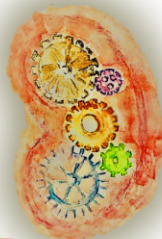


Anno VII  
**Cadernos  
de  
Patologia Renal**



*COMPLEMENTO E DOENÇAS RENAIIS.*

08 a 10 de maio, 2023  
Hospital do Rim,  
São Paulo, SP

Realização:



Apoio:



# Estado do Complemento

## Covid - 19

# Declaração de Conflito de Interesse

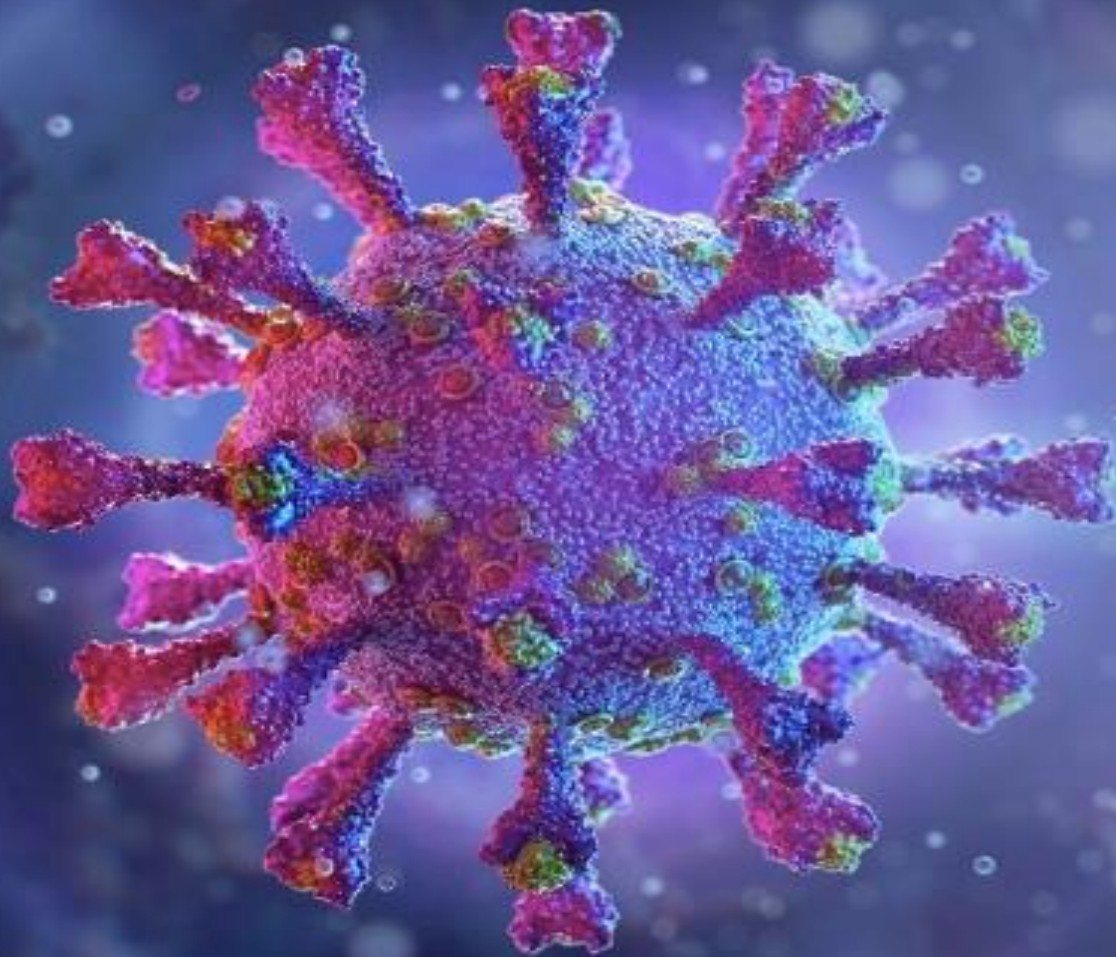
---

- Sem conflito de interesse

De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e a Resolução RDC 96/2008 da Agência de Vigilância Sanitária



<u>Co</u> -investigador	Estudo Controlado randomizado de fase III para determinar a segurança, eficácia e <u>Imunogenicidade</u> da vacina CHADOX1 NCOV-19 não replicante	2020 - 2022
<u>Co</u> -investigador	Estudo de fase IV, simples cego para avaliar a <u>imunogenicidade</u> e a segurança de uma terceira dose de reforço <u>heterólogo</u> com a vacina covid-19 recombinante (AstraZeneca; Pfizer ou Janssen) em indivíduos previamente vacinados com duas doses de <u>Sinovac</u> em comparação com uma terceira dose de reforço homólogo de vacina <u>Sinovac</u>	2021- 2022



# A G E N D A

- ✓ História: 2019-2023
- ✓ Complemento

# Definição

SARS-COV-2

Desregulação do Sistema Imune

assintomático/gripe – pneumonia – danos sistêmicos – hospitalização

Recuperação - covid longa - óbito

**Idade**  
**Genética**  
**DM, IS, Obeso**

Hiperinflamação + Resposta pró Trombótica

**Citocinas**  
**Complemento**  
**Coagulação**

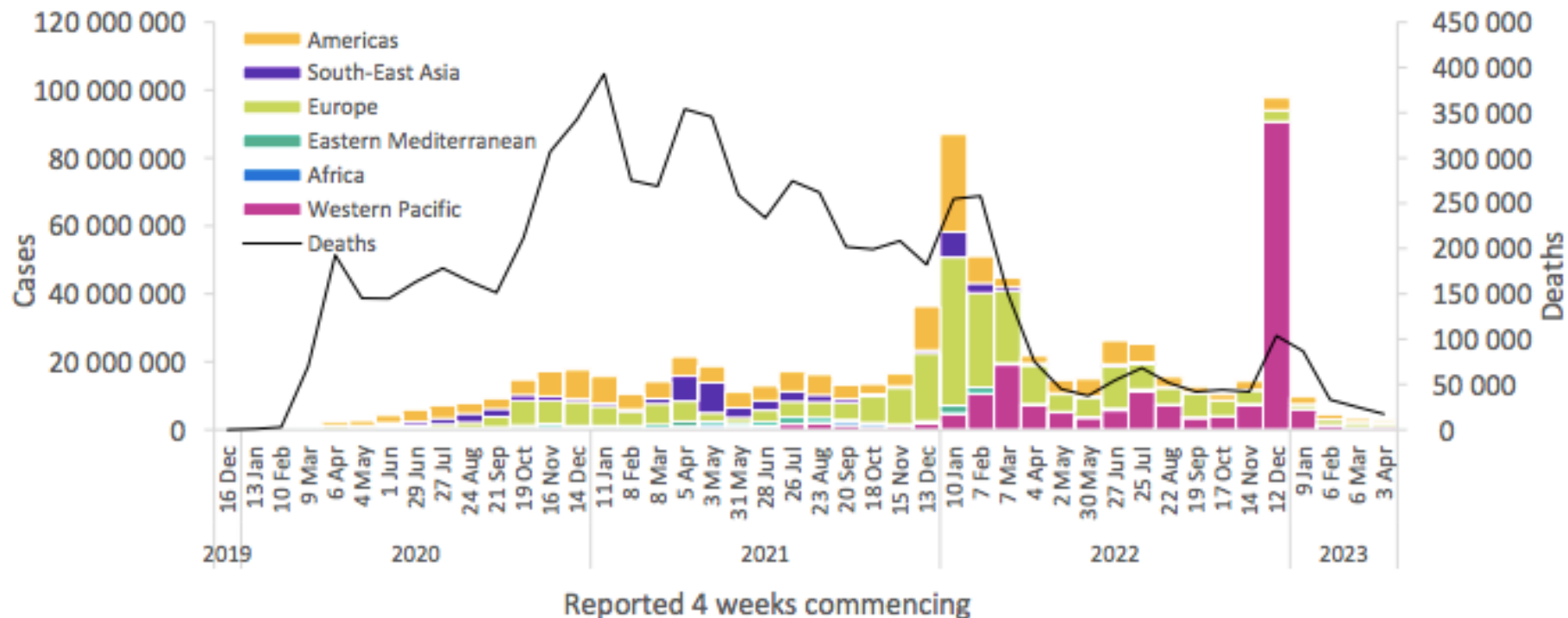


# Epidemiologia

- Infectados: 765 milhões
- Óbitos: 6.9 milhões

- Infectados: 2.8 milhões
- Óbitos: 17 mil

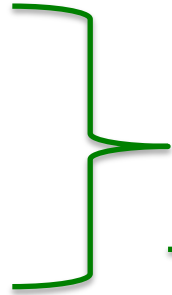
Figure 1. COVID-19 cases reported by WHO Region, and global deaths by 28-day intervals, as of 30 April 2023\*\*





# Evolução

- 1- NL63 - alfa
- 2- 229E - alfa
- 3- HKU1 - beta
- 4- OC43 – beta



Resfriado, zoonose

→ 1890 – Pandemia de gripe na Russia?

