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# COVID-19 Literature Updates

September 22, 2020


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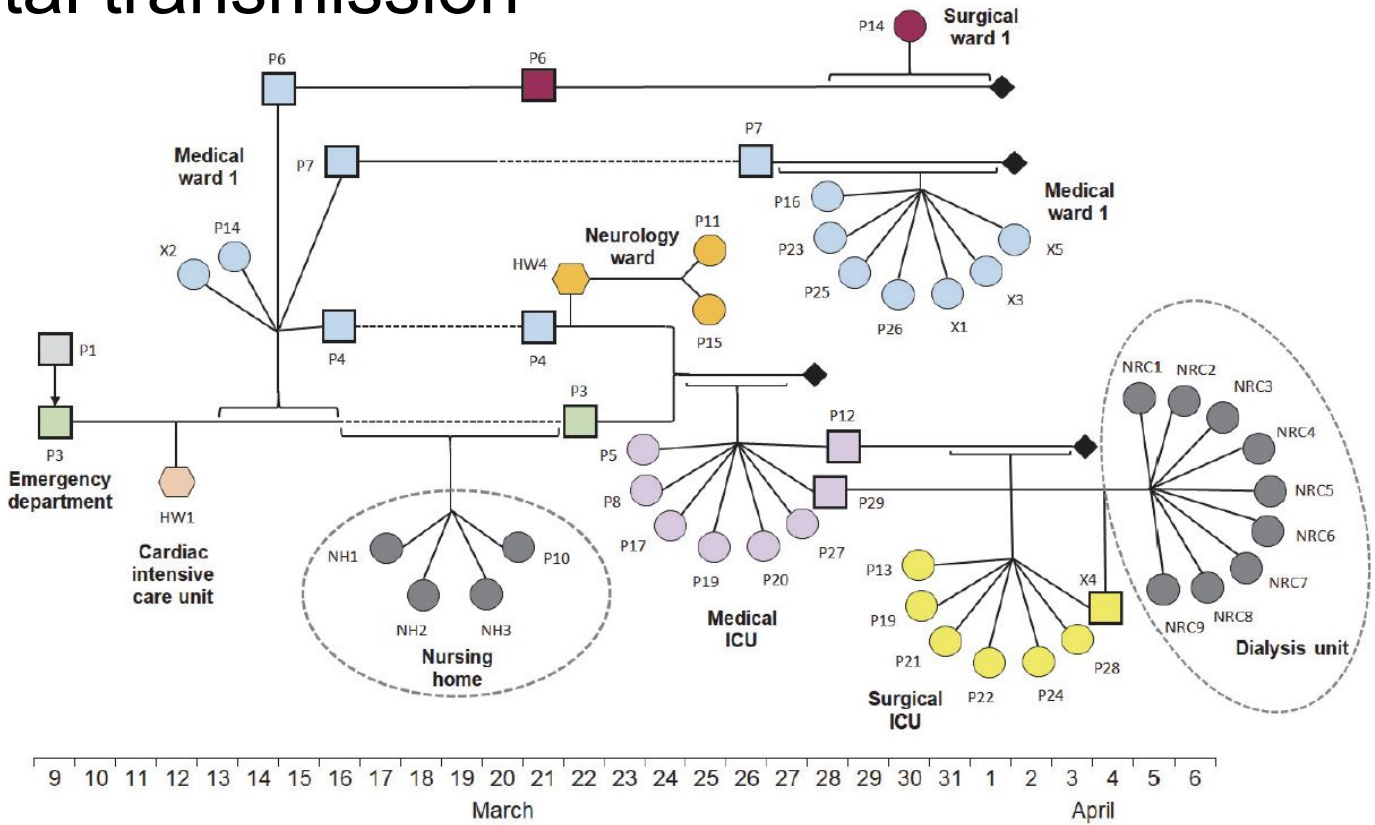
# Agenda

- Lessons from the evolving landscape of hospital-acquired infection
- Tracing the global spread of SARS-CoV-2
- The importance of viral load and disease severity
- Classifying the adaptive immune response to SARS-CoV-2
- Proposed updated model for COVID-19 pathogenesis
- Reinfection: insights from other human coronaviruses and reflections on reports of SARS-CoV-2 re-infection

# Lessons (and Questions) from the Evolving Landscape of Hospital-Acquired Infection

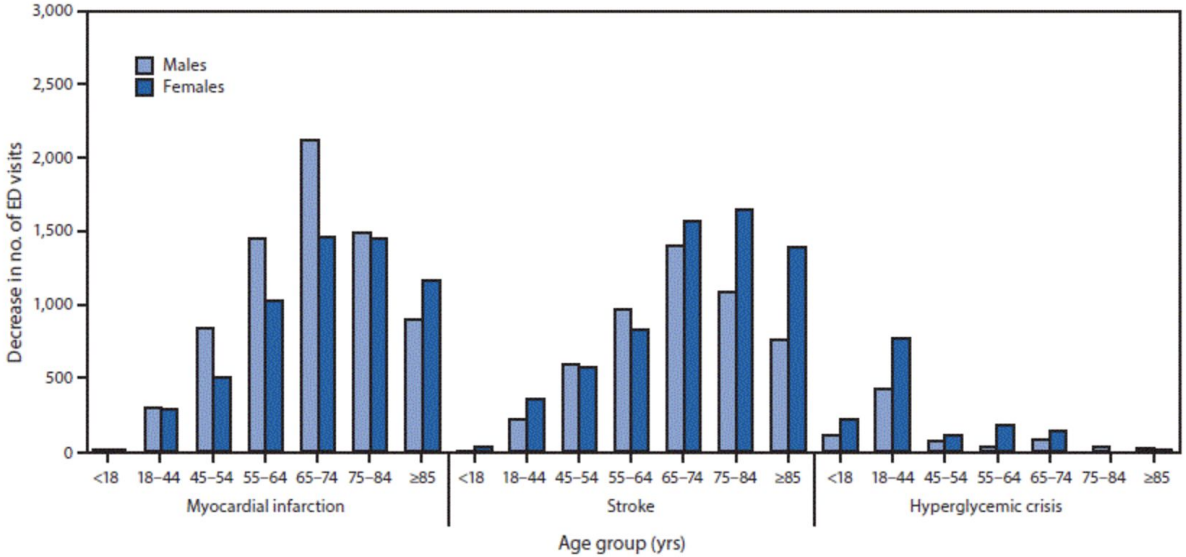
# Abundant early evidence for devastating potential of in-hospital transmission




Zhou ATM doi: 10.21037/atm-20-3324

Lessels https://www.krisp.org.za/manuscripts/StAugustinesHospitalOutbreakInvestigation_FinalReport_15may2020_comp.pdf

# Transmission concerns led to large decreases in patients presenting for acute / urgent illness worldwide

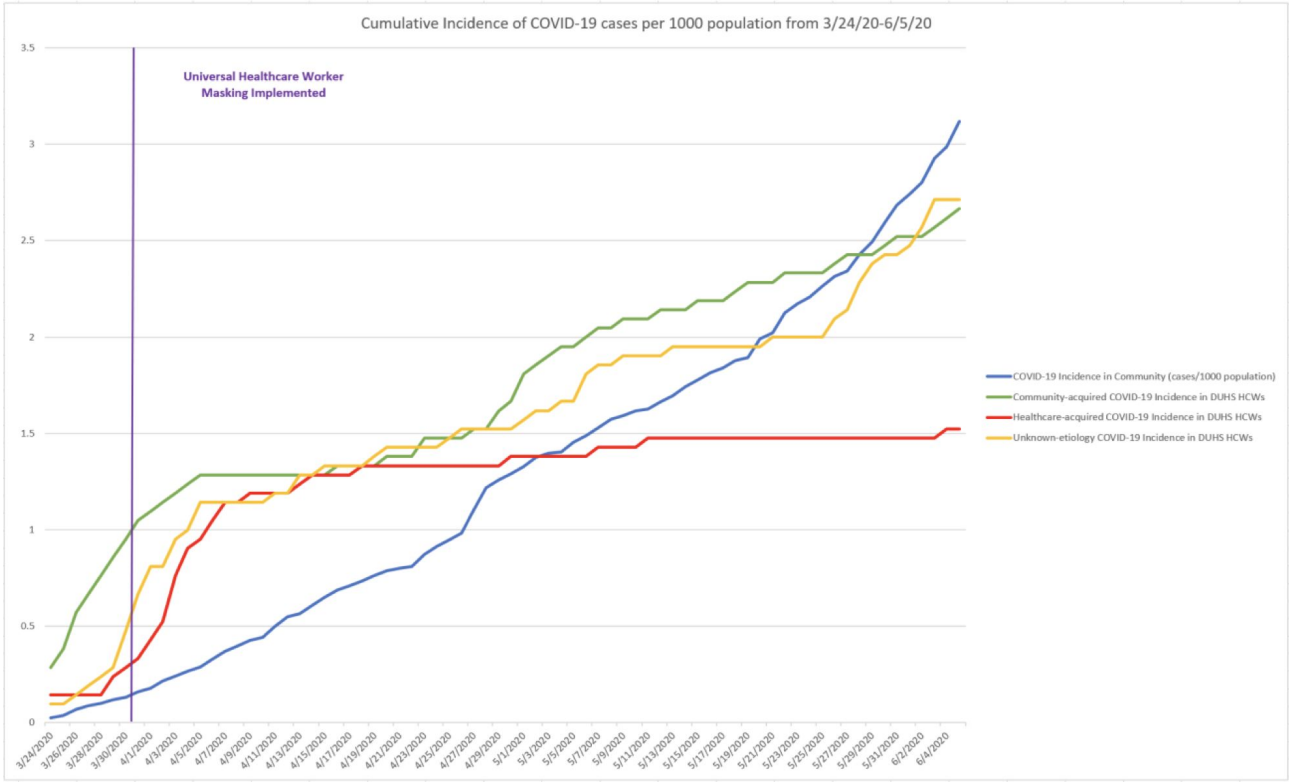



37 TB centers in 16 countries on 5 continents:

- 84% - decrease in new cases
- 75% - decrease in outpatient visits

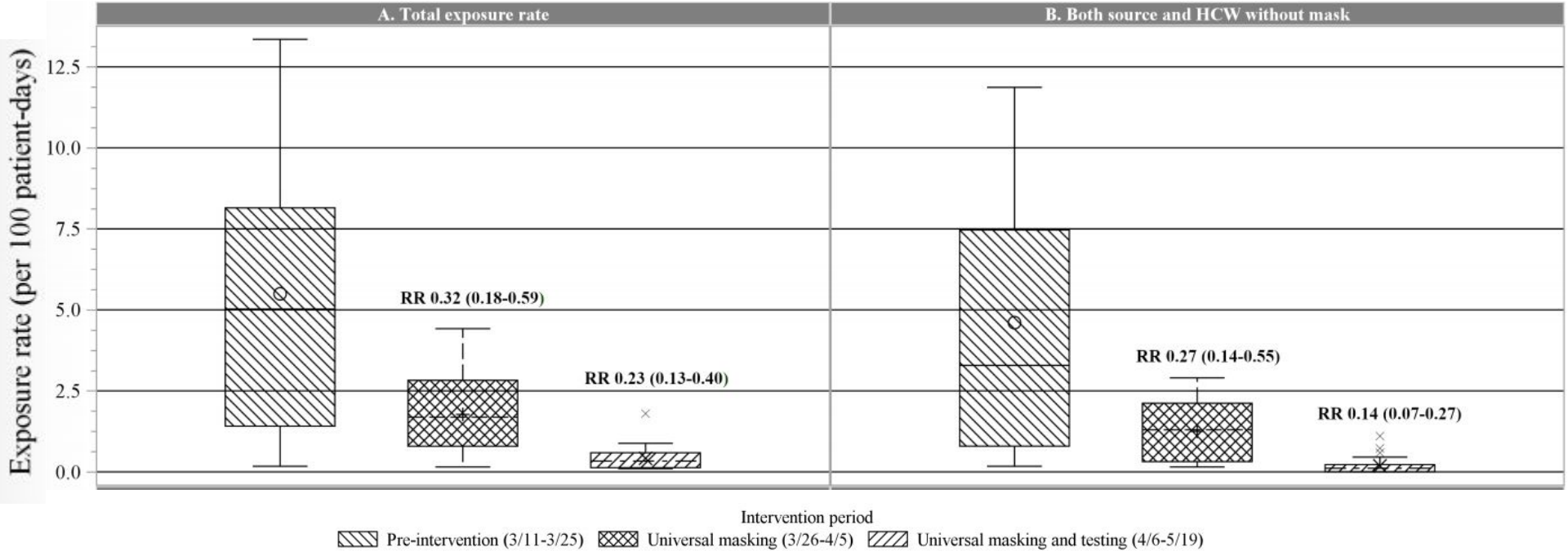
Lange MMWR http://dx.doi.org/10.15585/mmwr.mm6925e2
Mogliori Emerg Infect Dis https://doi.org/10.3201/eid2611.203163

