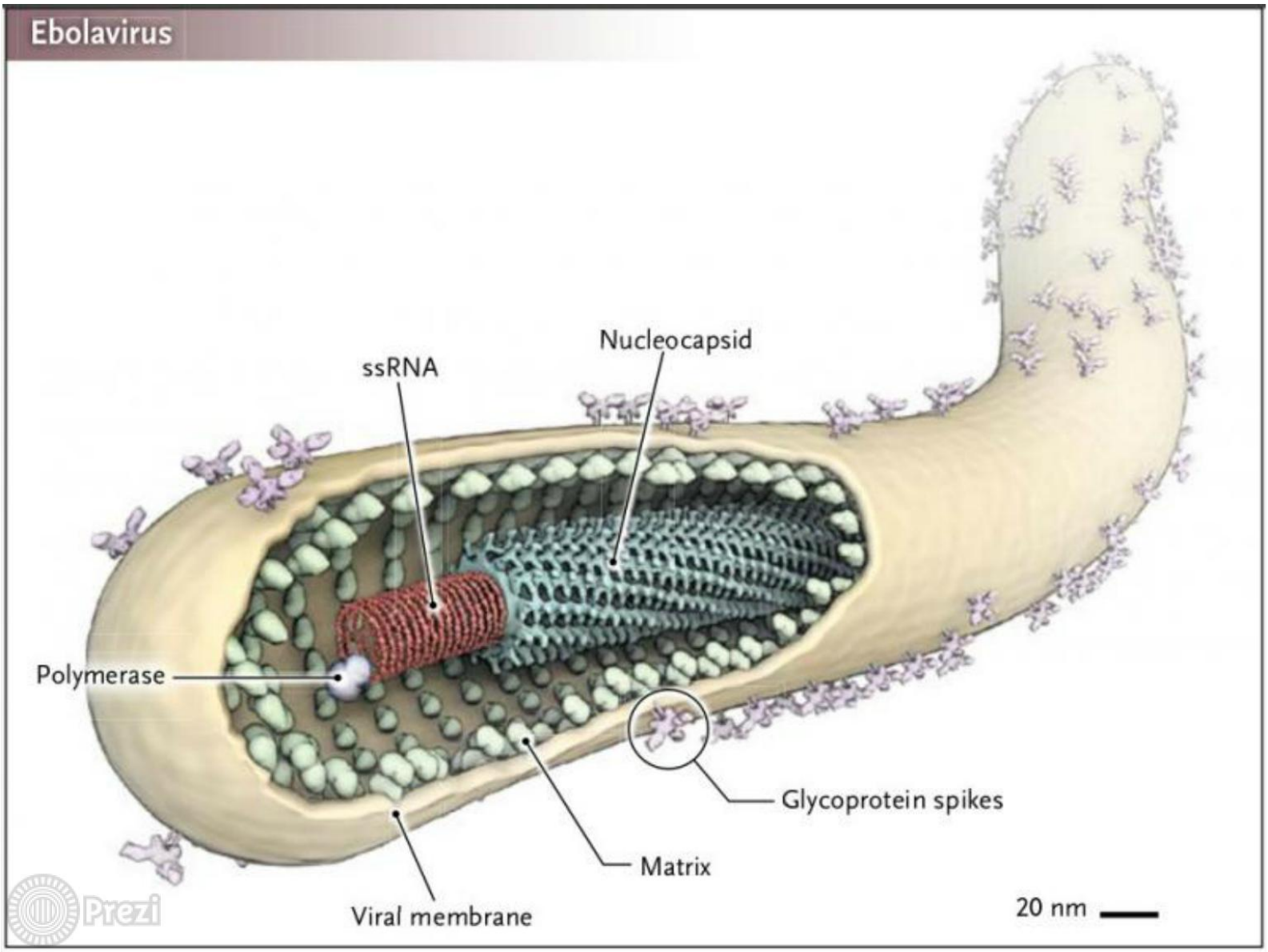

Article

Ebola Virus VP24 Targets a Unique NLS Binding Site on Karyopherin Alpha 5 to Selectively Compete with Nuclear Import of Phosphorylated STAT1


1µm
B
100nm


VIRION
Minor Nucleoprotein
(VP30)
Glycoprotein (GP)
Nucleoprotein (N)
© 2008
Swiss Institute of Bioinformatics
Polymerase complex
protein (VP35)
Genomic RNA
Polymerase (L)
VP24
Matrix (VP40)


(-) strand RNA genome
3'-OH
Leader
NP
vp35
vp40
GP
sGP
RNA
editing
vp30
vp24
L
5'
Trailer


Ebolavirus
Nucleocapsid
ssRNA
Polymerase
Glycoprotein spikes
Matrix
Viral membrane
20 nm


Prezi

Cell Host & Microbe
Article

Ebola Virus VP24 Targets a Unique NLS Binding Site on Karyopherin Alpha 5 to Selectively Compete with Nuclear Import of Phosphorylated STAT1

