



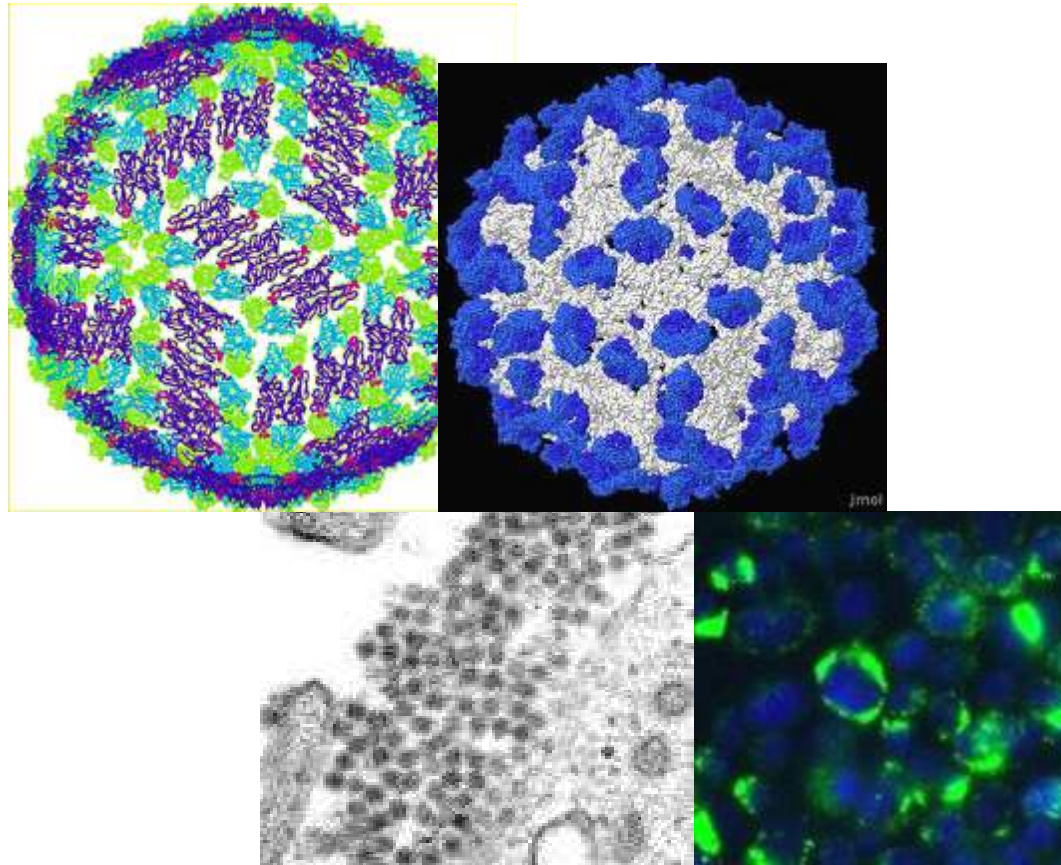
# VIRAL HEMORRHAGIC FEVERS



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2<sup>nd</sup> Yr PG Microbiology  
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# What are Viral Hemorrhagic Fevers (VHFs)?

- A group of illnesses that are caused by several distinct families of viruses
- A severe multisystem syndrome (multiple organ systems in the body are affected)
- Vascular system damaged : **SHOCK syndromes**
- Body 's ability to regulate itself (Homeostasis) is impaired
- Many cause severe and life-threatening disease.



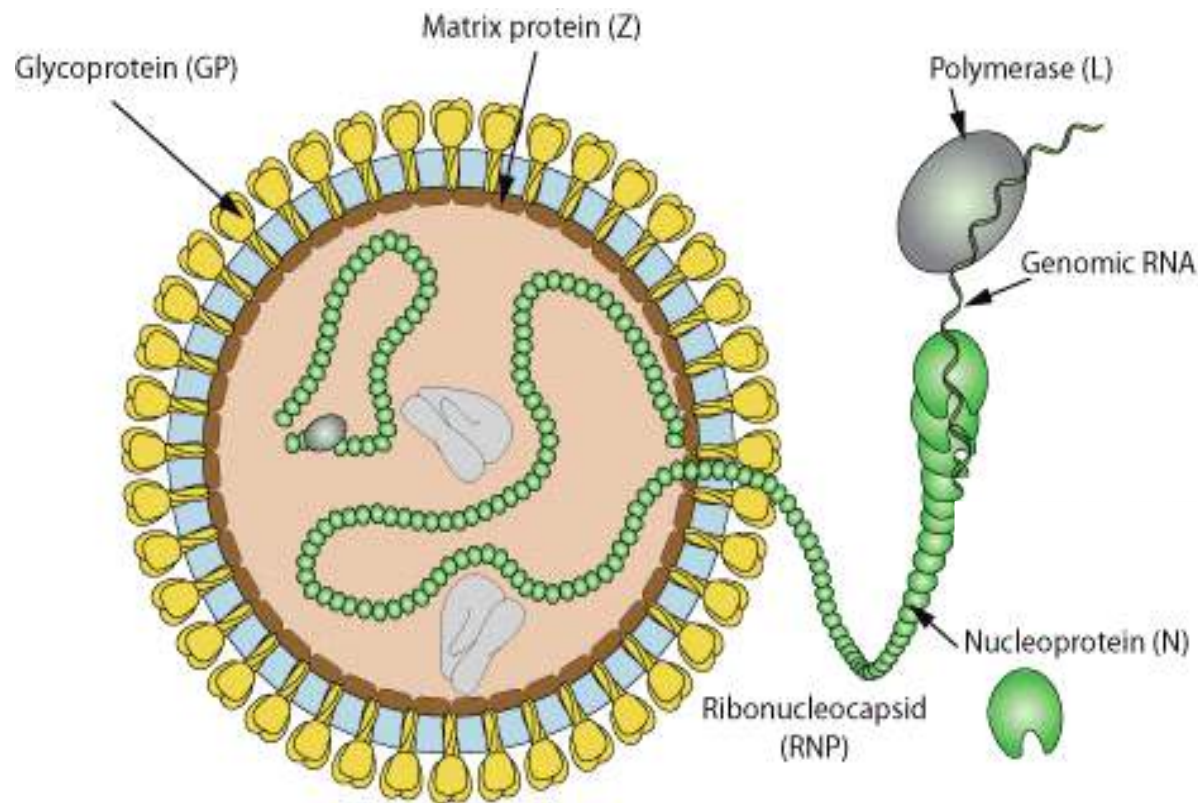
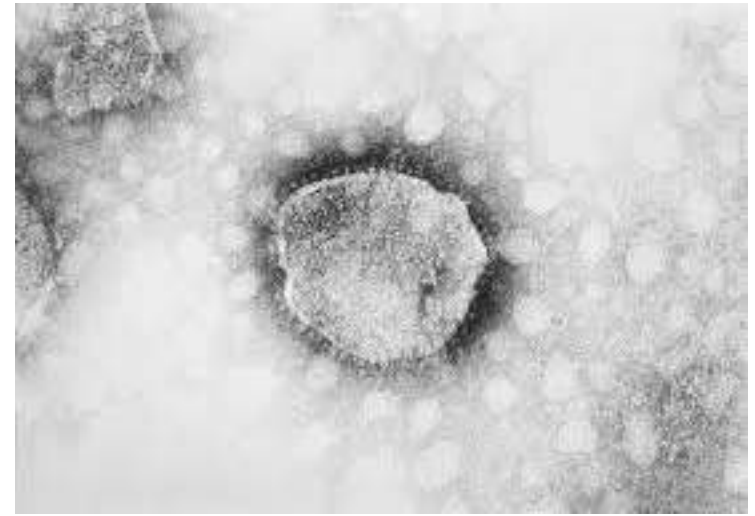
# Etiological Agents