# Early evidence that universal masking markedly reduces hospital-acquired infection



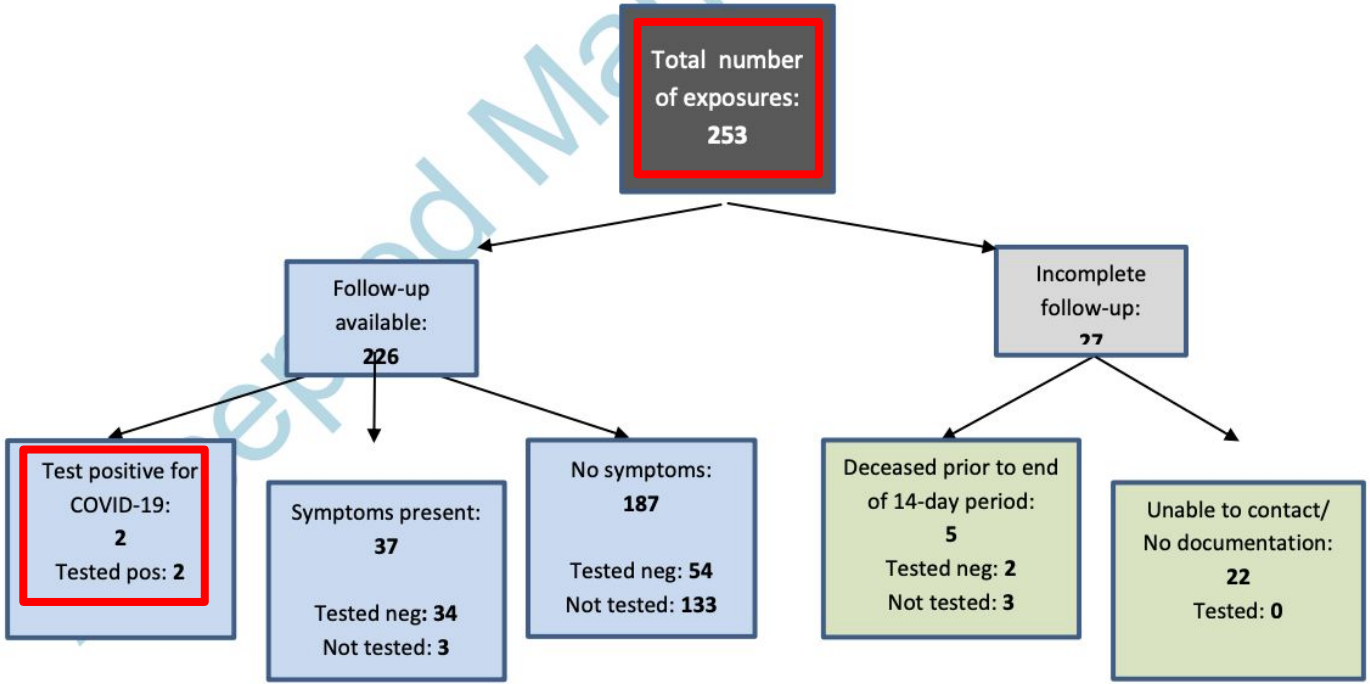

Seidelman ICHE DOI: 10.1017/ice.2020.313

# Major reduction in exposures after implementation of universal masking




Walker CID DOI: 10.1093/cid/ciaa1358

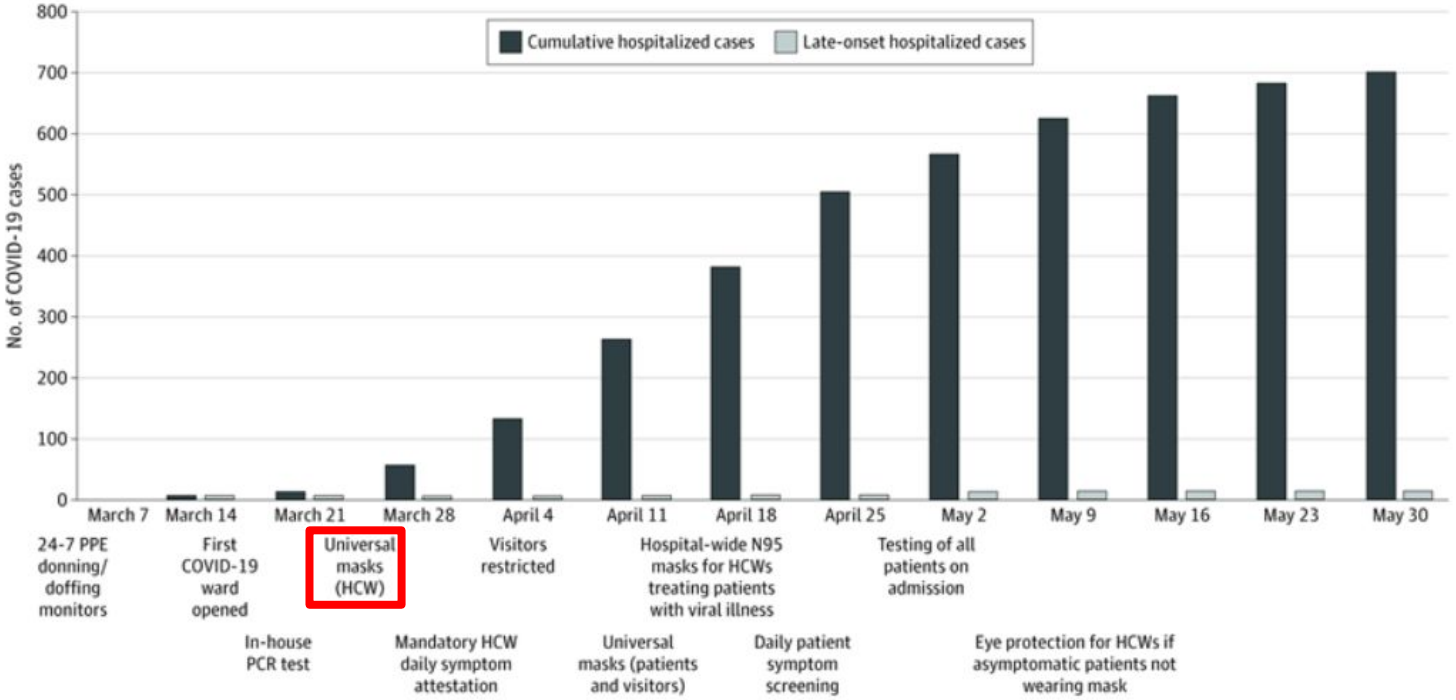
# In the universal masking era, provider to patient transmission is extremely rare






Baker CID DOI 10.1093/cid/ciaa1269

# Similarly, risk of nosocomial infection is very low with universal masking



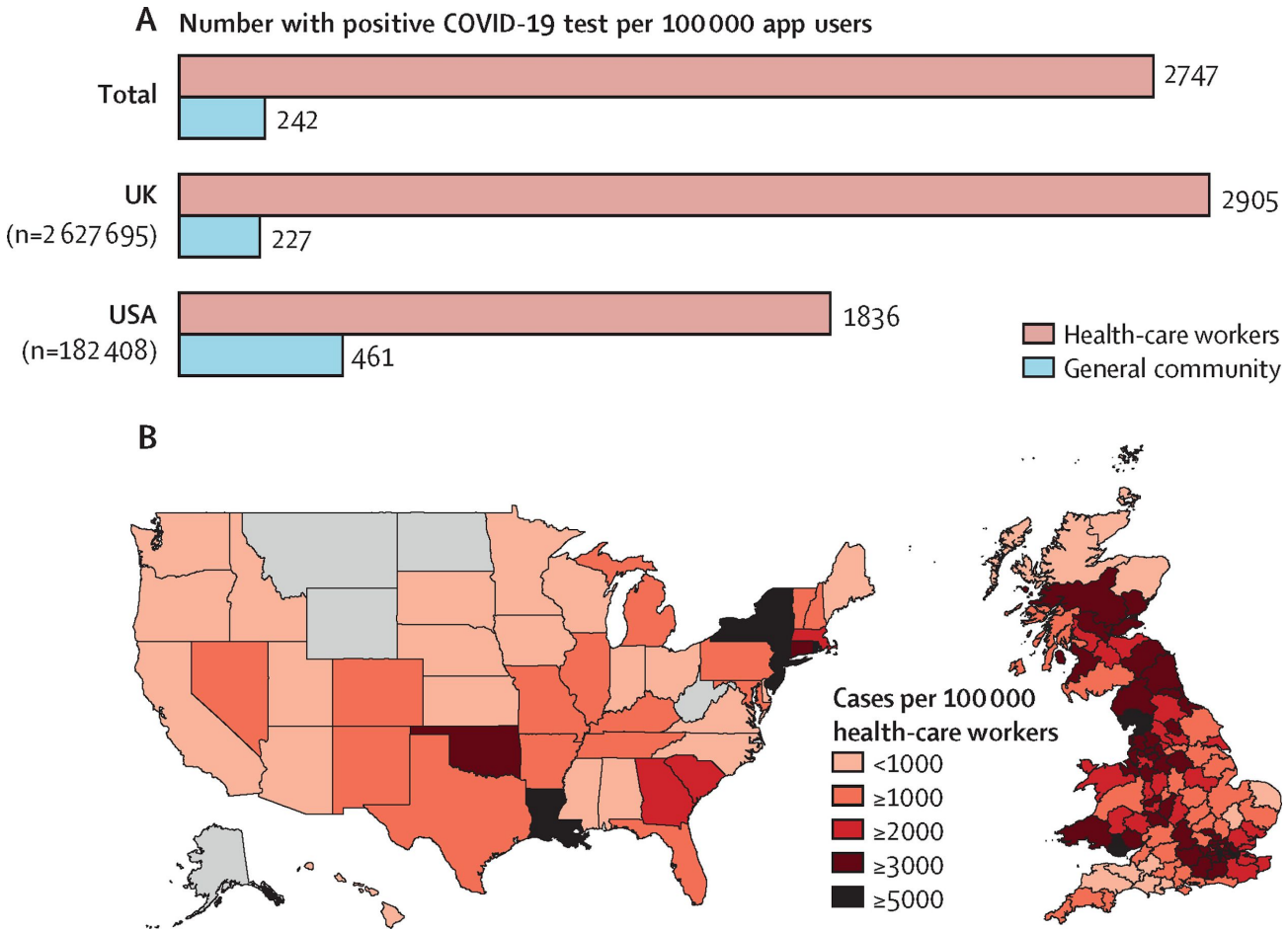

Rhee JAMA Open DOI 10.1001/jamanetworkopen.2020.20498

World

# Health-care workers make up 1 in 7 covid-19 cases recorded globally, WHO says

September 17, 2020 at 1:52 p.m. EDT

But then how to explain healthcare workers having higher risk of a positive test?




