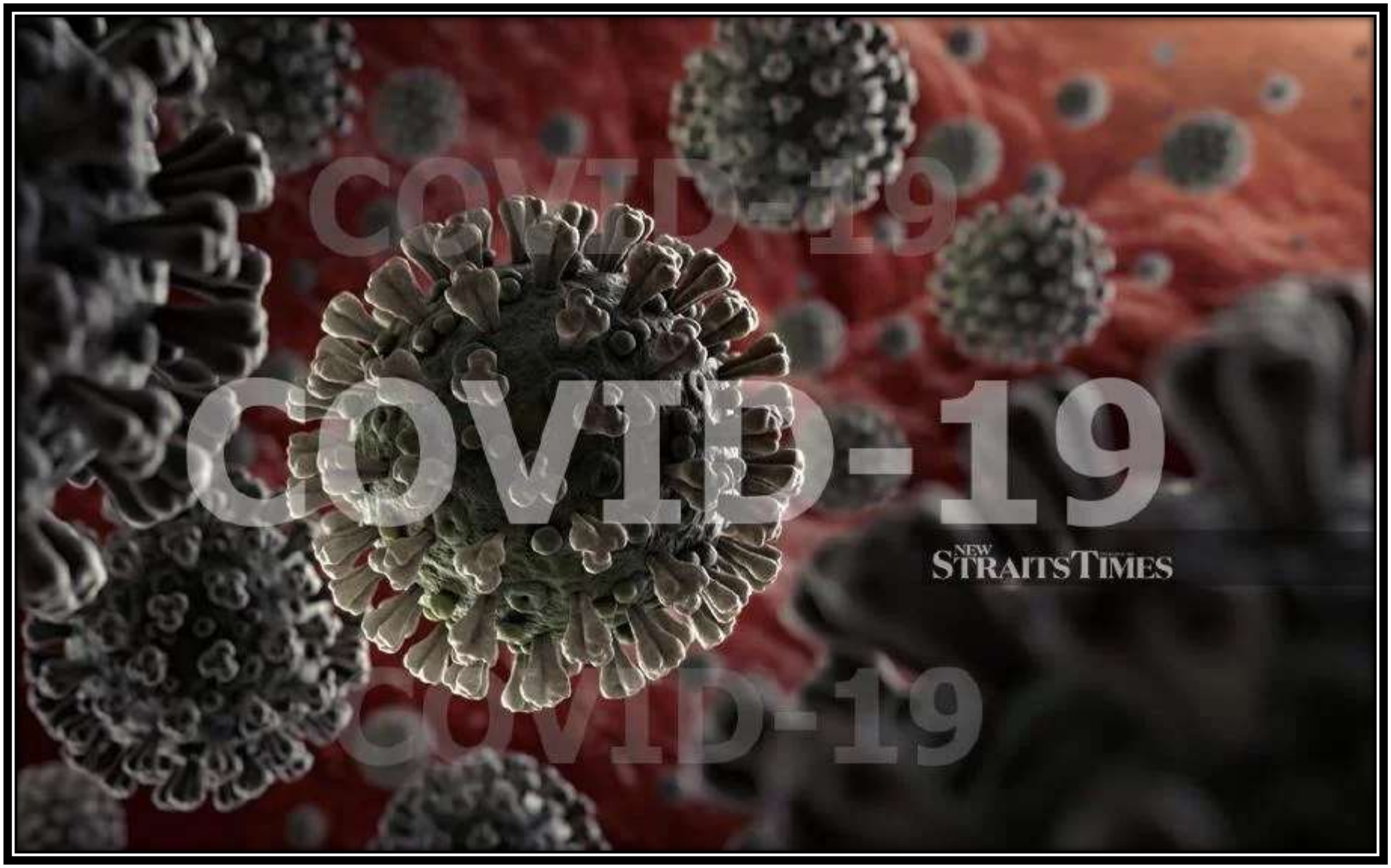
بسم الله الرحمن الرحيم

Bismillah al rahman al rahim


COVID-19
COVID-19
COVID-19
NEW STRAITS TIMES

The new name of this disease is coronavirus disease 2019, abbreviated as **COVID-19**. In COVID-19, 'CO' stands for 'corona,' 'VI' for 'virus,' and 'D' for disease. Formerly, this disease was referred to as "2019 novel coronavirus" or "2019-nCoV."

Types Human coronaviruses

There are **7** known strains of human coronaviruses:

I. 229E alpha coronavirus

II. NL63 alpha coronavirus

III. OC43 beta coronavirus

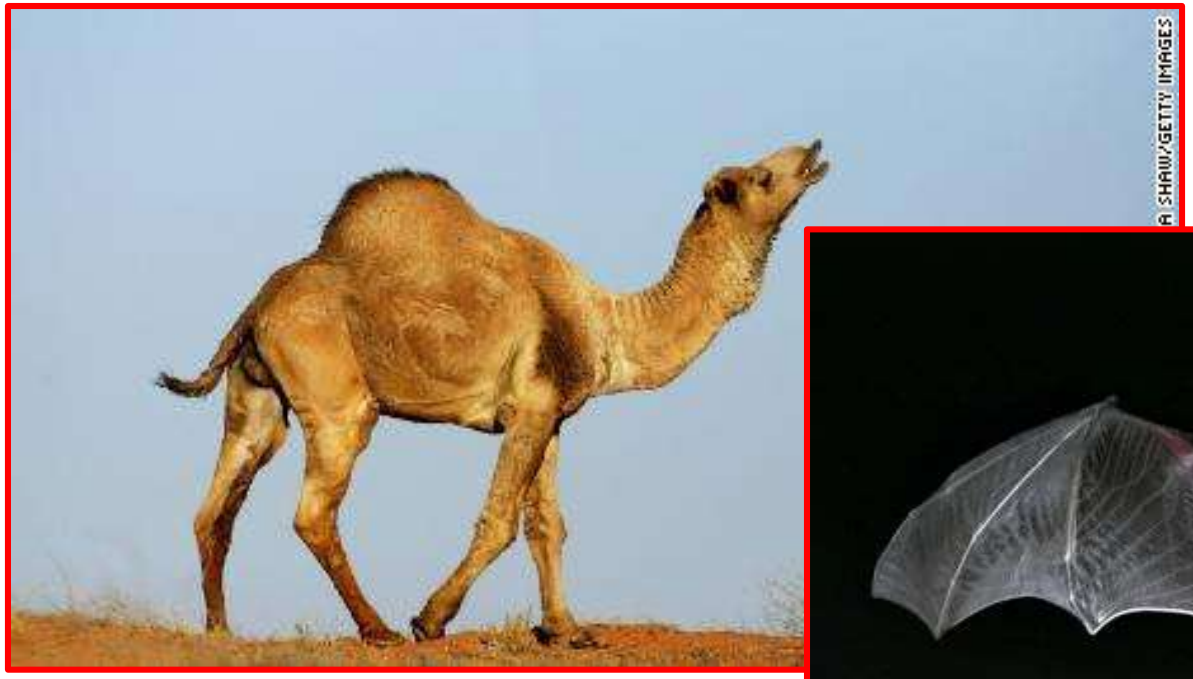
IV. HKU1 beta coronavirus

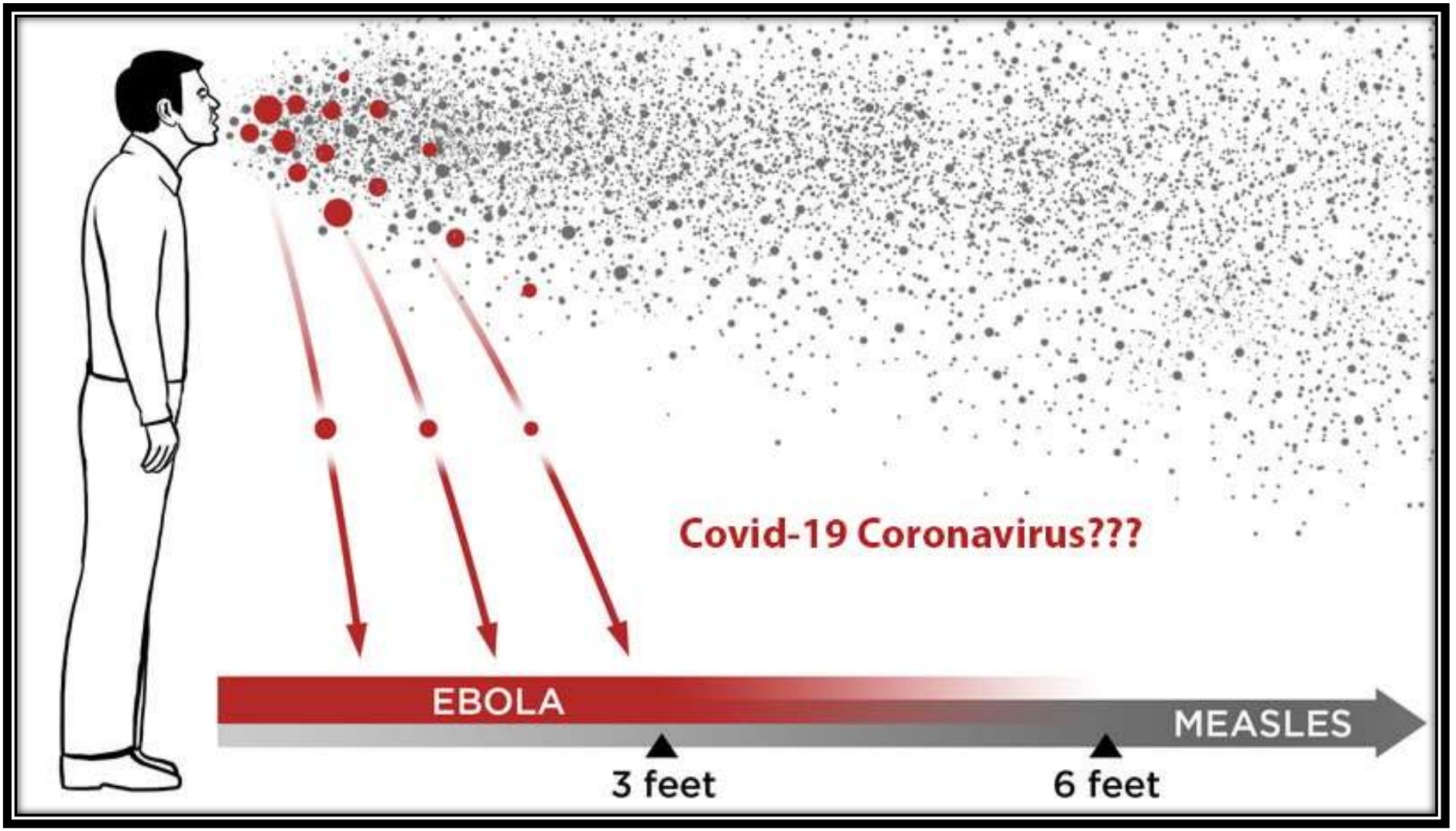
V. MERS-CoV (beta CoV)

VI. SARS-CoV (beta CoV)

VII. 2019 Novel CoV (nCoV)


FROM TRACEY CAUTHEN/FWC/FACEBOOK

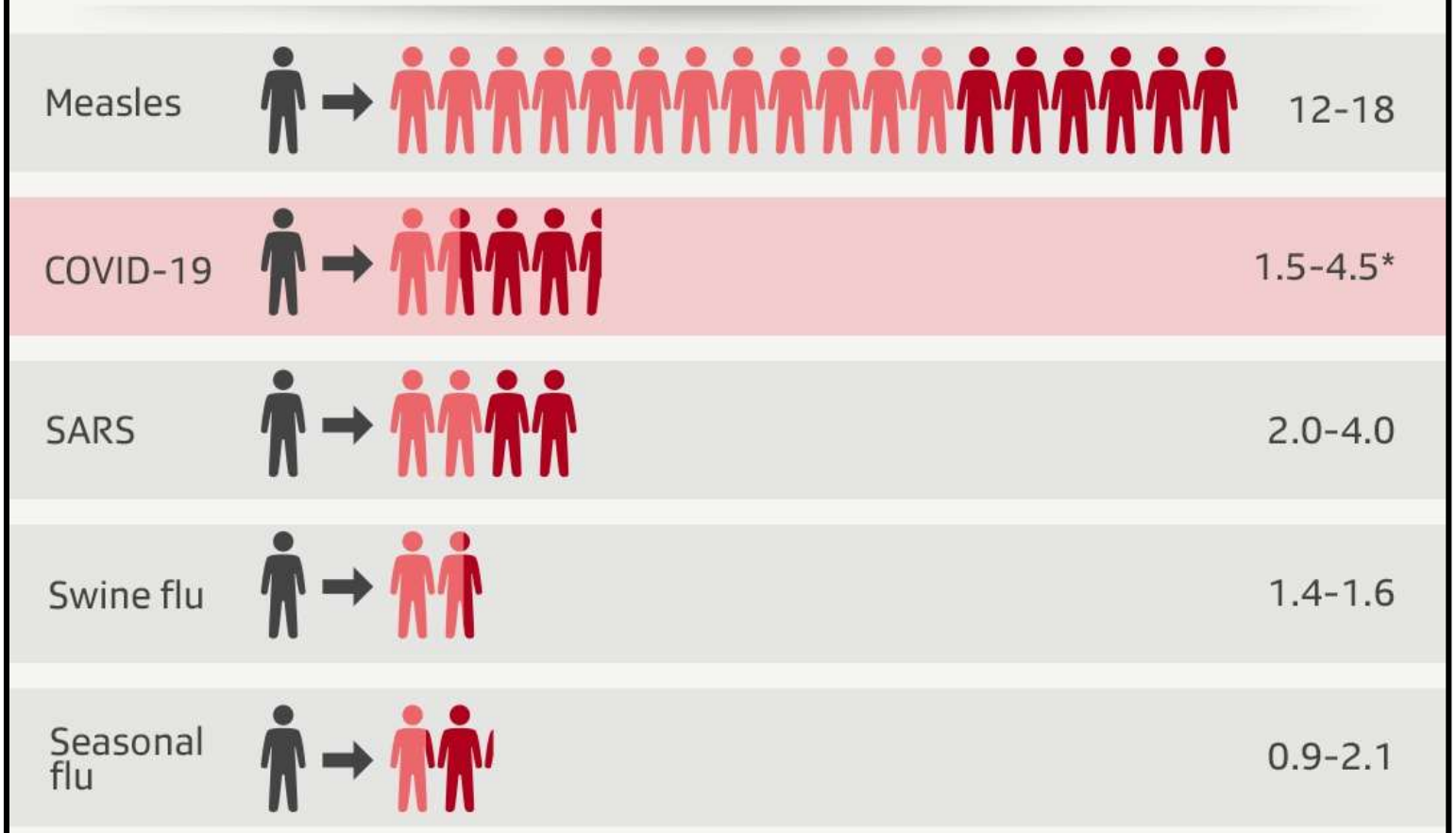

A SHAW/GETTY IMAGES



Aerosol transmission is a type of airborne transmission and refers to the mixing of the virus with **droplets in the air** to form aerosols, which causes infection after inhalation.

