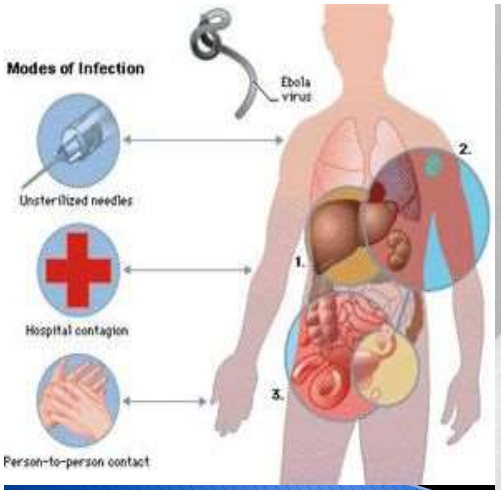
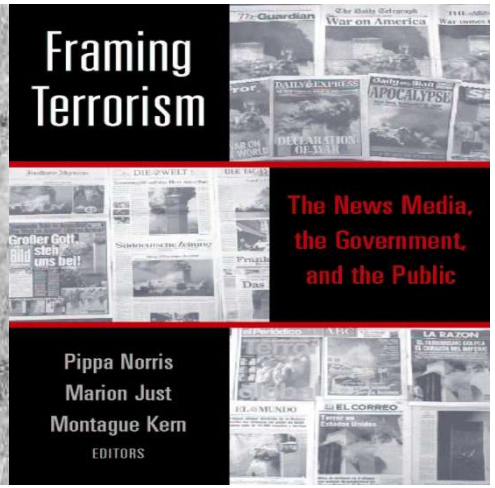
بسم الله الرحمن الرحیم