Nguyen Lancet Public Health https://doi.org/10.1016/S2468-2667(20)30164-X

But then how to explain healthcare workers having higher risk of a positive test?

| | Multivariate-adjusted hazard ratio (95% CI) | Inverse probability-weighted hazard ratio (95% CI) |
|---|---|---|
| **Overall (primary analysis)** | | |
| General community | 1 (ref) | 1 (ref) |
| Front-line health-care worker | 11·61 (10·93–12·33) | 3·40 (3·37–3·43) |

Nguyen Lancet Public Health https://doi.org/10.1016/S2468-2667(20)30164-X

# But then how to explain healthcare workers having higher risk of a positive test?

- Available data do not differentiate community vs hospital acquisition

  Kluytmans-van der Bergh JAMA Open doi 10.1001/jamanetworkopen.2020.9673

- Much of the data are not in the context of universal masking

- Residual confounding related to probability of receiving a test?

- Patients admitted with COVID-19 past peak infectiousness - importance of a/presymptomatic transmission (from healthcare workers?) in hospital settings?

# Lessons from the Evolving Landscape of Hospital-Acquired Infection

1. **In the context of pre-pandemic infection control, healthcare settings are major sites of SARS-CoV-2 transmission**

   - Much of this may be driven by a/pre-symptomatic (or early symptomatic) healthcare workers and patients *rather* than COVID-19 patients, many of whom will be minimally or non-infectious

# Lessons from the Evolving Landscape of Hospital-Acquired Infection

**2. Early evidence that universal masking has extremely high effectiveness in well-ventilated hospital settings with so-so ability to social distance =>**

- Need to emphasize this fact to the public, discourage avoidance of necessary healthcare
- Proof of concept for broader use of universal masking in indoor settings
- Await confirmation via high-quality contact tracing study of healthcare workers in a large hospital system during universal masking era

# Lessons from the Evolving Landscape of Hospital-Acquired Infection

## 3. Need to understand *context* of residual transmissions

*Infection Control & Hospital Epidemiology* (2020), 1–2
doi:10.1017/ice.2020.333

**Letter to the Editor**

### Are we forgetting the "universal" in universal masking? Current challenges and future solutions

Sonali D. Advani MBBS, MPH[1,2], Michael E. Yarrington MD[1,2], Becky A. Smith MD, Deverick J. Anderson MD, MPH[1,2] and Daniel J. Sexton MD[1,2]

*"Unmasked exposure to another HCP rather than exposure to known infected patients resulted in most of the COVID-19 cases among staff after implementation of this policy... We also determined that actual compliance with universal masking policies was suboptimal, particularly among staff outside of clinical care settings, including administrative offices, shared work rooms, and break rooms."*

Baystate Health

*"staff who convened in a breakroom and removed their masks without observing proper social distancing protocols"*

**A hospital-wide response to multiple outbreaks of COVID-19 in Health Care Workers**
**Lessons learned from the field**

Kirsty Buising[1,2], Deborah Williamson[2,3,4], Benjamin Cowie [1,2,5], Jennifer MacLachlan[2,5], Liz Orr[6], Chris MacIsaac[7,8], Eloise Williams[3], Katherine Bond[3], Stephen Muhi[1], James McCarthy[1,2], Andrea B. Maier [9,10], Louis Irving [11], Denise Heinjus [12], Cate Kelly [13], Caroline Marshall[1,2, 6]

*"On one occasion, staff congregation in a tearoom was identified as a likely opportunity for transmission between staff. On other occasions, staff noted that particular behaviours in infected patients appeared to be linked to transmission events (distressed patients shouting, vigorous coughing)."*

# Tracing the Global Spread of SARS-CoV-2

RESEARCH ARTICLE

# The emergence of SARS-CoV-2 in Europe and North America

Michael Worobey[1,*], Jonathan Pekar[2,3], Brendan B. Larsen[1], Martha I. Nelson[4], Verity Hill[5], Jeffrey B. Joy[6,7,8], Andrew Rambaut[5], Marc A. Suchard[9,10,11,*], Joel O. Wertheim[12,*], Philippe Lemey[13,*]

Worobey Science DOI: 10.1126/science.abc8169

# Phylogenetic inference - testing two hypotheses

1. Establishment of SARS-CoV-2 in North America took place much earlier (mid-January, “WA1” virus) than initially known (late February, “WA2” virus)

2. Failure of early contact tracing efforts in Germany in late January (“BavPat1” virus) led to the Lombardy outbreak and dissemination of SARS-CoV-2 across Europe

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# Phylogenetic inference - testing two hypotheses

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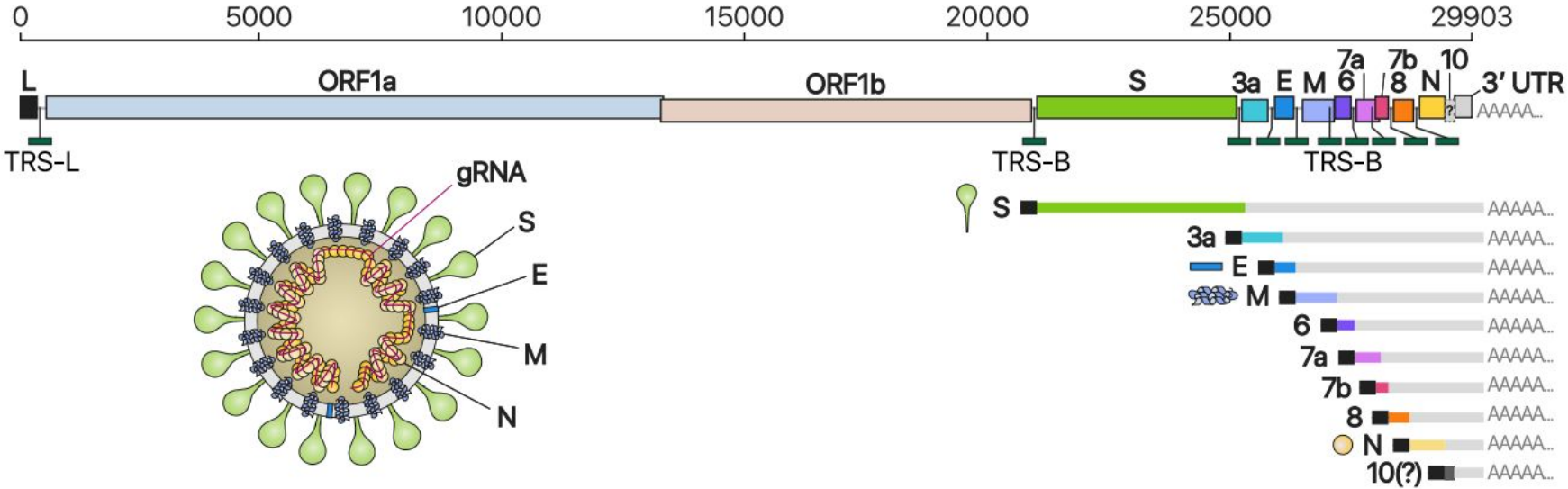
Worobey Science DOI: 10.1126/science.abc8169

# A long genome with a slow mutation rate

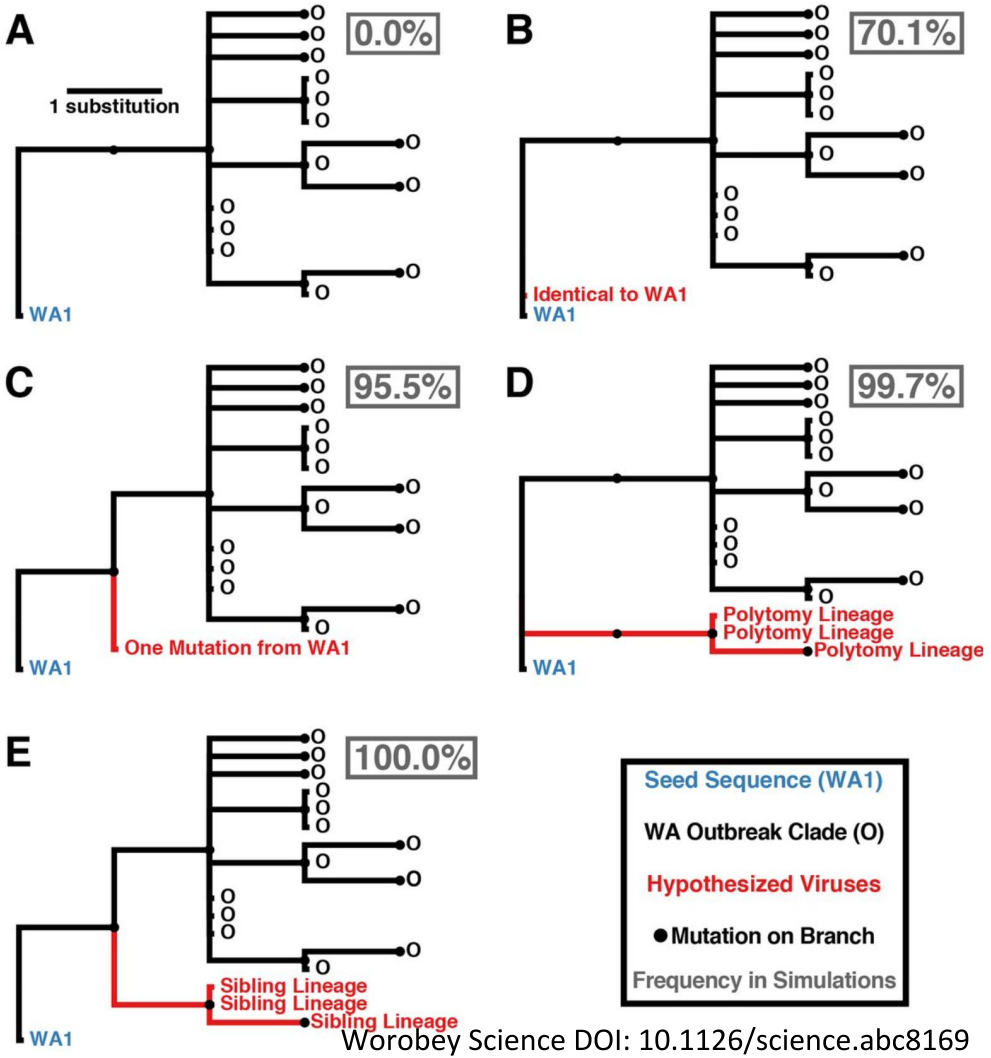



Phylogenetic inference limited by:
-Relatively small differences in viral genomes
-Low availability of sequence data in areas experiencing early outbreaks
-Rapid dissemination of virus

Worobey Science DOI: 10.1126/science.abc8169
Kim Cell https://doi.org/10.1016/j.cell.2020.04.011