# Viral hemorrhagic fever (...contd)

- Viruses of **four** distinct families
  - Arenaviridae
  - Filoviridae
  - Bunyaviridae
  - Flaviviridae
- **RNA viruses (single stranded)**
  - lipid capsulated
  - zoonotic
- Survival dependent on an animal or insect host, for the natural reservoir



# Arenaviridae



Junin virus  
Machupo virus  
Guanarito virus  
Lassa virus  
Sabia virus

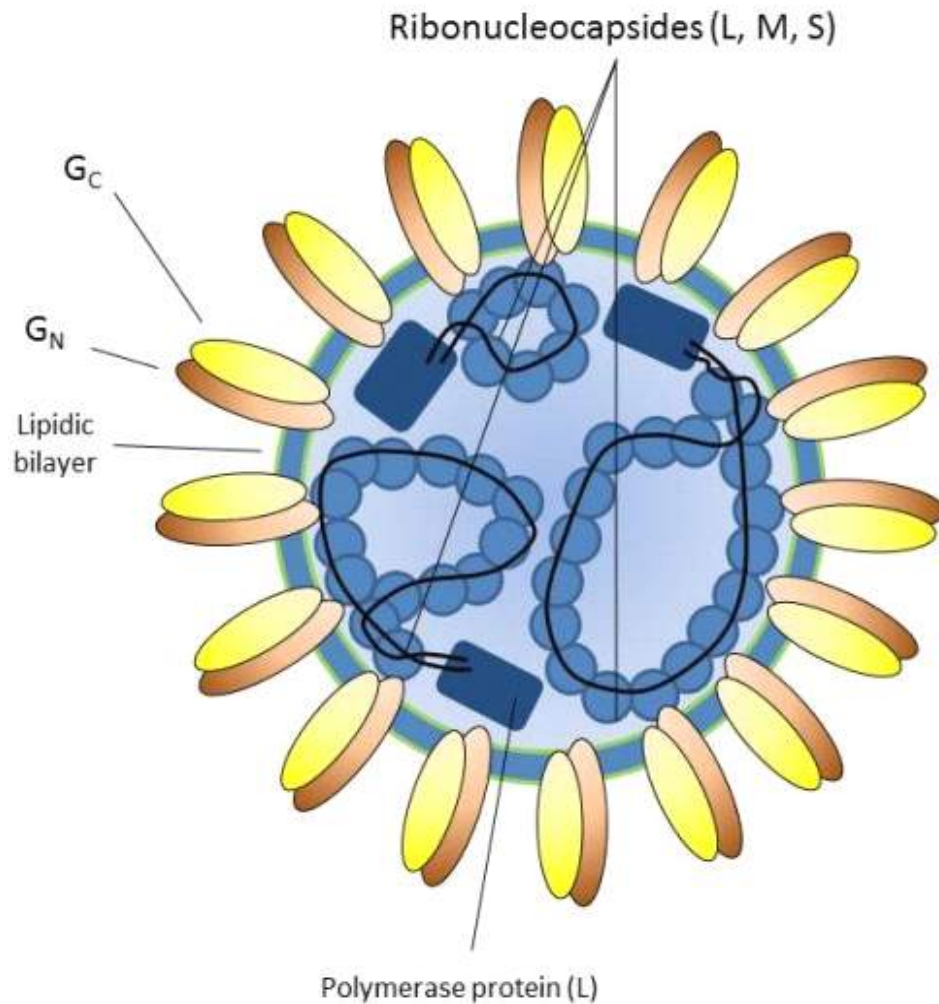
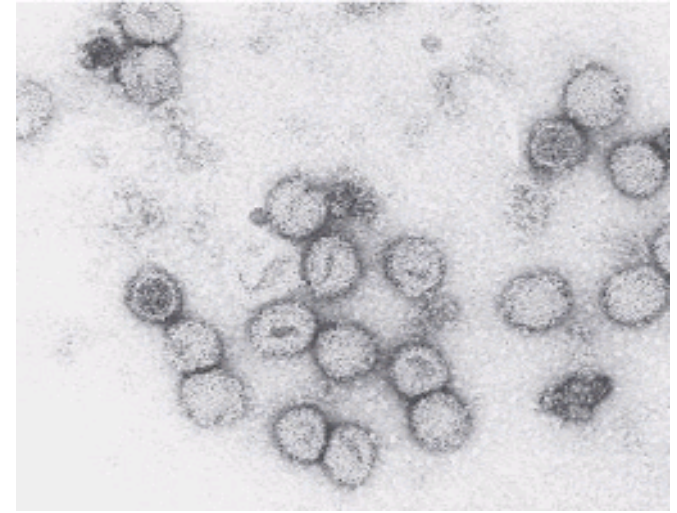


# Arenaviridae Transmission

- Virus transmission and amplification occurs in rodents
- Shed virus through urine, feces, and other excreta
- Human infection
  - Contact with excreta
  - Contaminated materials
  - Aerosol transmission
- Person-to-person transmission



# Bunyaviridae



Rift Valley Fever virus  
Crimean-Congo  
Hemorrhagic Fever virus  
Hantavirus

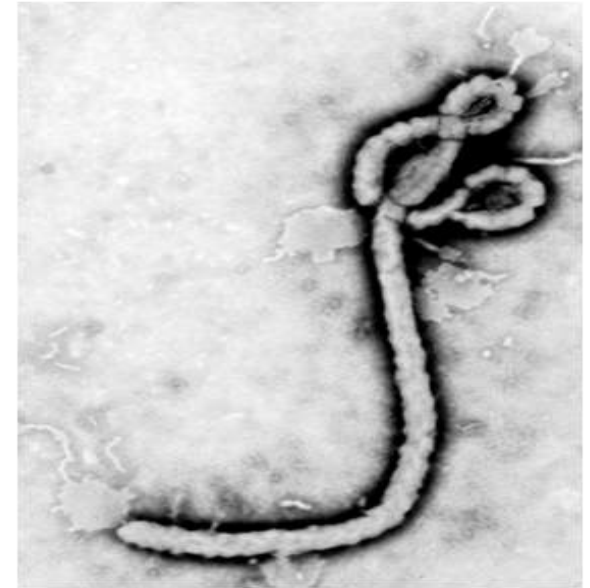
# Bunyaviridae Transmission

- Arthropod vector
  - Exception - Hantaviruses
- RVF - *Aedes* mosquito
- CCHF - Ixodid tick
- Hantavirus - Rodents
- Less common
  - Aerosol
  - Exposure to infected animal tissue

