

Human Coronaviruses

Structure, pathogenesis, pulmonary morphology, and
clinicopathologic consequences

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Learning objectives

- Distinguish mild seasonal human coronavirus infections from severe coronavirus pneumonias.
- Explain SARS-CoV-2 entry, replication, and evasion of type I interferon defenses.
- Relate viral and immune-mediated injury to diffuse alveolar damage, hypoxemia, and thrombosis.
- Apply morphology and diagnostic principles to clinical scenarios.

The clinical spectrum spans two extremes

Usually mild

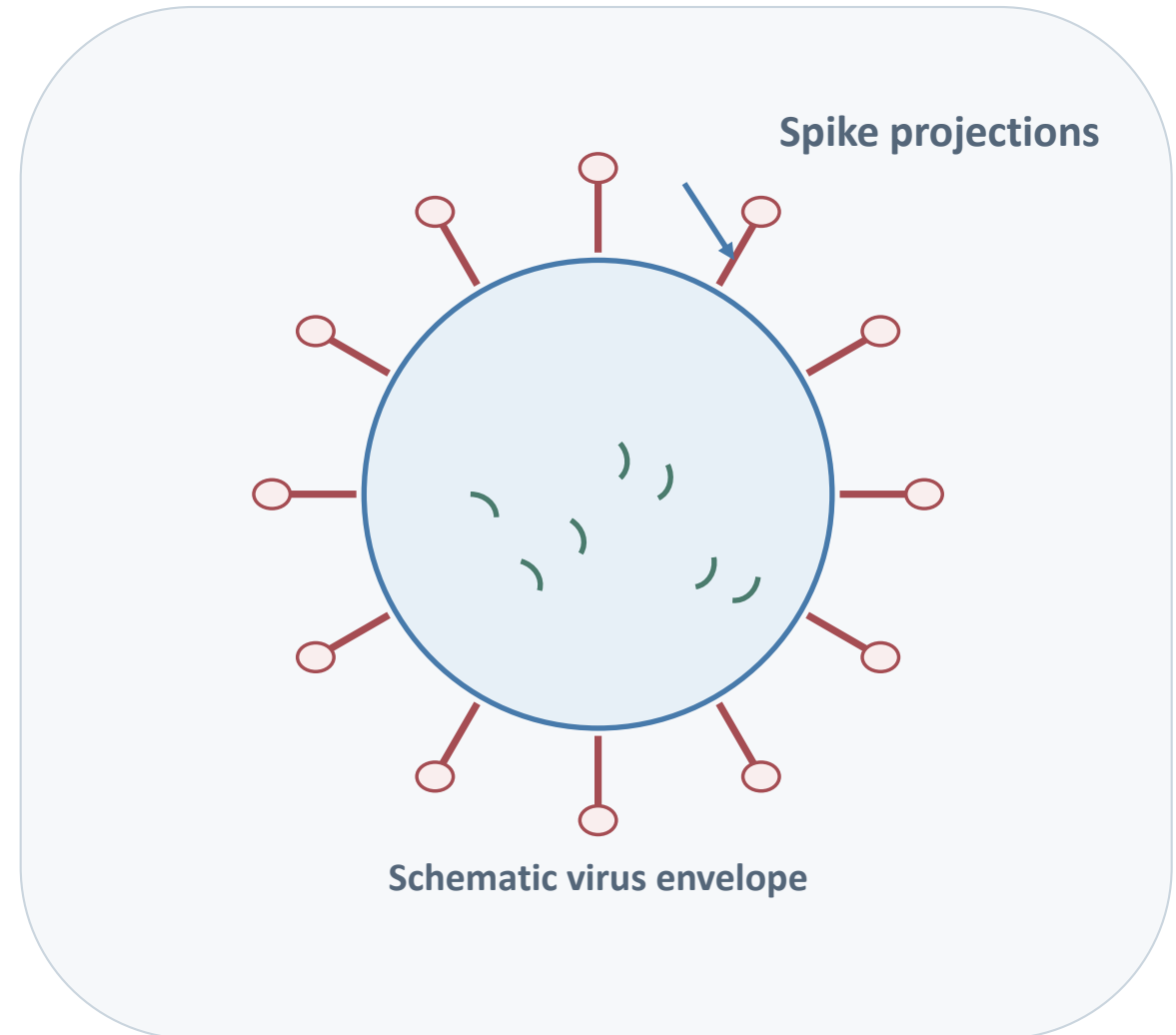
- Endemic human coronaviruses
- Upper respiratory tract infection
- Cold-like illness

Potentially severe

- Highly pathogenic coronaviruses
- Lower respiratory tract injury
- Pneumonia, diffuse alveolar damage, ARDS

Coronaviruses are enveloped RNA viruses

- Their genome is single-stranded, positive-sense RNA.
- A lipid envelope carries proteins needed for host-cell infection.
- Human and other vertebrate hosts can be infected.



Pathogenicity differs among coronaviruses

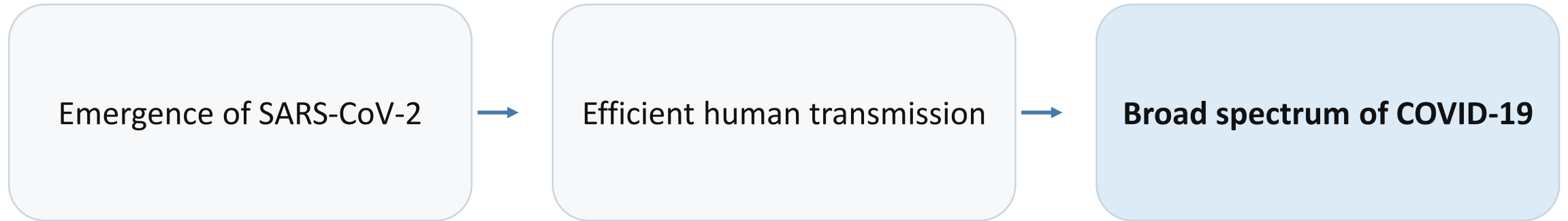
Common endemic strains

- Mostly restricted to upper airways in the Robbins account
- Mild, cold-like presentation
- Usually limited tissue injury

SARS, MERS, SARS-CoV-2

- Can cause severe lower-respiratory disease
- Inflammation amplifies epithelial injury
- Severe cases may develop ARDS

SARS-CoV-2 illustrates severe coronavirus disease



- COVID-19 emerged in late 2019 and became a global pandemic.
- The virus subsequently became endemic in humans.

SARS and MERS provide clinical contrasts

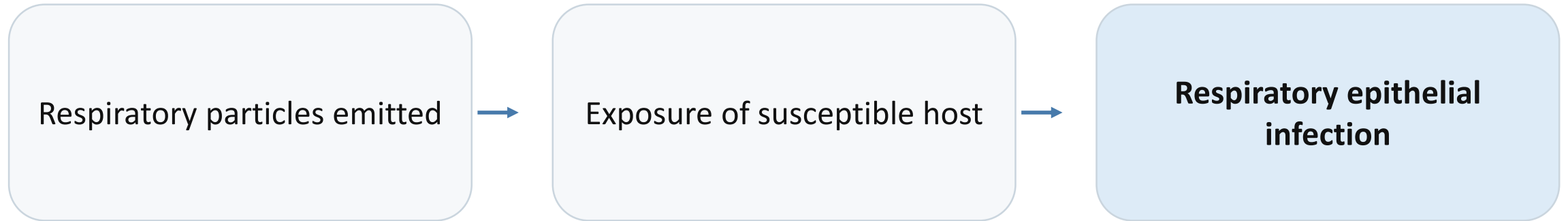
SARS and MERS

- Zoonotic coronaviruses
- Severe infections possible
- Less efficient sustained human spread account

SARS-CoV-2

- Extensive person-to-person transmission
- Endemic circulation after pandemic spread
- Illness from asymptomatic infection to ARDS

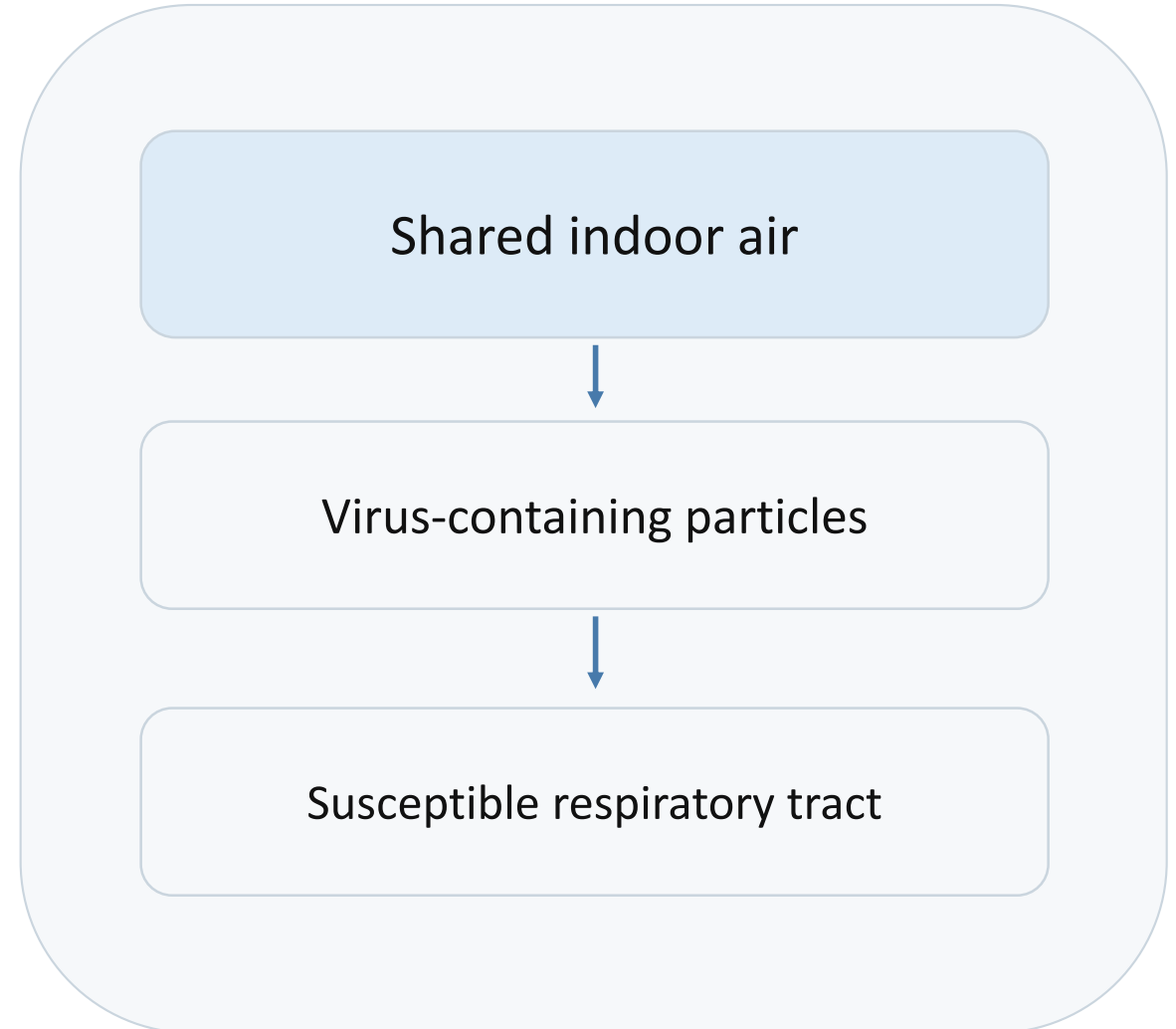
Transmission occurs through respiratory particles



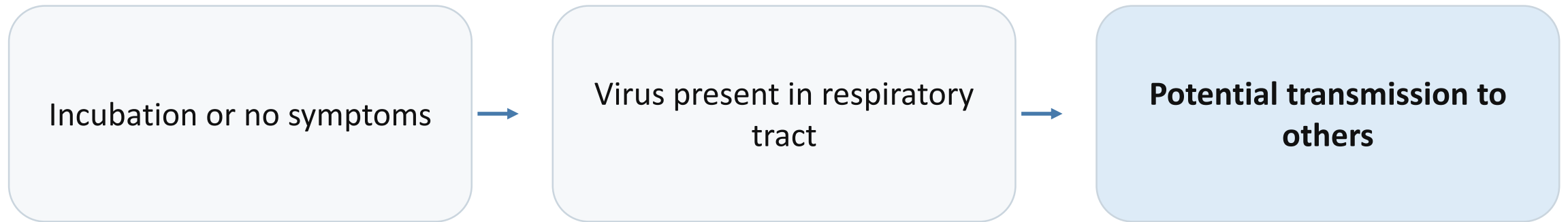
- Respiratory droplets and aerosols both transmit infection.
- Poor ventilation favors accumulation of infectious airborne particles.