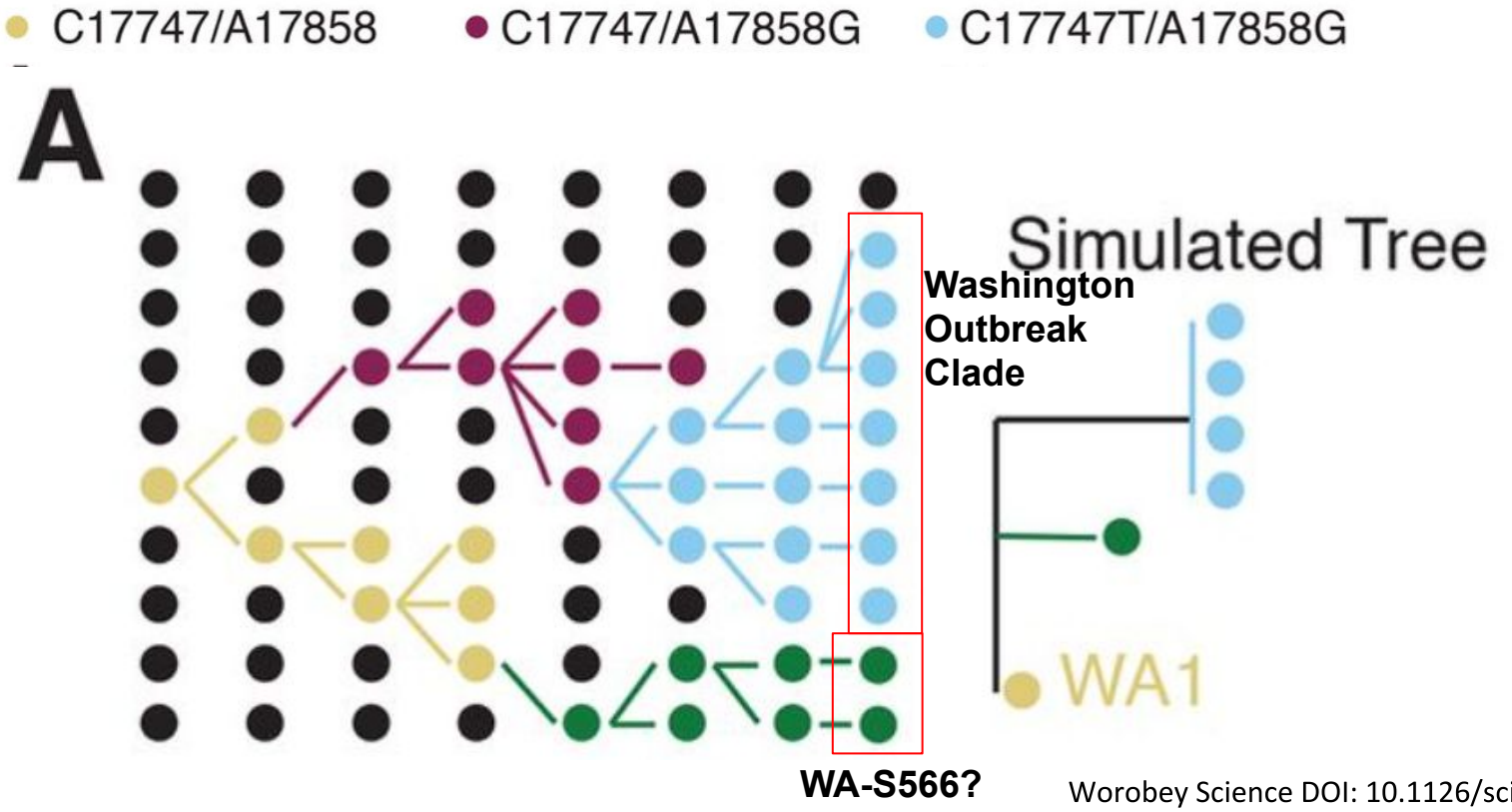
For the Washington outbreak clade to have descended from WA1, would need to have experienced two mutations prior to establishing outbreak clade -

C17747T and A17858G



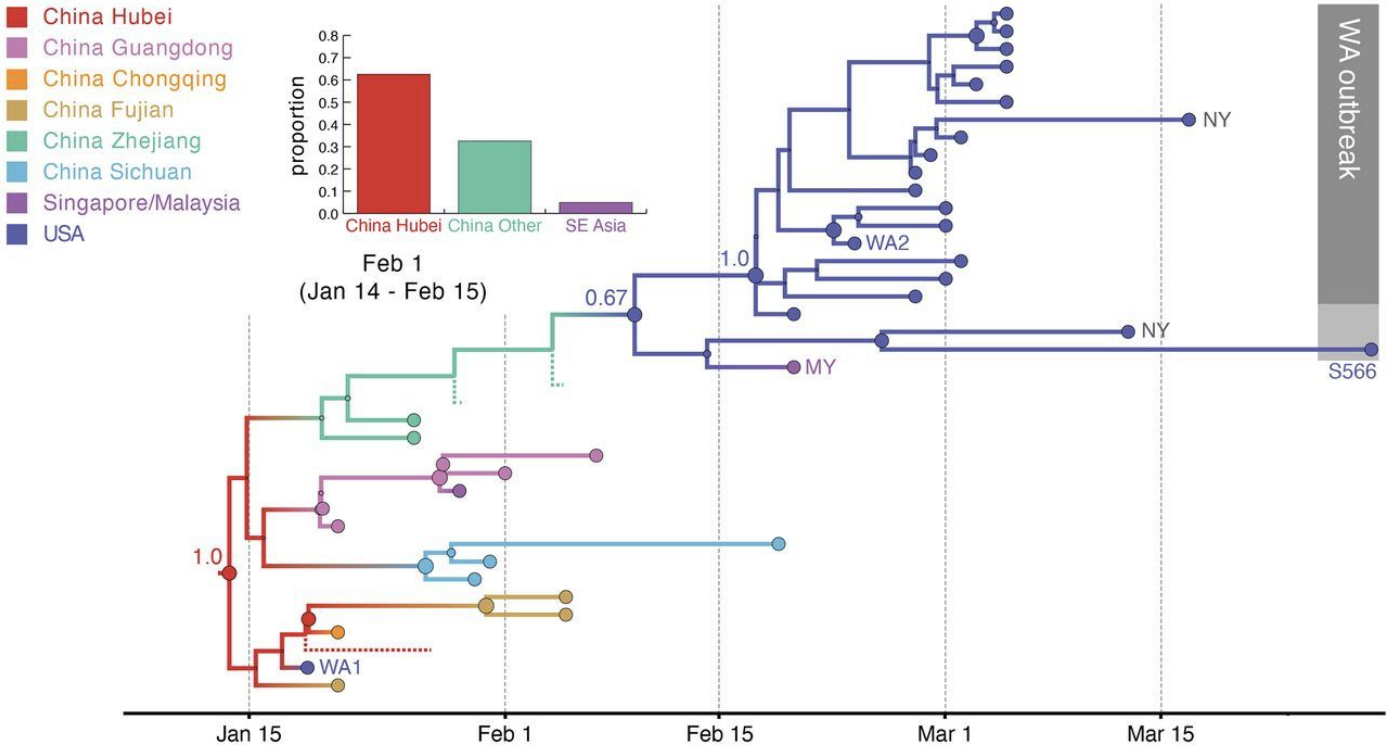

Worobey Science DOI: 10.1126/science.abc8169

# An exhaustive look at viral genomes in Washington points to multiple introductions *after* WA1



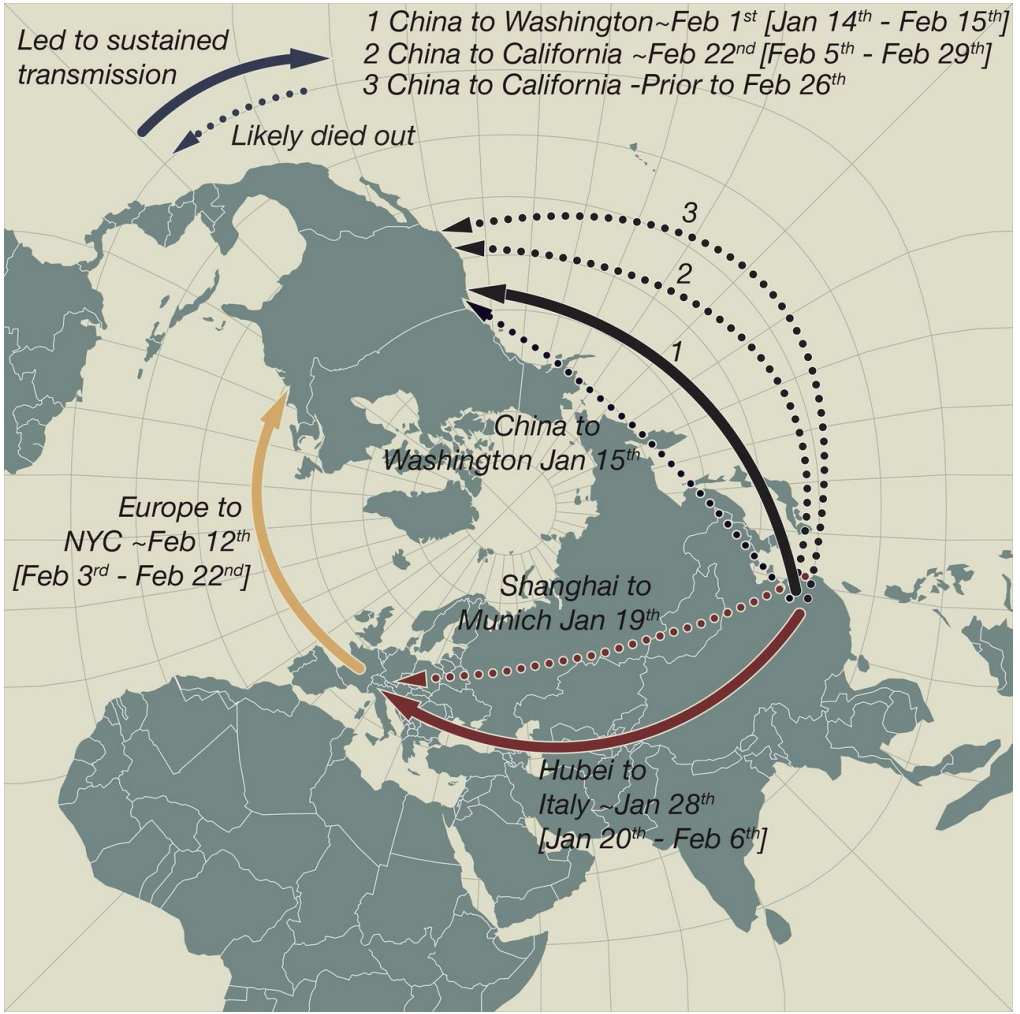

Worobey Science DOI: 10.1126/science.abc8169

Phylogeographic analysis incorporating temporal, epidemiological, geographic data suggests that WA outbreak clade and S566 arose from a single introduction around Feb 1




Worobey Science DOI: 10.1126/science.abc8169

Using phylogeographic analyses to create projections of the early introduction of SARS-CoV-2 to Europe and the US