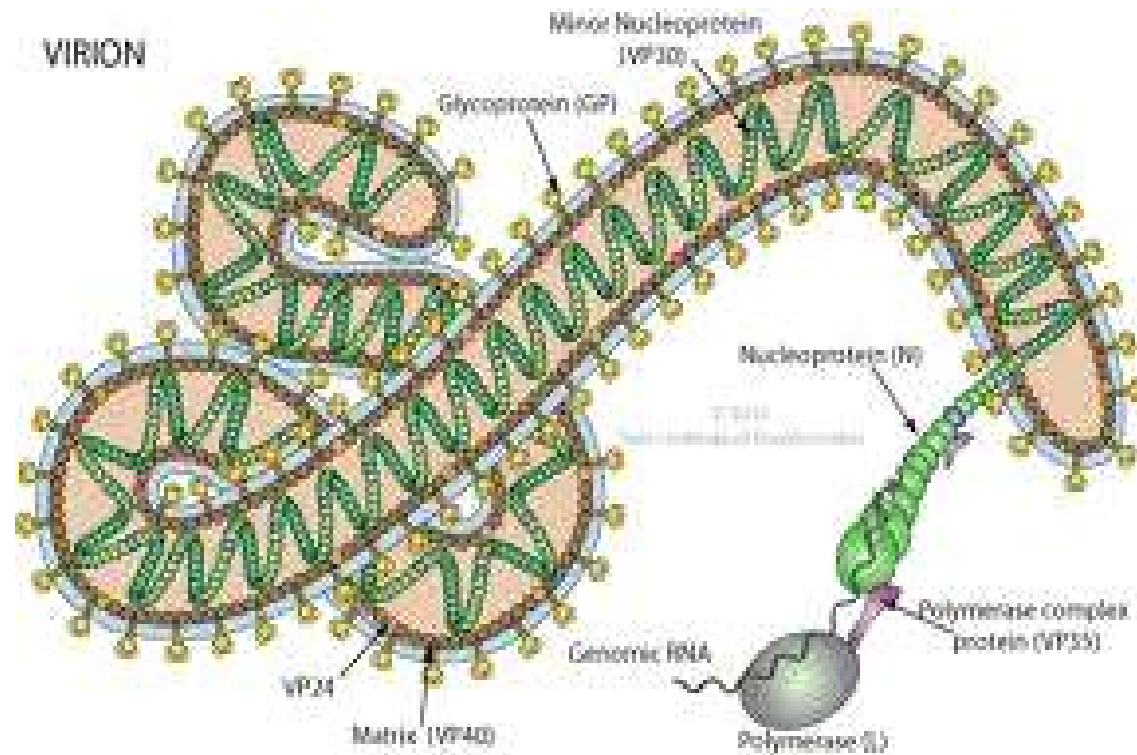




# Filoviridae



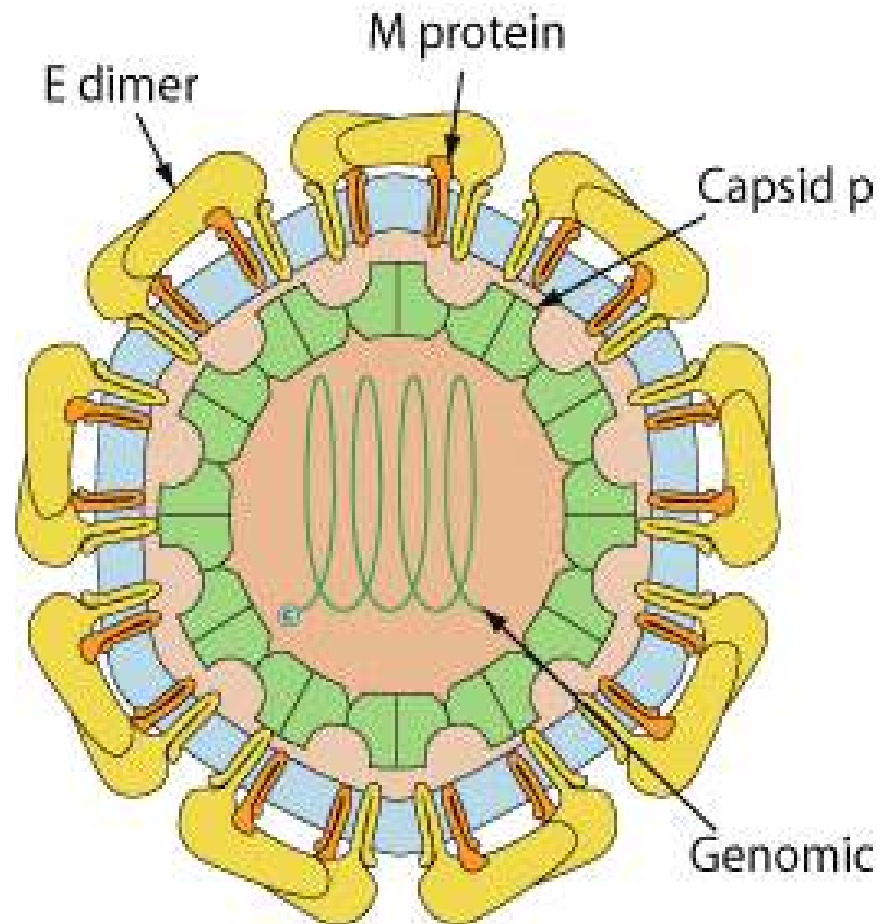
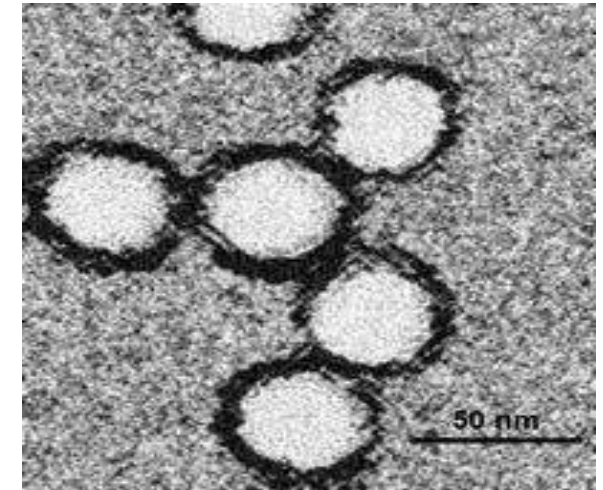
Marburg virus  
Ebola virus



# Filoviridae Transmission

- Reservoir is UNKNOWN
  - Fruit Bats implicated with Marburg
- Intimate contact
- Nosocomial transmission
  - Reuse of needles and syringes
  - Exposure to infectious tissues, excretions, and hospital wastes
- Aerosol transmission
  - Primates

# Flaviviridae



Dengue virus  
Yellow Fever virus  
Omsk Hemorrhagic Fever  
virus  
Kyasanur Forest Disease  
virus

# Flaviviridae Transmission

- Arthropod vector
- Yellow Fever and Dengue viruses
  - *Aedes aegypti*
  - Sylvatic cycle
  - Urban cycle
- Kyasanur Forest Virus
  - Ixodid tick
- Omsk Hemorrhagic Fever virus
  - Tick

# TARGET CELLS AND TISSUE

- Virus spreads from site of infection to regional lymph nodes, liver and spleen.
- Virus exploit host cell endocytic machinery to access the replication
- Macrophage, dendritic cells, endothelial cells, hepatocytes and adreno-cortical cell support replication.



