# General Intro & update of COVID-19

**김 예 진**
성균관의대 소아청소년과

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## Coronaviruses

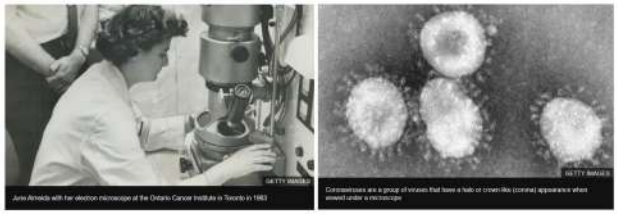
- Enveloped positive sense single-stranded RNA viruses sized 80–220 nm
- MW 26 to 31 kilobases, the largest of any RNA virus group

Coronaviridae (family)

- α-coronavirus: 229E, NL63
- β coronavirus: Lineage A: OC43, HKU-1
  Lineage B: SARS-CoV (mortality 10%), SARS-CoV-2
  Lineage C: MERS-CoV (mortality 30%)
- γ-coronavirus: avian infectious bronchitis virus
- δ-coronavirus: porcine epidemic diarrhea virus

Self-limiting upper respiratory infection

## June Almeida and visualization of coronavius



Back to St. Thomas's hospital medical school in 1967

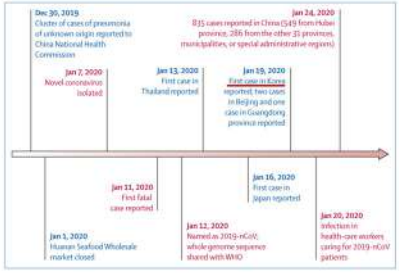
https://www.bbc.com/news/uk-scotland-52278716

## History of human coronaviruses

| Coronavirus | Year(s) Identified | First Identification |
|---|---|---|
| Alpha coronavirus: group 1 | | |
| HCoV-229E | 1960s | Boy with cold, United Kingdom: B814 isolate; medical students with colds, Chicago, Illinois: 229E (note: B814 isolate described here not further propagated) |
| HCoV- NL63 | 2004 | 7-month-old and 8-month-old infants with bronchiolitis in the Netherlands |
| Beta coronavirus group 2, lineage A | | |
| HCoV-OC43 | 1967–1972 | Acute respiratory infections in adults at the National Institutes of Health |
| HCoV-HKU1 | 2004 | 71-year-old man with pneumonia in Hong Kong |
| Beta coronavirus group 2, lineage B | | |
| SARS-CoV | 2003–2004 | Humans with severe pneumonia in China; natural host, Chinese horseshoe bats; presumed intermediate host, palm civet |
| SARS-CoV-2 | 2019–2020 | Adults with acute respiratory distress syndrome/pneumonia from Wuhan, China; potential bat origin and related to SARS-CoV |
| Beta coronavirus group 2, lineage C | | |
| Middle East respiratory syndrome-CoV | 2012 | Adults with acute respiratory distress syndrome in Saudi Arabia; dromedary camel as reservoir/intermediary |

Ogimi C. et al., J Pediatric Infect Dis Soc. 2020 Apr 21.

## Timeline of COVID-19 at early stage



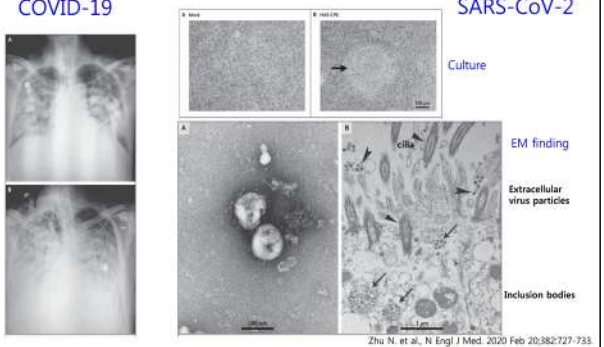

Wang C. et al., Lancet. 2020 Feb 15;395:470-473

## Global epidemiology of COVID (07.21.2020)

Case fatality rate, 4.2%


https://gisanddata.maps.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6

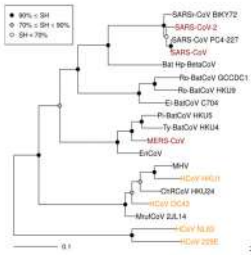
## COVID-19 SARS-CoV-2




Zhu N. et al., N Engl J Med. 2020 Feb 20;382:727-733.

