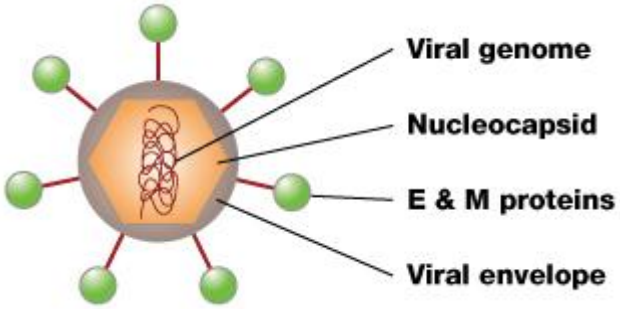
Dengue

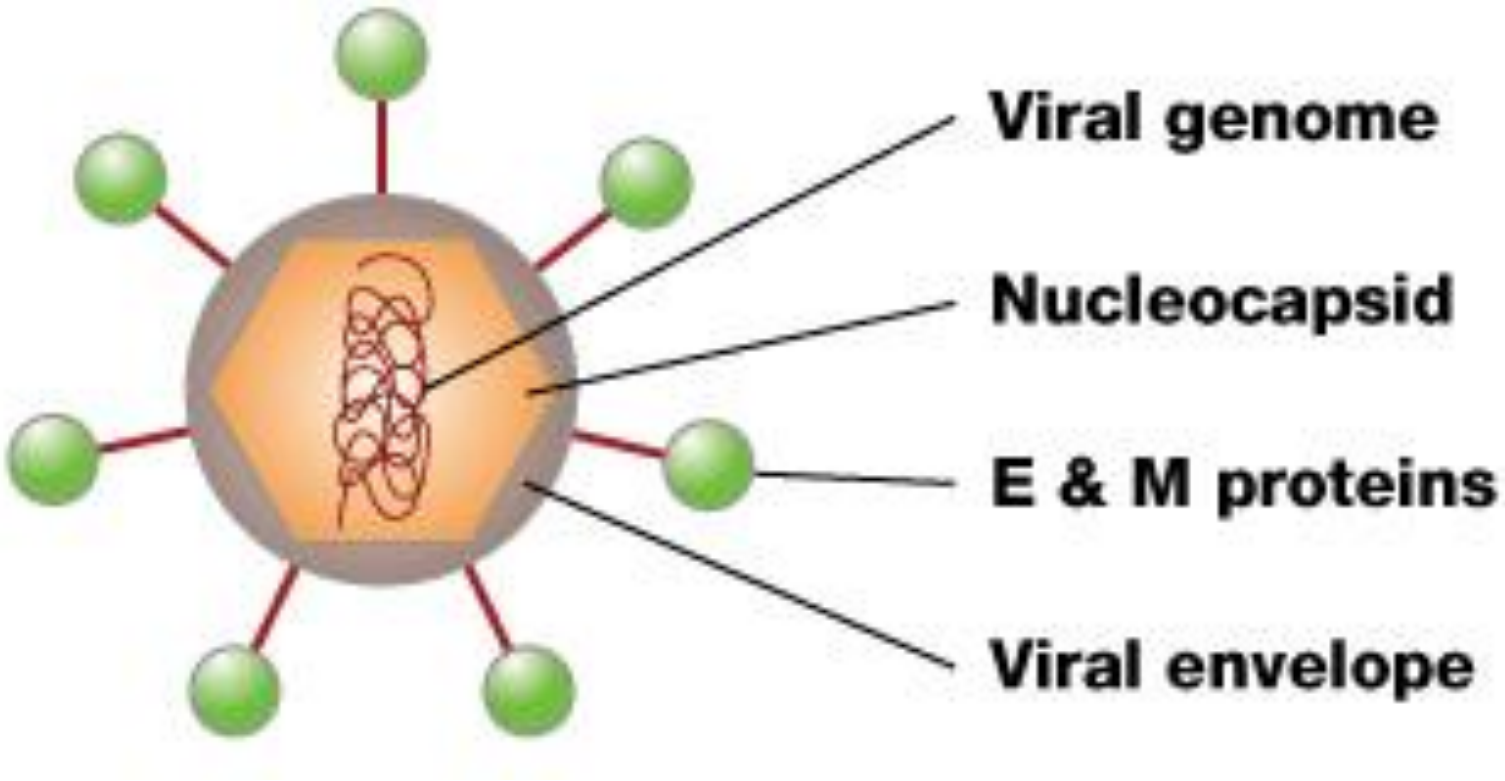
Dengue

- The word Dengue is derived from African word ‘Denga’ that means ‘fever with hemorrhage’.
- Dengue (break bone fever) is a viral infection that spreads from mosquitoes to people.
- It is an Arbovirus of Genus- Flavivirus.



Dengue

Structure of Dengue virus:



Dengue

- Dengue virus, which has 4 distinct serotypes, i.e. DEN-1, DEN-2, DEN-3 and DEN-4.
- Infection with one serotype confers lifelong immunity to that serotype and cross immunity to other serotypes for 2-3 months only.
- Dengue is transmitted by **Aedes aegypti and Aedes albopictus** to human.

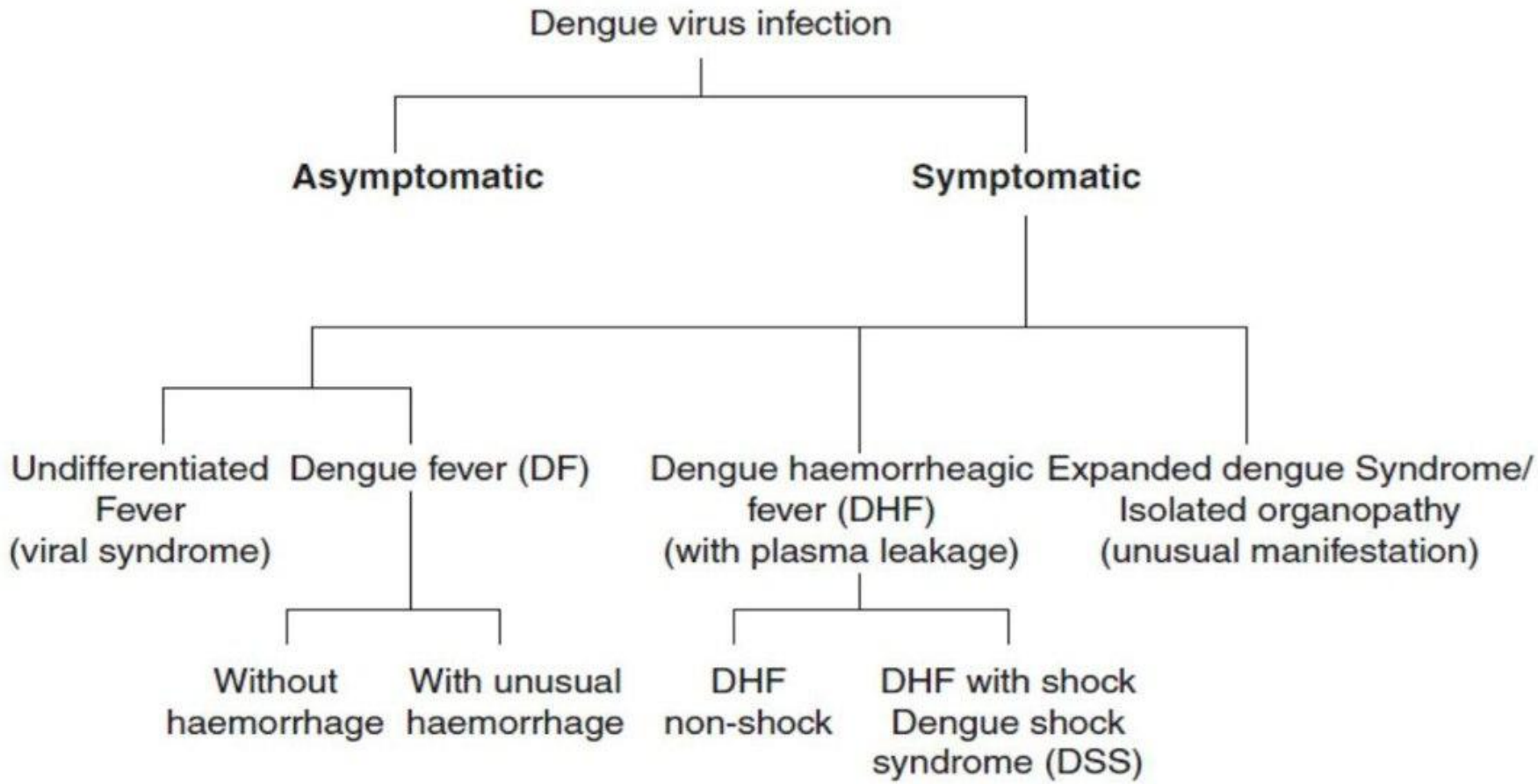


Figure 12: WHO and SEARO 2001 or WHO 1999 criteria for dengue classification. (Source: adopted from WHO criteria for dengue classification)

