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targeting emerging infectious diseases

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# Scientific update on COVID-19

**Updated on October 13th 2020**

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The objective of this slideshow is to answer various essential questions related to COVID-19 with the focus on:

- **EPIDEMIOLOGY**
- **VIROLOGY**
- **CLINICAL**
- **THERAPEUTIC**

Color code

EPIDEMIOLOGY VIROLOGY CLINICAL THERAPEUTIC

# EPIDEMIOLOGY



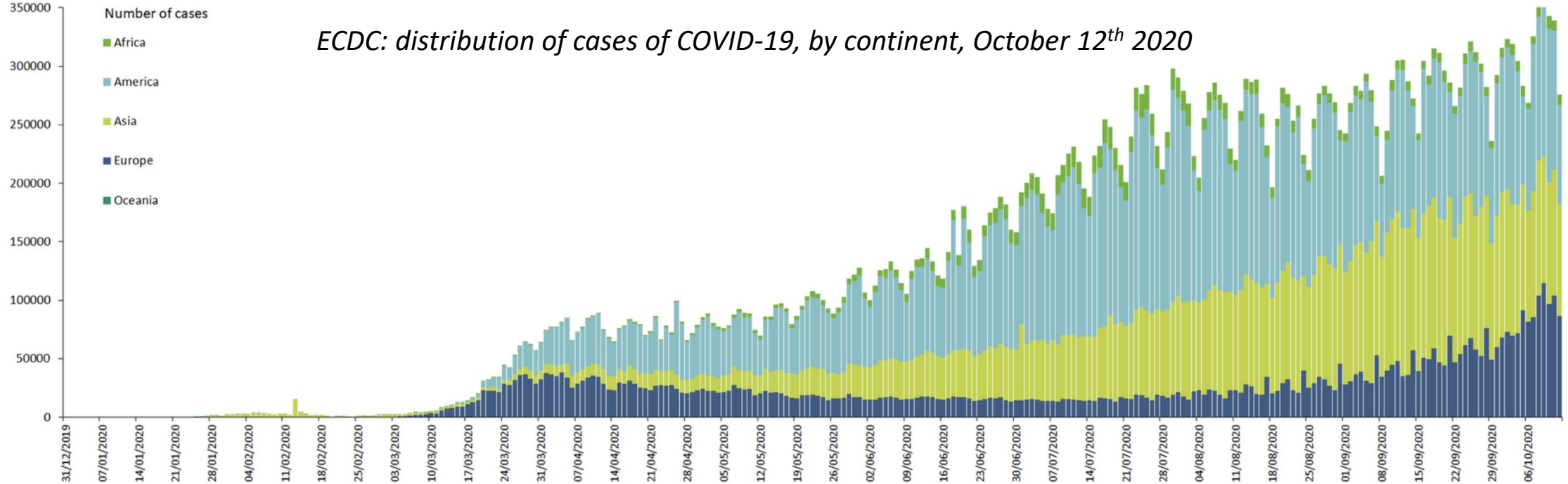
**Questions:**

- What is the situation in the World?
- What is the incubation period & $R_0$?
- What do we know about the risk of transmission & the mode of transmission?
- What is the impact of the different measures taken by countries?

# Situation update

- ***Santé publique France:*** *https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/articles/infection-au-nouveau-coronavirus-sars-cov-2-covid-19-france-et-monde*
- ***Johns Hopkins University:*** *https://reliefweb.int/report/world/coronavirus-covid-19-global-cases-johns-hopkins-csse*
- ***OMS:*** https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/
- ***ECDC :*** https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases