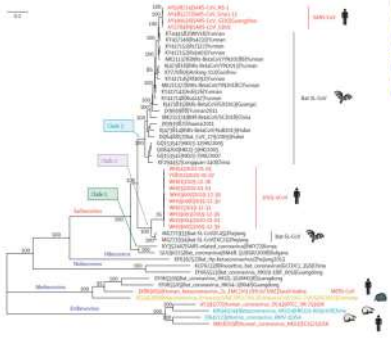
## Phylogenetic analysis of SARS-CoV-2 and other coronavirus genomes

The Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses (ICTV) named the new coronavirus SARS-CoV-2 based upon its genetic relationship to the original SARS-CoV that caused an outbreak of disease in 2002—2003.




biorxiv.org/content/10.1101/2020.02.07.937862v1

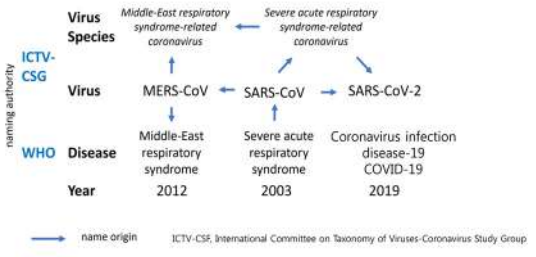
## Phylogenetic analysis of full-length genomes of SARS-CoV-2 and representative viruses of the genus betacoronavirus



- Whole genome
  - 88% identity with bat-derived Coronavirus
  - 79% with SARS-CoV
  - About 50% with MERS-CoV

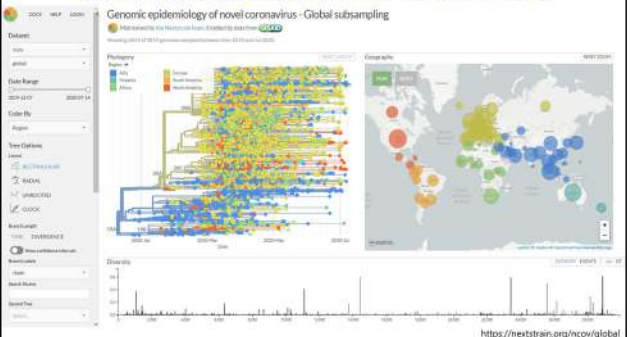
Lu R. et al., Lancet. 2020 Feb 22;395(10224):565-574.

## History of coronavirus naming during the three zoonotic outbreaks in relation to virus taxonomy and disease




Gorbalenya AE. et al., https://www.biorxiv.org/content/10.1101/2020.02.07.937862v1

## Genomic epidemiology of novel coronavirus - Global subsampling




https://nextstrain.org/ncov/global

## Human coronaviruses and their cellular receptors

| Coronavirinae Genera | Strains | Discovery | Cellular receptor |
|---|---|---|---|
| Alpha-corovavirus | HCoV-229E | 1966 | Human Aminopeptidase N (CD13) |
| | HCoV-NL63 | 2004 | ACE2 |
| Beta-coronavirus | HCoV-OC43 | 1967 | 9-O-Acetylated sialic acid |
| | HCoV-HKU1 | 2005 | 9-O-Acetylated sialic acid |
| | SARS-CoV | 2003 | ACE2 |
| | MERS-CoV | 2012 | DPP4 (CD26) |
| | SARS-CoV-2 | 2020 | ? |

DPP4, Dipeptidyl peptidase-4; ACE2, Angiotensin-converting enzyme 2

Lim YX. et al., Diseases. 2016 Jul 25;4(3).
Hoffmann M Cell. 2020 Apr 16;181(2):271-280.e8.

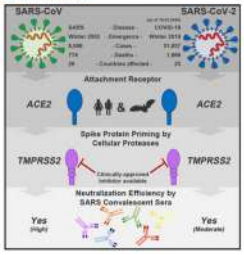
Article

**Cell**

**SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor**

- SARS-CoV-2 uses the SARS-CoV receptor ACE2 for host cell entry
- The spike protein of SARS-CoV-2 is primed by TMPRSS2.
- Antibodies against SARS-CoV spike may offer some protection against SARS-CoV-2.

