VIRAL HEMORRHAGIC FEVERS

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2nd Yr PG Microbiology

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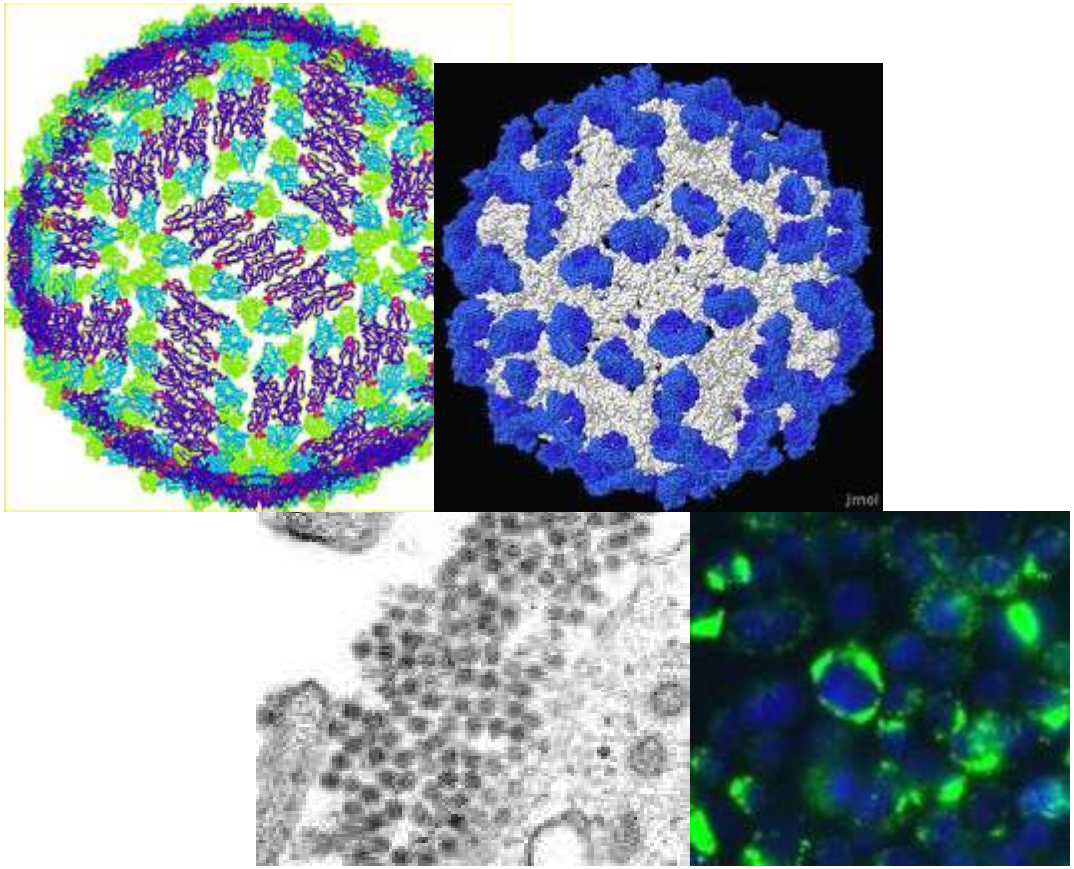
What are Viral Hemorrhagic Fevers (VHFs)?

- 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.



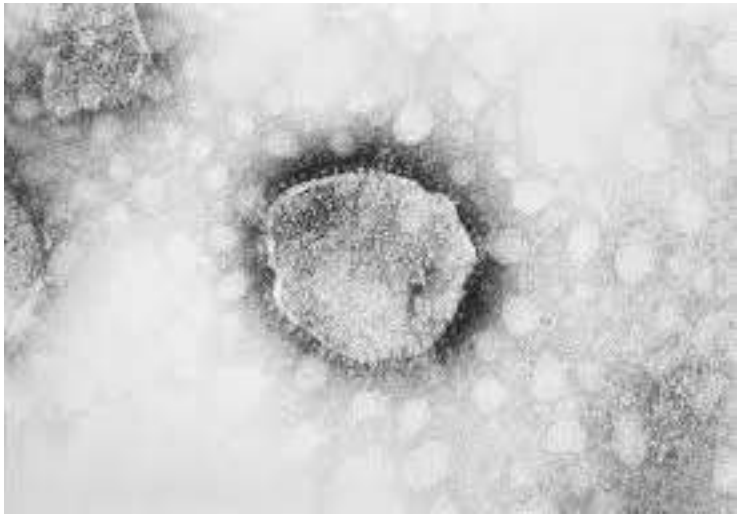
Etiological Agents

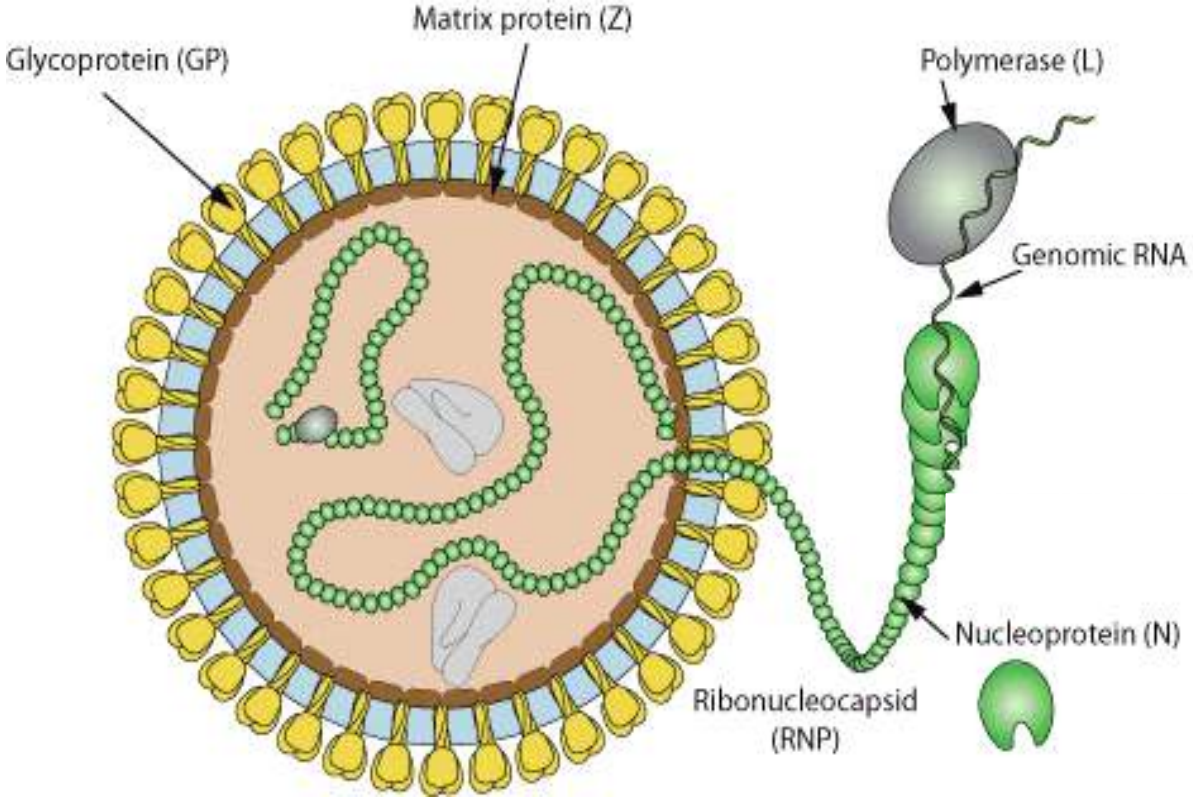
Viral hemorrhagic fever (…contd)

