Neurological Complications of COVID-19

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Brief Introduction

- **Coronaviruses infect humans and animals**
- **Typically cause disease of the respiratory tract, gastrointestinal tract, liver, and nervous system**
- **CoVs that can infect humans include:**
  HCoV-OC43, HCoV–229E, HCoV-NL63, HCoV-HKU1, MERS-CoV, SARS-CoV-1, and SARS-CoV-2
- **Three prior HuCoVs can infect neurons:**
  HCoV-OC43, HCoV-229E, and SARS-CoV-1

Zubair et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.2065
Glass et al, J Immunol. 2004. doi:10.4049/jimmunol.173.6.4030
Su et al, Trends Microbiol. 2016. doi:10.1016/j.tim.2016.0[illegible]03
Zhu et al, N Engl J Med. 2020. doi:10.1056/NEJMoa2001017

	SARS-CoV	MERS-CoV	SARS-CoV-2
Systemic manifestations	• Mild to severe • Fever and lower respiratory illness • ICU care required in ~30% patients • ARDS in ~20% patients • Gastrointestinal infection	• Mild to severe clinical signs • Fever and lower respiratory illness and acute renal failure • ICU care required in ~43% patients • ARDS in ~3% patients • Gastrointestinal infection	• Mild to severe clinical signs • Fever and lower respiratory illness • ICU care required in ~10% patients • ARDS in ~5% patients • Gastrointestinal infection
Pulmonary pathology	Consistent with pneumonia and acute lung injury	Samples not available for investigation	Consistent with pneumonia and acute lung injury
Human ligand	Protein S1 binds to ACE2 protein of the host cell surface	DPP4 (also known as CD26)	Protein S1 binds to ACE2 protein (10- to 20-fold higher affinity compared with SARS-CoV)
Neurological manifestations	Sporadic case reports	Sporadic case reports	34% of hospitalized patients and sporadic case reports
CNS involvement	Human neurons are infectible [53] and ACE2 neuronal expression has been identified in human CNS [54]	Capable of infecting human neuronal cells in *in-vitro* cell lines [55]. DDP4 has a low expression in the brain [56]	–
Neuropathology	SARS genome sequences detected in the brain in autopsies; also, edema and scattered red degeneration of neurons [17]	Samples not available for investigation	–
Mortality	9.6%	34.4%	5.3%[a]

Natoli et al, Eur J Neurol. 2020. DOI: 10.1111/ene.14277

Nervous System Symptoms in Wuhan

Characteristic	No. (%)	COVID-19 Infection		P value[a]
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07

- **Those with CNS symptoms had fewer platelets (p=0.005), lymphocytes (p=0.049), and higher blood urea nitrogen (p=0.04) and possibly creatinine (p=0.06)**

Mao et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.1127

Neurologic Manifestations in Bergamo

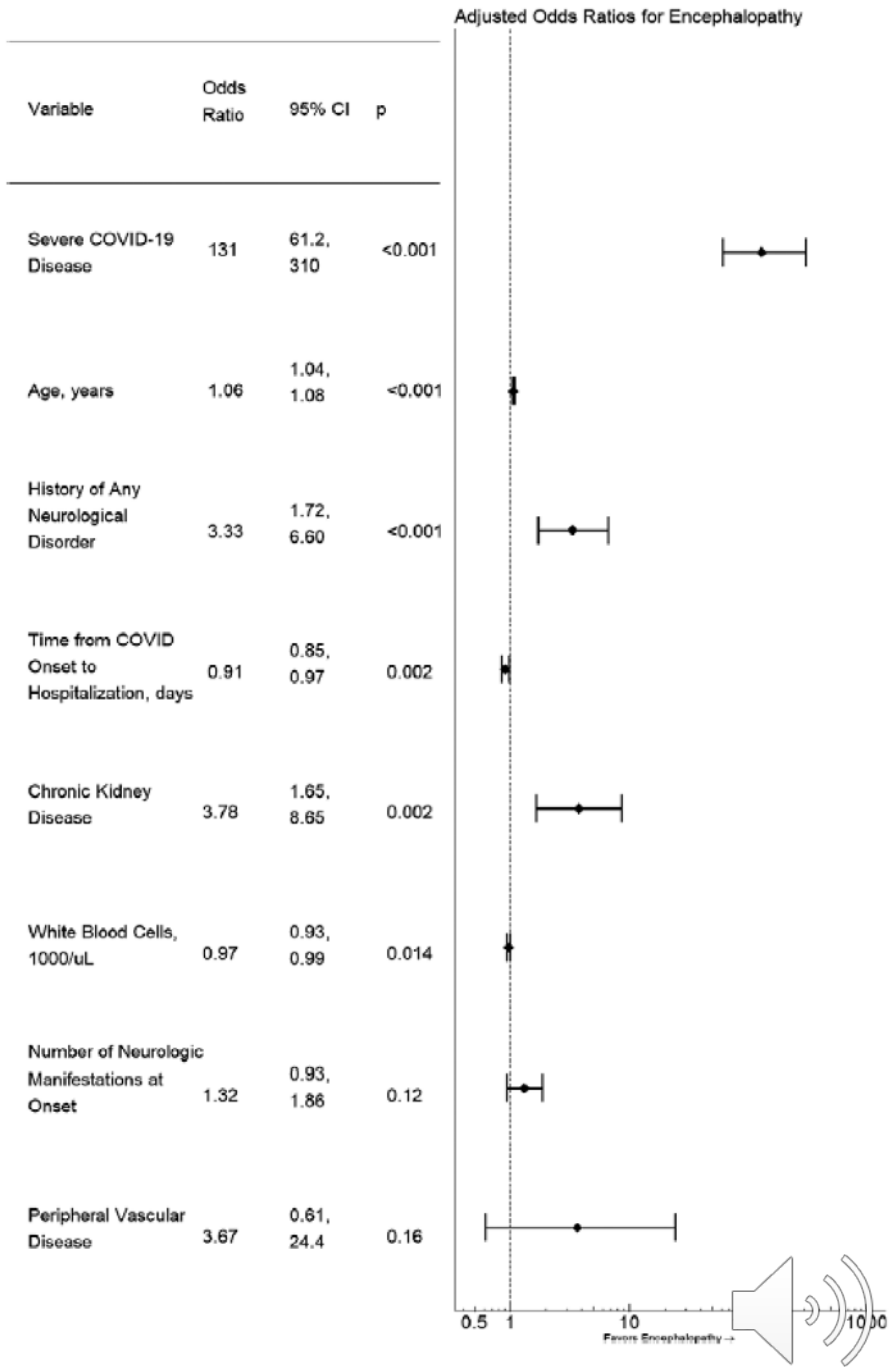
- **137 of 1760 (7.8%) COVID-19 patients had neurologic manifestations**
  - Presenting symptom in 39 (2.2%)
  - Presented after COVID-19 in 98 (5.6%)
- **Neurological manifestations**
  - Cerebrovascular disease (38.7%)
  - Peripheral nervous system diseases (22.6%)
  - Altered mental status (35.8%)
  - Miscellaneous disorders
    - 2 with myelopathy with anti-SARS-CoV-2 antibody in CSF

Neurological complications	*N* (%)			
	All patients (*N* = 137)	*N* of females (%)	Average age	Average *n* of comorbidities
Cerebrovascular diseases	53 (38.7%)	20 (37.7%)	68.6	3.1
Ischemic stroke	37 (27.0%)	15 (40.5%)	70.3	3
Haemorrhagic stroke	11 (8%)	4 (36.3%)	65.9	3.5
Transient ischemic attacks	4 (2.9%)	1 (25%)	63.5	3.4
Cerebral venous thrombosis	1 (0.7%)	0 (0%)	55	3
Peripheral neuropathies	31 (22.6%)	6 (19.3%)	56.3	2.1
Guillain–Barrè syndrome	17 (12.4%)	4 (23.5%)	55.6	2.2
Critical illness polyneuropathy	9 (6.6%)	1 (1.1%)	60.7	1.7
Others	5 (3.6%)	1 (20.0%)	54.2	3.6
Altered mental status	49 (35.8%)	17 (34.7%)	65.6	2.7
Encephalitis	5 (3.6%)	1 (40%)	66	2.4
Myelitis	2 (1.4%)	0 (0%)	64.5	3.5
Headache	3 (2.2%)	1 (33.3%)	61.5	0.7
Seizures	10 (7.3%)	3 (30.0%)	64.4	2.9
Syncope	3 (2.2%)	2 (66.7%)	72.6	3.7
Movement disorders	7 (5%)	3 (42.8%)	70.3	3.8
Other	5 (3.6%)	1 (20.0%)	61.2	4.6