Graphical Abstract




Authors
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Correspondence
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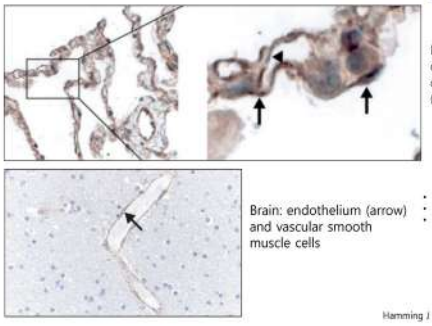
In Brief
The emerging SARS-coronavirus 2 (SARS-CoV-2) threatens public health. Hoffmann and coworkers show that SARS-CoV-2 infection depends on the host cell factors ACE2 and TMPRSS2 and can be blocked by a clinically proven protease inhibitor. These findings might help to establish options for prevention and treatment.

Hoffmann M Cell. 2020 Apr 16;181(2):271-280.e8.

## ACE2 distribution in the body



Lung: alveolar epithelial cells (arrow) capillary endothelium (arrow-head)

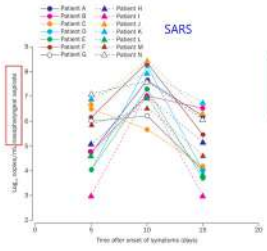


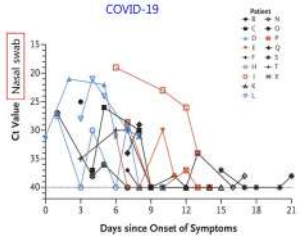
Brain: endothelium (arrow) and vascular smooth muscle cells

- Enterocytes of the small intestine
- Arterial and venous endothelial cells
- Arterial smooth muscle cells in organs studied (oral and nasal mucosa, nasopharynx, lung, stomach, small intestine, colon, skin, lymph nodes, thymus, bone marrow, spleen, liver, kidney, and brain)

Hamming I et al., J Pathol. 2004 Jun;203(2):631-7.

## Difference in viral kinetics: SARS-CoV vs. SARS-CoV-2



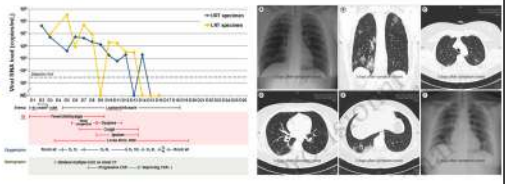




Peiris JS. et al., Lancet. 2003 May 24;361(9371):1767-72.

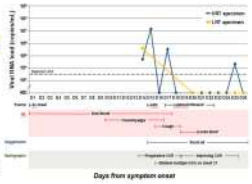
Zou L. et al., N Engl J Med. 2020 Feb 19. doi: 10.1056/NEJMc2001737.

## Viral load kinetics in Korean pts

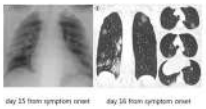
Pt 1



Pt 2



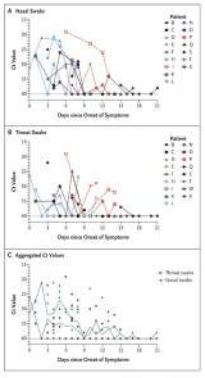




day 15 from symptom onset day 16 from symptom onset

Kim JY. et al., JKMS. 2020 Feb 24;35(7):e86. doi: 10.3346/jkms.2020.35.e86.

Days from symptom onset



## Viral load detected in nasal and throat swabs obtained from patients with SARS-CoV-2

Symptomatic (n=17), asymptomatic (n=1)

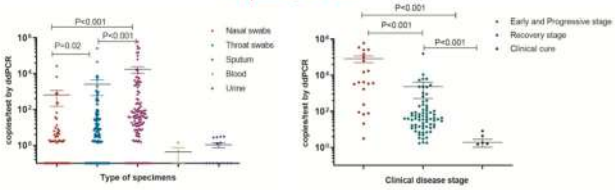
Ct values of
30.76, $1.5\times10^4$ copies per milliliter
27.67, $1.5\times10^5$ copies per milliliter
24.56, $1.5\times10^6$ copies per milliliter
21.48 $1.5\times10^7$ copies per milliliter
Negative samples are denoted with a Ct of 40, limit of detection

- Higher viral loads were detected soon after symptom onset, with higher viral loads detected in the nose than in the throat.
- The viral load that was detected in the asymptomatic patient was similar to that in the symptomatic patients (transmission potential of asymptomatic or minimally symptomatic patients).