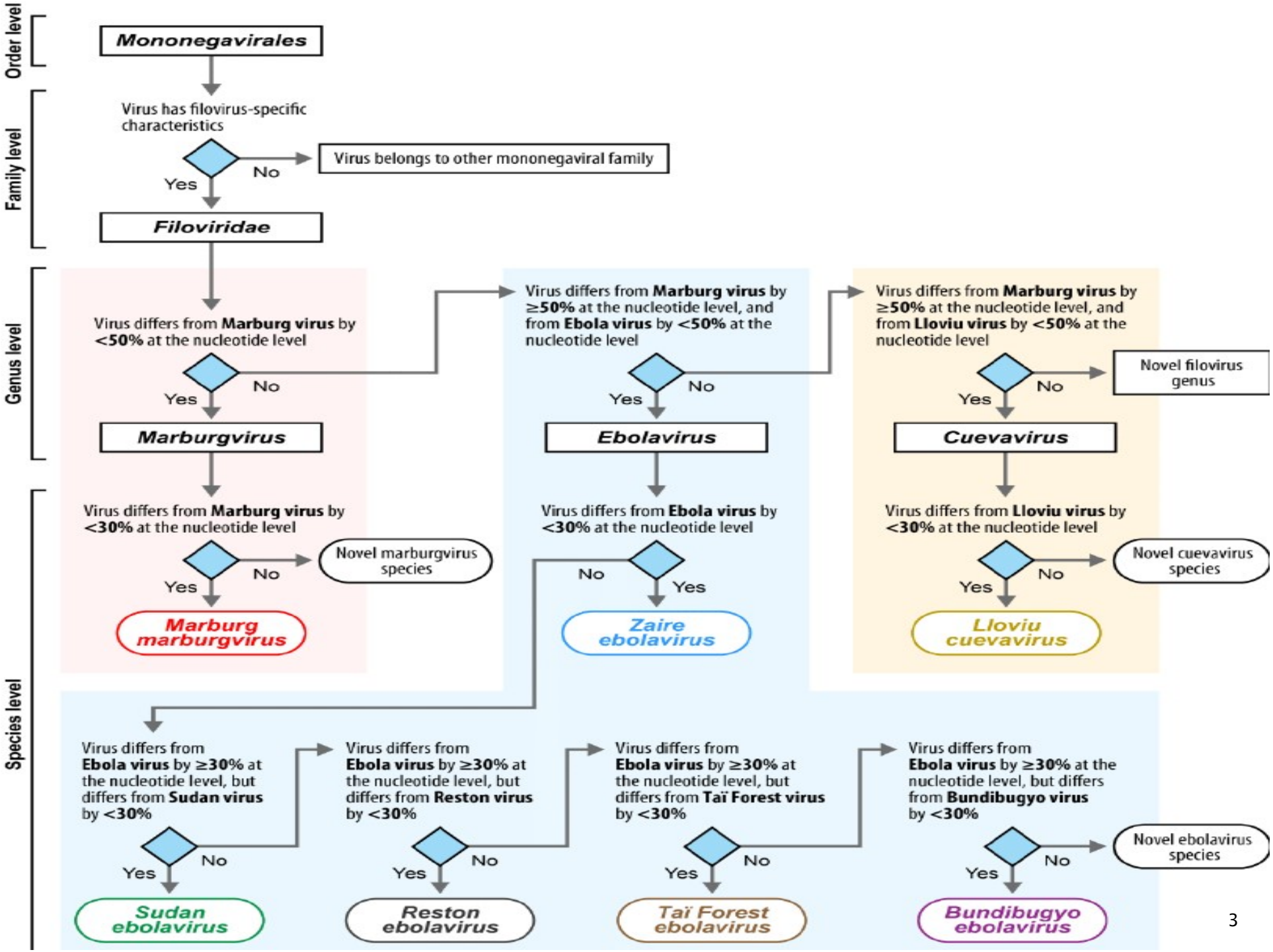
باغ فین کاشان

Ebola and Marburg

Ruhollah Dorostkar
Virologist

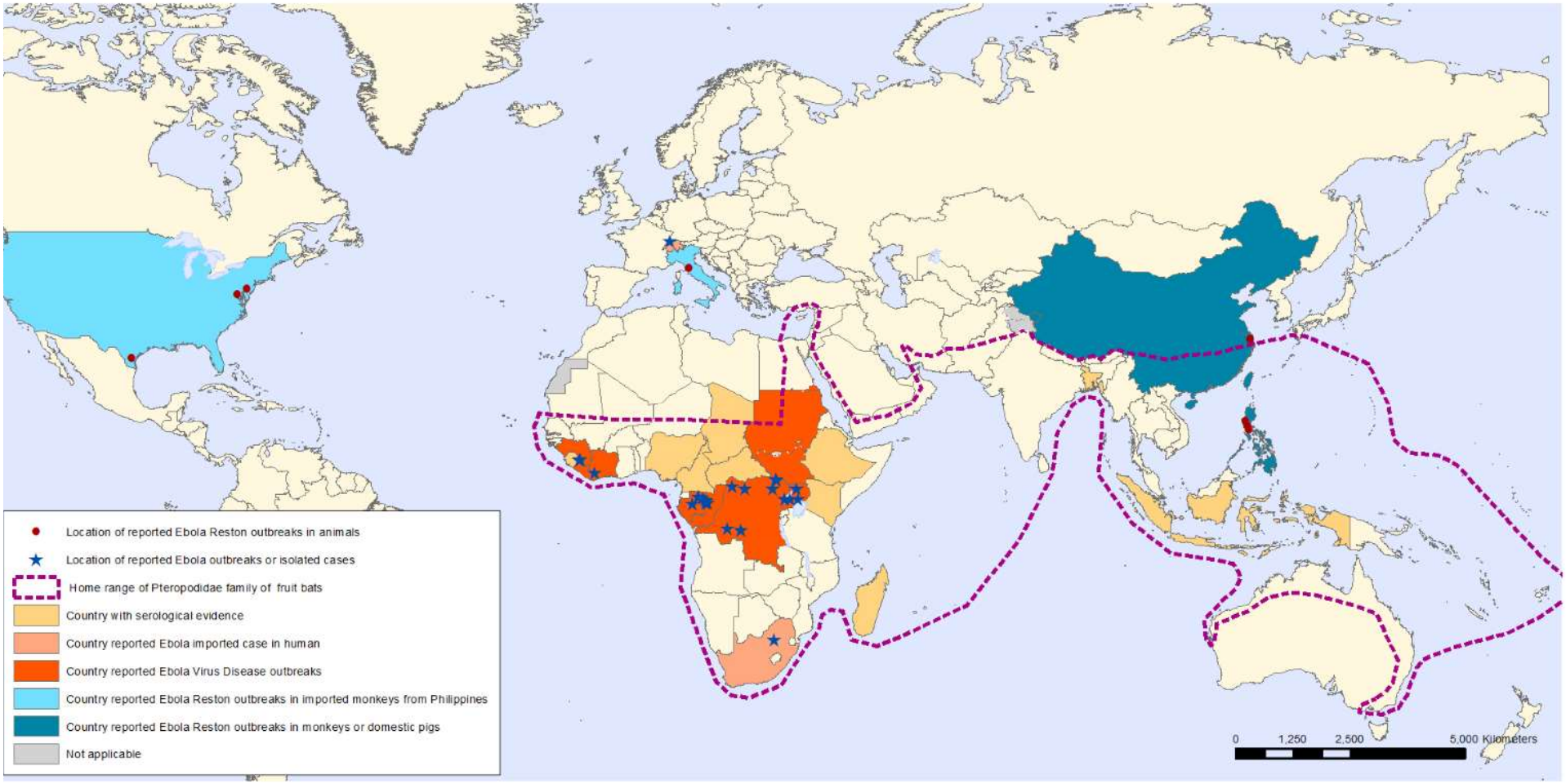





Order level
Mononegavirales
Family level
Virus has filovirus-specific characteristics
Yes
No
Virus belongs to other mononegaviral family
Filoviridae
Genus level
Virus differs from Marburg virus by <50% at the nucleotide level
Yes
No
Marburgvirus
Virus differs from Marburg virus by ≥50% at the nucleotide level, and from Ebola virus by <50% at the nucleotide level
Yes
No
Ebolavirus
Virus differs from Marburg virus by ≥50% at the nucleotide level, and from Lloviu virus by <50% at the nucleotide level
Yes
No
Novel filovirus genus
Cuevavirus
Species level
Virus differs from Marburg virus by <30% at the nucleotide level
Yes
No
Novel marburgvirus species
Marburg marburgvirus
Virus differs from Ebola virus by <30% at the nucleotide level
No
Yes
Zaire ebolavirus
Virus differs from Lloviu virus by <30% at the nucleotide level
Yes
No
Novel cuevavirus species
Lloviu cuevavirus
Virus differs from Ebola virus by ≥30% at the nucleotide level, but differs from Sudan virus by <30%
Yes
No
Sudan ebolavirus
Virus differs from Ebola virus by ≥30% at the nucleotide level, but differs from Reston virus by <30%
Yes
No
Reston ebolavirus
Virus differs from Ebola virus by ≥30% at the nucleotide level, but differs from Taï Forest virus by <30%
Yes
No
Taï Forest ebolavirus
Virus differs from Ebola virus by ≥30% at the nucleotide level, but differs from Bundibugyo virus by <30%
Yes
No
Novel ebolavirus species
Bundibugyo ebolavirus

- Named after the Ebola River in the Democratic Republic of the Congo (formerly Zaire), near the first epidemics.
- Two species were identified in 1976:
  - Zaire ebolavirus (ZEBOV) and
  - Sudan ebolavirus (SEBOV)
- Case fatality rates of 83% and 54% respectively.
- A third species, Reston ebolavirus (REBOV), was discovered in November 1989 in a group of monkeys (Macaca fascicularis) imported from the Philippines