5- Cov: Inglaterra 1965 (1º covid identificado em humano)

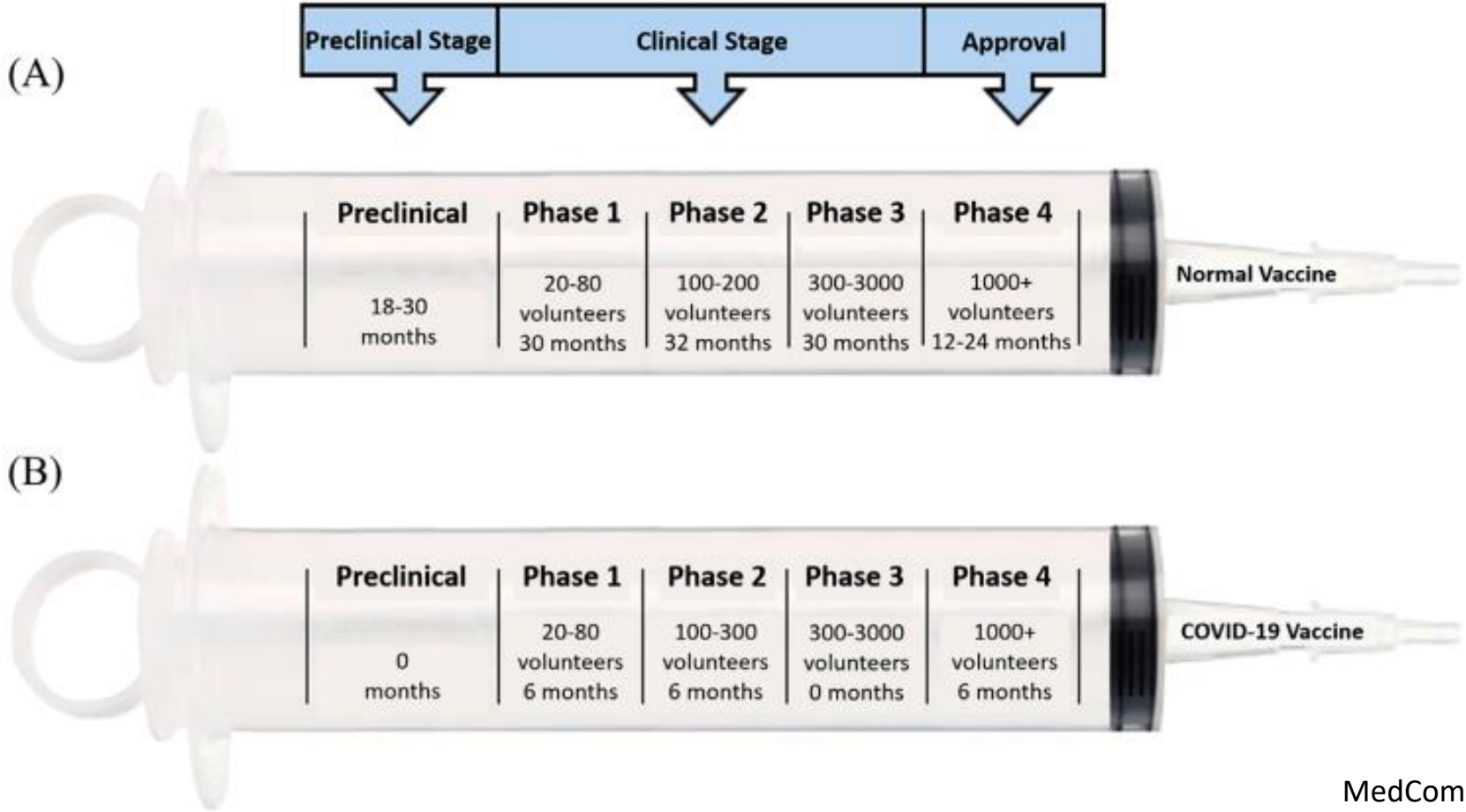
5- SARS-CoV-1: China, 2002 – 2004 – vírus erradicado (estudo)  
03/2020: 800.000 casos descritos (4.8% letal)

6- MERS-CoV: Oriente, 2012 - pesquisa para vacina  
até 2018: 2.500 casos (34% letal)

**7- SARS-CoV-2: beta coronavírus, 2019**

**07/01/2021: sequenciamento (80% com SARS-Cov 1; 50% MERS)**

# Vacinas





1200 x 754

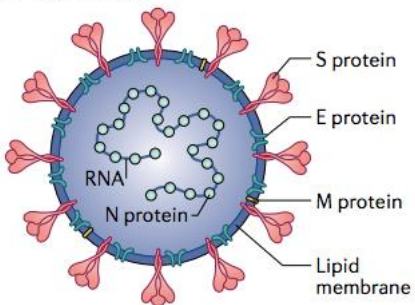


AstraZeneca

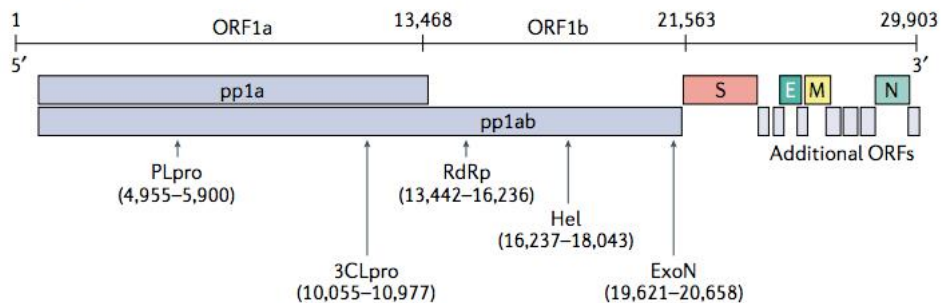


# Estrutura Viral

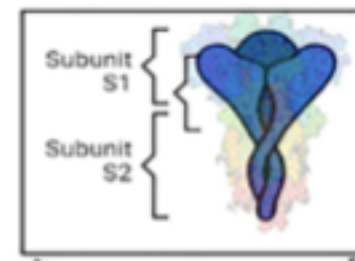
**a SARS-CoV-2**



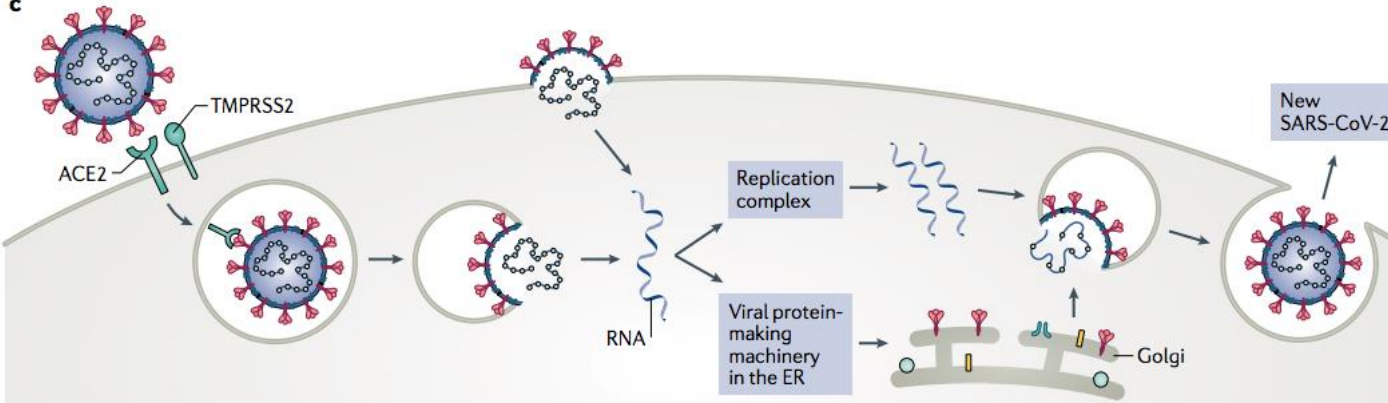
**b Single-stranded RNA genome of SARS CoV-2 (29,903 bases)**