Rifino et al, J Neurol. 2020 doi:10.1007/s00415-020-10251-5

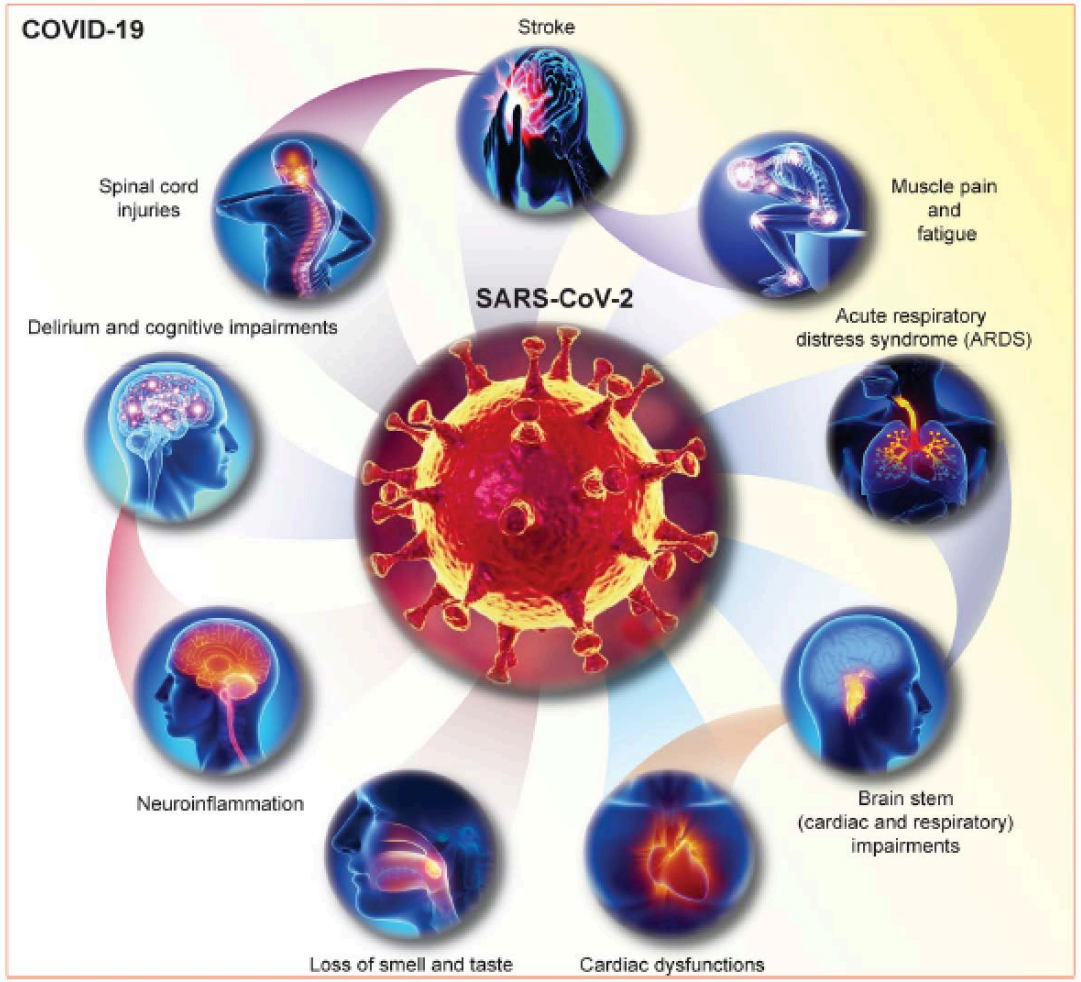
Encephalopathy in Chicago

- **509 consecutive COVID-19 hospitalizations**
- **Neurologic manifestations present in 82.3%**
  - At onset in 215 (42.2%), at hospitalization in 319 (62.7%)
- **Most frequent neurologic manifestations**
  - Myalgias (44.8%), headaches (37.7%), encephalopathy (31.8%), dizziness (29.7%), dysgeusia (15.9%), and anosmia (11.4%).
- **Less frequent:** Strokes, movement disorders, motor and sensory deficits, and seizures
- **Risk factors for a neurologic complication**
  - Severe COVID-19 (OR 4.02; P < 0.001)
  - Younger age (OR 0.982; P = 0.014)
- **Encephalopathy independently associated with worse functional outcome and higher mortality**



Liotta et al, ACTN. 2020 doi:10.1002/acn3.51210

Neurological Complications of SARS-CoV-2 Infection

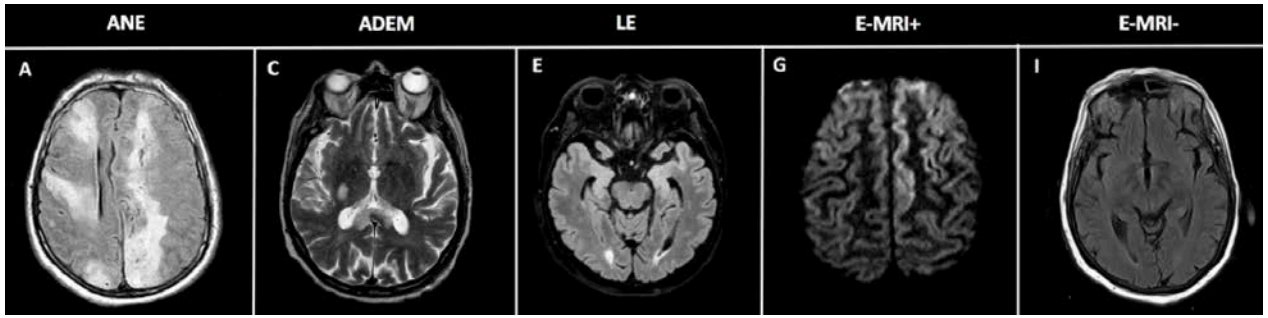


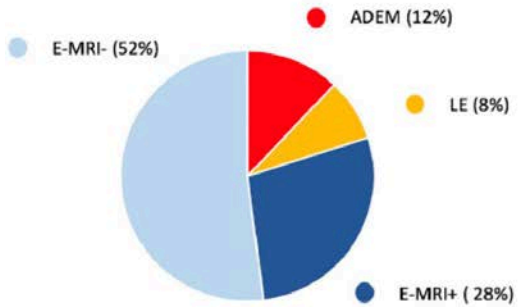
- **Most common conditions**
  - Anosmia/Hyposmia
  - Ageusia/Hypogeusia
  - Headache
- **Less common conditions**
  - Delirium/impaired consciousness
  - Stroke (ischemic, hemorrhagic)
  - Seizure
  - Demyelinating polyneuropathy
  - Cranial neuropathy
  - Acute disseminated encephalomyelitis
  - Hearing Loss
- **Uncertain contribution**
  - Reduced respiratory drive

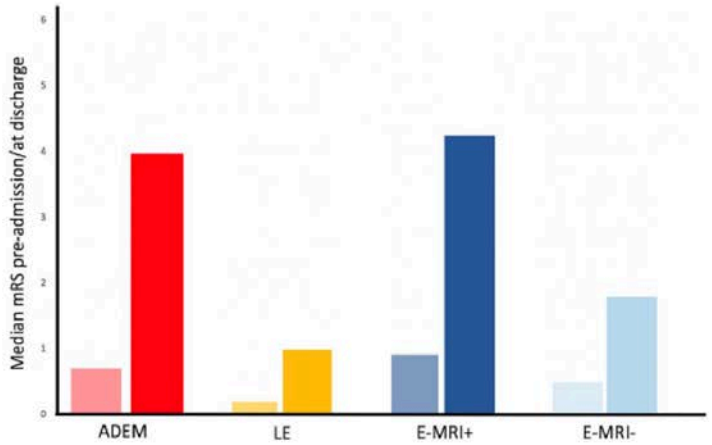
Zubair et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.4565
Costello & Dalakas, Neurology 2020, doi: 10.1212/WNL.0000000000009921
Acharya et al, J Neuroimm Pharmacol 2020. doi: 10.1007/s11481-020-09924-9

ENCOVID Encephalitis Case Series

- **25 COVID-19 patients with encephalitis**
  - 68% had hyperproteinorrachia or pleocytosis
- **SARS-CoV-2 RNA not detected in CSF**
- **Four principal categories**
  - ADEM (n=3), limbic encephalitis (n=2), encephalitis with MRI alterations (n=7), and encephalitis with normal imaging (n=13)
- **ADEM and LE** had delayed onset vs. others (p=0.001) and were associated with more severe COVID-19
- **Patients with MRI alterations had worse response to therapy and final outcomes than others**







ADEM, acute disseminated encephalomyelitis; ANE, acute necrotizing encephalitis; E-MRI-, encephalitis with negative MRI; E-MRI+, encephalitis with MRI alterations; LE, Limbic encephalitis; mRS, modified Rankin scale.

Pilotto et al, J Infect Dis 2020. doi:10.1093/infdis/jiaa609

SARS-CoV-2 RNA Detected in CSF

- 6 patients with moderate to severe COVID-19 and neurological symptoms in Göteborg, Sweden
- **SARS-CoV-2 RNA was detected in the plasma of 2 patients (Cycle threshold [Ct]value 35.0-37.0) and in CSF at low levels (Ct 37.2, 38.0, 39.0) in 3 patients in one rtPCR assay but not in a second.**
- CSF neopterin (median, 43.0 nmol/L) and β2-microglobulin (median, 3.1 mg/L) were increased in all.
- Median IgG-index (0.39), albumin ratio (5.35) and CSF white blood cell count (<3 cells/μL) were normal in all, while CSF NfL was elevated in 2 patients.