Indoor congregation increases exposure

- Prolonged close contact indoors facilitates transmission.
- Households and shared residential or care facilities illustrate exposure settings.
- Ventilation modifies the environment in which aerosols accumulate.

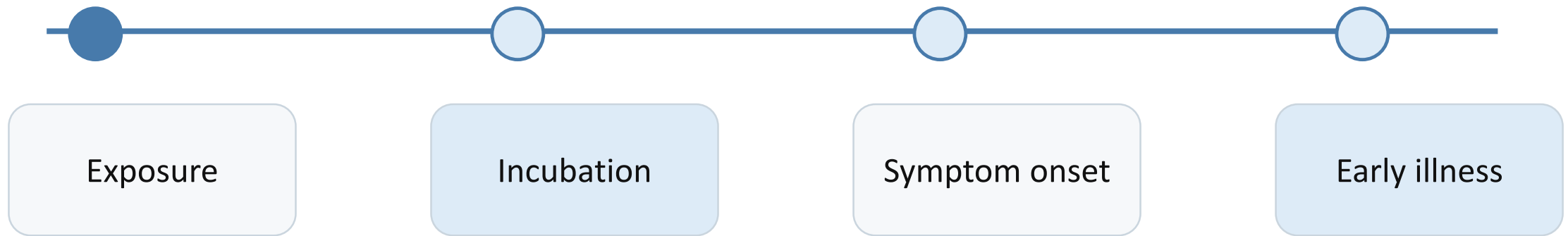


Asymptomatic infection does not prevent spread



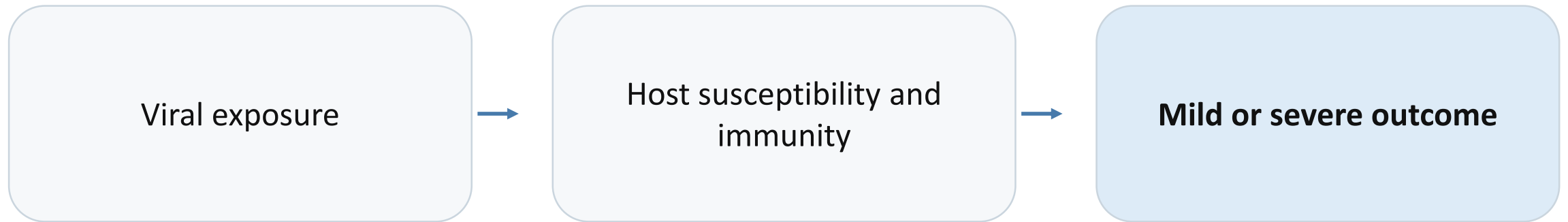
- Transmission can occur before symptoms and in asymptomatic people.
- Symptoms may increase the likelihood of onward spread.

Incubation precedes the clinical phenotype



- An incubation range of 2–14 days, with median onset around 4–5 days.
- Viral load is generally highest early in the infection.
- These are source-era observations, not a variant-specific contemporary prediction.

Host susceptibility strongly modifies disease

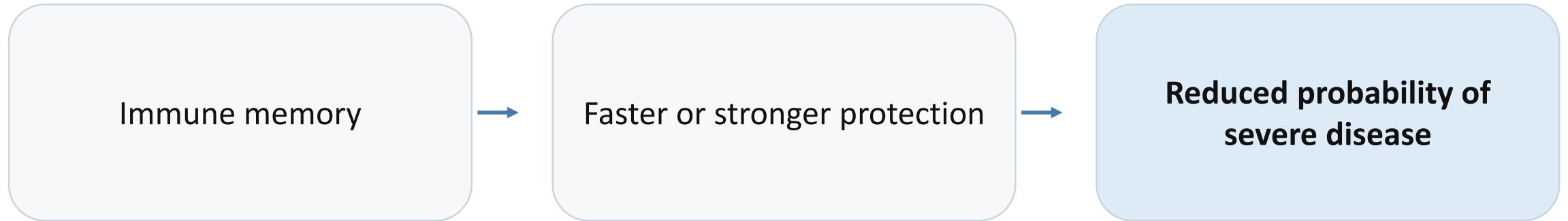


- Older age is a major determinant of severe COVID-19.
- Host factors alter whether infection remains controlled or progresses.

Comorbid disease increases risk

- Underlying cardiopulmonary disease and diabetes contribute to severe-disease susceptibility.
- Cancer, immunocompromise, and chronic renal or hepatic disease also matter.
- Obesity, smoking, and pregnancy are additional risk factors.
- Risk reflects a combination of exposure, host biology, and access to care.

Prior immunity changes the natural history



- Previous infection or vaccination may modify the immune response.
- Population immunity and clinical treatment altered disease severity during the pandemic.
- Severity estimates from early pandemic periods are not fixed biological constants.

Coronavirus severity is not a binary property

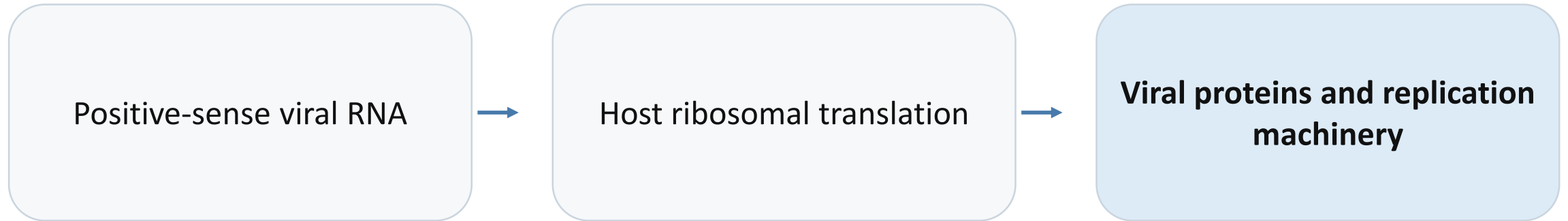
Virus-associated determinants

- Cell entry and tissue tropism
- Viral replication and immune evasion
- Genetic variation of the virus

Host-associated determinants

- Age and comorbidities
- Innate antiviral competence
- Prior adaptive immunity

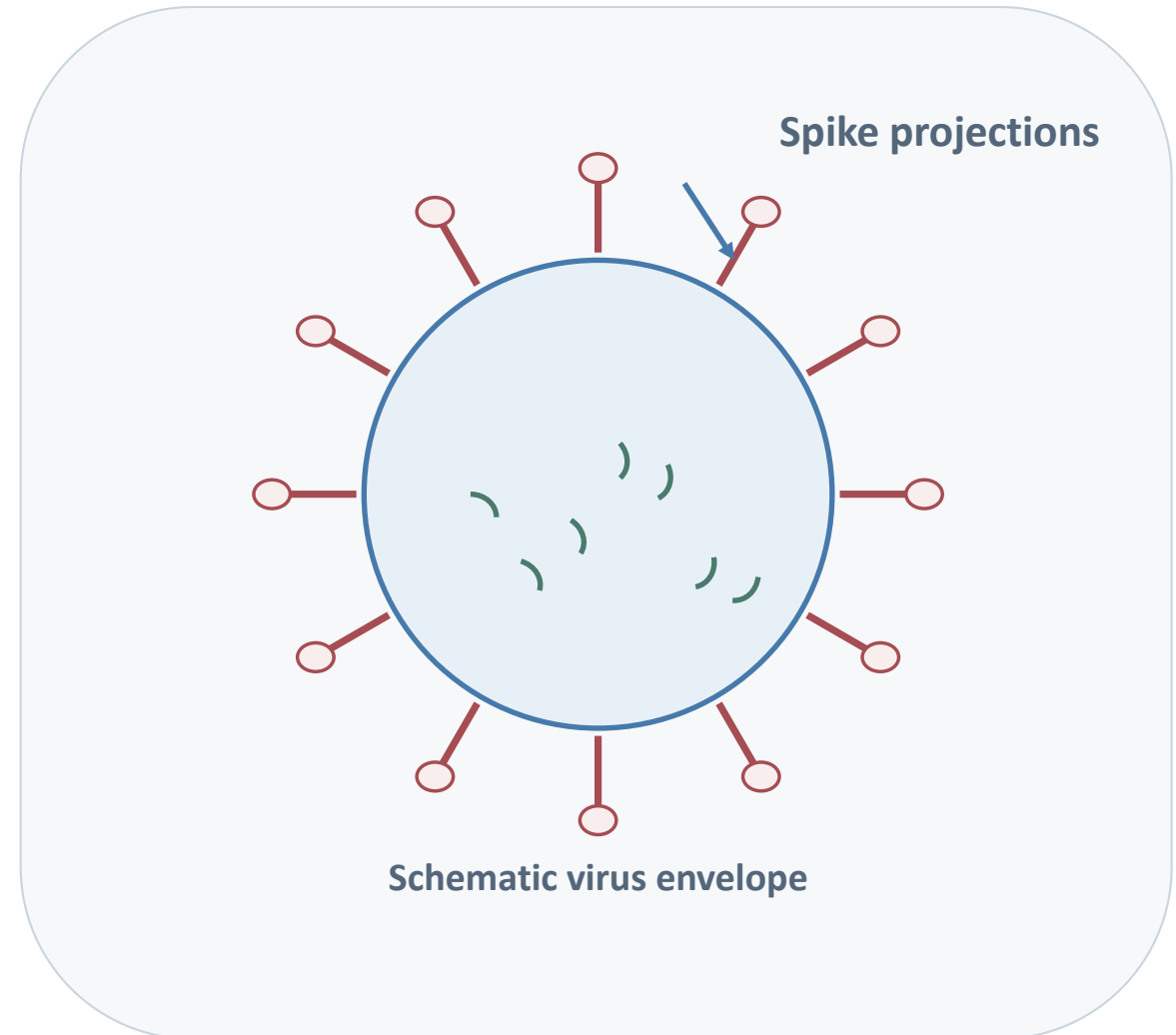
SARS-CoV-2 genome supports direct translation



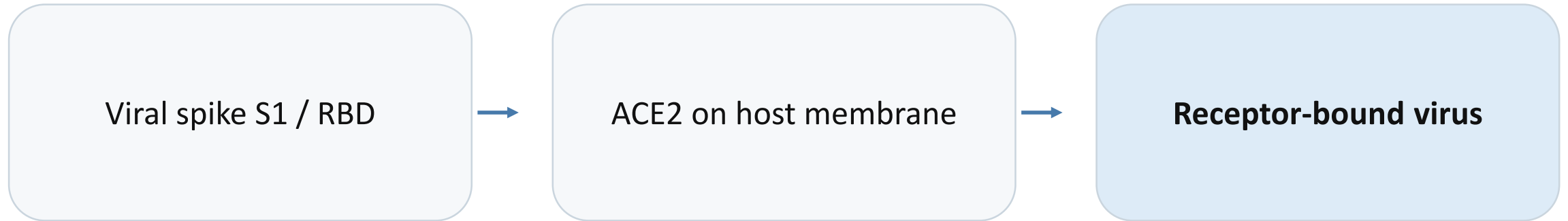
- The positive-sense RNA genome is approximately 30 kilobases account.
- After entry, host ribosomes translate viral RNA into proteins.