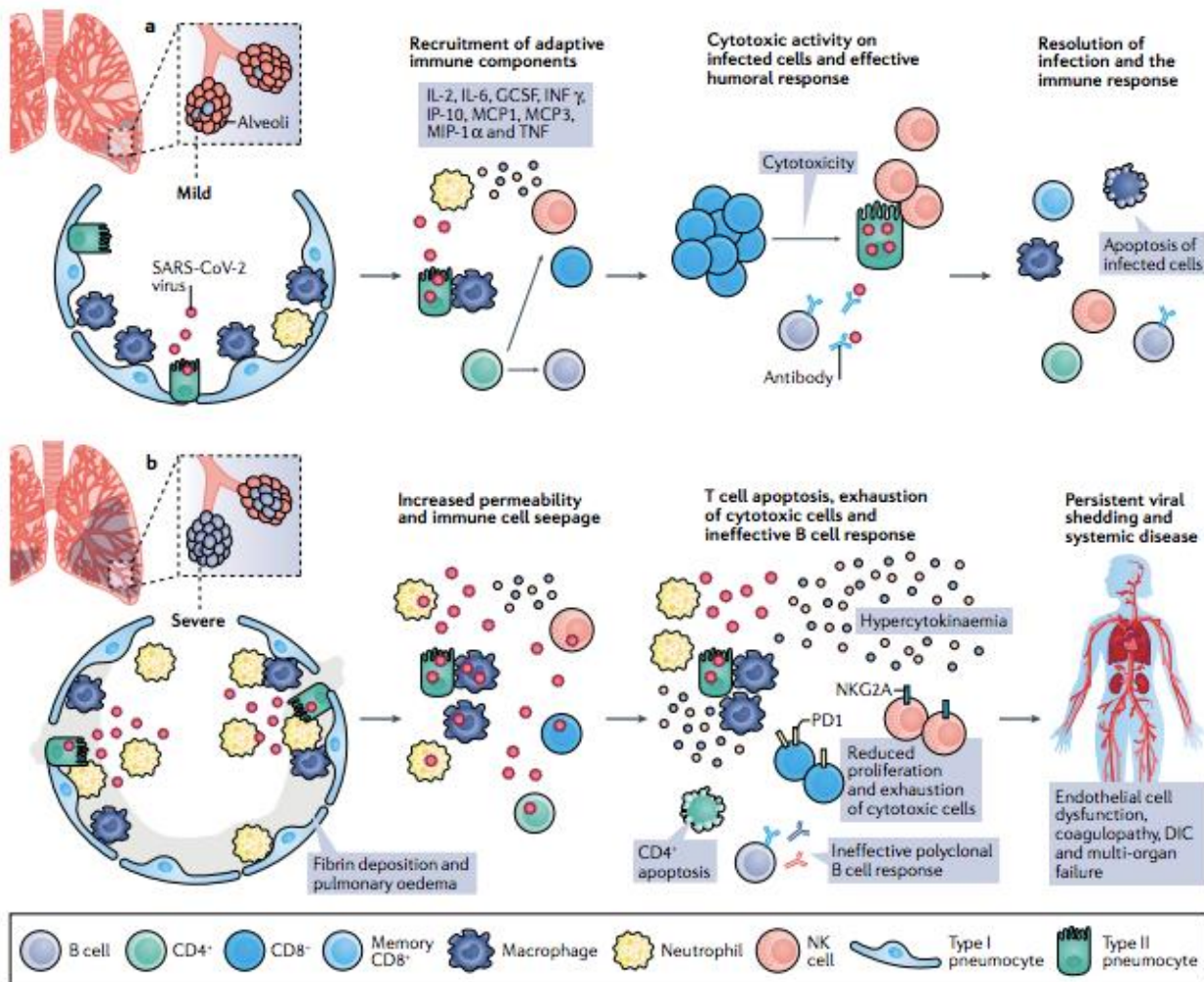
**(c) SARS-CoV-2 spike protein**



**c**

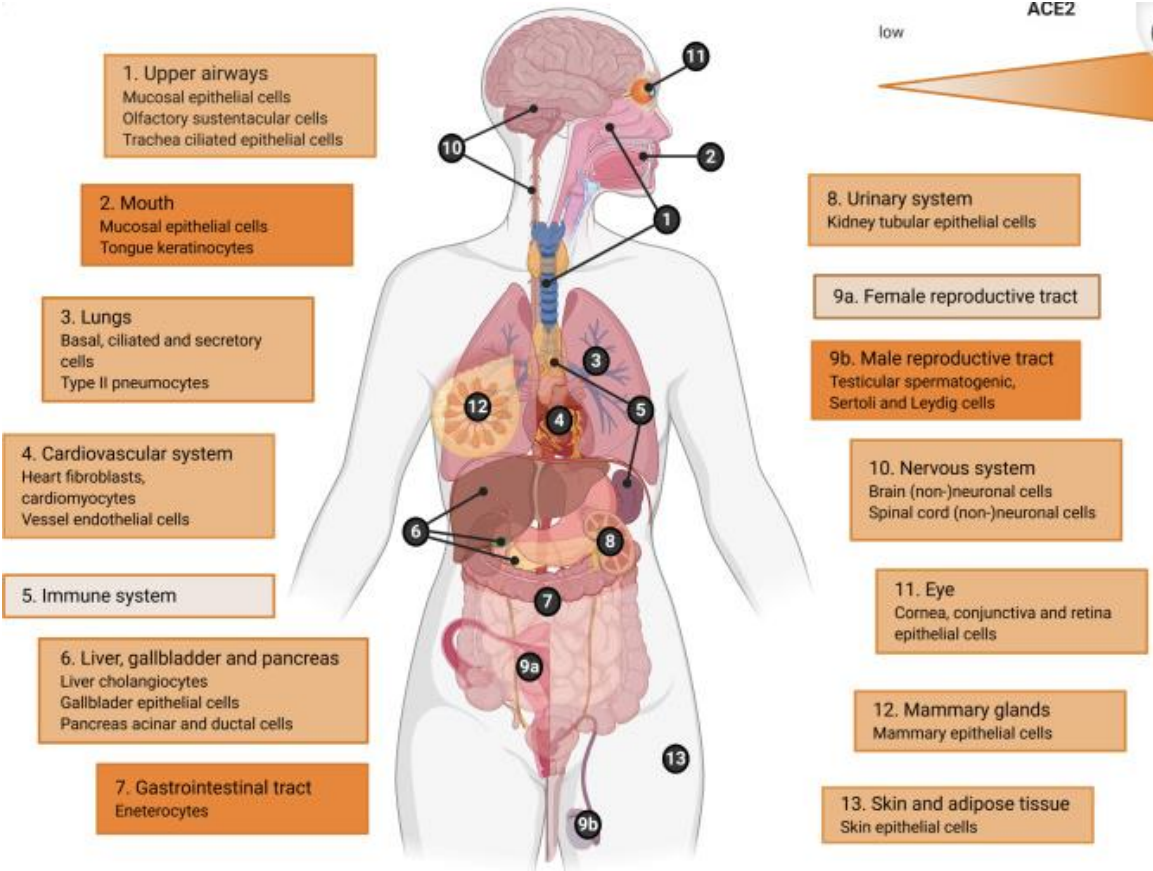


# Fisiopatogenia



# Quadro Clínico

Symptoms	ALLERGIES	COLD	INFLUENZA	COVID-19
Symptoms begin	Gradually	Gradually	Abruptly	Within 14 days of exposure
Symptoms last	Allergy season	4 – 10 days	5 – 7 days	Varies by Person
Body aches	–	✓	✓	Sometimes
Chills	–	Less Common	✓	Sometimes
Dry cough	✓	✓	✓	✓
Exposure to germs	–	✓	✓	✓
Fatigue/Weakness	Sometimes	✓	✓	✓
Fever	–	Less Common	✓	✓
Headaches	✓	Less Common	✓	Sometimes
Itchy eyes	✓	–	–	–
Nasal Congestion	✓	✓	✓	Less Common
Nausea/Vomiting/Diarrhea	–	Sometimes	Sometimes	Sometimes
New loss of taste or smell	Sometimes	Sometimes	Sometimes	✓
Repeated shaking with chills	–	Sometimes	Sometimes	Sometimes
Runny nose	✓	✓	✓	Less Common
Sneeze	✓	✓	✓	Sometimes
Sore throat	Sometimes	✓	✓	Sometimes



# Testes Diagnósticos

1- RT-PCR naso/orofaringe: **Sensível para as variantes**

2- RT-PCR saliva: SEN 94%      ESP 100%

3- Sorologias

Imunoglobulinas Totais: (IgA, IgM, IgG)

IgM: alvo principalmente nucleoproteína (pouco Spike)

IgG: alvo principalmente nucleoproteína (pouco Spike)

4- Anticorpo Neutralizante - contra Spike - contra RBD

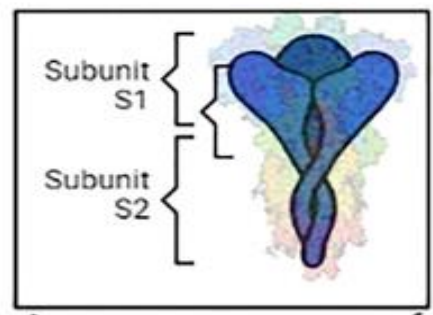
5- Antígeno nasal – teste de farmácia

L  
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F  
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P  
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N  
I  
A

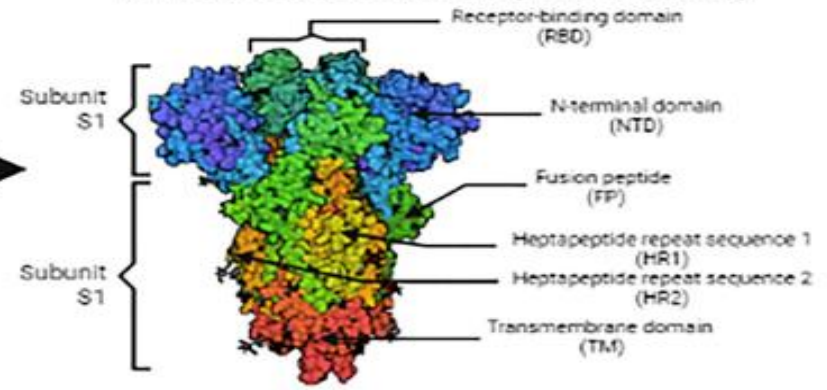


# Variantes

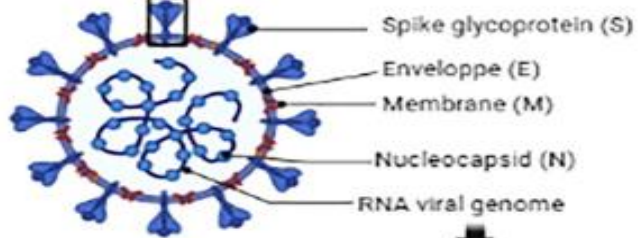
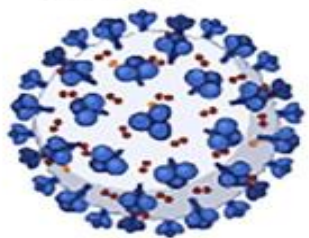
(c) SARS-CoV-2 spike protein



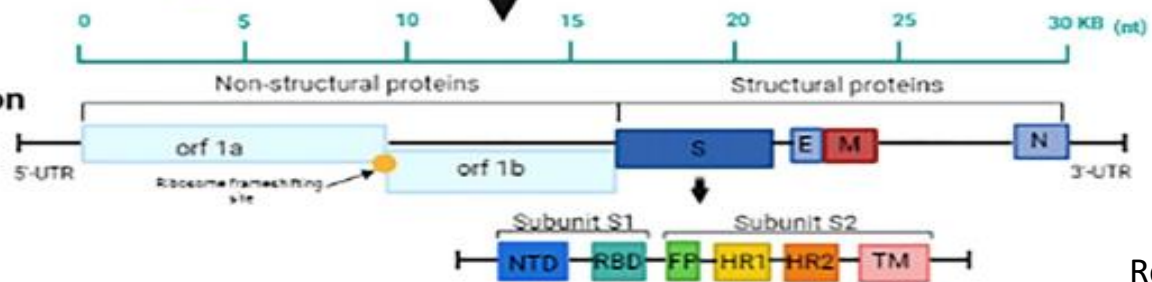
(d) SARS-CoV-2 spike protein  
Van Der Waals structure (PDB ID: 6VXX)



(a) SARS-CoV-2 structure



(b) SARS-CoV-2 genome organisation

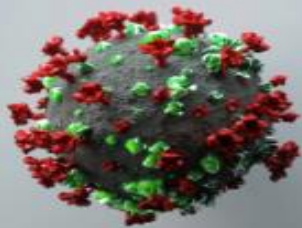


## VOCs – variantes de preocupação

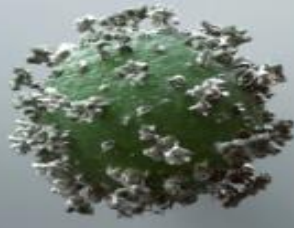
- Transmissibilidade
- Resistência a Testes diagnósticos
- Resistência vacinal
- Gravidade
- Reinfecção

## VOIs – variantes de interesse

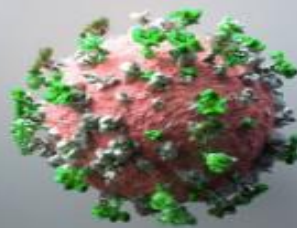
- 8



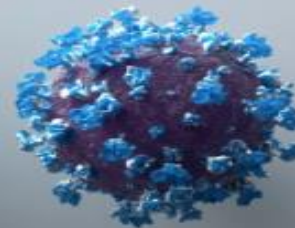
Alpha  
B.1.1.7



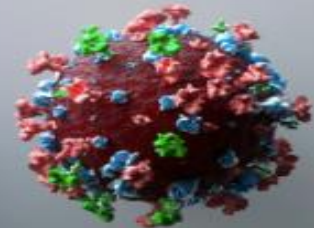
Beta  
B.1.351



Gamma  
P.1



Delta  
B.1.617.2




Omicron  
B.1.1.529

# Covid Longa


- 10-12 % vacinados
- 10-30% não hospitalizados
- 50-70% hospitalizados
- todas as idades