Eden et al, Neurol 2020. doi:10.1212/WNL.0000000000010977

Neuropsychiatric Complications of CoV Infection

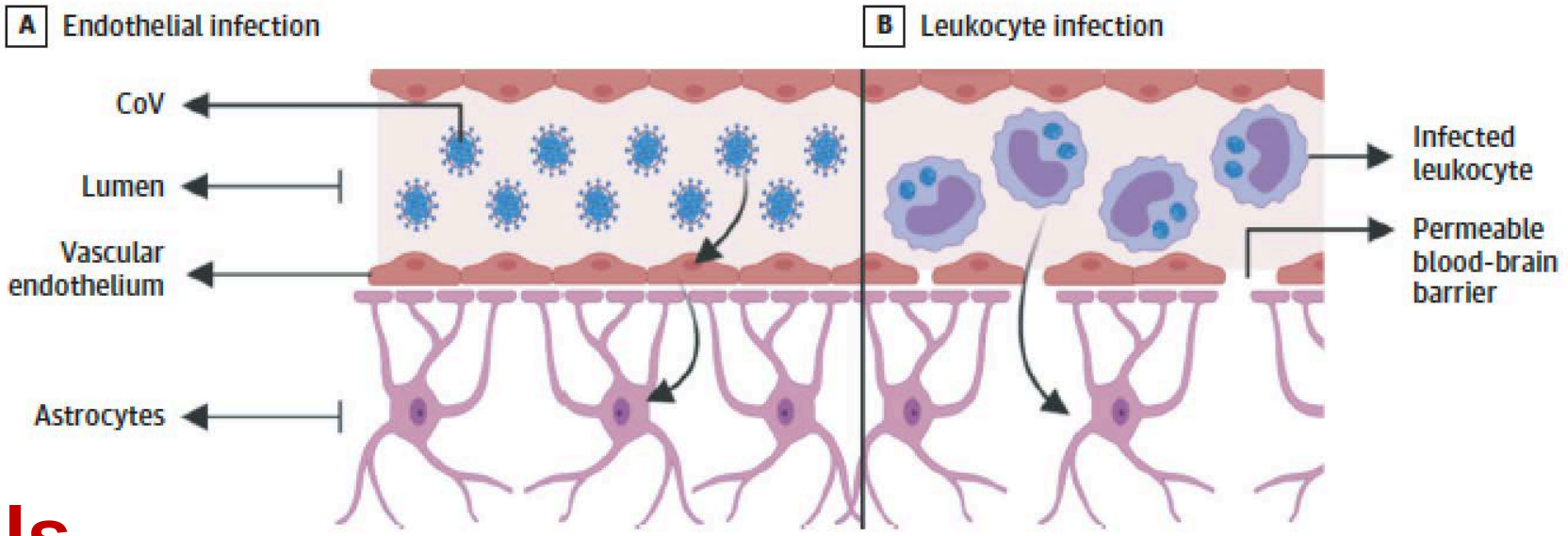
	Acute				Post-Illness			
	Studies	Cases	Sample size	Prevalence (95% CI)	Studies	Cases	Sample size	Prevalence (95% CI)
Insomnia	2	54	129	41·9% (22·5–50·5)	4	34	280	12·1% (8·6–16·3)
Anxiety	2	46	129	35·7% (27·6–44·2)	2	21	171	12·3% (7·7–17·7)
Impaired concentration or attention	1	39	102	38·2% (29·0–47·9)	2	34	171	19·9% (14·2–26·2)
Impaired memory	2	44	129	34·1% (26·2–42·5)	3	44	233	18·9% (14·1–24·2)
Depressed mood	2	42	129	32·6% (24·7–40·9)	5	35	332	10·5% (7·5–14·1)
Confusion	2	36	129	27·9% (20·5–36·0)	1	1	621	0·2% (0·0–0·7)
Emotional lability	1	30	102	29·4% (0·4–7·3)	1	24	102	23·5% (15·8–32·3)
Altered consciousness	1	17	82	20·7% (12·6–30·3)	NA	NA	NA	NA
Pressured speech	1	21	102	20·6% (13·3–29·0)	1	12	102	11·8% (6·1–18·8)
Euphoria	1	8	102	7·8% (3·3–14·0)	1	11	102	10·8% (5·4–17·6)
Aggression	1	2	27	7·4% (0·2–21·1)	1	1	102	1·0% (0·0–4·2)
Irritability	1	5	102	4·9% (1·4–10·1)	3	28	218	12·8% (8·7–17·6)
Auditory hallucinations	2	6	129	4·7% (1·6–9·1)	1	1	102	1·0% (0·0–4·2)
Persecutory ideas	1	4	102	3·9% (0·9–8·7)	1	2	102	2·0% (0·0–5·8)
Visual hallucinations	1	2	102	2·0% (0·0–5·8)	NA	NA	NA	NA
Suicidality	1	2	102	2·0% (0·0–5·8)	1	0	102	0 (0·0–1·7)
Fatigue	NA	NA	NA	NA	4	61	316	19·3% (15·1–23·9)
Frequent recall of traumatic memories	NA	NA	NA	NA	1	55	181	30·4% (23·9–37·3)
Sleep disorder	NA	NA	NA	NA	1	14	14	100% (88·0–100·0)
Psychotic symptoms (unspecified)	NA	NA	NA	NA	1	4	90	4·4% (1·0–9·9)
Self-harm	NA	NA	NA	NA	1	1	102	1·0% (0·0–4·2)

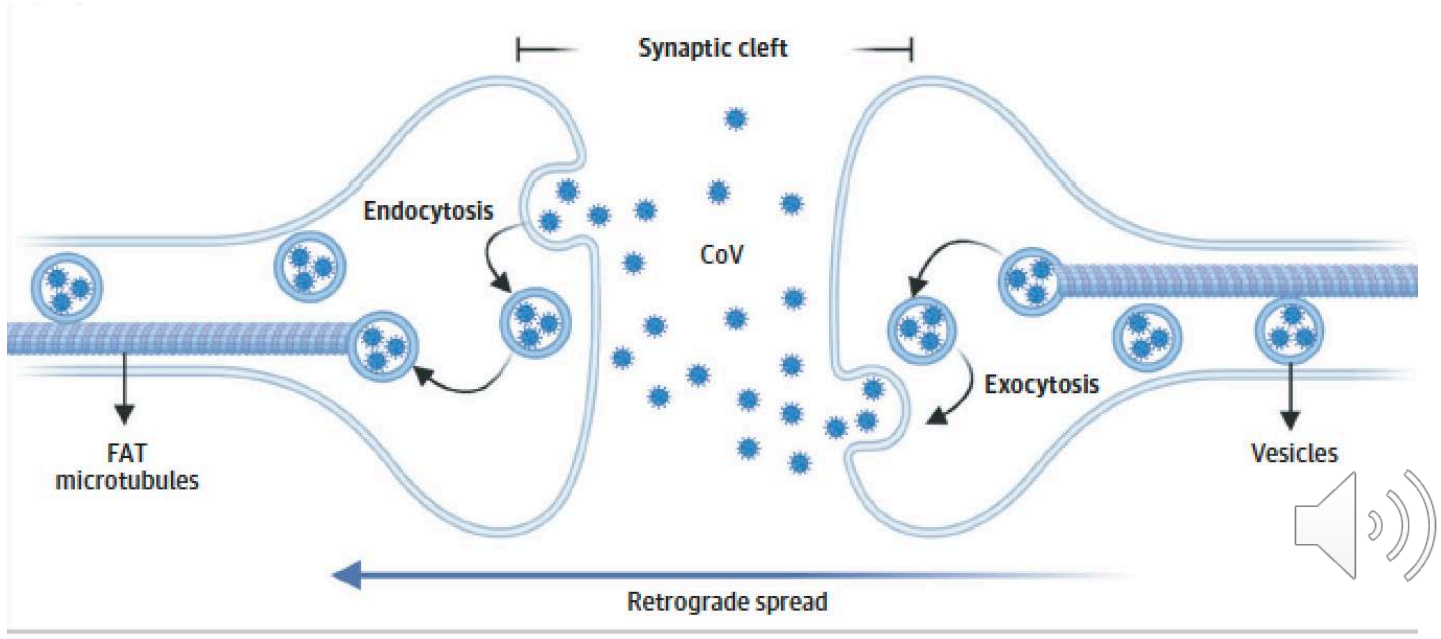
NA=not available.

Rogers et al, Lancet Psychiatry. 2020. doi: 10.1016/S2215-0366(20)30203-0

Entry Into the Central Nervous System

- **Via brain microvascular endothelial cells**
- **Within immune cells (Trojan horse)**
- **Intraneuronal and trans-synaptic**