Infection rate

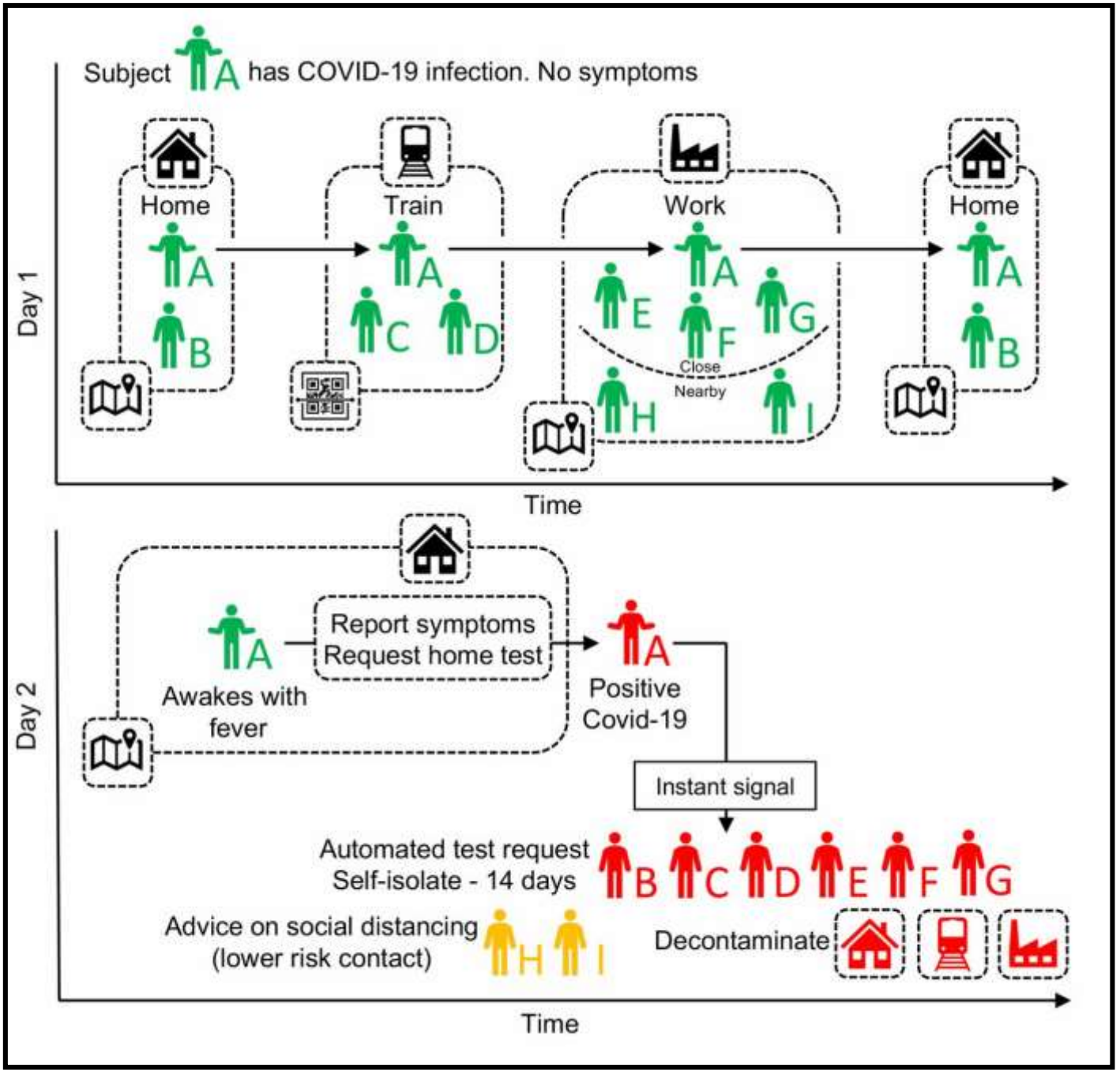
The average number of people an ill person infects



*according to data from Wuhan

Source: Estimates from the WHO, the CDC, the London School of Hygiene and Tropical Medicine and various studies

SWI


Subject A has COVID-19 infection. No symptoms
Day 1
Home
Train
Work
Home
A
B
C
D
E
F
G
H
I
Close
Nearby
Time
Day 2
Awakes with fever
Report symptoms
Request home test
Positive Covid-19
Instant signal
Automated test request
Self-isolate - 14 days
Advice on social distancing
(lower risk contact)
Decontaminate
Time

COVID-19 (Corona Virus Disease 2019): Pathophysiology and Clinical Findings

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Reviewers:
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Stephen Vaughan*
** MD at time of publication*

Respiratory droplet production (cough, sneeze, talking) by human host or animal vector infectedwith SARS-CoV-2

Droplet contact with mucus membrane (eyes, ears, nose, mouth) of recipient

Live viral particles adhere to inanimate objects called fomites (e.g. doorknobs, surfaces, clothing)

Recipient touching infected fomite subsequently touches any of their mucus membranes

Patient exposed to the virus (SARS-CoV-2)

Virus spreads directly on mucus membranes to surrounding cells (major mechanism)

Virus enters the blood stream (minor mechanism)

Virus adheres to angiotensin-converting enzyme 2 (ACE-2) receptor on body cells, mimics ACE-2, and gains access into the cell

Virus disassembles, releasing viral RNA, which uses host cell's ribosomes to make new viral proteins

Newly made viral RNA-polymerases use cell's own nucleotides to synthesize new viral RNA

Viral RNA & proteins packaged into new viral particles

New virus assembled and released from cell

Note: Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the name of the betacoronavirus (a positive sense, single stranded RNA virus). COVID-19 is the name of the disease caused by this virus.

Symptoms are on a continuum

Mild
- -Fever
- -Cough
- -Myalgia
- -Fatigue
- -Anorexia
- -Mild dyspnea

Moderate
- -Worsening dyspnea
- -Bilateral interstitial infiltrates on Chest X-ray

Severe
- -Acute Respiratory Distress Syndrome
- -Shock
- -Arrhythmia

COVID-19 Infection with SARS-CoV-2 and symptomatic

Average incubation period (time from initial infection to symptom onset) is 4-5 days; can be up to 14 days

Viral proliferation in cells of tissues with more ACE-2 receptors: **lungs** (type II pneumocytes); **vasculature** (endothelial cells), **kidneys** (proximal tubular epithelium), **heart** (myocardium), **GI tract** (enterocytes)

Neutrophils move to lungs, release reactive oxygen species and cytokines

Airway irritation → **Cough**

Alveolar/capillary damage

Fluid accumulates in interstitium and alveoli → **Bilateral ground-glass opacities (CT lung) & interstitial infiltrates on Chest X-ray**

↑ Distance for O2 to diffuse from alveoli to capillary → ↓ blood O2 saturation → **Dyspnea**

Heart tries to compensate for hypoxemia → ↑ cardiac output and strain on myocardium → **Arrhythmogenic state**

↑ myocardial cell damage → ↑ **Troponin**

Cell death and ↑ in inflammatory cytokines triggers immune response

Cytokines induce the hypothalamus to release prostaglandins → ↑ body temperature set point to fight infection → **Fever**

↑ skeletal muscle cell damage → **Myalgia**

Legend: Pathophysiology | Mechanism | Sign/Symptom/Lab Finding | Complications

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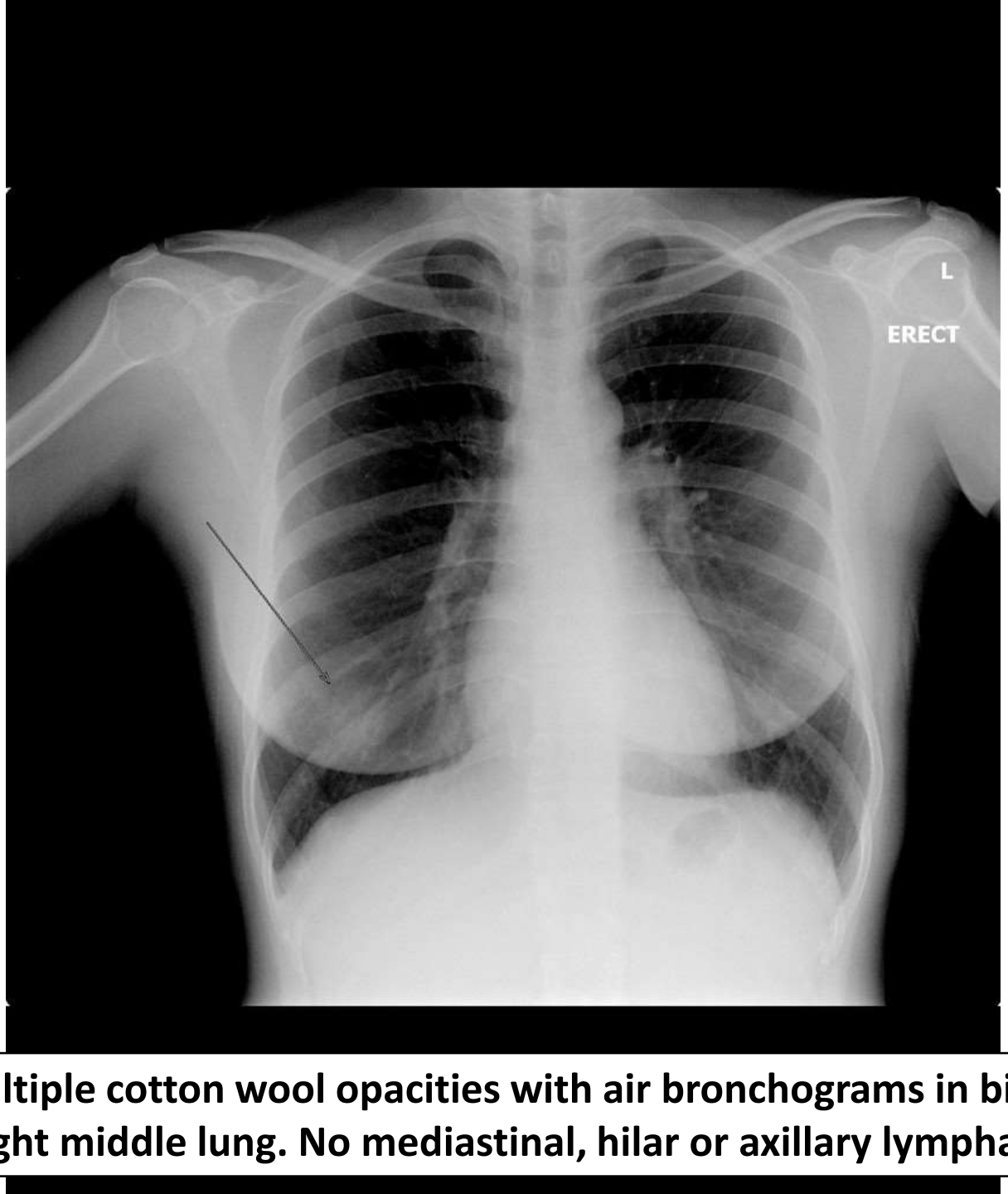
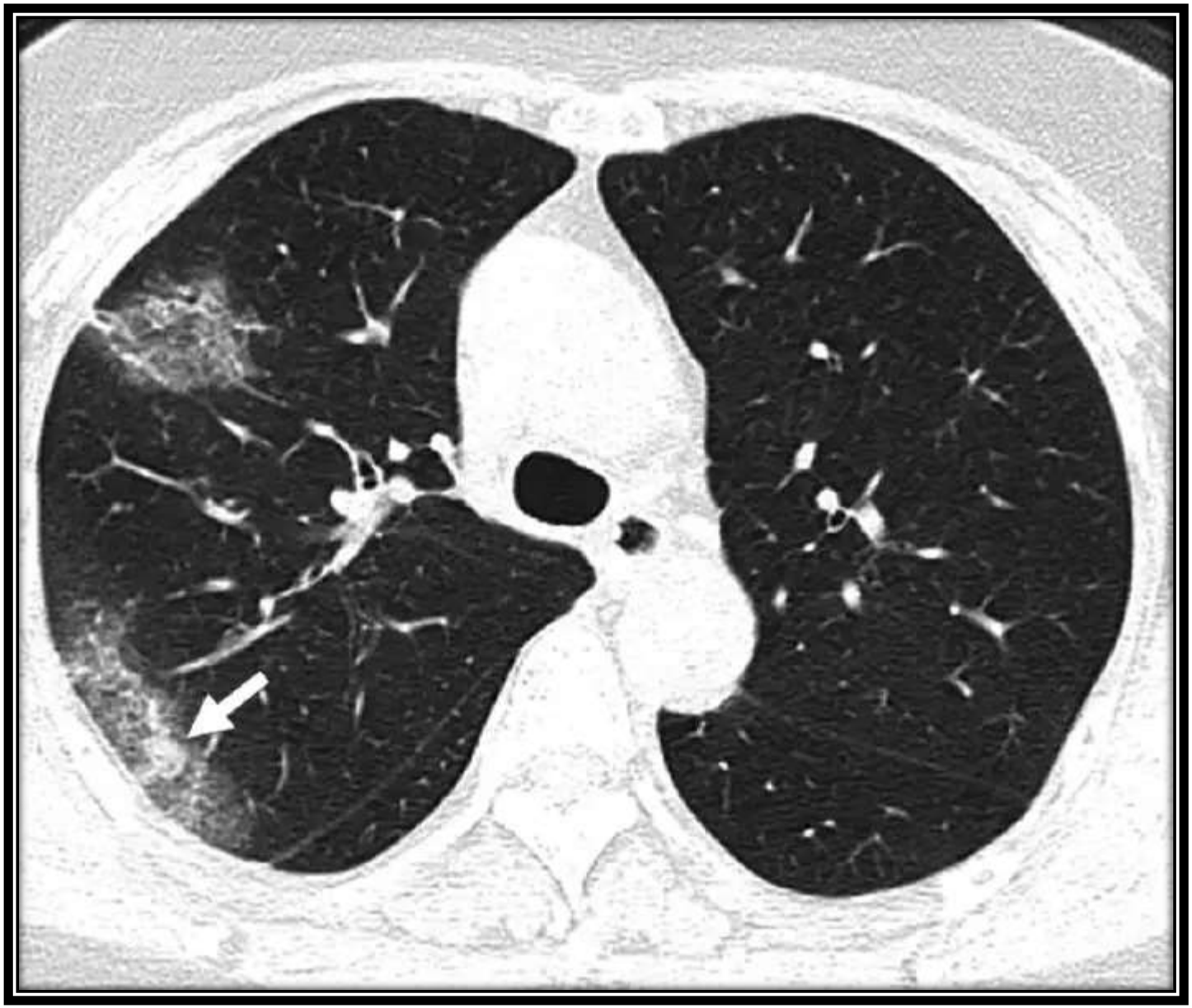
Mild disease	Severe disease	Critical disease
Dry Cough	Fever	Respiratory failure
Fever	Tachypnea	Fever
Sour throat	Dyspnea	Decreases blood oxygen saturation
With or without nasal congestion		Septic shock
Generalized body aches		Multiple organ failure
Headache		
Malaise and fatigue		