Asymptomatic Infection

- Majority of infections asymptomatic
- More common in children <15 years
- Minimal or no symptoms
- Contributes to silent transmission

Undifferentiated Fever

- Nonspecific febrile illness
- Mild symptoms, indistinguishable from other viral infections
- Common in primary dengue infection
- Often self-limiting

Classical Dengue Fever (DF)

- High fever (39-40°C, 102-104°F)
- Severe headache, retro-orbital pain
- Myalgia, arthralgia (break-bone fever)
- Rash, leucopenia, thrombocytopenia
- Occasionally unusual hemorrhages

(e.g., GI bleeding, hypermenorrhea, massive epistaxis)

Dengue Fever - Fever Characteristics

- Sudden onset, high-grade, continuous
- Temperature: 39-40°C (102-104°F)
- Biphasic pattern, lasts 2-7 days
- Associated symptoms: Flushing, nausea, myalgia

Dengue Fever - Rash Characteristics

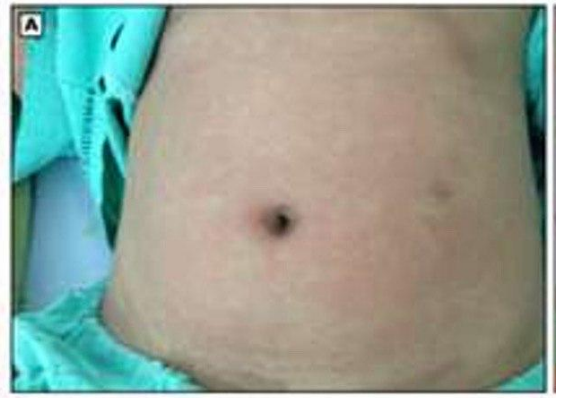
Febrile Phase (Days 2-3):

- Diffuse flushing or blanching erythema.
- Affects face, neck, chest.

Days 3-4:

- Maculopapular or rubelliform rash.
- Afebrile/Defervescence:
- Confluent erythematous/petechial rash.
- “Isles of white in a sea of red” on feet, legs, hands.
- Often pruritic.

Rash in dengue fever



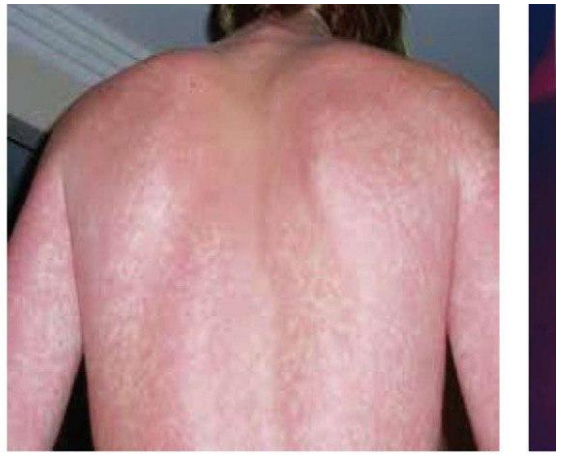


Figure13: Isles of White in the Sea of Red.

Warning signs of dengue fever:

- Intense continuous abdominal pain or pain when palpating abdomen.
- Persistent vomiting (≥3 episodes in 1 hr or ≥4 in 6 hrs).
- Fluid accumulation (pleural effusion, ascites, or pericardial effusion.
- Mucosal bleeding (gums, nose, vagina [metrorrhagia or hypermenorrhea], kidney [macroscopic hematuria])
- Altered mental status (irritability, drowsiness, GCS score <15)
- Hepatomegaly (≥2cm below costal margin)
- Progressive increase of the hematocrit (in at least 2 consecutive measurements taken 6 hours apart

Dengue Haemorrhagic Fever (DHF)

- Small proportion of cases progress to DHF
- Hallmarks: Plasma leakage, abnormal hemostasis
- Risk of Dengue Shock Syndrome (DSS) if severe
- Occurs around defervescence (fever settling)

Dengue Haemorrhagic Fever (DHF)

Phases of DHF:

1. **Febrile phase**: High fever (3–5 days), mild hemorrhage.
2. **Critical phase**: Plasma leakage (days 4–5), defervescence.
3. **Convalescent phase**: Recovery, reabsorption.

Optional: Equilibrium phase in some cases

Febrile Phase

- Fever: 39–40°C, lasting 3–7 days
- Symptoms: Myalgia, headache, nausea, vomiting
- Late febrile phase: Leucopenia (WBC<5000 mm^3) and mild thrombocytopenia(<150,000/mm^3).
- Tender hepatomegaly, significantly elevated transaminases indicate possibility of developing DHF.

Critical Phase (Leakage Phase)

- Onset: Around day 4–5 with defervescence
- Plasma leakage due to capillary permeability. Leads to hemoconcentration.
- Evidence: Rising hematocrit >10% is suggestive, >20% is indicative of severe form.
- Risk of shock if leakage severe.
- Ascites or pleural effusion.

Convalescent Phase

- Resolution of fever, improved appetite
- Diuresis, reabsorption of leaked fluid
- Risk of fluid overload if mismanaged

Dengue Shock Syndrome (DSS)

Clinical Signs

- Cool extremities, cyanosis, delayed capillary refill
- Tachypnoea or Kussmaul’s breathing
- Tachycardia, weak pulse, narrow pulse pressure (≤20 mmHg)
- Hypotension: <80 mmHg (<5 yrs) or 80–90 mmHg (older)
- Reduced urine output, lethargy/restlessness

Dengue Shock Syndrome (DSS)

Classification

- Compensated Shock: Pulse pressure ≤20 mmHg
- Decompensated Shock: SBP <90 mmHg or >20% drop, mean BP <60 mmHg
- Profound Shock: BP and pulse unrecordable

Expanded Dengue Syndrome (EDS)/ Isolated Organopathy

- Introduced by WHO in 2011 to describe rare dengue manifestations
- Involves severe damage to liver, kidneys, bone marrow, heart, or brain

High-Risk Groups

- Pregnant women, infants, elderly
- Patients with coronary artery disease, hemoglobinopathies, or immunocompromised status.

Expanded Dengue Syndrome (EDS)/ Isolated Organopathy

Key Features

- Organ impairment without fluid leakage
- Does not classify as DHF unless prolonged shock is present.

Management

- Organ-specific treatment required
- Not applicable if DHF complications arise from shock

Laboratory Tests for Diagnosis

- NS1 antigen: Detects early infection (days 1–3)
- IgM/IgG serology: Confirms recent/past infection.
- IgM- after day 5.
- IgG- after day 9.
- PCR: Identifies serotype, highly specific. Positive Within 5 days of onset of symptoms.

Biochemical Tests

- Liver function: Elevated ALT, AST. If severe, levels may rise 5-15 folds upwards.
- Serum Albumin: <3.5 gm/dl indicates plasma leakage.
- Renal function: Serum creatinine, urea. Elevated in shock.
- Electrolytes: Sodium, potassium imbalances

Coagulation Profile

- Prolonged PT, aPTT
- Reduced fibrinogen
- Indicators of coagulopathy and bleeding risk.