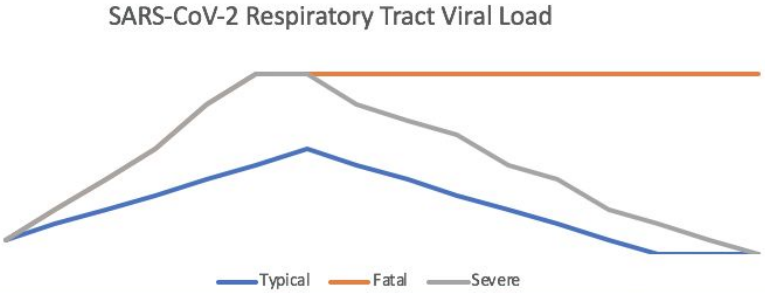



Worobey Science DOI: 10.1126/science.abc8169

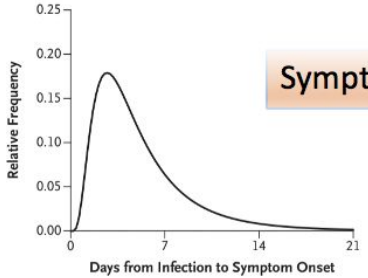
# Pathogenesis, Immunity, and Reinfection

[Proposed March 25, 2020]

# COVID-19 Disease Course




| 5.1 days (median) | 5-10 days | Days - weeks | |
|---|---|---|---|
| **Incubation Period** | **Acute Mild Phase *** | **ARDS/Pro-inflammatory Phase** | **Recovery** |




Symptom onset

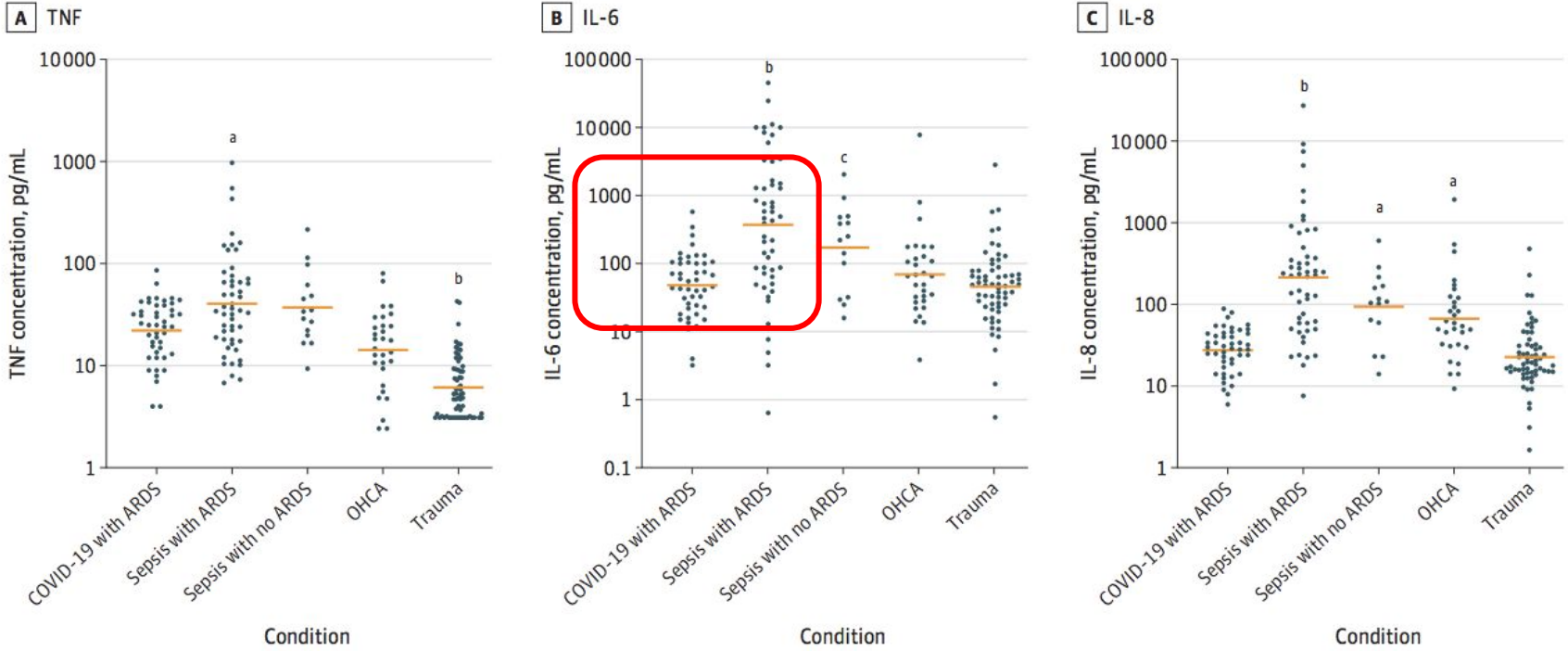
Hallmarks: dyspnea, tachypnea, hypoxemia

* Acute Mild Phase: nonspecific symptoms. Most commonly fevers, cough, myalgias, fatigue. Nausea, diarrhea reported <50% of the time

Pan Lancet ID 2020 https://doi.org/10.1016/S1473-3099(20)30113-4
Zou NEJM 2020 DOI: 10.1056/NEJMc2001737
Zhou Lancet 2020 https://doi.org/10.1016/S0140-6736(20)30566-3
Li NEJM 2020 DOI: 10.1056/NEJMoa2001316
Wang JAMA 2020 doi:10.1001/jama.2020.1585
Siddiqi JHLT 2020 doi:10.1016/j.healun.2020.03.012

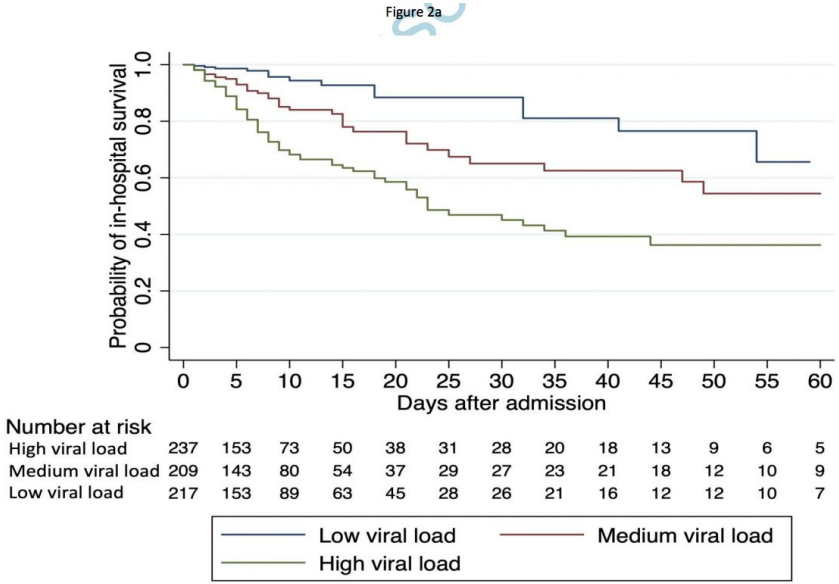
# Complicating the idea of “cytokine storm”

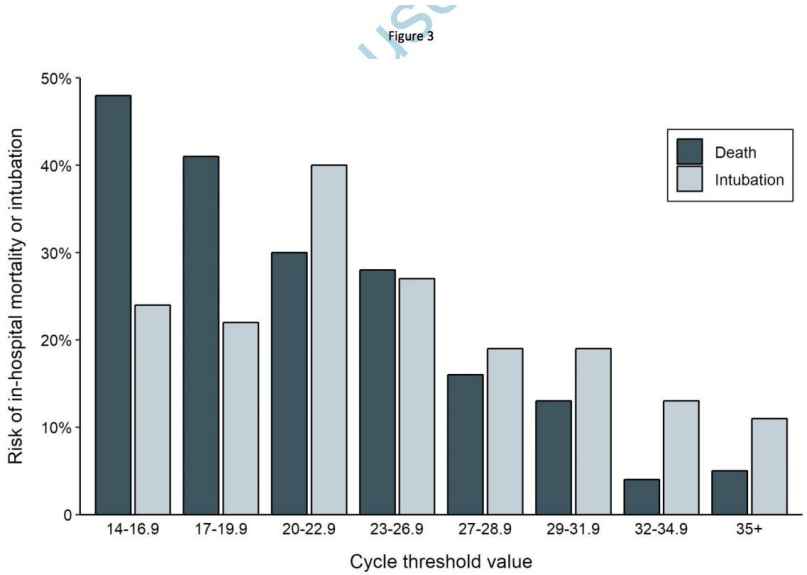
**Figure. Cytokine Levels in Critically Ill Patients With Coronavirus Disease 2019 (COVID-19) and Other Conditions**




Cox JAMA [doi:10.1001/jama.2020.17052](https://doi.org/10.1001/jama.2020.17052)

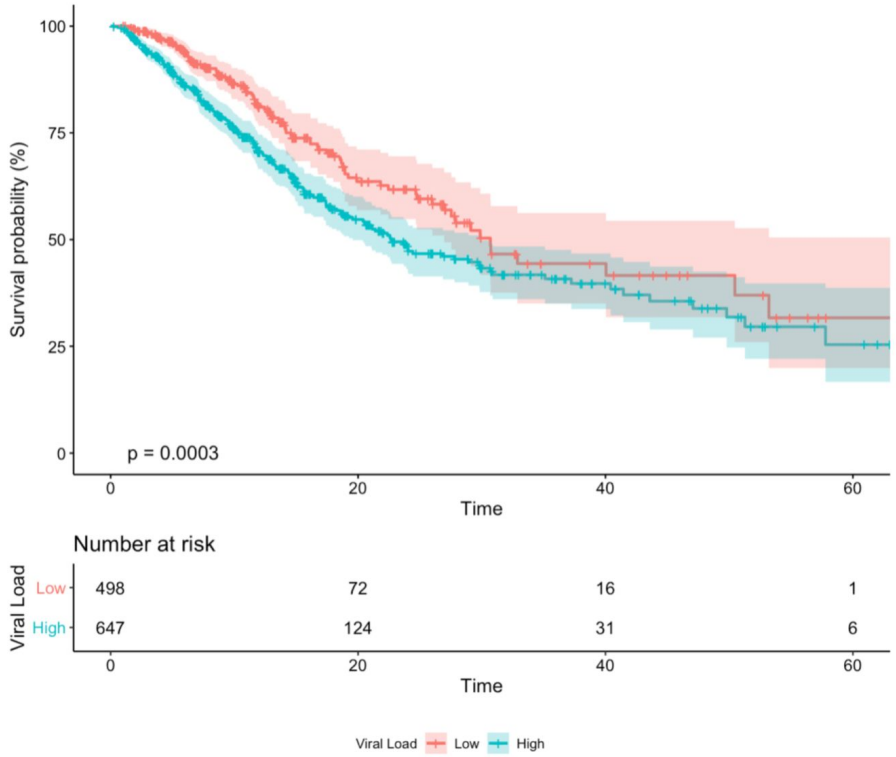
# Viral load clearly associated with disease severity and COVID-19 mortality




Magleby CID https://doi.org/10.1093/cid/ciaa851

# Higher viral load associated with increased mortality




Pujadas Lancet Resp Med https://doi.org/10.1016/S2213-2600(20)30354-4

# In multivariable model, high viral load had OR 5.00 for death

**Table 3 excerpt: Overall in-hospital mortality:**

| | cobas SARS-CoV-2 assay[a] |
|---|---|
| All patients | |
| High viral load (n=941) | 37.5%[c] |
| Medium viral load (n=825) | 23.5% |
| Low viral load (n=1248) | 12.4% |