- 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





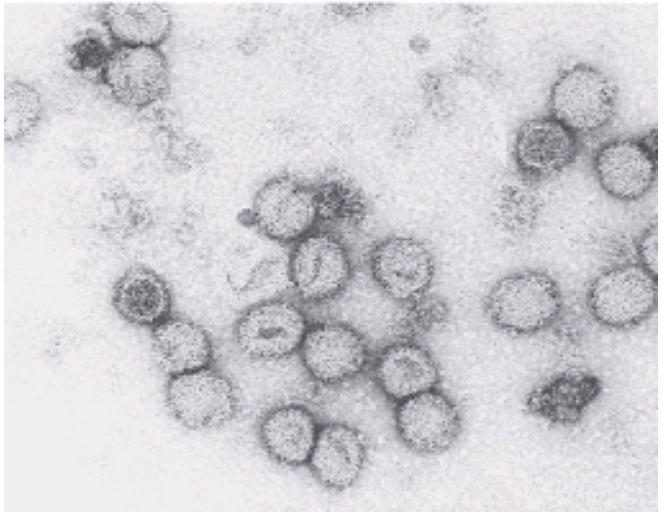
Junin virus
Machupo virus
Guanarito virus
Lassa virus
Sabia virus

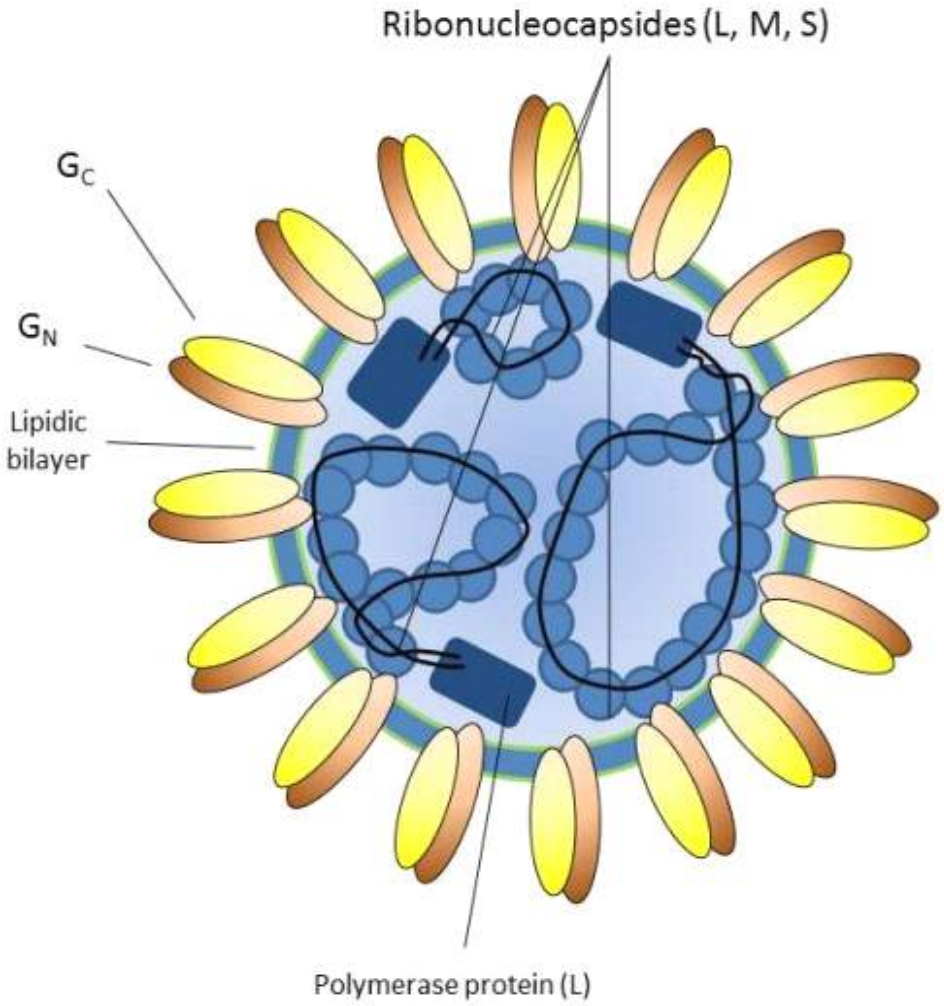
Arenaviridae Transmission

- 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

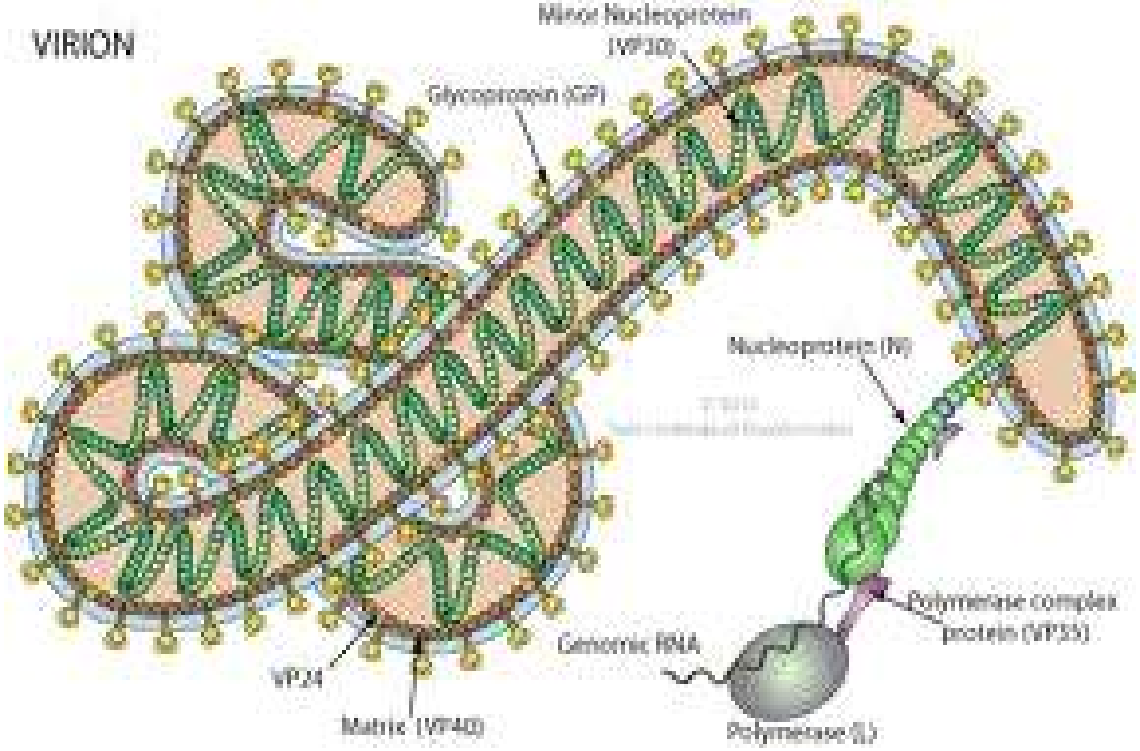
Hantavirus

Bunyaviridae Transmission

- Arthropod vector
  - Exception – Hantaviruses
- RVF – *Aedes* mosquito
- CCHF – Ixodid tick
- Hantavirus – Rodents