Three structural components orient the mechanism

- Spike protein mediates attachment and membrane fusion.
- Membrane protein is located in the viral envelope.
- Nucleocapsid protein associates with viral genomic RNA.



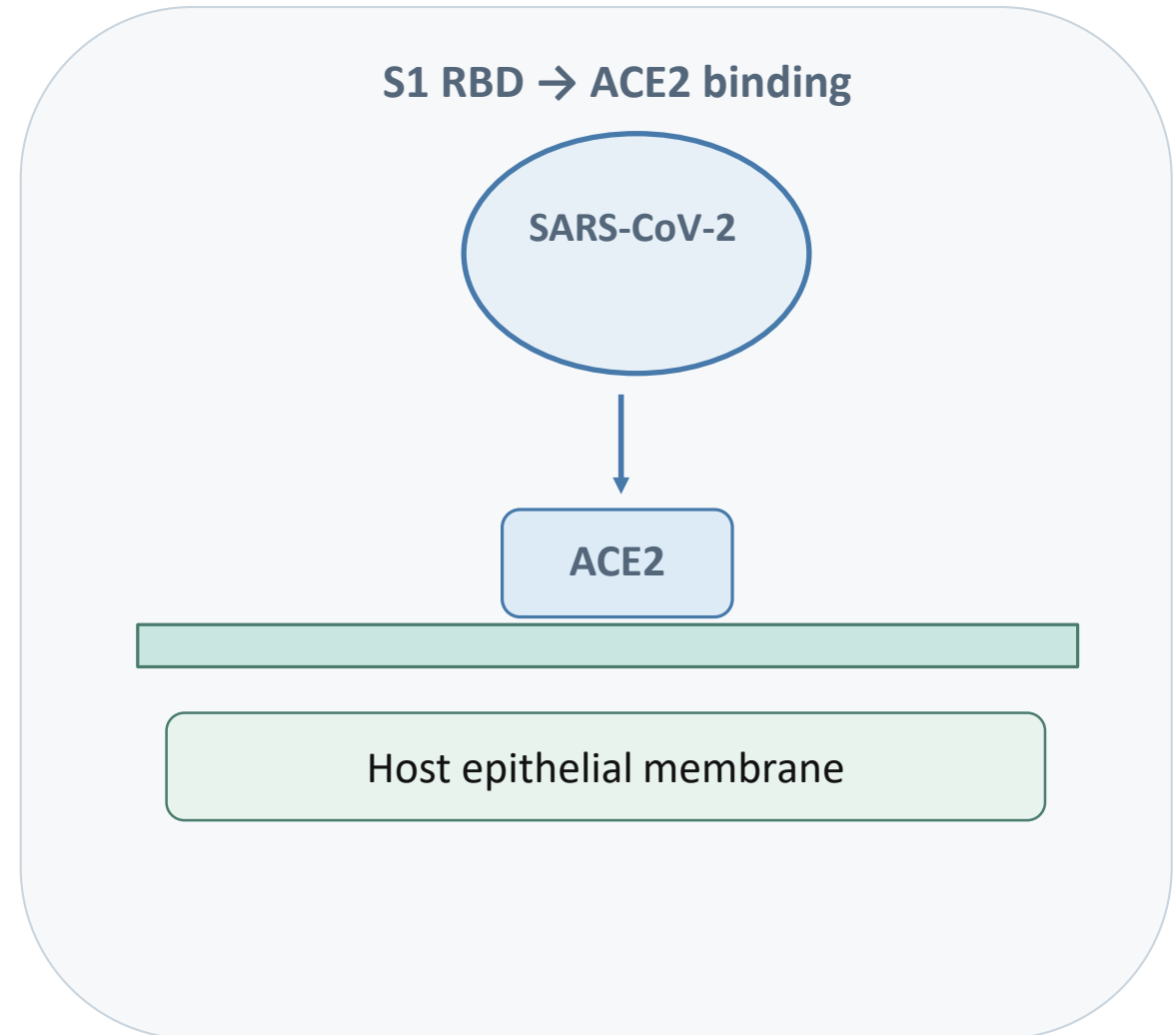
Spike S1 binds a cellular receptor



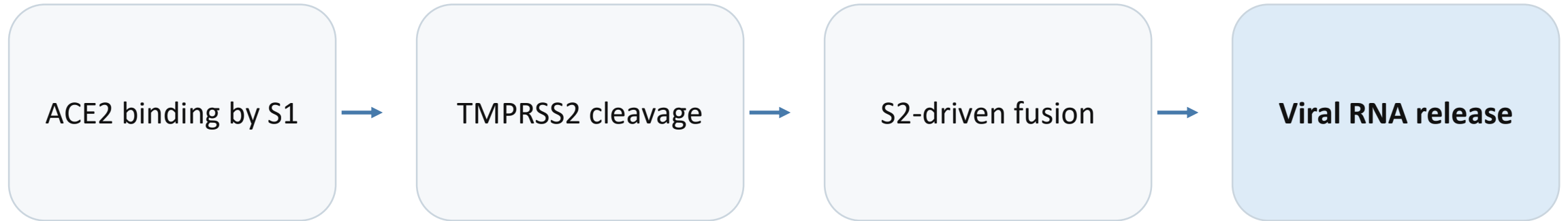
- The S1 subunit carries the receptor-binding domain (RBD).
- RBD recognition of ACE2 initiates cell-entry events.

ACE2 helps explain respiratory tropism

- ACE2 is expressed on respiratory epithelial cells.
- SARS-CoV-2 attachment is enabled where an accessible receptor and entry machinery are present.
- Receptor expression alone does not specify clinical severity.



TMPRSS2 primes membrane fusion



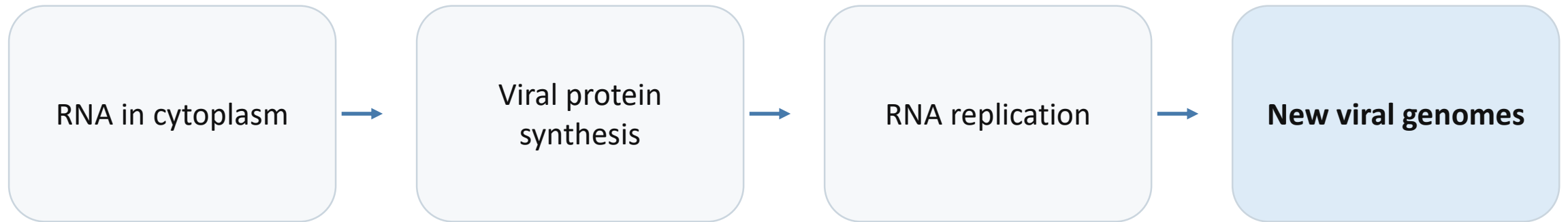
- Host-cell protease TMPRSS2 cleaves receptor-engaged spike.
- Cleavage activates the S2 fusion machinery.
- Viral and host membranes fuse to permit RNA entry.

Neutralizing antibodies target spike



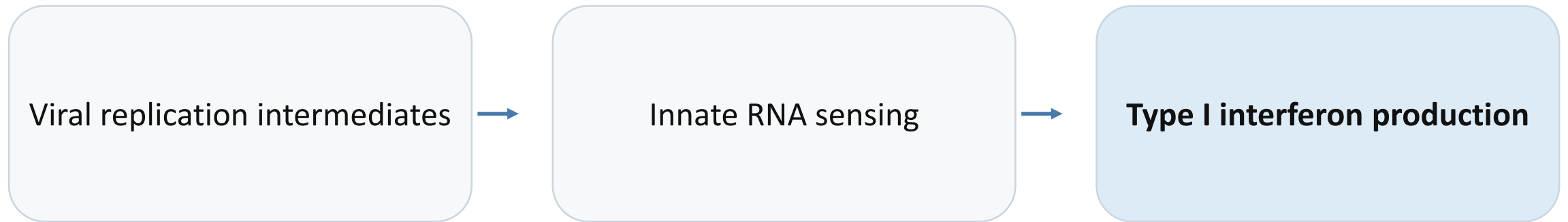
- Antibodies recognizing spike, particularly RBD, can block host-cell infection.
- This is a mechanism of immune protection, not a direct measure of lung injury.

Replication begins after viral RNA entry



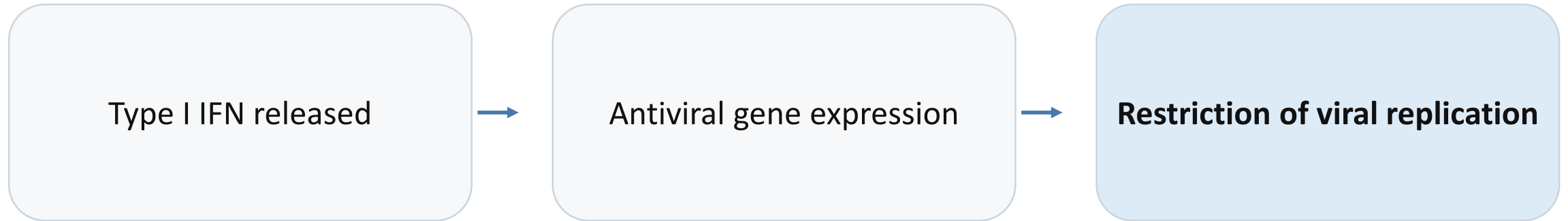
- Host-cell translation produces replication proteins.
- The viral RNA-dependent RNA polymerase copies the genome.
- New positive-strand RNAs supply subsequent viral replication.

Double-stranded RNA is an innate danger signal



- RNA replication generates intermediates recognized as nonself by innate sensors.
- Viral RNA structures stimulate type I interferon responses.
- These responses inhibit replication in infected and neighboring cells.

Type I interferon creates an antiviral state



- Interferon signaling activates defenses in infected and nearby cells.
- This response opposes viral replication rather than directly neutralizing virions.
- Effective early innate defense may contain infection before severe lung injury.

SARS-CoV-2 evades interferon defenses

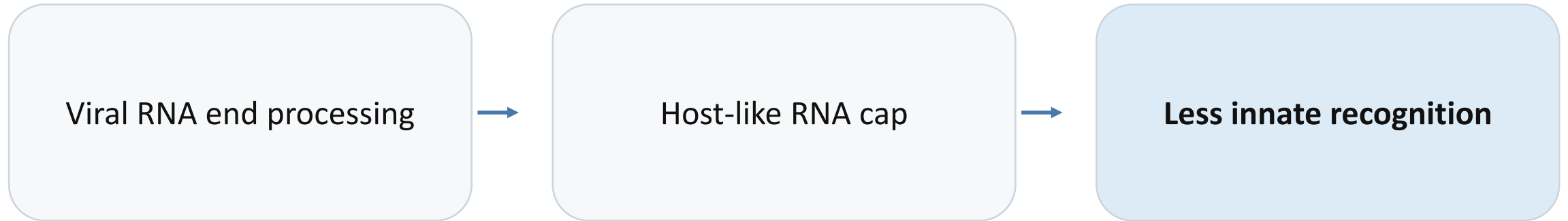
Host defense

- Detect unusual viral RNA
- Produce type I interferon
- Induce antiviral signaling

Viral countermeasures

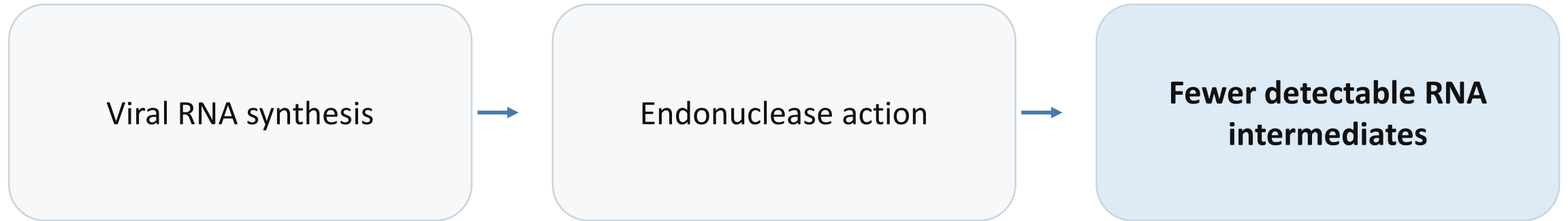
- Make RNA resemble host RNA
- Shelter replication intermediates
- Block signaling leading to interferon

Viral RNA modification conceals its identity



- The virus modifies and caps its RNA.
- These changes make viral RNA more similar to host transcripts.
- Reduced recognition by sensors such as RIG-I favors replication.