**Table 4 excerpt: Factors associated with death in multivariable model for those with cancer:**

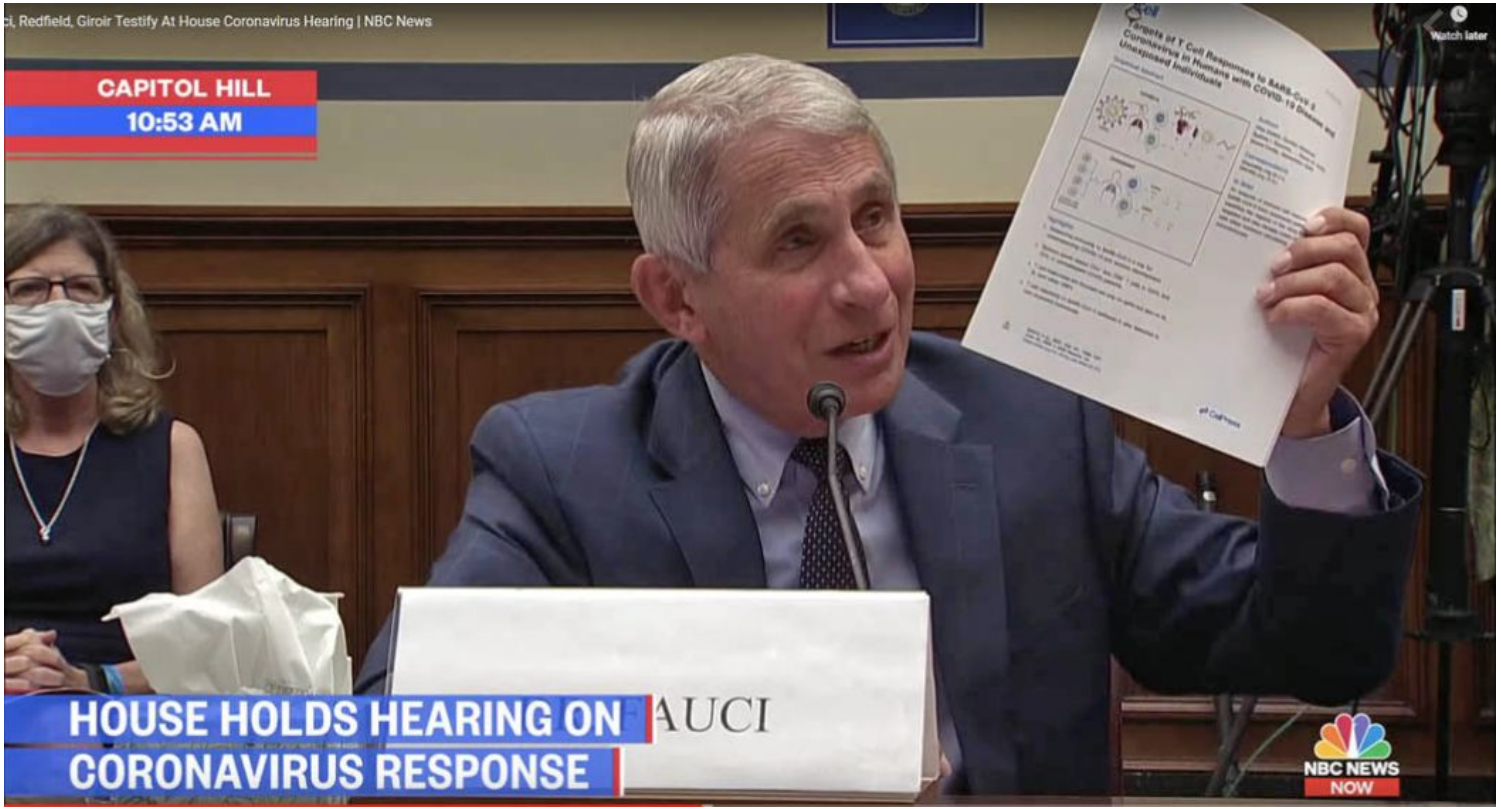
| | Multivariate model Adjusted OR (95% CI) | *P* value |
|---|---|---|
| Admission viral load[a, b] | | |
| Low (cobas, $C_T$ value >30; Xpert >32) | Reference | |
| Medium (cobas, $C_T$ value 25-30; value 27-32) | 2.13 (0.51-8.85) | 0.30 |
| High (cobas, $C_T$ value <25; Xpert <27) | 5.00 (1.42-17.61) | **0.012** |

Westblade Cancer Cell https://doi.org/10.1016/j.ccell.2020.09.007

# Factors associated with high viral load in multivariable model

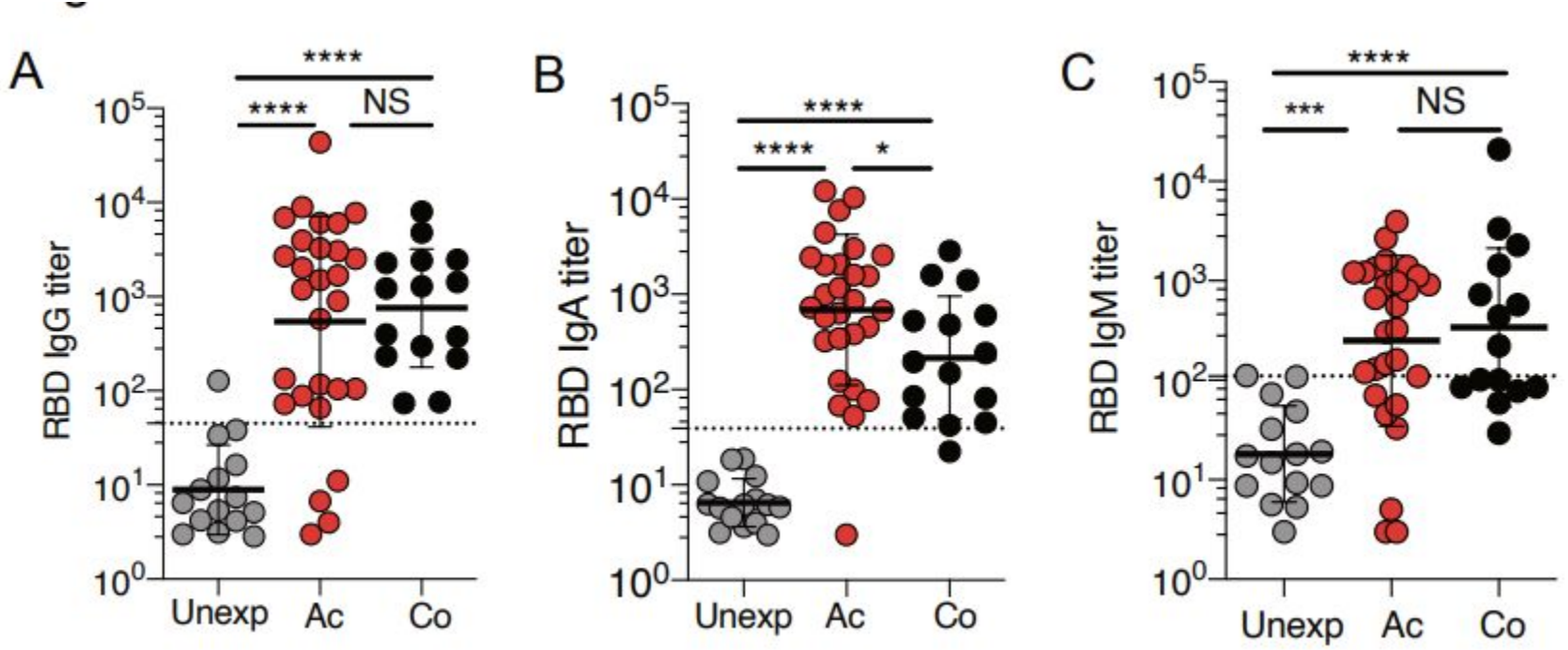
| Variable | Univariate model Unadjusted OR (95% CI) | *P* value | Multivariate model Adjusted OR (95% CI) | *P* value |
|---|---|---|---|---|
| Hematologic malignancy | 2.48 (1.33-4.63) | **0.004** | 2.52 (1.30-4.88)[b] | **0.006** |
| Age, per year increase | 1.03 (1.02-1.03) | **<0.001** | 1.02 (1.02-1.03) | **<0.001** |
| Congestive heart failure | 2.39 (1.79-3.21) | **<0.001** | 1.46 (1.06-2.00) | **0.019** |
| Diabetes mellitus | 1.64 (1.40-1.93) | **<0.001** | 1.68 (1.32-2.14) | **<0.001** |
| Hypertension | 1.54 (1.32-1.79) | **<0.001** | 0.78 (0.61-0.99) | **0.042** |
| Chronic pulmonary disease[a] | 1.53 (1.25-1.87) | **<0.001** | | |
| Chronic kidney disease | 2.41 (1.88-3.09) | **<0.001** | 2.00 (1.53-2.62) | **<0.001** |
| Home medications | | | | |
| Inhaled or nasal steroid | 1.89 (1.35-2.66) | **<0.001** | 1.64 (1.14-2.36) | **0.007** |
| Oral steroid | 1.86 (1.25-2.76) | **0.002** | 1.62 (1.06-2.48) | **0.025** |