- Less common
  - Aerosol
  - Exposure to infected animal tissue

Filoviridae

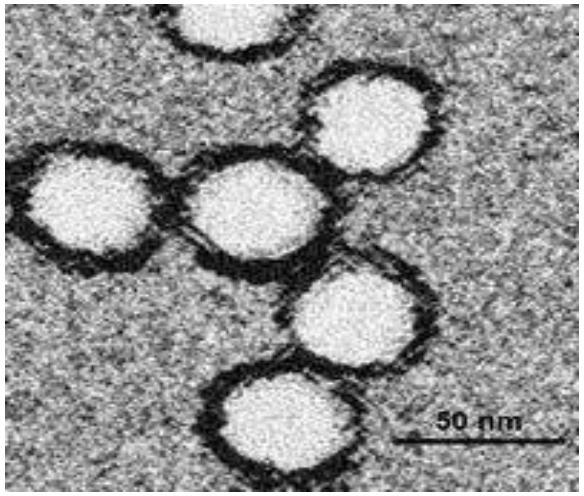


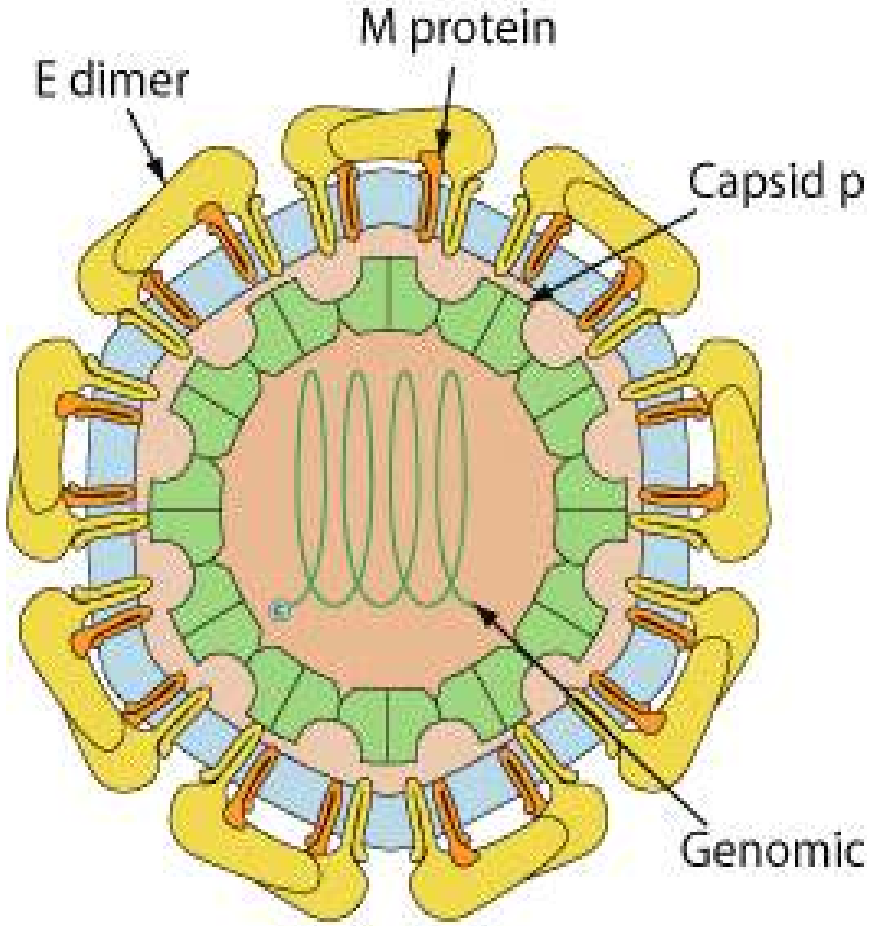
Marburg virus
Ebola virus

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

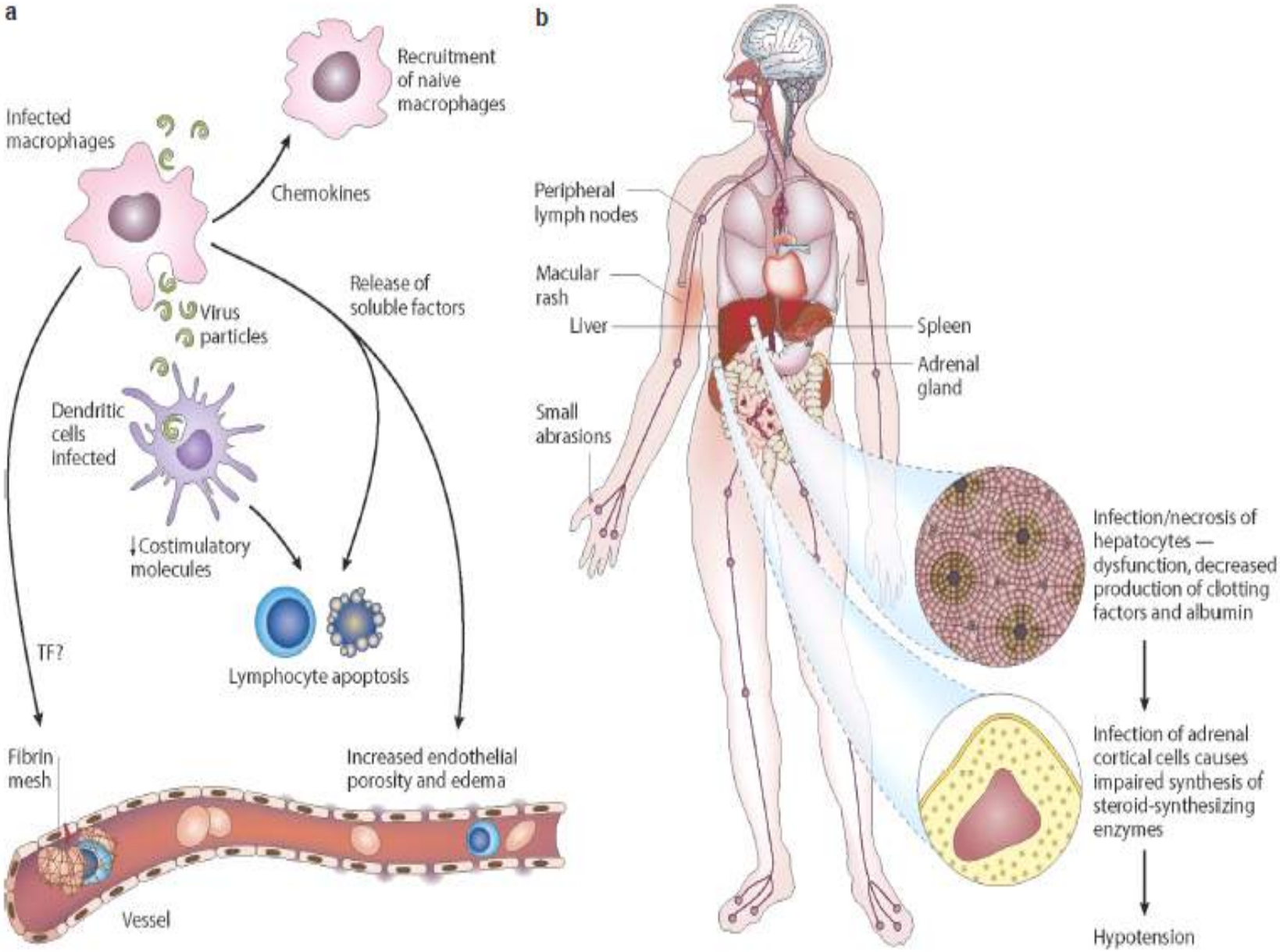
↓

Amplify dysregulated immune response

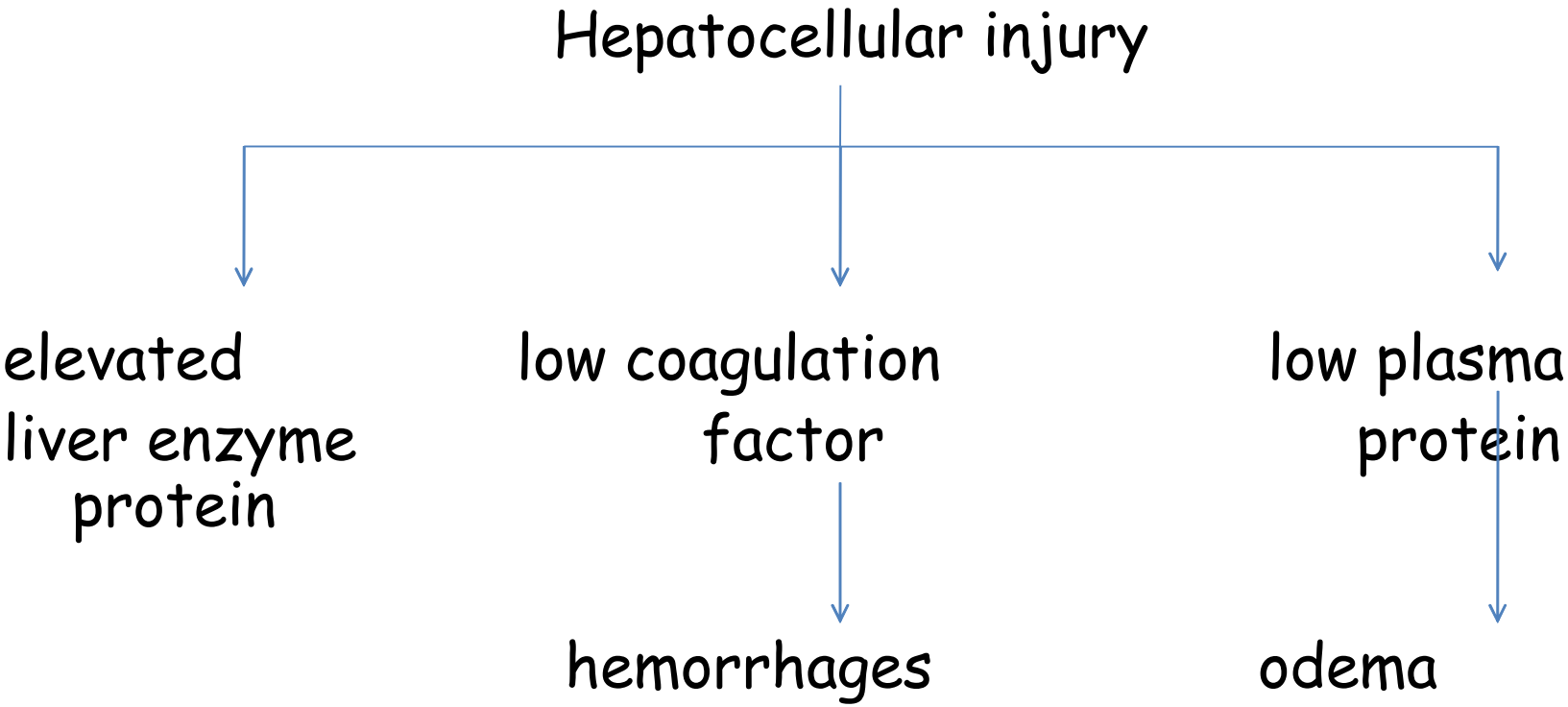
- Immunological mechanism → VASCULAR DAMAGE
- direct infection → VASCULAR DAMAGE

↓

Vascular impermeability


a
Recruitment of naive macrophages
Infected macrophages
Chemokines
Release of soluble factors
Virus particles
Dendritic cells infected
↓Costimulatory molecules
TF?
Lymphocyte apoptosis
Fibrin mesh
Increased endothelial porosity and edema
Vessel
b
Peripheral lymph nodes
Macular rash
Liver
Spleen
Adrenal gland
Small abrasions
Infection/necrosis of hepatocytes — dysfunction, decreased production of clotting factors and albumin
Infection of adrenal cortical cells causes impaired synthesis of steroid-synthesizing enzymes
Hypotension

- 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, pummala, 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 → IL-1, TNF♋, IFN♑
- Renal tubule blocked by cast cells and proteins
- Activation of angiotensin II

Dengue is a scare!!!