*ECDC: distribution of cases of COVID-19, by continent, October 12th 2020*

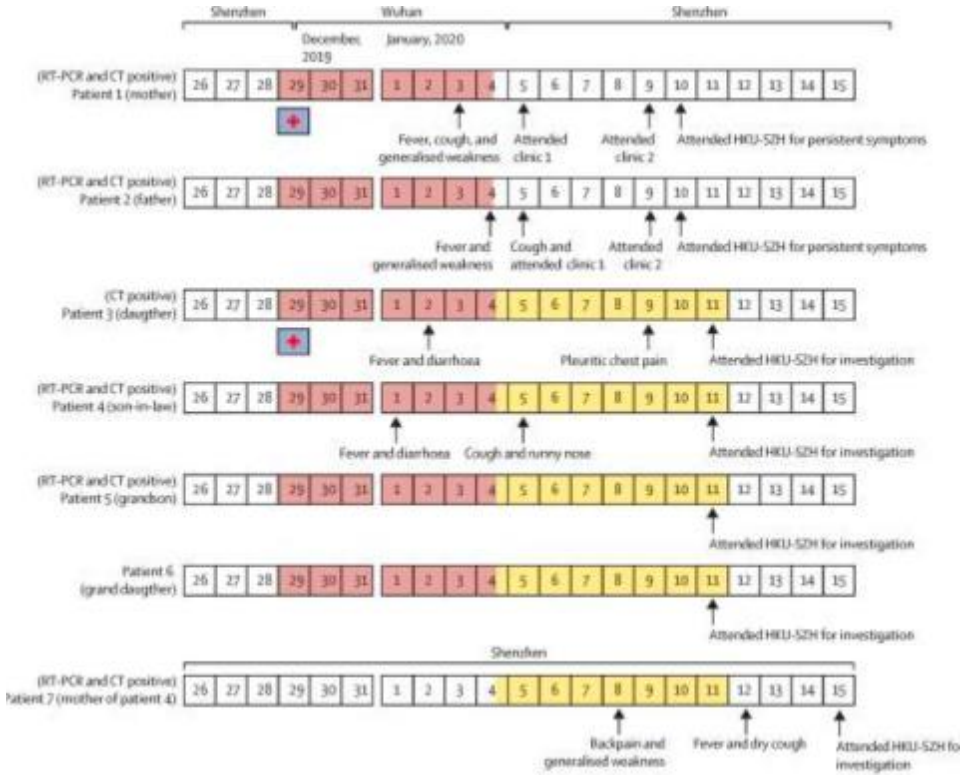



Day, month and year of reporting

# Epidemiology

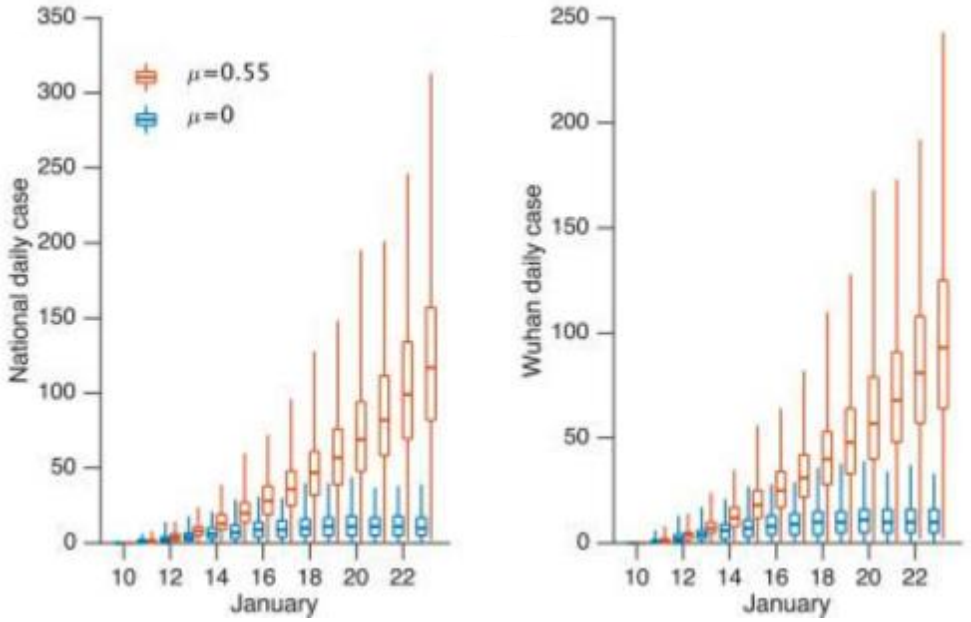


- Person to person transmission
- Contagious 2 days before symptoms : **pre-symptomatic phase**




*Chronology of symptom onset of the family cluster*

*Daily documented cases – simulation generated using some parameters*
*μ=factor applied to transmission rate due to undocumented infected persons*




- Very high rate of undocumented infection
- **Dissemination by undocumented infection** (asymptomatic, presymptomatic…)

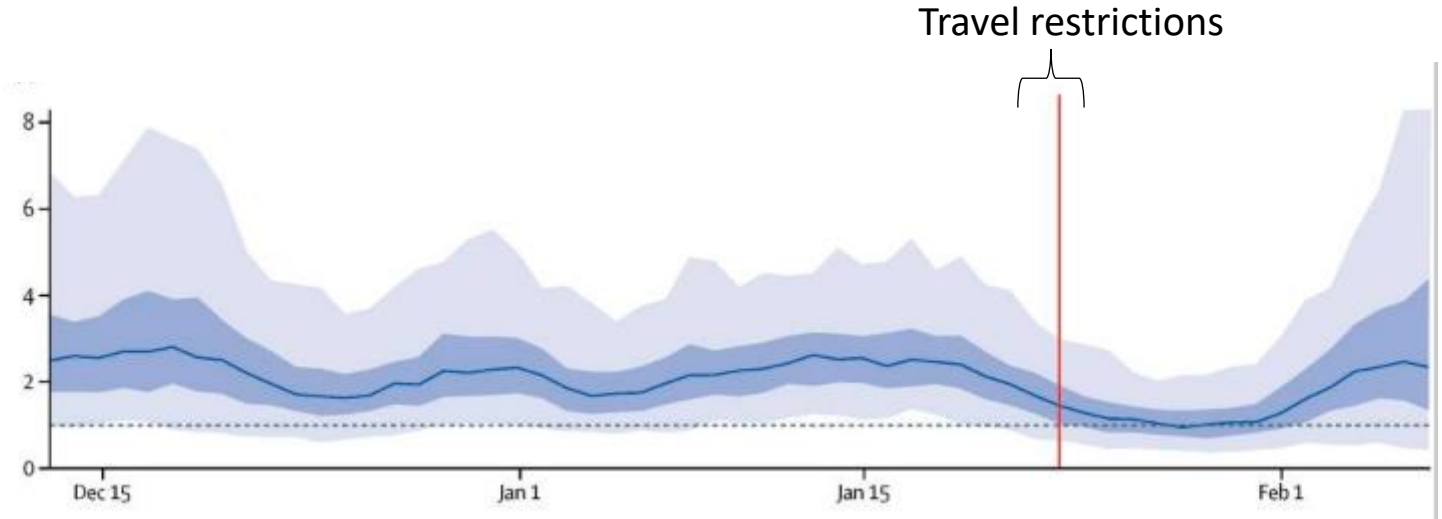
- He and colleagues estimation (slide 35): 44% ($CI_{95\%}$ [30 – 57%]) of secondary cases were infected during the index cases' presymptomatic stage