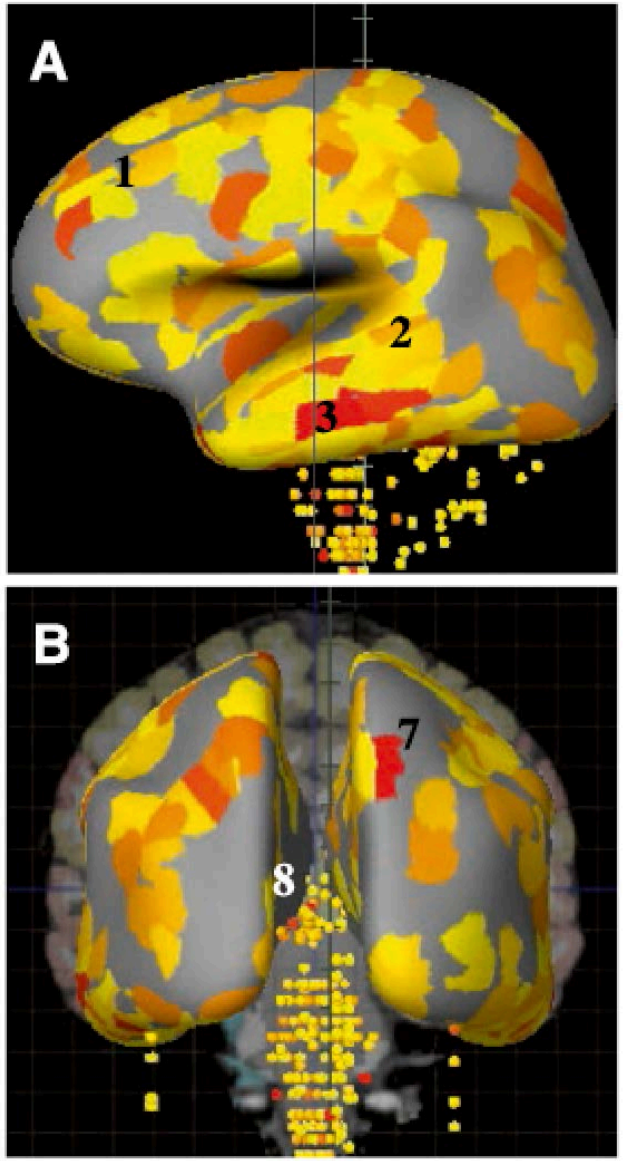


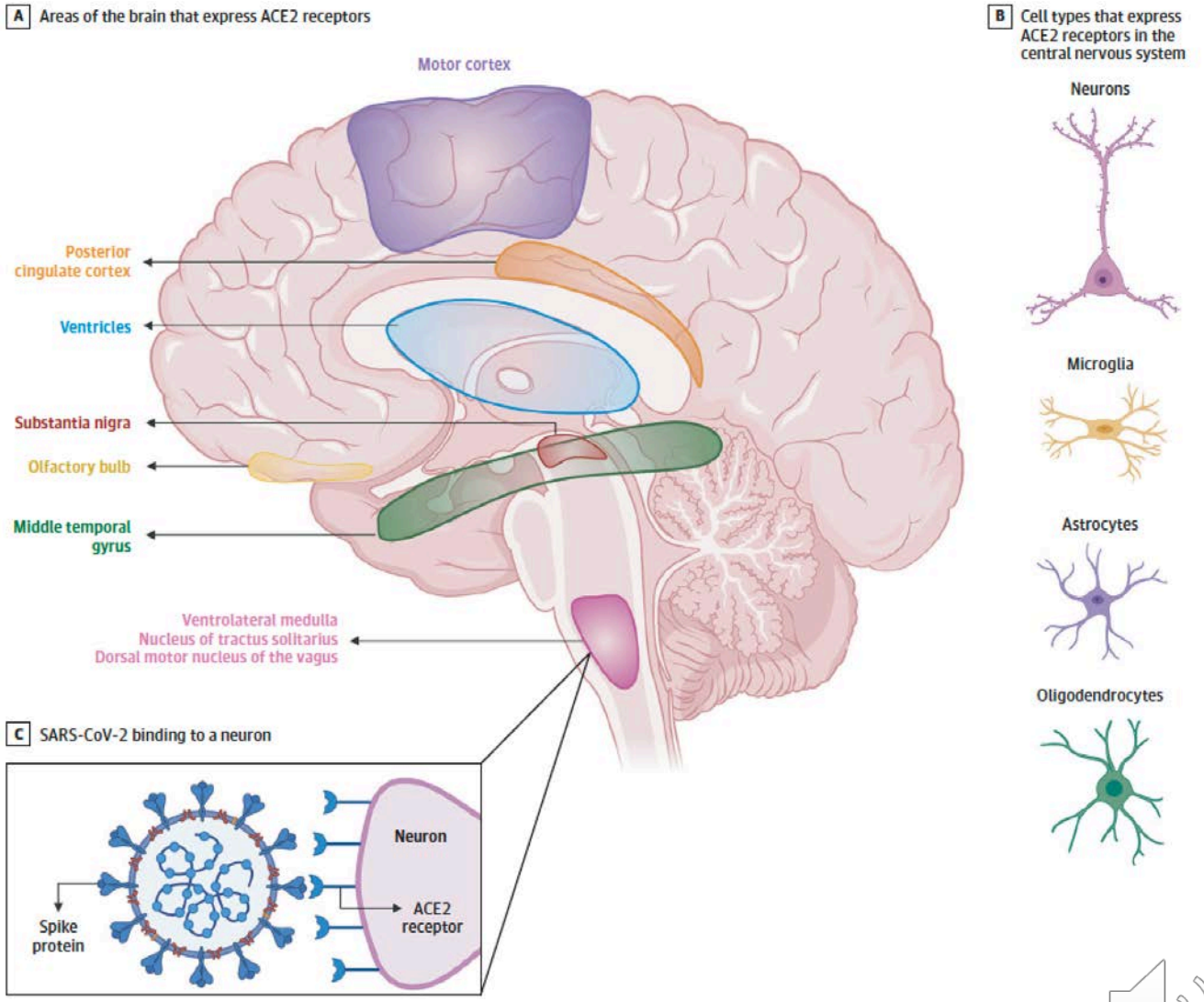


Zubair et al, JAMA Neurol.
doi:10.1001/jamaneurol.2020.2065

ACE2 Receptor Distribution in Brain

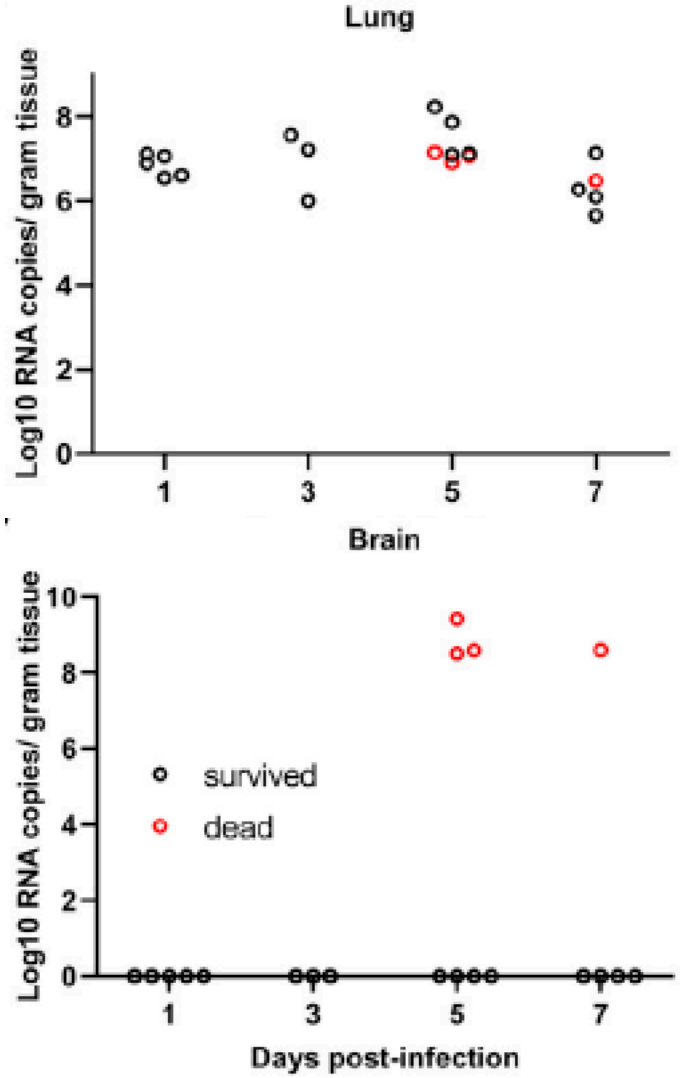
1. Motor Cortex
2. Auditory Cortex
3. Temporal Gyrus
4. Hippocampus
5. Caudate Nucleus
6. Hypothalumus
7. Somatosensory Cortex
8. Lateral Ventricle
9. Medula
10. Brainstem



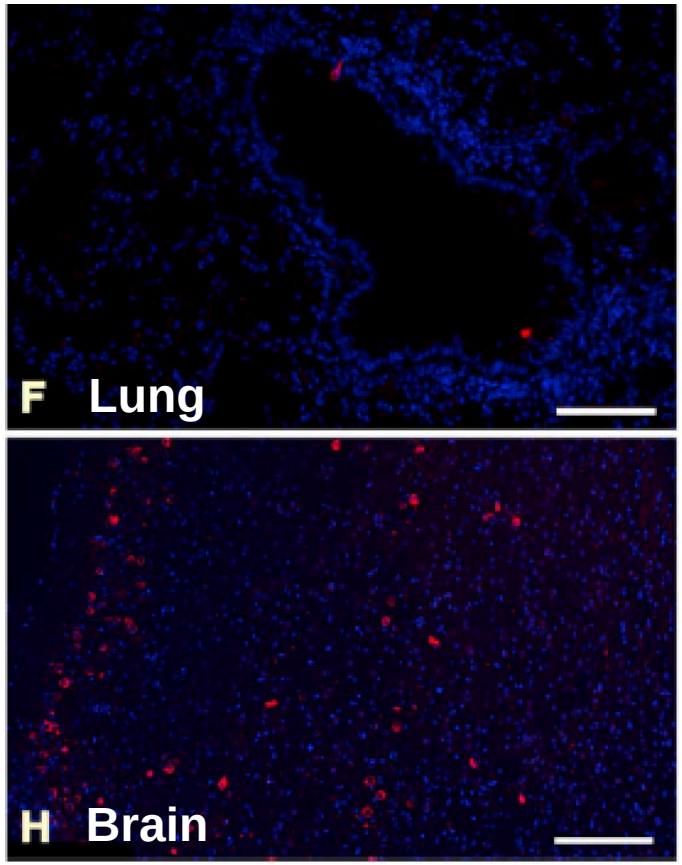


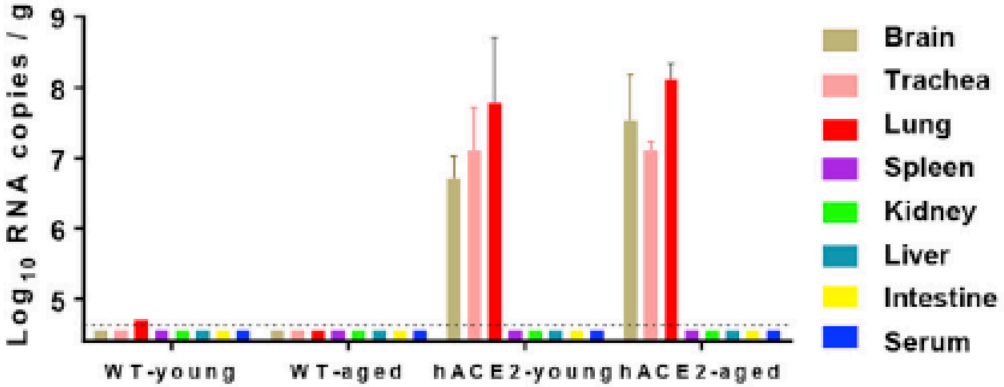
Zubair et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.2065
Kabbani & Olds, Mol Pharmacol. 2020. doi.org/10.1124/molpharm.120.000014