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

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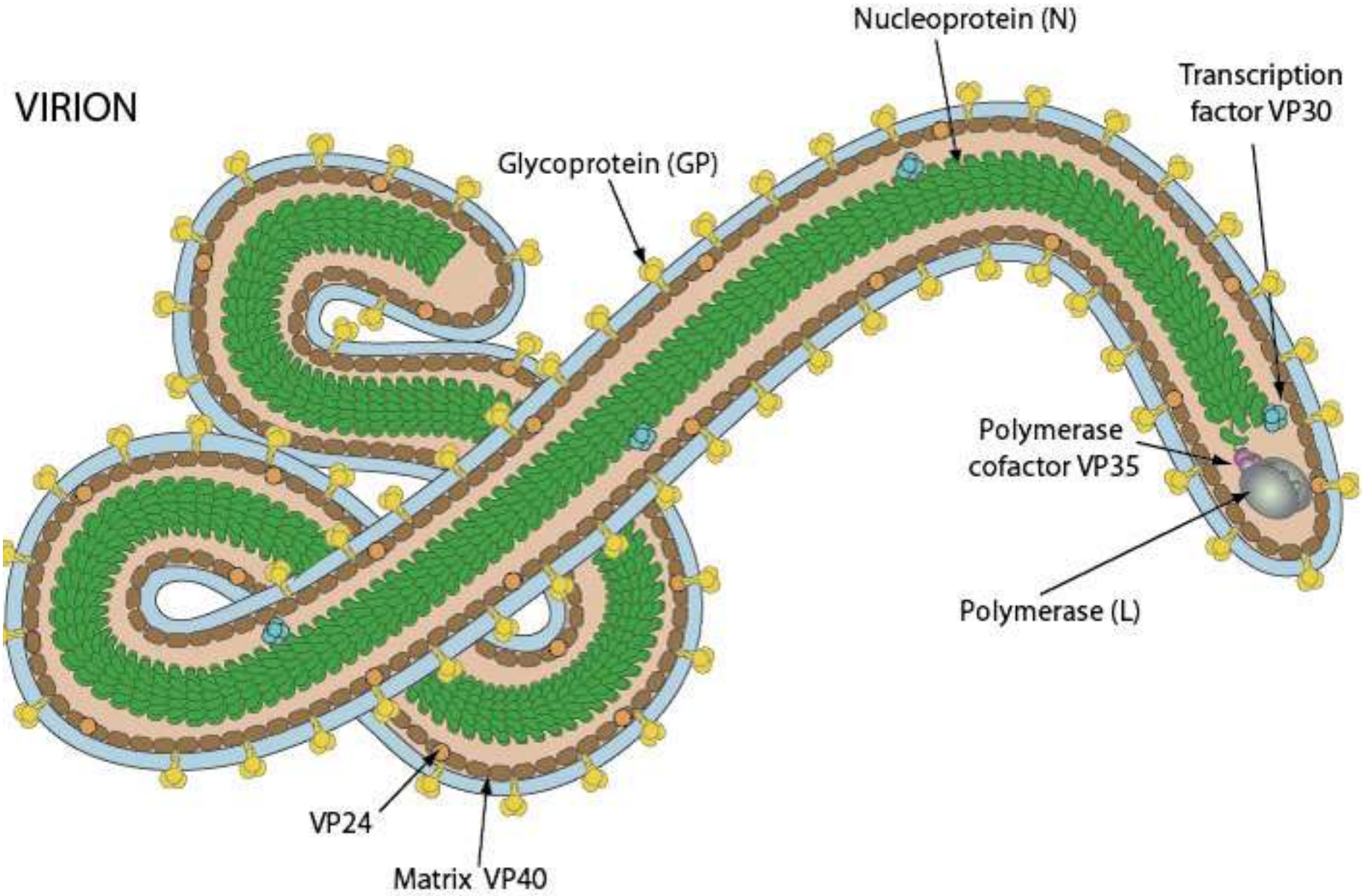
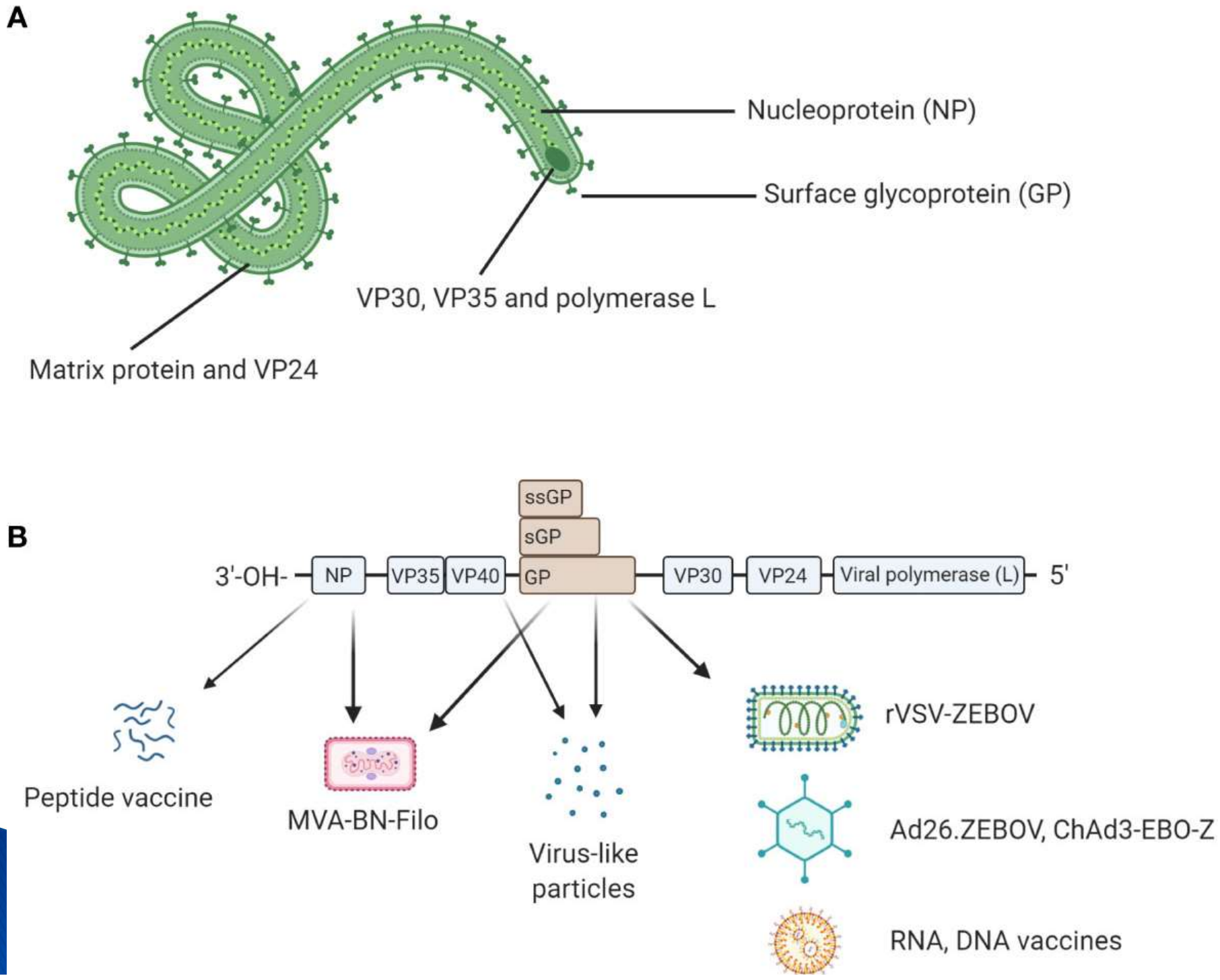
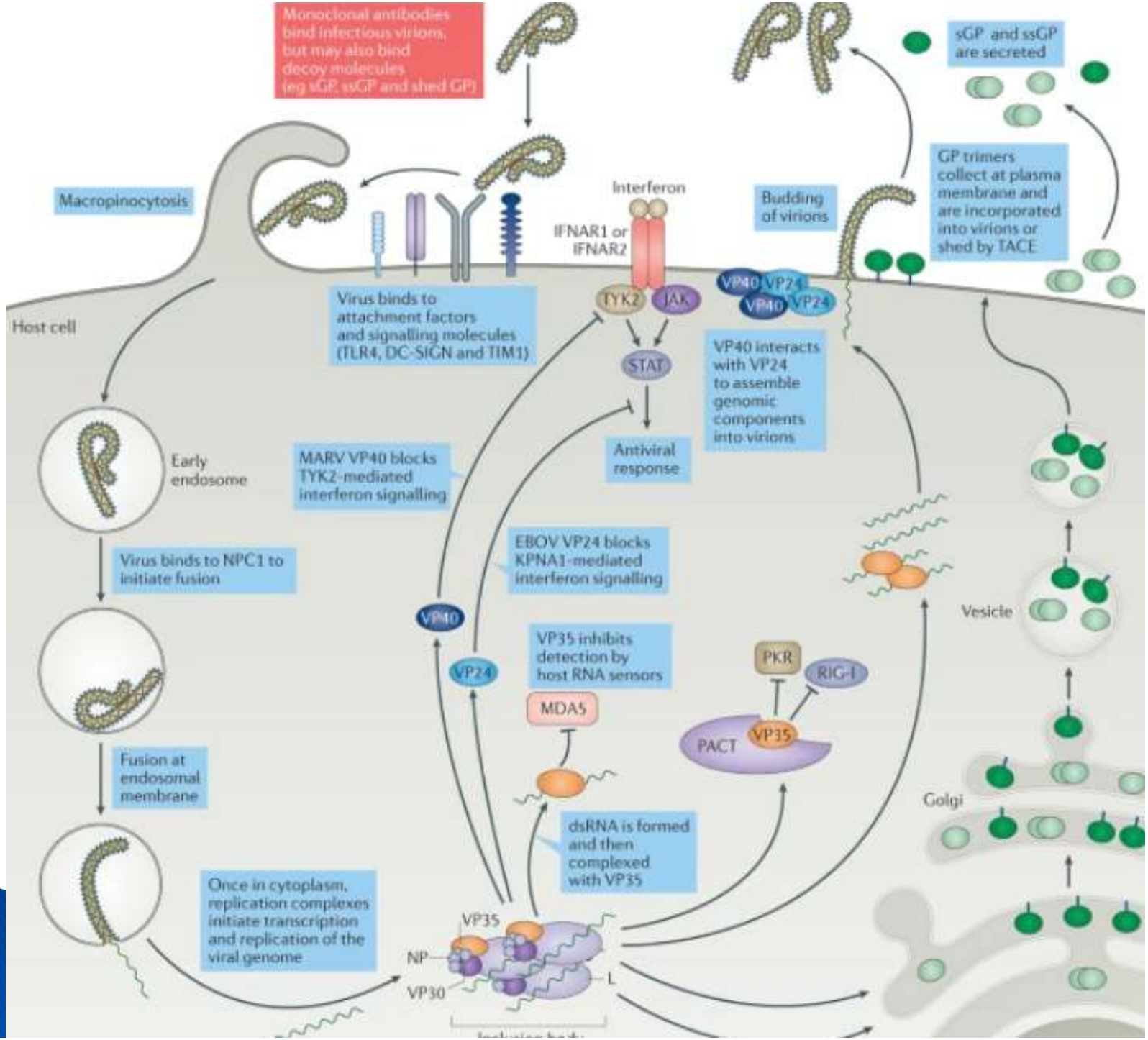
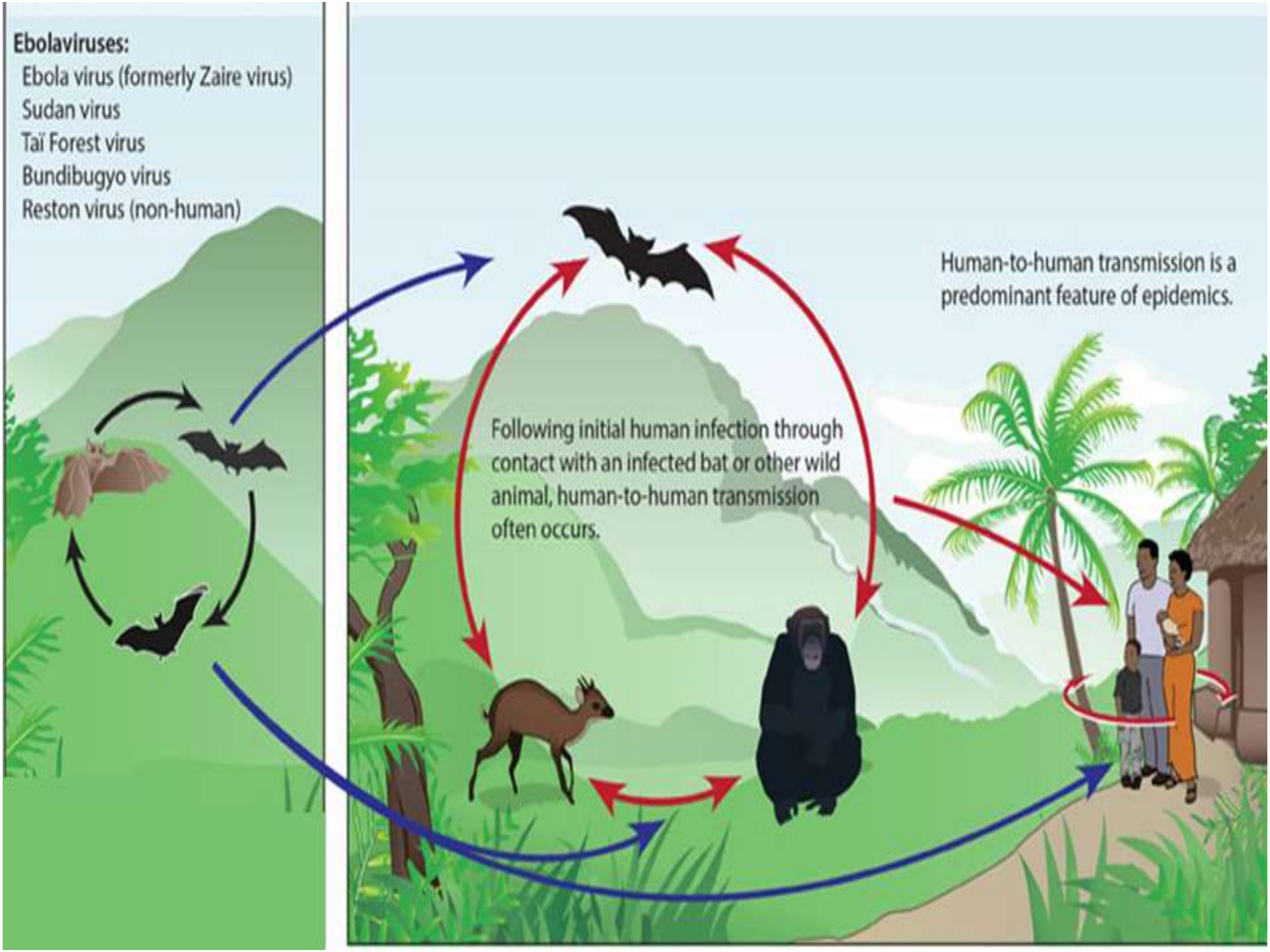
VIRION