Infectiousness was estimated to decline quickly within 7 days

# Epidemiology

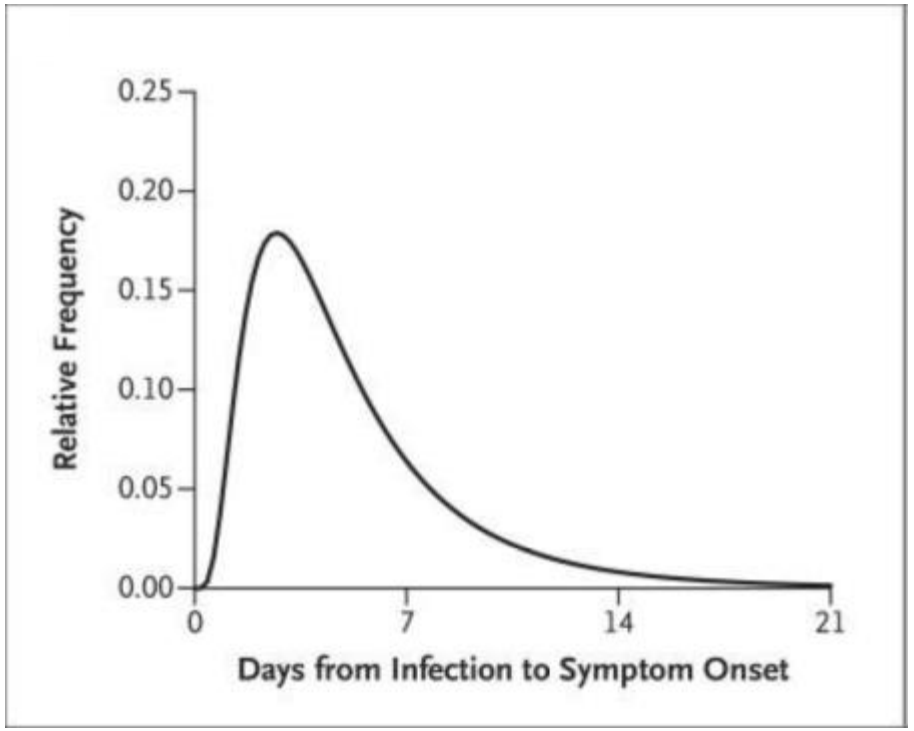
<u>At beginning & before controls measures:</u>

- Basic reproduction number **($R_0$)**: 2,2 to 6,4
- $R_0$ depends on
  - Geographic location
  - Stage of outbreak
- $R_e$ depends on
  - Control measures
- Doubling time : 2,9 to 7,3 days