SARS-CoV-2 in ACE2 Transgenic Mouse Model

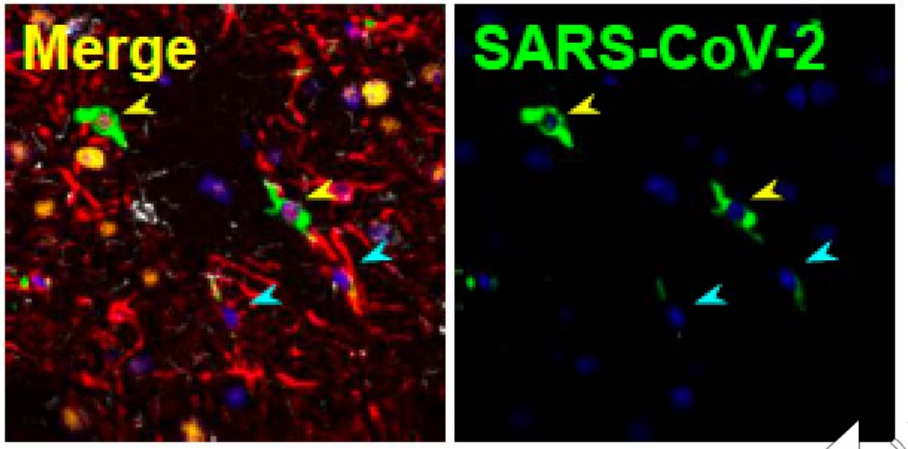


SARS-CoV-2 Antigen in Lung and Brain





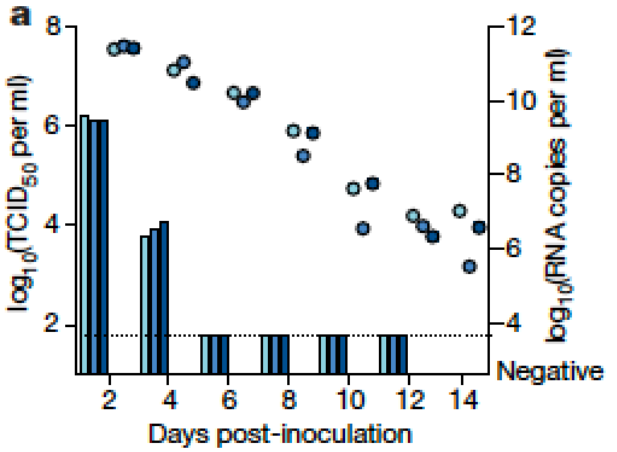
S Protein in Neurons, Astrocytes, & Microglia

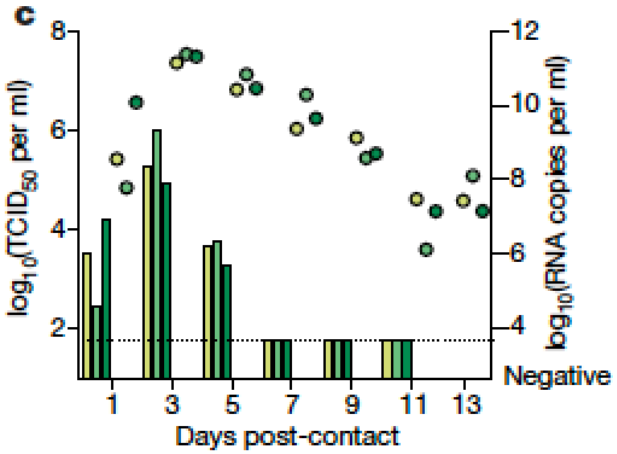


Jiang et al, Cell. 2020. doi:10.1016/j.cell.2020.05.027
Sun et al, Cell Host & Microbe. 2020. 10.1016/j.chom.2020.05.020