Nucleoprotein (N)
Transcription factor VP30
Glycoprotein (GP)
Polymerase cofactor VP35
Polymerase (L)
VP24
Matrix VP40


A
Nucleoprotein (NP)
Surface glycoprotein (GP)
VP30, VP35 and polymerase L
Matrix protein and VP24
B
ssGP
sGP
3'-OH-
NP
VP35
VP40
GP
VP30
VP24
Viral polymerase (L)
5'
Peptide vaccine
MVA-BN-Filo
Virus-like particles
rVSV-ZEBOV
Ad26.ZEBOV, ChAd3-EBO-Z
RNA, DNA vaccines


Monoclonal antibodies bind infectious virions, but may also bind decoy molecules (eg sGP, ssGP and shed GP)
sGP and ssGP are secreted
Macropinocytosis
Interferon
IFNAR1 or IFNAR2
Budding of virions
GP trimers collect at plasma membrane and are incorporated into virions or shed by TACE
Virus binds to attachment factors and signalling molecules (TLR4, DC-SIGN and TIM1)
TYK2
JAK
VP40
VP24
VP40
VP24
Host cell
STAT
VP40 interacts with VP24 to assemble genomic components into virions
Antiviral response
Early endosome
MARV VP40 blocks TYK2-mediated interferon signalling
EBOV VP24 blocks KPNA1-mediated interferon signalling
Virus binds to NPC1 to initiate fusion
VP40
VP24
VP35 inhibits detection by host RNA sensors
PKR
RIG-I
MDA5
PACT
VP35
Vesicle
Fusion at endosomal membrane
Golgi
dsRNA is formed and then complexed with VP35
Once in cytoplasm, replication complexes initiate transcription and replication of the viral genome
VP35
NP
VP30
L


Ebolaviruses:
Ebola virus (formerly Zaire virus)
Sudan virus
Taï Forest virus
Bundibugyo virus
Reston virus (non-human)
Following initial human infection through contact with an infected bat or other wild animal, human-to-human transmission often occurs.
Human-to-human transmission is a predominant feature of epidemics.

Natural Reservoir

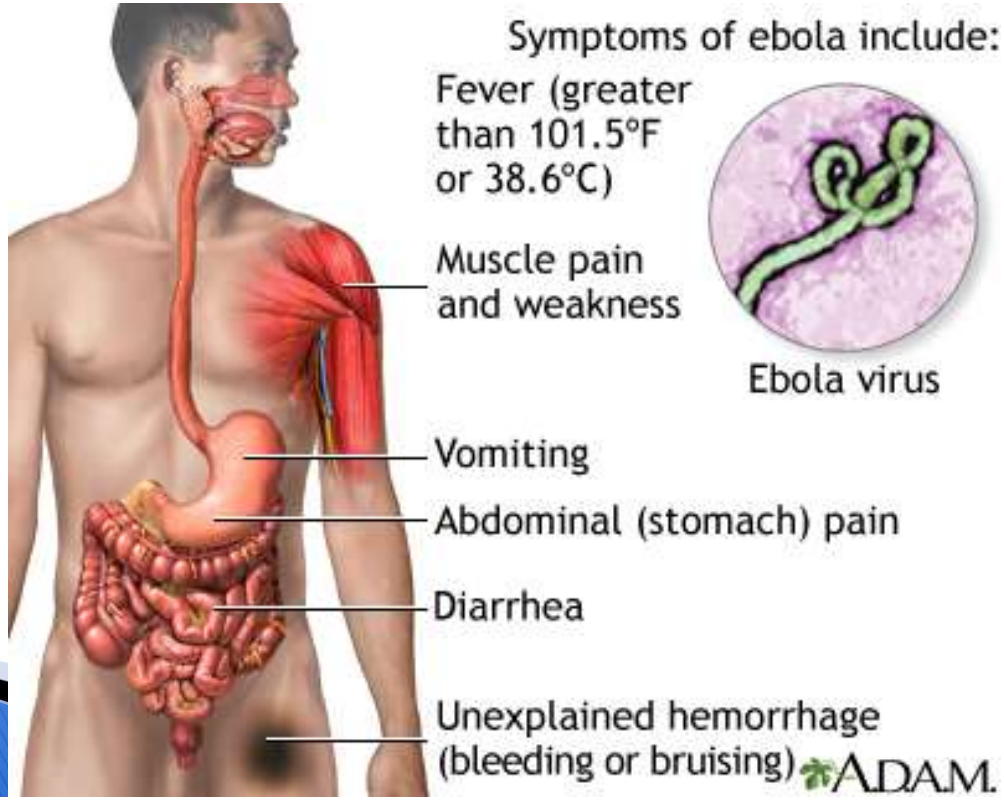
Suspected to be a zoonotic (animal-borne)

However, it is unknown what organism carries it naturally without being infected

<u>Suspected vectors</u>

- Bats
- Primates (in some cases, have been confirmed)
- Basically any other animal native to Africa, including mosquitoes, ticks, birds, reptiles

- Early symptoms
  - muscle aches, fever, vomiting
  - red eyes, skin rash, diarrhea, stomach pain
- Acute symptoms
  - bleeding/hemorrhaging from skin, orifices, internal organs



Target Organs and Damage Methods

Target mainly small capillary vessels. Attach to walls, cause leakage of blood and serum into surrounding tissue.

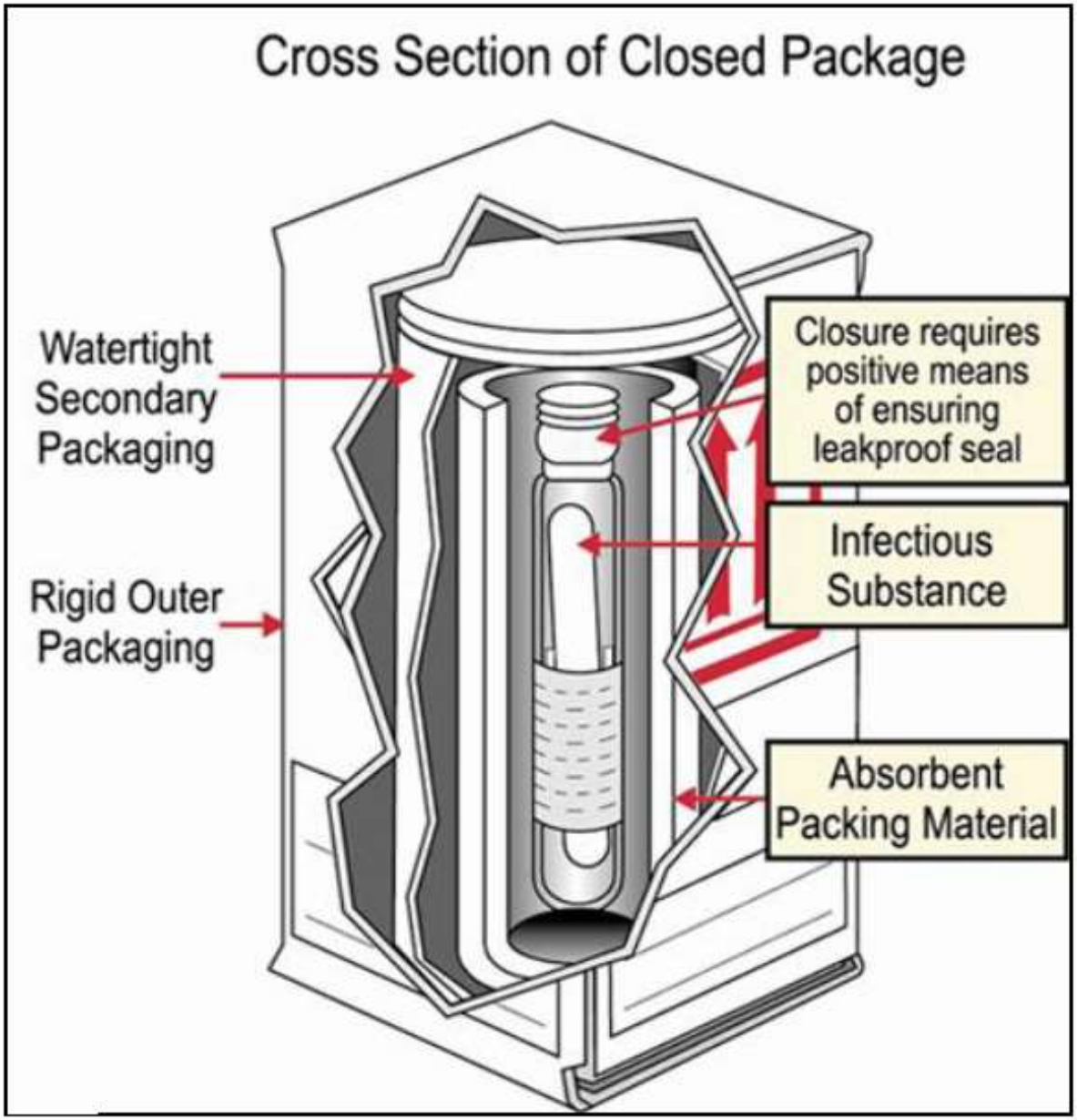
When white blood cells attack the virus, they dissolve – this releases a chemical into the blood stream that signals the release of other chemicals (pro-inflammatory cytokines, pro-coagulants, and anticoagulants)

These injure blood vessels even worse, resulting in permanent bleeding.