# PATHOGENESIS

- Virus infects tissue macrophages (Kupffer cells) and dendritic cells

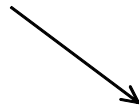


Recruit more macrophages



Amplify dysregulated immune response

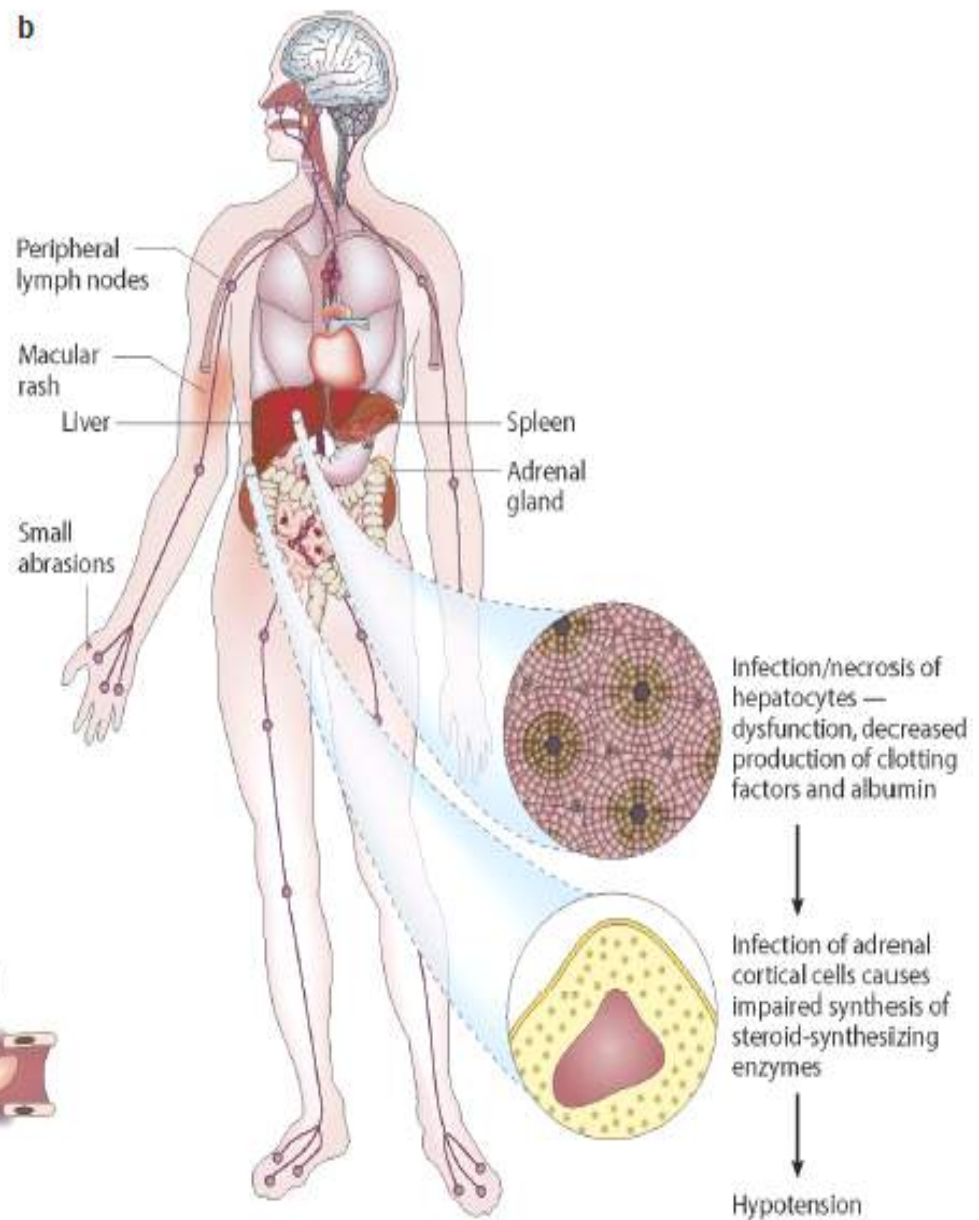
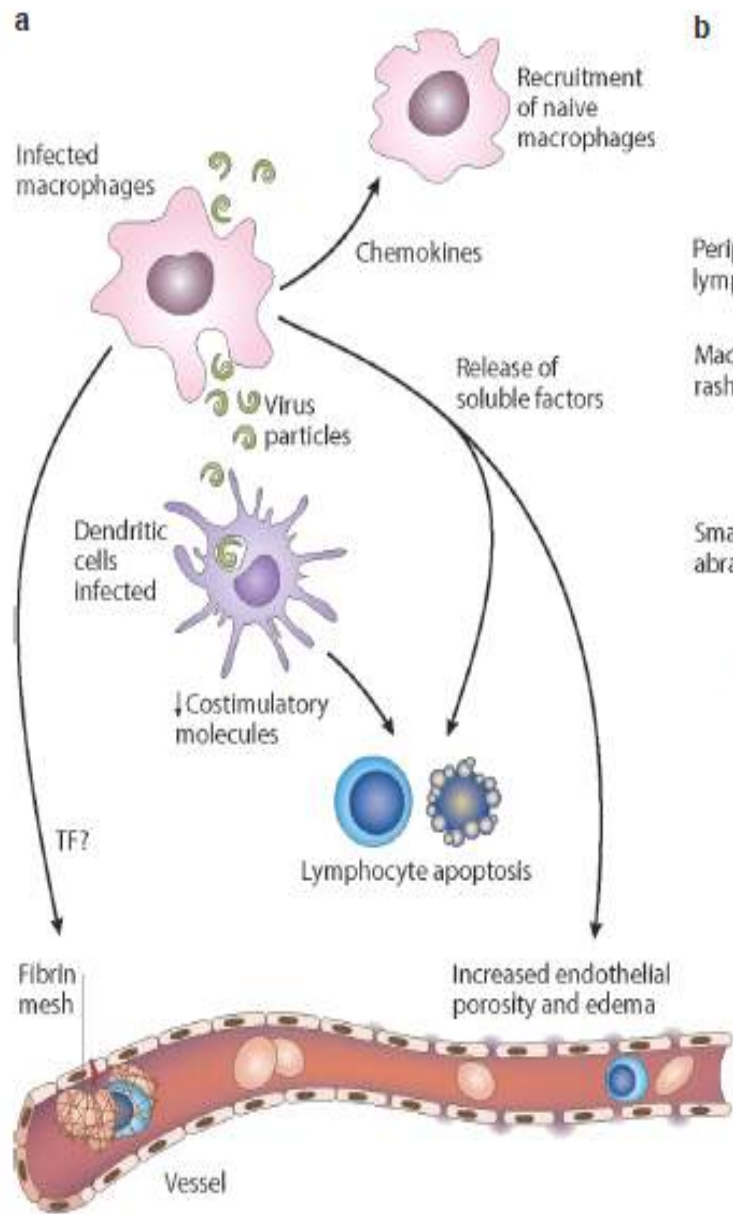
- Immunological mechanism      direct infection