Clinical features of patients with a varying degree of disease

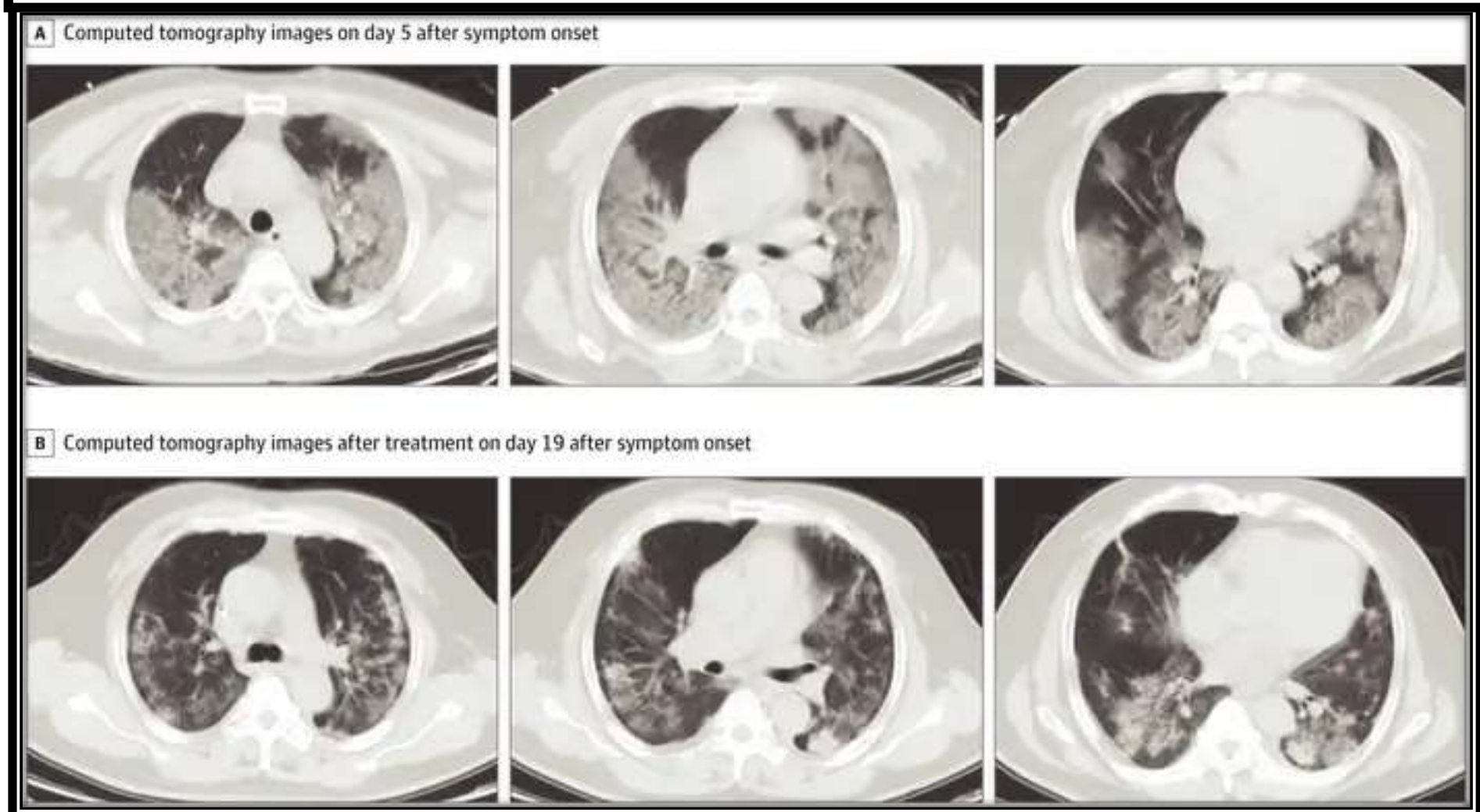


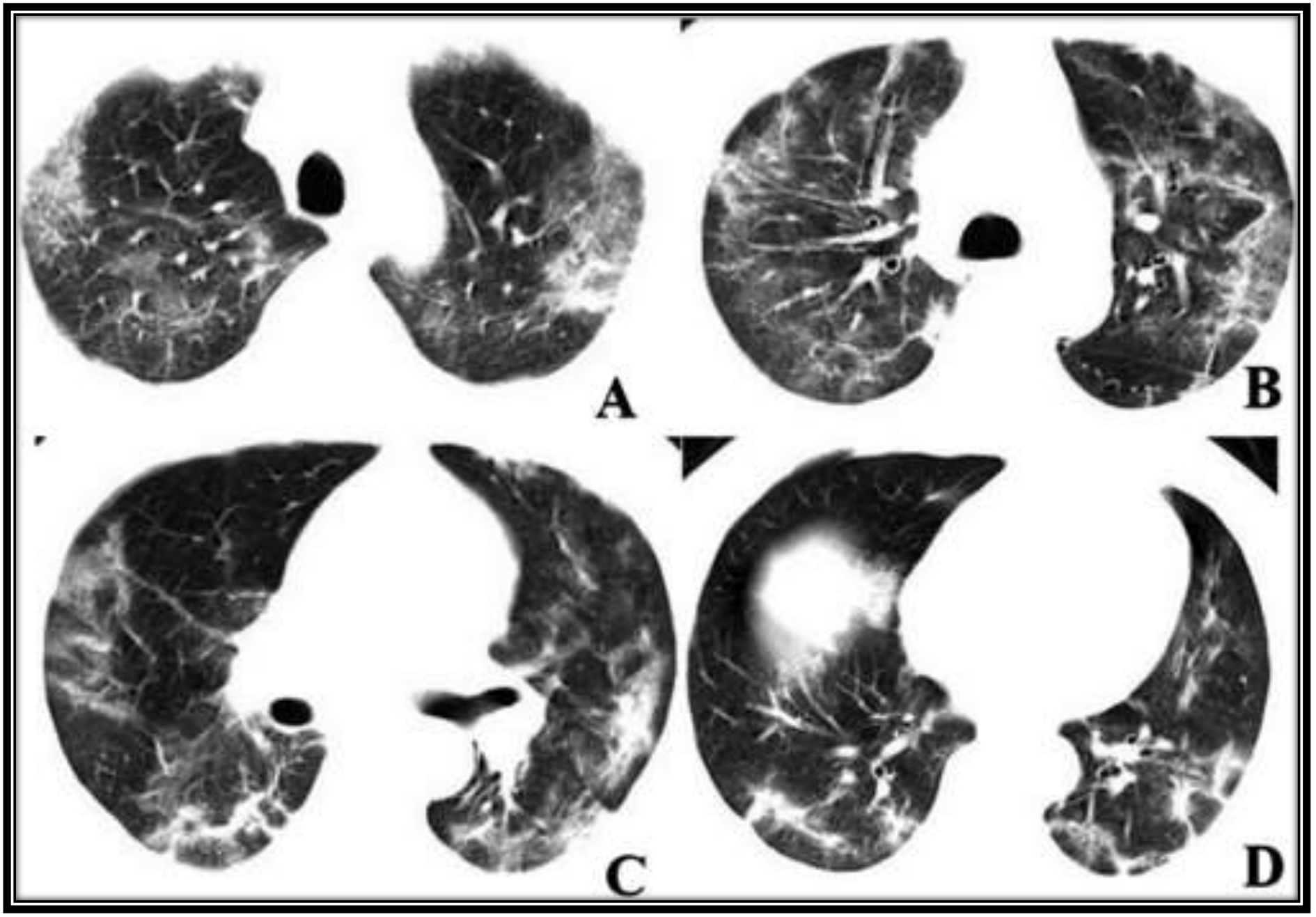
There are multiple cotton wool opacities with air bronchograms in bilateral lower lungs and right middle lung. No mediastinal, hilar or axillary lymphadenopathy.

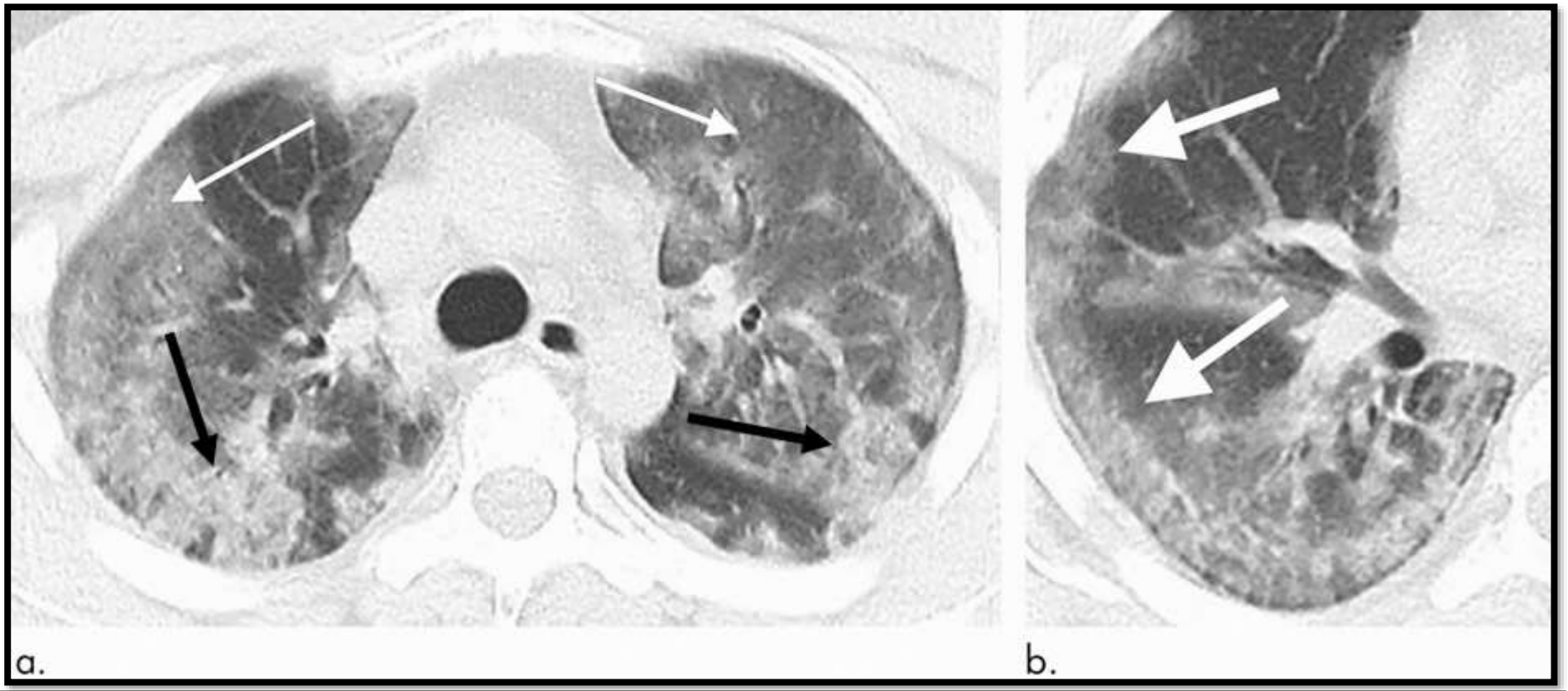
Coronavirus scans tend to have white patches that radiologists refer to as "ground glass opacity."



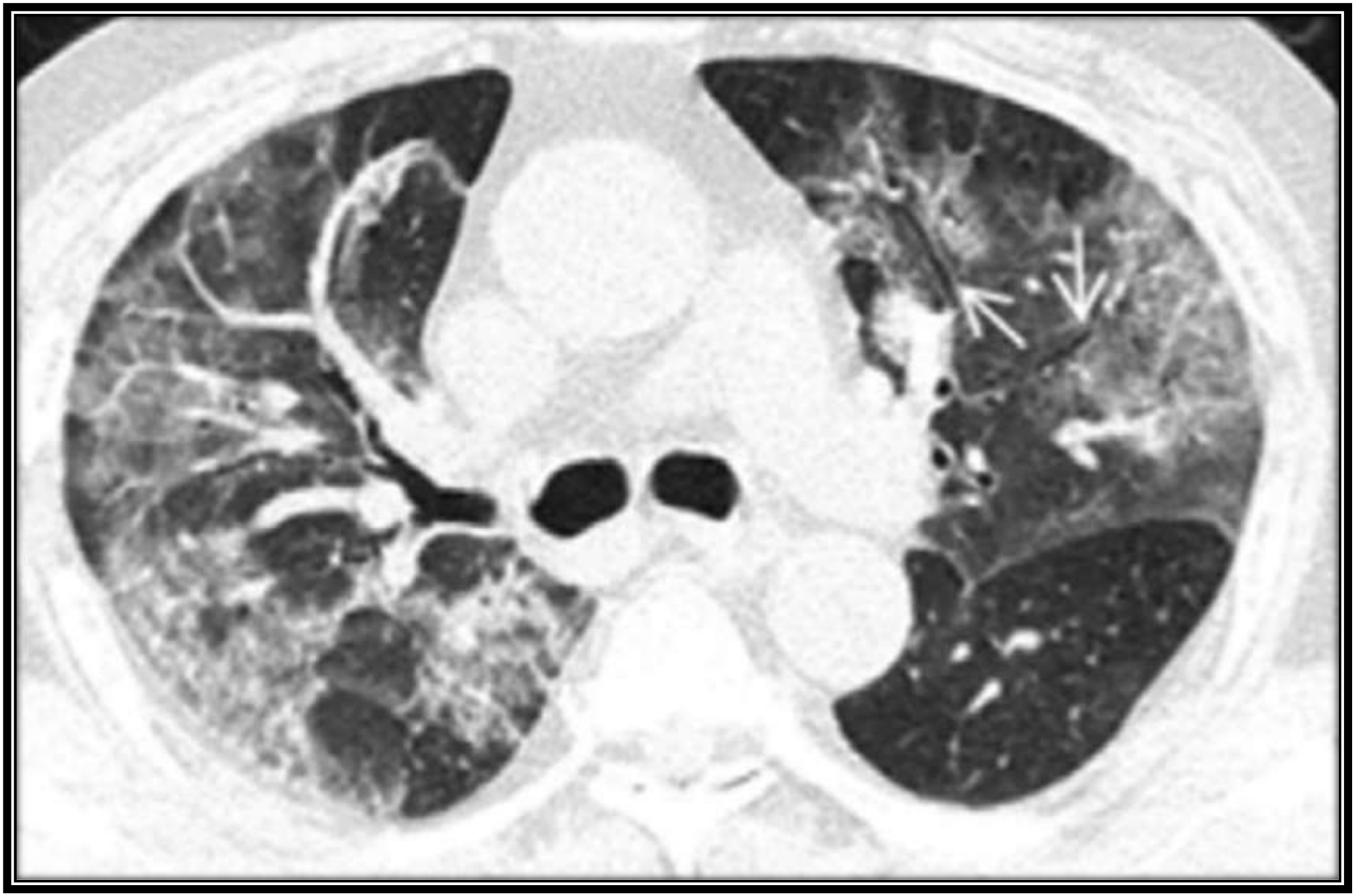
An analysis of nearly 140 coronavirus scans said patches of ground glass (GGO)on both lungs were a hallmark of the virus.