Zou L. et al., N Engl J Med. 2020 Feb 19. doi: 10.1056/NEJMc2001737.

## Viral load of different tissue samples and clinical stages

76 patients, 646 tests

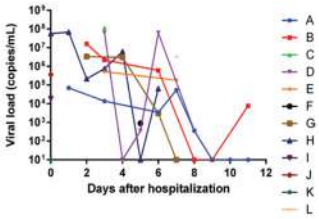



Average viral load in
- Sputum: 17,429 ± 6,920 copies/test
- Throat swabs 2,552 ± 1,965 copies/test
- Nasal swabs 651 ± 501 copies/test

Viral load in sputum
- Early and progressive stages 46,800 ± 17,272 copies/test
- Recovery stage 1,252 ± 1,027 copies/test

Yu F. et al., Clin Infect Dis. 2020 Mar 28. pii: ciaa345.

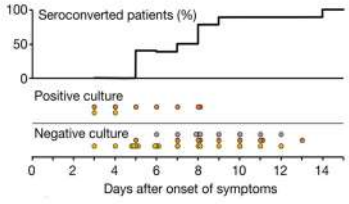
## Saliva viral load in patients with COVID-19




- 12 hospitalized patients
- 91.7% (11/12) patients was positive in self-collected saliva.
- Median 2 days (range, 0-7 days) after hospitalization
- Median viral load of the first available saliva specimens: 3.3 × $10^6$ copies/mL (range, 9.9 × $10^2$ to 1.2 × $10^8$ copies/mL)
- Serial saliva viral load monitoring generally showed a declining trend.
- Live virus was detected in saliva by viral culture (n=3).
- Saliva is a promising noninvasive specimen for diagnosis, monitoring, and infection control in patients with COVID-19.

T KKW. et al., Clin Infect Dis. 2020 Feb 12 : ciaa149

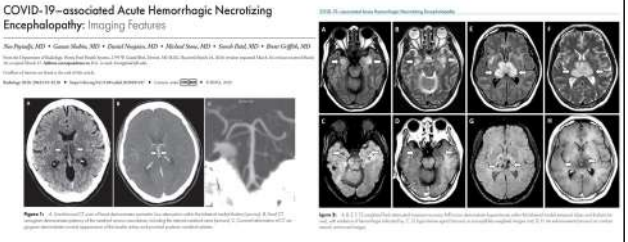
## Virus isolation and seroconversion




Wölfel R et al., Nature. 2020 May;581(7809):465-469.

## First presumptive case of encephalitis linked to COVID-19

COVID-19–associated Acute Hemorrhagic Necrotizing Encephalopathy: Imaging Features



Poyiadji N et al., Radiology: 2020 Aug;296(2):E119-E120. Published Online:Mar 31 2020

## Multisystem Inflammatory Syndrome – children and adolescents (MIS-C) associated with COVID-19

Jones VG. et al., Hosp Pediatr. 2020 Apr 7.