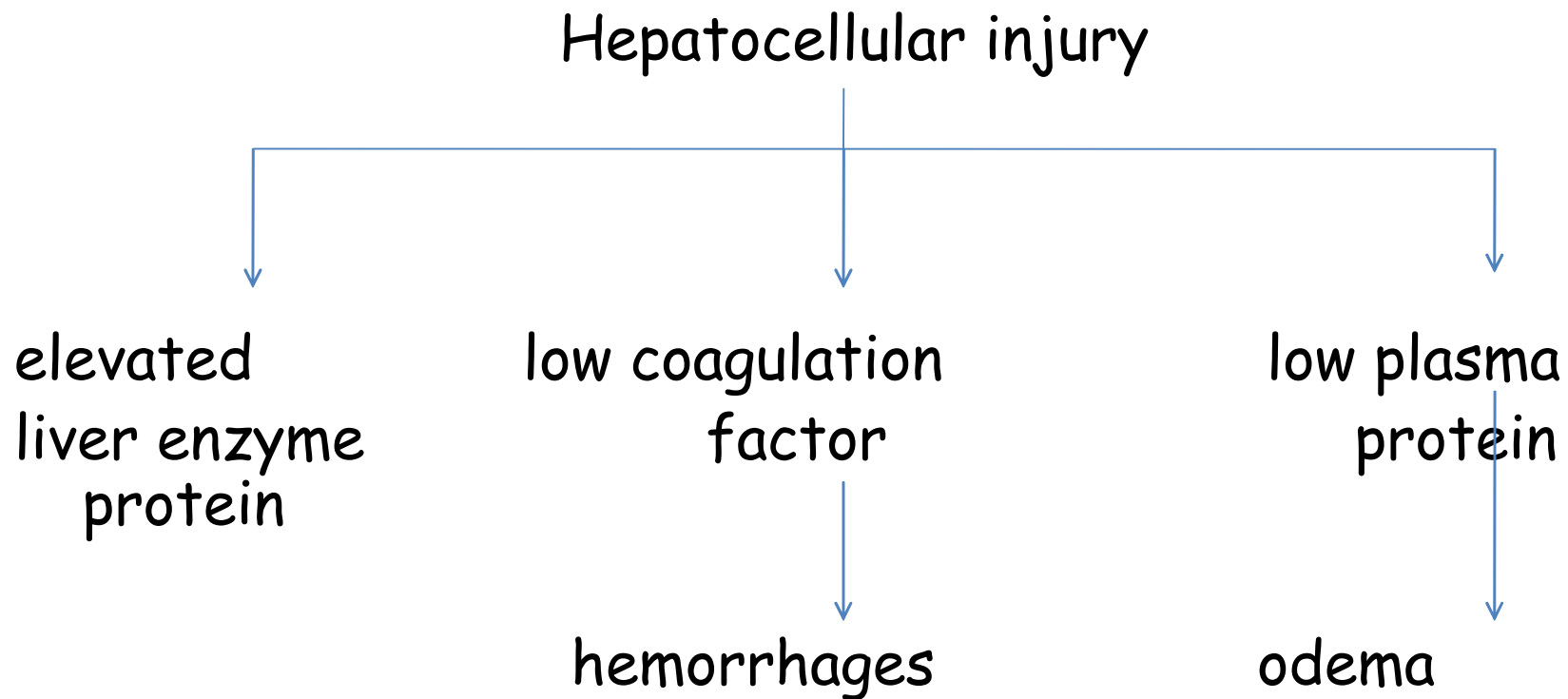
VASCULAR DAMAGE



Vascular impermeability



- Target organs are macrophage -rich lymphoid tissue, liver and adrenal gland.



Adrenocortical dysfunction by viral infection plays important role in evolution of shock (late phase of VHF)

# Immunosuppression

- Lymphopenia is the most consistent finding (except hanta viruses).
- Undergo apoptosis leads to lymphoid depletion.
  - TRAIL : **T**NF **R**elated **A**poptosis **I**nduced **L**igand
  - and Fas related receptor pathways
  - dysfunction of infected dendritic cells
  - increased NO production.



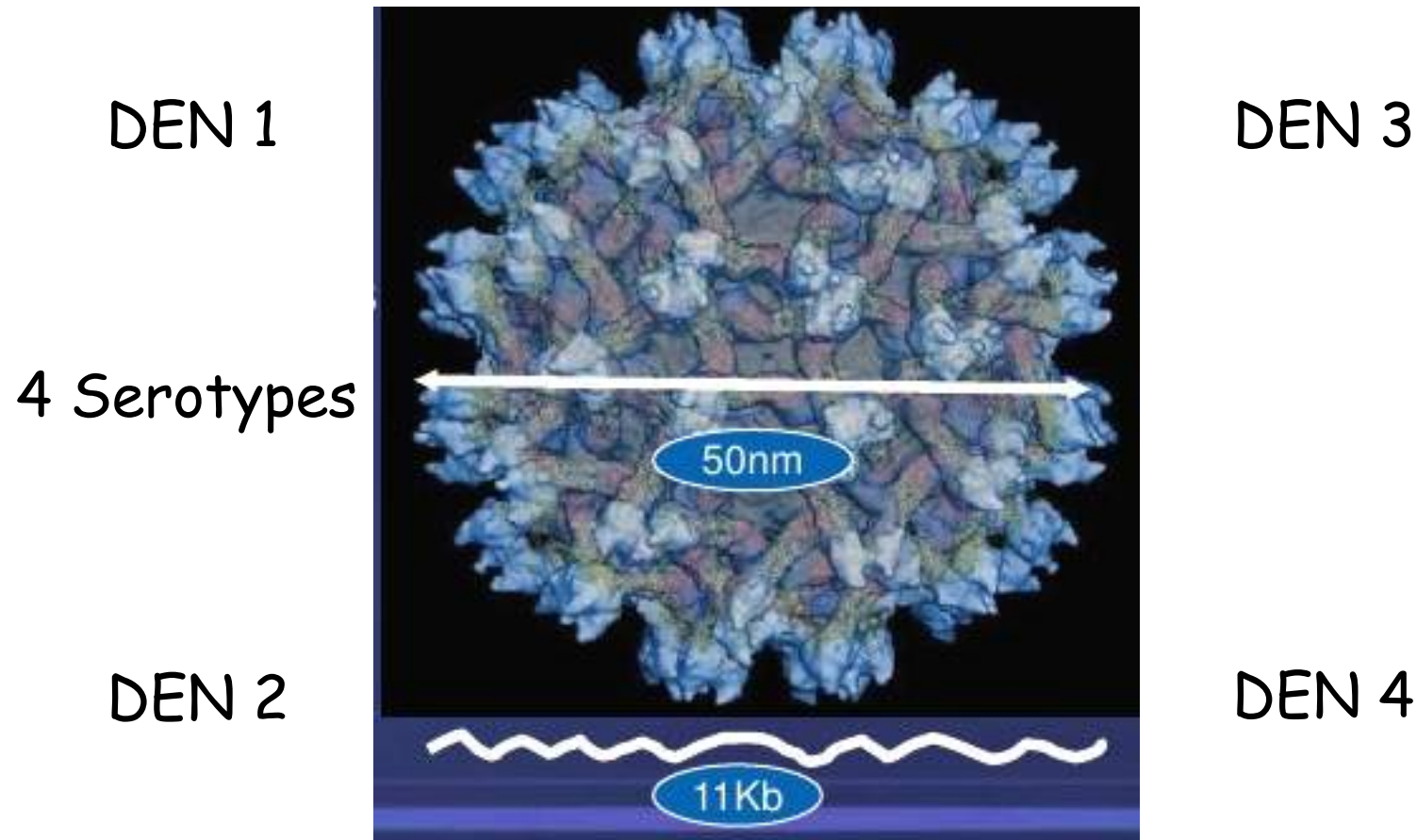
# HF WITH RENAL FAILURE

- Caused by hantaan, pummla, seoul virus.
- Both humoral and cell mediated immunity
- Direct damage by hanta virus
- Accumulation of immune complex
- Hypersensitivity reaction (Ig E, Ig G)
- Activated CD8 T cell  $\rightarrow$  IL-1, TNF $\alpha$ , IFN $\gamma$
- Renal tubule blocked by cast cells and proteins
- Activation of angiotensin II

Dengue is a scare!!!