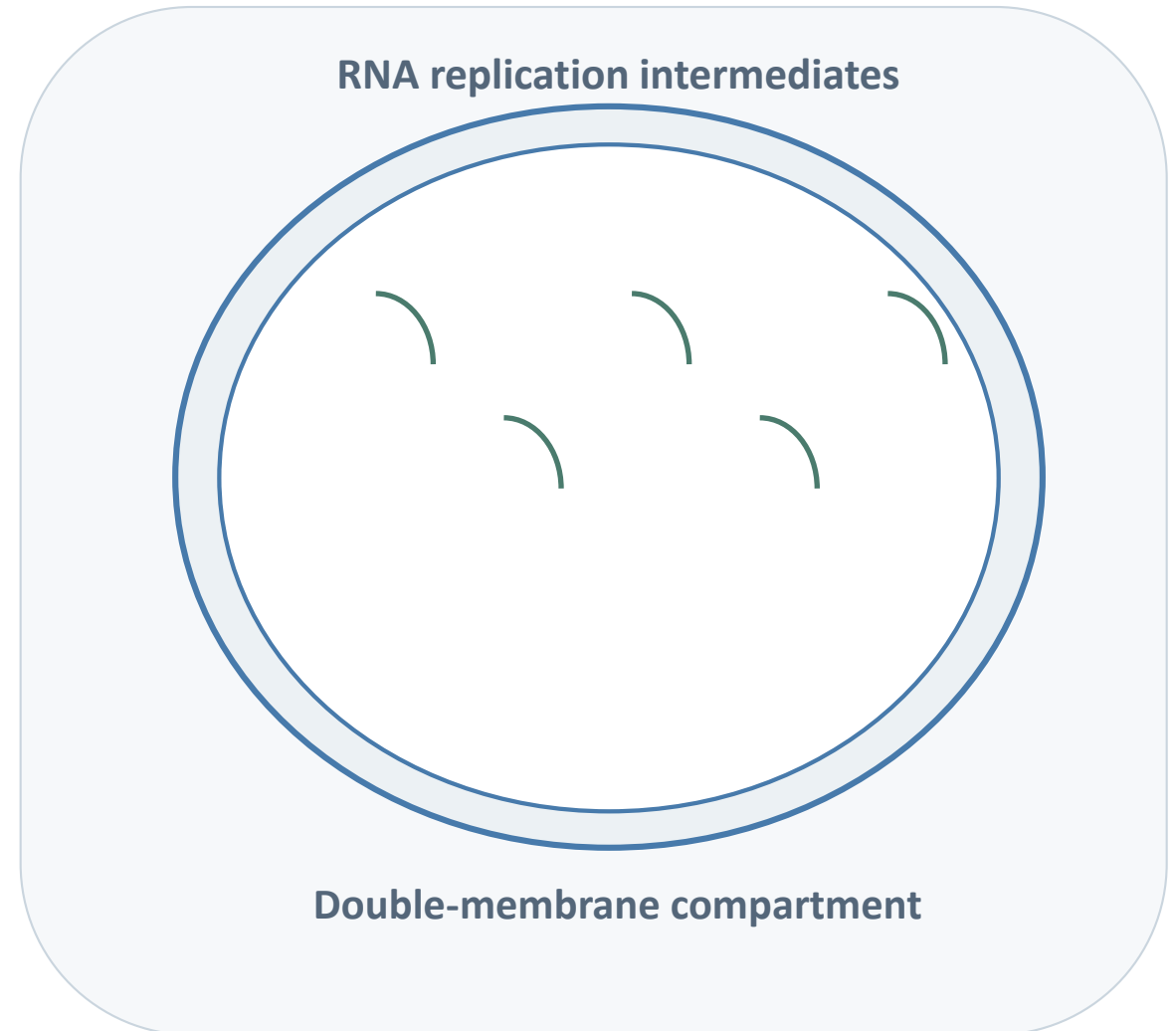
Viral endonuclease limits RNA alarm signals



- Viral RNA endonuclease activity minimizes accumulation of negative-strand and double-stranded RNA.
- This helps decrease detection of replication intermediates.

Membrane vesicles shield replicating RNA

- Viral proteins recruit endoplasmic reticulum membranes.
- Double-membrane compartments contain RNA replication intermediates.
- Sequestration limits access of cytoplasmic RNA sensors.



Interferon signaling is also directly inhibited



- Several viral proteins interfere with host proteins involved in interferon-production pathways.
- Immune evasion acts at multiple steps rather than through one isolated target.

Failure of interferon defense predicts vulnerability

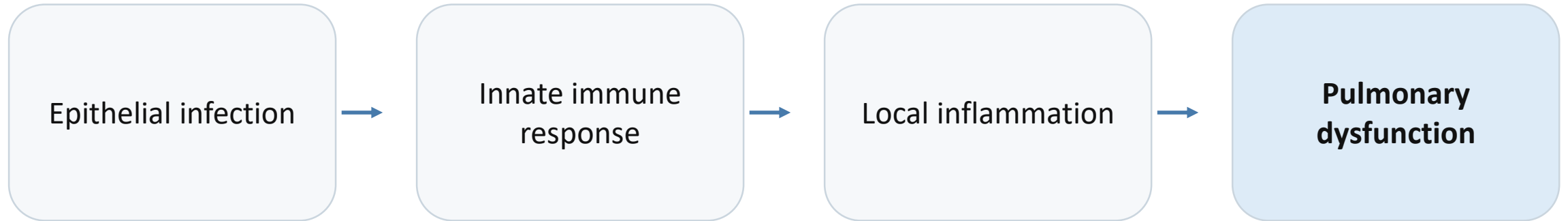
Intact type I IFN pathway

- Earlier recognition of viral RNA
- Antiviral state in affected tissue
- Limits spread when effective

Defective type I IFN response

- Genetic defects in IFN pathways
- Autoantibodies against type I IFN
- Increased risk of severe COVID-19

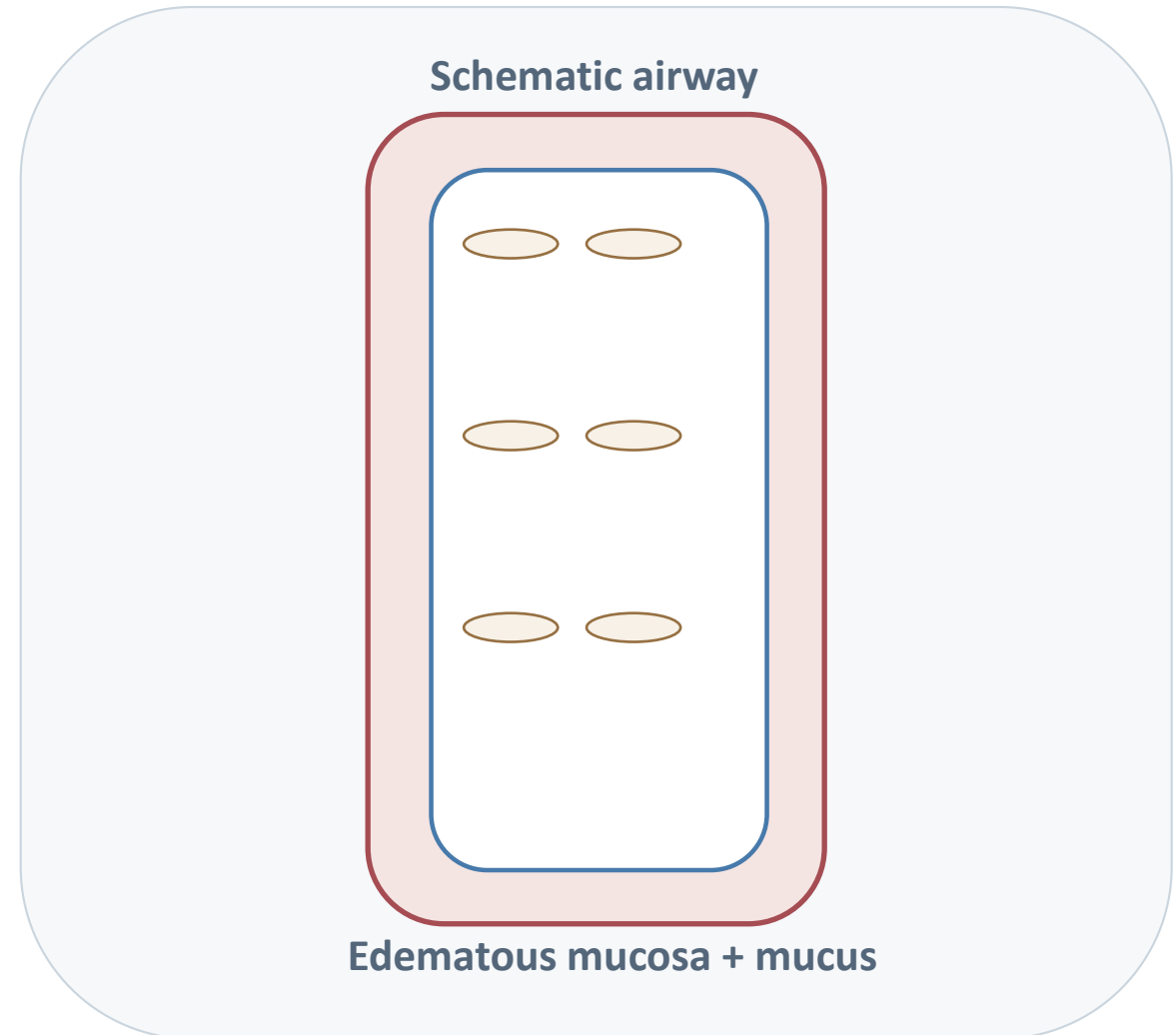
Virus–host interactions determine lung injury



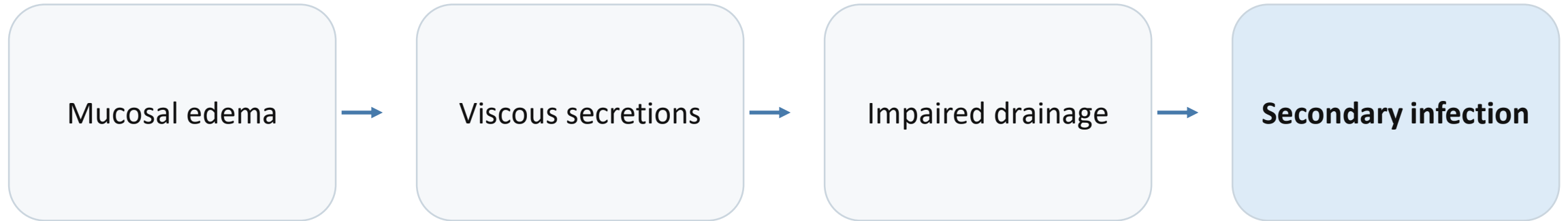
- Direct viral replication causes epithelial damage.
- Host responses amplify inflammation and vascular injury.
- The resulting lesion can progress beyond the infected epithelium.

Upper-airway infection produces mucosal inflammation

- Mucosal hyperemia and swelling reflect local inflammation.
- Submucosal mononuclear cells include lymphocytes and monocytes.
- Excess mucus contributes to congestion and obstruction.