# Adaptive immunity is more than antibodies



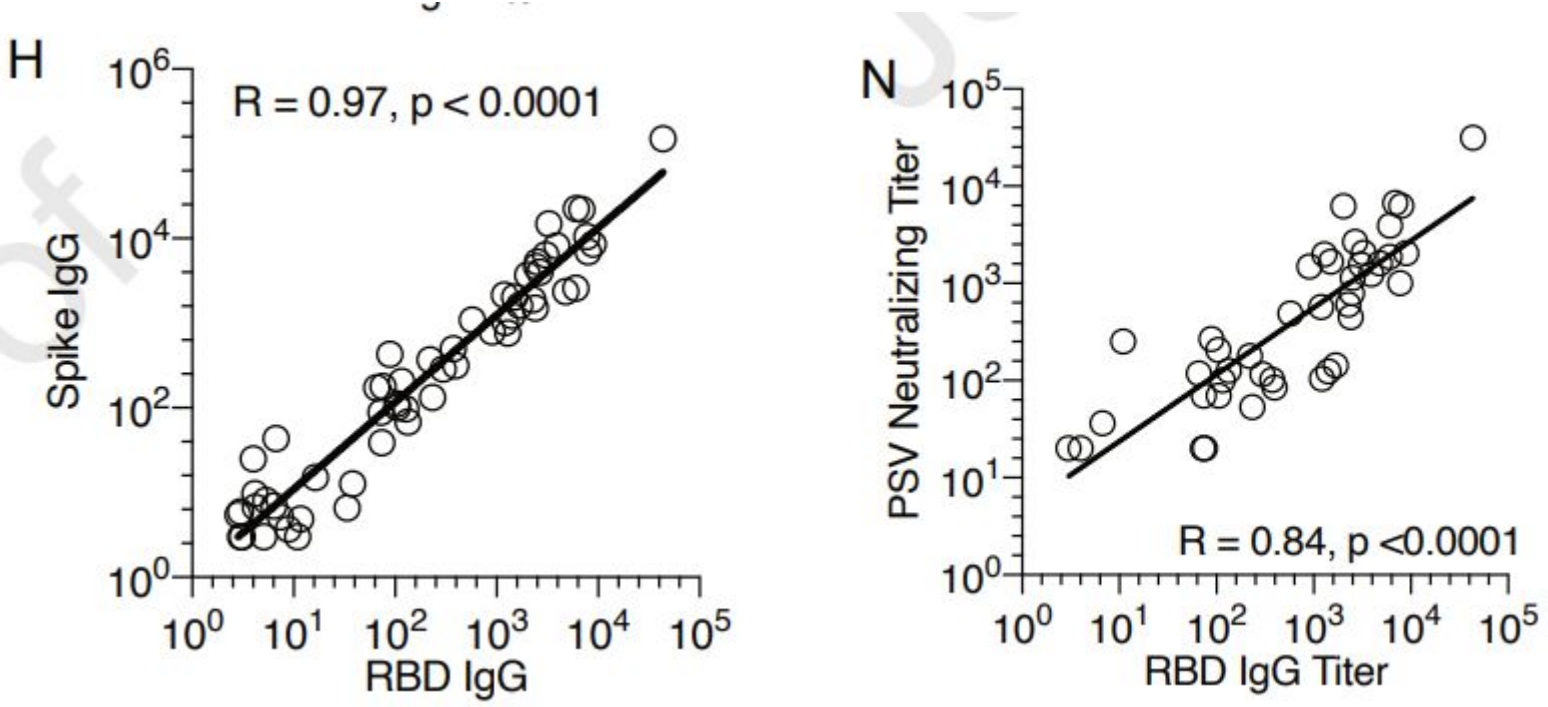

Grifoni Cell https://doi.org/10.1016/j.cell.2020.05.015

# RBD IgG and IgA present in most people with COVID-19



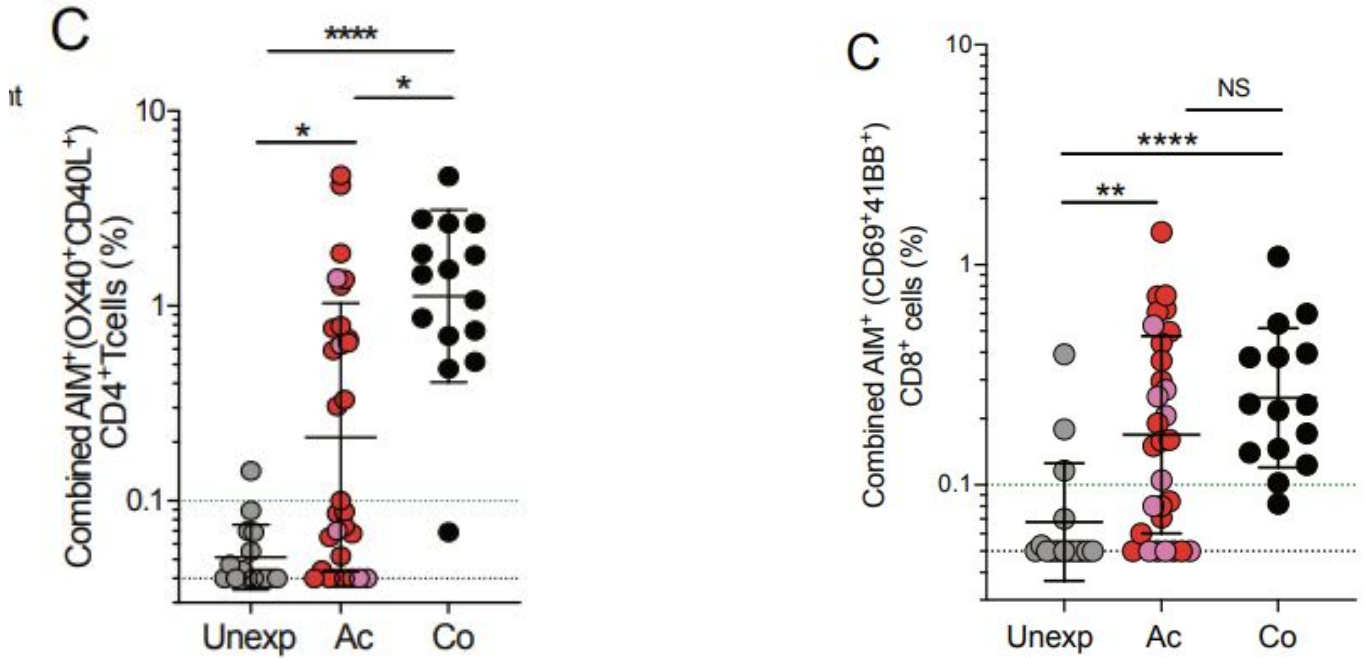

Morderbacher Cell https://doi.org/10.1016/j.cell.2020.09.038

# RBD IgG correlates with Spike IgG and Neutralizing Abs



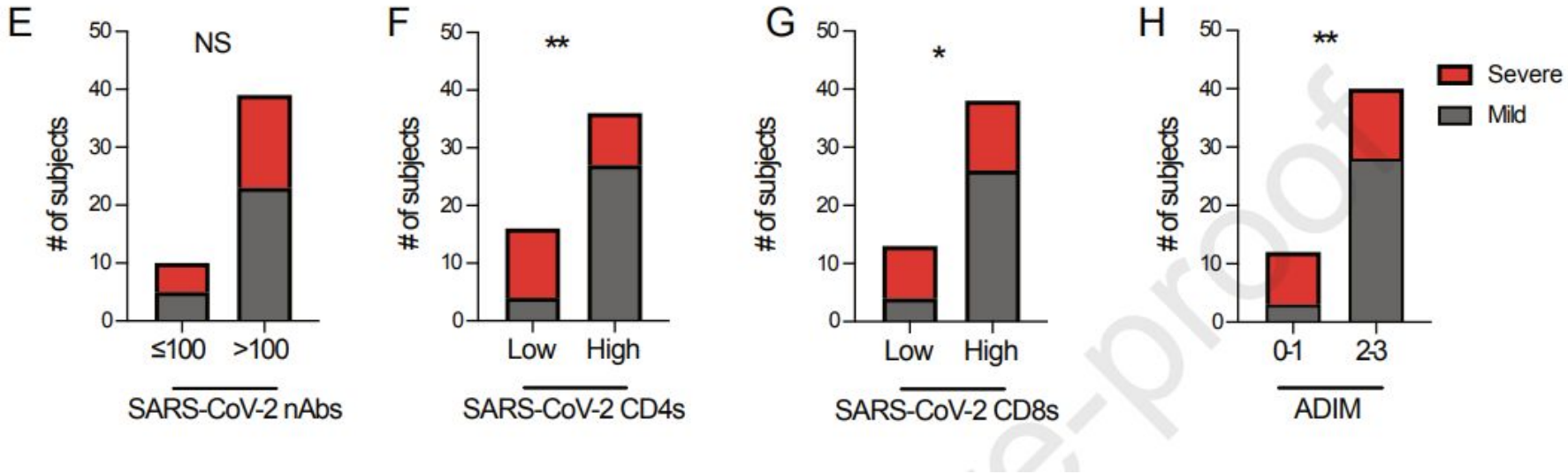

Morderbacher Cell https://doi.org/10.1016/j.cell.2020.09.038

# Specific CD4 and CD8 T cell responses found in most convalescent but fewer acute patients




Morderbacher Cell https://doi.org/10.1016/j.cell.2020.09.038

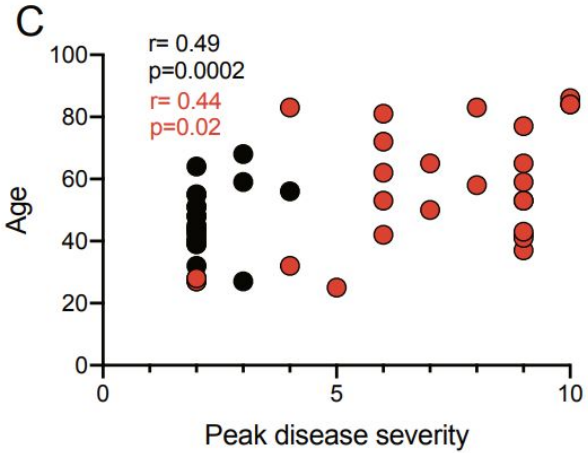
# Peak disease severity and association with adaptive immune responses

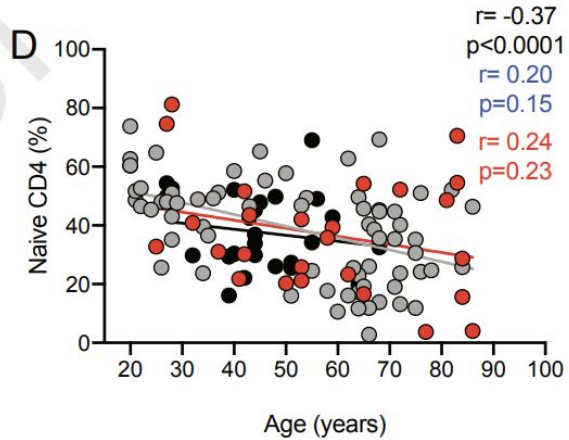


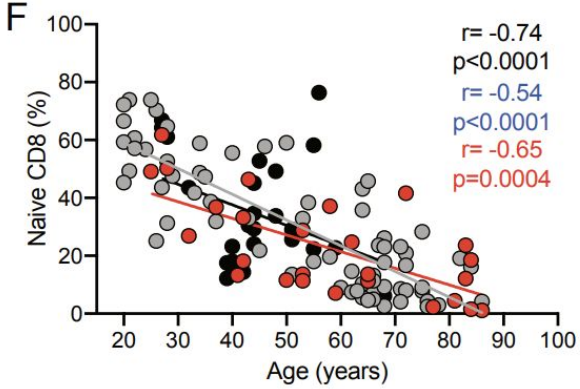


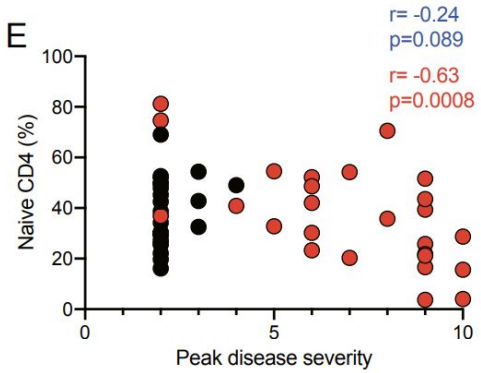

Morderbacher Cell https://doi.org/10.1016/j.cell.2020.09.038

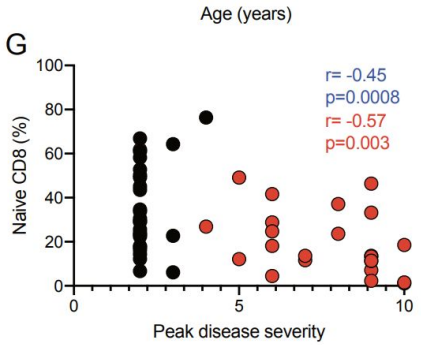
# Explaining the age dependent illness severity spectrum




Morderbacher Cell https://doi.org/10.1016/j.cell.2020.09.038

# Key Points:

A “coordinated” adaptive immune response is necessary to limit disease severity

Neutralizing antibodies are not associated with disease severity

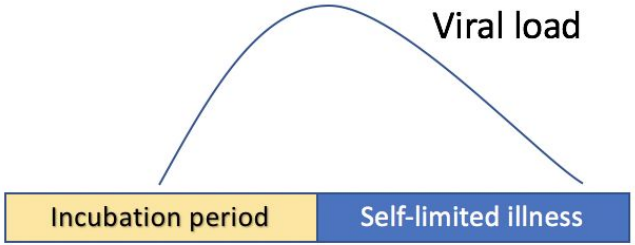
Naive T cells, particularly CD8 cells, may be needed to quickly respond to novel SARS-CoV-2 antigens to limit disease severity

Lack of naive T cells that comes with aging may explain some of age dependent severity spectrum