# Dengue Virus - Flaviviridae

Infection with one serotype produces life long immunity



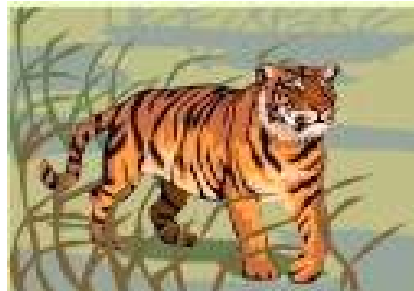
But only temporarily and partial immunity against other types

# Vectors - Aedes Mosquito

**Aedes albopictus**



**Aedes aegypti**

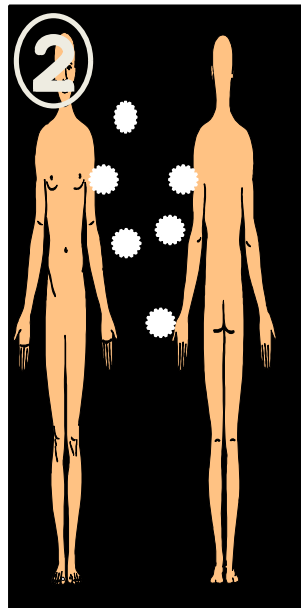


# Dengue Transmission

1. Mosquitoes transmit Dengue virus to human dendritic cells.



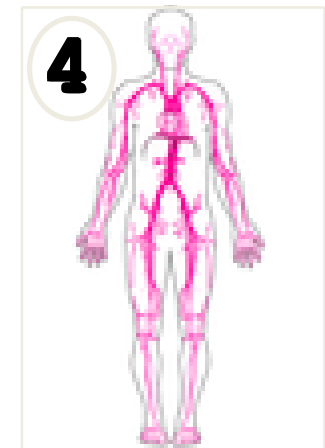
2. Virus targets areas with high WBC counts (liver, spleen, lymph nodes, bone marrow, And glands)