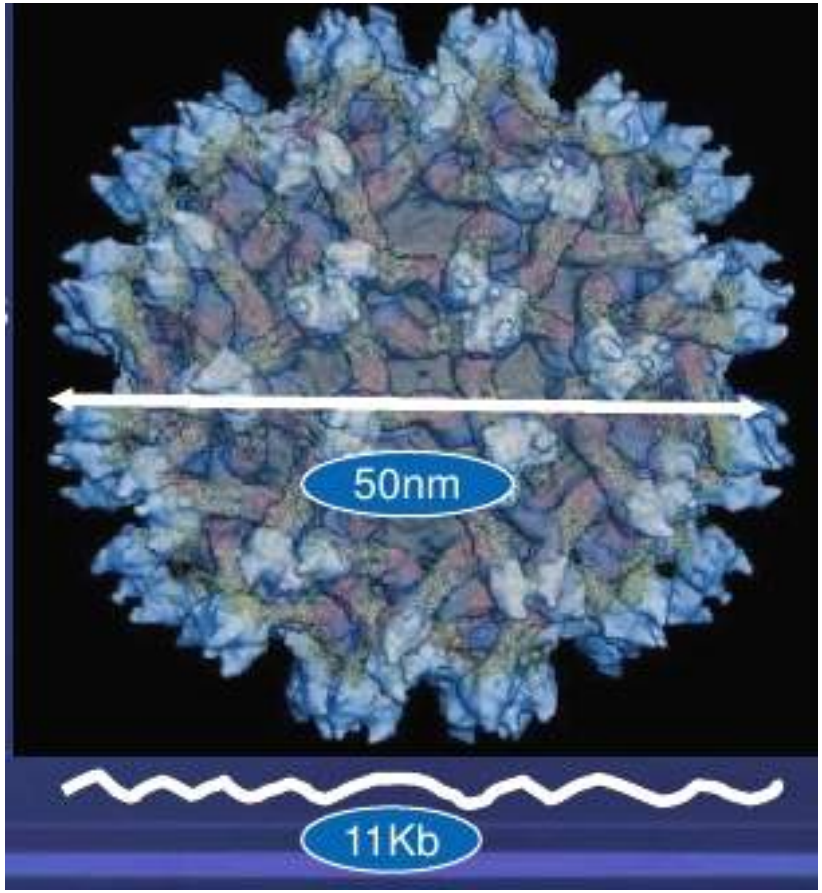
Dengue Virus - Flaviviridae

Infection with one serotype produces life long immunity

DEN 1

4 Serotypes

DEN 2



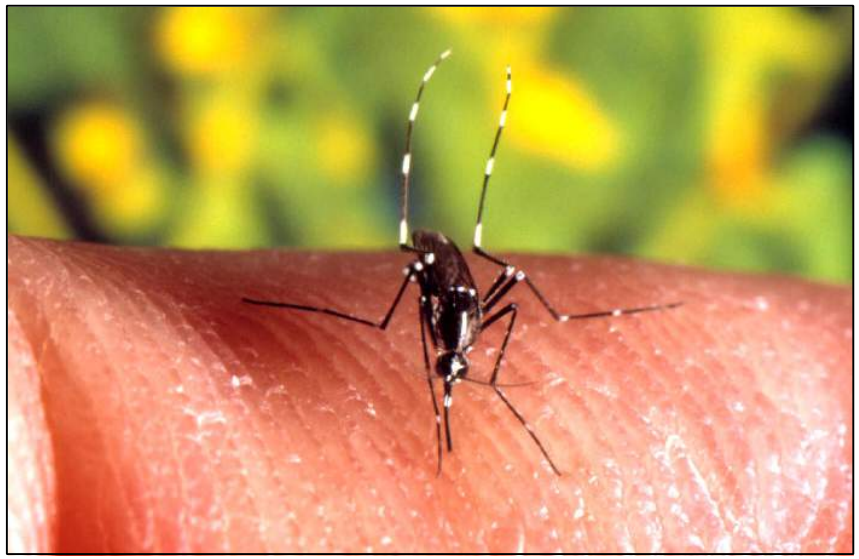
DEN 3

DEN 4

But only temporarily and partial immunity against other types

Vectors – Aedes Mosquito

Aedes albopictus



Aedes aegypti

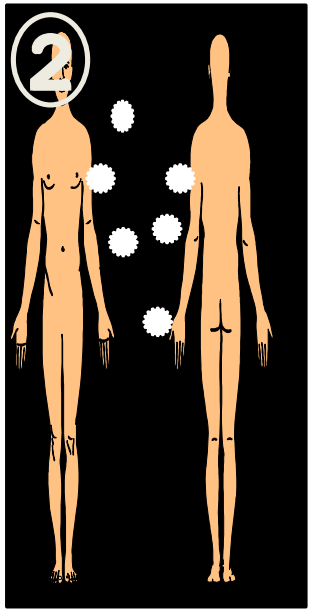
Dengue Transmission

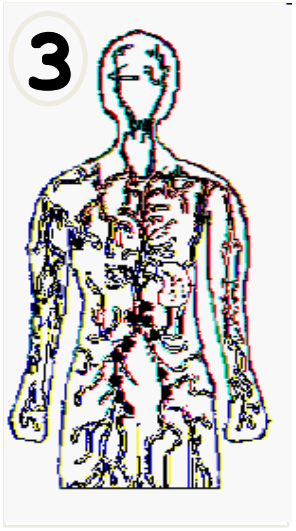
1. Mosquitoes transmit Dengue virus to human dendritic cells.