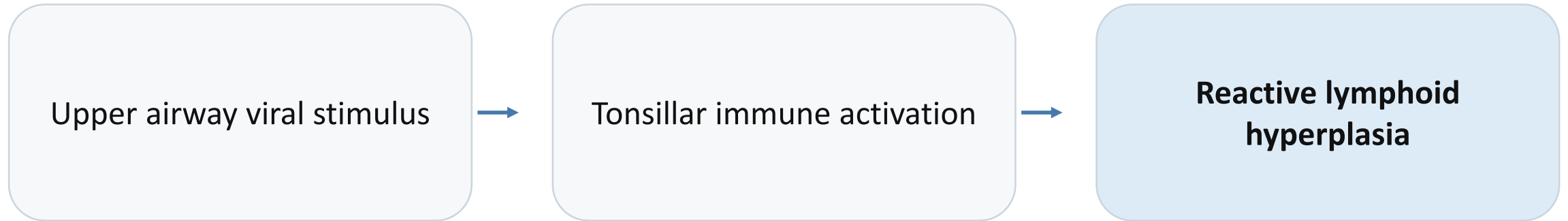


Mucus obstruction explains some complications



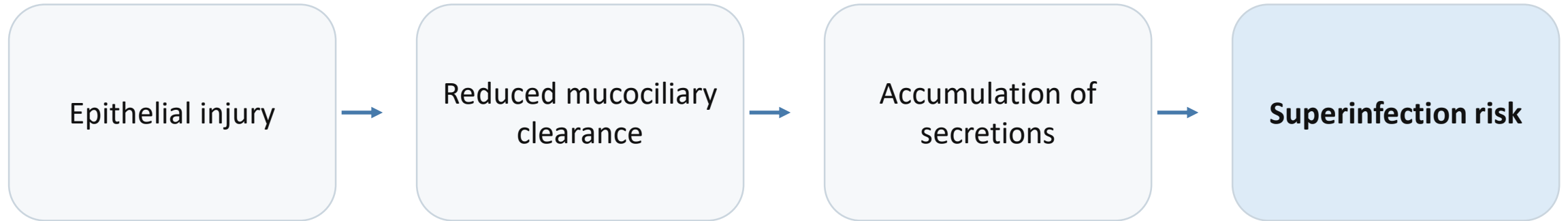
- Swelling and viscous secretion can obstruct nasal channels, sinuses, or Eustachian tubes.
- Obstruction may facilitate secondary suppurative bacterial infection.

Waldeyer-ring reactivity is a pediatric feature



- Virus-associated tonsillitis can produce lymphoid tissue hyperplasia.
- This reflects a local mucosal immune response in children.
- Lymphoid hyperplasia is not a coronavirus-specific diagnostic finding.

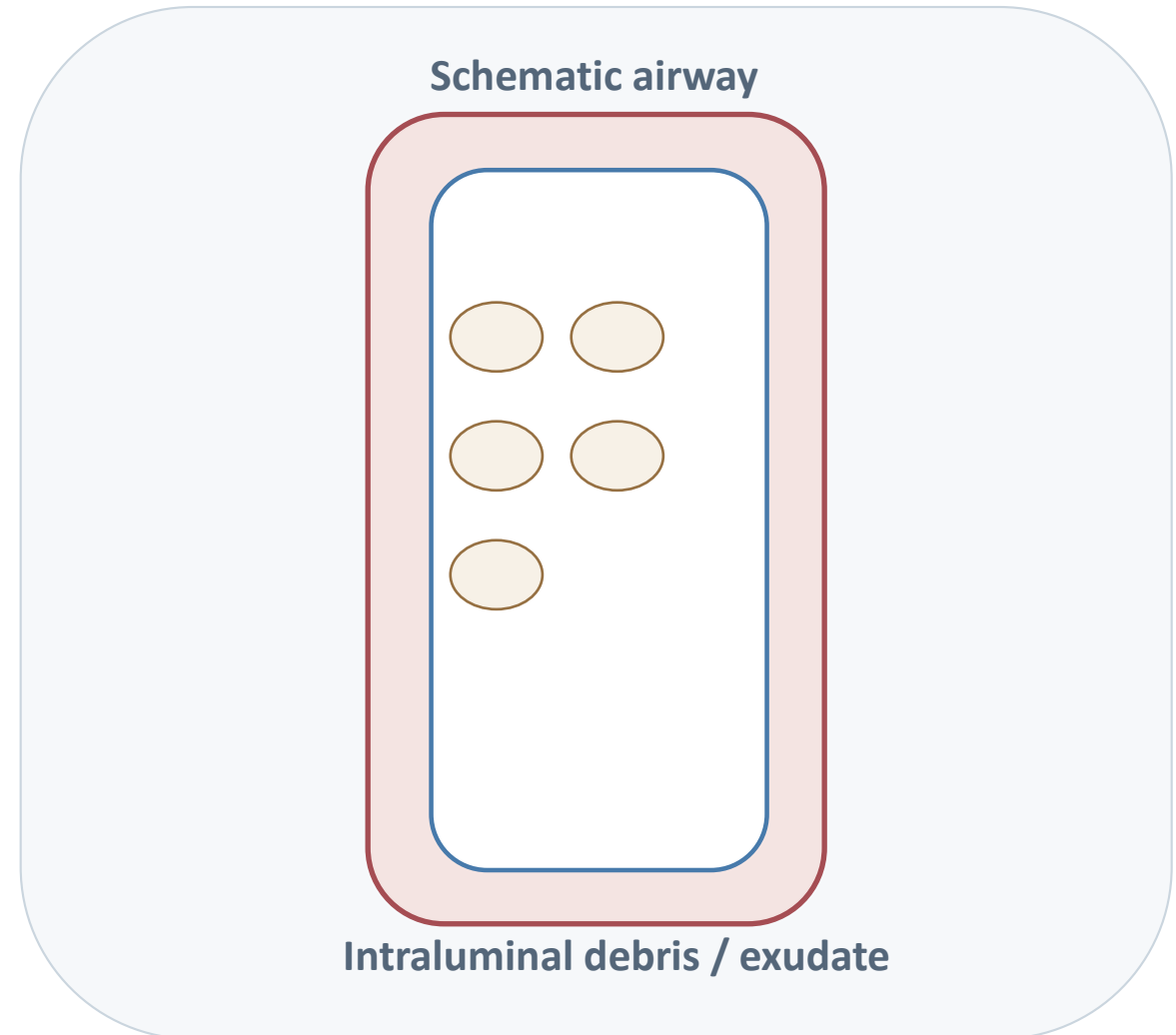
Large-airway disease impairs mucociliary function



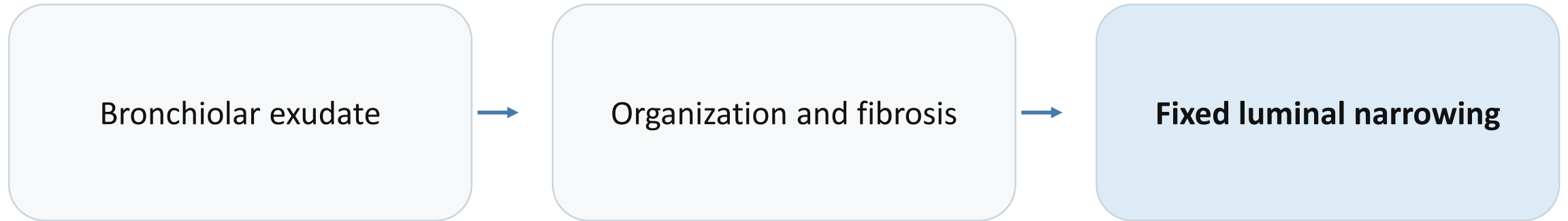
- Viral laryngotracheobronchitis may cause vocal cord edema and mucus hypersecretion.
- Compromised bronchociliary clearance favors bacterial superinfection.

Bronchiolar plugging has mechanical effects

- Cell debris, fibrin, mucus, and inflammatory exudate can obstruct small airways.
- Segmental or focal atelectasis can follow distal airway blockage.
- Severe prolonged damage may heal by organization and fibrosis.



Persistent bronchiolitis can leave structural damage



- Prolonged exudate organization may narrow or obliterate airway lumina.
- This pathway can lead to obliterative bronchiolitis and permanent impairment.
- It is a severe viral airway outcome, not inevitable in routine COVID-19.

Viral pneumonia need not be spatially uniform

Patchy involvement

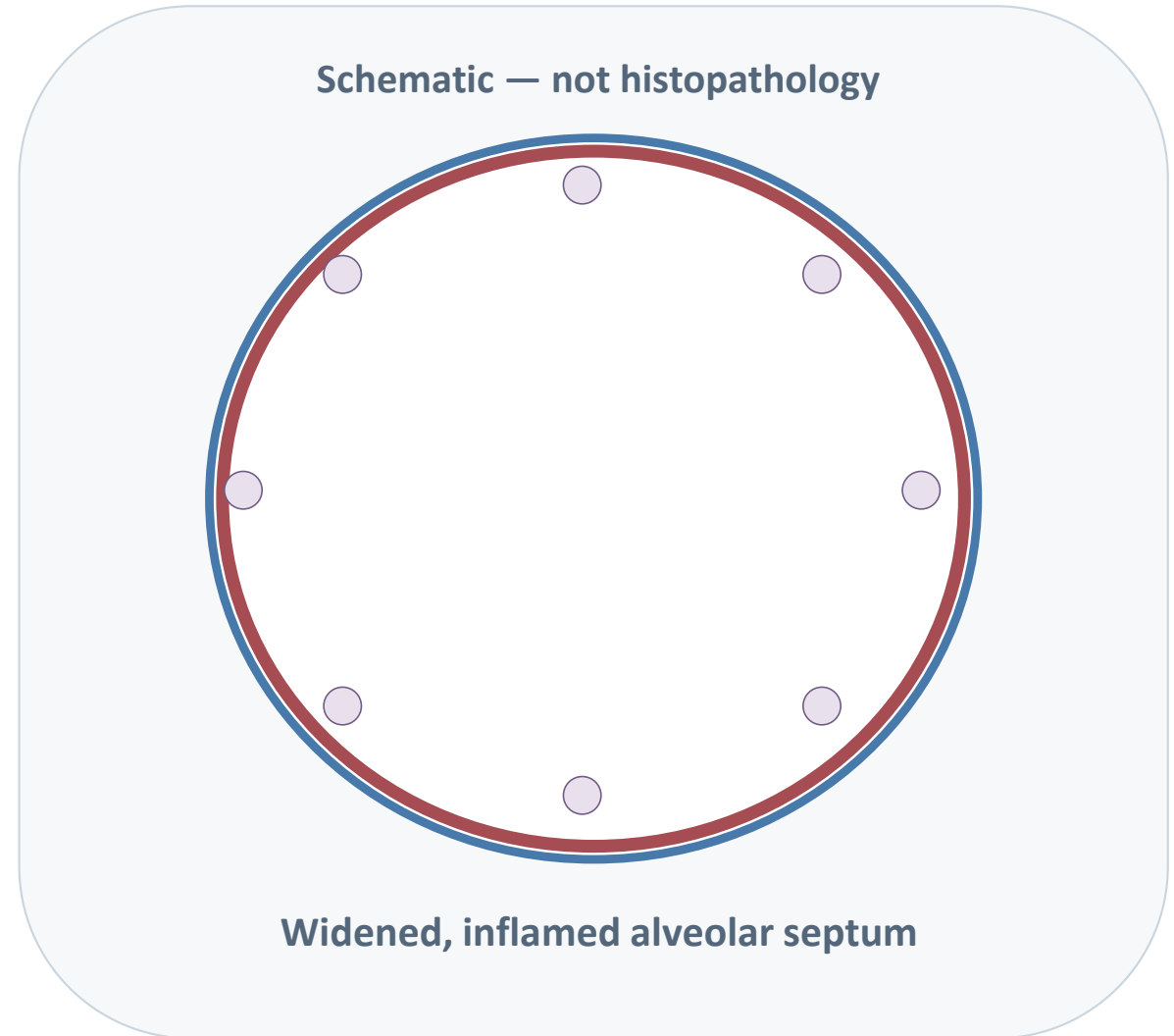
- Discrete affected parenchymal regions
- Adjacent relatively aerated lung
- Heterogeneous ventilation

Extensive involvement

- Lobar or bilateral disease possible
- Red-blue congested lung tissue
- Greater loss of functioning gas exchange

Interstitial inflammation is a central pattern

- Alveolar septa become widened and edematous.
- Mononuclear inflammatory cells infiltrate alveolar walls.
- The process is centered on the interstitium, not simply the alveolar lumen.