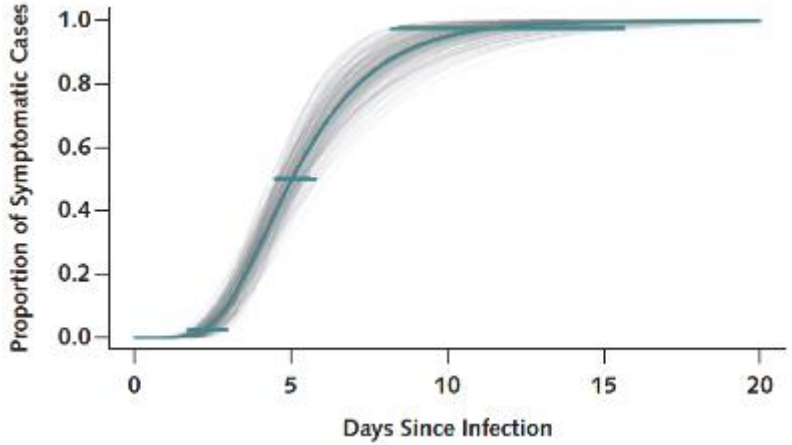

*Estimated $R_t$ over time*

- Incubation period SARS-CoV-2
  - Median: 5 days
  - 2 to 14 days

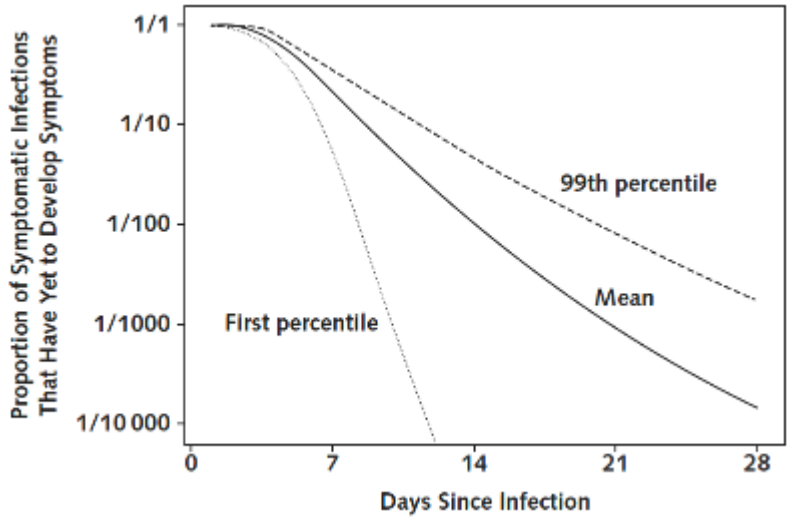


# Epidemiology

- 185 cases of confirmed COVID-19 – before Feb 24th
- 24 countries – 89% had recent history of travel to Wuhan
- Median incubation period (days) : 5,1 [4,5 – 5,8]
  - < 2,5% of infected persons will shows symptoms within 2,2 days
  - 97.5% of symptomatic patients developing symptoms within 11.5 days
- <u>Analysis specific for cases detected outside of China</u>
  - Median incubation (days): 5,5 [4,4 – 7,0]
  - 95% range spanning from 2,1 to 14,7 days




- After 14 d → we would not miss a symptomatic infection among high risk persons




*Proportion of known symptomatic SARS-CoV-2 infections that have yet to develop* symptoms by number of days since infection, using bootstrapped

- High risk = A 1-in-100 chances of developing a symptomatic infection after exposure

| Monitoring Duration | Mean Estimated Number of Undetected Symptomatic Infections per 10 000 Monitored Persons (99th Percentile) | | | |
|---|---|---|---|---|
| | Low Risk (1 in 10 000) | Medium Risk (1 in 1000) | High Risk (1 in 100) | Infected (1 in 1) |
| 7 d | 0.2 (0.4) | 2.1 (3.6) | 21.2 (36.5) | 2120.6 (3648.5) |
| 14 d | 0.0 (0.0) | 0.1 (0.5) | 1.0 (4.8) | 100.9 (481.7) |
| 21 d | 0.0 (0.0) | 0.0 (0.1) | 0.1 (0.8) | 9.5 (82.5) |
| 28 d | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.2) | 1.4 (17.8) |

Lauer SA et *al. Ann Intern Med.* May 2020

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# Distanciation measures to prevent transmission

**The effects of physical distance, face masks, and eye protection on virus transmission?**

Systematic revue (172 studies) & meta-analysis (44 comparatives studies)

16 countries & 6 continents

25 697 patients in the meta-analysis

Included COVID-19, SARS & MERS

Did not identify any randomized trials

Unadjusted, adjusted, frequentist, and bayesian meta-analyses all supported the main findings,

| | Studies and participants | Relative effect (95% CI) | Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission | | Difference (95% CI) | Certainty* | What happens (standardised GRADE terminology)[29] |
|---|---|---|---|---|---|---|---|
| | | | Comparison group | Intervention group | | | |
| Physical distance ≥1 m *vs* <1 m | Nine adjusted studies (n=7782); 29 unadjusted studies (n=10 736) | aOR 0·18 (0·09 to 0·38); unadjusted RR 0·30 (95% CI 0·20 to 0·44) | Shorter distance, 12·8% | Further distance, 2·6% (1·3 to 5·3) | −10·2% (−11·5 to −7·5) | Moderate† | A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2·02 times |
| Face mask *vs* no face mask | Ten adjusted studies (n=2647); 29 unadjusted studies (n=10 170) | aOR 0·15 (0·07 to 0·34); unadjusted RR 0·34 (95% CI 0·26 to 0·45) | No face mask, 17·4% | Face mask, 3·1% (1·5 to 6·7) | −14·3% (−15·9 to −10·7) | Low‡ | Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks§ |
| Eye protection (faceshield, goggles) *vs* no eye protection | 13 unadjusted studies (n=3713) | Unadjusted RR 0·34 (0·22 to 0·52)¶ | No eye protection, 16·0% | Eye protection, 5·5% (3·6 to 8·5) | −10·6% (−12·5 to −7·7) | Low‖ | Eye protection might result in a large reduction in virus infection |

*Population comprised people possibly exposed to individuals infected with SARS-CoV2, SARS-CoV or MERS-CoV*

Physical distancing of 1 m or more → lower transmission of viruses compared with a distance of less than 1 m
Protection was increased as distance was lengthened → **distance of 2 m might be more effective**
The use of face mask → reduction in risk of infection → **wearing face mask protects people**