Limitations: relatively small study, levels of adaptive immune cells found in blood samples may not correlate with levels found in end organ tissue like the lungs

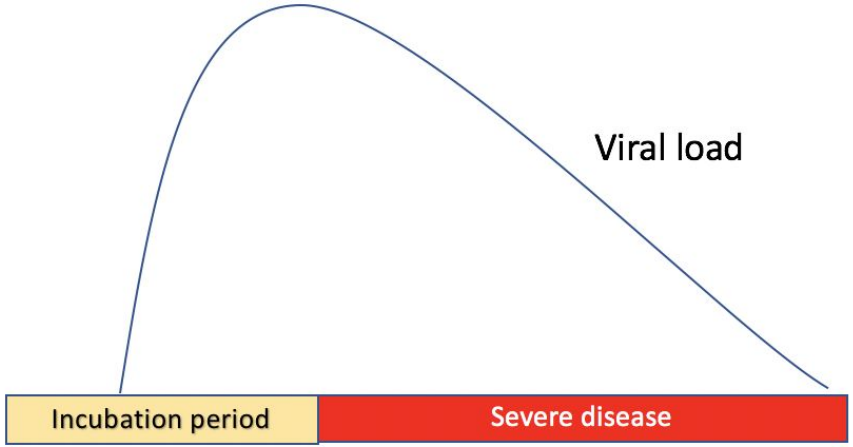
Morderbacher Cell https://doi.org/10.1016/j.cell.2020.09.038

# Proposed updated model for COVID-19 pathogenesis




✓ *SARS-CoV-2 specific CD4 cell response*
✓ *SARS-CoV-2 specific CD8 cell response*
✓ *SARS-CoV-2 specific antibody response*

*Early, coordinated, effective adaptive immune response*




✗ *SARS-CoV-2 specific CD4 cell response*
✗ *SARS-CoV-2 specific CD8 cell response*
✗ *SARS-CoV-2 specific antibody response*

*Uncoordinated, poor adaptive immune response*

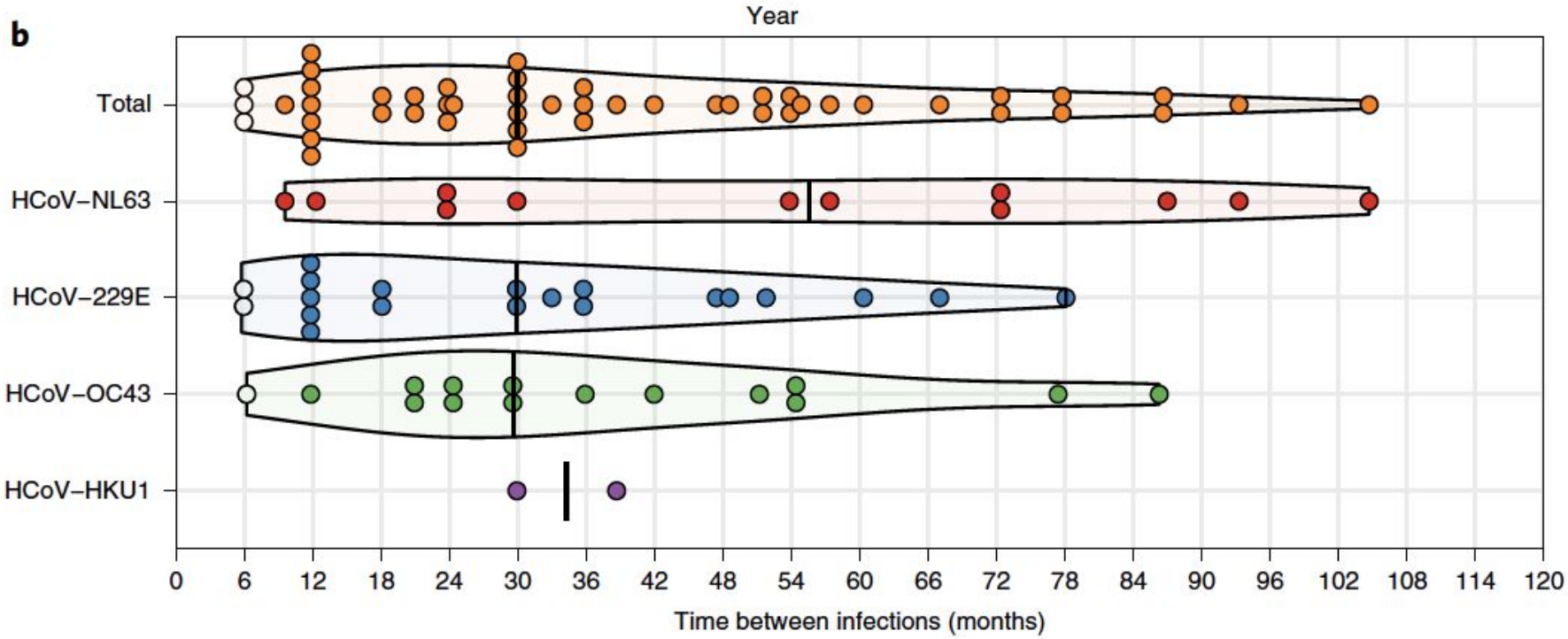
# Reinfection and the common human coronaviruses

**Table 1 | Study individuals and seasonal coronavirus infections during follow-up**

| Individual | Year | | Age | | Continuous follow-up period | | Coronavirus infections | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Start | End | Start | End | Months | Years | Total* | NL63 | 229E | OC43 | HKU1 |
| 1 | 1985 | 2017 | 32 | 64 | 265 | 22.1 | 11 | 2 | 2 | 6 | 1 |
| 2 | 1985 | 2019 | 30 | 64 | 310 | 25.9 | 11 | 4 | 3 | 1 | 3 |
| 3 | 1985 | 2020 | 29 | 64 | 340 | 28.3 | 5 | 2 | 2 | 1 | 0 |
| 4 | 1985 | 2010 | 33 | 59 | 230 | 19.2 | 17 | 1 | 12 | 4 | 0 |
| 5 | 1985 | 2010 | 27 | 53 | 232 | 19.3 | 6 | 3 | 2 | 0 | 1 |
| 6 | 1985 | 1997 | 37 | 49 | 144 | 12.0 | 3 | 1 | 1 | 1 | 0 |
| 7 | 1985 | 2003 | 32 | 49 | 138 | 11.5 | 12 | 3 | 4 | 4 | 1 |
| 8 | 1986 | 2014 | 34 | 62 | 256 | 21.3 | 8 | 1 | 5 | 2 | 0 |
| 9 | 1985 | 2010 | 40 | 75 | 342 | 28.6 | 16 | 6 | 3 | 6 | 1 |
| 10 | 1985 | 2011 | 35 | 60 | 233 | 19.4 | 12 | 2 | 4 | 5 | 1 |
| Total | | | | | 2,473 | 205.6 | 101 | 25 | 38 | 30 | 8 |

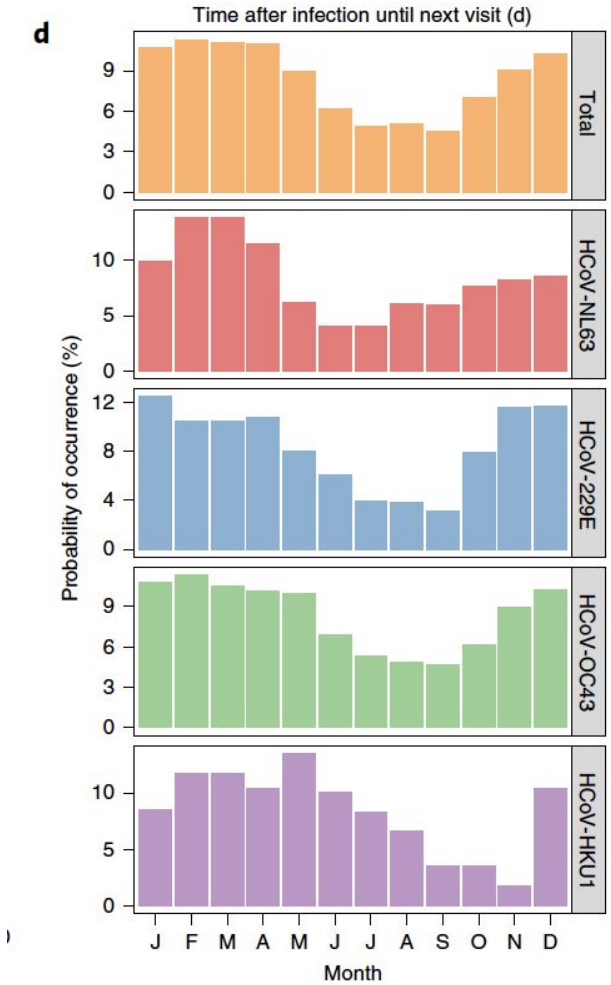
Eldridge Nature https://doi.org/10.1038/s41591-020-1083-1

# Reinfections occurred commonly starting at 12 months




Eldridge Nature https://doi.org/10.1038/s41591-020-1083-

# Seasonality




Eldridge Nature https://doi.org/10.1038/s41591-020-1083-

# SARS-CoV-2 reinfection case reports to date: more details needed

BNO News - Coronavirus : Re-infection

| CASES | DEATHS | RECOVERED | AVERAGE INTERVAL |
|---|---|---|---|
| 10 | 0 | 8 | 64 days |

| Reported | Location | Patient | Interval | Symptoms (1st case) | Symptoms (2nd case) | Recovered | Links |
|---|---|---|---|---|---|---|---|
| Sept. 15 | India | 28/F | 101 days | None | None | Yes | Details |
| Sept. 15 | India | 25/M | 100 days | None | None | Yes | Details |
| August 30 | Ecuador | 46/M | 47 days | Mild | Moderate | Yes | Details |
| August 28 | United States | 25/M | 31 days | Mild | Serious | N/A | Details |
| August 26 | Netherlands | 60s/M | Several days | Mild | Serious | Yes | Details |
| August 26 | Netherlands | 80s/M | 21 days | Mild | Mild | Yes | Details |
| August 26 | Netherlands | 60+ | 60 days (estimate) | N/A | N/A | Yes | Details |
| August 24 | Netherlands | 60+ | N/A | N/A | N/A | N/A | Details |
| August 24 | Belgium | 51/F | 93 days | Mild | Mild (less intense) | Yes | Details |
| August 24 | Hong Kong | 33/M | 123 days | Mild | None | Yes | Details |
| TOTAL | 10 | 0 | 64 days | 75% | 62% | 8 | |
| | Cases | Deaths | Average interval | Symptomatic (1st case) | Symptomatic (2nd case) | Recovered | |

https://bnonews.com/index.php/2020/08/covid-19-reinfection-tracker/

Hong Kong Case:
To CID
https://doi.org/10.1093/cid/ciaa1275

# Summary

- While evidence has pointed to healthcare setting as an important site of transmission, there is emerging evidence of the high efficacy of universal masking in reducing hospital-acquired infection
- Detailed genomic analyses indicated multiple “dead-end” introductions into the US and Europe prior to the establishment of SARS-CoV-2
- High viral loads are markers of disease severity, supporting an early antiviral approach to treatment; evidence suggests there is no true “cytokine storm” in severe COVID-19
- A robust coordinated multi-pronged adaptive immune response (not just antibodies) may be important for limiting disease severity. Age-related immune changes may help explain the age-dependent severity spectrum
- Reinfection of other common coronaviruses is common by 12 months; there are now reports of SARS-CoV-2 reinfection, but we need more details