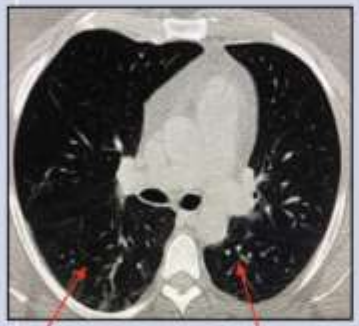
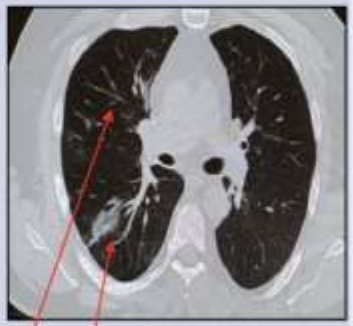
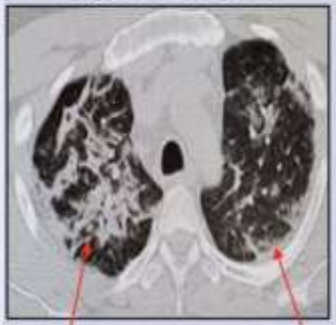
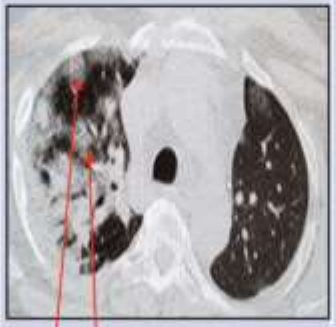
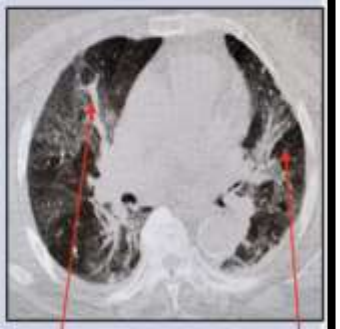


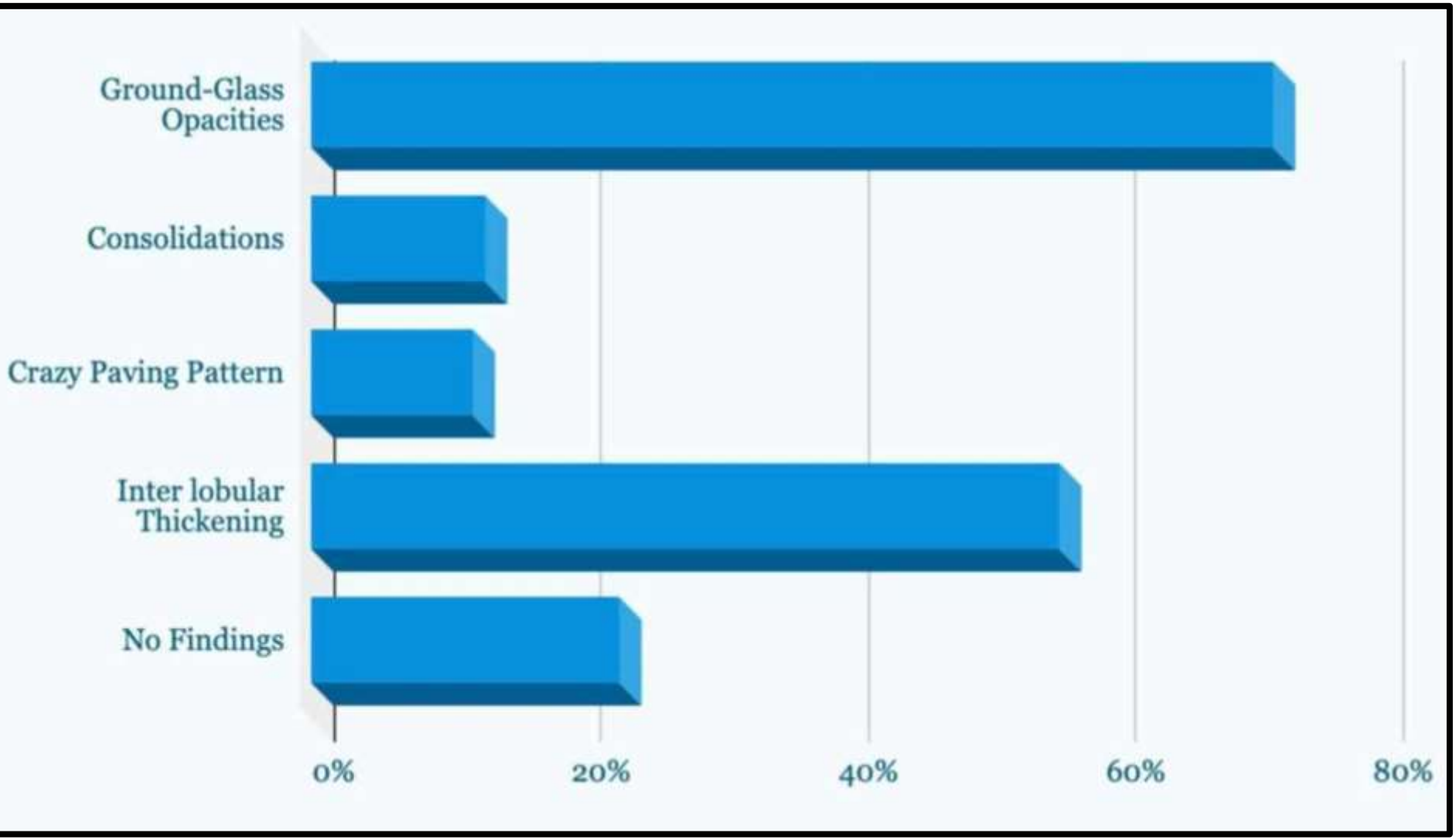

A
B
C
D

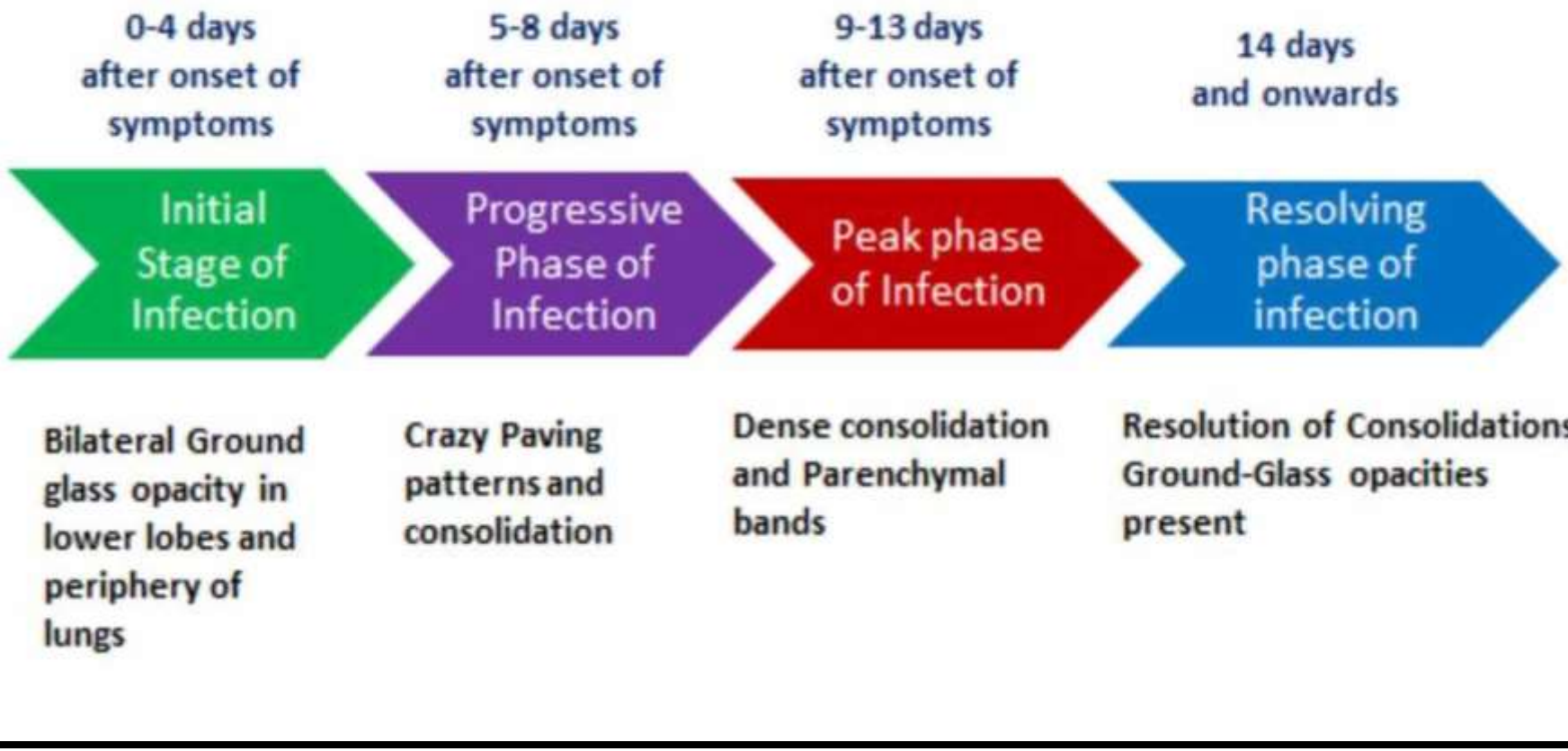


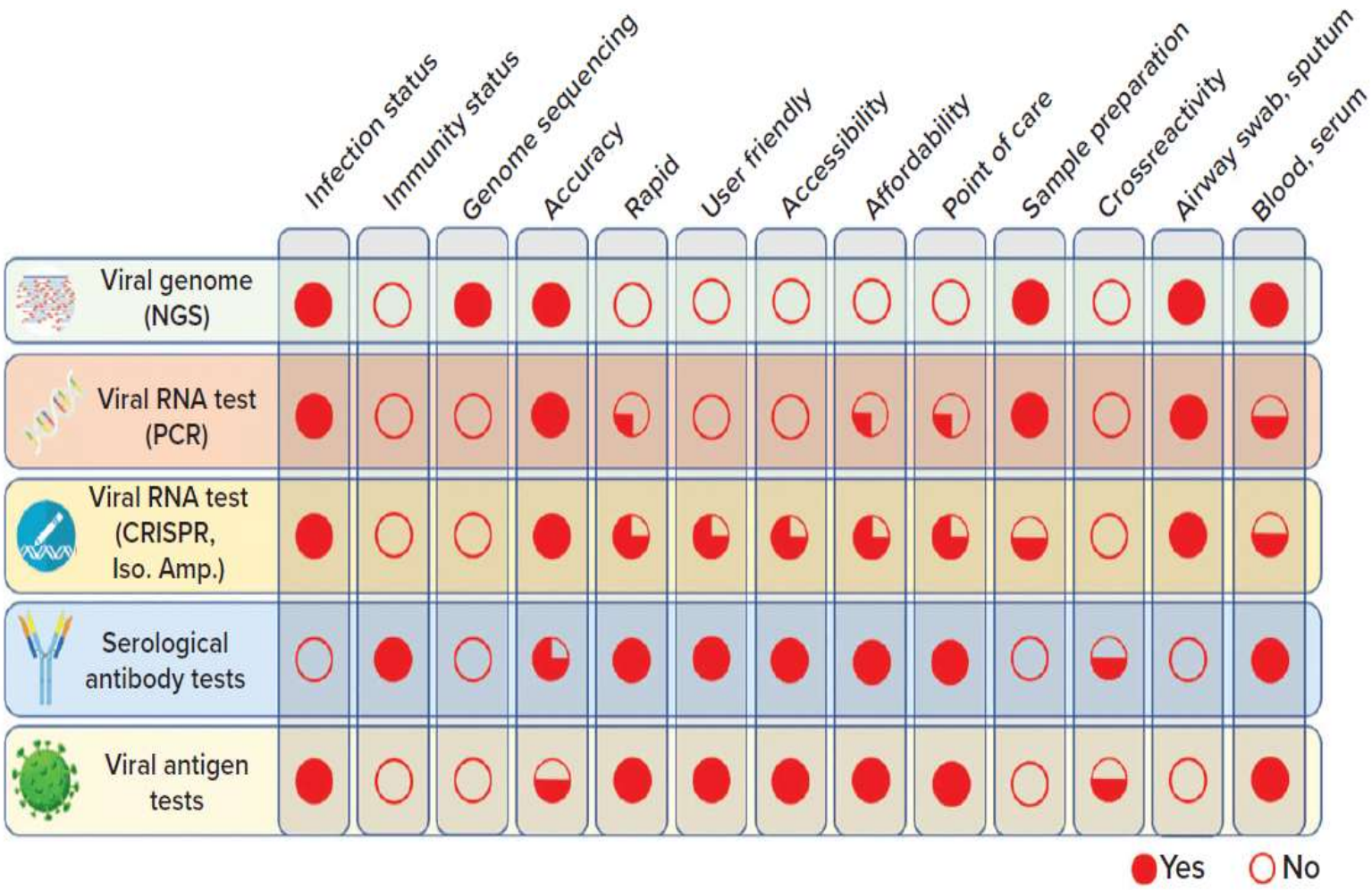
29-year old male with unknown exposure history, presenting with fever and cough, ultimately requiring intensive care unit admission: (a) axial thin-section non-contrast CT scan shows **diffuse bilateral confluent and patchy ground-glass** and **consolidative pulmonary opacities**; (b) the disease in the right middle and lower lobes has a striking peripheral distribution.



	Ultra-Early Stage	Early Stage	Rapid progression Stage	Consolidation Stage	Dissipation Stage
Findings	• Prior to symptom onset. • Throat swab positive, laboratory negative • Usually within 1-2 weeks of exposure.	• Patients present with symptoms (within 1-3 days of symptoms like fever, dry cough). • On histopathology - There is congestion of alveolar capillaries resulting in alveolar and interlobular interstitial edema.	• This stage follows within 3-7 days of symptomatic presentation. • There is an escalation in the hyperinflammatory response. Fibrous extensions that connect the alveoli begin to develop.	• This phase coincides with 2nd week of clinical symptoms. • The vascular congestion diminishes and fibrosis predominates.	• It occurs about 2-3 weeks after initial symptomatic presentation. • There is more of a healing and repair response within the lungs .
Images					
	CT scan demonstrates Bilateral, subpleural, multiple scattered ground glass opacities.	CT scan shows multiple, bilateral ground glass opacities. Irregular, interlobular septa begin to develop.	CT findings include subpleural, posterior consolidations, dispersed air bronchograms along with superimposed irregular septa.	There is a decrease in size and density of consolidations.	CT scan shows patchy consolidation, reticular opacities (strip-like opacities), bronchial and interlobular septal thickening.