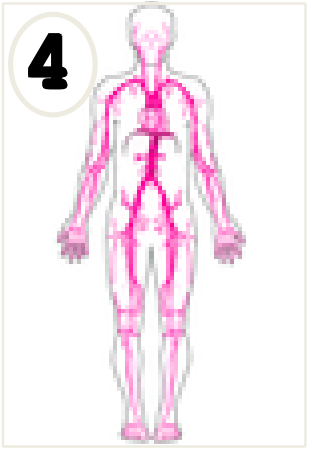
2. Virus targets areas with high WBC counts (liver, spleen, lymph nodes, bone marrow, And glands)

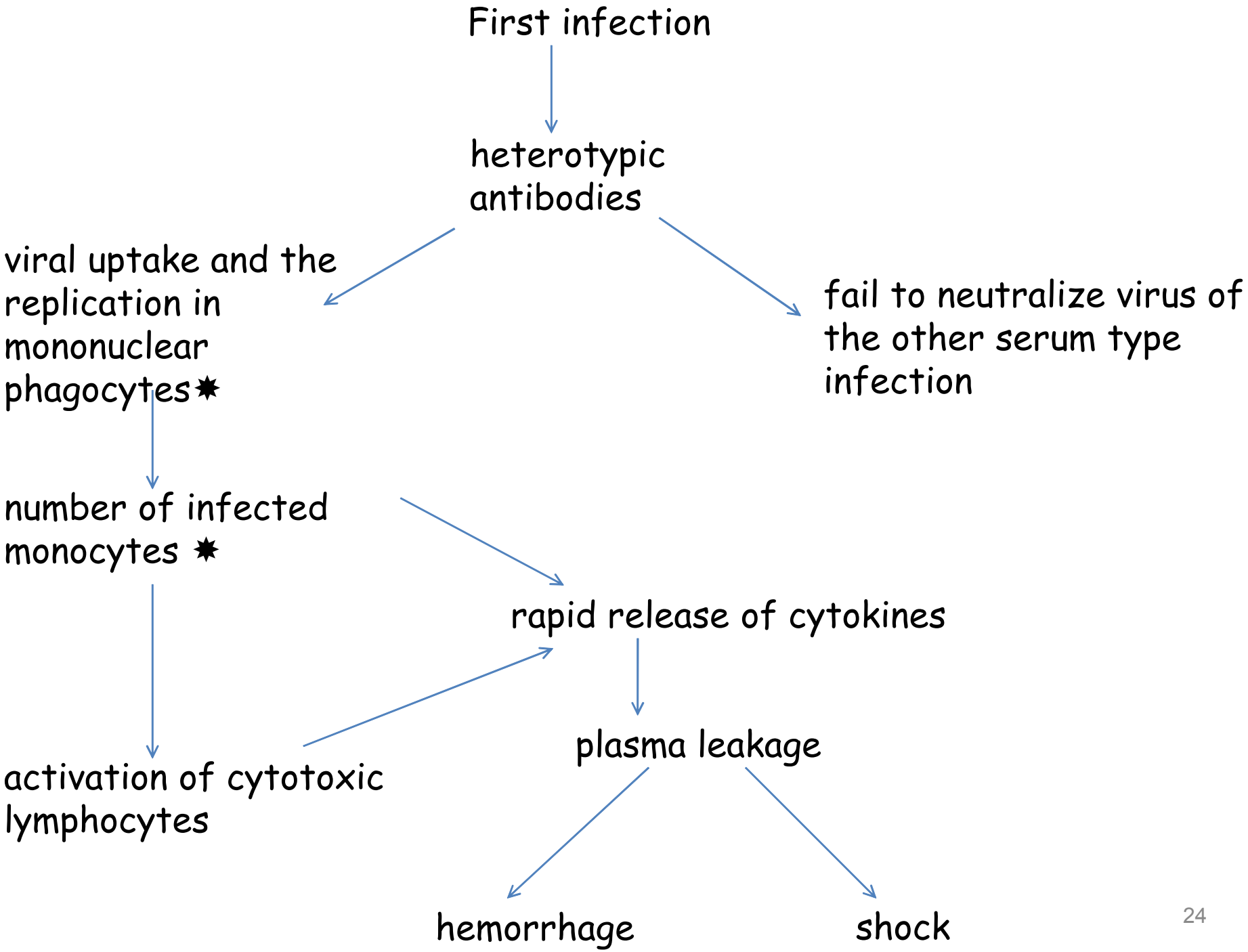
3. Virus enters WBCs & lymphatic Tissue

4. Dengue virus enters blood Circulation.

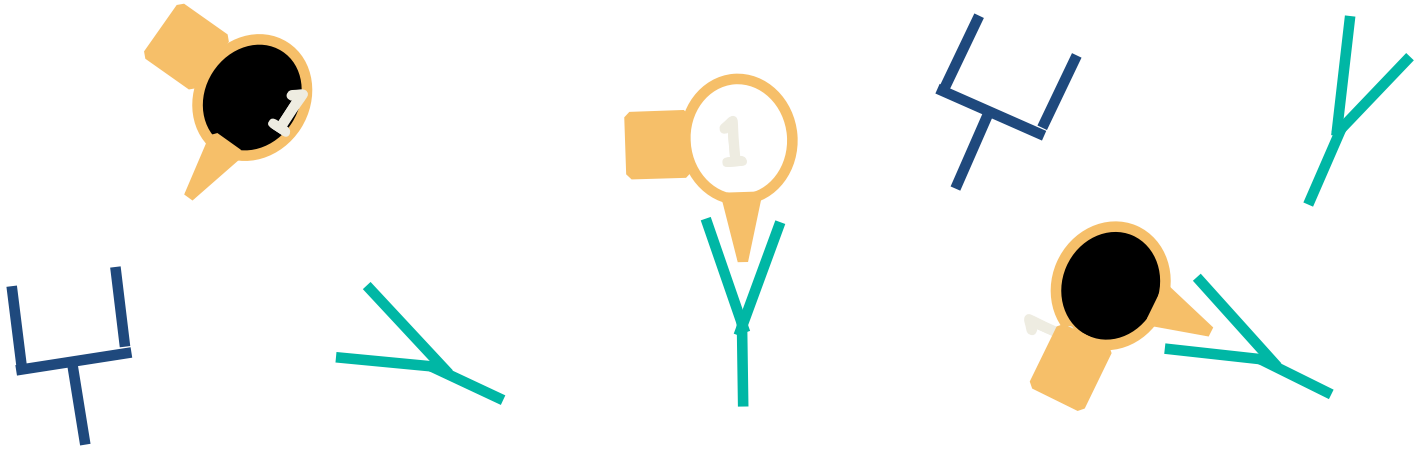







First infection
heterotypic antibodies
viral uptake and the replication in mononuclear phagocytes✸
fail to neutralize virus of the other serum type infection
number of infected monocytes ✸
rapid release of cytokines
plasma leakage
activation of cytotoxic lymphocytes
hemorrhage
shock