SARS-CoV-2 in Syrian Golden Hamster

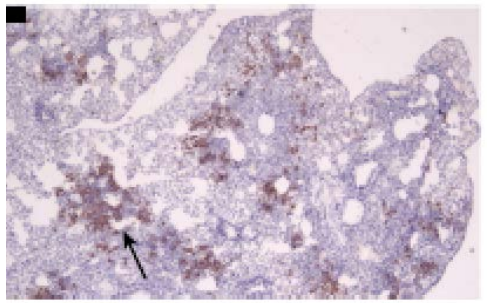
Primarily inoculated animal



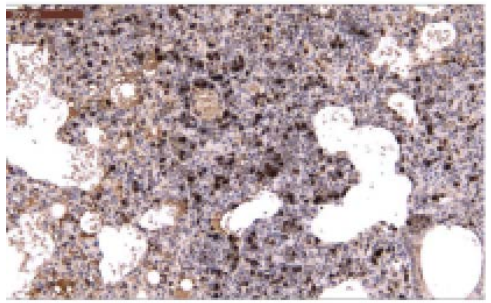


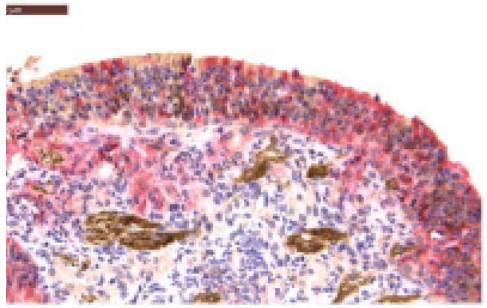
Infected Cage Mate

N Protein in Pneumocytes

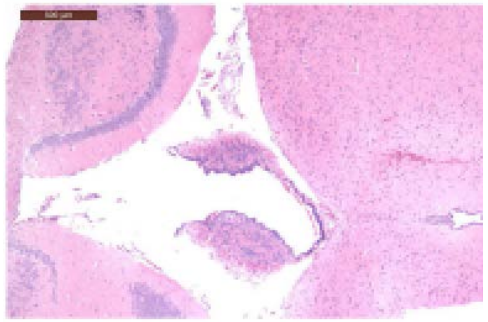


CD3+ Cells in Lungs



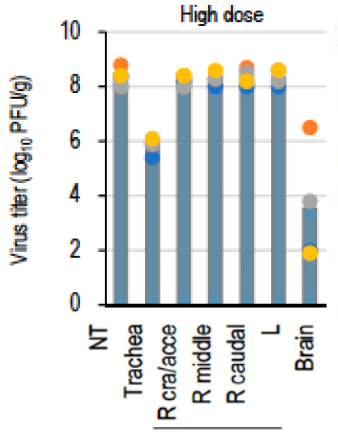


N Protein in Olfactory Neurons

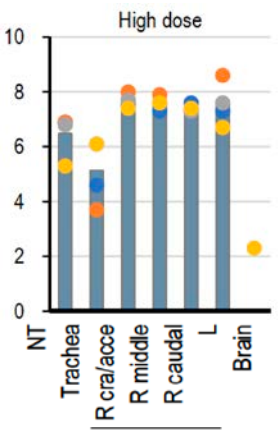


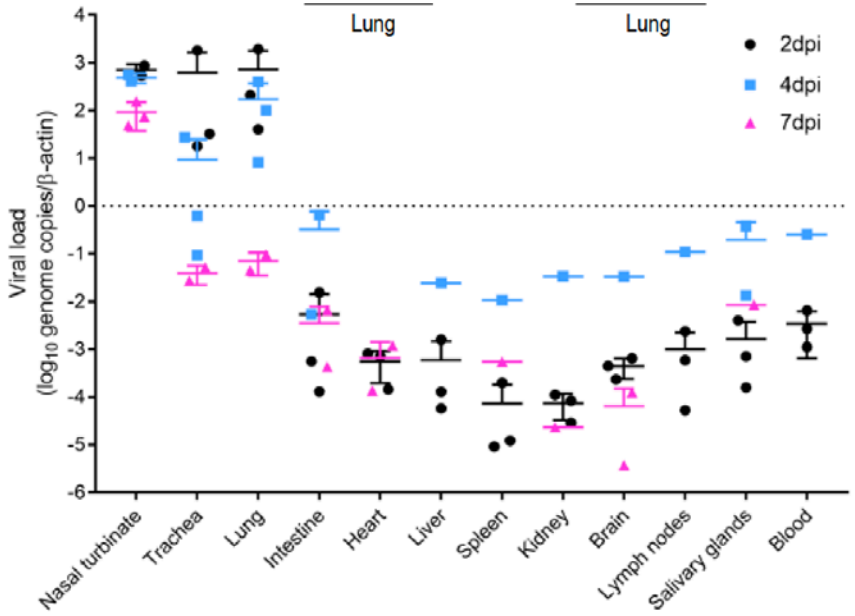
No SARS-CoV-2 or Pathology in Brain

1 month old



8 month old

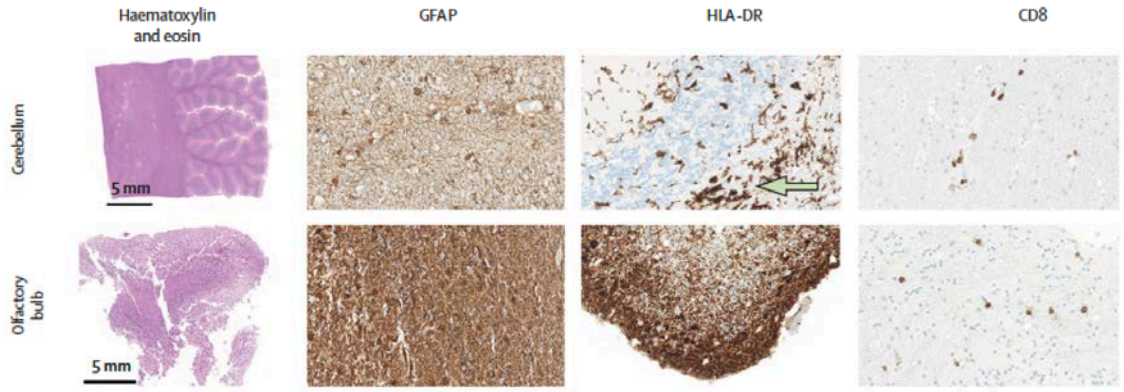


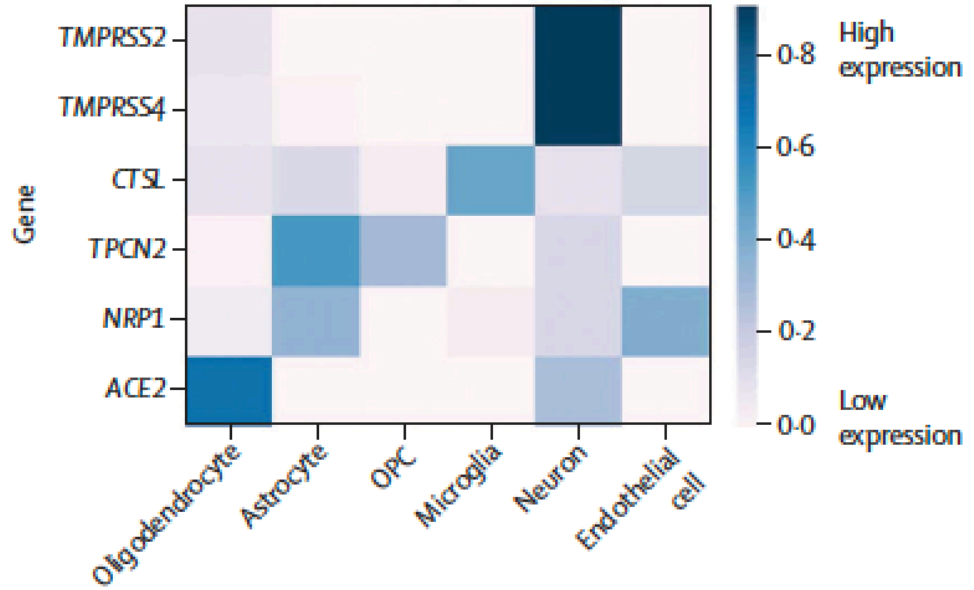


Sia et al, Nature. 2020. DOI: 10.1038/s41586-020-2342-5
Chan et al. Clin Infect Dis 2020. doi: 10.1093/cid/ciaa325
Imai et al, PNAS 2020. doi: 10.1073/pnas.2009799117

Post-Mortem Case Series from Germany

- 43 patients, median age 76 years
- Territorial ischemic lesions in 14%
- 86% had astrogliosis in all assessed regions
- Microglial activation and infiltration by cytotoxic T cells was greatest in brainstem and cerebellum
- 79% had meningeal cytotoxic T cell infiltration
- SARS-CoV-2 detected in the brains of 21 (53%) of 40





Matschke et al, Lancet Neurol. 2020. doi: 10.1016/ S1474-4422(20)303[illegible]1-9

COVID-19 in PWH

Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

We are still learning about COVID-19 and how it affects people with HIV. Based on limited data, we believe people with HIV who are on effective HIV treatment have the same risk for COVID-19 as people who do not have HIV.

Older adults and **people of any age who have serious underlying medical conditions** might be at increased risk for severe illness. This includes people who have weakened immune systems. The risk for people with HIV getting very sick is greatest in

- People with a low CD4 cell count, and
- People not on effective HIV treatment (antiretroviral therapy or ART).

- **276,807 COVID-19 diagnostic tests in San Francisco**
  - 193 of 4,252 (4.5%) positive in PWH
  - 9,626 of 272,555 (3.5%) positive in people without HIV ($p<0.001$)
- **Homelessness and congregate living more common among PWH than among people without HIV**
  - 45.4% of PWH were marginally housed
- **Rate of severe illness was not higher among PWH**

Sachdev et al, JAIDS. 2020. doi: 10.1097/QAI.0000000000002531

Severity of COVID-19 Among PWH

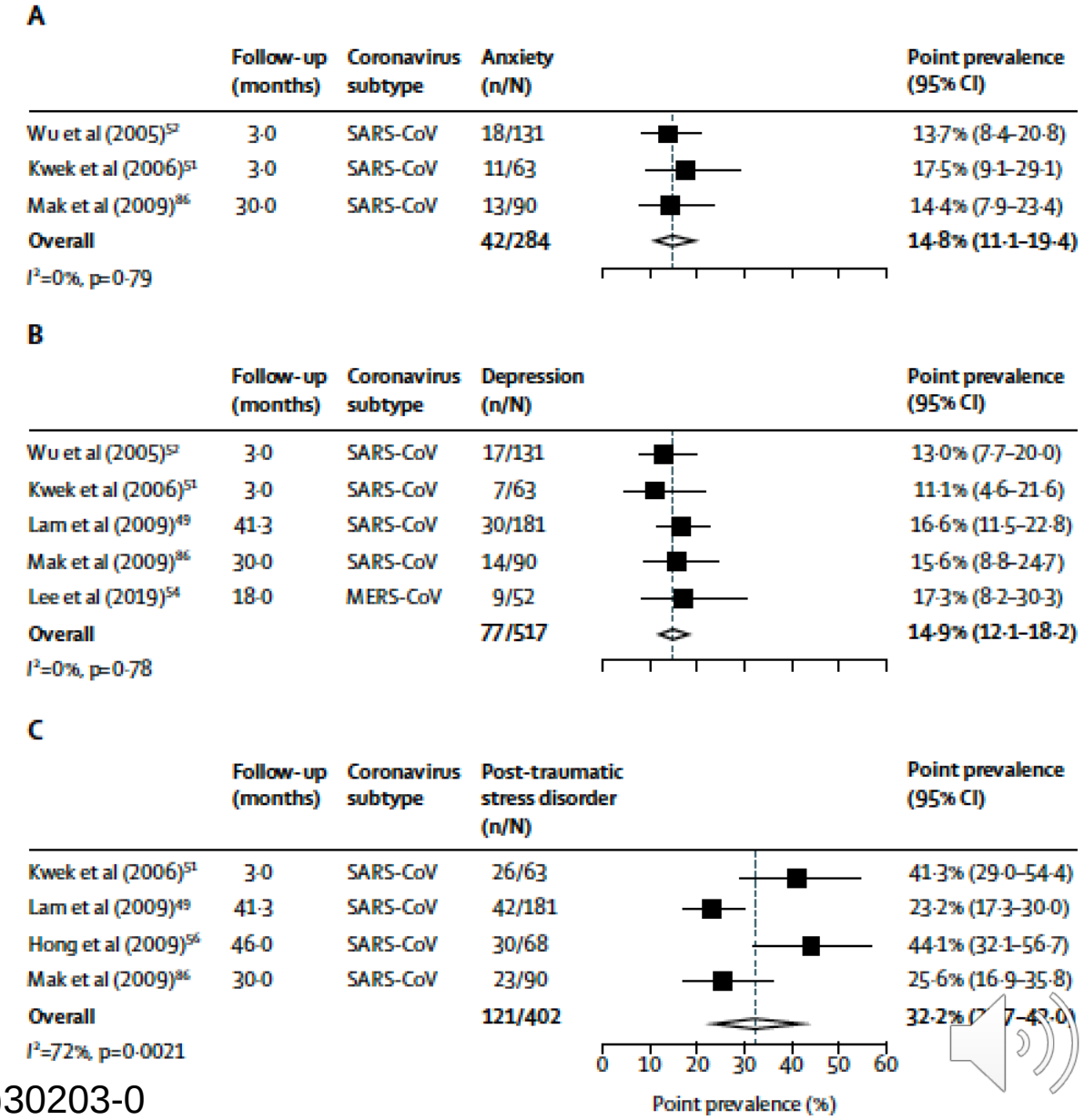
- **Reviewed 25 published reports of COVID-19 in PWH**
  - **Mean age 52.7 years**
  - **98% on ART**
- **Comorbidities**
  - **Hypertension (39.3%)**
  - **COPD (18.0%)**
  - **Diabetes (17.2%)**
- **Two-thirds had mild-to-moderate symptoms**
- **Among those who died, 90.5% were older than 50 years, 85.7% were men, and 64.3% had multimorbidity**

First author (Reference)	Setting	Publication date	Study type	Data type[a]	Sample size	Case definition	Quality assess-ment
Zhu [22]	Wuhan, China	12/03/20	Case report	Individual	1	Confirmed	5/8
Guo [23]	Wuhan, China	03/04/20	Cross-sectional	Aggregate	8	Confirmed	7/9
Zhao [24]	Shenzhen, China	10/04/20	Case report	Individual	1	Confirmed	6/8
Chen [25]	Guizhou, China	15/04/20	Case report	Individual	1	Confirmed	6/8
Su [26]	China	17/04/20	Case report	Individual	1	Confirmed	6/8
Schweitzer [27]	Italy	18/04/20	Case report	Individual	1	Confirmed	4/8
Blanco [28]	Barcelona, Spain	19/04/20	Case series	Individual	5	Confirmed	8/10
Riva [29]	Italy	24/04/20	Case series	Individual	3	Confirmed	4/10
Wang [30]	Wuhan, China	27/04/20	Case report	Individual	1	Confirmed	6/8
Altuntas Aydin [31]	Istanbul, Turkey	30/04/20	Case series	Individual	4	Confirmed	7/10
Haerter [32]	Germany	01/05/20	Case series	Individual	33	Confirmed	8/10
Karmen [33]	New York, USA	12/05/20	Retrospective cohort	Aggregate	21	Confirmed	8/11
Wu [34]	Wuhan, China	13/05/20	Case series	Individual	2	Confirmed	4/10
Gervasoni [35]	Italy	15/05/20	Cross-sectional	Aggregate	47	Confirmed/Probable	6/9
Benkovic [36]	New York, USA	20/05/20	Case series	Individual	4	Confirmed	4/10
Haddad [37]	Wynnewood, USA	20/05/20	Case report	Individual	1	Confirmed	7/8
Baluku [38]	Uganda	22/05/20	Case report	Individual	1	Confirmed	6/8
Patel [39]	USA	23/05/20	Case report	Individual	1	Confirmed	6/8
Iordanou [40]	Cyprus	25/05/20	Case report	Individual	1	Confirmed	7/8
Kumar [41]	Chicago, USA	27/05/20	Case report	Individual	1	Confirmed	7/8
Childs [42]	UK	28/05/20	Case series	Aggregate	18	Confirmed	4/10
Suwanwongse [43]	New York, USA	29/05/20	Case series	Individual	9	Confirmed	5/10
Ridgway [44]	Chicago, USA	30/05/20	Case series	Individual	5	Confirmed	7/10
Shalev [45]	New York, USA	31/05/20	Case series	Aggregate	31	Confirmed	8/10
Vizcarra [20]	Madrid, Spain	01/06/20	Prospective cohort	Aggregate	51	Confirmed, probable	9/11