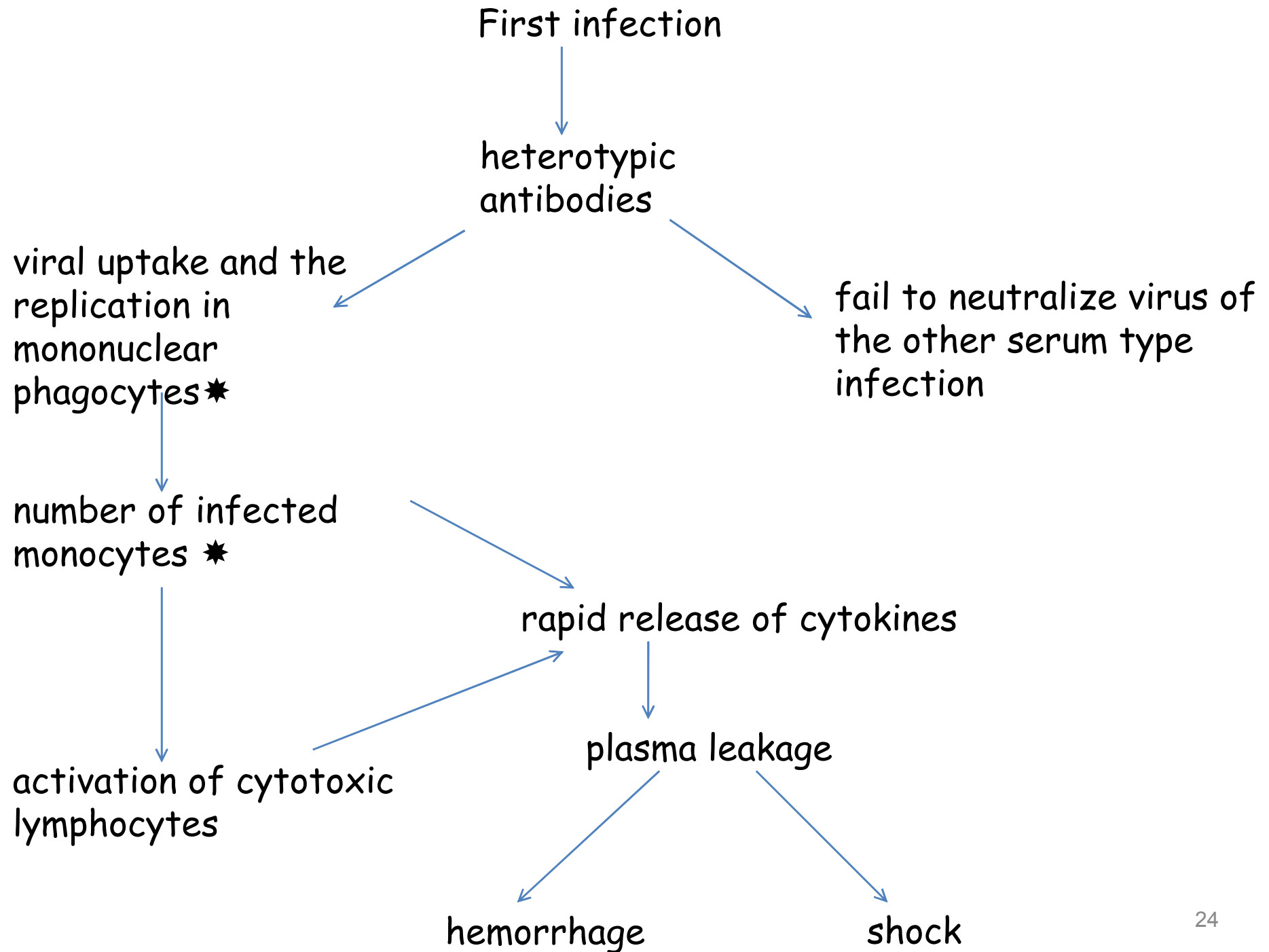
3. Virus enters WBCs & lymphatic Tissue



4. Dengue virus enters blood Circulation.

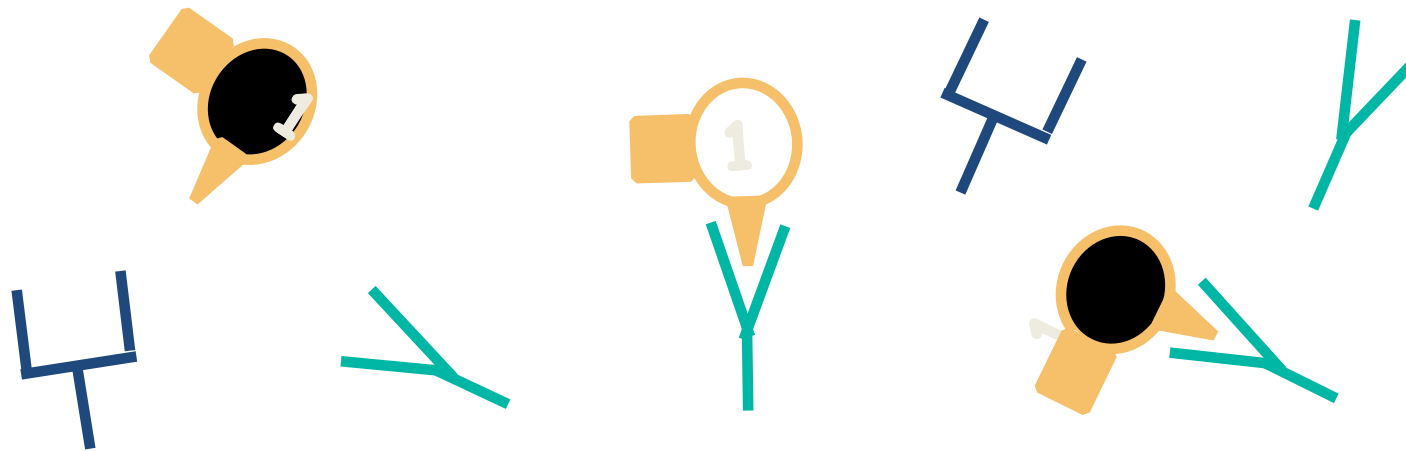






# Pathogenesis of DHF

## STEP 1- Homologous Antibodies Form Non-infectious Complexes



Dengue 1 virus



Neutralizing antibody to Dengue 1 virus

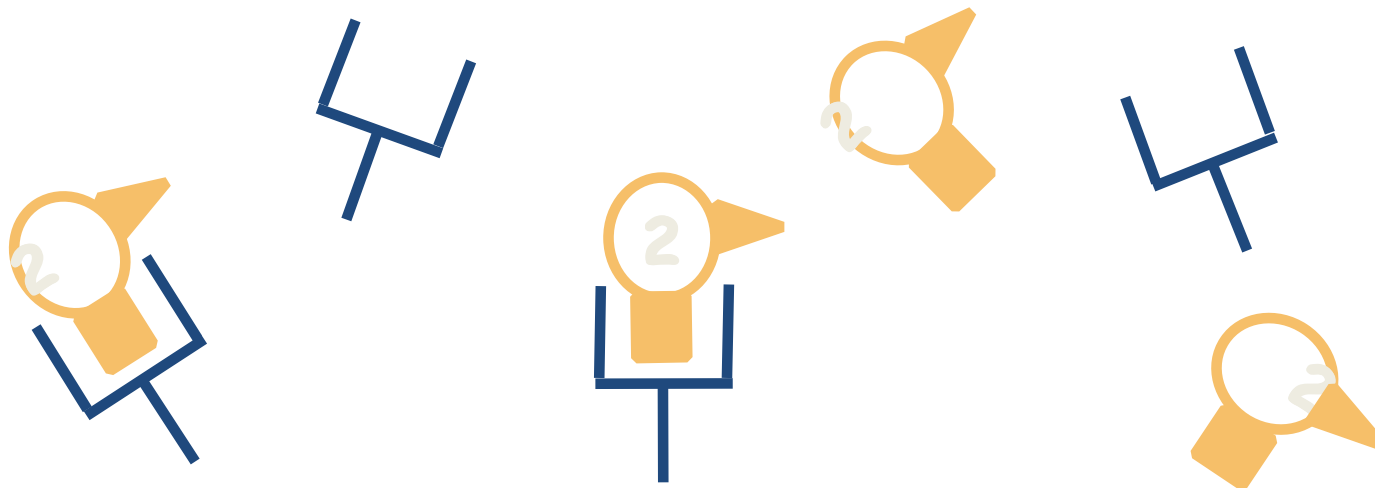





Non-neutralizing antibody



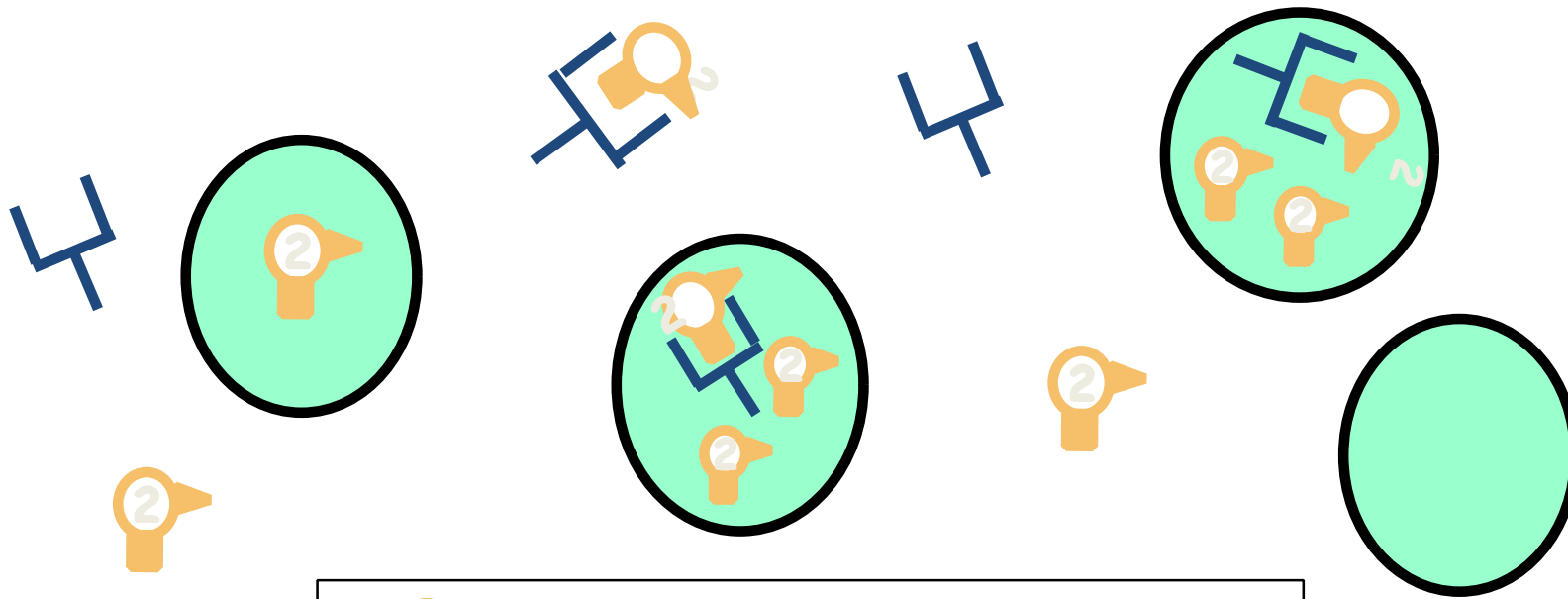
Complex formed by neutralizing antibody and virus