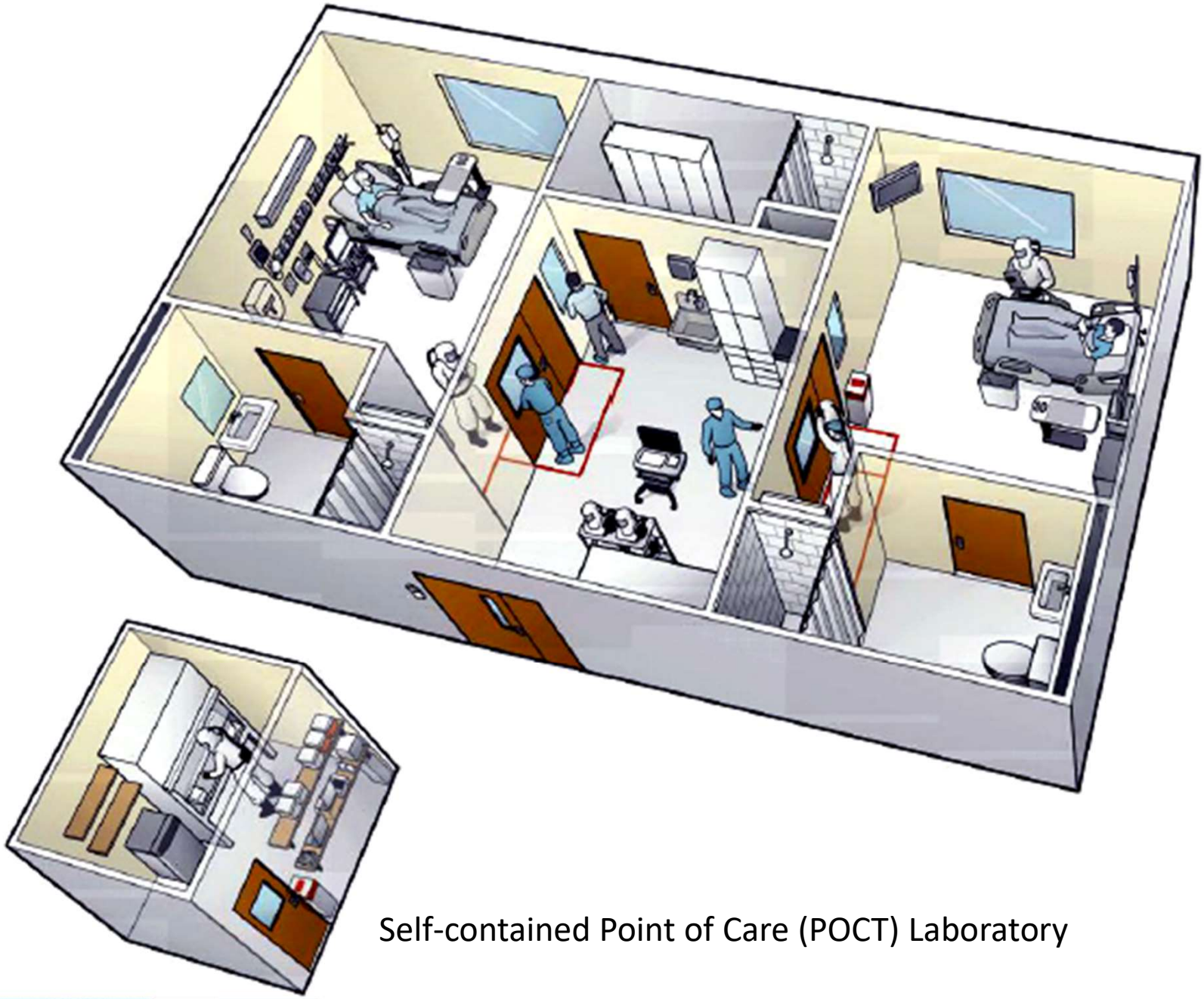
Eventually, the entire body is leaking and dissolving

- Early Diagnosis
  - very difficult
  - signs & symptoms very similar to other infections
- Laboratory Test
  - PCR detection
  - ELISA (enzyme-linked immuno-absorbant) assay

Cate



Category A Shipping Containment



Self-contained Point of Care (POCT) Laboratory

THERE IS NO CURE FOR EBOLA

- There are no known curative medications for Ebola.
- However, there have been very recent developments in preventative medications.

Care of Infected Persons:

Supportive therapy

Maintain oxygen status

Balance fluids and electrolytes

Treatment of complicating infections

Antiviral Research 105 (2014) 17–21

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Antiviral Research

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

Short Communication

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

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

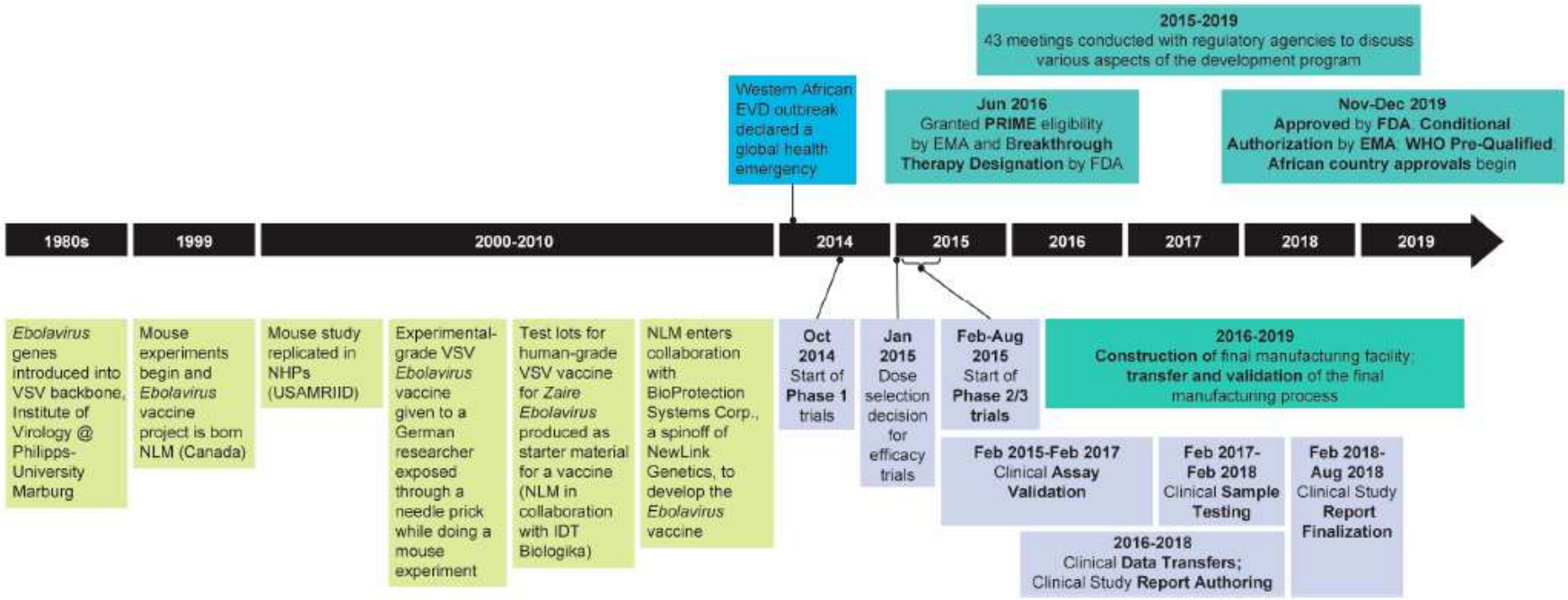
[a] Bernhard-Nocht-Institute for Tropical Medicine, Bernhard-Nocht-Strasse 74, 20359 Hamburg, Germany
[b] German Centre for Infection Research (DZIF), Partner Site Hamburg, Germany
[c] Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Martinistrasse 52, 20251 Hamburg, Germany

Table 1. Clinical manifestations in different animal models of filovirus infections [30].

Manifestation	Immuno-Competent Mouse	Immuno-Compromised Mouse	Guinea Pig	Syrian Hamster	Ferret	NHP	Human
Lymphopenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Liver damage	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Thrombocytopenia	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Coagulopathy	No	Unknown	Yes	Yes	Yes	Yes	Yes
Cytokine Storm	Yes	Yes	Unknown	Yes	Unknown	Yes	Yes
Rash	No	No	No	Yes	Yes	Yes	Yes
Hemorrhage signs	No	Yes	Unknown	Yes	Yes	Yes	Yes

NHP: Non-human primates; Virus is host-adapted for mouse, guinea pig, and Syrian hamster and wild-type for ferret, NHP, and Human.