Symptoms  
Pathology

### Heart

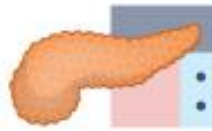


• Chest pain	• Cardiac impairment
• Palpitations	• Myocardial inflammation
	• POTS



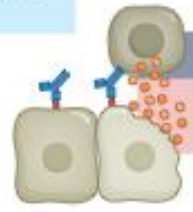
### Lungs

• Cough	• Abnormal gas exchange
• Dyspnoea	



### Pancreas

• Diabetes
• Pancreas injury




### Immune system

• Autoimmunity
• MCAS



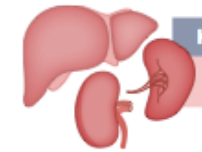
### Gastrointestinal tract

• Abdominal pain	• Gut dysbiosis
• Nausea	• Viral persistence and viral reservoir




### Neurological system

• Cognitive impairment	• Dysautonomia
• Fatigue	• ME/CFS
• Disordered sleep	• Neuroinflammation
• Memory loss	• Reduced cerebral blood flow
• Tinnitus	• Small fibre neuropathy



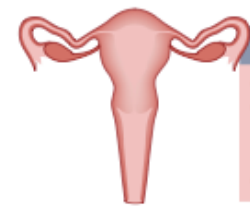
### Kidneys, spleen and liver

• Organ injury
----------------



### Blood vessels

• Fatigue	• Coagulopathy
	• Deep vein thrombosis
	• Endothelial dysfunction
	• Microangiopathy
	• Microclots
	• Pulmonary embolism
	• Stroke

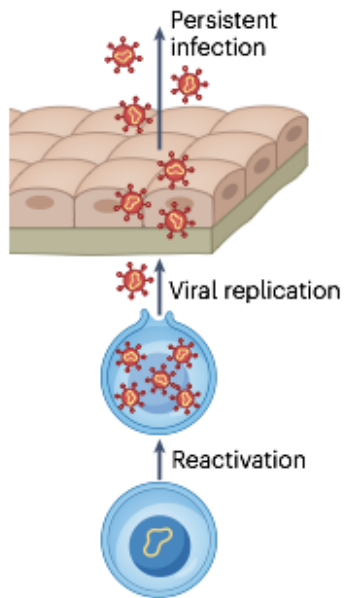


### Reproductive system

• Erectile dysfunction	• Reduced sperm count
• Increased severity and number of premenstrual symptoms	
• Irregular menstruation	

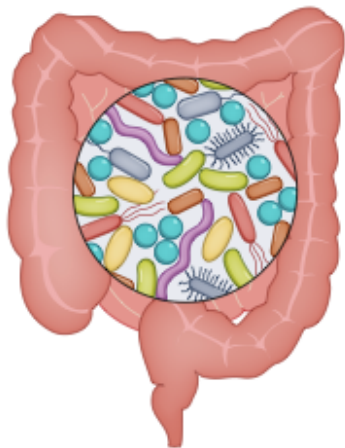
# Covid Longa

## Immune dysregulation



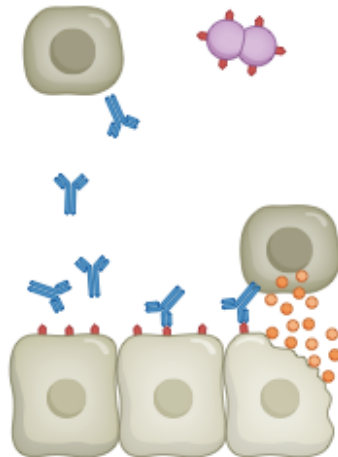
EBV  
Herpes simples

## Microbiota dysbiosis



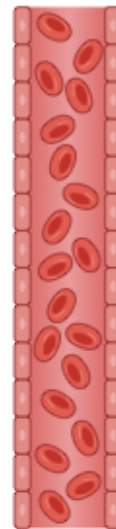
3.8% RNA fezes  
7 meses apósCovid

## Autoimmunity and immune priming



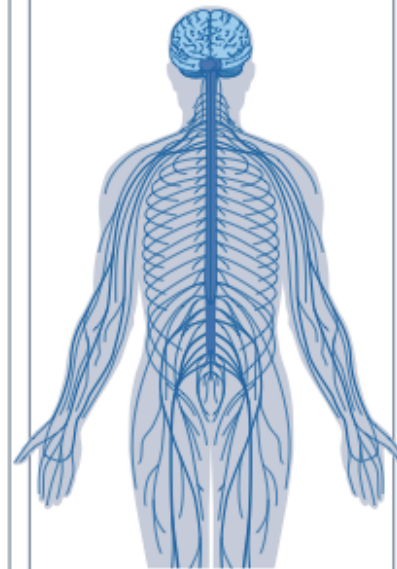
AutoAc: recep. musc  
Citocinas: CCL11  
citotoxicid. neuronal

## Blood clotting and endothelial abnormalities



Ac anti plaqueta;C  
microtrombos

## Dysfunctional neurological signalling



↓ cortisol, de  
massa cinzenta

POTS	Pharmacological: $\beta$ -blockers, pyridostigmine, fludrocortisone, midodrine	POTS and ME/CFS literature	Options can be prioritized on the basis of a specific constellation of symptoms
	Non-pharmacological: increase salt and fluid intake, intravenously administered salt, compression stockings	POTS and ME/CFS literature	-
Fatigue	Coenzyme Q <sub>10</sub> , D-ribose	ME/CFS literature	-
Abnormal clotting	Anticoagulants	Long COVID pilot study	Additional trials in progress
Viral persistence and antivirals (COVID-19)	Paxlovid	Long COVID case reports	No active trials, despite strong evidence for viral persistence
Gastrointestinal symptoms	Probiotics	Long COVID pilot study	Resolved gastrointestinal and other symptoms



TABLE 2 Characteristics of post-vaccination COVID-19 kidney injury based on literature review (n = 82).

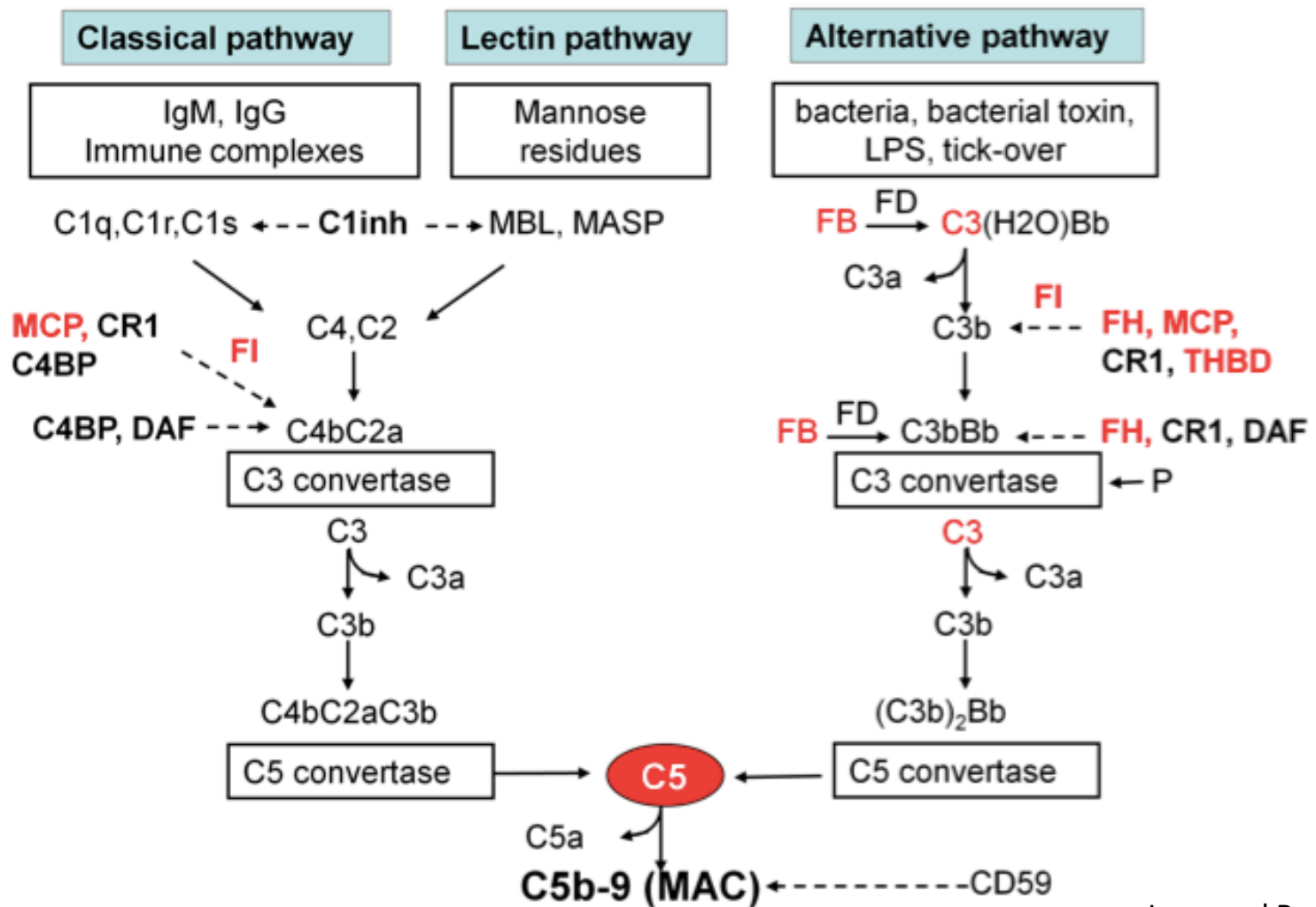
Glomerular injury	N	Vaccine	Number of cases per dose	Time from vaccine to diagnosis
IgA nephropathy (7, 39, 40, 68–72)	27	Pfizer–12	1st dose: 5	3 h to 6 weeks
		Moderna–10	2nd dose: 22	
		Sinopharm–1		
		Astrazeneca–1		
Minimal change disease (6, 7, 39, 40, 44, 54, 55, 63, 73–75)	21	RNAm*–3	1st dose: 11	2 days to 4 weeks
		Pfizer–11	2nd dose: 8	
		Moderna–7		
		Astrazeneca–2		
Crescentic glomerulonephritis (40, 42, 76–79)	12	RNAm*–1	1st dose: 2	2 days to 4 weeks
		Pfizer–6	2nd dose: 8	
		Moderna–5		
		Covaxin–1		
Membranous nephropathy (7, 40, 80)	7	Pfizer–3	1st dose: 2	1 day to 4 weeks
		Moderna–3	2nd dose: 5	
		Johnson–1		
		Moderna–5		
Lupus nephritis (40, 80–83)	5	Pfizer–2	1st dose: 4	2 days to 1 week
		Astrazeneca–2	2nd dose: 1	
		Moderna–1		
Collapsing glomerulopathy (37, 38)	4	Moderna–2	1st dose: 2	1 s to 3 weeks
		Astrazeneca–2	2nd dose: 2	
Anti-glomerular basement membrane (7, 39)	3	Pfizer–2	1st dose: 1	1 day to 2 weeks
		Moderna–1	2nd dose: 2	
Focal segmental glomerulosclerosis (7)	1	Pfizer–1	2nd dose: 2	3 weeks
Scleroderma renal crisis (38)	1	Pfizer–1	1st dose: 1	1 day
C3 glomerulonephritis (84)	1	Astrazeneca–1	1st dose: 1	1 week

\*Pfizer and Moderna were the available vaccines at the time of publication.