Mirzaei et al, AIDS & Behavior. 2020. doi: 10.1007/s10461-020-029[illegible]3-2

Long-Term Complications of CoV Infections

- **Patients with stroke, encephalitis, and other severe complications will likely have residual sequelae**
- **Patients with milder disease may not but may still suffer from PTSD and other mental health disorders**
- **People affected by COVID-19 may also suffer long-term mental health effects from social isolation, stress, & addiction**



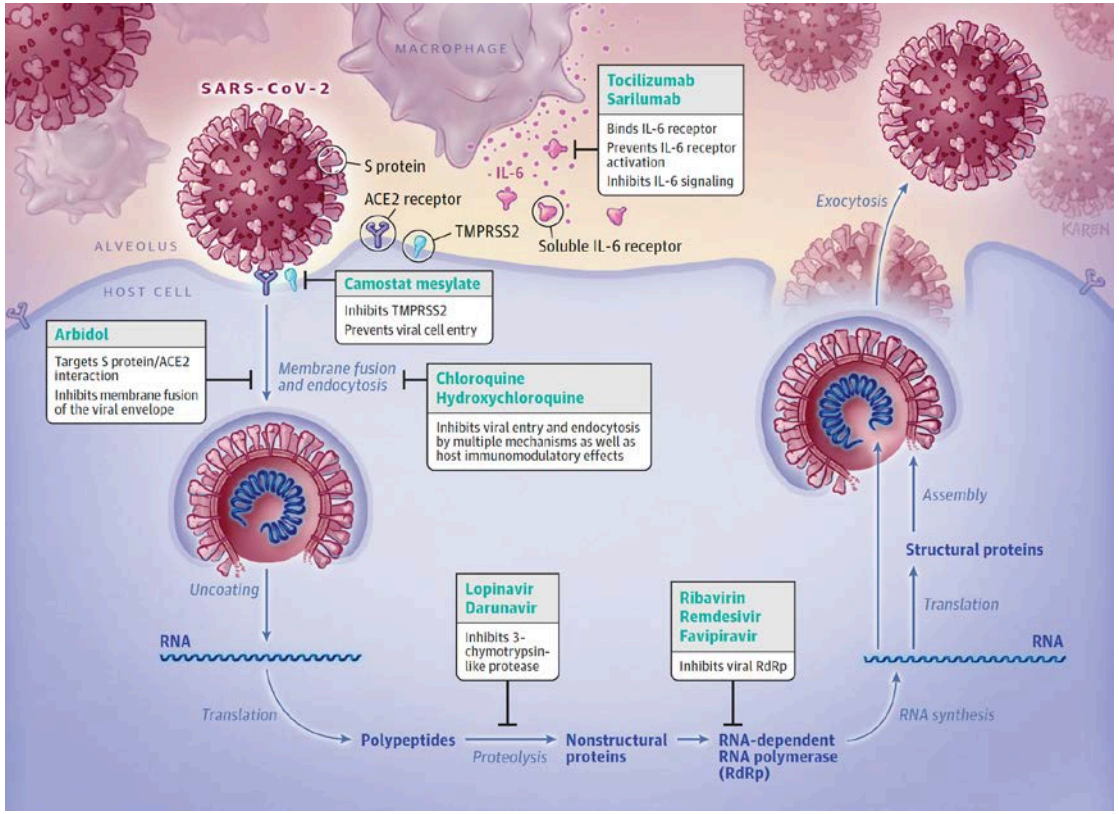
Rogers et al, Lancet Psychiatry. 2020. doi: 10.1016/S2215-0366(20)30203-0

Secondary Consequences Among PWH

- Increased stigma, social isolation, housing & food insecurity
- Increased drug and alcohol use
- Redirection of human, financial, & manufacturing resources
- Reduced in-person medical assessments
- Reduced diagnosis of new infections and diseases
- Reduced availability of ART drugs, other therapies, & pre-exposure prophylaxis
- Worsened HIV disease progression and transmission

Adadi & Kanwugu, J Med Virol. 2020. doi: 10.1002/jm[illegible]61.18
World Health Organization, 11 May 2020, Joint News Release

CNS Safety of SARS-CoV-2 Treatments



Sanders et al, JAMA. 2020. doi: 10.1001/jama.2020.6019

- **Remdesivir**
  - Few data on neurologic adverse events (AEs)
  - Molecular weight 602.6, XLogP3-AA 1.9, P-gp Substrate
- **Dexamethasone**
  - Neuropsychiatric AEs include depression, sleep disturbance, irritability, seizure, stroke, and others
- **Hydroxychloroquine**
  - Neurologic AEs include psychosis, irritability, neuropathy, and neuromyopathy
  - Lowers the seizure threshold and interacts with several antiepileptic drugs, including lacosamide and lamotrigine
- **Tocilizumab**
  - Poor penetration into the CNS
  - Neurologic AEs include headache and dizziness; Rare cerebral microangiopathy

Antiretroviral Drugs and COVID-19

Ford N et al. Journal of the International AIDS Society 2020, 23:e25489
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25489/full | https://doi.org/10.1002/jia2.25489

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REVIEW

Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS or COVID-19: initial assessment

Nathan Ford[1,§], Marco Vitoria[1], Ajay Rangaraj[1], Susan L Norris[2], Alexandra Calmy[3,*] and Meg Doherty[1,*]

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

ANTIVIRAL AGENTS

Atazanavir, Alone or in Combination with Ritonavir, Inhibits SARS-CoV-2 Replication and Proinflammatory Cytokine Production

Natalia Fintelman-Rodrigues,[a,j] Carolina Q. Sacramento,[a,j] Carlyle Ribeiro Lima,[i] Franklin Souza da Silva,[b,i] André C. Ferreira,[a,c,i] Mayara Mattos,[a,i] Caroline S. de Freitas,[a,i] Vinicius Cardoso Soares,[a] Suelen da Silva Gomes Dias,[a] Jairo R. Temerozo,[d,e] Milene D. Miranda,[f] Aline R. Matos,[i] Fernando A. Bozza,[g,h] Nicolas Carels,[i] Carlos Roberto Alves,[b] Marilda M. Siqueira,[f] Patrícia T. Bozza,[a] Thiago Moreno L. Souza[a,j]

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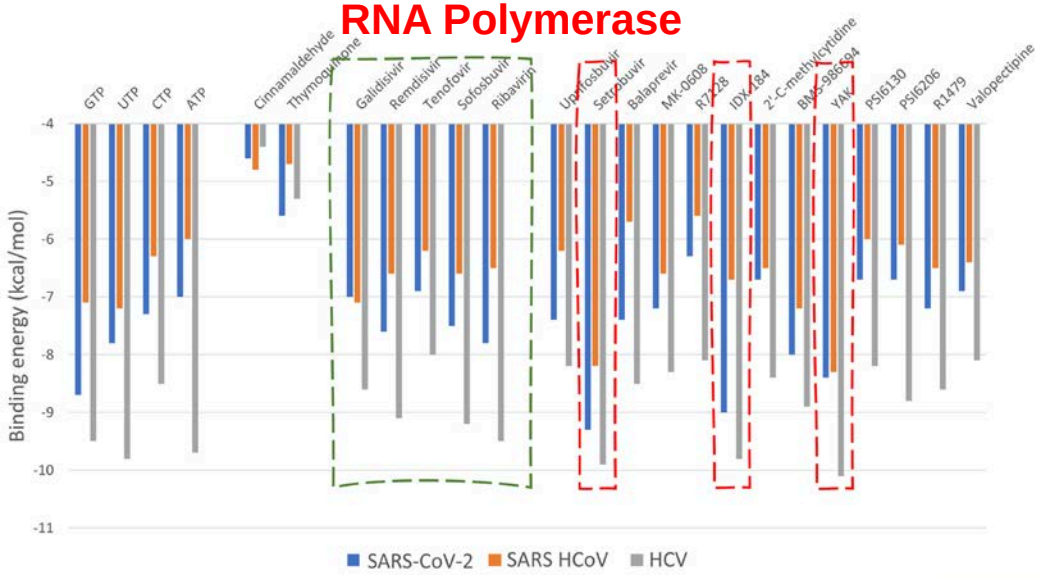
Lack of antiviral activity of darunavir against SARS-CoV-2

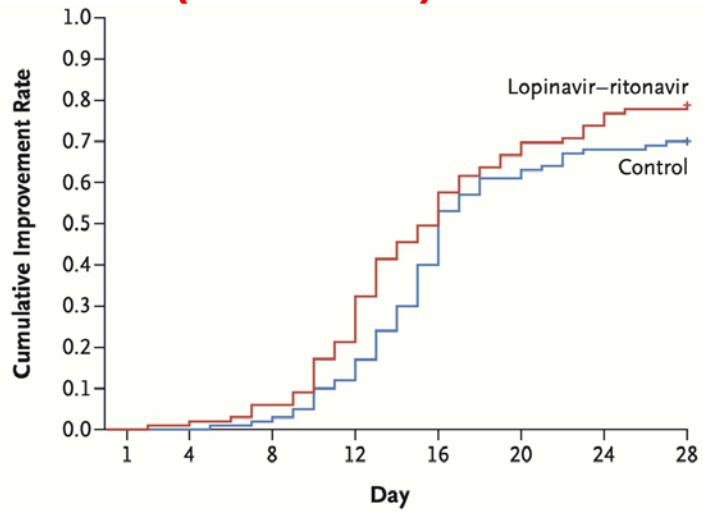
Sandra De Meyer[a,*], Denisa Bojkova[b], Jindrich Cinatl[b], Ellen Van Damme[a], Christophe Buyck[a], Marnix Van Loock[a], Brian Woodfall[c], Sandra Ciesek[b,d]