Species	Features	Pro	Con
	Survivor studies have proved invaluable to our understanding of the immune response directed towards EBOV	Natural host	Controlled challenge experiments are not possible
	Recapitulates human disease and is susceptible to EBOV in the wild, many vaccine and challenge studies have been performed using NHP and this data has been invaluable to supporting vaccine licensure	Gold standard, recapitulates human disease	Ethical issues, study expense and facilities expertise
	Relatively recent model that is susceptible to EBOV and shows many aspects of human disease	Challenge with WT EBOV	Lack of reagents
	A Guinea pig-adapted strain of EBOV is needed to (GA-EBOV) to see severe disease in these animals	Established	Fails to fully recapitulate human disease
	A mouse-adapted strain of EBOV is needed to (MA-EBOV) to see severe disease in these animals. The use of transgenic mice and adoptive transfer techniques allows for the study of human cell subsets in an *in vivo* setting	Cost-effective and versatile	Fails to fully recapitulate human disease


2015-2019
43 meetings conducted with regulatory agencies to discuss various aspects of the development program
Western African EVD outbreak declared a global health emergency
Jun 2016
Granted PRIME eligibility by EMA and Breakthrough Therapy Designation by FDA
Nov-Dec 2019
Approved by FDA; Conditional Authorization by EMA; WHO Pre-Qualified; African country approvals begin
1980s
1999
2000-2010
2014
2015
2016
2017
2018
2019
Ebolavirus genes introduced into VSV backbone, Institute of Virology @ Philipps-University Marburg
Mouse experiments begin and Ebolavirus vaccine project is born NLM (Canada)
Mouse study replicated in NHPs (USAMRIID)
Experimental-grade VSV Ebolavirus vaccine given to a German researcher exposed through a needle prick while doing a mouse experiment
Test lots for human-grade VSV vaccine for Zaire Ebolavirus produced as starter material for a vaccine (NLM in collaboration with IDT Biologika)
NLM enters collaboration with BioProtection Systems Corp., a spinoff of NewLink Genetics, to develop the Ebolavirus vaccine
Oct 2014 Start of Phase 1 trials
Jan 2015 Dose selection decision for efficacy trials
Feb-Aug 2015 Start of Phase 2/3 trials
2016-2019
Construction of final manufacturing facility; transfer and validation of the final manufacturing process
Feb 2015-Feb 2017
Clinical Assay Validation
Feb 2017-Feb 2018
Clinical Sample Testing
Feb 2018-Aug 2018
Clinical Study Report Finalization
2016-2018
Clinical Data Transfers; Clinical Study Report Authoring

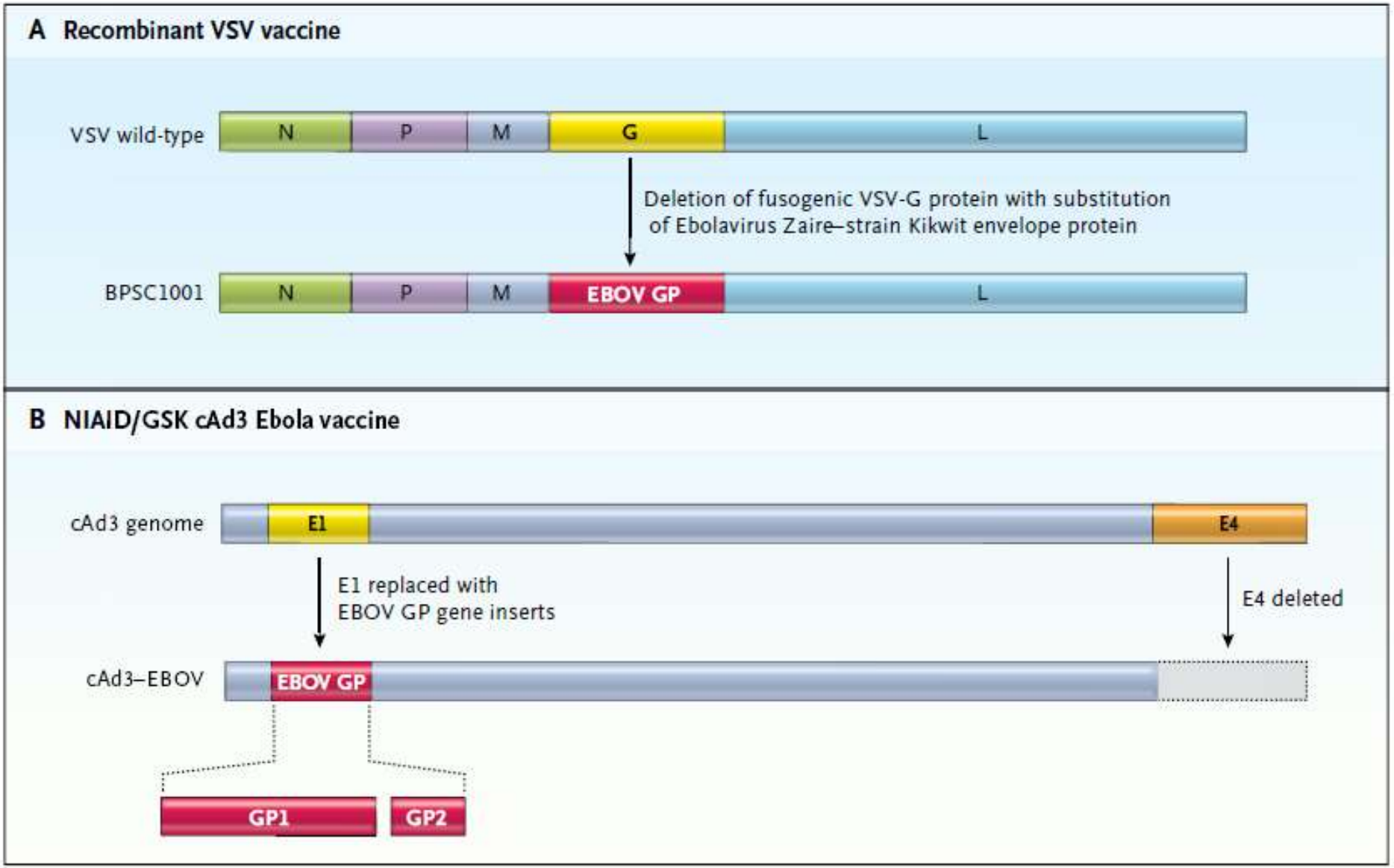
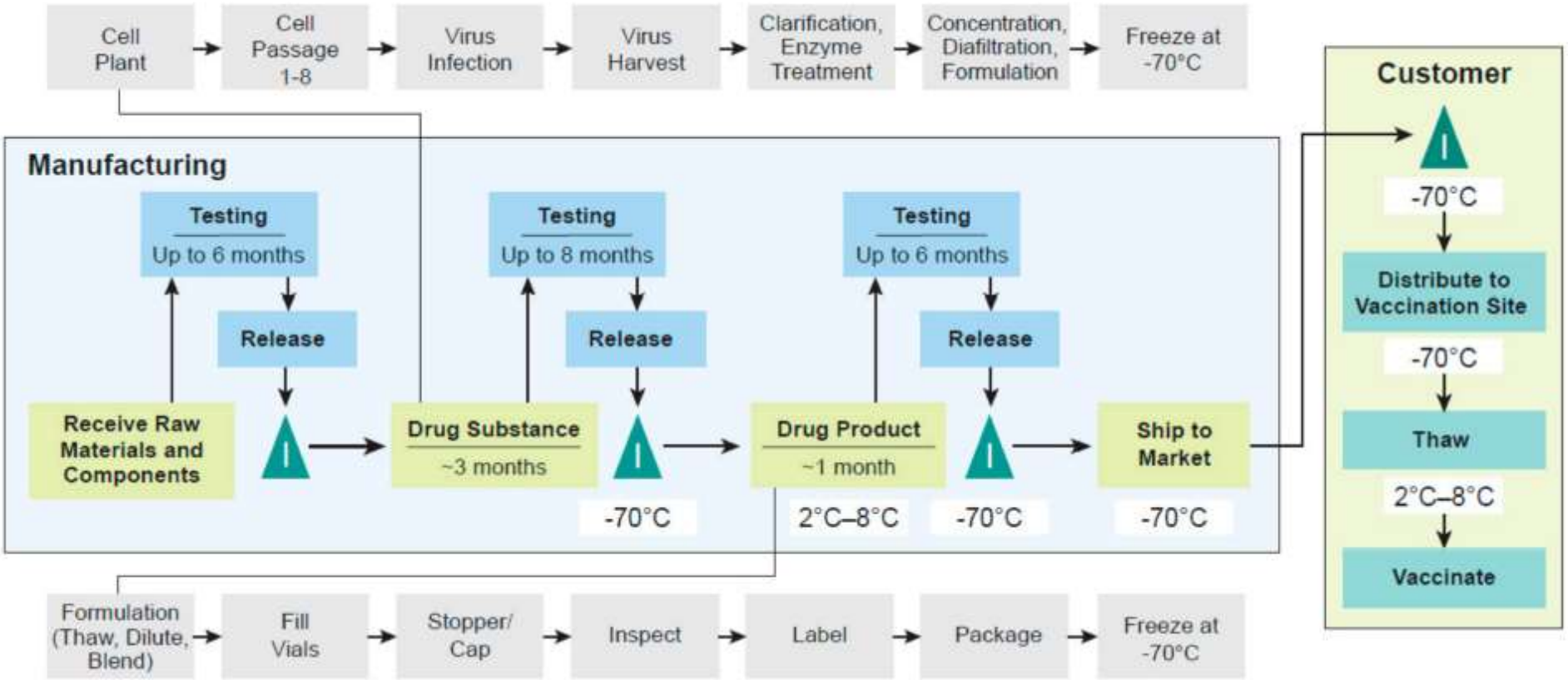
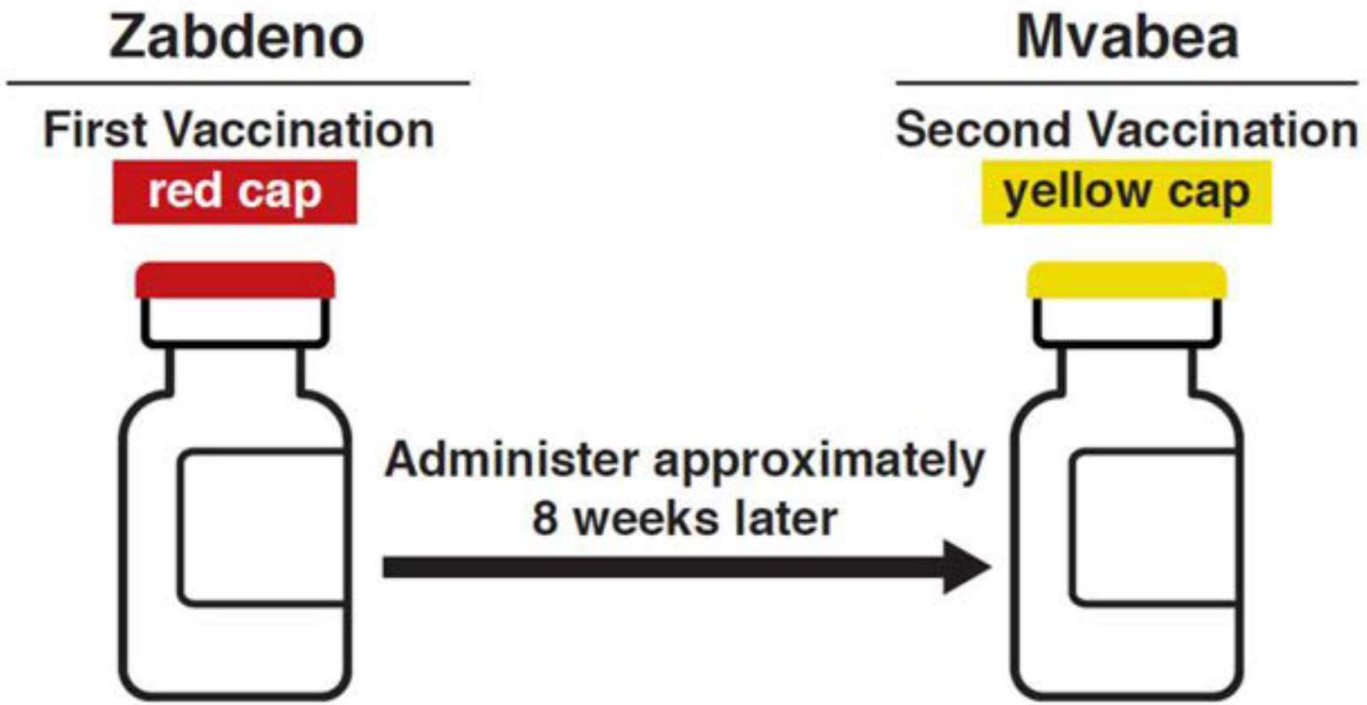