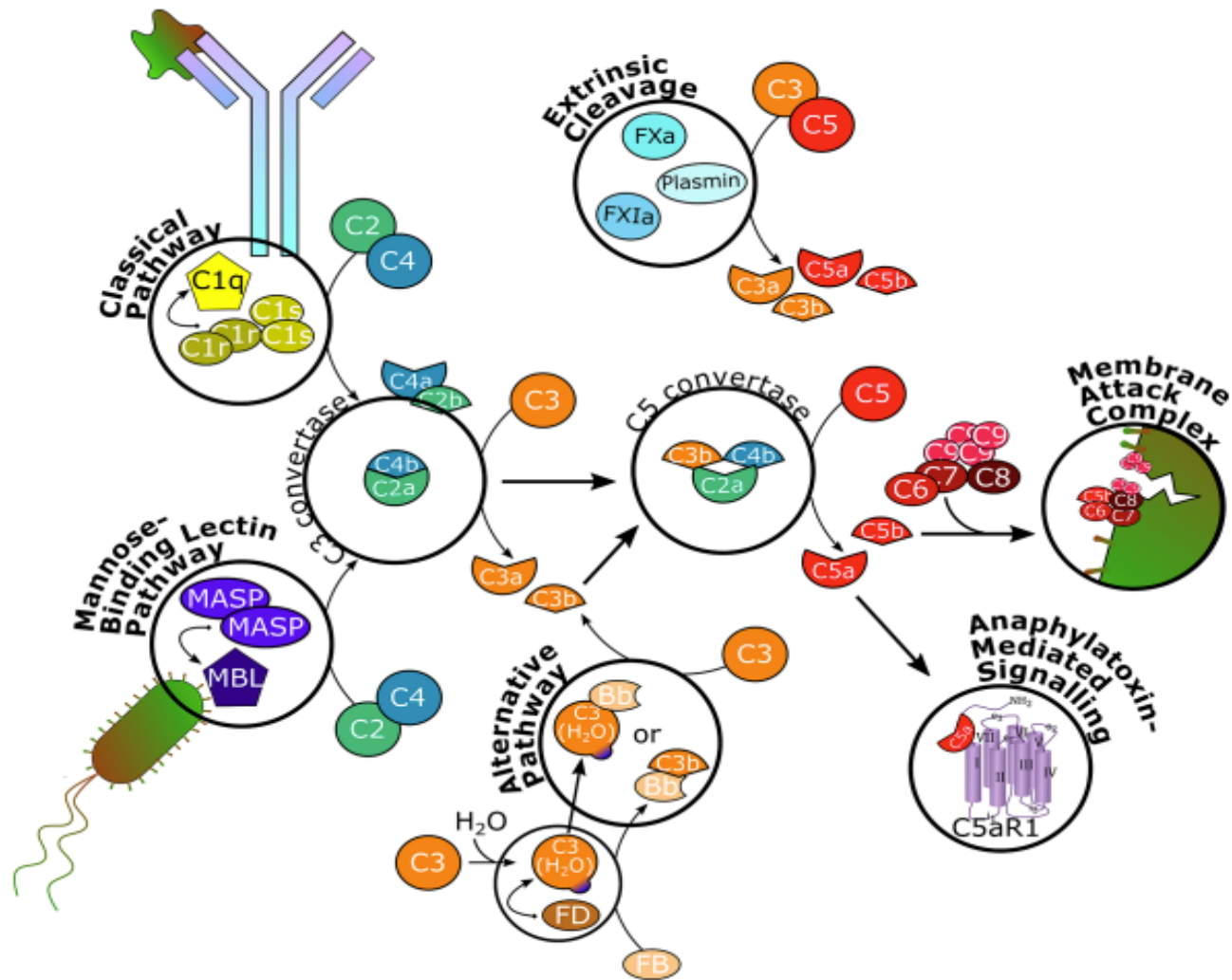
TABLE 1 Biopsy findings of native kidney in patients with COVID-19: Review of case-series reports (n = 331) (14, 18, 62–67).

Diagnosis	Number of cases	%
Collapsing glomerulopathy	94	28.4
Acute tubular injury	46	13.9
Diabetic nephropathy	32	9.7
Focal segmental glomerulosclerosis (FSGS)	25	7.6
Minimal change disease	18	5.4
Membranous nephropathy	15	4.5
Pauci-immune crescentic glomerulonephritis	13	3.9
Thrombotic microangiopathy	12	3.6
Infection-associated glomerulonephritis (GN)	9	2.7
Myoglobin cast nephropathy	9	2.7
IgA nephropathy	9	2.7
Arteritis/Arterionephrosclerosis	9	2.7
Lupus nephritis	7	2.1
Amyloidosis	5	1.5
Proliferative glomerulonephritis with monoclonal IgG deposits	4	1.2
Acute interstitial nephritis	4	1.2
Cryoglobulinemic glomerulonephritis	3	0.9
HSP nephritis	2	0.6
Cortical infarct	2	0.6
Anti-glomerular basement membrane antibody disease	2	0.6
Acute pyelonephritis	2	0.6
Light chain cast nephropathy	2	0.6
C3 glomerulonephritis	1	0.3
Membranous-like glomerulopathy with monoclonal IgG kappa deposits	1	0.3
Fibrillary glomerulopathy	1	0.3
Light chain deposition disease	1	0.3
Hemoglobin cast nephropathy	1	0.3
Thin glomerular basement membrane disease	1	0.3
Sickle cell nephropathy	1	0.3

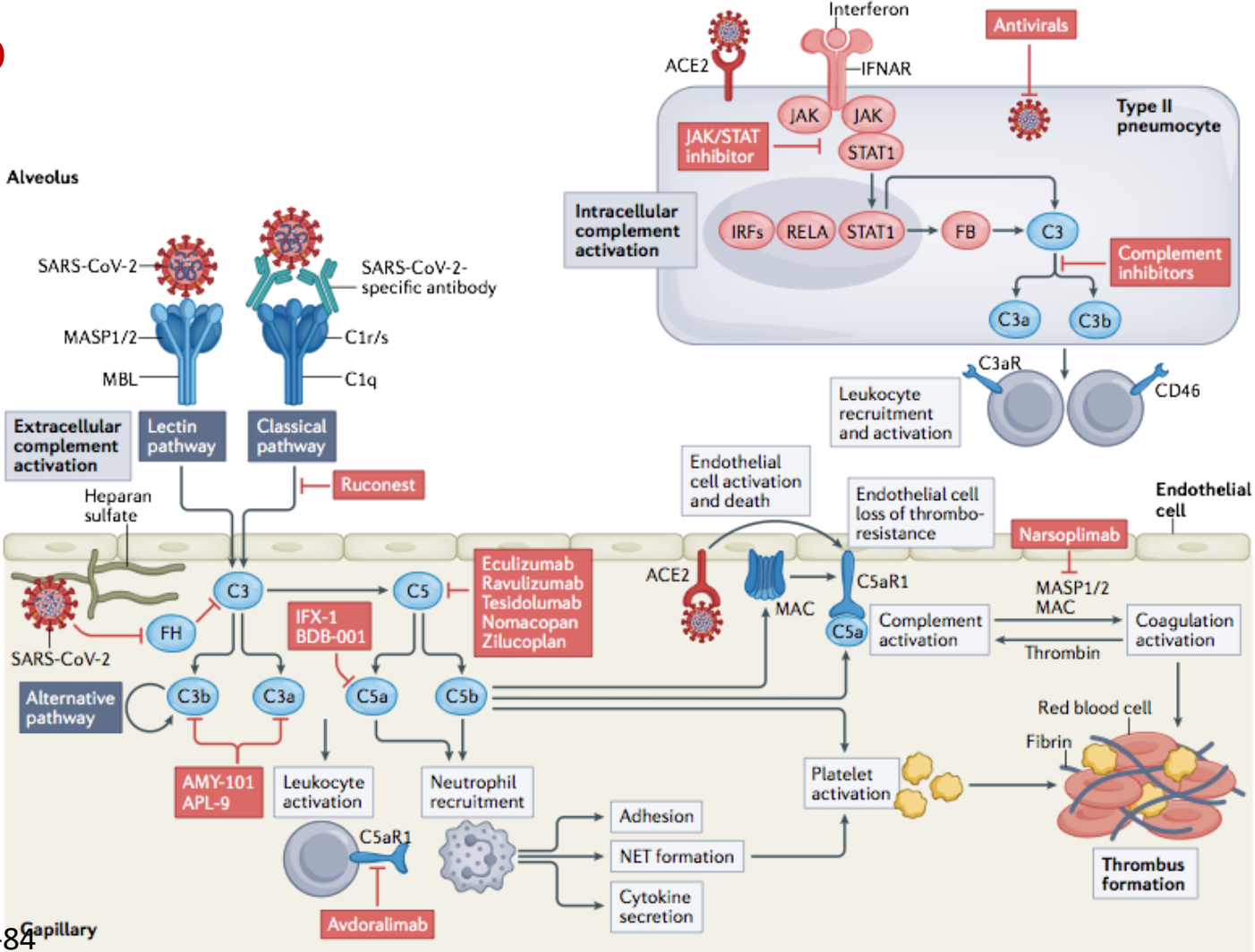
COVID-19, coronavirus disease 2019; HSR, Henoch-Schönlein purpura.