Other Tests

- Chest X-ray: Pulmonary edema
- Ultrasound: Pleural effusion, ascites
- ECG: Arrhythmias in severe cases
- Urine R/M/E: Albuminurea, hematuria
- CSF: in dengue encephalitis

Timing and Frequency of Investigations

- Within first 5 days: CBC, haematocrit, dengue NS1 antigen, ALT, AST.
- Daily CBC, hematocrit during critical phase
- Repeat coagulation profile if bleeding suspected
- Ultrasound: As needed for plasma leakage

Chikungunya Fever

Introduction

- Chikungunya fever is a re-emerging viral illness caused by Chikungunya virus (CHIKV).
- It belongs to genus alphavirus in the Togaviridae family.
- The name 'Chikungunya' comes from the Makonde word 'kungunyala', meaning 'to bend up', referring to the bent posture caused by severe joint pain during the illness.

Epidemiology – Bangladesh & Global

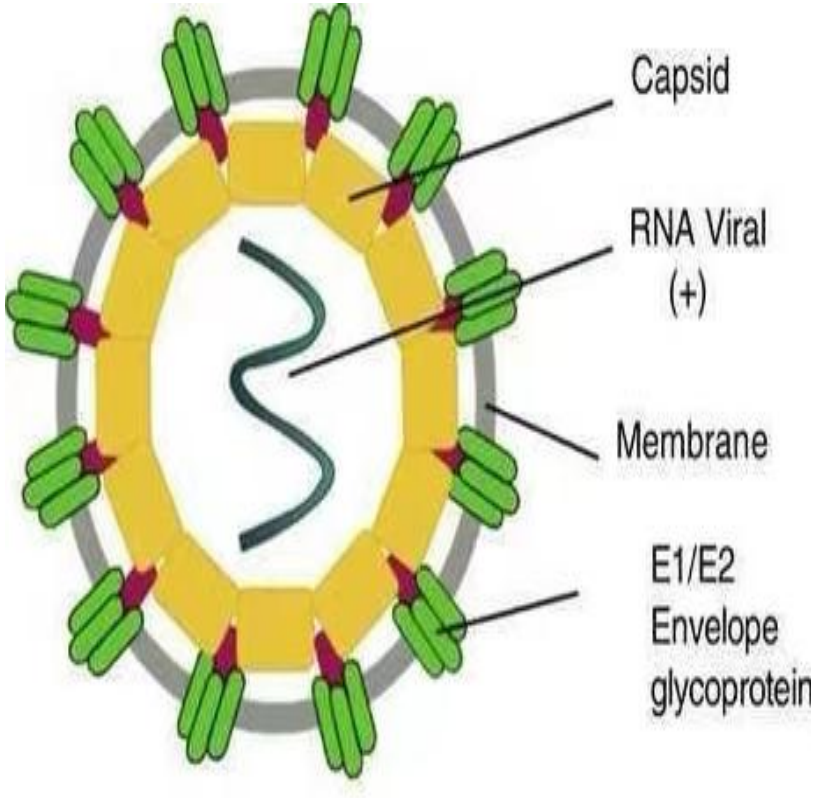
- First identified: Tanzania, 1952.
- Global outbreaks: India, Thailand, Southeast Asia.
- Chikungunya fever in Bangladesh
  - First reported in Bangladesh: 2008.
  - Outbreaks: 2009, 2011, 2012, major in 2017 (13,176 cases)
  - Re-emerged in Dhaka, October 2024 (Nasif et al., 2025).
  - Current Strain: ECSA genotype with E1-K211E mutation.
  - This mutation enhances transmission by Aedes aegypti.

Structure

- **Genome:** Single-stranded, **positive-sense RNA (~11.8 kb)**
- **Capsid:** Icosahedral
- **Envelope:** Lipid bilayer derived from host cell membrane
- **Structural proteins:**

  -Capsid protein (C) – forms the nucleocapsid

  -Envelope glycoproteins (E1 & E2)– essential for host cell attachment and membrane fusion. They form heterodimeric spikes on the virion surface.
- **Non-structural proteins** (nsP1–nsP4): Involved in viral replication
- **Replication site:** Cytoplasm of host cells.



Transmission

- **Primary vector: *Aedes aegypti, Aedes albopictus*** (day-biting)
- Rare modes: Vertical transmission, blood transfusion, organ transplant

Since it is transmitted by arthropods- namely mosquitoes—chikungunya is classified as an **arbovirus** (arthropod-borne virus).

During outbreaks, humans act as the primary reservoir for chikungunya, enabling transmission to mosquitoes due to high viremia in the early acute phase.

In inter-epidemic periods, non-human vertebrates—including primates and birds—may serve as secondary reservoirs, sustaining viral circulation in nature.

Clinical Manifestations

The incubation period is about 5 days (3–7 days)

Acute stage: up to 3 weeks.

- Fever
- Severe joint pain (worsens in the morning): bilateral, symmetric, migratory, and affects small wrist and ankle joints with swelling.
- Headache
- Nausea/ vomiting
- Muscle pain
- Tenosynovitis
- Morbilliform (measles-like) skin rashes

Clinical Manifestations

- **Subacute cases:** Fatigue and articular symptoms between 21 and 90 days after symptom onset.
- **Chronic stage**: For some (10–15%), the arthralgia can persist for months or years with debilitating polyarthralgia and polyarthritis.

Rare **complications** include: uveitis, retinitis, myocarditis, hepatitis, nephritis, bullous skin lesions, hemorrhage, meningoencephalitis, myelitis, Guillain-Barré syndrome, and cranial nerve palsies.

Mortality is rare and occurs mostly in older adults. Persons at risk for severe disease include: Newborn, older adults (≥65 years), persons with underlying hypertension, diabetes, or heart disease.

Diagnostic Approaches for Chikungunya

1. **Viral Isolation:**
   - Performed in mosquito cell lines
   - Most effective within 0–7 days of symptom onset
   - Limited to reference laboratories
   - Requires 1–2 weeks for results
2. **Serological Testing:**
   - **IgM antibodies** detectable after 4 days; persist for ~3 months
   - **IgG antibodies** appear after 2 weeks; may persist for years
   - A **fourfold rise in IgG** or presence of **IgM** indicates recent infection
   - Methods: **MAC-ELISA**, standard **ELISA**, or **rapid tests (ICT)**

Diagnostic Approaches for Chikungunya

3. Molecular Testing:

- Reverse-transcriptase PCR (RT-PCR) allows early and specific detection of viral RNA

4. Hematological Findings:

- **Leukopenia** with lymphocyte predominance
- Occasionally **thrombocytopenia**
- Elevated **ESR** and **C-reactive protein (CRP)** levels

Treatment

- **No specific antiviral treatment** is currently available.
- Supportive care remains the mainstay:
  - Adequate Hydration
  - Rest
  - Pain and fever management using paracetamol (acetaminophen)
- Avoid NSAIDs (e.g. ibuprofen, aspirin) until dengue is ruled out due to the risk of bleeding.
- Vaccination- Two chikungunya vaccines have received regulatory approval in select countries. However, they are not yet widely available or in general use.