Wei Xu,[1] Megan R. Edwards,[2] Dominika M. Borek,[3] Alicia R. Feagins,[2] Anuradha Mittal,[4] Joshua B. Alinger,[1] Kayla N. Berry,[1] Benjamin Yen,[2] Jennifer Hamilton,[2] Tom J. Brett,[5] Rohit V. Pappu,[4] Daisy W. Leung,[1] Christopher F. Basler,[2] and Gaya K. Amarasinghe[1,*]
[1]Department of Pathology and Immunology, Washington University School of Medicine, St Louis, MO 63110, USA
[2]Department of Microbiology, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA
[3]Departments of Biophysics and Biochemistry, University of Texas Southwestern Medical Center at Dallas, Dallas, TX 75390, USA
[4]Department of Biomedical Engineering and Center for Biological Systems Engineering, Washington University, St. Louis, MO 63110, USA
[5]Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA
*Correspondence: gamarasinghe@path.wustl.edu
http://dx.doi.org/10.1016/j.chom.2014.07.008

SUMMARY

During antiviral defense, interferon (IFN) signaling triggers nuclear transport of tyrosine-phosphorylated STAT1 (PY-STAT1), which occurs via a subset of karyopherin alpha (KPNA) nuclear transporters. Many viruses, including Ebola virus, actively antagonize STAT1 signaling to counteract the antiviral effects of IFN. Ebola virus VP24 protein (eVP24) binds KPNA to inhibit PY-STAT1 nuclear transport and render cells refractory to IFNs. We describe the structure of human KPNA5 C terminus in complex with eVP24. In the complex, eVP24 recognizes a unique nonclassical nuclear localization signal (NLS) binding site on KPNA5 that is necessary for efficient PY-STAT1 nuclear transport. eVP24 binds KPNA5 with very high affinity to effectively compete with and inhibit PY-STAT1 nuclear transport. In contrast, eVP24 binding does not affect the transport of classical NLS cargo. Thus, eVP24 counters cell-intrinsic innate immunity by selectively targeting PY-STAT1 nuclear import while leaving the transport of other cargo that may be required for viral replication unaffected.

INTRODUCTION

Interferons (IFNs) generate innate and adaptive immune responses to viral infections through a signaling cascade that requires the activation of signal transducer and activator of transcription (STAT) family transcription factors (Goodbourn et al., 2000). Type I IFNs activate STAT1 and STAT2 through phosphorylation by the Janus kinase (JAK) family members, and type II IFN only activates STAT1 (Reich and Liu, 2006). Phosphorylation of tyrosine 701 on STAT1 (PY-STAT1) results in a conformation that is recognized by a subset of the karyopherin alpha (KPNA) family of nuclear transport factors (Chen et al., 1998; McBride et al., 2002; Meyer et al., 2002). Nuclear transport of PY-STAT1 and binding to IFN-stimulated response elements (ISRE) or interferon-gamma-activated site (GAS) elements induce expression of IFN-stimulated genes (ISG) that confer an antiviral state.

All KPNAs contain ten armadillo (ARM) repeats and are divided into subfamilies based on sequences that dictate cargo specificity (Conti and Kuriyan, 2000; Conti et al., 1998). Cargo that contain a classical nuclear localization signal (cNLS), which consists of mostly basic amino acids, bind KPNA near ARMs 2–4 (major site) and 6–8 (minor site) (Chook and Blobel, 2001; Conti and Izaurralde, 2001; Cook et al., 2007). In contrast, the NPI-1 subfamily (KPNA1, KPNA5, and KPNA6; also known as importin α5, importin α6, and importin α7, respectively) mediates PY-STAT1 nuclear transport, which depends on a nonclassical NLS (ncNLS) (Sekimoto et al., 1997). Use of a distinct nuclear transporter binding site presumably allows PY-STAT1 to translocate to the nucleus without impacting regular nucleocytoplasmic trafficking processes. Viruses target IFN signaling by inhibiting distinct steps in the STAT1 activation and nuclear translocation process, but these mechanisms vary, and many are poorly defined (Yarbrough et al., 2014).

A hallmark of infection by filoviruses (Ebola virus [EBOV] and Marburg virus [MARV]) is the rapid and potent suppression of innate antiviral immune responses, which facilitates uncontrolled viral replication and cytokine storm (Bray and Murphy, 2007; Geisbert et al., 2003). As a result, high case fatality rates of up to 90% are observed during outbreaks (Feldmann and Geisbert, 2011). EBOV mediates immune suppression through at least three virally encoded proteins: surface glycoprotein (GP), virus protein 35 (eVP35), and virus protein 24 (eVP24) (Basler and Amarasinghe, 2009; Kaletsky et al., 2009; Leung et al., 2010; Zhang et al., 2012a). Among these, eVP24 acts in a cell-intrinsic manner to inhibit IFN signaling and render cells refractory to exogenous IFN treatment by targeting the NPI-1 subfamily of KPNAs, but the molecular mechanism of this process is unknown.