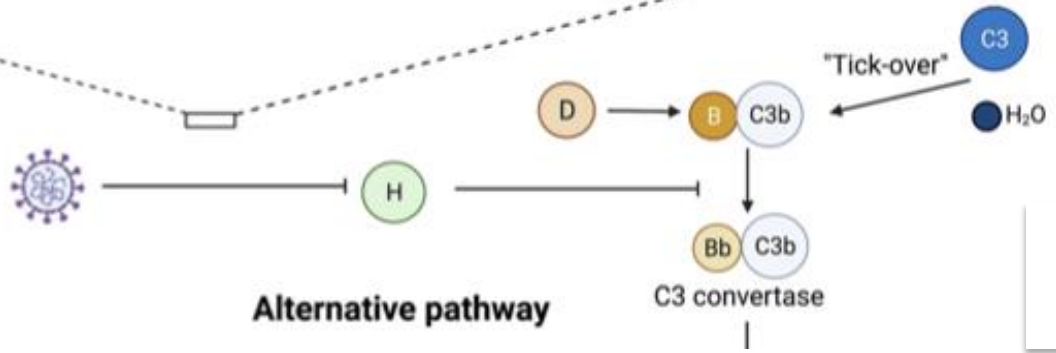
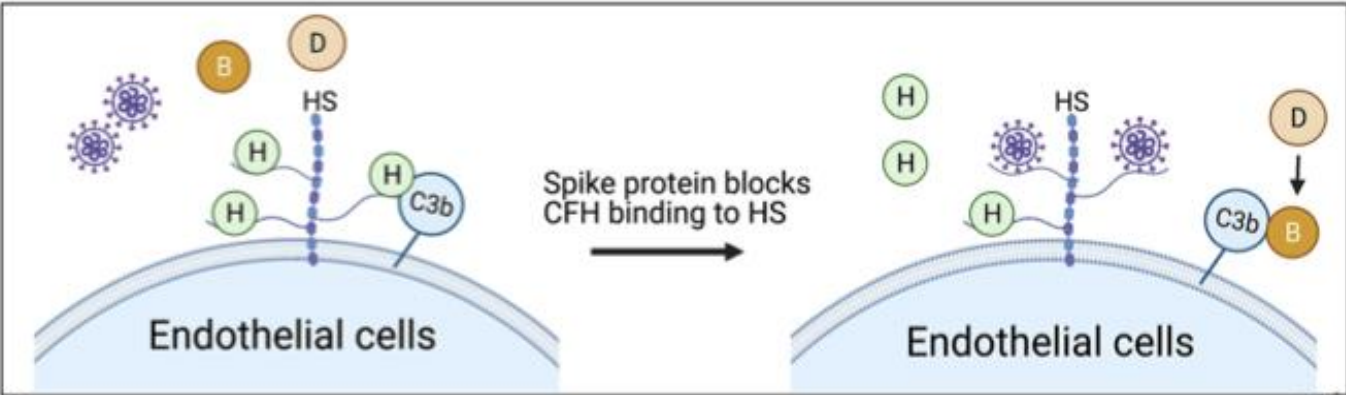




# Complemento



# Complemento – via alternativa



# Complemento: via alternada

ISARIC4C - UK

N = 682 hospitalizados

302 UTI

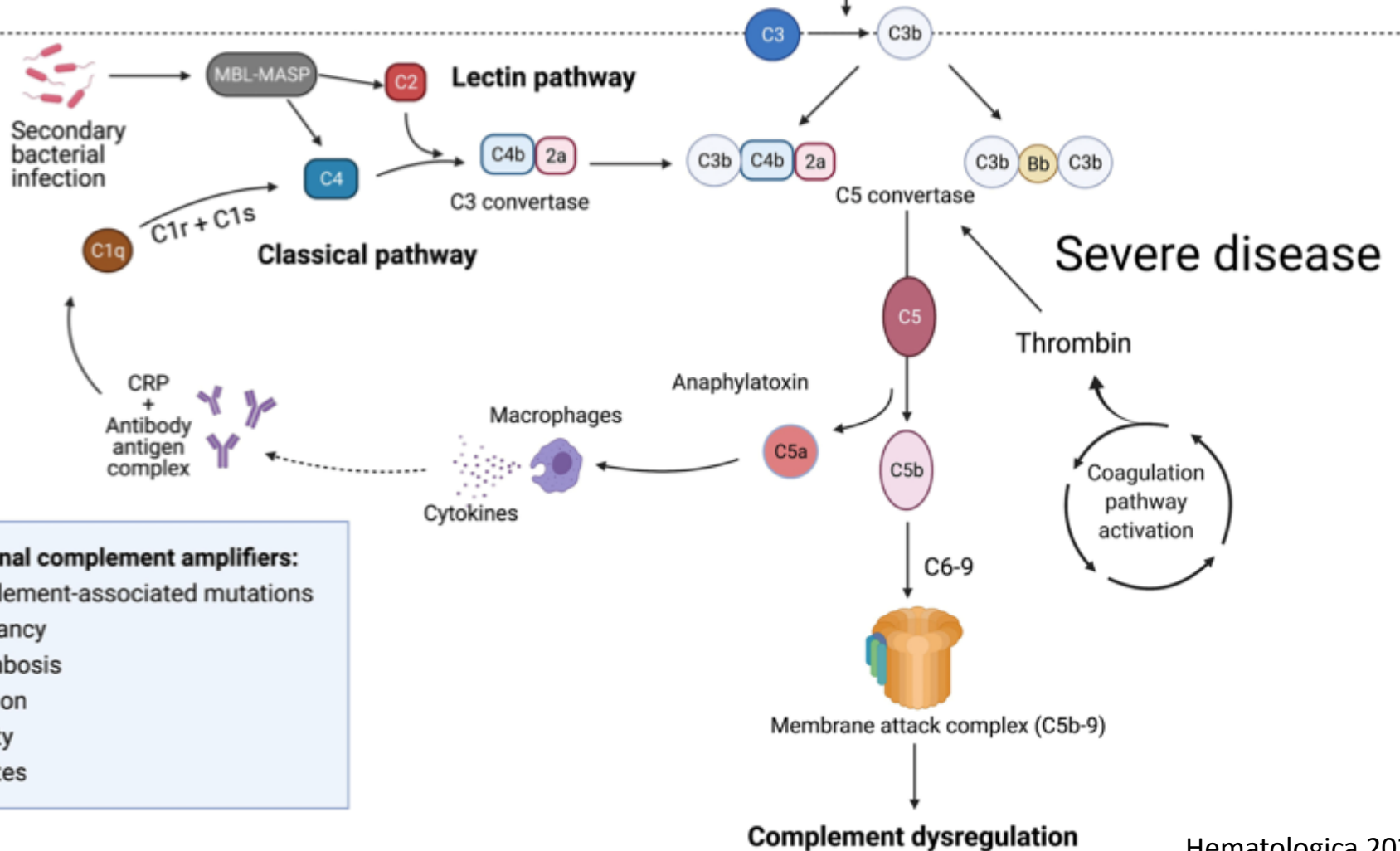
104 óbitos

N= 49 sadios

Via alternada: 16 proteínas

Event	<i>p</i> value
Death	<0.0001
Discharged alive	<0.0001

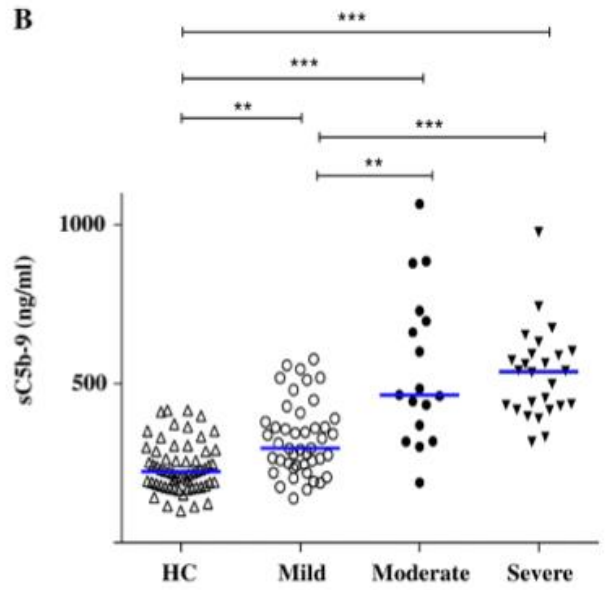
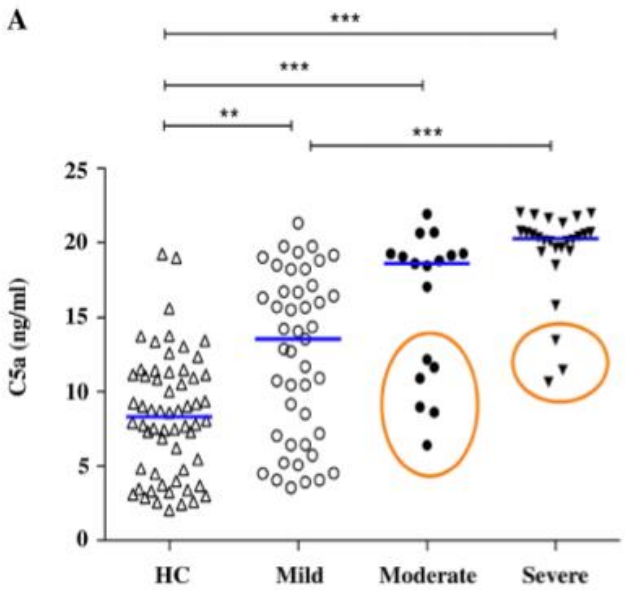
Variable (reference)	Hazard ratio	95% CI	<i>p</i> value
Ba class (2)	4.32	2.68; 6.96	<0.001
Age	1.03	1.01; 1.04	0.001
Sex (Male)	1.49	0.82; 2.72	0.19
Obesity (Yes)	1.24	0.57; 2.68	0.59
Any Comorbidity (Yes)	1.01	0.49; 2.12	0.97