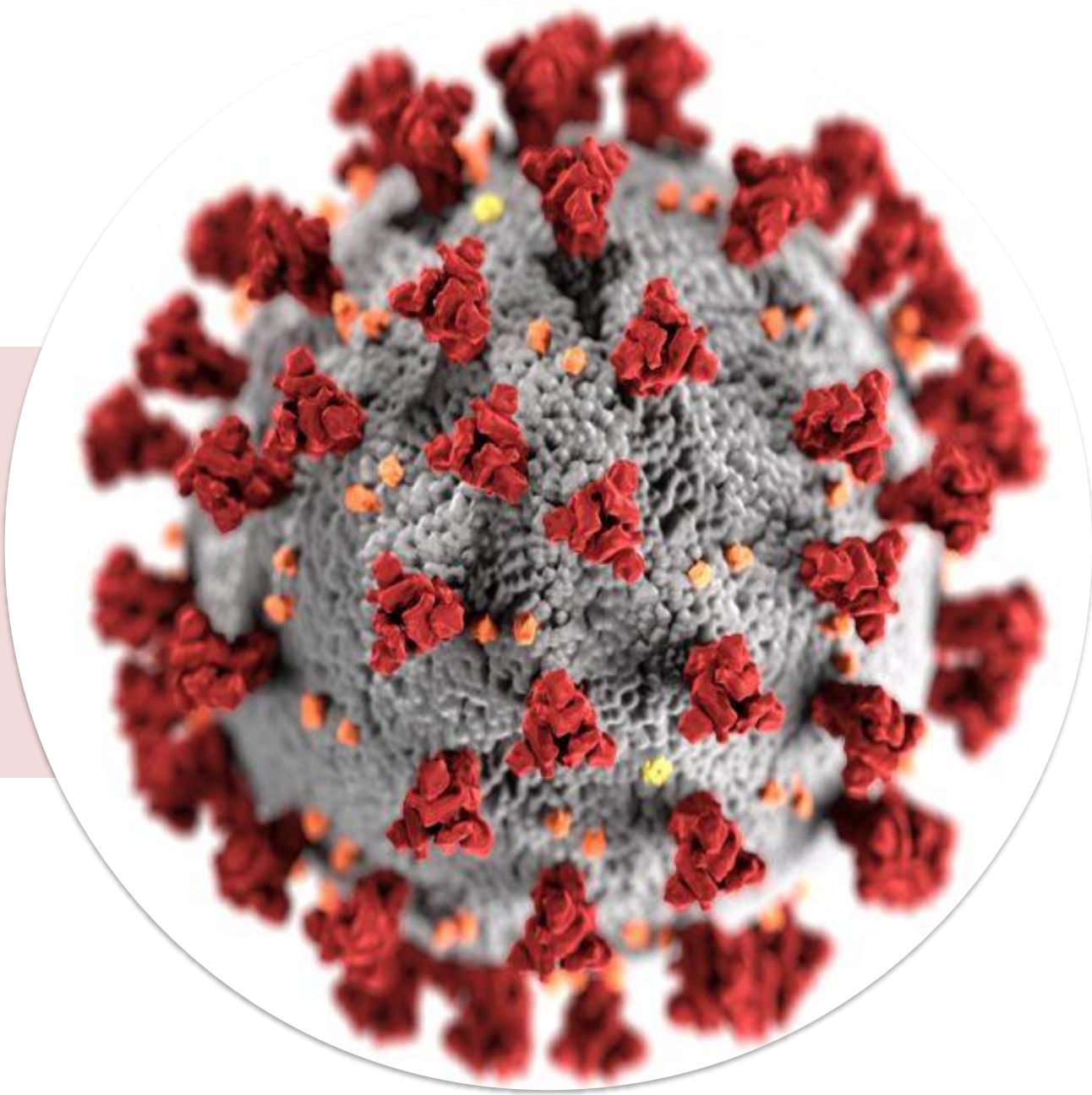
Prevention

- **Source Control:** Weekly elimination of Aedes breeding sites through community-led water container management and solid waste disposal is essential.
- **Vector Control**: Use of adulticides, larvicides, and residual insecticides during outbreaks reduces mosquito density and transmission risk.
- **Personal Protection:** People in affected areas should wear clothing that covers the skin, use window and door screens, and apply mosquito repellents containing DEET, IR3535, or icaridin according to instructions.
- **Infected Case Management:** CHIKV-suspected individuals must avoid mosquito exposure during the first 7 days to interrupt human–mosquito–human transmission.
- Insecticide-treated mosquito nets should be used to protect children, elderly, and bedridden individuals sleeping during the day.

Comparison of Clinical Manifestations: Chikungunya vs Dengue

Feature	Chikungunya	Dengue
Fever (onset, duration)	Acute onset, 2–4 days	Gradual onset, 5–7 days
Polyarthritis	Frequent; may last >1 month	Less common; short duration
Tenosynovitis	Common	None
Rash	Day 1–4; maculopapular	Day 3–7; petechiae or maculopapular
Myalgia	Possible	Common
Leukopenia	Common	Infrequent
Thrombocytopenia	Infrequent	Common
Retro-orbital pain	Rare	Common
Hypotension and shock	Possible	Common
Minor bleeding	Rare	Common
Hematocrit	Normal	Increased

Corona virus



- Corona viruses are enveloped, carrying petal or club-shaped or crown-like peplomer spikes giving the appearance of solar corona.
- They are large (120–160 nm) spherical viruses having a helical symmetry
- They possess linear, positive-sense ssRNA of 26 to 32 kbp size, largest among the non-segmented RNA viruses.
- Family: Coronaviridae; Subfamilies: Coronavirinae (α, β, γ, δ genera), Torovirinae.

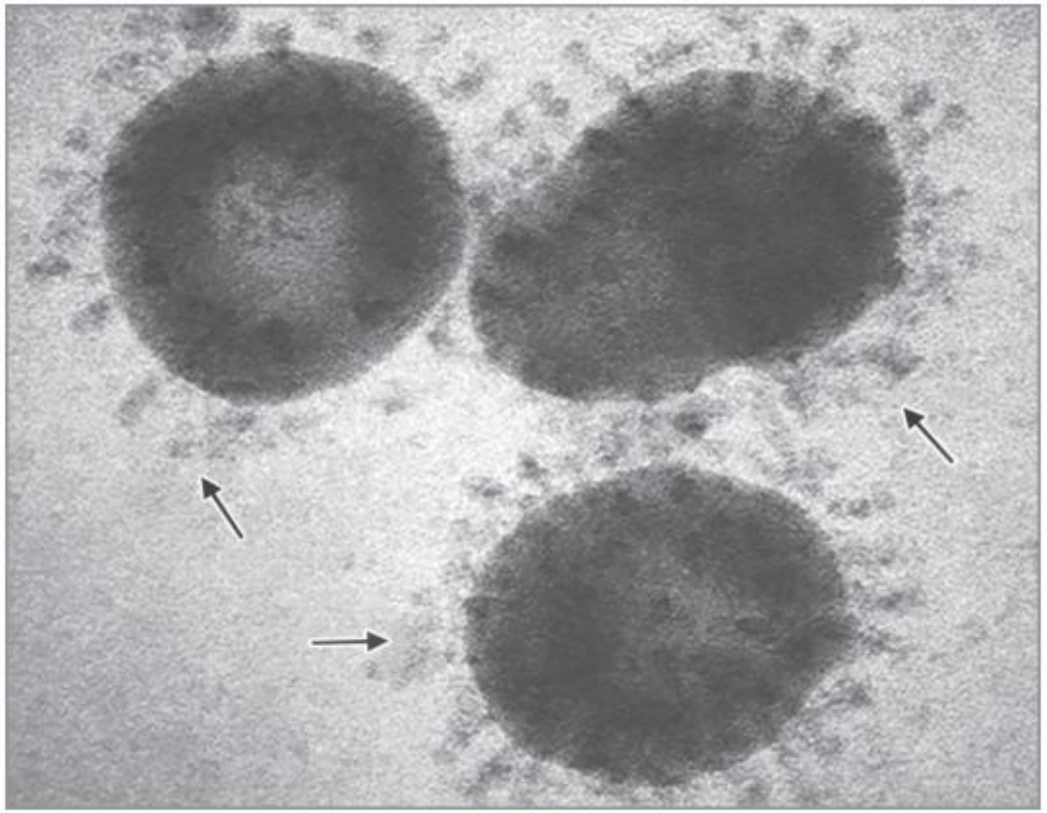


Fig. 67.1: Electron micrograph of coronavirus (petal or club-shaped peplomers) (arrows showing).