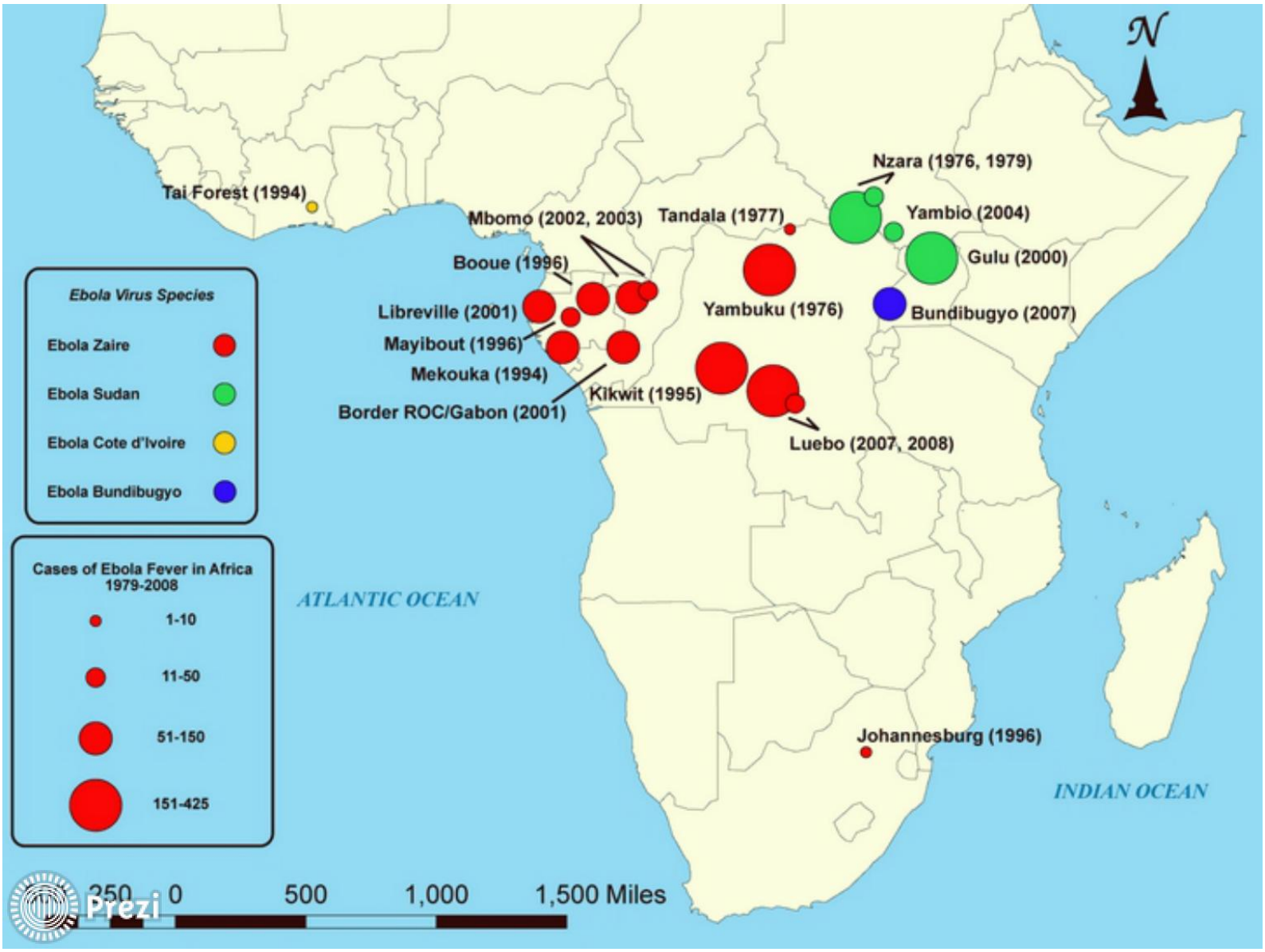
Cargo containing ncNLS sequences are often difficult to identify because ncNLS sequences lack consensus motifs. As a result, the exact ncNLS binding site for PY-STAT1 as well as viral

cate to the nucleus without impacting regular nucleocytoplasmic trafficking processes. Viruses target IFN signaling by inhibiting distinct steps in the STAT1 activation and nuclear translocation process, but these mechanisms vary, and many are poorly defined (Yarbrough et al., 2014).