The interstitial infiltrate is usually mononuclear

Typical viral interstitial process

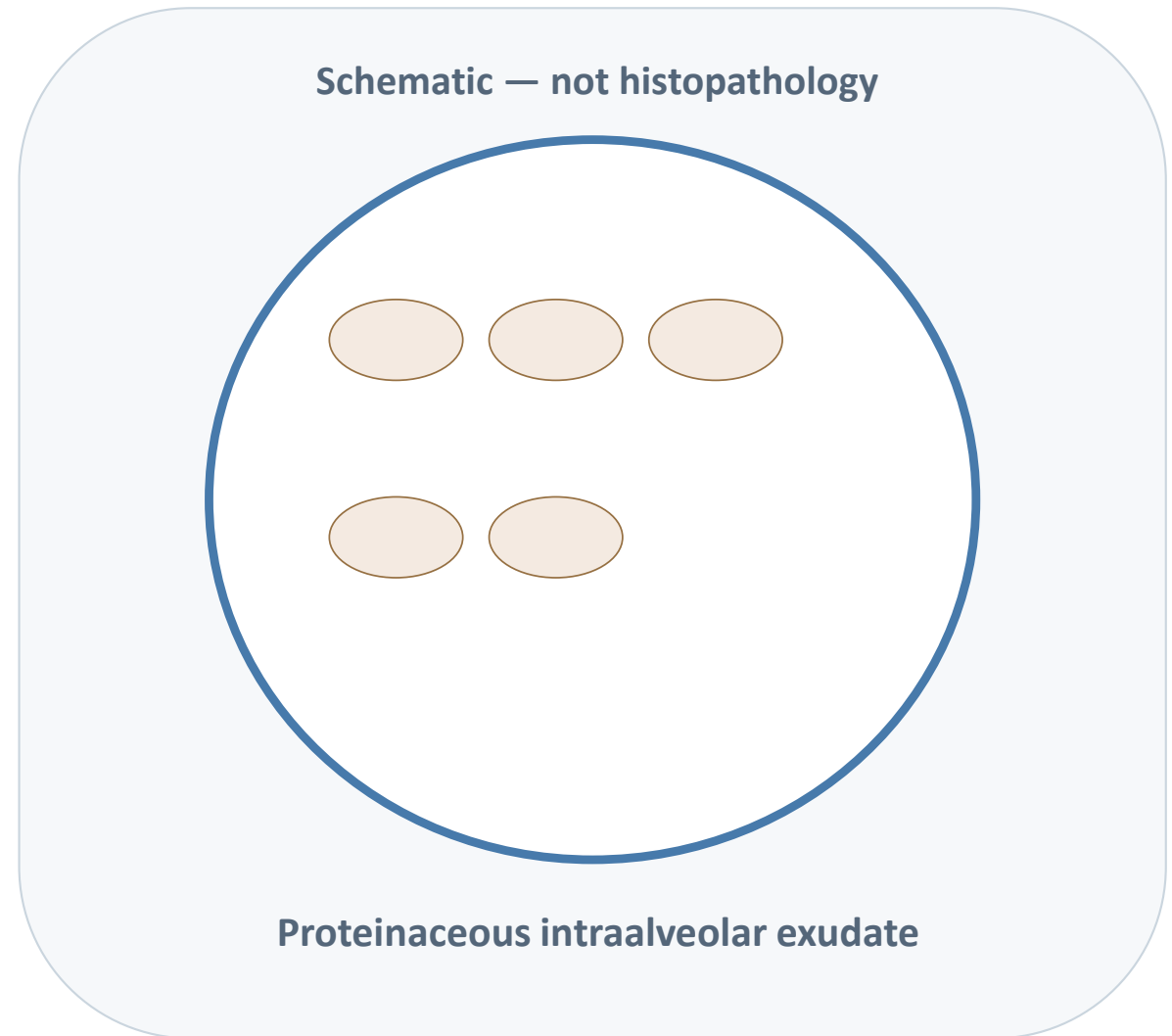
- Lymphocytes and macrophages
- Occasional plasma cells
- Septal edema and widening

Severe or modified pattern

- Neutrophils may also be present
- Superimposed bacteria change exudate composition
- Histology alone may not identify the virus

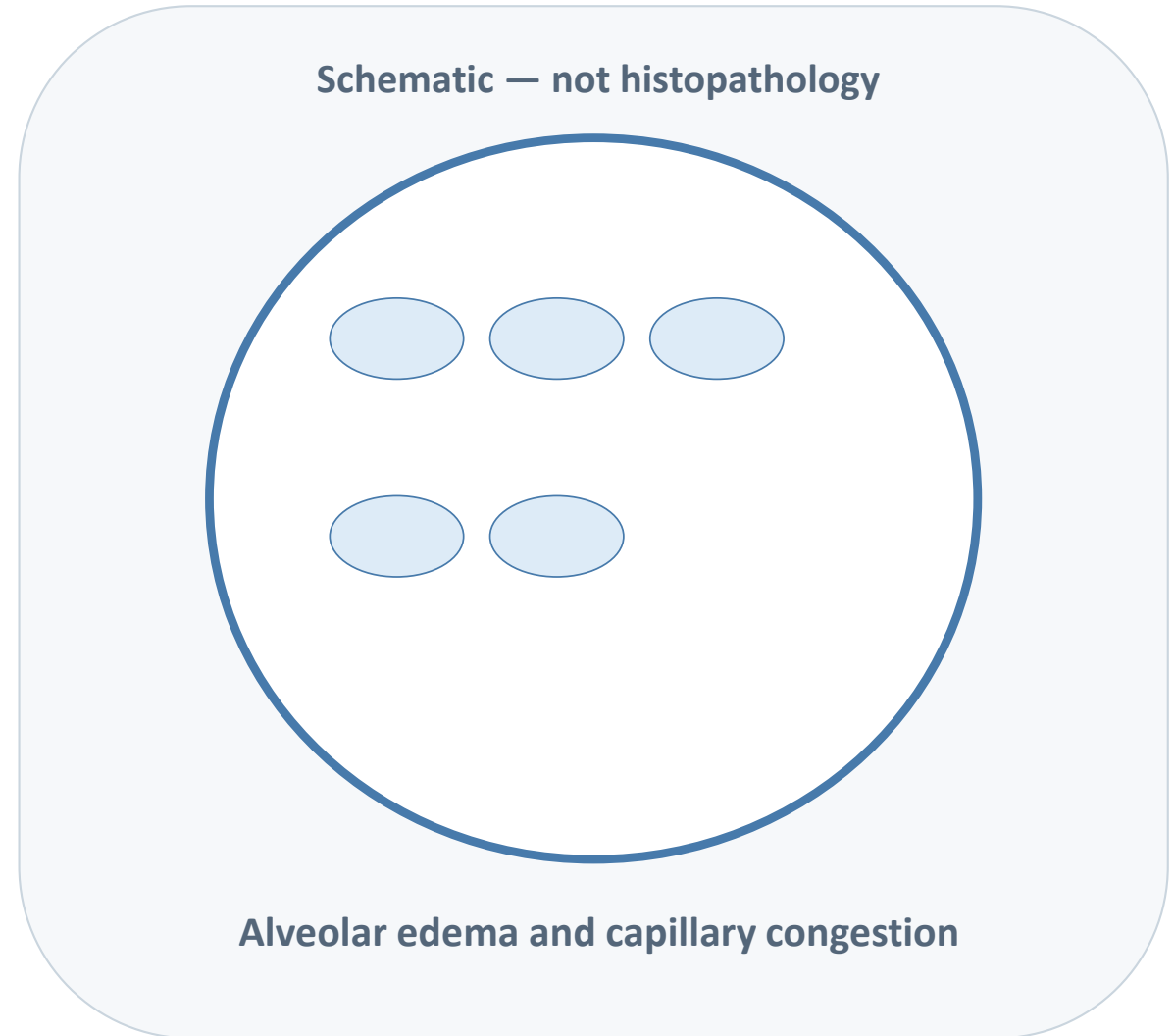
Alveolar exudate varies across cases

- Some viral pneumonias have minimal intraalveolar material.
- Others contain protein-rich fluid and inflammatory cells.
- Increasing exudation compromises aeration and diffusion.

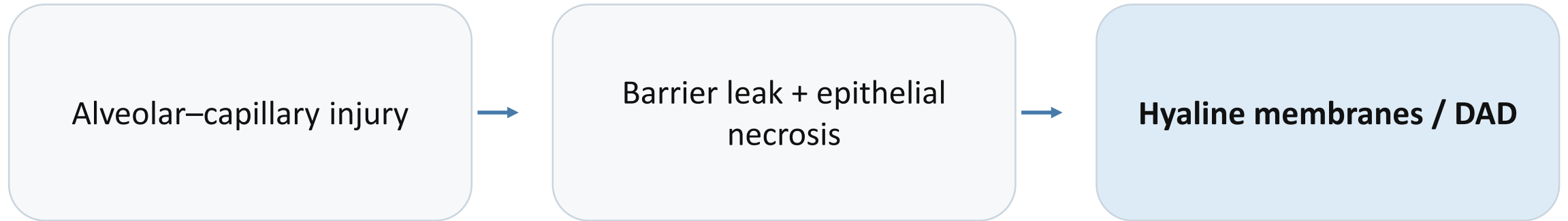


Severe COVID-19 may produce congested, edematous lungs

- In fatal cases, gross lungs are congested and edematous.
- Vascular congestion accompanies alveolar and septal fluid accumulation.
- These findings are not specific to one viral pathogen.