# STEP2- Heterologous Antibodies of first serotype infection form Infectious Complexes with second serotype



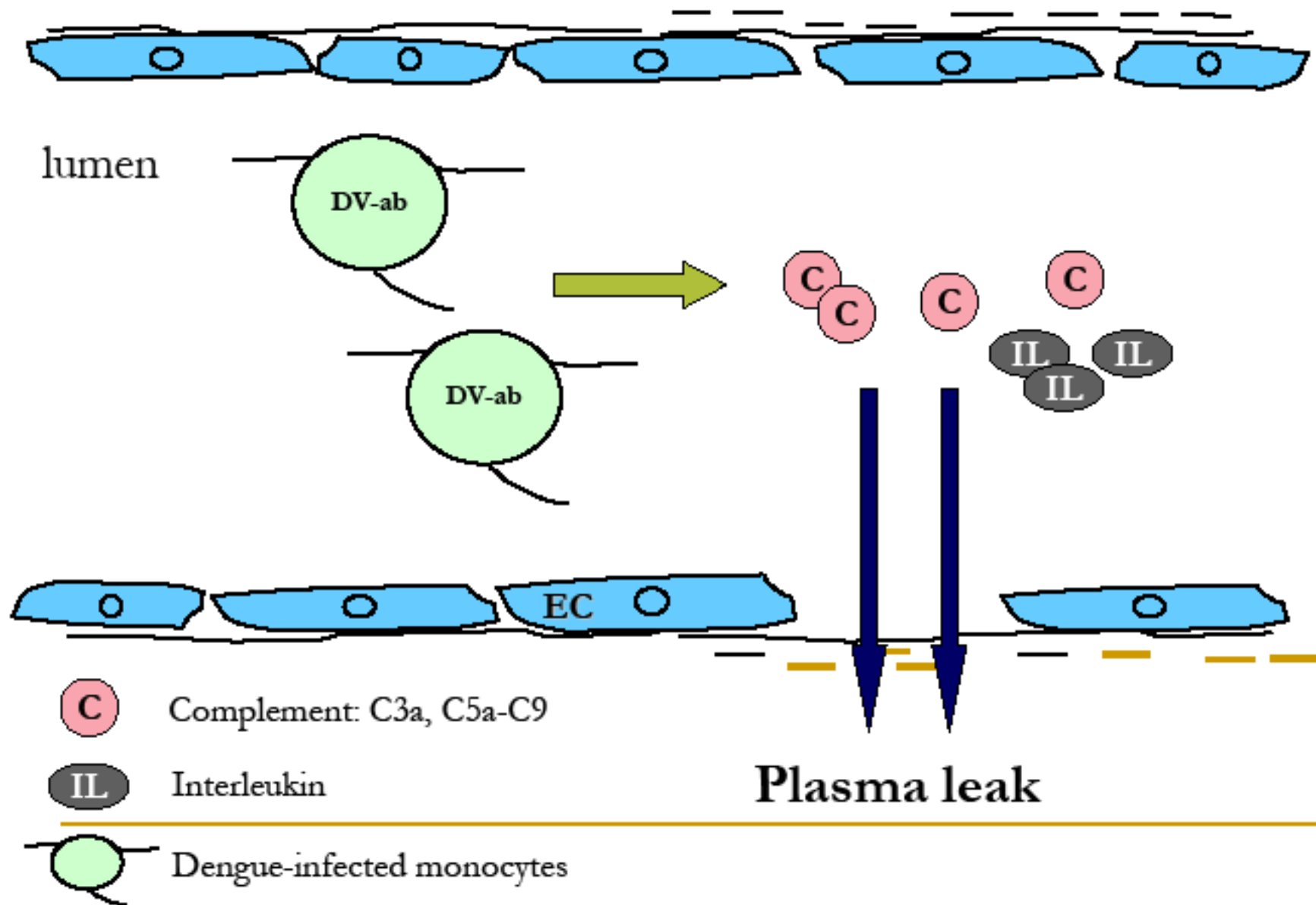
	Dengue 2 virus
	Non-neutralizing antibody to Dengue 1 virus
	Complex formed by non-neutralizing antibody and virus

# STEP3 - Heterologous Complexes Enter More Monocytes, Where Virus Replicates



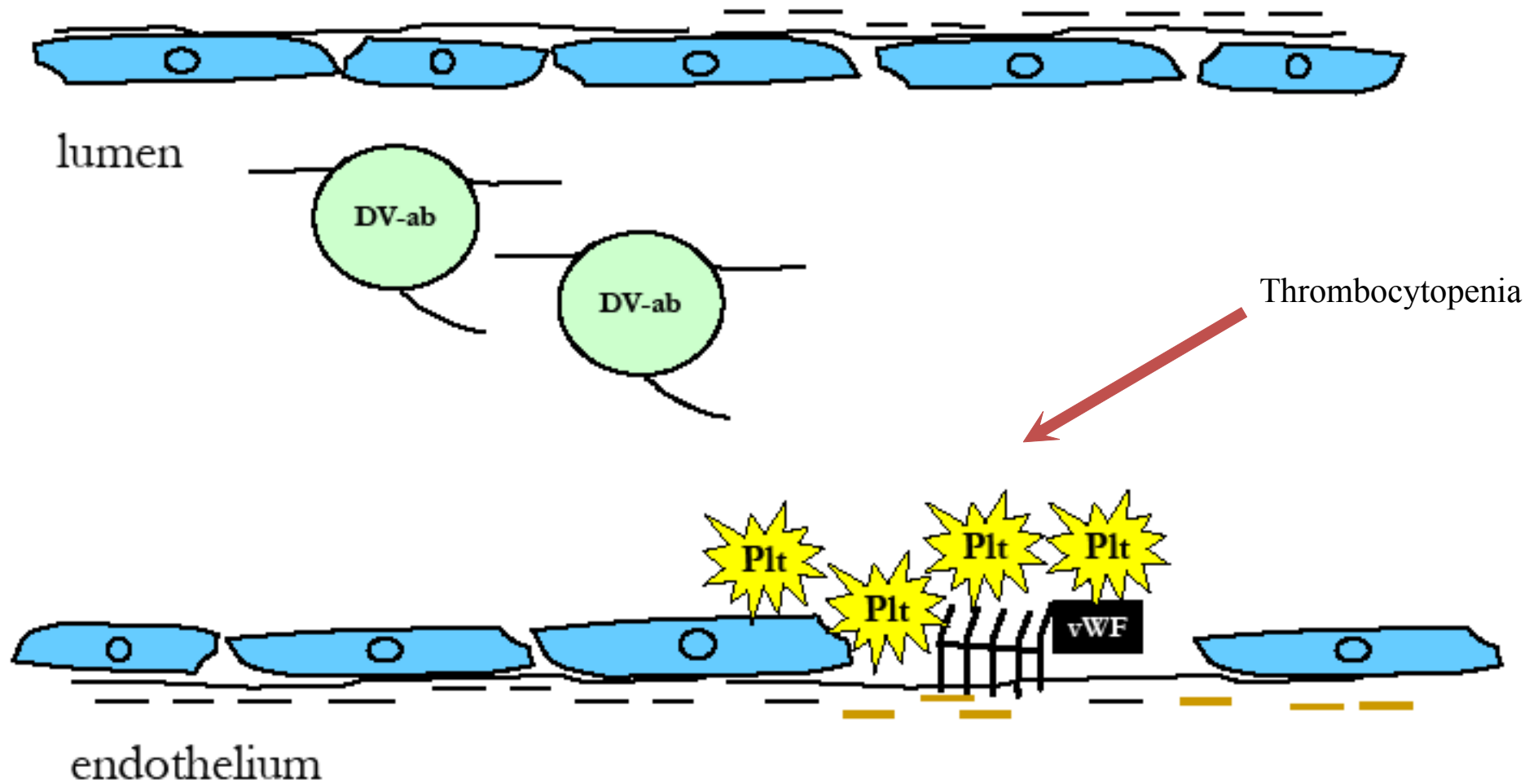
	Dengue 2 virus
	Non-neutralizing antibody
	Complex formed by non-neutralizing antibody and Dengue 2 virus

# Endothelial activation





# Platelet activation



- Impaired and ineffective immune response leads to high level of viremia and the proinflammatory mediators in the late stage of disease plays important role .
- CDC categorized most of these viruses under "category A bioweapon agents" except for dengue virus, CCHF virus and viruses causing renal failure.



**All that are round and spiculated are  
not Dengue**



**Thank you...**