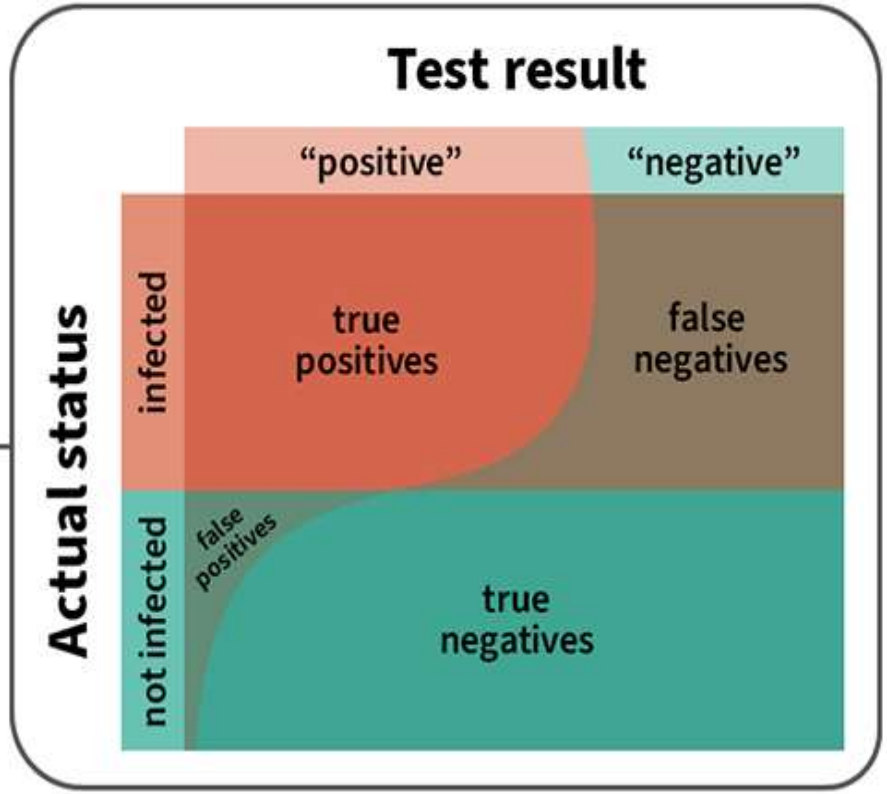

Ground-Glass Opacities
Consolidations
Crazy Paving Pattern
Inter lobular Thickening
No Findings
0%
20%
40%
60%
80%


0-4 days after onset of symptoms
5-8 days after onset of symptoms
9-13 days after onset of symptoms
14 days and onwards
Initial Stage of Infection
Progressive Phase of Infection
Peak phase of Infection
Resolving phase of infection
Bilateral Ground glass opacity in lower lobes and periphery of lungs
Crazy Paving patterns and consolidation
Dense consolidation and Parenchymal bands
Resolution of Consolidations Ground-Glass opacities present


Infection status
Immunity status
Genome sequencing
Accuracy
Rapid
User friendly
Accessibility
Affordability
Point of care
Sample preparation
Crossreactivity
Airway swab, sputum
Blood, serum
Viral genome (NGS)
Viral RNA test (PCR)
Viral RNA test (CRISPR, Iso. Amp.)
Serological antibody tests
Viral antigen tests
Yes
No

The COVID-19 swab test is highly **specific** but not as **sensitive.**

That means a positive result is almost always true, but a negative result is sometimes false.

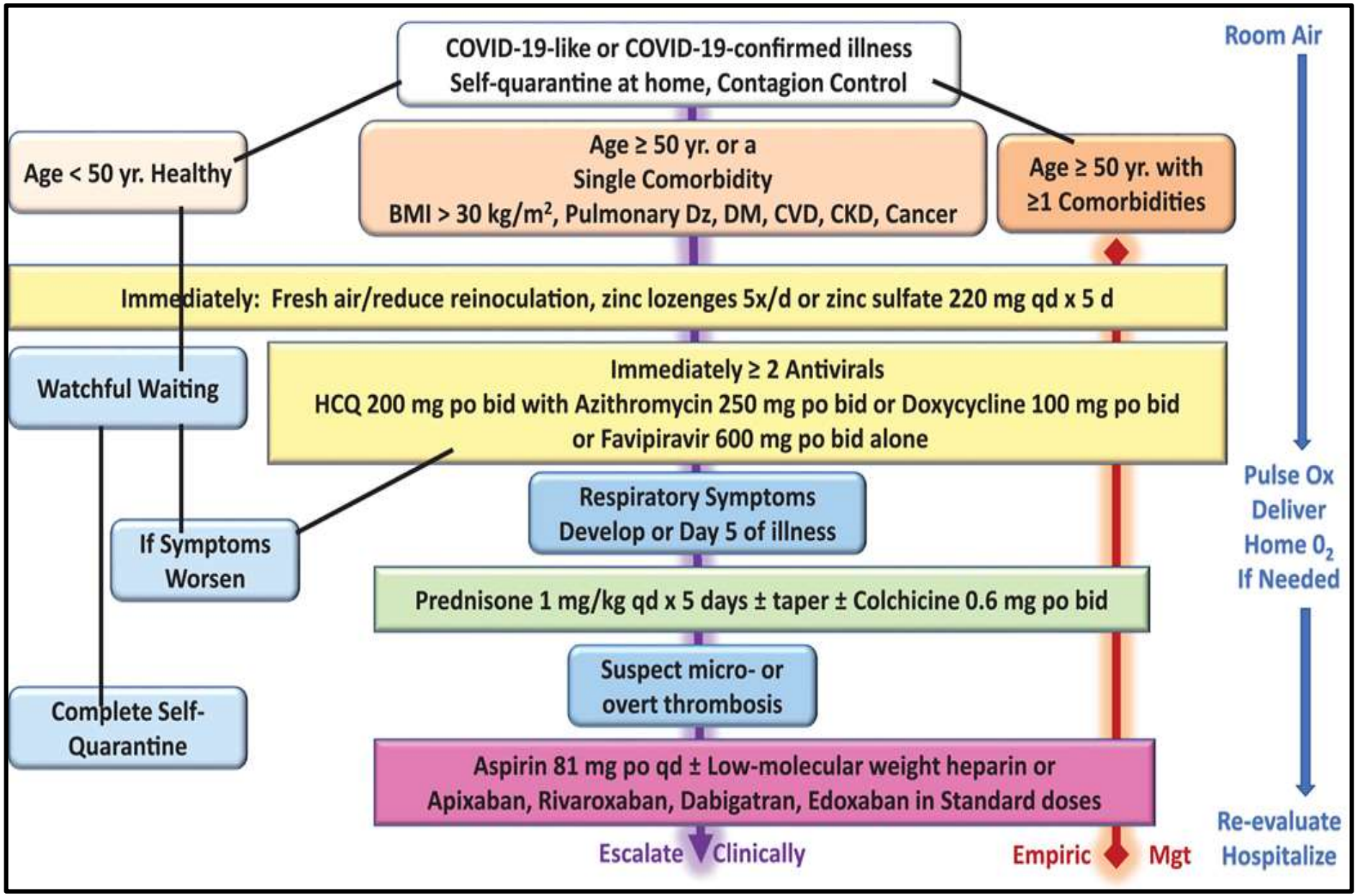


Sensitivity = number of **true positives** / number of those tested who **really are infected** = **"how many of the infections did we find?"**

Specificity = number of **true negatives** / number of those tested who **really are not infected** = **"how many of the healthy people did we clear?"**

Table 1 Types of diagnostic approaches in COVID-19[54,65]; *- still in experimental phase, now available for research; POC – point of care

Test	Mechanism of detection	Testing material	Availability for POC	Positive Test indicates	Use of tests
Nucleic acid amplification tests (NAAT)	RT-PCR and NGS detection of genetic sequences of conserved regions for regions of the virus e.g. N, E, S and RdRP genes. Two independent sequences need to be detected	Ambulatory: nasopharyngeal swabs, sputum In hospital: sputum, endotracheal aspirate, BAL blood, feces	No; Needs to be performed in the lab	Confirms current SARS-CoV2 infection	Individual testing
Antibody based immunoassay*	ELISA detecting IgM or IgG anti- SARS-CoV-2 antibodies	Serum	Yes (depending on test design)	IgM+: 3-5 days post onset IgG: past infection	Overall infection/ immunity rates in a community
Antigen based immunoassay*	ELISA detecting viral proteins e.g. S (spike protein) or N protein (nucleocapsid)	nasopharyngeal swabs, sputum and other lower respiratory tract secretions, BAL blood, feces.	Yes (depending on test design)	Confirms current SARS-CoV2 infection	Individual testing
Clinical tests	Clinical symptoms (fever/ cough) Epidemiologial history Imaging (CT)	CT – detection of radiological features	Yes	Infection possible	Triage to identify candidates for further testing


COVID-19-like or COVID-19-confirmed illness
Self-quarantine at home, Contagion Control
Room Air
Age < 50 yr. Healthy
Age ≥ 50 yr. or a
Single Comorbidity
BMI > 30 kg/m², Pulmonary Dz, DM, CVD, CKD, Cancer
Age ≥ 50 yr. with
≥1 Comorbidities
Immediately: Fresh air/reduce reinoculation, zinc lozenges 5x/d or zinc sulfate 220 mg qd x 5 d
Watchful Waiting
Immediately ≥ 2 Antivirals
HCQ 200 mg po bid with Azithromycin 250 mg po bid or Doxycycline 100 mg po bid
or Favipiravir 600 mg po bid alone
Pulse Ox
Deliver
Home 0_2
If Needed
Respiratory Symptoms
Develop or Day 5 of illness
If Symptoms
Worsen
Prednisone 1 mg/kg qd x 5 days ± taper ± Colchicine 0.6 mg po bid
Suspect micro- or
overt thrombosis
Complete Self-
Quarantine
Aspirin 81 mg po qd ± Low-molecular weight heparin or
Apixaban, Rivaroxaban, Dabigatran, Edoxaban in Standard doses
Re-evaluate
Hospitalize
Escalate
Clinically
Empiric
Mgt

Treatments	Dosing regimens	Route of administration	Mode of action	Common adverse events	Contraindications	Major drug interactions	Use in specific populations
Specific immunomodulators							
Anakinra	**IV: 100 mg every 6 h (total daily dose: 400 mg) for 15 days; 200 mg every 8 h for 7 days; 300 mg od for 4 days, followed by 100 mg od SC: 100 mg od for 10 or 28 days. Alternative regimen: 100 mg every 12 h on days 1–3, then 100 mg od from days 4–10**	**IV, SC Note: IV route is currently not FDA-approved**	**Anti-cytokine, IL-1 receptor antagonist**	**Injection site reactions, upper respiratory tract infections, headache, nausea, diarrhea, sinusitis, flu-like symptoms, abdominal pain**	**Known hypersensitivity to *Escherichia coli*-derived proteins, anakinra, or any component of the product**	**Avoid use with anti-TNF agents due to higher rates of infections and neutropenia**	**Use caution in the elderly due to higher rates of infections in the elderly population In patients with CrCl < 30 and ESRD, use extended dosing intervals (every other day)**
Tocilizumab	**4–8 mg/kg (maximum single dose: 800 mg), may repeat after 12 h**	**IV No trials evaluating the SC form**	**Anti-cytokine, IL-6 receptor antagonist**	**Injection site reactions, upper respiratory tract infections (including tuberculosis), nasopharyngitis, headache, hypertension, increased ALT, hematological effects**	**Known hypersensitivity to tocilizumab**	**May decrease serum concentration of CYP3A4 substrates**	**Safety during pregnancy and lactation is unknown**
Sarilumab	**Not described**	**IV Note: IV route is currently not FDA-approved**	**Anti-cytokine, IL-6 receptor antagonist**	**Neutropenia, increased ALT, injection site erythema, upper respiratory infections, urinary tract infections**	**Known hypersensitivity to sarilumab or any of its inactive ingredients**	**May decrease serum concentration of CYP3A4 substrates**	**Safety during pregnancy and lactation is unknown**

Treatments	Dosing regimens	Route of administration	Mode of action	Common adverse events	Contraindications	Major drug interactions	Use in specific populations
Ruxolitinib	**Various regimens under investigation 5 mg bid for 14 days; 10 mg bid; 2 × 10 mg bid dose at day 1 and can be increased up to 2 × 15 mg bid from day 2 to day 28; 5 mg bid from day 1 to day 3 then 10 mg bid from day 4 to day 10; 10 mg bid, for 14 days followed by 5 mg bid for 2 days and 5 mg od for 1 day**	**PO**	**Anti-cytokine, JAK1/JAK2 inhibitor**	**Thrombocytopenia, neutropenia, anemia, infections, edema, headache, dizziness**	**None**	**CYP3A4 substrate. Serum roxulitinib levels may increase when used with CYP3A4 inhibitors (i.e. ritonavir)**	**Use in pregnant and lactating women is not recommended May require starting dose reduction in hepatic and renal impairment**
Baricitinib	**2 or 4 mg od for 14 days**	**PO**	**Anti-cytokine, JAK1/JAK2 inhibitor**	**Upper respiratory tract infections, nausea, herpes simplex, herpes zoster**	**None**	**Substrate of BCRP/ABCG2, CYP3A4, OAT1/3, P-gp/ABCB1 Avoid use with strong OAT3 inhibitors**	**Avoid use in patients with severe hepatic impairment, and in patients with moderate or severe renal impairment**
Adalimumab	**Not described**	**Injection, specifics not described**	**Anti-cytokine, anti-TNFα**	**Upper respiratory tract infections, sinusitis, increased macrophage-dependent infection, tuberculosis, opportunistic infections, injection site reactions, increased creatine phosphokinase, headache, rash**	**None**	**Avoid use with anakinra due to higher rates of infections and neutropenia**	**Use with caution in patients with heart failure or decreased left ventricular function; may cause myocardial toxicity or exacerbate underlying myocardial dysfunction Use caution in elderly patients; may increase infection risk**

Treatments	Dosing regimens	Route of administration	Mode of action	Common adverse events	Contraindications	Major drug interactions	Use in specific populations
Sargramostim	**125 µg bid for 5 days**	**Nebulized inhalation**	**Recombinant humanized GM-CSF**	**Fever, hypertension, edema, pericardial effusion, chest pain, peripheral edema, tachycardia, central nervous system effects, dermatologic effects, endocrine and metabolic changes, GI effects, urinary tract infections, hyperbilirubinemia, neuromuscular and skeletal effects, retinal hemorrhage, increased serum creatinine, pharyngitis, epistaxis, dyspnea**	**Hypersensitivity to human GM-CSF, yeast-derived products, or any component of the formulation**	**May enhance myeloproliferative effects when administered with products that induce myeloproliferation (e.g. corticosteroids)**	**Use with caution in patients with pre-existing cardiac disease; may cause supraventricular arrhythmia Safety during pregnancy and lactation is unknown**
Gimsilumab (investigational molecule)	**High dose on day 1 and low dose on day 8, specifics not described**	**IV**	**Anti-GM-CSF**	**Not described**	**Not described**	**Not described**	**Not described**
Convalescent plasma	**One or two infusions. Titer depends on donor**	**IV**	**Neutralizing antibodies provide short-term passive immunity**	**Inadvertent transmission of infectious agents, allergic reactions, thrombotic complications, transfusion-associated circulatory overload, transfusion-related acute lung injury**	**Allergy to human plasma, sodium citrate, methylene blue IgA-deficient patients with antibodies to IgA and a history of hypersensitivity**	**None**	**Not recommended in patients with heart failure, chronic kidney failure in the dialysis phase, and organ transplant**