Pathogenesis of DHF
STEP 1- Homologous Antibodies Form Non-infectious Complexes



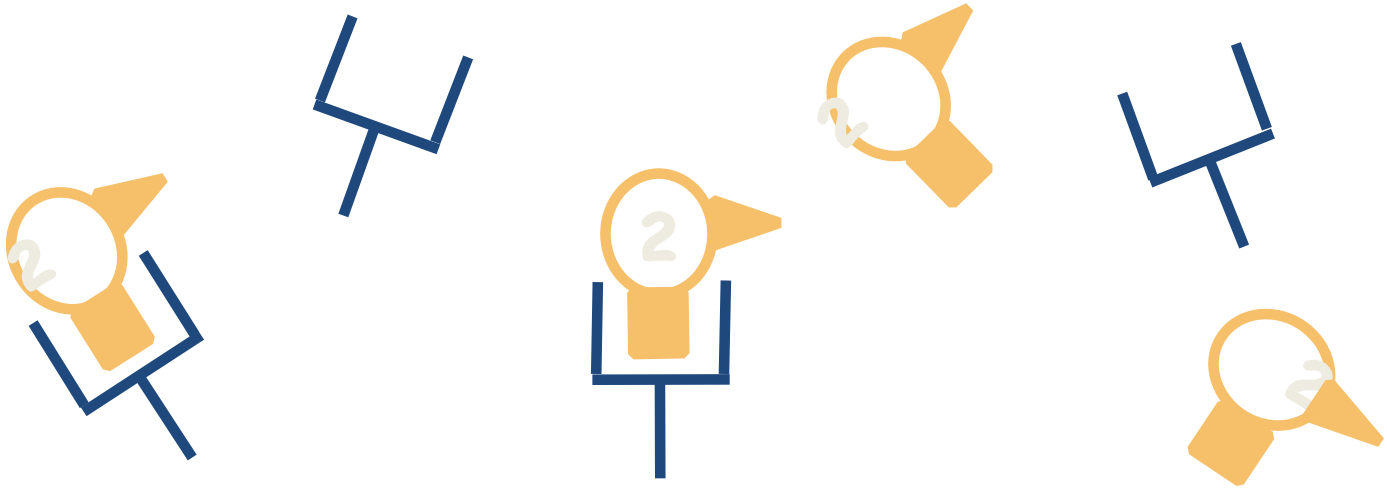
Dengue 1 virus

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

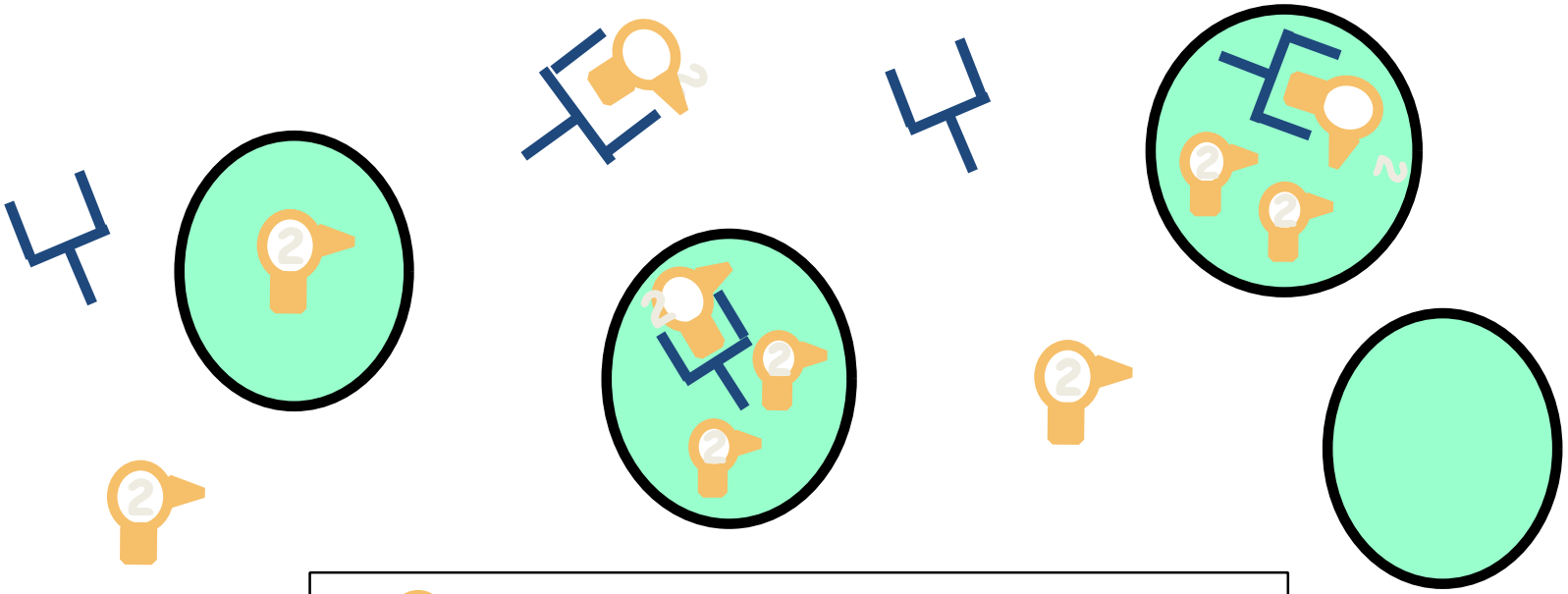


Dengue 2 virus

Non-neutralizing antibody to Dengue 1 virus