Human coronaviruses

There are **seven** recognized coronaviruses that are known to cause **human infections**. Coronaviruses that that are widespread in distributionand **cause mild upper respiratory tract infections** are:

1. Human coronavirus 229E
2. Human coronavirus NL63
3. Human coronavirus OC43
4. Human coronavirus HKU1

Coronaviruses that **caused explosive outbreaks of severe respiratory disease** with higher mortality are:

5. SARS-CoV (Severe acute respiratory syndrome coronavirus)
6. MERS-CoV (Middle East respiratory syndrome coronavirus)
7. SARS-CoV-2 (Severe acute respiratory syndrome coronavirus-2)- COVID-19

SARS-CoV (2003)

- Origin: China; spread to 29 countries
- Reservoirs: Civets, raccoon dogs, possibly bats
- Transmission: Respiratory droplets, contact
- Symptoms: Fever, myalgia, cough, dyspnea, pneumonia
- Outcomes: ~8,098 cases, 774 deaths (9.6% CFR)

MERS-CoV (2012)

- Origin: Saudi Arabia; zoonotic from camels
- Reservoirs: Camels (intermediate), bats (primary)
- Transmission: Zoonotic and limited human-to-human
- Symptoms: Fever, cough, dyspnea, GI symptoms
- Outcomes: ~2,519 cases, 858 deaths (~34.3% CFR)

SARS-CoV-2

First Identified: December 2019, Wuhan, China

Origin: SARS-CoV-2 is a Betacoronavirus, sharing approximately 96% genome similarity with bat coronaviruses. While the natural reservoir is believed to be bats, the exact intermediate host remains uncertain. Early studies have suggested possible roles for pangolins, civets, or other wild mammals commonly found in live animal markets.

Transmission Routes: Respiratory droplets (primary mode), Contact transmission (direct/indirect via fomites), Aerosols during medical procedures

Global Impact : Declared a Public Health Emergency of International Concern (PHEIC) on 30 Jan 2020 and a pandemic on 11 March 2020. Reached over 200 countries within months; largest pandemic since the 1918 influenza pandemic

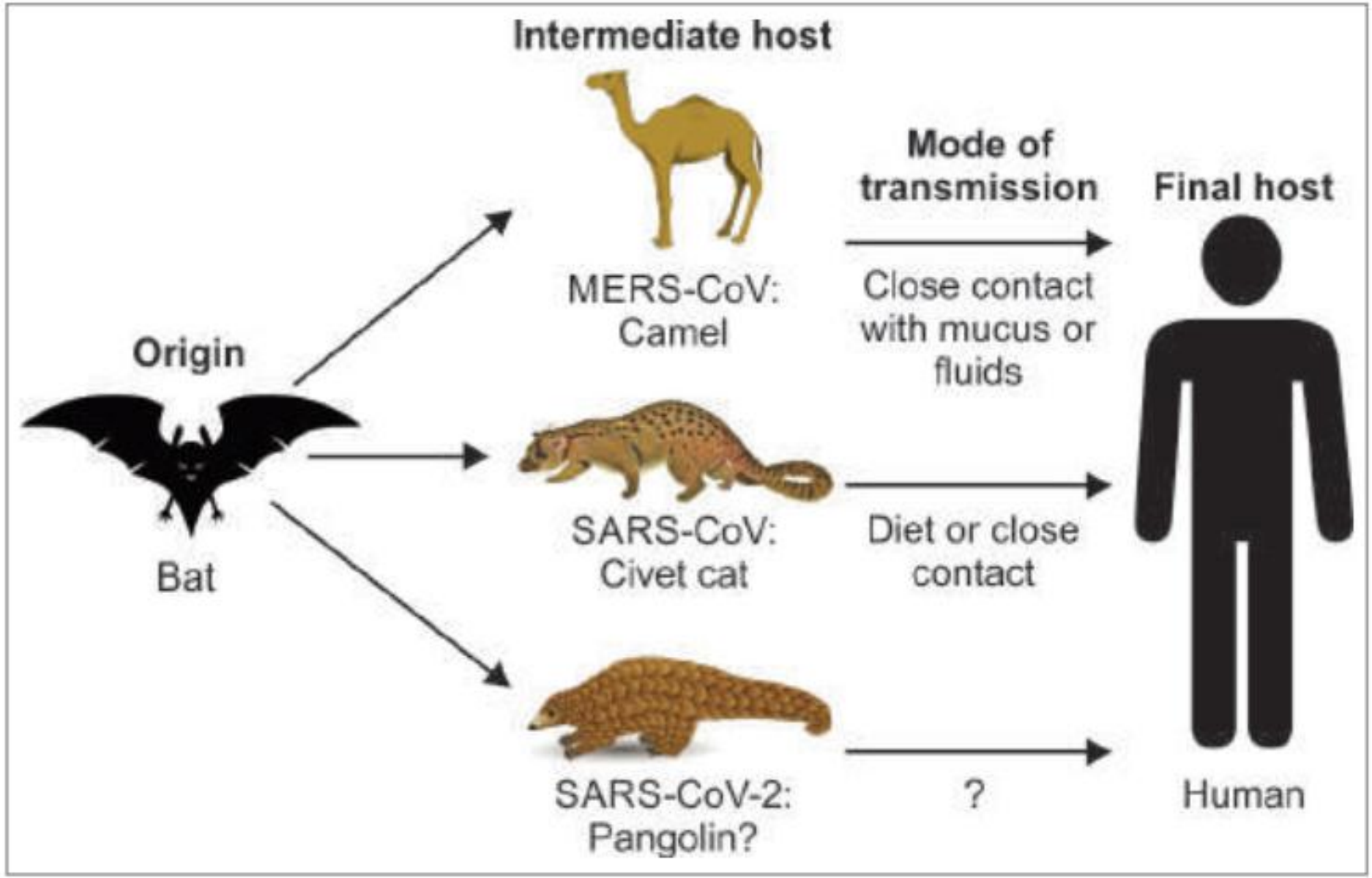


Fig. 67.2: Origin of MERS-CoV, SARS-CoV and SARS-CoV-2.

Structure of SARS-CoV-2

SARS-CoV-2 is an **enveloped, spherical virus** with a diameter of approximately **120 nm** and exhibits **helical nucleocapsid symmetry**.

- **Nucleocapsid:** consists of RNA surrounded by nucleocapsid protein (N)
- **Genomic Composition:** Contains a **single-stranded, positive-sense RNA genome (~30 kb).** The genome encodes **structural, non-structural,** and **accessory proteins**.
- **Envelope:** It is lipoprotein in nature; the lipid part is host-derived, into which a number of proteins are embedded such as Spike protein (S), Membrane glycoprotein (M), Envelope protein (E)

Structure of SARS-CoV-2

It possesses 4 structural proteins (N, S, M and E), 16 nonstructural proteins and several other accessory proteins

Structural Proteins:

- **Spike (S) Protein**
  - Club-shaped projections giving a crown-like appearance. It has two Subunits: S1 subunit and S2 subunit
  - Binds to **ACE2 receptors** (via S1 subunit) and mediates **membrane fusion** (via S2 subunit)
- **Membrane (M) Protein**
  - Most abundant protein; shapes the envelope and supports assembly
- **Envelope (E) Protein**
  - Small protein; involved in **virus assembly, release**, and acts as an **ion channel**

- **Nucleocapsid (N) Protein:** Binds and protects RNA genome; supports replication and immune modulation
- **Non-structural proteins (nsp1–16):** They include several enzymes which help in replication of the virus, e.g. RNA-dependent RNA polymerase (RdRp), helicase, etc.