**None of these interventions afforded complete protection from infection**

Chu DK et *al. Lancet.* Jun 2020

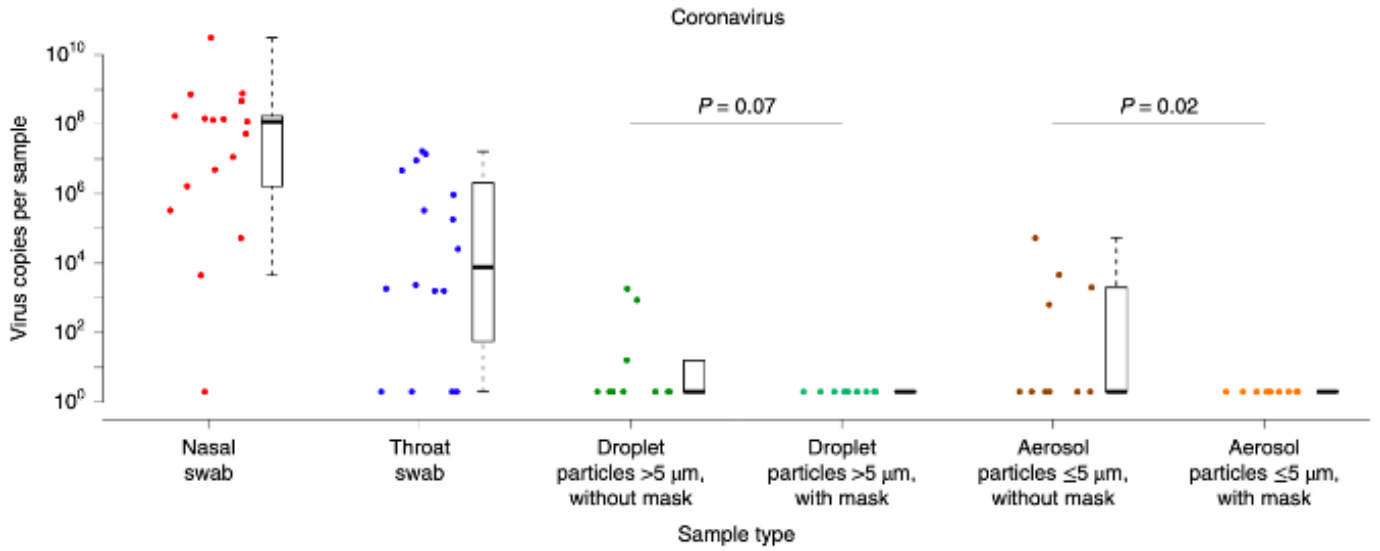
# Face masks' effectiveness

- 246 participants
  - 122 without face masks and 124 with face mask
  - Provided exhaled breath samples
- 123 were infected by
  - HCoV (17), influenza (43) and rhinovirus (54)
- Test viral shedding
  - Nasal swab, throat swab
  - Respiratory droplet sample
  - Aerosol sample
- Detection of coronavirus
  - 30% (droplets) and 40% (aerosol) without mask
  - 0 %(droplet or aerosol) with mask

→Aerosol transmission is possible

→ Face masks reduce coronavirus detection in aerosol (significantly) and respiratory droplet

→ **Face masks could prevent transmission of human coronaviruses and influenza viruses.**




**Limits**

- Human coronavirus, not SARS-CoV-2
- Large proportion of undetectable viral shedding
- Detected Coronavirus' infectivity not confirmed

Leung NHL et *al. Nature Med.* May 2020

# Projection - Transmission dynamics

Model of SARS-CoV-2 transmission

Projected that recurrent wintertime outbreaks will probably occur after the initial outbreak

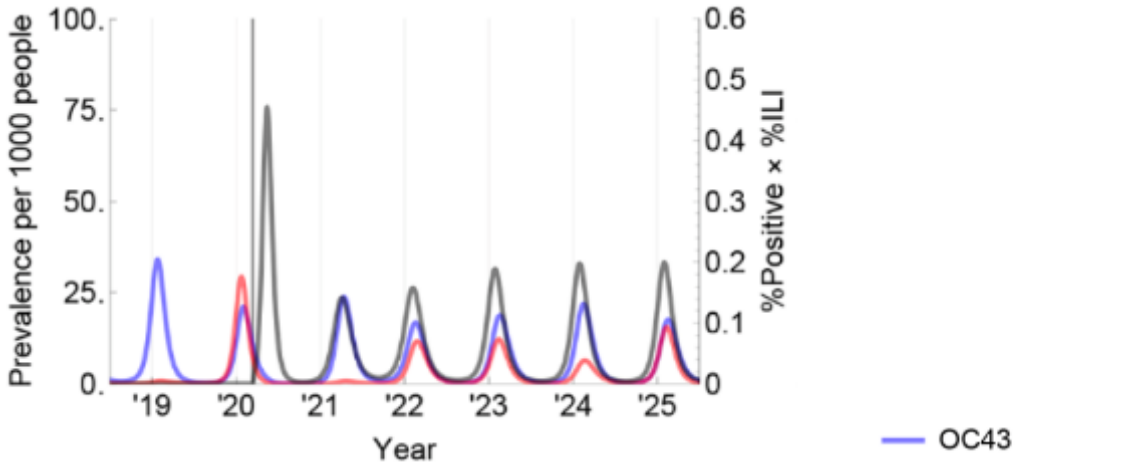
Used estimates of seasonality, immunity and cross-immunity for beta coronaviruses (OC43 & HKU1)