- Additional complement amplifiers:**
- Complement-associated mutations
  - Pregnancy
  - Thrombosis
  - Infection
  - Obesity
  - Diabetes

# Complemento: via final C5a e C5b-9

Norte da Itália  
N = 97 pacientes  
54 leve  
17 moderada  
26 severa  
N= 50 sadios



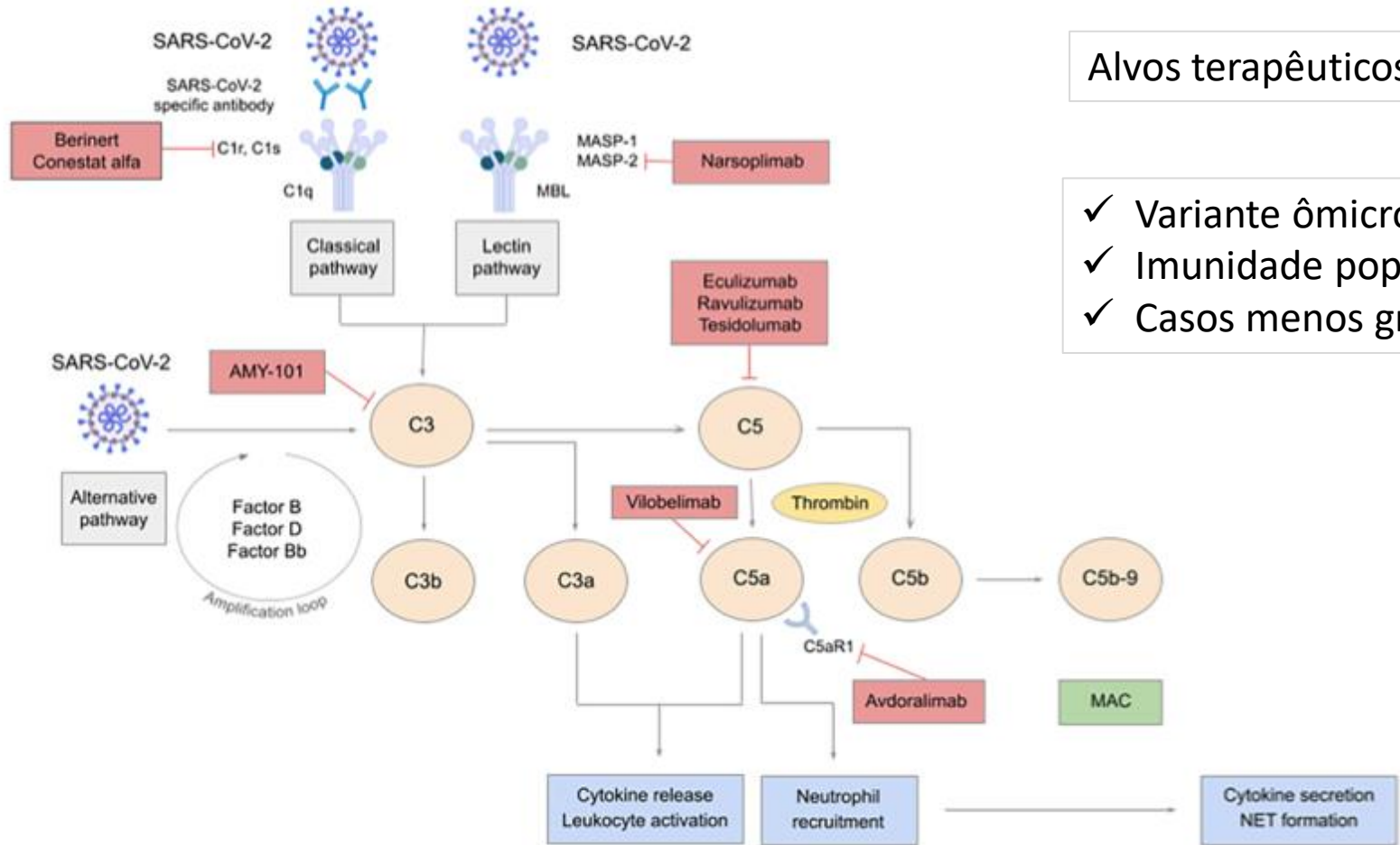
Complemento foi preditivo de severidade

# Complement activation in COVID-19 and targeted therapeutic options: A scoping review

Metanálise 157 estudos, indivíduos > 16 anos

- 1- Estudos histopatológicos (16): Pele- C3d; C4d; C5b-9    Vasos- C4d e fibrina    Coração-C5b-9  
Pulmão-3 vias    Rim- C5b9 arteríolas, túbulos; Via ML
- 2- Estudos pré clínicos (células): 3 vias do complemento estão hiperativadas; knock-out C3
- 3- Multiomics: expressão de 28 genes do SC em 32 pacientes:  
Via Clássica correlacionou com doença moderada  
Vias Alternada e Manose/Lectina correlacionaram com doença severa
- 4- Estudos observacionais (81): C3a e C5a correlacionaram com inflamação e  
C5b-9 com inflamação, coagulação e mortalidade
- 5- Estudos clínicos de intervenção (13 mas 2 RTC fase II): 3 vias hiperativadas





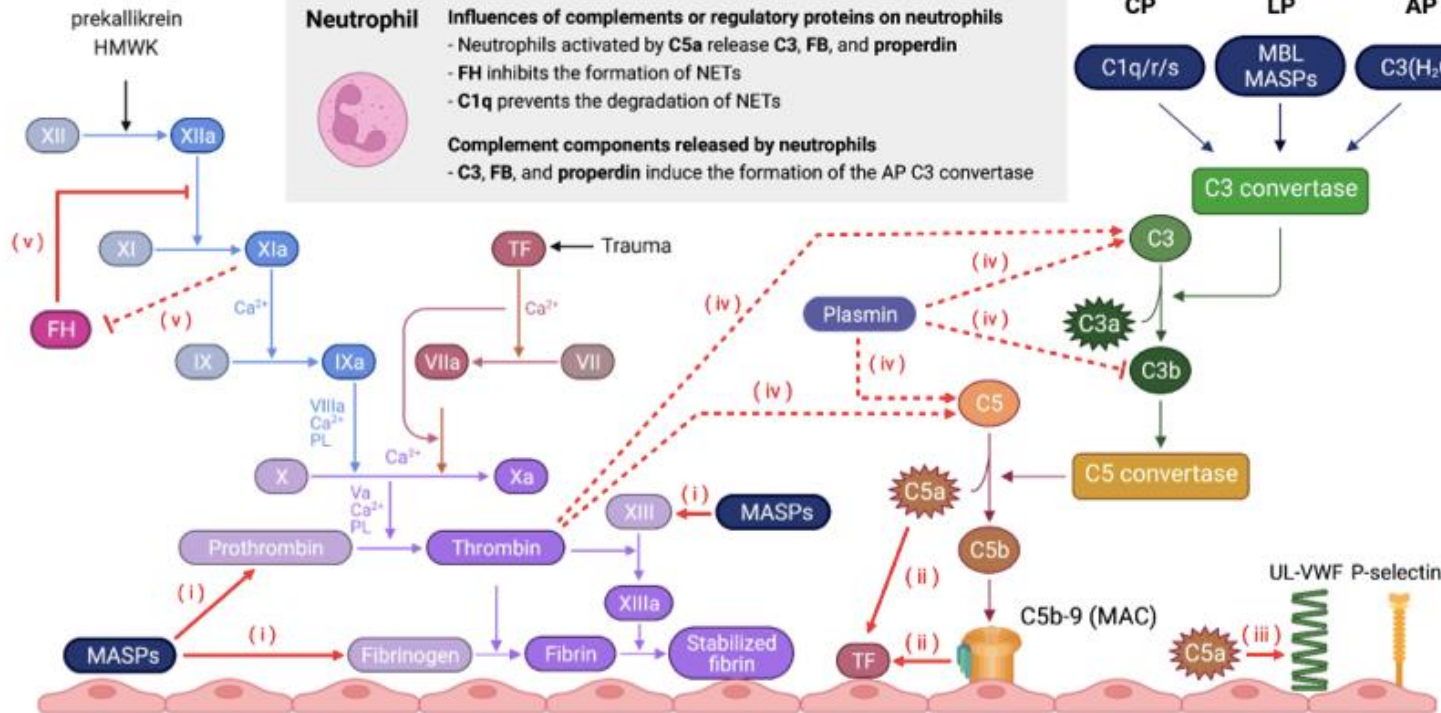
## Alvos terapêuticos

- ✓ Variante ômicron
- ✓ Imunidade populacional
- ✓ Casos menos graves

# Complemento

- ✓ Ativação das 3 vias      Lectina/Manose: ação direta do vírus (proteína S e N)  
                                    Clássica: IgG/IgM anti RBD  
                                    Alternada: ligação com heparan sulfato (competição com FH)
- ✓ Ativação extra celular e intracelular; sistêmico e local
- ✓ Fator de risco independente de mortalidade
- ✓ Alvo terapêutico
- ✓ Associação com trombose

## Coagulation



**Platelet**

**Influences of complements on platelets**

- C3a and C5a induce platelet activation and aggregation
- C1q and C5b-9 are likely to contribute to thrombotic events

**Substances released by activated platelets**

- CS and PMPs activate the CP
- P-selectin activates the AP

**Complement components released by activated platelets**

- C3, C5, C6, C7, C8, and C9 are secreted under the specific stimulation

**Neutrophil**

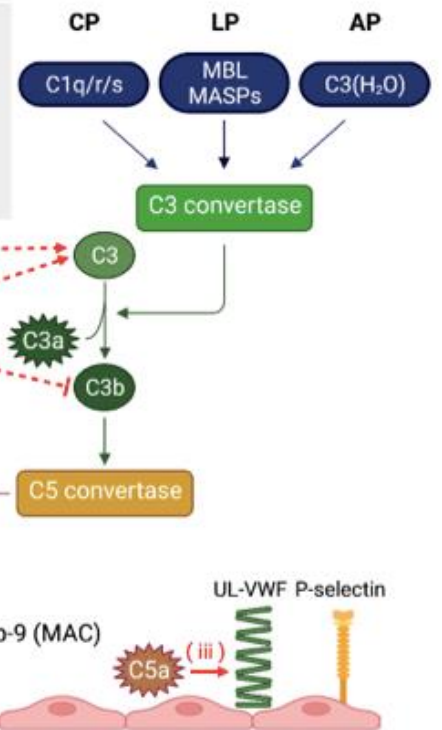
**Influences of complements or regulatory proteins on neutrophils**