Figure 1. Structures of Ebola Vaccine Candidates rVSV (Panel A) and cAd3 (Panel B).

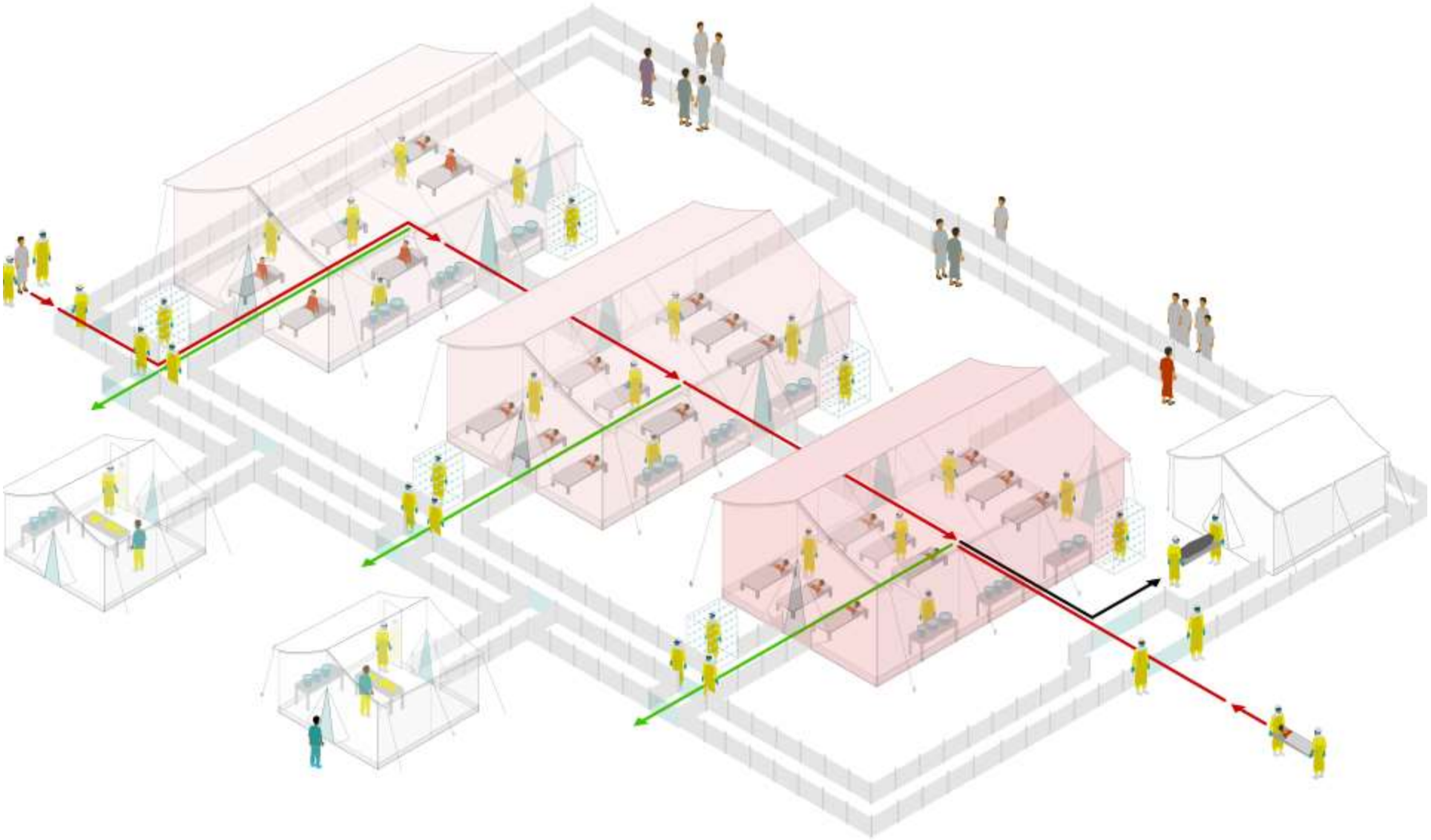

Cell Plant
Cell Passage 1-8
Virus Infection
Virus Harvest
Clarification, Enzyme Treatment
Concentration, Diafiltration, Formulation
Freeze at -70°C
Manufacturing
Testing
Up to 6 months
Release
Testing
Up to 8 months
Release
Testing
Up to 6 months
Release
Receive Raw Materials and Components
Drug Substance
~3 months
Drug Product
~1 month
Ship to Market
-70°C
2°C–8°C
-70°C
-70°C
Customer
-70°C
Distribute to Vaccination Site
-70°C
Thaw
2°C–8°C
Vaccinate
Formulation (Thaw, Dilute, Blend)
Fill Vials
Stopper/ Cap
Inspect
Label
Package
Freeze at -70°C