<u>Post-pandemic transmission dynamics will depend on:</u>

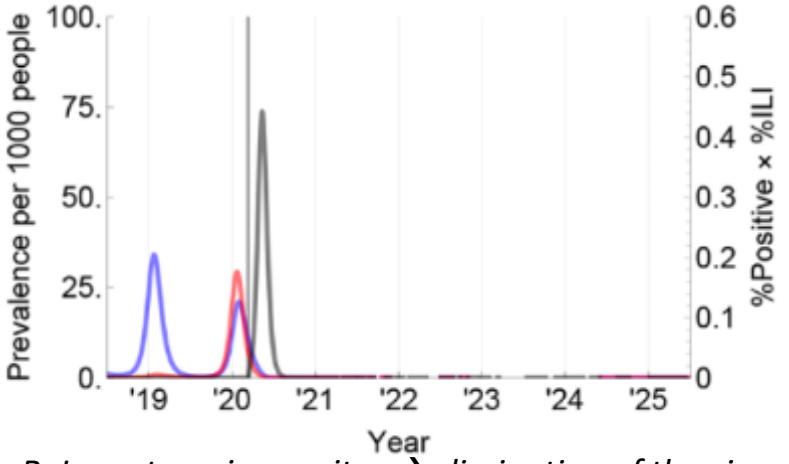
- Degree of season variation in transmission
- Duration of immunity
- Degree of cross-immunity between SARS-CoV-2 and other coronaviruses
- Intensity and timing of control measures

**Presentation of different scenarios**

*Invasion scenario for SARS-CoV-2 in temperate regions*




*A: Short duration of immunity → annual outbreak*

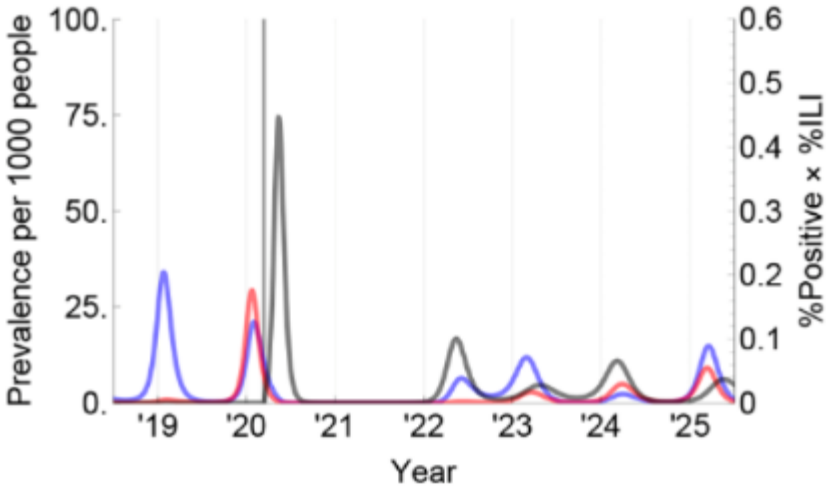


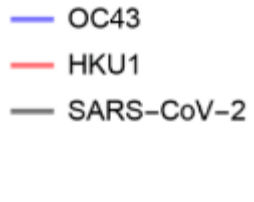

*B: Long-term immunity → elimination of the virus*

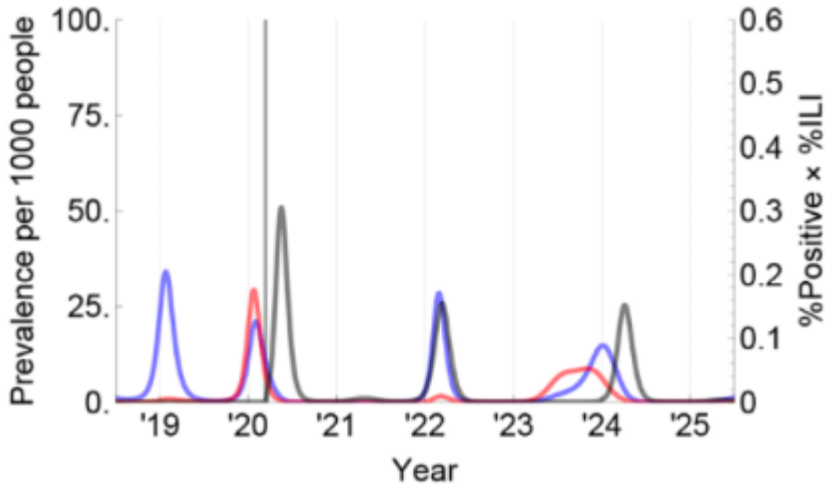
Kissler SM et *al. Science.* Apr 2020

# Projection - Transmission dynamics

*Invasion scenario for SARS-CoV-2 in temperate regions*




*C: Longer-term immunity → biennial outbreaks*
*Possibly with smaller outbreak*

*D: Higher seasonal variation in transmission → reduce the peak size of the invasion wave*
***BUT** more severe wintertime outbreaks thereafter compare with C*

<u>Total incidence of COVID-19 illness over next years will depend on</u>

- Regular circulation after the initial pandemic wave
- Duration of immunity that SARS-CoV-2 infection imparts
- Social distancing strategies
- Effective therapeutic

# Community and close contact exposures

Comparison between (random sampling 1:2):

- Exposure reported by case-patients: adults with laboratory confirmed COVID-19 (= 154)
- Exposure reported by control-participants (= 160)

All were symptomatic

Identified and contact 14-23 days after results of SARS CoV2 testing.