Treatments	Dosing regimens	Route of administration	Mode of action	Common adverse events	Contraindications	Major drug interactions	Use in specific populations
Non-specific immunomodulators							
IVIG	**0.3–0.5 g/kg daily for 5 days**	**IV**	**Antibodies from pooled plasma provide short-term passive immunity**	**Headache, nausea, fever, chills, dyspnea, cough, sore throat, malaise, myalgia, arthralgia, abdominal pain, leukopenia, aseptic meningitis, infections, acute renal failure, stroke, myocardial infarction, deep vein thrombosis, pulmonary embolism, anaphylactic shock**	**History of anaphylactic or severe systemic reaction to human immune globulin Patients with hyperprolinemia ; IVIG contains stabilizer L-proline IgA-deficient patients with antibodies to IgA and a history of hypersensitivity**	**Live virus vaccines (measles, mumps, rubella, varicella)**	**Use with caution in elderly patients; may be at higher risk for renal failure and thromboembolic events. Administer the minimum dose at the lowest infusion rate practical**
Dexamethasone	**RECOVERY trial: 6 mg daily for 10 days; DEXA-COVID19 trial: 20 mg od from day 1 to day 5, followed by 10 mg od from day 6 to day 10**	**IV or PO**	**Provide anti-inflammatory and antifibrotic effects to prevent extended cytokine response**	**Sodium and water retention (less than methylprednisolone), hypertension, hyperglycemia, osteoporosis, cardiac hypertrophy, edema, hypokalemia, bruising, diaphoresis, urticaria, allergic rash, euphoria, psychosis, infections, myasthenia gravis**	**Hypersensitivity to corticosteroids or any component of the formulation, systemic fungal infection**	**Substrate of CYP3A4 and P-gp/ABCB1. Live or attenuated virus vaccines (if using immunosuppressive doses of corticosteroids)**	**Use with caution in the elderly with the smallest possible effective dose for the shortest duration**

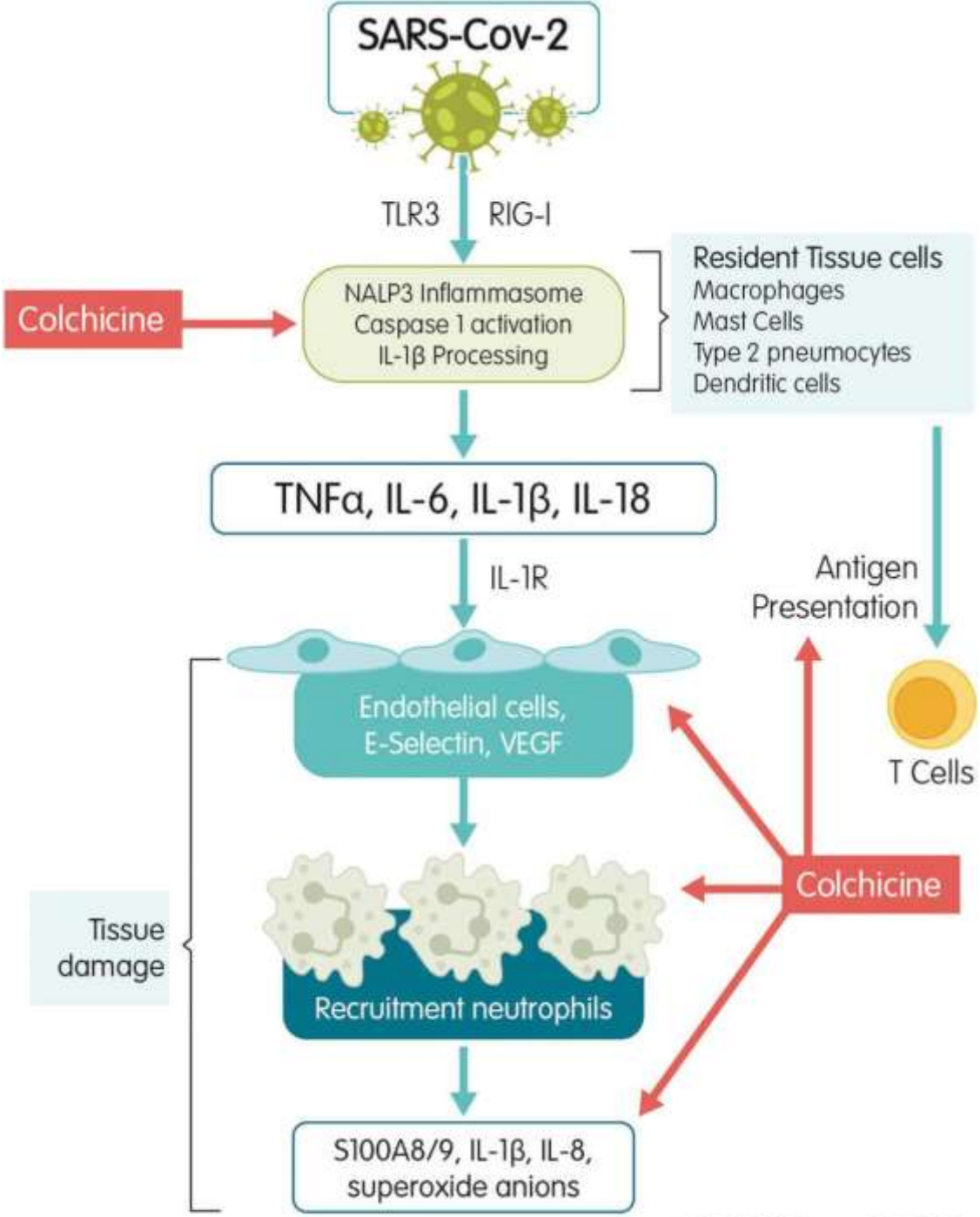
Treatments	Dosing regimens under investigation	Route of administration under investigation	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Methylprednisolone	**0.5–1 mg/kg daily or 1–2 mg/kg daily (of methylprednisolone or equivalent) have been proposed Higher doses (cytokine storm): 60–125 mg (methylprednisolone) every 6 h for up to 3 days**	**IV**	**Provide anti-inflammatory and antifibrotic effects to prevent extended cytokine response**	**Sodium and water retention, hypertension, hyperglycemia, osteoporosis, cardiac hypertrophy, edema, hypokalemia, bruising, diaphoresis, urticaria, allergic rash, euphoria, psychosis, infections, myasthenia gravis**	**Hypersensitivity to corticosteroids or any component of the formulation, systemic fungal infection**	**CYP3A4 substrate Live or attenuated virus vaccines (if using immunosuppressive doses of corticosteroids)**	**Use with caution in the elderly, with the smallest possible effective dose for the shortest duration Note: Oral corticosteroids should be continued in COVID-19 patients with an underlying condition (e.g. primary or secondary adrenal insufficiency, rheumatologic diseases) Inhaled corticosteroids should be continued in COVID-19 patients with asthma and COPD Corticosteroid treatment in pregnant women should be individualized; benefits should be weighed with potential harm**

Treatments	Dosing regimens under investigation	Route of administration under investigation	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Interferon-β-1b	**0.25 mg (8 million units) for 3 days; days 1, 2, 3, or days 1, 3, 5**	**SC**	**Antiviral and immunomodulator**	**Peripheral edema, skin rash, abdominal pain, urinary urgency, leukopenia, lymphocytopenia, neutropenia, increased ALT, injection site reaction, ataxia, chills, headache, hypertonia, insomnia, asthenia, myalgia, flu-like symptoms, fever**	**History of hypersensitivity to natural or recombinant interferonβ, albumin (human), or any component of the formulation**	**No formal drug interaction studies have been conducted**	**Use with caution in patients with bone marrow suppression, cardiovascular disease, hepatic impairment**
Interferon-α-2b	**5 million units bid**	**Nebulized**	**Antiviral and immunomodulator**	**Skin rash, abdominal pain, leukopenia, lymphocytopenia, neutropenia, increased ALT, injection site reaction, ataxia, chills, headache, hypertonia, insomnia, asthenia, myalgia, flu-like symptoms, fever, hemolytic anemia**	**Hypersensitivity to interferon-α or any component of the formulation, decompensated liver disease, autoimmune hepatitis**	**Not fully evaluated**	**Use with caution in patients with a history of neuropsychiatric, autoimmune, ischemic, infectious disorders, and patients with pre-existing heart disease and organ transplant**

Treatments	Dosing regimens under investigation	Route of administration under investigation	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Miscellaneous							
Statins	**Simvastatin 40 mg od for 14 days, simvastatin 80 mg od, atorvastatin 40 mg od**	**PO**	**Anti-inflammatory and immunomodulatory effects**	**Hepatotoxicity, myopathies, GI effects, rhabdomyolysis, increased risk of diabetes**	**Hypersensitivity to statin or any component of the formulation, active liver disease; unexplained persistent elevations of serum transaminases; pregnancy, breastfeeding**	**Inhibitors/substrates of CYP3A4 may increase statin concentrations**	**Use with caution in elderly patients; may be at higher risk for myopathy Statins may need to be withheld for a short time period in COVID-19 patients with severe rhabdomyolysis**
ACEi/ARB	**Various dosing regimens: telmisartan 80 mg bid, telmisartan 40 mg bid, ramipril 2.5 mg od for 14 days, losartan 100 mg od, valsartan 80 or 160 mg for 14 days (max: 160 mg bid), captopril 25 mg, losartan 25 mg od, losartan 50 mg od**	**PO**	**Anti-inflammatory and immunomodulatory effects**	**Cough (more common with ACEi), hyperkalemia, edema, angioedema (more common with ACEi), photosensitivity, renal failure, dysgeusia, headache**	**Previous angioneurotic edema (ACEi), pregnancy, hyperkalemia, bilateral renal stenosis, pregnancy**	**Risk of hyperkalemia may be increased when combined with potassium-increasing medications**	**Treatment should be continued in COVID-19 patients with an indication for ACEi/ARB; abrupt withdrawal may lead to clinical instability**

Treatments	Dosing regimens under investigation	Route of administration under investigation	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Azithromycin	**500 mg on day 1, then 250 mg od on days 2–5 in conjunction with a 10-day regimen of hydroxychloroquine**	**PO**	**Anti-inflammatory and immunomodulatory effects**	**QTc prolongation and ventricular arrhythmias, diarrhea, nausea, abdominal pain, vomiting**	**Hypersensitivity to azithromycin or other macrolides, history of cholestatic jaundice/hepatic dysfunction associated with prior azithromycin use**	**Inhibits P-gp/ABCB1**	**Elderly patients may be more susceptible to development of Torsades de pointes arrhythmias**
Hydroxychloroquine	**400 mg bid on day 1, then 200 mg bid on days 2–5; 400 mg od for 5 days; 200 mg tid for 10 days; 100–200 mg bid for 5–14 days**	**PO**	**Anti-inflammatory and immunomodulatory effects**	**QTc prolongation, abdominal pain, decreased appetite, diarrhea, nausea, vomiting, hemolysis in G-6-PD deficiency, hypoglycemia, retinopathy, nervous system disorders, psychiatric disorders**	**Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivatives, or any component of the formulation**	**CYP2D6, CYP2C8, CYP3A4, CYP3A5 Coadministration of chloroquine phosphate or hydroxychloroquine sulfate and remdesivir may result in reduced antiviral activity of remdesivir**	**Caution should be exercised when administering to pregnant and nursing mothers**
Colchicine	**0.5 mg bid for 3 days, then 0.5 mg od for 27 days**	**PO**	**Anti-inflammatory and immunomodulatory effects**	**GI symptoms (diarrhea, nausea, vomiting, abdominal pain), neuromuscular toxicity, hematological effects, elevated AST and ALT**	**Renal or hepatic impairment in conjunction with drugs that inhibit both CYP3A4 and P-gp (e.g. clarithromycin)**	**Substrate of CYP3A4, P-gp/ABCB1 Dose adjustment of colchicine is required in patients taking protease inhibitors (e.g. lopinavir/ritonavir)**	**Dose adjustment is required in patients with renal or hepatic function**

ACEi angiotensin-converting enzyme inhibitors, ALT alanine aminotransferase, ARB angiotensin II receptor blockers, AST aminotransferase, bid twice daily, COPD chronic obstructive pulmonary disease, COVID-19 coronavirus disease 2019, CrCl creatinine clearance, CYP cytochrome P450, ESRD end-stage renal disease, G-6-PD glucose-6-phosphate dehydrogenase, GI gastrointestinal, GM-CSF granulocyte–macrophage colony-stimulating factor, IgA immunoglobulin A, IL interleukin, IV intravenous, IVIG intravenous immunoglobulin, JAK Janus kinase, max maximum, OAT organic anion transporter, od once daily, P-gp P-glycoprotein, PO oral, SC subcutaneous, tid three times daily, TNF tumor necrosis factor