## Hyperinflammatory shock in children during COVID-19 pandemic

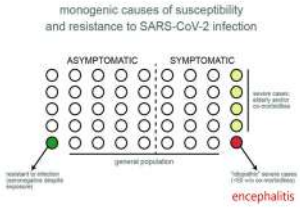
| | Age; weight; BMI; comorbidities | Clinical presentation | | Organ support | Pharmacological treatment | Imaging results | Laboratory results | Microbiology results | PICU length of stay; outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | Initial | PICU referral | | | | | | |
| Patient 1 (male, Afro-Caribbean) | 14 years; 95 kg; BMI 33 kg/m²; no comorbidities | 4 days >40°C; 3 days non-bloody diarrhoea; abdominal pain; headache | BP 80/40 mmHg; HR 130 beats/min; RR 40 breaths per min; work of breathing; SatO2 99% NCO2 | MV, RRT, VA-ECMO | Dopamine, noradrenaline, angiotensin, adrenaline milrinone, hydrocortisone, IVIG, ceftriaxone, clindamycin | RV dysfunction/ elevate RVSP; ileitis, GB oedema and dilated biliary tree, ascites, bilateral basal lung consolidations and diffuse nodules | Ferritin 4220 µg/L; D-dimers 13·4 mg/L; troponin 675 ng/L; proBNP >35 000; CRP 556 mg/L; procalcitonin>100 µg/L; albumin 20 g/L; platelets 123×10⁹ | SARS-CoV-2 positive (post mortem) | 6 days; demise (right MCA and ACA ischaemic infarction) |
| Patient 2 (male, Afro-Caribbean) | 8 years; 30 kg; BMI 18 kg/m²; no comorbidities | 5 days >39°C; non-bloody diarrhoea; abdominal pain; conjunctivitis; rash | BP 81/37 mmHg; HR 165 beats/min; RR 40 breaths/ min; SVA | MV | Noradrenaline, adrenaline, IVIG, infliximab, methylprednisolone, ceftriaxone, clindamycin | Mild biventricular dysfunction, severely dilated coronaries; ascites, pleural effusions | Ferritin 277 µg/L; D-dimers 4·8 mg/L; troponin 25 ng/L; CRP 295 mg/L; procalcitonin 9·4 µg/L; albumin 18 g/L; platelets 61×10⁹ | SARS-CoV-2 negative; likely COVID-19 exposure from mother | 4 days; alive |
| Patient 3 (male, Middle-Eastern) | 4 years; 18 kg; BMI 17 kg/m²; no comorbidities | 4 days >39°C; diarrhoea and vomiting; abdominal pain; rash; conjunctivitis | BP 90/30 mmHg; HR 170 beats/min; RR 35 breaths/ min; SVA | MV | Noradrenaline, adrenaline, IVIG, ceftriaxone, clindamycin | Ascites, pleural effusions | Ferritin 574 µg/L; D-dimers 11·7 mg/L; troponin 45 ng/L; CRP 322 mg/L; procalcitonin 10·3 µg/L; albumin 27 g/L; platelets 103×10⁹ | Adenovirus positive; HERV positive | 4 days; alive |
| Patient 4 (female, Afro-Caribbean) | 13 years; 64 kg; BMI 33 kg/m²; no comorbidities | 5 days >39°C; non-bloody diarrhoea; abdominal pain; conjunctivitis | BP 77/41 mmHg; HR 127 beats/min; RR 24 breaths/ min; SVA | HFNC | Noradrenaline, milrinone, IVIG, ceftriaxone, clindamycin | Moderate-severe LV dysfunction; ascites | Ferritin 631 µg/L; D-dimers 3·4 mg/L; troponin 250 ng/L; proBNP 13427 ng/L; CRP 307 mg/L; procalcitonin 12·1 µg/L; albumin 21 g/L; platelets 146×10⁹ | SARS-CoV-2 negative | 5 days; alive |

Riphagen S. et al., Lancet. 2020 May 23;395(10237):1607-1608.

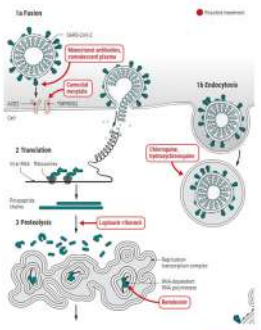
## COVID-19 associated Kawasaki-like MIS in an adult

Sokolovsky S. Am J Emerg Med. 2020 Jun 25;S0735-6757(20)30542-8.
Shaigany S, et al. Lancet. 2020.

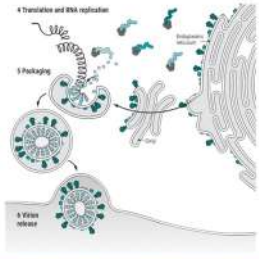
## COVID Human Genetic Effort




https://www.covidhge.com/

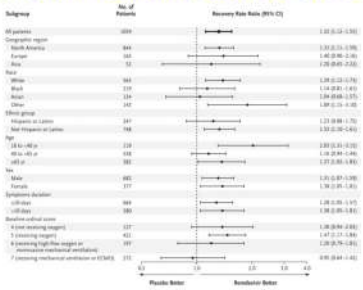


Experimental treatment strategies being tested by a large WHO study and other clinical trials attempt to interfere with different steps (numbered) in the coronavirus replication cycle.