Interview by telephone:

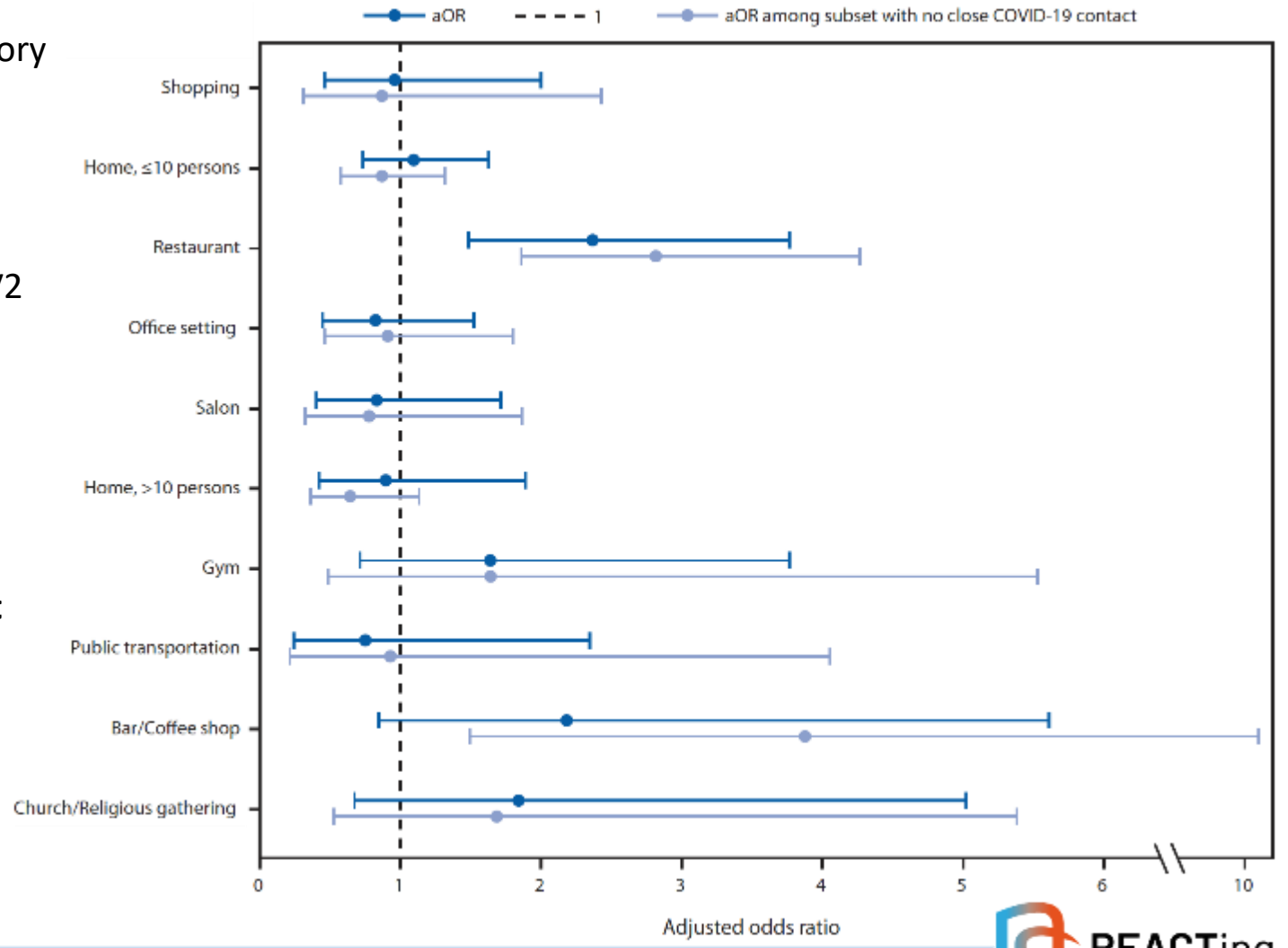
- Mask-wearing behavior, community activities <14 days before symptom onset (shopping, dining at restaurant, salon, gym, coffee/bar…) …

**Case-patients were more likely to have reported dining at restaurant (aOR: 2,4, $IC_{95\%}$: 1,5 – 3,8).**

Analysis restricted to 225 participants:

- Dining at restaurant (aOR: 2,8, $CI_{95\%}$: 1,9 – 4,3)
- Going bar/coffee shop (aOR: 3,9, $CI_{95\%}$: 1,5 – 10,1)

*Adjusted odds ratio (aOR) and 95% confidence intervals for community exposures*




Fisher KA et *al. MMWR.* Sep 2020

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# Community and close contact exposures

Most close contact exposures were to family members

Continued assessment of various types of activities and exposures as communities, schools, and workplaces reopen is important

Efforts to reduce possible exposures at location that offer on-site eating and drinking options should be considered

**Limits**:

- Ratio 1:2 could not be reached → unmatched analysis was performed
- Interview on behaviors one month before → memorization bias
- Participants were aware of their SARS-CoV-2 test results → could influence their responses
- At restaurant: not distinguish between outdoor and indoor
- In coffee shop/bar: not distinguish between venues or service delivery method
- Distanciation measures could not be accounted for restaurant & bar → extrapolate to other countries?
- No explanation about the result difference between dining at restaurant and going to coffee/bar in the full analysis?