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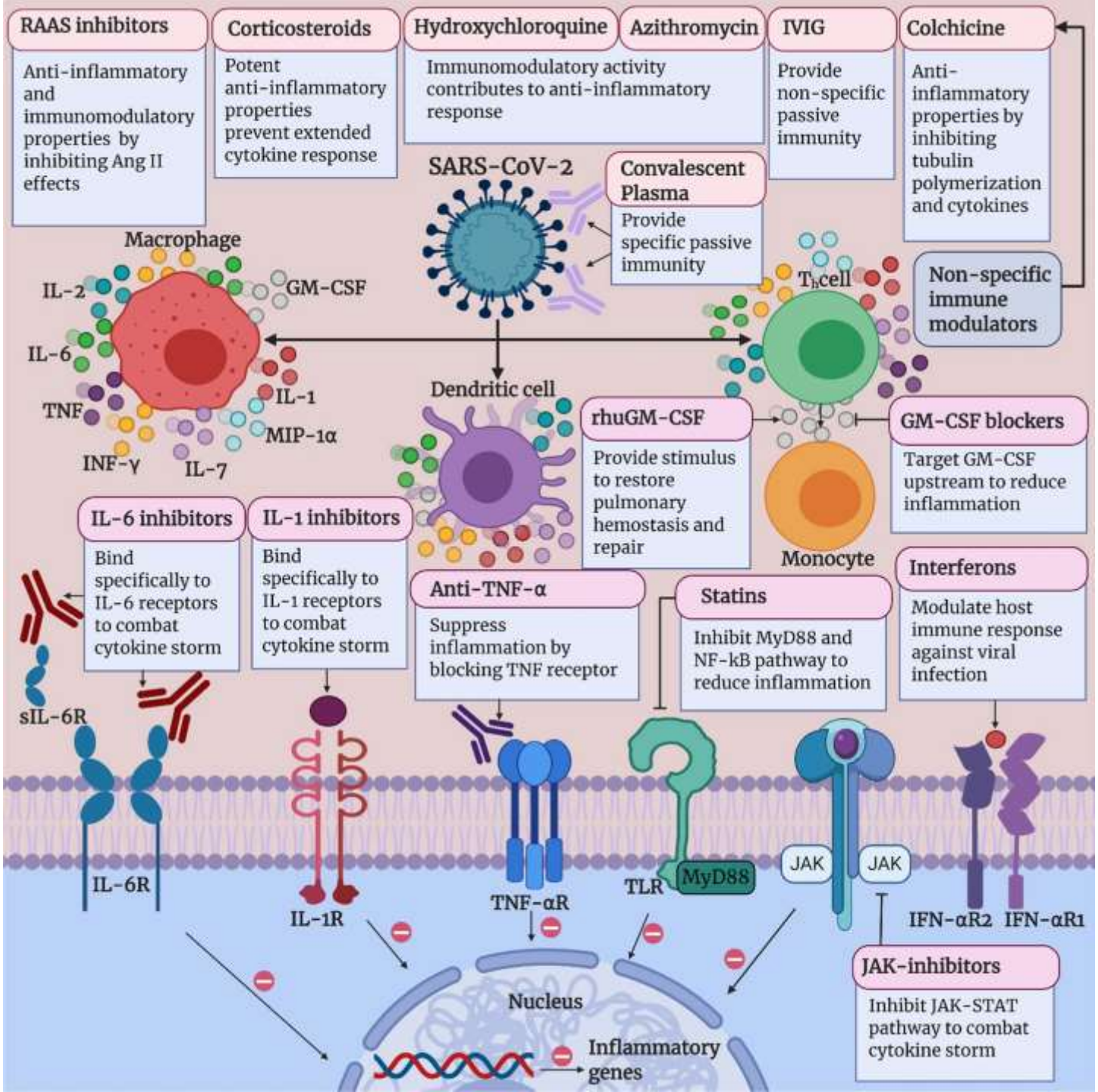
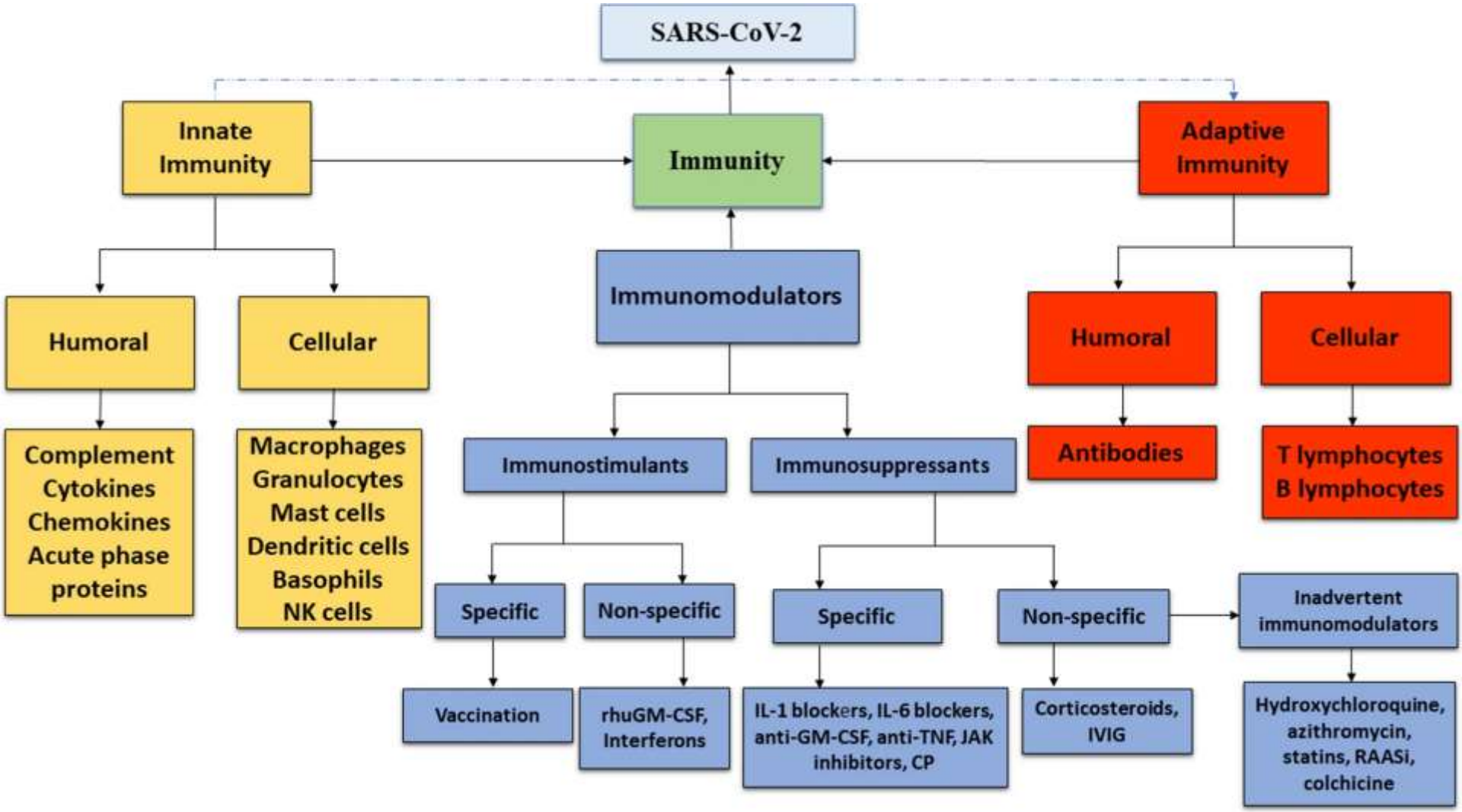

RAAS inhibitors
Anti-inflammatory and immunomodulatory properties by inhibiting Ang II effects
Corticosteroids
Potent anti-inflammatory properties prevent extended cytokine response
Hydroxychloroquine
Azithromycin
Immunomodulatory activity contributes to anti-inflammatory response
IVIG
Provide non-specific passive immunity
Colchicine
Anti-inflammatory properties by inhibiting tubulin polymerization and cytokines
SARS-CoV-2
Convalescent Plasma
Provide specific passive immunity
Macrophage
IL-2
GM-CSF
IL-6
IL-1
TNF
MIP-1α
INF-γ
IL-7
Dendritic cell
Th cell
Non-specific immune modulators
rhuGM-CSF
Provide stimulus to restore pulmonary hemostasis and repair
GM-CSF blockers
Target GM-CSF upstream to reduce inflammation
Monocyte
IL-6 inhibitors
Bind specifically to IL-6 receptors to combat cytokine storm
IL-1 inhibitors
Bind specifically to IL-1 receptors to combat cytokine storm
Anti-TNF-α
Suppress inflammation by blocking TNF receptor
Statins
Inhibit MyD88 and NF-kB pathway to reduce inflammation
Interferons
Modulate host immune response against viral infection
sIL-6R
IL-6R
IL-1R
TNF-αR
TLR
MyD88
JAK
JAK
IFN-αR2
IFN-αR1
Nucleus
Inflammatory genes
JAK-inhibitors
Inhibit JAK-STAT pathway to combat cytokine storm

Schematic representation of the immunomodulators' site of action.
Hydroxychloroquine, azithromycin, statins, RAASi and their combinations have not been reliably shown to be of benefit in hospitalized patients with COVID-19, and therefore are represented here to define a potential pathophysiological target for therapy.
This should not be seen as endorsement for use of such agents. The use of hydroxychloroquine and azithromycin in COVID-19 patients may be associated with harm. Whether such agents are beneficial in other stages of infection remains a matter of study.
Ang II angiotensin II, GM-CSF granulocyte–macrophage colony-stimulating factor, IFN interferon, IL interleukin, IL-6R interleukin-6 receptor, IVIG intravenous immunoglobulin, JAK Janus kinase, JAK-STAT Janus kinase-signal transducer and activator of transcription, MIP-1α macrophage inflammatory protein 1-α, MyD88 myeloid differentiation primary response 88, NF-κB nuclear factor-κB, RAAS renin–angiotensin–aldosterone system, rhuGM-CSF recombinant human granulocyte–macrophage colony-stimulating factor, sIL-6R soluble IL-6 receptor, TLR toll-like receptor, TNF tumor necrosis factor reserve


SARS-CoV-2
Innate Immunity
Immunity
Adaptive Immunity
Humoral
Cellular
Immunomodulators
Humoral
Cellular
Complement
Cytokines
Chemokines
Acute phase proteins
Macrophages
Granulocytes
Mast cells
Dendritic cells
Basophils
NK cells
Immunostimulants
Immunosuppressants
Antibodies
T lymphocytes
B lymphocytes
Specific
Non-specific
Specific
Non-specific
Inadvertent immunomodulators
Vaccination
rhuGM-CSF, Interferons
IL-1 blockers, IL-6 blockers, anti-GM-CSF, anti-TNF, JAK inhibitors, CP
Corticosteroids, IVIG
Hydroxychloroquine, azithromycin, statins, RAASi, colchicine

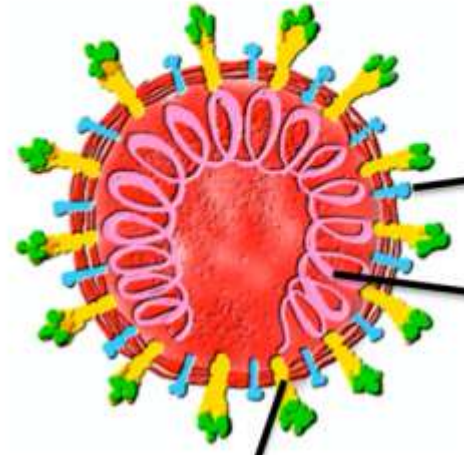
The immune system is classically divided into innate and adaptive components. The innate immune system provides nonspecific resistance to pathogens, whereas adaptive immunity is characterized by antigen specificity and immunologic memory. Immunomodulators are drugs that either stimulate or suppress the immune system. The two immune systems, along with immunomodulators, work together to prevent and control infection.

CP convalescent plasma, IL interleukin, GM-CSF granulocyte–macrophage colony-stimulating factor, IVIG intravenous immunoglobulin, JAK Janus kinase, NK natural killer, RAASi renin–angiotensin–aldosterone system inhibitors, rhuGM-CSF recombinant human granulocyte–macrophage colony-stimulating factor, TNF tumor necrosis factor

Vaccine Candidate	Platform, Route of Administration	Target (SARS-Cov-2)	Developer	Trial Phase, Registry Number, Study Start, Link
Synthetic minigene transfected APCs Covid-19/aAPC	Artificial antigen presenting cells (APCs) modified with lentiviral vector, s.c..	Selected conserved structural and protease protein domains	Shenzhen Geno-immune Medical Institute, China	Phase 1/2, NCT04299724, 15 February 2020 http://szgimi.org/en/news.php
Synthetic minigene transfected APCs + cytotoxic T cells LV-SMENP-DC	Dendritic cells modified with lentiviral vector, s.c., plus i.v. infusion of cytotoxic T cells	Viral structural proteins and a polyprotein protease	Shenzhen Geno-immune Medical Institute, China	Phase 1/2, NCT04276896, 24 March 2020 http://szgimi.org/en/news.php
Recombinant adenovirus, Ad5-nCoV	Viral vector, Adenovirus 5, i.m.	Spike protein	CanSino Biologics, China	Phase 2, NCT04341389, 12 April 2020 http://www.cansinotech.com/homes/article/plist/56.html
Recombinant adenovirus, AZD1222	Viral vector (non-replicating) Chimpanzee Adenovirus, i.m.	Spike protein	University of Oxford, UK, & AstraZeneca	Phase 2b/3, 2020-001228-32, 4 May 2020 https://www.ox.ac.uk/news-and-events/for-journalists
Recombinant adenovirus, Gam-COVID-Vac (Lyo)	Viral vector, Adenoviruses 5 and 26, i.m.	Spike protein	Gamaleya Research Institute, Russia	Phase 1, NCT04436471, 17 June 2020 http://gamaleya.org/
Plasmid, INO-4800	DNA, i.d., followed by electroporation	Spike protein	Inovio Pharmaceuticals USA, & CEPI	Phase 1, NCT04336410, 3 April 2020, and Phase 2, https://www.inovio.com/our-focus-serving-patients/covid-19/
Plasmid + adjuvant, AG0301-COVID19	DNA, i.m.	Spike protein	AnGes and Osaka University, Japan	Phase 1/2, NCT04463472, 29 June 2020 https://www.anges.co.jp/en/
Plasmid, GX-19	DNA, i.m.	Spike protein	Genexin Inc., Korea	Phase 1/2, NCT04445389, 17 June 2020 http://www.genexine.com/m62.php?cate=1
Lipid nanoparticle encapsulated RNA, mRNA 1273	mRNA, i.m.	Spike protein	Moderna and Natl Inst Allergy & Infectious Diseases (NIAID), USA	Phase 2, NCT04405076, 25 May 2020 https://www.niaid.nih.gov/clinical-trials/safety-immunogenicity-study-vaccine-covid-19
Lipid nanoparticle encapsulated RNA, BNT162	mRNA, i.m.	Various viral ags (4 vaccine candidates)	BioNTech, Germany, & Pfizer, USA	Phase 1/2, NCT04368728, 29 April 2020 https://investors.biontech.de/press-releases
Lipid nanoparticle encapsulated RNA. CVnCoV	mRNA, i.m.	Spike protein	CureVac, Germany	Phase 1, NCT04449276, 18 June 2020 https://www.curevac.com/covid-19
COVAC1 (LNP-nCoVsaRNA)	mRNA in lipid nanoparticle, i.m.	Spike protein	Imperial College London, UK	Phase 1, ISRCTN17072692, 1 April 2020 http://www.imperial.ac.uk/news
Protein + adjuvant, NVX-CoV2373	Protein subunit vaccine, i.m.	Spike protein and Matrix-M adjuvant	Novavax, USA	Phase 1/2, NCT04368988, 25 May 2020 http://ir.novavax.com/press-releases
Protein + adjuvant, SCB-2019	Protein trimeric subunit vaccine, i.m.	Spike protein, AS03, CpG, alum adjuvant	Clover Biopharma, Australia, GSK, Dynavax	Phase 1, NCT04405908, 19 June 2020 http://www.cloverbiopharma.com/
SARS-CoV-2 inactivated virus, PiCoVacc	Inactivated virus + alum adjuvant	Entire virus	Sinovac Research and Development Co, China	Phase 1/2, 16 April 2020, and Phase 3 http://www.sinovacbio.com/?optionid=754&auto_id=904
SARS-CoV-2 inactivated virus	Inactivated virus	Entire virus	Chinese Academy of Medical Sciences	Phase 1/2, NCT04412538, 15 May 2020 http://english.cas.cn/newsroom/news/
SARS-CoV-2 inactivated virus	Inactivated virus	Entire virus	Sinopharm	Phase 1/2, ChiCTR2000031809, 11 April 2020 http://www.chinacdc.cn/en/