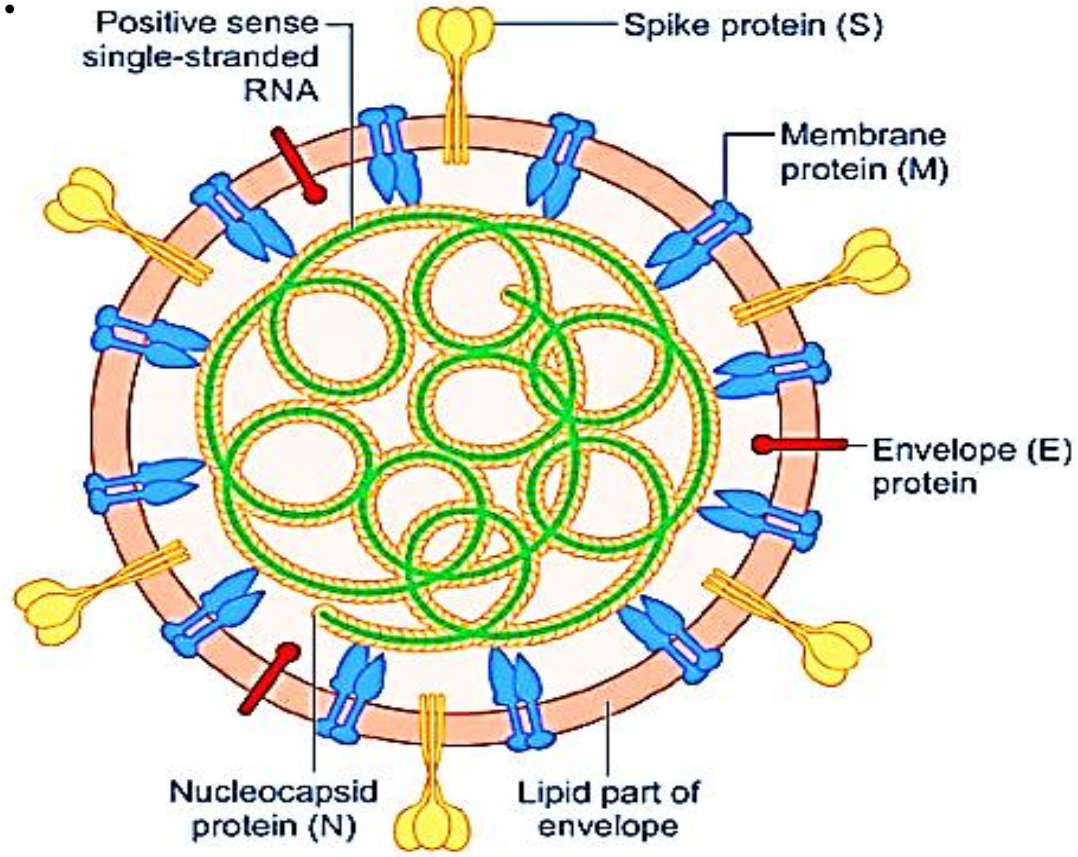
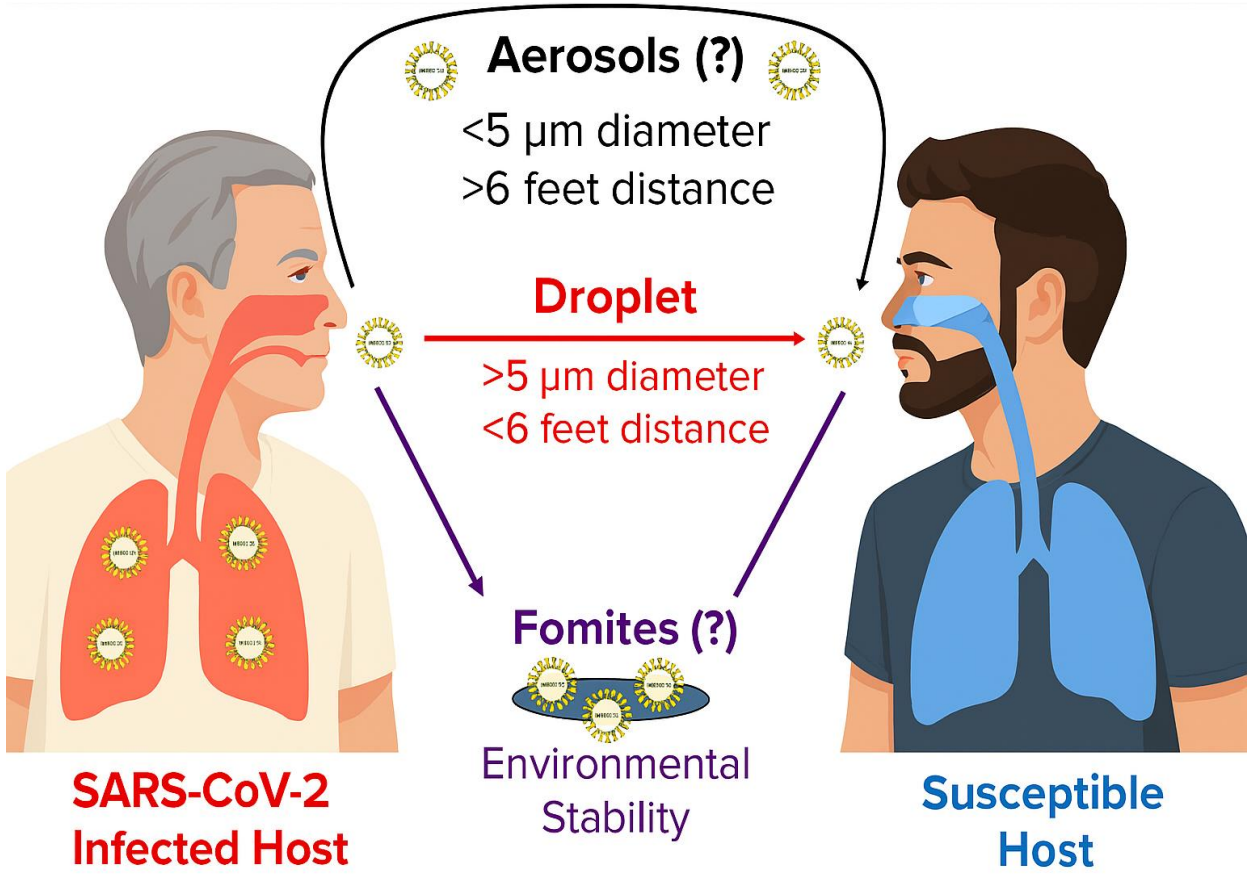


Fig. 67.3: Structure of SARS-CoV-2.

Transmission Routes

1. **Droplet:** Primary mode; occurs via coughing, sneezing, or close contact (<1 meter). Masking reduces risk.
2. **Contact:** Via contaminated surfaces, objects (fomites), or direct physical contact. Hand hygiene is essential.
3. **Aerosol:** Possible during aerosol-generating procedures (e.g., intubation). N95 masks recommended.
4. **Pre-symptomatic:** Transmission occurs 1–3 days before symptom onset; viral load peaks around symptom onset.



Viral Entry & Host Cell Invasion

- **Receptor binding:** Spike (S) protein binds to **ACE2 receptors** on host cells.
- **Priming:** Host enzyme **TMPRSS2** cleaves the S protein to enable viral entry via membrane fusion or endocytosis.
- **Tropism:** ACE2 is expressed in lungs (type II alveolar cells), oral mucosa, heart, kidneys, intestines, and endothelium—explaining multisystem involvement.

Stages of Disease Progression

1. **Initial Stage (ILI):**

   Viral replication in pharyngeal mucosa → sore throat, fever, cough.