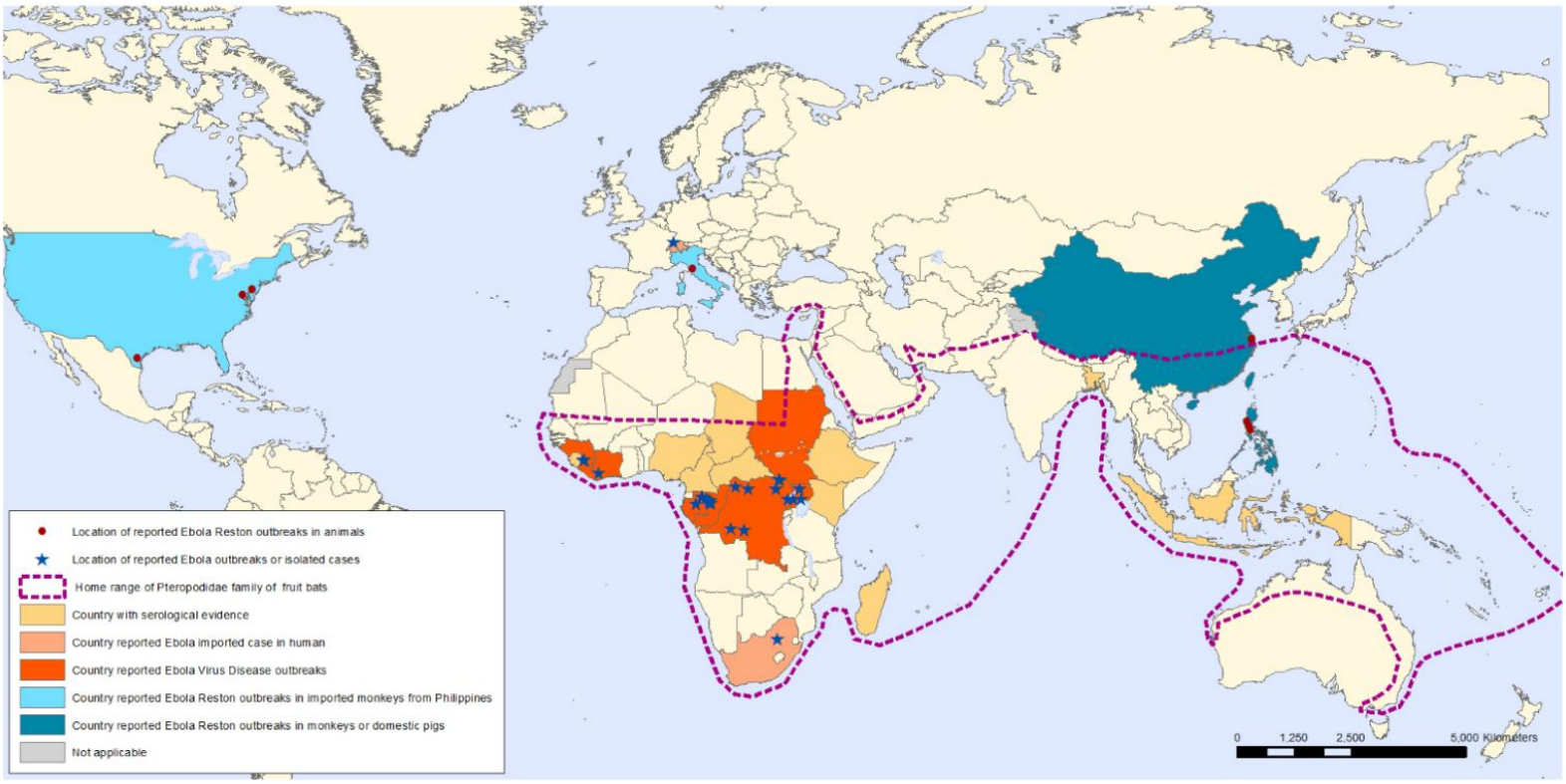
A hallmark of infection by filoviruses (Ebola virus [EBOV] and Marburg virus [MARV]) is the rapid and potent suppression of innate antiviral immune responses, which facilitates uncontrolled viral replication and cytokine storm (Bray and Murphy, 2007; Geisbert et al., 2003). As a result, high case fatality rates of up to 90% are observed during outbreaks (Feldmann and Geisbert, 2011). EBOV mediates immune suppression through at least three virally encoded proteins: surface glycoprotein (GP), virus protein 35 (eVP35), and virus protein 24 (eVP24) (Basler and Amarasinghe, 2009; Kaletsky et al., 2009; Leung et al., 2010; Zhang et al., 2012a). Among these, eVP24 acts in a cell-intrinsic manner to inhibit IFN signaling and render cells refractory to exogenous IFN treatment by targeting the NPI-1 subfamily of

Filoviridae

1. Бундибуджио - Bundibugyo ebolavirus (BDBV)
2. Заир - Zaire ebolavirus (EBOV)
3. Судан - Sudan ebolavirus (SUDV)
4. Рестон - Reston ebolavirus (RESTV)
5. Таи Форест - Taï Forest ebolavirus (TAFV)


N
Nzara (1976, 1979)
Tai Forest (1994)
Mbomo (2002, 2003)
Tandala (1977)
Yambio (2004)
Booue (1996)
Gulu (2000)
Libreville (2001)
Yambuku (1976)
Bundibugyo (2007)
Mayibout (1996)
Mekouka (1994)
Kikwit (1995)
Border ROC/Gabon (2001)
Luebo (2007, 2008)
Ebola Virus Species
Ebola Zaire
Ebola Sudan
Ebola Cote d'Ivoire
Ebola Bundibugyo
Cases of Ebola Fever in Africa 1979-2008
1-10
11-50
51-150
151-425
ATLANTIC OCEAN
Johannesburg (1996)
INDIAN OCEAN
250 0 500 1,000 1,500 Miles

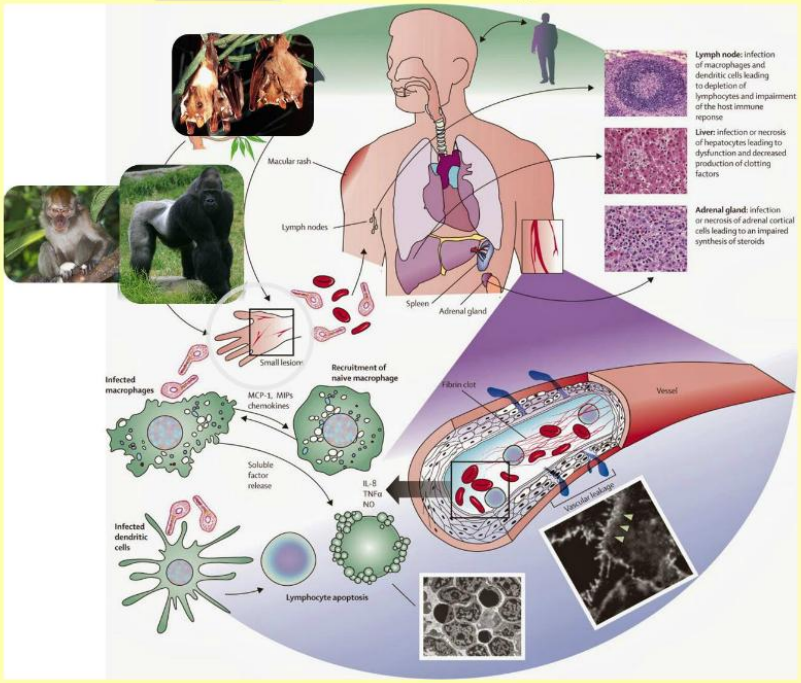
Geographic distribution of Ebola virus disease outbreaks in humans and animals