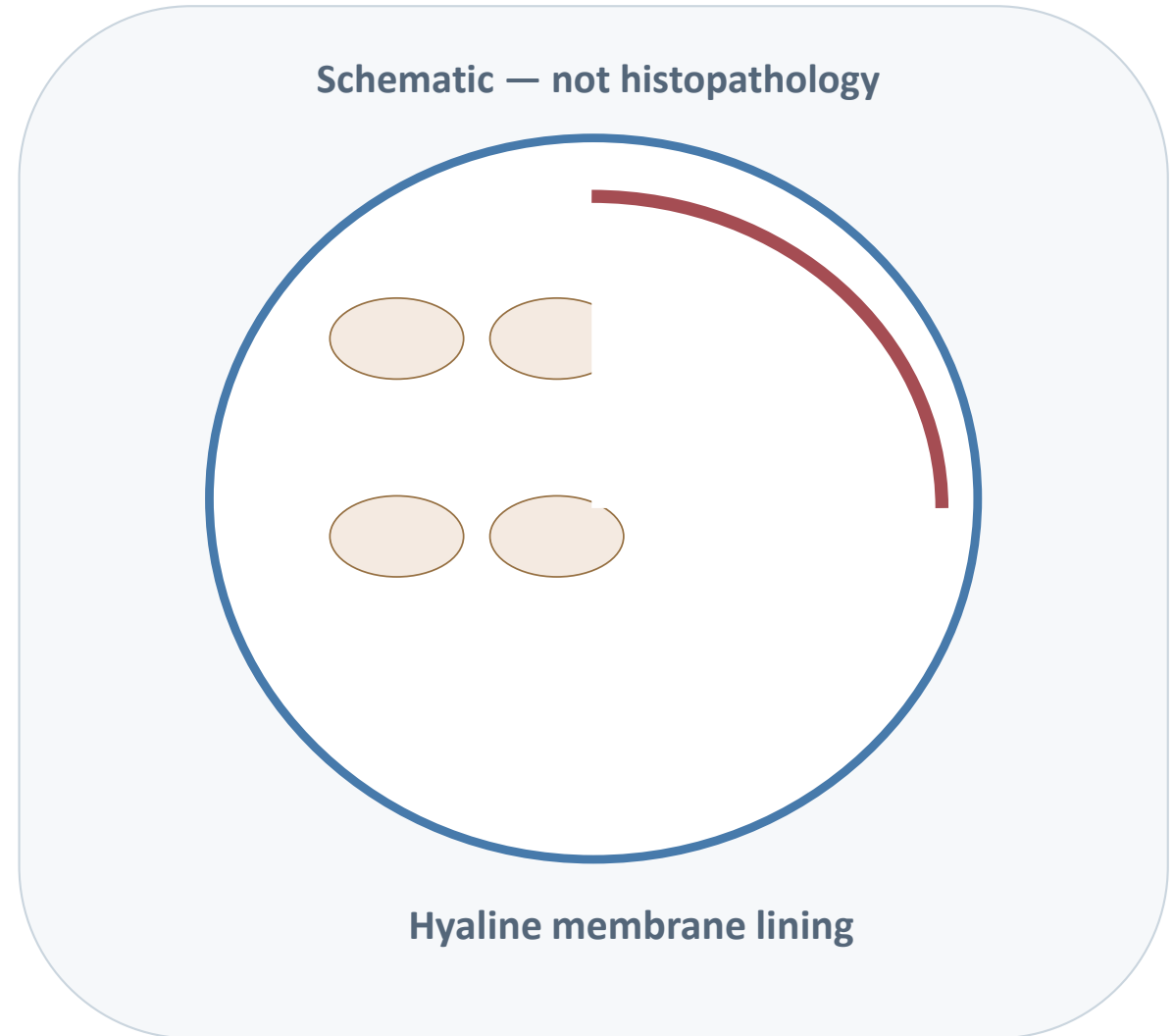
Diffuse alveolar damage defines the ARDS lesion



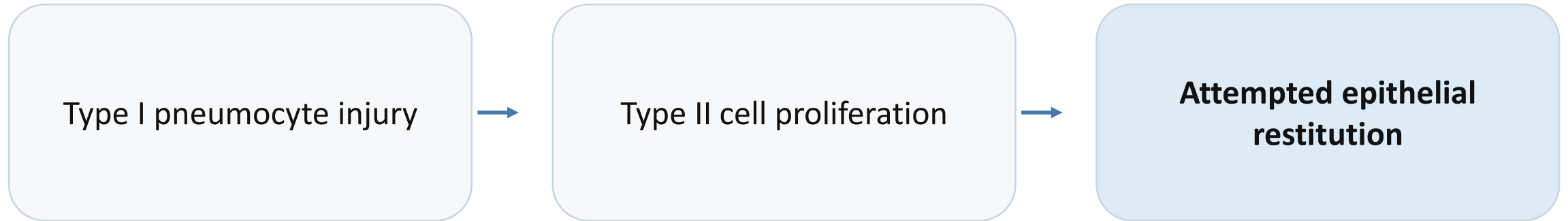
- Severe epithelial and endothelial injury culminates in diffuse alveolar damage (DAD).
- Hyaline membranes, edema, and epithelial injury characterize the exudative phase.
- DAD represents an injury pattern, not a pathogen-specific signature.

Hyaline membranes form from leaked proteins and debris

- Capillary leak delivers fibrin-rich plasma proteins into alveolar spaces.
- Necrotic epithelial debris mixes with the exudate.
- Condensed material lines alveolar walls as eosinophilic hyaline membranes.



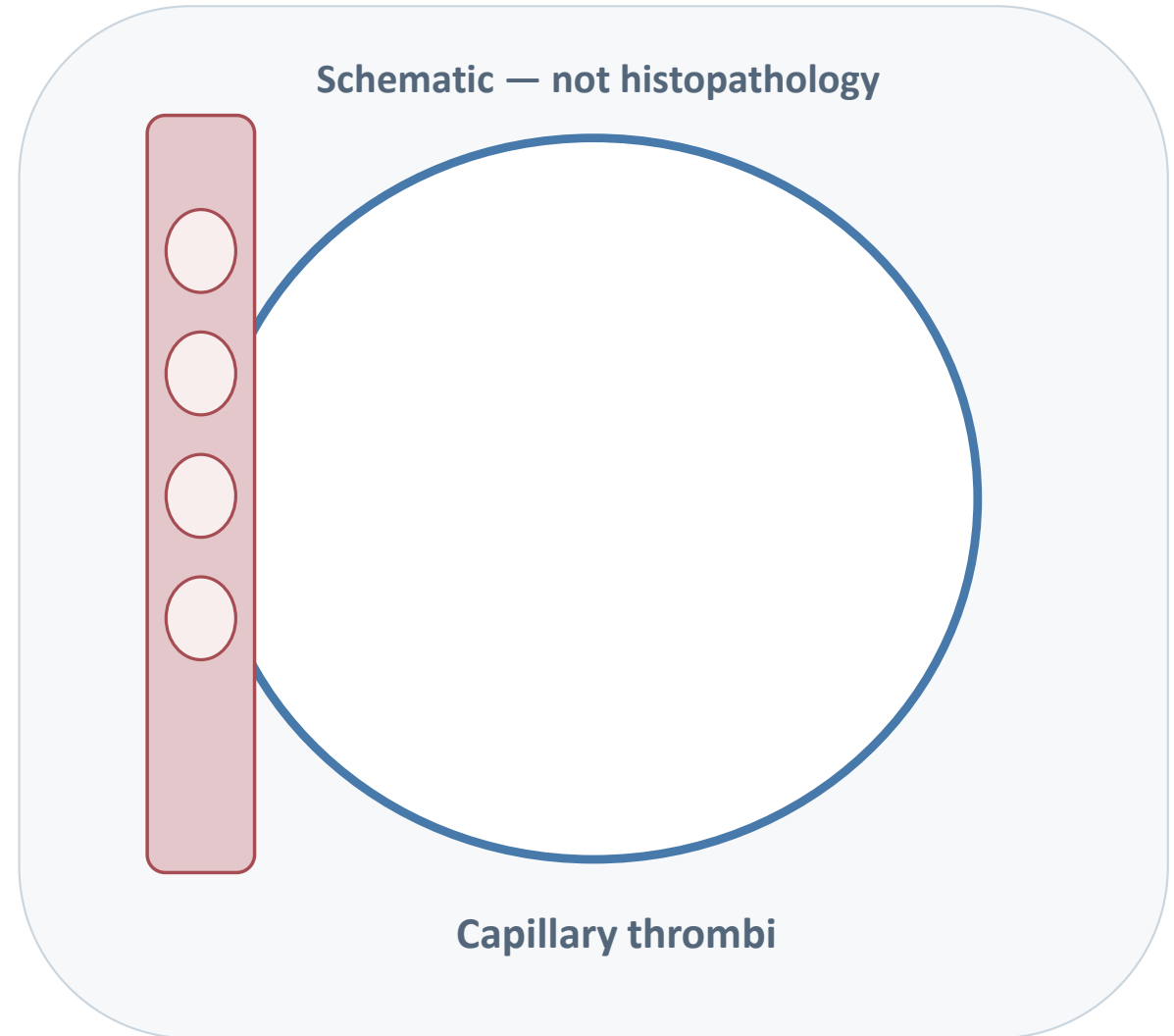
Type II pneumocyte hyperplasia signals epithelial repair



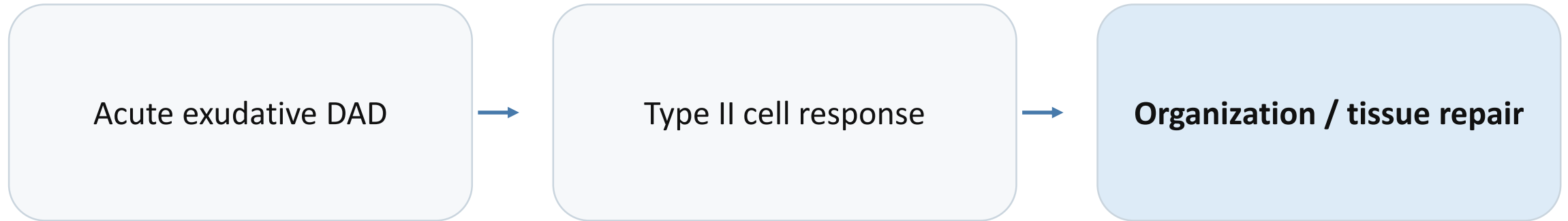
- Severe COVID-19 may show hyperplasia of type II pneumocytes.
- Surviving type II cells proliferate during alveolar epithelial restoration.
- This accompanies evolving or organizing diffuse alveolar damage.

Pulmonary microthrombi link inflammation to perfusion

- Thrombi occur in pulmonary arterioles and alveolar capillaries in severe fatal COVID-19.
- Vascular thrombosis adds perfusion abnormalities to impaired alveolar ventilation.
- The coexistence of DAD and microthrombi is diagnostically informative but not exclusive.



Acute lung injury can enter an organizing phase



- The acute phase shows edema, epithelial necrosis, fibrin, and hyaline membranes.
- The organizing phase includes type II pneumocyte hyperplasia and granulation tissue.
- The trajectory depends on persistence or resolution of injury.

Recovery and fibrosis are alternative trajectories

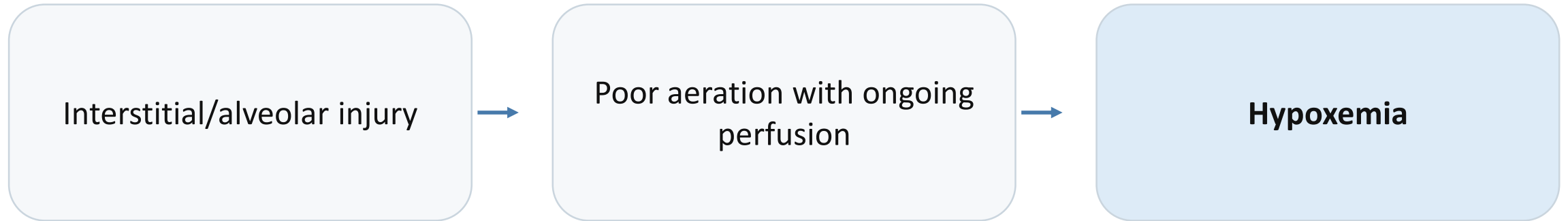
Recovery

- Trigger and inflammation abate
- Macrophages clear debris
- Alveolar lining reconstituted

Fibroproliferative outcome

- Persistent injury and organizing exudate
- Fibroblast activation and collagen deposition
- Possible chronic functional impairment

Ventilation–perfusion mismatch causes hypoxemia



- Edema and alveolar exudate reduce ventilation of perfused regions.
- Patchy parenchymal injury creates regional V/Q inequality.
- Gas exchange failure can be prominent despite limited focal signs.

Symptoms can exceed the physical examination

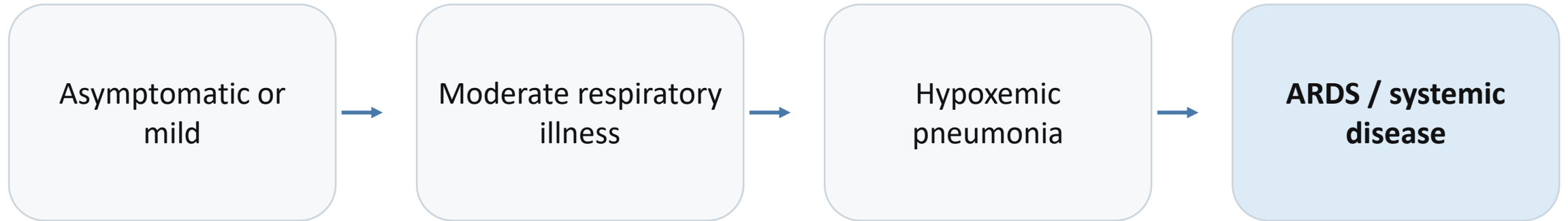
Reported symptoms

- Fever and myalgia
- Headache and fatigue
- Dyspnea or cough; Cough may be absent

Pathologic explanation

- Interstitial edema and inflammation
- V/Q mismatch
- Impaired oxygenation despite scant localizing signs

Clinical severity ranges from silent to critical



- Asymptomatic infection can occur.
- Most recognized cases present with an acute respiratory/systemic illness.
- Severe cases progress to hypoxemia and respiratory failure.