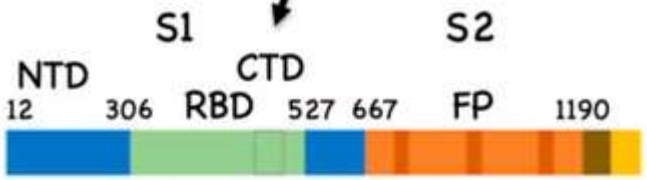
A

SARS-CoV-2



M/E = Membrane and envelope proteins

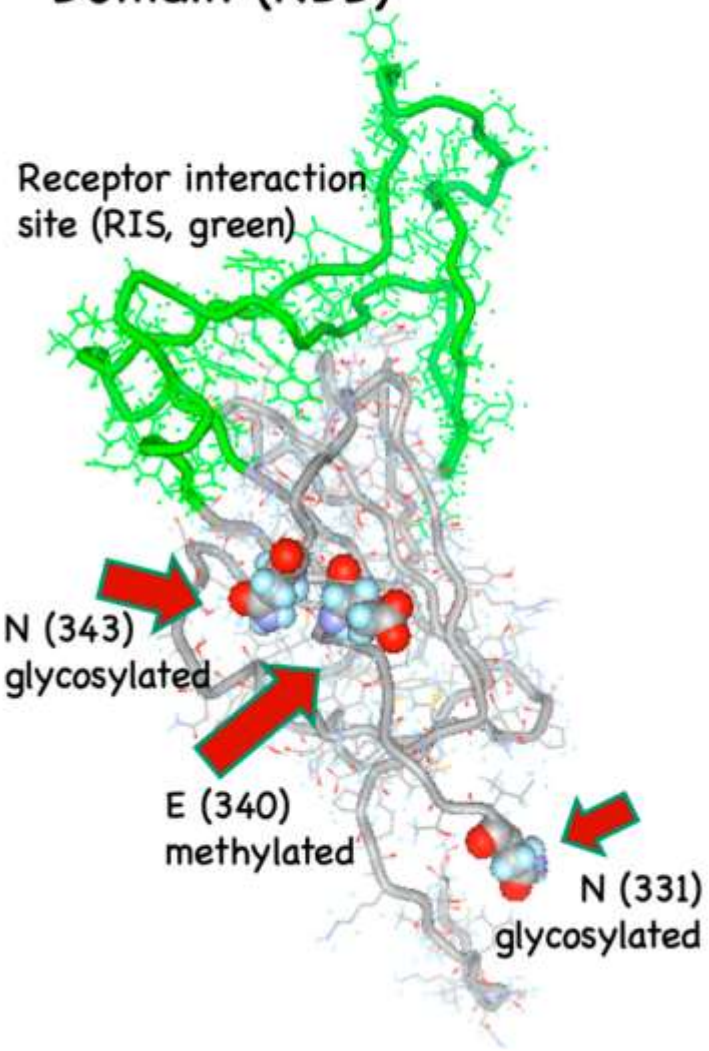
N/RNA = Nucleocapsid protein and RNA



Spike (S) protein, with S1 & S2:
S1 surface unit, with N-terminal domain (NTD), and CTD containing the RBD
S2 unit that fuses with cellular membrane, including the internal membrane fusion peptide (FP)

B

Receptor Binding Domain (RBD)



SARS-CoV-2, the spike (S) protein and its receptor binding domain (RBD).
(A) Coronaviruses have their name because they are decorated by prominent S proteins (yellow/green).
It is the only viral protein that interacts with host cells and is the most diverging protein between different coronaviruses, particularly in its receptor binding domain (RBD, green).
RBD binds to angiotensin converting enzyme 2 (ACE2, not shown) on the host's cell surface. The fusion peptide (FP) fuses with the host cell membrane. Specific antibodies against RBD and FP can neutralize SARS-CoV-2 NTD/CTD, N-/C-terminal domains.
(B) RBD is glycosylated and methylated, which may hinder the induction of neutralizing antibodies. In contrast, the receptor interaction site (RIS, green) is not glycosylated.

Types of coronavirus vaccine approaches

Scientists are casting a wide net to see what works best against the novel coronavirus.

Types of vaccines	DNA and RNA	Live attenuated	Inactivated	Subunit	Viral vector
					
How it works	This vaccine uses DNA or RNA molecules to teach the immune system to target key viral proteins.	This is a weakened version of the actual virus.	An inactivated vaccine uses the whole virus after it has been killed with heat or chemicals.	This vaccine uses a piece of a virus' surface to focus your immune system on a single target.	This approach takes a harmless virus and uses it to deliver viral genes to build immunity.
Advantages	Easy and quick to design.	Stimulates a robust immune response without causing serious disease.	Safe because the virus is already dead and is easy to make.	Focuses the immune response on the most important part of the virus for protection and cannot cause infection.	Live viruses tend to elicit stronger immune responses than dead viruses or subunit vaccines.
Disadvantages	Never been done before. There are no licensed DNA or RNA vaccines currently in use.	May not be safe for those with compromised immune systems.	Not as effective as a live virus. Some previous inactivated vaccines have made the disease worse; safety for the novel coronavirus needs to be shown in clinical trials.	May not stimulate a strong response, other chemicals may need to be added to boost long-term immunity.	Important to pick a viral vector that is truly safe. An immune response to the viral vector could make the vaccine less effective.
Existing examples	• None	• Measles, Mumps and Rubella • Chickenpox	• Polio	• Pertussis • Hepatitis B • Human papillomavirus (HPV)	• Ebola • Veterinary medicine
Group testing this approach for COVID-19	• Moderna (RNA) • Inovio (DNA)	• Codagenix • Indian Immunologicals Ltd.	• Sinovac • Sinopharm	• Novavax • AdaptVac	• University of Oxford & AstraZeneca • CanSino Biologics • Johnson & Johnson

Sources: CDC; NIAID; FDA

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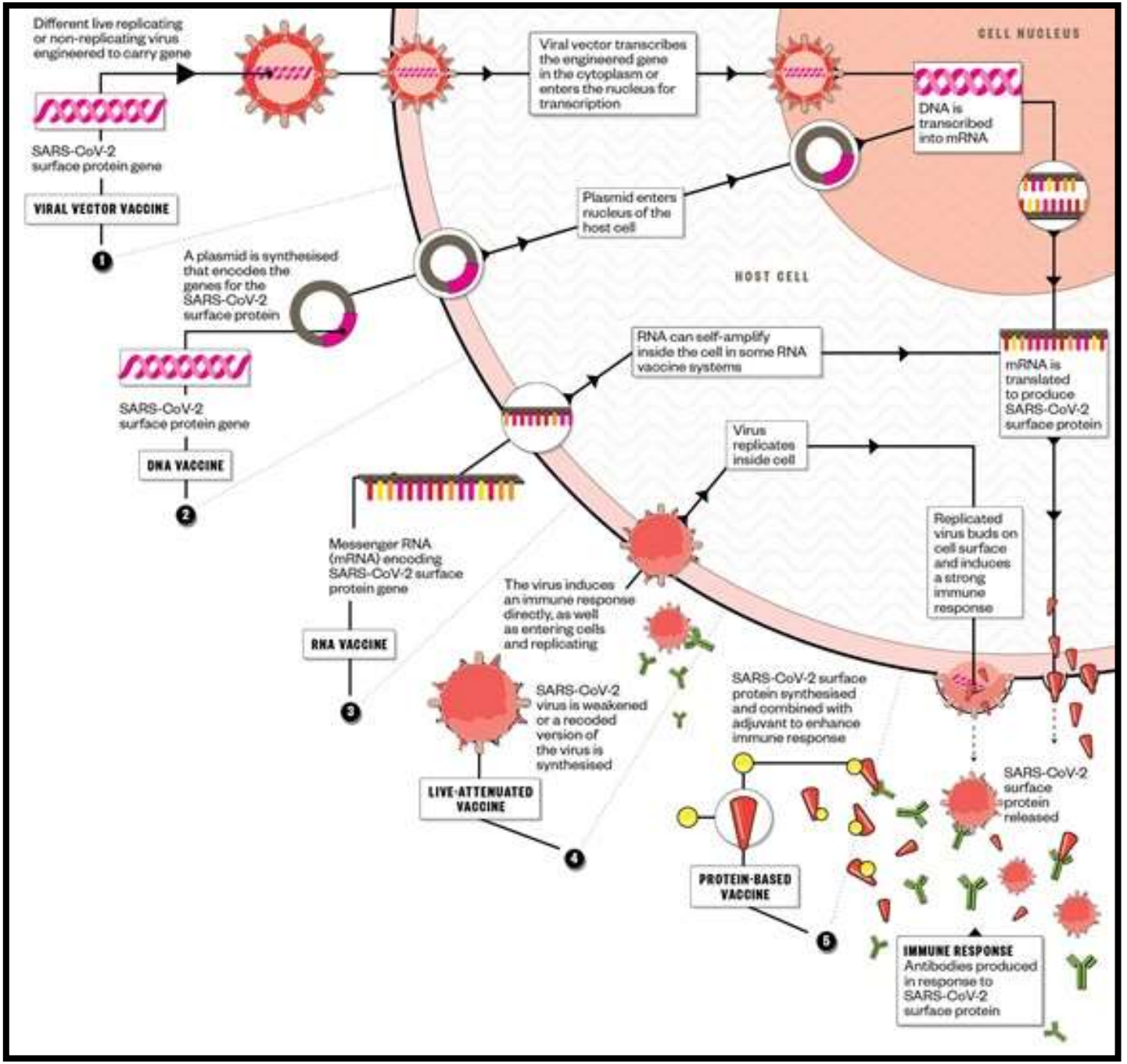
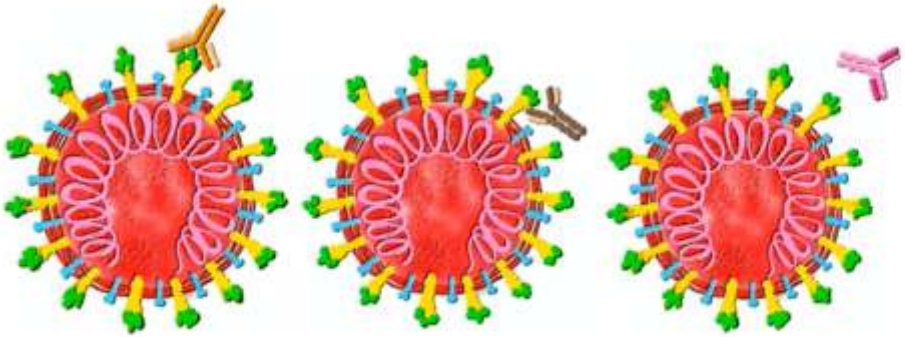
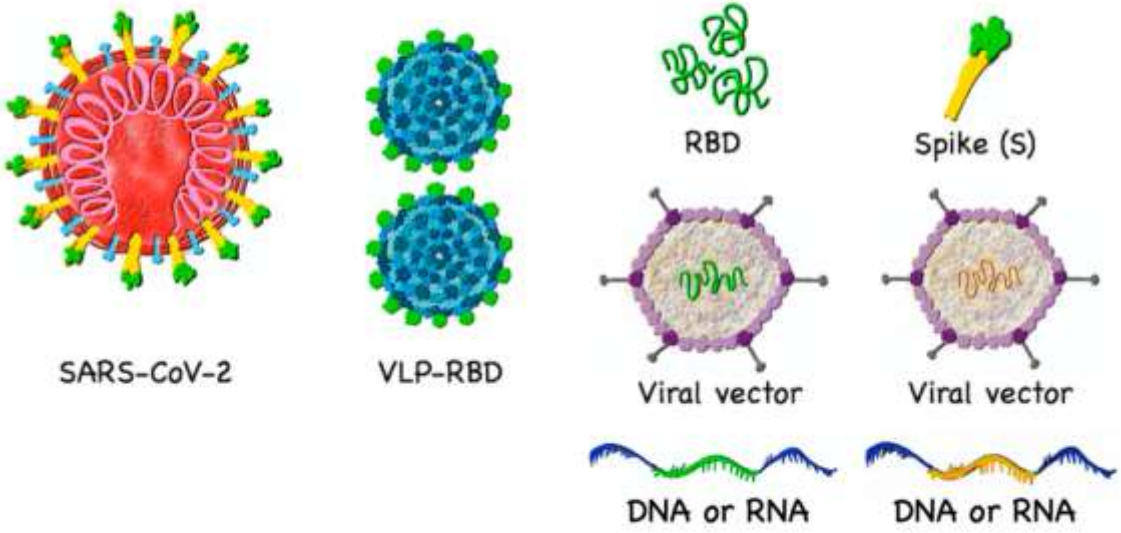

Different live replicating or non-replicating virus engineered to carry gene
SARS-CoV-2 surface protein gene
VIRAL VECTOR VACCINE
1
Viral vector transcribes the engineered gene in the cytoplasm or enters the nucleus for transcription
CELL NUCLEUS
DNA is transcribed into mRNA
Plasmid enters nucleus of the host cell
HOST CELL
A plasmid is synthesised that encodes the genes for the SARS-CoV-2 surface protein
SARS-CoV-2 surface protein gene
DNA VACCINE
2
RNA can self-amplify inside the cell in some RNA vaccine systems
mRNA is translated to produce SARS-CoV-2 surface protein
Virus replicates inside cell
Replicated virus buds on cell surface and induces a strong immune response
Messenger RNA (mRNA) encoding SARS-CoV-2 surface protein gene
RNA VACCINE
3
The virus induces an immune response directly, as well as entering cells and replicating
SARS-CoV-2 virus is weakened or a recoded version of the virus is synthesised
LIVE-ATTENUATED VACCINE
4
SARS-CoV-2 surface protein synthesised and combined with adjuvant to enhance immune response
SARS-CoV-2 surface protein released
PROTEIN-BASED VACCINE
5
IMMUNE RESPONSE
Antibodies produced in response to SARS-CoV-2 surface protein

A Antibody binding and virus neutralization:



Antibody specific for	S_{RBD}	S_{other}	N
can bind the virus	+	+	-
can neutralize the virus	+	+/-	-

B Induction of antibodies by: Infection — Vaccination



Virus-binding antibodies	+	+	+	+
Virus-neutralizing antibodies	++	+++	++	+

Different types of antibodies and induction of antibodies by infection and vaccination. (A) Antibodies (orange or brown) specific for viral surface proteins can bind to SARS-CoV-2, in contrast to antibodies (pink) specific for the viral nucleoprotein (N), which is not accessible in viable viruses.
Antibodies (orange) that bind to RBD are likely neutralizing, as they block the attachment of the virus to its receptor (ACE2) on the surface of host cells (not shown). Most antibodies (brown) binding to other moieties of the spike (S) protein (and antibodies binding to envelope or membrane proteins of SARS-CoV-2; not shown) may not neutralize the virus. +, yes; +/- eventually; - no. (B) Virus-binding antibodies may be induced by infection or vaccine candidates.
Virus-like particles displaying RBD (VLP-RBD) have a high likelihood of inducing neutralizing antibodies, provided that they display RBD (green) in a repetitive and thus highly immunogenic manner. Alternatively, RBD-based vaccines may be produced with RBD peptide, or viral vectors, DNA or RNA encoding RBD.
The same vaccine types may incorporate alternative antigens such as the full S protein (yellow), which may differ in the degree of immunogenicity but may also be more likely to trigger virus-binding non-neutralizing antibodies, possibly increasing the risk for antibody-dependent enhancement (ADE).

Inactivated and live-attenuated viruses (not shown) are expected to have relatively similar antigenic profiles to wild-type virus. +++, strong; ++ intermediate; + weak.