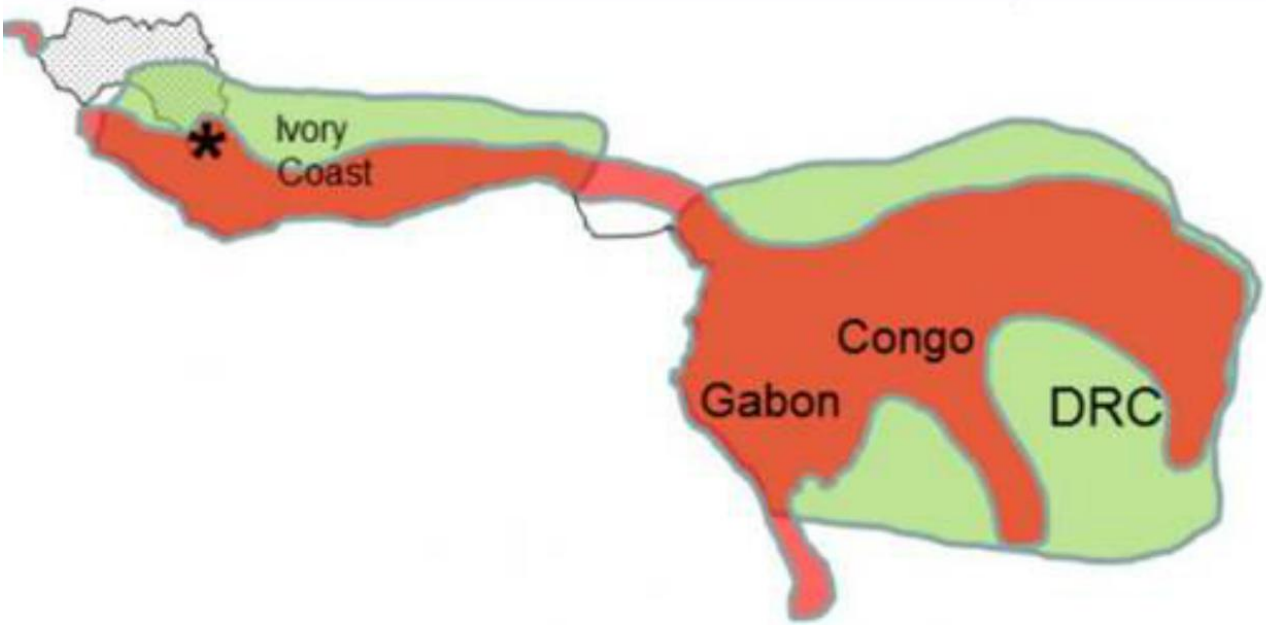


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers 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