Severe disease includes hyperinflammation



- Severe COVID-19 may show elevated proinflammatory cytokines, including TNF and IL-6.
- These signals amplify inflammatory cell activation and tissue injury.
- Inflammation is one component of disease, not the sole explanation.

Lymphopenia reflects immune dysregulation

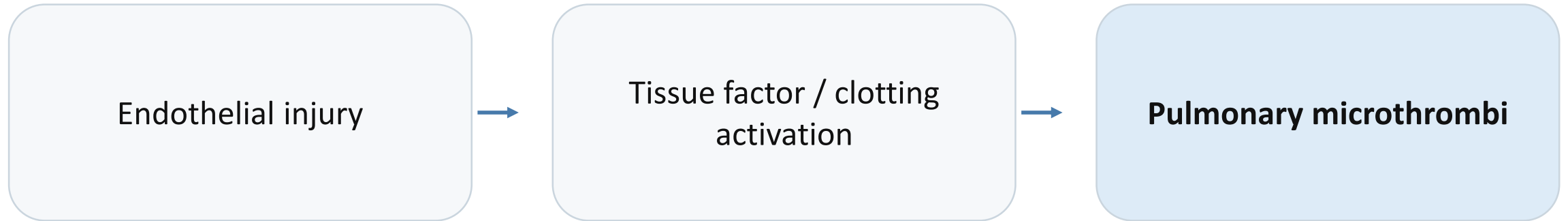
Clinical laboratory pattern

- Reduced circulating lymphocytes
- Altered myeloid cell populations
- Reduced T- and NK-cell numbers in severe disease

Interpretive caution

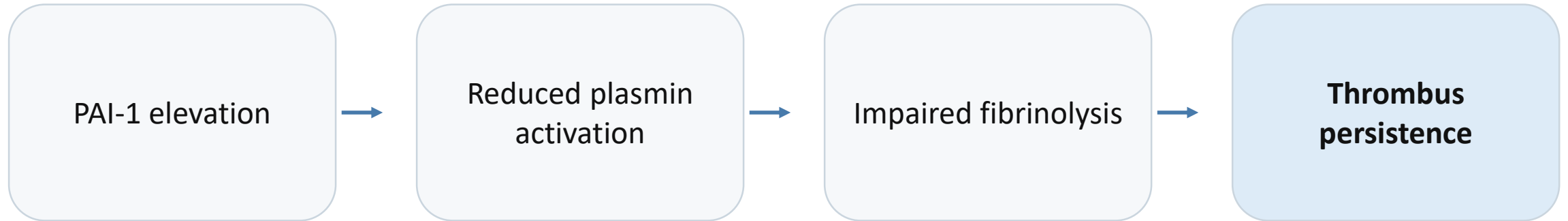
- Supports systemic immune disturbance
- Not a standalone diagnostic test
- Must be interpreted with infection confirmation and clinical context

COVID-associated coagulopathy promotes thrombosis



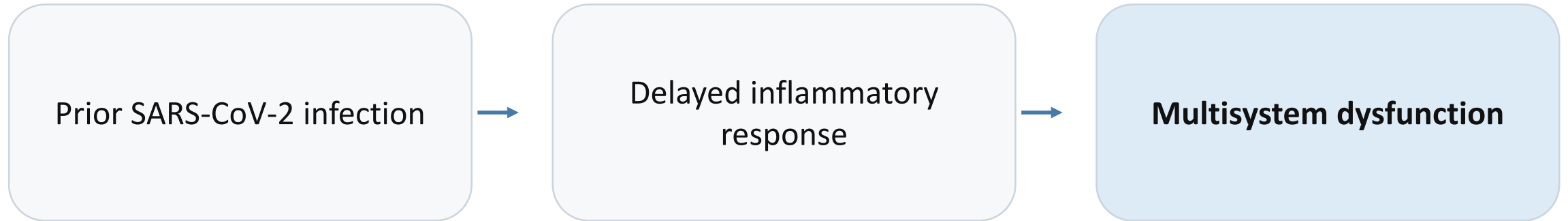
- Inflammation or endothelial damage can expose tissue factor.
- Coagulation activation favors intravascular thrombus formation.
- Vascular injury and lung injury can reinforce each other.

Reduced fibrinolysis may intensify thrombosis



- PAI-1 can inhibit tissue plasminogen activator and urokinase.
- Less plasmin generation impairs fibrin degradation.
- The combined effect can shift the balance toward thrombosis.

MIS-C is a delayed pediatric inflammatory syndrome



- Onset commonly 2–6 weeks after acute COVID-19.
- Gastrointestinal, mucocutaneous, neurologic, and cardiac abnormalities may coexist.
- Shock can occur, but most affected children recover.

Adult systemic inflammation has diverse patterns

- Some severe adult cases show an HLH-like syndrome with cytopenias and acute-phase reactant elevation.
- Vasculitis may involve skin, CNS, lungs, or gastrointestinal tract.
- Myositis and arthritis may accompany systemic inflammation.
- These complications should not be inferred from pulmonary histology alone.

Long COVID extends beyond acute viral pneumonia

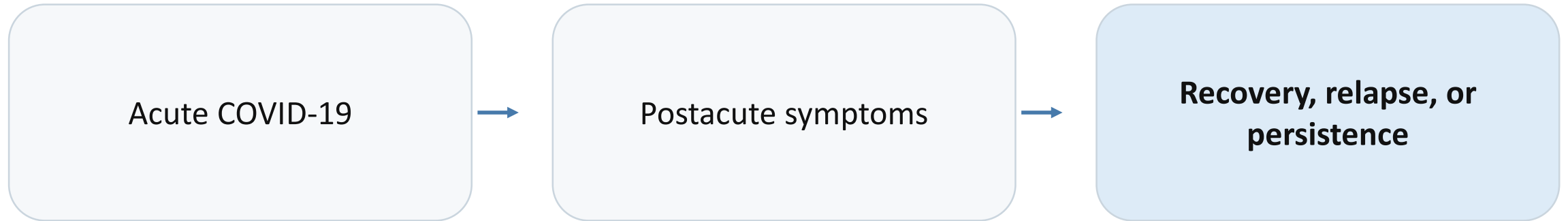
Physical symptoms described

- Fatigue and weakness
- Dyspnea and chest pain
- Cough

Neuropsychological symptoms

- Impaired memory or concentration
- Anxiety and depression
- Posttraumatic stress manifestations

Long COVID trajectories are heterogeneous



- Symptoms may persist or relapse after acute infection.
- Definitions vary across studies, complicating prevalence estimates.
- Some recover while others have relapsing-remitting or progressive symptoms.

Bacterial superinfection changes morphology

Predominantly viral injury

- Interstitial mononuclear infiltrate
- Variable proteinaceous alveolar exudate
- Possible diffuse alveolar damage

Superimposed bacterial infection

- Suppurative bronchitis / bronchiolitis
- More neutrophil-rich exudation
- Bacterial pneumonia may become dominant

Antigen tests and PCR detect different analytes

Antigen assay

- Antibody-based detection of nucleocapsid protein
- Usually performed on upper-airway swabs
- Detects viral protein

Molecular assay

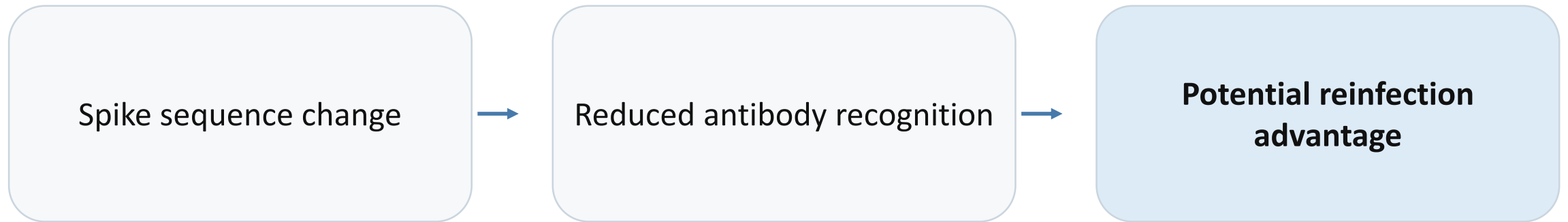
- PCR-based detection of viral RNA
- Targets nucleic acid rather than protein
- Method performance depends on specimen and timing

Genetic changes continually generate variants



- Mutations, insertions, deletions, and recombination change viral sequences.
- Variant phenotype depends on effects on transmissibility, pathogenicity, and immune recognition.

Spike changes can modify immune escape



- Changes in spike may impair recognition by existing neutralizing antibodies.
- The textbook uses the emergence of Omicron as an example of immune escape.
- A named historical variant should not be mistaken for the current dominant lineage.

Clinical application: Mild respiratory infection

Clinical problem

- A patient has coryza, sore throat, and mild cough without hypoxemia.
- What epithelial changes best explain congestion and impaired drainage?
- Why should a histology pattern not be labeled coronavirus-specific?

Teaching interpretation

Mucosal hyperemia/edema, submucosal mononuclear inflammation, and mucus hypersecretion; Similar findings occur with many respiratory viruses.

Clinical application: Rapidly progressive hypoxemia

Clinical problem

- An older patient with comorbid illness develops dyspnea and diffuse opacities after confirmed SARS-CoV-2 infection.
- Which pattern of lung injury should be considered?
- How do hyaline membranes and microthrombi affect gas exchange?

Teaching interpretation

Diffuse alveolar damage with alveolar edema/hyaline membranes, often with pulmonary microthrombi; Both ventilation and perfusion become disturbed.

Morphology exercise: Diagnose an injury pattern

Clinical problem

- Lung sections show septal edema, intraalveolar fibrin-rich exudate, hyaline membranes, and reactive type II pneumocytes.
- Name the morphologic pattern; Then identify what this pattern cannot establish by itself.
- Which additional data would support a SARS-CoV-2 etiology?

Teaching interpretation

Diffuse alveolar damage. It is nonspecific as to etiology; Clinical context and SARS-CoV-2 antigen/PCR results support causation.

Integrating mechanisms with diagnostic findings

Early / less severe infection

- Virus attaches and replicates
- Upper airway symptoms predominate
- Mucosal edema and mononuclear reaction

Severe pulmonary involvement

- Immune dysregulation and vascular injury
- Hypoxemia and possible ARDS
- DAD, hyaline membranes, microthrombi

Core conclusions

- Human coronaviruses span mild upper-airway infections and severe lower-respiratory disease.
- ACE2–spike binding and TMPRSS2-dependent fusion initiate SARS-CoV-2 entry.
- Type I interferon defenses oppose replication; Viral proteins interfere with recognition and signaling.
- Severe lung disease is mediated by epithelial injury, inflammation, diffuse alveolar damage, and vascular thrombosis.

References and source boundaries

Robbins, Cotran & Kumar. Pathologic Basis of Disease. 11th ed. 2026. Sections: Human Coronaviruses and viral pneumonia.

Robbins, Cotran & Kumar. Pathologic Basis of Disease. Section: COVID-19 (Infectious Diseases).

Robbins, Cotran & Kumar. Pathologic Basis of Disease. Section: Acute Lung Injury and ARDS (The Lung).

Schematic visuals are original editable teaching diagrams; no clinical images or histology specimens are presented.