https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments#

## Remdesivir for the Treatment of Covid-19 - Preliminary Report

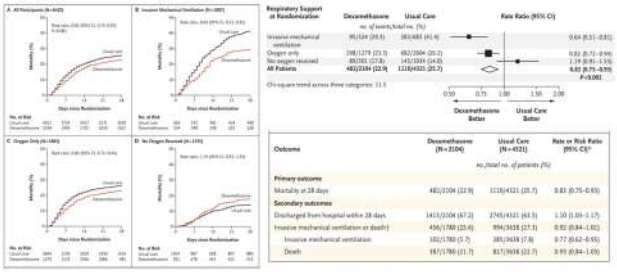


- 1059 patients (538 assigned to remdesivir and 521 to placebo): up to 10 days
- Median recovery time
  - Remdesivir: 11 days (95% confidence interval [CI], 9 to 12)
  - Control: 15 days (95% CI, 13 to 19)
  - Rate Ratio for recovery, 1.32; (95% CI, 1.12 to 1.55; P<0.001).
- Kaplan Meier estimates of mortality by 14 days
  - Remdesivir: 7.1%
  - Placebo: 11.9%
  - Hazard ratio for death, 0.70 (95% CI, 0.47 to 1.04).

Beigel J et al., N Engl J Med . 2020 May 22;NEJMoa2007764.

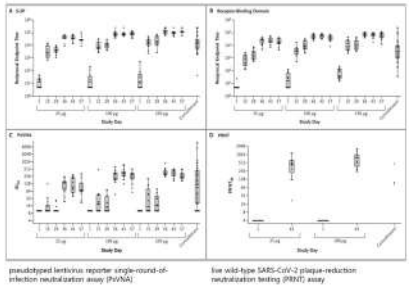
## Dexamethasone in hospitalized patients with Covid-19 - Preliminary Report

Effect of Dexamethasone on 28-Day Mortality



RECOVERY Collaborative Group: Horby P et al., N Engl J Med. 2020 Jul 17

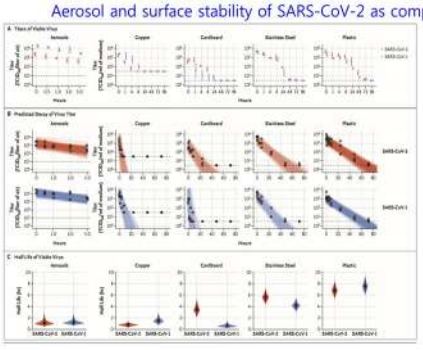
## An mRNA Vaccine against SARS-CoV-2 - Preliminary Report



- mRNA-1273 encodes the stabilized prefusion SARS-CoV-2 spike protein
- Phase 1, dose-escalation, open-label trial including 45 healthy adults, 18 to 55 years of age
- Two vaccinations, 28 days apart, with mRNA-1273 in a dose of 25 μg, 100 μg, or 250 μg

Jackson L et al., N Engl J Med. 2020 Jul 14.

## Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1



- 21-23°C, 40% relative humidity
- over 7 days

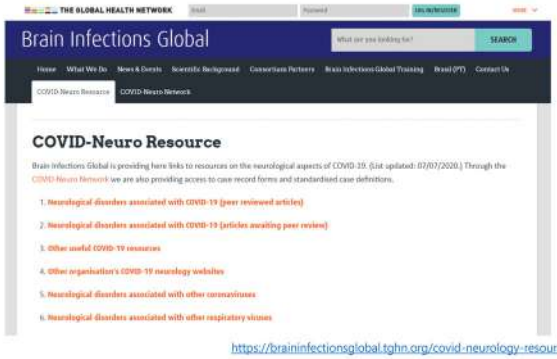
- SARS-CoV-2 was more stable on plastic and stainless steel than on copper and cardboard, and viable virus was detected up to 72 hours after application to these surfaces
- Plastic: from 103.7 to 100.6 TCID50 per milliliter of medium after 72 hours (SARS-CoV-2)
- Stainless steel: from 103.7 to 100.6 TCID50 per milliliter after 48 hours (SARS-CoV-2)
- Copper: no viable SARS-CoV-2 after 4 hours and no viable SARS-CoV-1 after 8 hours.
- Cardboard: no viable SARS-CoV-2 after 24 hours and no viable SARS-CoV-1 after 8 hours

van Doremalen N. et al., N Engl J Med; 2020 Apr 16;382(16):1564-1567.

## Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis

## Summary

- Second pandemic caused by coronavirus in human history
- ACE2 is the receptor for the virus infection.
- Viral load is high during the early phase of infection.
- New options for treatment and prevention are being studied.
- Non-pharmaceutical intervention (social distancing, personal hygiene, and wearing a mask) is still very important.
- Several neurologic complications have been reported.
- Mechanisms for neurologic complications need further study.




https://braininfectionsglobal.tghn.org/covid-neurology-resource/