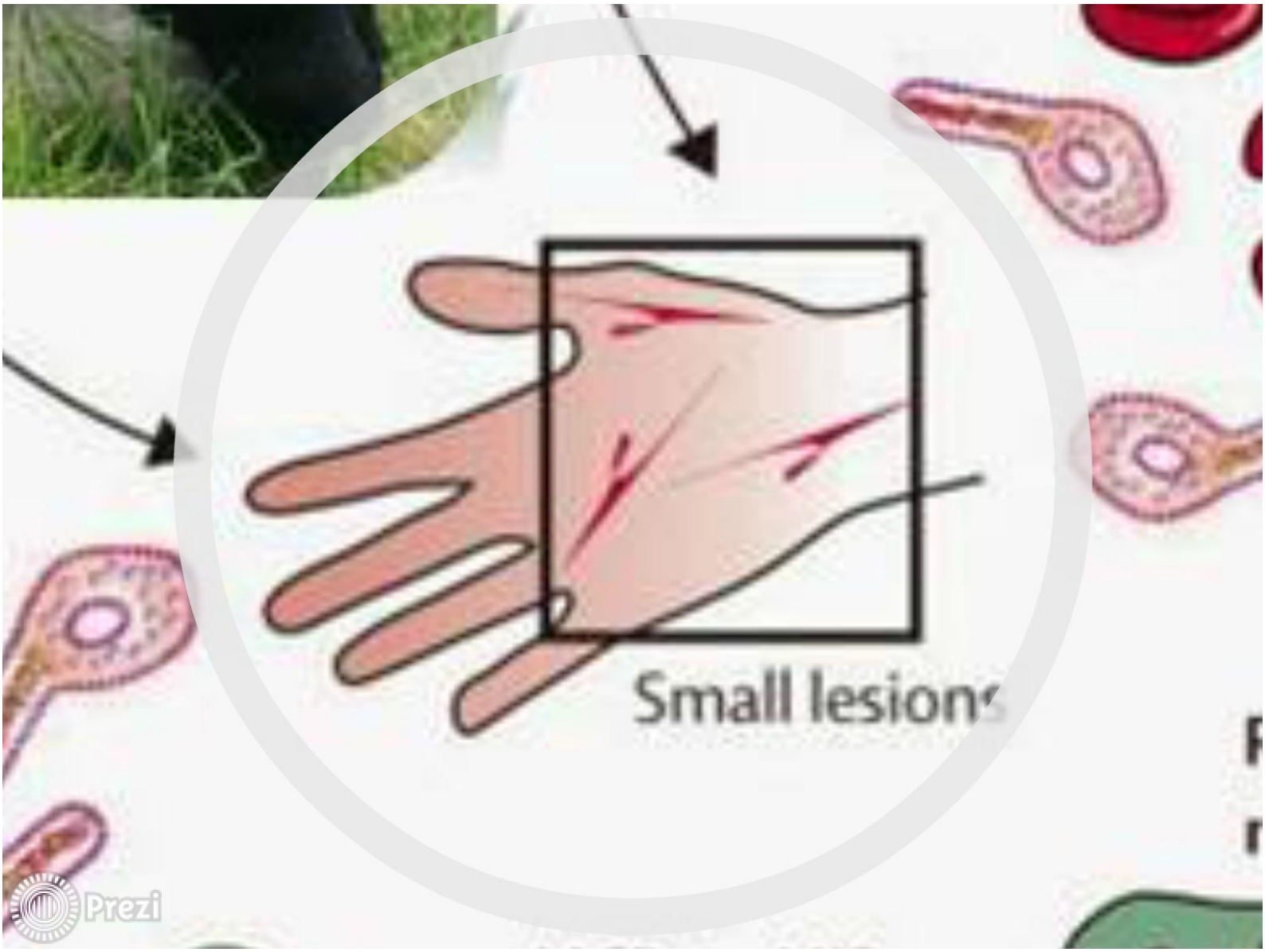
World Health Organization

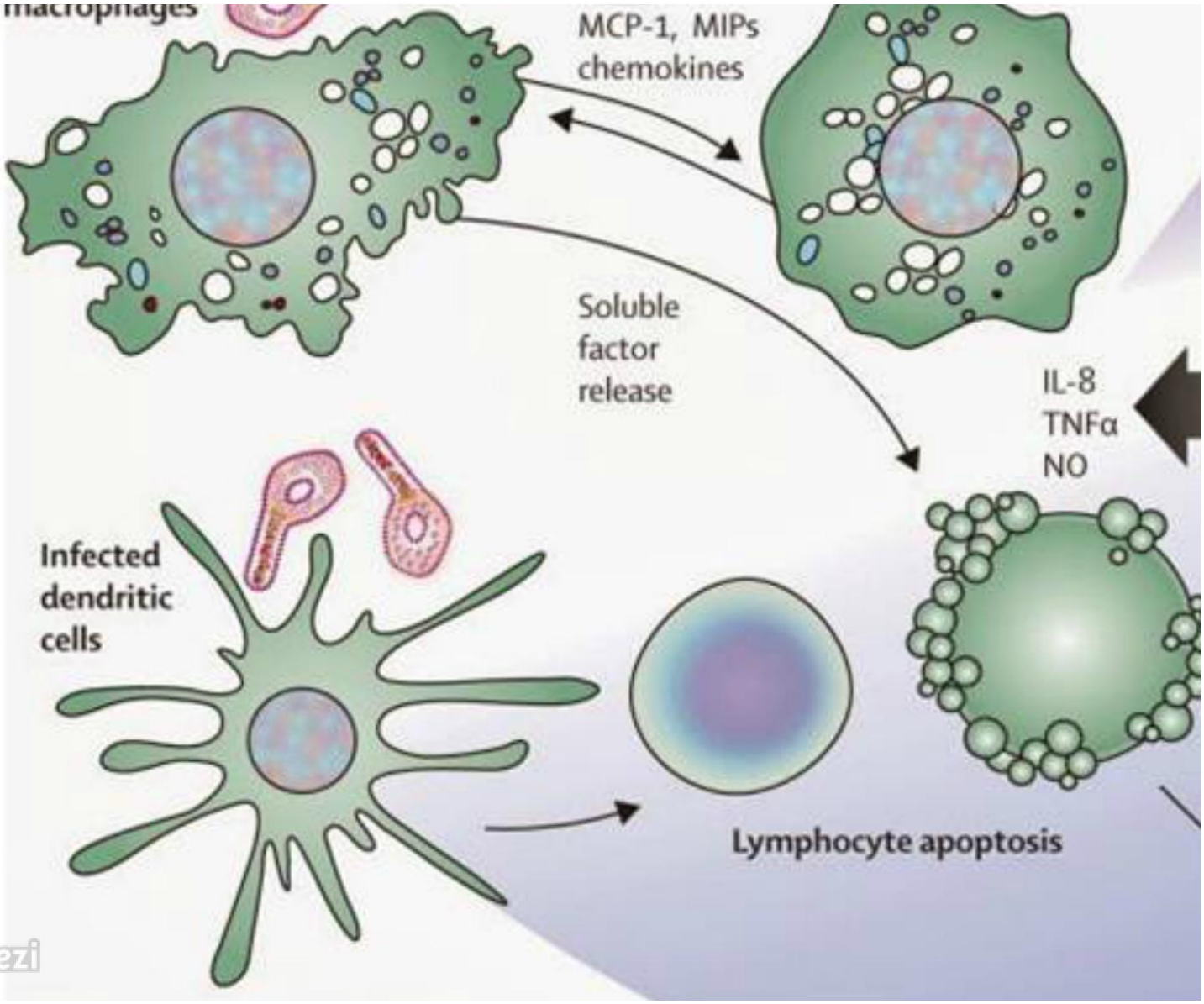

Macular rash
Lymph nodes
Spleen
Adrenal gland
Small lesion
Infected macrophages
Recruitment of naïve macrophage
MCP-1, MIPs chemokines
Soluble factor release
IL-8
TNFα
NO
Infected dendritic cells
Lymphocyte apoptosis
Fibrin clot
Vessel
Vascular leakage
Lymph node: infection of macrophages and dendritic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