Binding of Tenofovir to SARS-CoV-2 RNA-Dependent RNA Polymerase



Elfiky AA, Life Sciences. 2020.
doi: 10.1016/j.lfs.2020.117592

Lopinavir/ritonavir vs. Standard of Care (No Placebo)



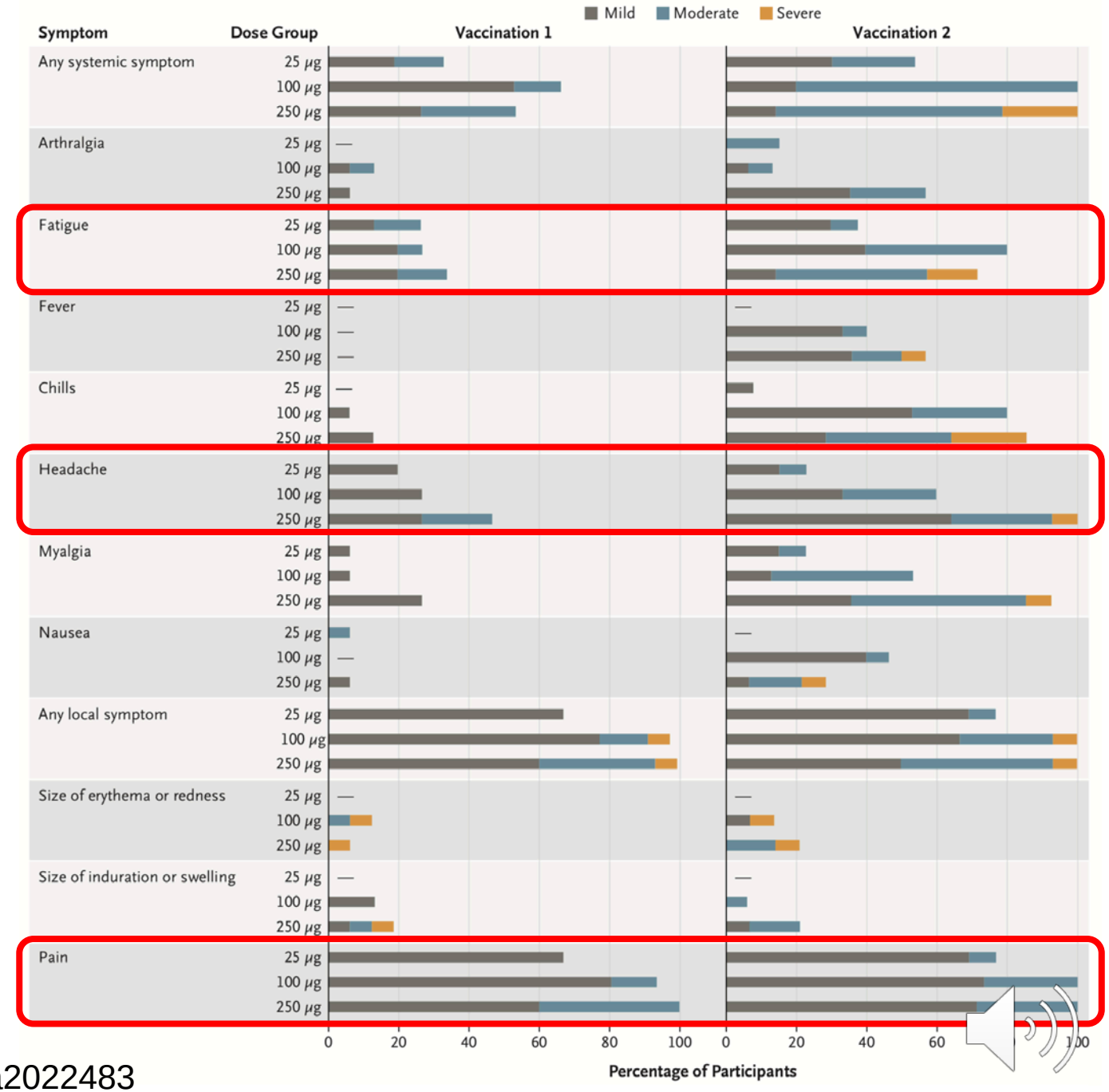
No. at Risk

Lopinavir–ritonavir	99	98	93	78	50	33	26	22
Control	100	100	98	88	60	39	32	30

Cao et al, N Engl J Med. 2020.
doi: 10.1056/NEJMoa2001282

CNS Safety of SARS-CoV-2 mRNA Vaccine

- **Phase 1, dose escalation, open-label trial of 45 adults who received two doses (25 µg, 100 µg, or 250 µg) of mRNA-1273 (Moderna)**
- **3 participants (21%) in the 250-µg dose group reported a severe adverse event**



Jackson et al, N Engl J Med, 2020. DOI: 10.1056/NEJMoa2022483

CNS Safety of SARS-CoV-2 Ad5 Vaccine

- **Phase 2, randomized, placebo-controlled trial of an adenovirus type-5 (Ad5)-vectored COVID-19 vaccine**
  - CanSino vaccine containing replication-defective Ad5 vectors expressing the full-length spike gene based on Wuhan-Hu-1
- **508 adults who received placebo or one of two doses**
  - 1 x 10^{11} or 5 x 10^{10} viral particles
- **Severe adverse reactions in 24 (9%) in the higher dose group and 1 (< 1%) in the lower dose group (p=0.001)**

	Vaccine at 1×10^{11} vp (n=253)	Vaccine at 5×10^{10} vp (n=129)	Placebo (n=126)	p value
Solicited adverse reactions within 14 days				
Any	183 (72%)	96 (74%)	46 (37%)	<0·0001
Grade 3	24 (9%)	1 (1%)	0	<0·0001
Injection site adverse reactions				
Pain	145 (57%)	72 (56%)	11 (9%)	<0·0001
Induration	12 (5%)	2 (2%)	0	0·014
Grade 3 induration	2 (1%)	0	0	0·75
Redness	5 (2%)	1 (1%)	2 (2%)	0·81
Swelling	10 (4%)	5 (4%)	0	0·049
Grade 3 swelling	1 (<1%)	0	0	1·0
Itch	14 (6%)	3 (2%)	0	0·0075
Systemic adverse reactions				
Fever (all grades)	82 (32%)	21 (16%)	12 (10%)	<0·0001*
Grade 3 fever	20 (8%)	1 (1%)	0	0·0001†
Headache	73 (29%)	36 (28%)	17 (13%)	0·0031
Grade 3 headache	2 (1%)	0	0	0·75
Fatigue	106 (42%)	44 (34%)	21 (17%)	<0·0001
Grade 3 fatigue	1 (<1%)	0	0	1·0
Vomiting	4 (2%)	1 (1%)	1 (1%)	0·88
Diarrhoea	19 (8%)	10 (8%)	4 (3%)	0·22
Muscle pain	39 (15%)	23 (18%)	3 (2%)	0·0002
Grade 3 muscle pain	1 (<1%)	0	0	1·0
Joint pain	34 (13%)	13 (10%)	4 (3%)	0·0074
Grade 3 joint pain	1 (<1%)	0	0	1·0
Oropharyngeal pain	22 (9%)	7 (5%)	6 (5%)	0·27
Cough	12 (5%)	2 (2%)	3 (2%)	0·24
Nausea	20 (8%)	6 (5%)	4 (3%)	0·14
Hypersensitivity	0	0	2 (2%)	0·061
Dyspnoea	1 (<1%)	0	0	1·0
Grade 3 dyspnoea	1 (<1%)	0	0	1·0
Appetite impaired	27 (11%)	7 (5%)	3 (2%)	0·0089
Syncope	1 (<1%)	1 (1%)	0	1·0
Mucosal abnormality	2 (1%)	2 (2%)	2 (2%)	0·65
Pruritus	6 (2%)	4 (3%)	6 (5%)	0·40
Unsolicited adverse reactions within 14 days				
Any	19 (8%)	7 (5%)	7 (6%)	0·65
Grade 3	1 (<1%)	0	0	1·0
Overall adverse events within 28 days				
Any	196 (77%)	98 (76%)	61 (48%)	<0·0001
Grade 3	24 (9%)	1 (1%)	2 (2%)	0·0002

Zhu et al, Lancet 2020; 396: 479–88

Transverse Myelitis in the AstraZeneca Trial

AstraZeneca Covid-19 vaccine study put on hold due to suspected adverse reaction in participant in the U.K.

By REBECCA ROBBINS @rebeccadrobbins, ADAM FEUERSTEIN @adamfeuerstein, *and* HELEN BRANSWELL @HelenBranswell
/ SEPTEMBER 8, 2020

WORLD NEWS SEPT. 18, 2020 / 11:29 AM

AstraZeneca: No link between adverse reactions and COVID-19 vaccine

Covid-19 Vaccine Trial From AstraZeneca, Oxford Can Resume in U.S.

Late-stage trial of coronavirus vaccine had been on hold in the U.S. while FDA reviewed mysterious neurological conditions in two subjects

Conclusions

- **Spectrum of neuropsychiatric complications occurs in COVID-19**
  - **The most severe are life-threatening but uncommon. If patients survive, they could have persistent sequelae**
  - **Less severe complications are more common and their persistence is uncertain. Longer term follow-up is warranted**
- **Pathogenesis of many complications are likely due to robust immune and endothelial responses to the virus**
- **Hyposmia may be more likely to be due to infection of olfactory neurons and inflammation**
- **If SARS-CoV-2 does replicate in the human CNS, the efficacy of therapies is uncertain**
- **No major CNS safety signal has clearly emerged for vaccines in development so far**

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