2. **Pulmonary Phase (ARDS):**
   - **Alveolar damage** → ↓ surfactant → alveolar collapse
   - Interstitial fluid accumulation → pulmonary edema
   - Hypoxemia → respiratory failure

3. **Hyperinflammatory Phase (Cytokine Storm):** Massive immune activation → release of cytokines (IL-6, TNF-α, IFN-γ, etc.) The elevated cytokines lead to various consequences:
   - Tissue damage and necrosis
   - Further recruitment of leukocytes
   - Impaired gas exchange, which leads to reduced blood oxygenation and tissue hypoxia
   - Endothelial damage of pulmonary vasculature, leading to vasodilation, microvascular thrombosis and hemorrhage, and hypercoagulability

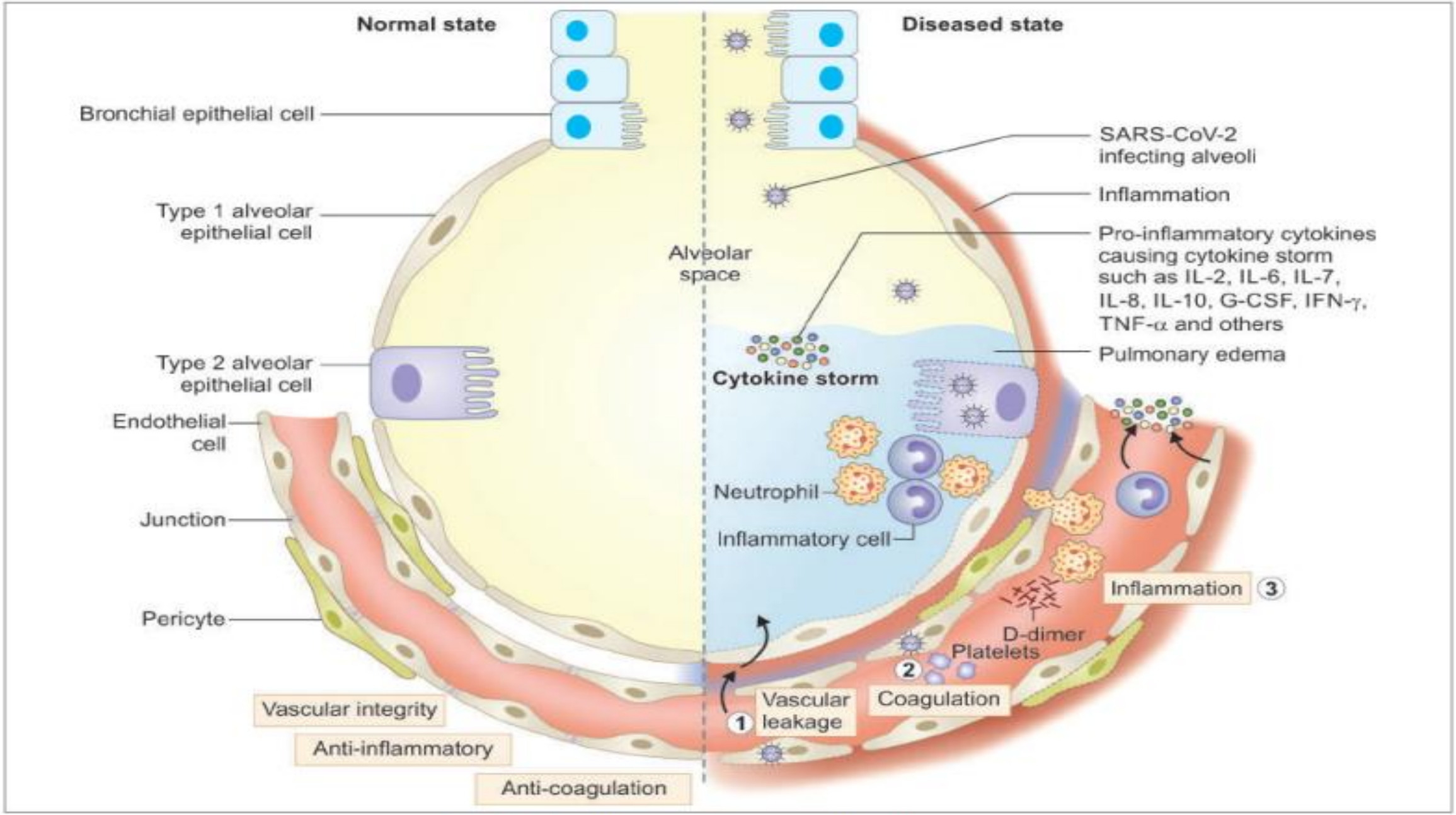


Fig. 67.4: Cytokine storm seen in COVID-19 patients.

Dilatation of blood vessels underlying the alveoli: This allows passage of fluid from the blood vessels to lungs which leads to pulmonary oedema. These infiltrates in the lungs appear as **‘ground-glass’** in chest imaging

Fibrosis: In the later stage, there occurs recruitment of fibroblast, which causes lung fibrosis, and ultimately, leads to respiratory failure. This stage is called as *acute respiratory distress syndrome (ARDS)*, eventually leading to respiratory failure

Multiorgan failure: Cytokines can also induce damage to other organs of the body such as heart, kidney, liver, etc.

There occur several catastrophic events such as sepsis, septic shock and multiorgan failure including acute kidney injury and cardiac injury

Risk factors

The major risk factors for severe disease are:

- **Age** > 60 years (risk increases with age)
- **Underlying comorbidities** such as diabetes, hypertension, cardiac disease, chronic obstructive lung disease, cerebrovascular disease, chronic kidney disease, immune-suppression and cancer.

Clinical Features

- Incubation: 5–6 days (up to 14 days)
- **Common features:**
  Fever, cough with expectoration, fatigue, shortness of breath, myalgia, rhinorrhea, sore throat, diarrhea. Loss of smell or taste sensation may occasionally occur preceding the onset of respiratory symptoms
- **Atypical symptoms:** Particularly seen in older people and immune-suppressed patients—such as fatigue, reduced alertness, reduced mobility, diarrhea, loss of appetite, delirium, and absence of fever. Children might not develop fever or cough as frequently as adults.

Clinical severity of COVID-19 disease

- Mild (influenza-like illness: Fever, cough, myalgia, fatigue, sore throat
- Moderate: Dyspnea, fever and cough, Hypoxia, SpO2 <94%, respiratory rate ≥ 24 per minute
- Severe: Clinical signs of pneumonia plus one of the following sign of severe respiratory distress: (i) Respiratory rate >30 /min or (ii) SpO2<90%
- Complications: ARDS, Sepsis, shock

Laboratory diagnosis

- Specimens: Throat and nasal swabs
- NAAT: Nucleic acid amplification testing
  - Formats: Real time RT-PCR, automated formats (CBNAAT and Truenat)
  - Gene targets: Screening (E, N, M genes), confirmatory (RdRp,N2 genes, etc.)
- Antigen detection assay: Point-of-care test; detects nucleocapsid protein antigen in nasopharyngeal swab
- Antibody (IgG) detection assay: Used for serosurveillance and survey in high-risk and vulnerable group; not for clinical diagnosis
- **Sequencing:** To determine mutations in the viral genome