- Mvabea suspension for injection
- Ebola vaccine (MVA-BN-Filo [recombinant])

- *Zaire ebolavirus* (EBOV) Mayinga variant glycoprotein (GP)
- *Sudan ebolavirus* Gulu variant GP
- *Taï Forest ebolavirus* nucleoprotein
- *Marburg marburgvirus* Musoke variant GP


Zabdeno
First Vaccination
red cap
Mvabea
Second Vaccination
yellow cap
Administer approximately
8 weeks later

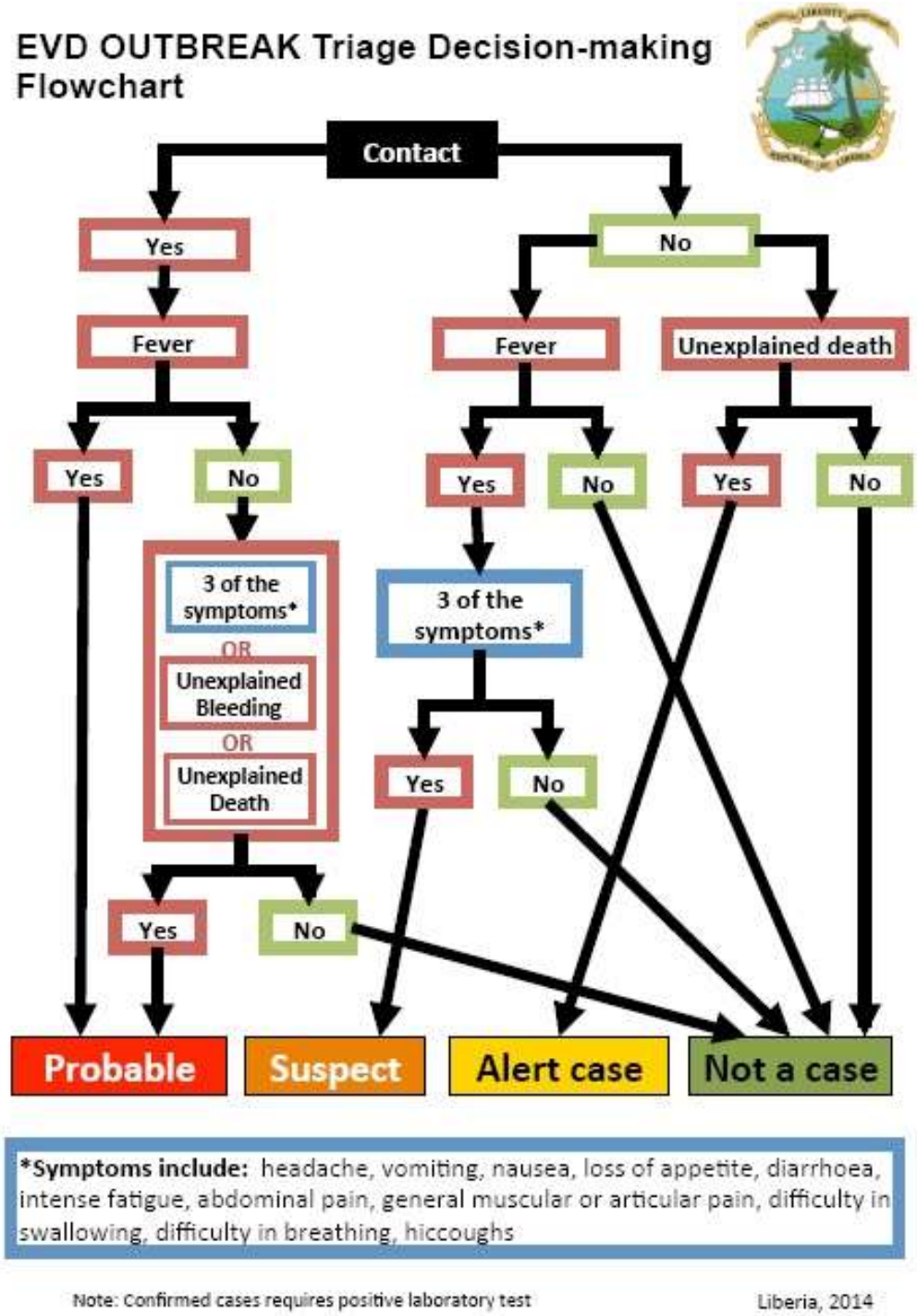
گینه بیمارستان دونکا



Source: MSI


MEDECINS
SANS FRONTIERE

- Triage process for epidemiological purposes
- May change the threshold for clinical purposes

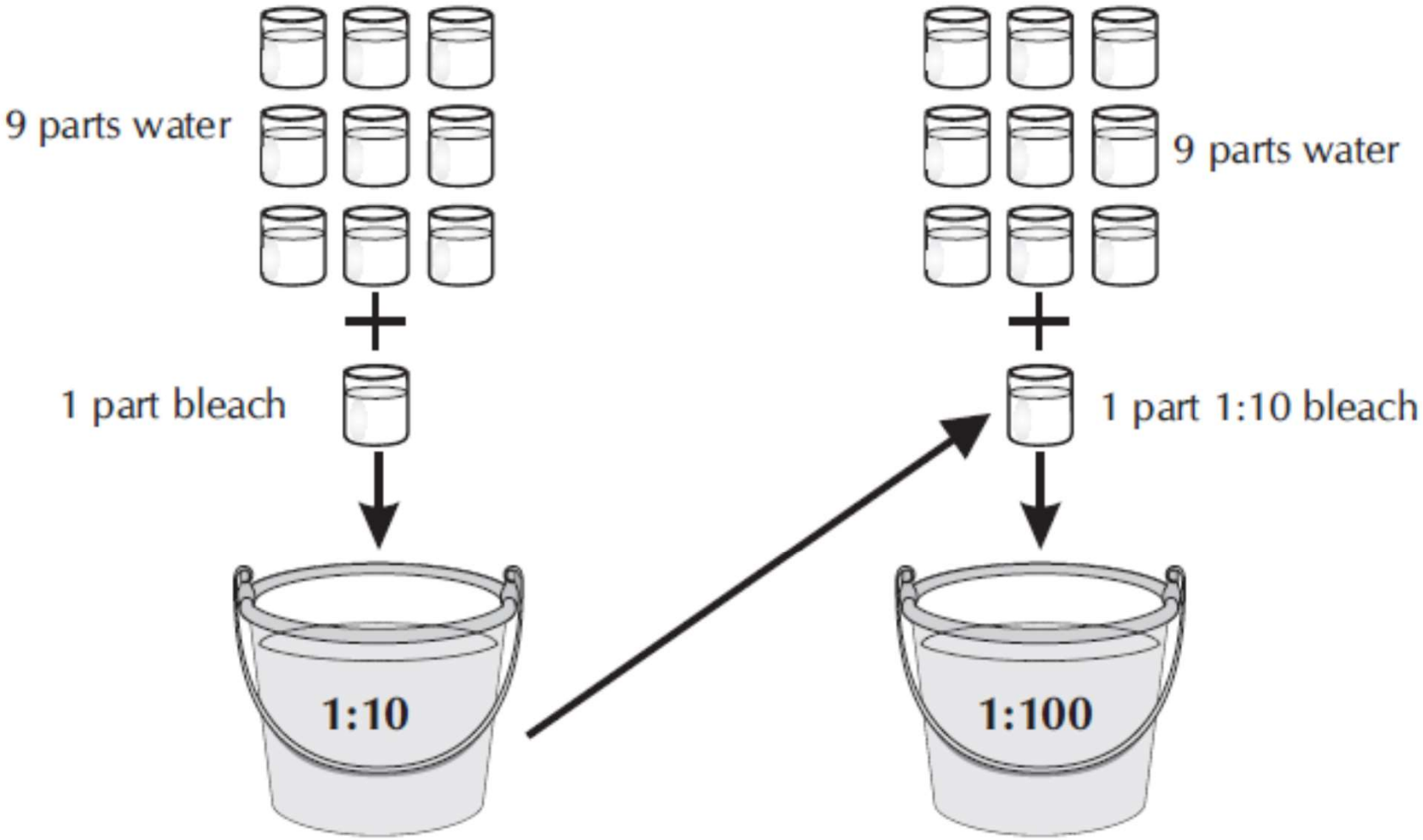



UECINS
S FRONTIERES


AFP

Disinfection with chlorine

Solution	Uses
0.5%	Disinfection of body fluids; Disinfection of corpses; Disinfection of toilets & bathrooms; Disinfection of gloved hands; Disinfection of floors; Disinfection of beds & mattress covers; Footbaths;
0.05%	Disinfection of bare hands and skin; Disinfection of medical equipment; Disinfection of laundry; Washing up of plates and eating utensils;


9 parts water
1 part bleach
1:10
9 parts water
1 part 1:10 bleach
1:100

Thanks for your attention