Complex formed by non-neutralizing antibody and virus

STEP3 - Heterologous Complexes Enter More Monocytes, Where Virus Replicates

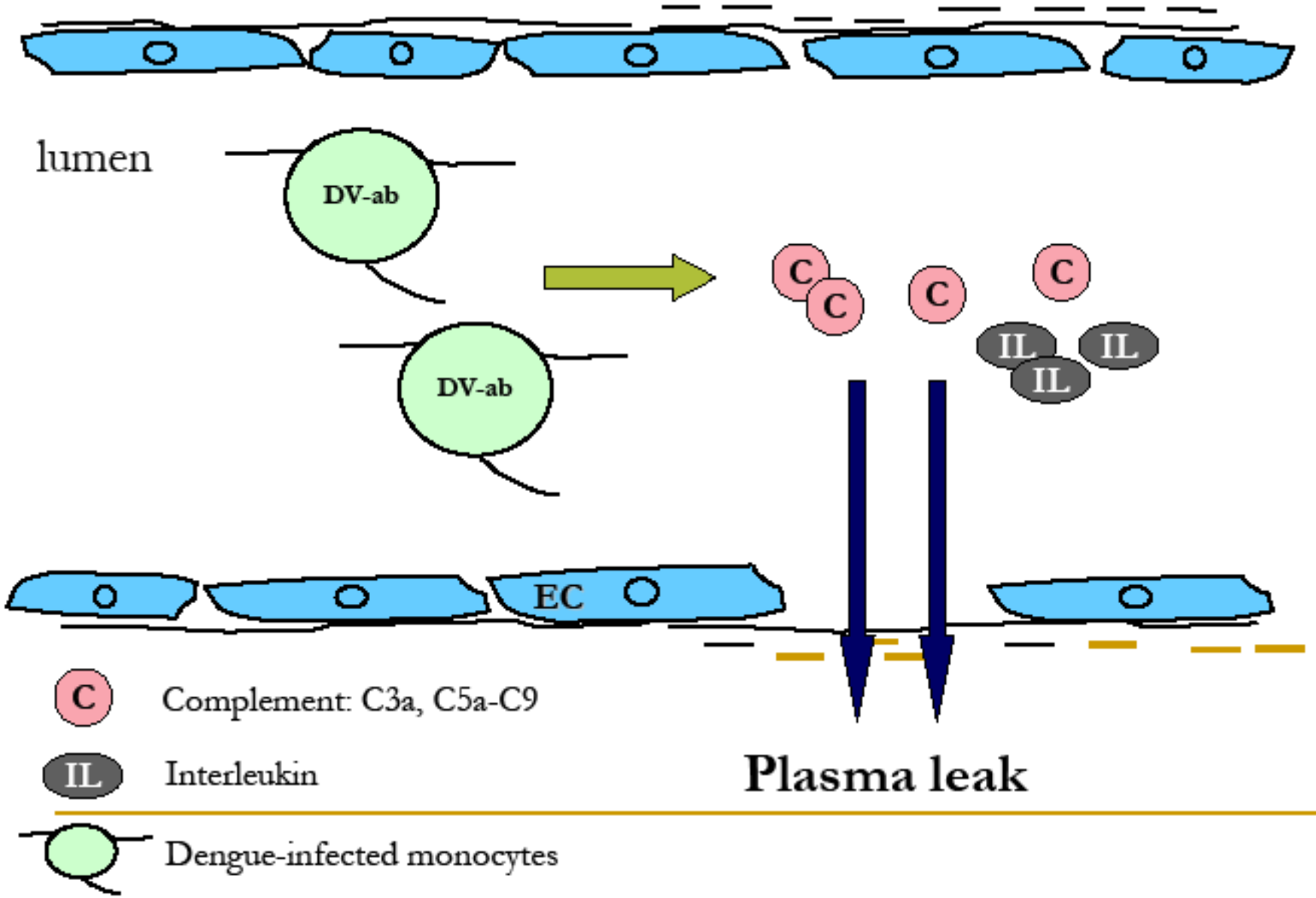


Dengue 2 virus

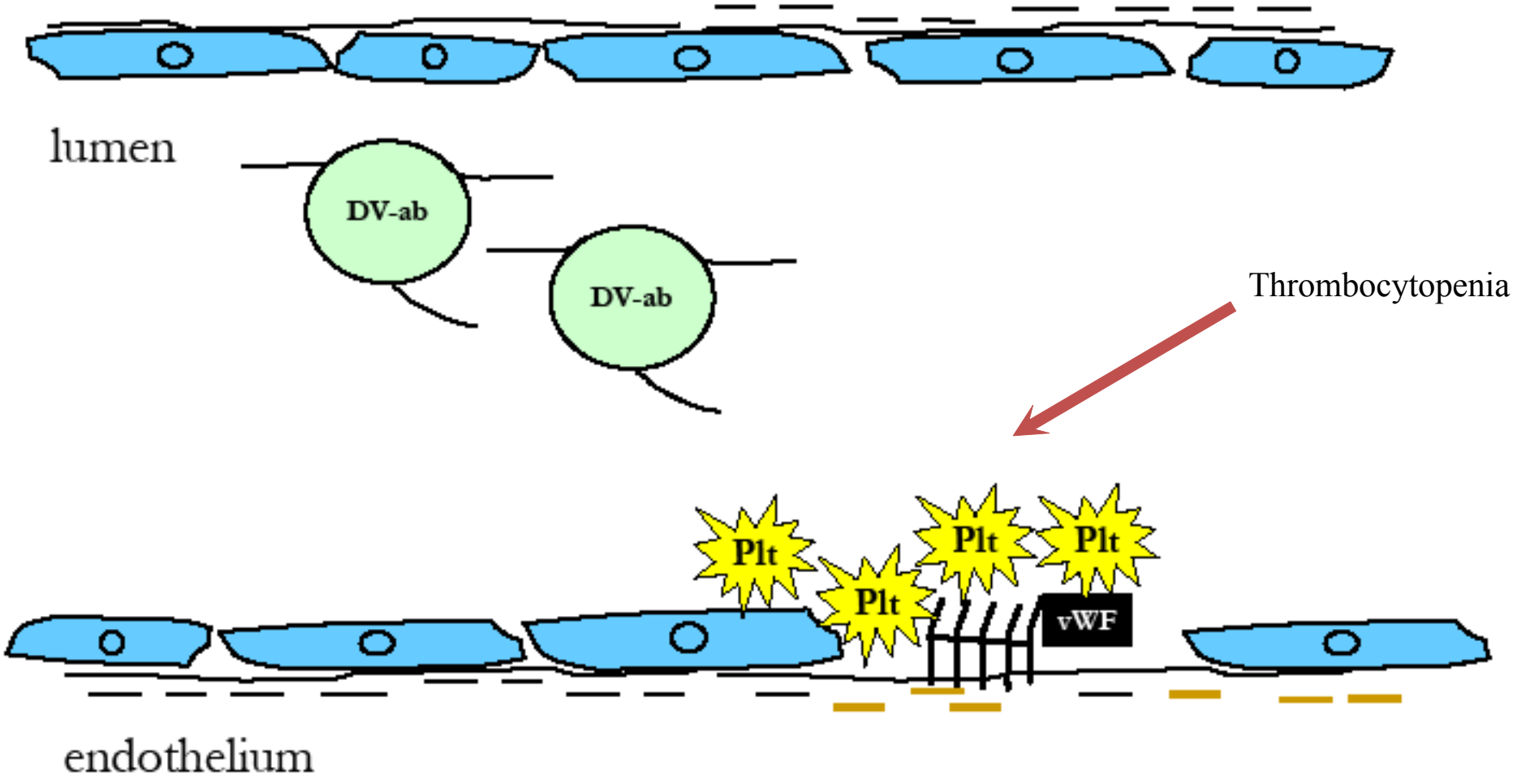
Non-neutralizing antibody

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...