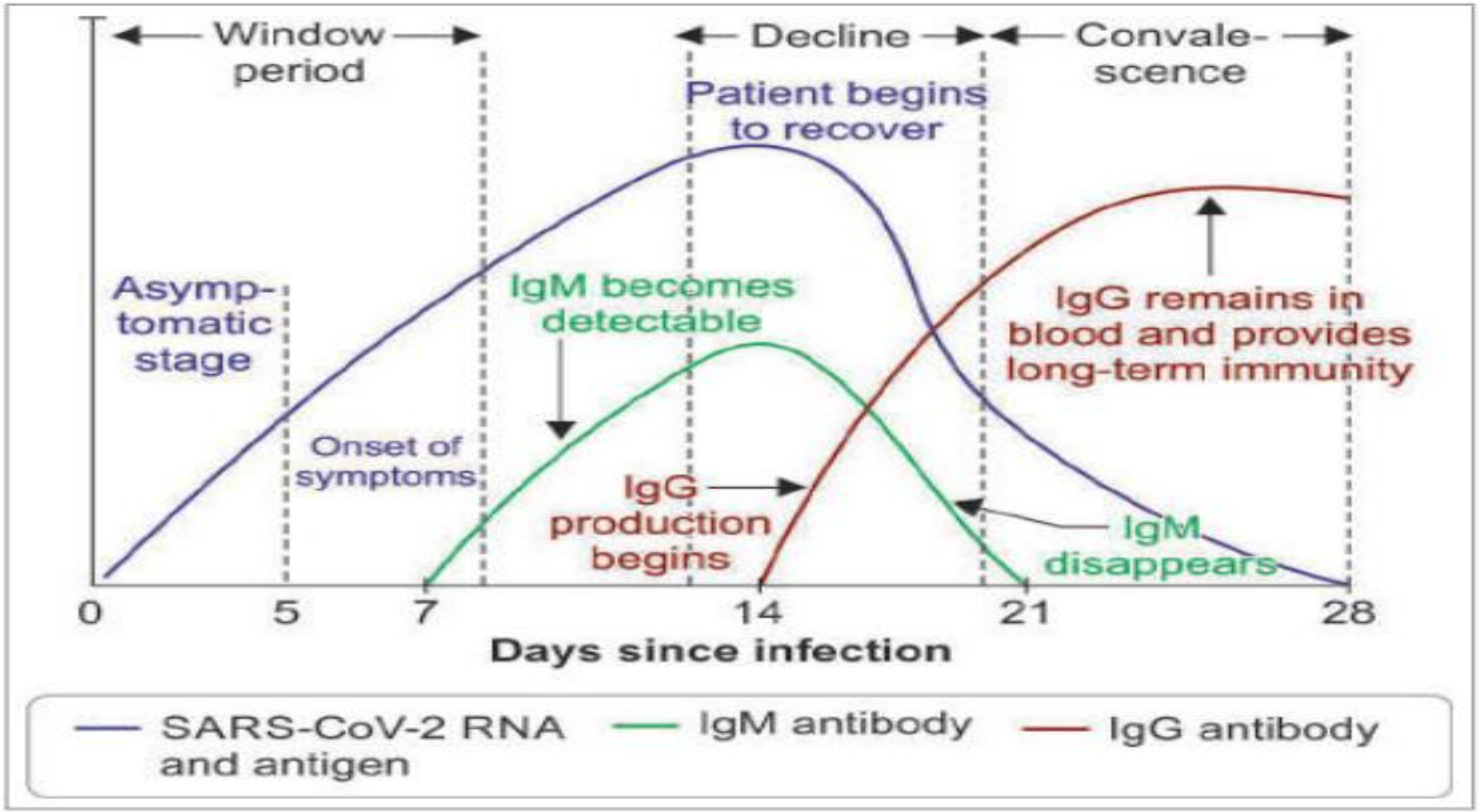
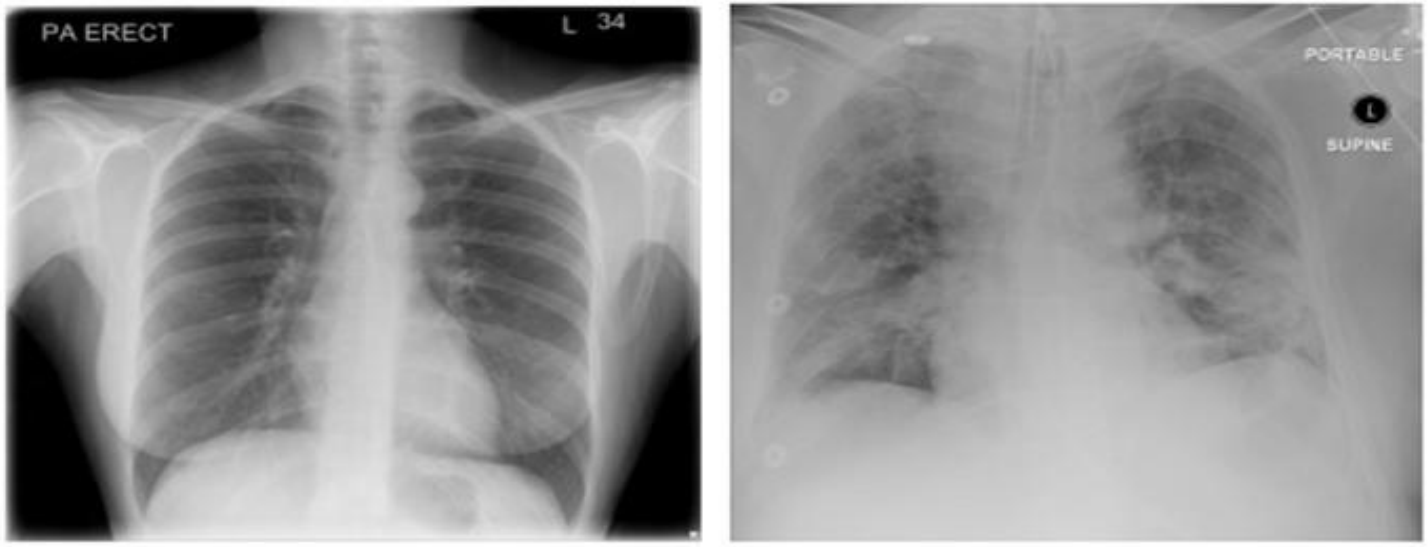


Fig. 67.6: Course of the diagnostic markers in COVID-19.

Laboratory diagnosis

- **Viral culture:** Used for research purpose
- **Nonspecific tests** include:
  - Radiology (X-ray, chest CT scan): Ground-glass appearance,
  - Biomarkers: IL-6, D-dimer, Elevated serum ferritin: Indicates inflammation, Severe lymphopenia, Elevated C-reactive protein.



(a) 'NORMAL' (b) 'CLASSIC' COVID-19

COVID-19 Treatment

- Supportive: Oxygen therapy, ventilation, fluids
- Antivirals
- Immunomodulators: Tocilizumab (IL-6 inhibitor)
- Plasma therapy
- Corticosteroids in severe cases

Drug / Category	Mechanism of Action
Favipiravir	Converted to active form in cells; inhibits RNA polymerase activity
Remdesivir	Converted to active form (GS-441524); inhibits viral RNA-dependent RNA polymerase
Lopinavir / Ritonavir	Protease inhibitors; block viral replication
Hydroxychloroquine	Used for prophylaxis against COVID-19
Anti-cytokines	Useful for ARDS, prevents cytokine storm
– Tocilizumab / Sarilumab	IL-6 receptor blockers
– Tofacitinib	Jak3 inhibitor
Convalescent Plasma Plasma from recovered patients contains neutralizing antibodies against SARS-CoV-2These antibodies may eliminate the virus completely	
Other Investigational Drugs	
– Camostat Mesylate	Inhibits TMPRSS2 (a host protease involved in viral entry)
– Hesperidin	Inhibits binding of spike protein to ACE-2 receptor

Vaccination

Currently, there are several vaccines available against COVID-19, which are approved for human use after being proven safe and effective in large (phase III) clinical trials. Moreover, **200+ candidates** are developing, with more than 60 in clinical trials.

Types of COVID-19 Vaccines

1. **Inactivated/Weakened Virus Vaccines**
    1. Use inactivated virus to elicit immune response.
    2. Examples: *Covaxin*, *CoroVac*, *BBIBP-CorV*
2. **Protein-based Vaccines**
    - Use viral protein fragments to mimic virus.
    - Example: *EpiVacCorona*

3. Viral Vector Vaccines

- Use harmless virus to deliver genetic material.
- Examples: *Covishield*, *Oxford-AstraZeneca*, *Sputnik V, Johnson & Johnson*

Vaccination

4. RNA/DNA Vaccines

- Use genetic material to generate viral proteins and immune response.
- Examples: *Pfizer-BioNTech*, *Moderna*

- **Adverse Effects**

Mostly mild: pain at injection site, fever, fatigue, headache, myalgia- more pronounced after second dose for RNA vaccines.

- Most given in 2-dose schedules; J&J is single-dose
- Storage: Varies (2–8°C for most, -70°C for Pfizer)

Prevention & Control

- Hand hygiene, masking, and physical distancing
- Disinfection of high-touch surfaces
- PPE for healthcare workers
- Quarantine, isolation, lockdowns
- Cluster containment strategies in hotspots- to contain the disease within a defined geographic area by early detection of cases, breaking the chain of transmission and thus preventing its spread to new areas causing community transmission

Quarantine

Quarantine refers to restriction on the movement of healthy people who are exposed to a confirmed case; aims at preventing the transmission if they develop disease subsequently. Quarantine period is usually kept as maximum incubation period (i.e. 14 days in case of COVID-19).

Isolation

Isolation separates sick people with a contagious disease from people who are not sick.