- Neutrophils activated by C5a release C3, FB, and properdin
- FH inhibits the formation of NETs
- C1q prevents the degradation of NETs

**Complement components released by neutrophils**

- C3, FB, and properdin induce the formation of the AP C3 convertase

## Complement



# Tromboinflamação

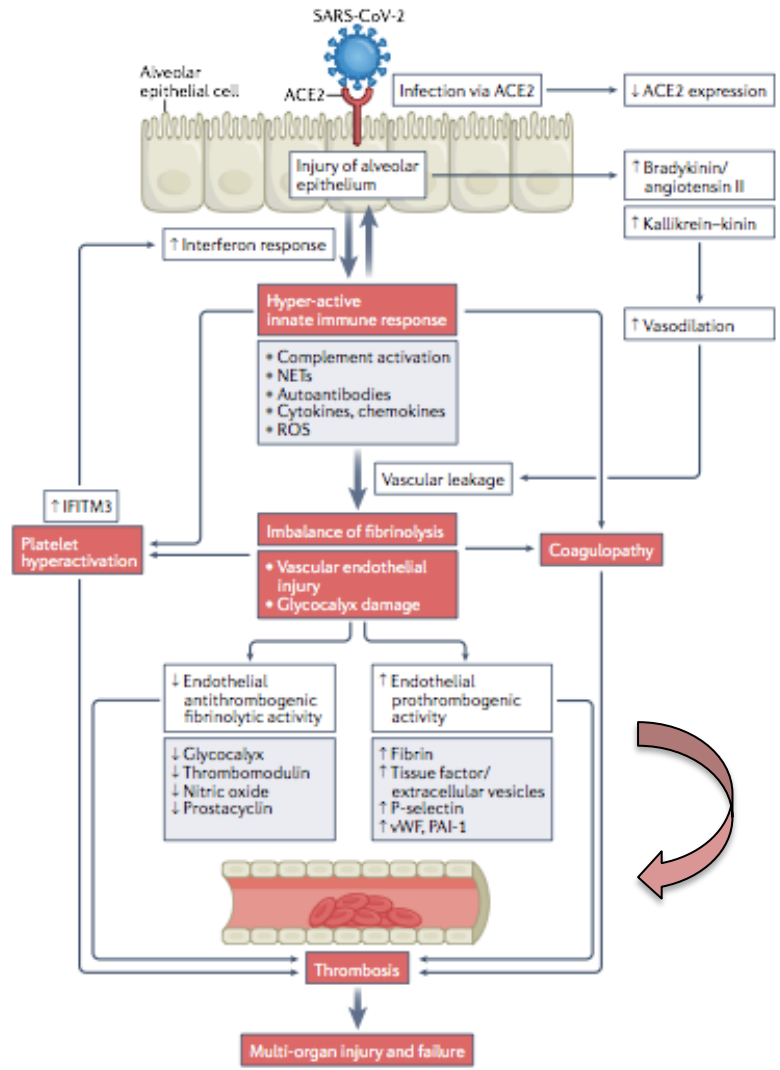
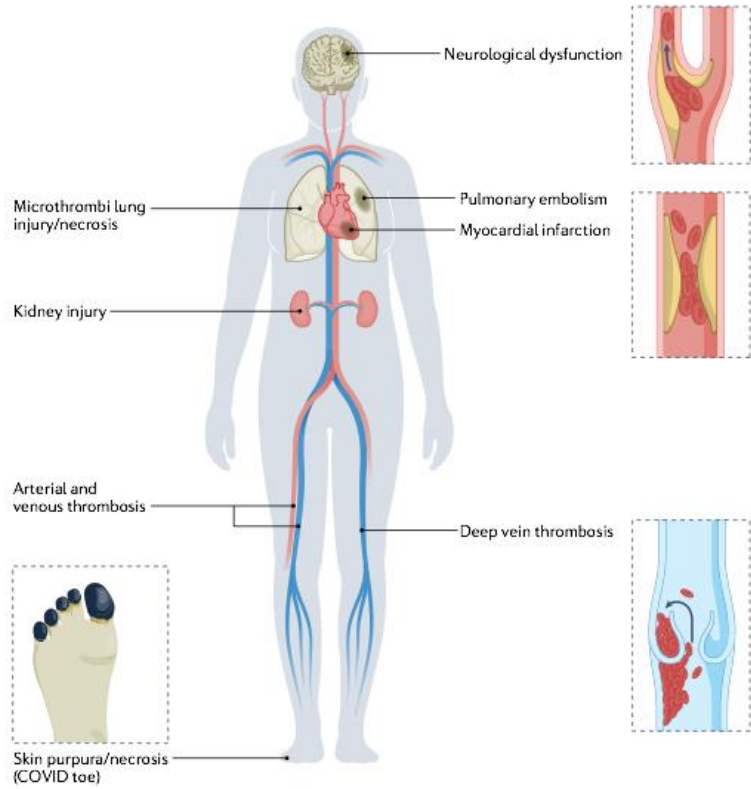




Figure 2 Vesico-bullous lesions in a patient with COVID-19.

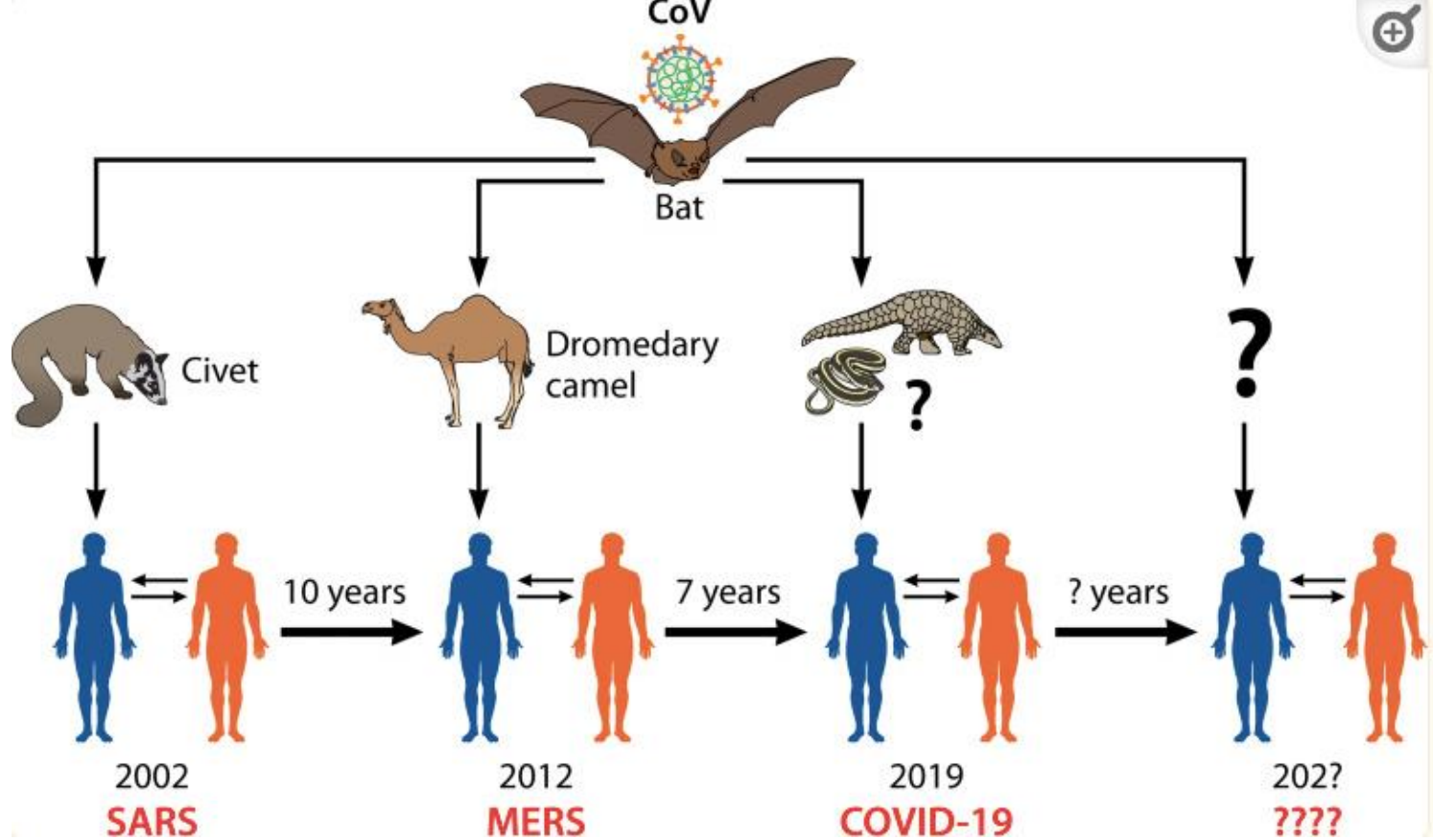


# Tromboinflamação

- ✓ considerada a maior complicação COVID e associada a óbito
- ✓ inicia no pulmão e pode se espalhar; a despeito da trombofilaxia
- ✓ 10% dos indivíduos hospitalizados tem complicações trombóticas
- ✓ 79% pac que faleceram observou microangiopatia pulmonar
- ✓ lab: ↑ D-dímero (degradação da fibrina), trombomodulina, vWF;
- ✓ histologia: fibrina; C5b-9 = MAT

# Vacinas

- VIIT – trombocitopenia trombótica imune induzida por vacina
- Vacina monovalente vetor adenovírus: AZ; Janssen
- primeiros 25 casos descritos na Europa AZ; até maio/2021 110 casos
- AZ 3.2 – 16.1 casos pmp                      Janssen: 1.7 – 3.7 casos pmp
- Trombocitopenia: IgG anti F4P (pac. com anomalias primárias do complemento)  
Trombose: IgG/F4P ativa via clássica complemento (não se inicia no pulmão)
- Diagnóstico: D-dímero > 4.000; Ac anti F4P +; plaqueta < 150.000; ↓ fibrinogênio  
4 – 28 dias após vacina
- Tratamento: Ig e anticoagulação não heparina e inibidores de C5



variante Omicron dominante  
População imunizada