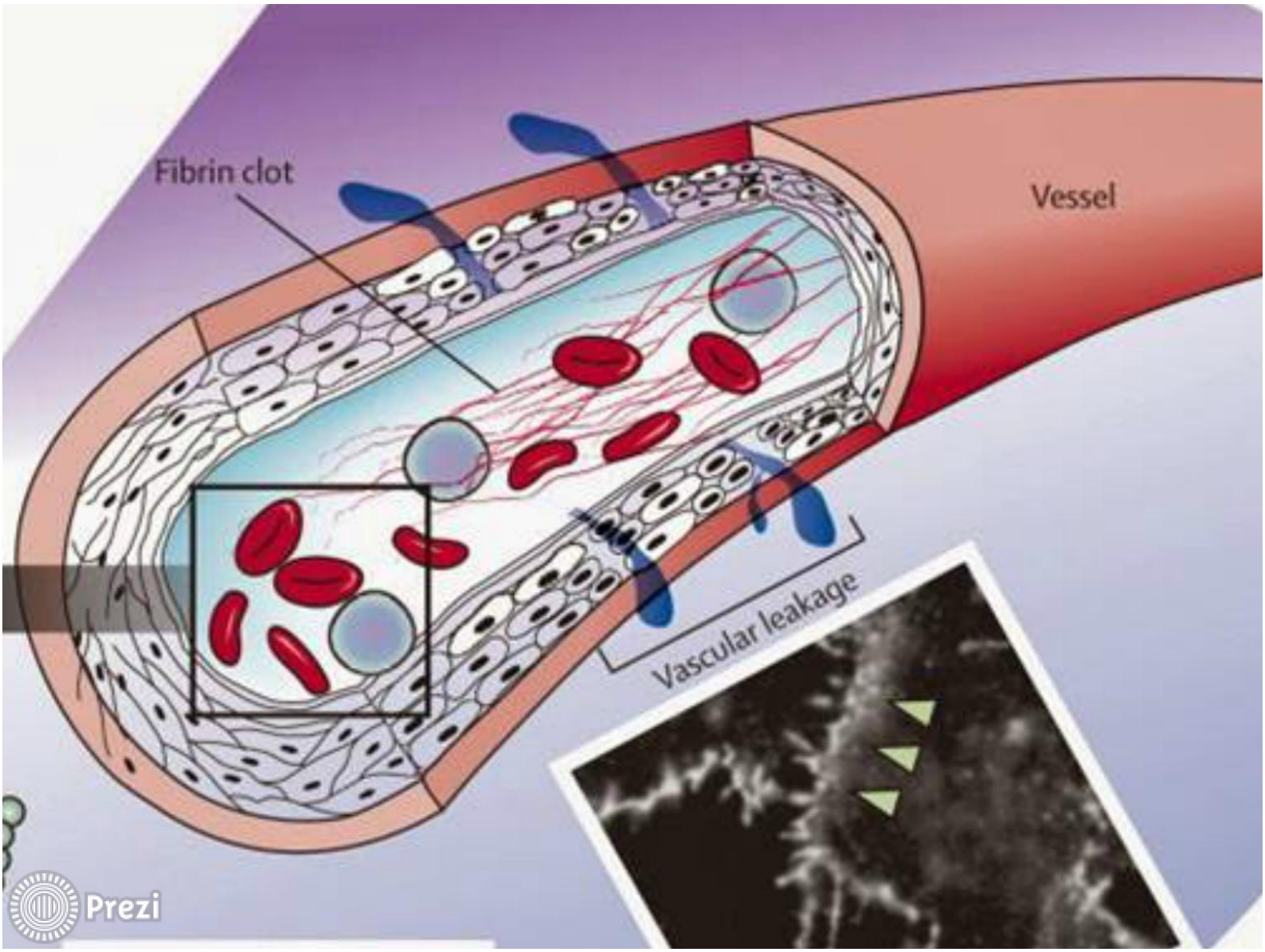


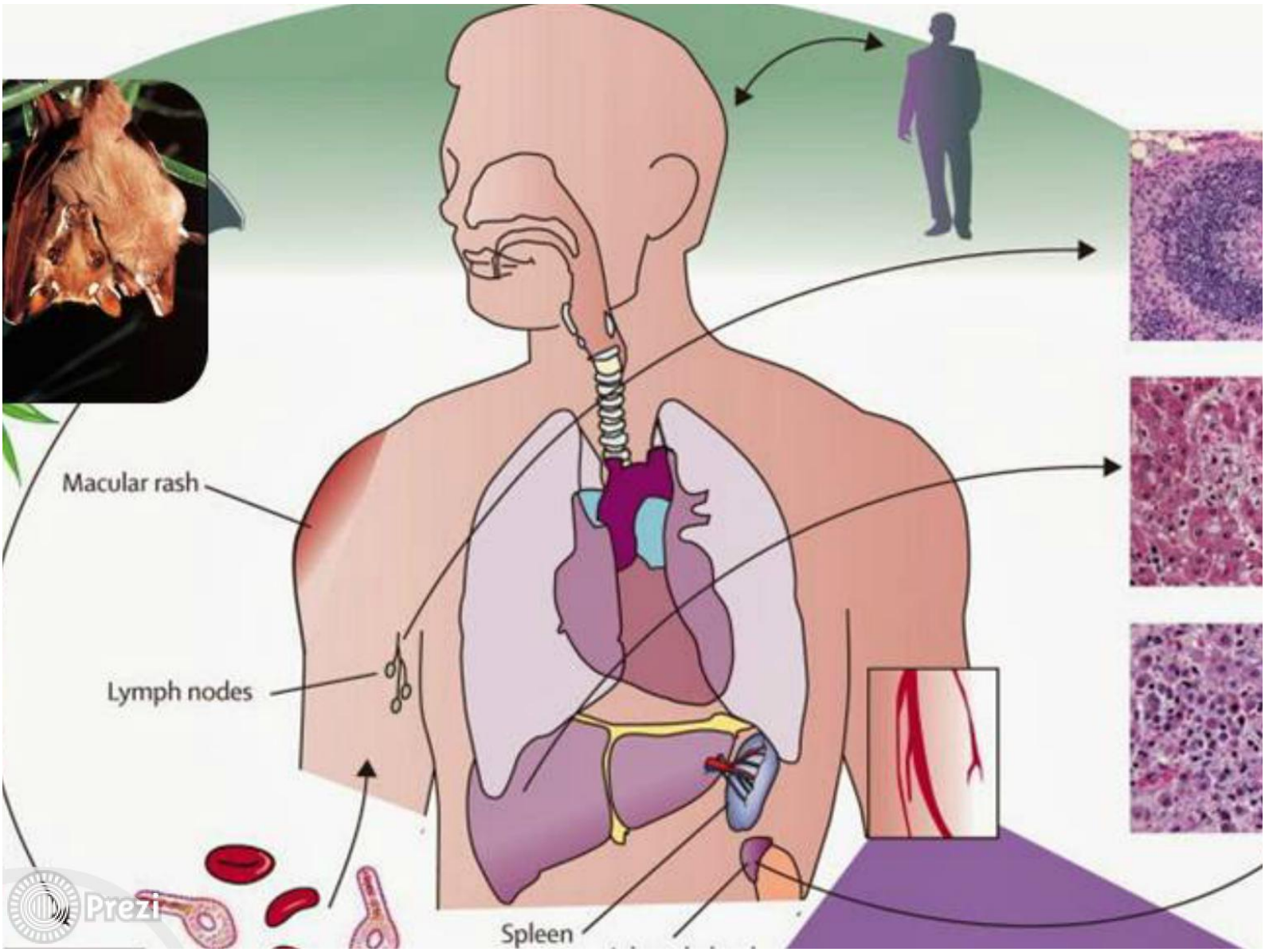

Guinea
Liberia
Nigeria
AFRICA
Dem. Rep. Congo
Angola
Prezi

кровь
слюна
мокрота
фекалии
моча
пот
семенная жидкость
кожа


Small lesions


macrophages
MCP-1, MIPs
chemokines
Soluble
factor
release
IL-8
TNFα
NO
Infected
dendritic
cells
Lymphocyte apoptosis


Fibrin clot
Vessel
Vascular leakage


Macular rash
Lymph nodes
Spleen

Инкубация

2 - 21 день

Не заразен

Клиника
Симптомы и признаки

Острое начало

Лихорадка с ознобом или без(95%),

Симптомы и признаки

Острое начало
Лихорадка с ознобом или без(95%),
Головная боль (50%-74%)
Миалгии или артралгии (85%-95%)
Слабость (50%-79%)
Анорексия (45%)
Боль в горле
Макулопапулезная сыпь

Дифференциальная диагностика

Малярия
Брюшной тиф
Шигеллез
Холера
Лептоспироз

Риккетсиозы
Возвратный тиф
Менингит
Гепатит
Геморрагические
вирусные

Малярия
Брюшной тиф
Шигеллез
Холера
Лептоспироз
Чума

Риккетсиозы
Возвратный тиф
Менингит
Гепатит
Геморрагические вирусные лихорадки

Через 3 – 5 дней

Рвота (65%)

Диарея (85%)

Боль в животе (68%-73%)

Боль в грудной клетке

Нарушения функций почек и печени

Геморрагический синдром

Шок


Medscape®
www.medscape.com


Prezi

кровь
слюна
мокрота
фекалии
моча
пот
семенная жидкость
кожа

ЛАБОРАТОРНАЯ ДИАГНОСТИКА

- ELISA;
- тесты на выявление антигенов;
- реакция сывороточной нейтрализации;
- полимеразная цепная реакция ;
- электронная микроскопия;
- изоляция вируса в клеточных культурах

Лечение

Лечение

Симптоматическая
Поддерживающая
Интенсивная терапия


HIGH RISK
ZONE

Вакцин лицензированных нет

СПАСИБО ЗА ВНИМАНИЕ