# COVID-19 & social and leisure activities

Description study of the outbreak in Spain

Transmission declined in early May 2020

Cases' number increased during June and mild July:

- Mild June up to August 2nd: 673 COVID-19 outbreak = 8300 persons
- 76% were small outbreak (<10 cases)
- 2% had more than 100 cases

Social setting = 35% of all active outbreaks

- Family gathering or private party
- Leisure facility

Occupational setting = 20% of all active outbreaks

- Agriculture seasonal worker

| Setting | | Total | | | | Active | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Oubreaks | | Cases | | Oubreaks | | Cases | |
| | | N | % | N | % | N | % | N | % |
| Healthcare facility | | 20 | 3.0 | 274 | 3.3 | 17 | 3.1 | 219 | 3.5 |
| Long-term care facility | | 59 | 8.8 | 829 | 9.9 | 39 | 7.1 | 376 | 6.1 |
| Vulnerable social group | | 44 | 6.5 | 576 | 6.9 | 32 | 5.8 | 337 | 5.4 |
| Family- different households | | 65 | 9.7 | 406 | 4.8 | 52 | 9.4 | 315 | 5.1 |
| Occupational | Total | 146 | 21.7 | 2,331 | 27.8 | 110 | 20.0 | 1,269 | 20.4 |
| | Slaughterhouse/meat plant | 19 | NA | 767 | NA | 12 | NA | 365 | NA |
| | Agriculture seasonal worker/fruit-vegetable company | 45 | NA | 1,022 | NA | 31 | NA | 500 | NA |
| | Other/not specified | 82 | NA | 542 | NA | 67 | NA | 404 | NA |
| Social | Total | 206 | 30.6 | 2,627 | 31.3 | 193 | 35.0 | 2,546 | 41.0 |
| | Organised event/public space | 31 | NA | 349 | NA | 29 | NA | 324 | NA |
| | Family/friends reunion or private party | 120 | NA | 900 | NA | 112 | NA | 854 | NA |
| | Leisure facility (restaurant, bar, club…) | 35 | NA | 1,234 | NA | 34 | NA | 1,231 | NA |
| | Other/not specified | 20 | NA | 144 | NA | 18 | NA | 137 | NA |
| Mixed | | 111 | 16.5 | 1,218 | 14.5 | 92 | 16.7 | 1,050 | 16.9 |
| Other | | 22 | 3.3 | 129 | 1.5 | 16 | 2.9 | 96 | 1.5 |
| Total | | 673 | 100 | 8,390 | 100 | 551 | 100 | 6,208 | 100 |

<u>Two main settings to target efforts</u>:

- Social gatherings
- Workers in vulnerable situations

New cases and cumulative incidence are currently increasing in all regions

# Infectiousness of children

A nationwide COVID-19 contact tracing program in South Korea

Index patient were eligible if they identified ≥ 1 contact.

Compared the difference in detected cases between household and nonhousehold contacts across the stratified age groups.

| | Household | |
|---|---|---|
| Index patient age, y | No. contacts positive/ no. contacts traced | % Positive (95% CI) |
| 0–9 | 3/57 | 5.3 (1.3–13.7) |
| 10–19 | 43/231 | 18.6 (14.0–24.0) |
| 20–29 | 240/3,417 | 7.0 (6.2–7.9) |
| 30–39 | 143/1,229 | 11.6 (9.9–13.5) |
| 40–49 | 206/1,749 | 11.8 (10.3–13.4) |
| 50–59 | 300/2,045 | 14.7 (13.2–16.3) |
| 60–69 | 177/1,039 | 17.0 (14.8–19.4) |
| 70–79 | 86/477 | 18.0 (14.8–21.7) |
| ≥80 | 50/348 | 14.4 (11.0–18.4) |
| Total | 1,248/10,592 | 11.8 (11.2–12.4) |

*Rates of coronavirus disease among household*

59 073 contacts of 5 706 COVID-19 index patients:

- 10 592 household contacts → **11,8% ($CI_{95\%}$ [11,2% - 12,4%]) had COVID-19**
  - with an index patient 10–19 years, 18.6% ($CI_{95\%}$ [14.0%–24.0%]) of contacts had COVID-19
- 48 481 nonhousehold contacts → 1,9% ($CI_{95\%}$ [1,8% - 2,0%]) had COVID-19

→ Higher secondary attack rate among household than non household contacts
→Highest COVID-19 rate for household contacts of school-aged children (10-19y)

**Limits**:

- Underestimation of the number of cases,
- Exposure outside the household,
- Difference of testing policy between household and nonhousehold contacts,

→ **Transmission potential in both children and adolescents,**
→ **Possibly more effective transmission in adolescents than in adults.**

Park YJ. *Emerg Infect Dis.* Oct 2020

# Risk of COVID-19: health-care workers & general community

Prospective – observational cohort study (UK & USA)
Data from the COVID Symptom Study smartphone application:

- Baseline demographic info
- Daily info on symptoms
- COVID-19 testing

2 135 190 participants, whom 99 795 front-line health-care workers

Primary outcome: positive COVID-19 test (self report)

→ **Recorded 5 545 positive COVID-19 test** over 34 435 272 person-days
→ Testing ratio (health care workers vs general community):
  → UK: ratio 5,5 [1,1 % vs 0,2%]
  → USA: ratio 3,7 [4,1% vs 1,1%]

| | Event/person-days | Incidence (30-day) | Multivariate-adjusted hazard ratio (95% CI) | Inverse probability-weighted hazard ratio (95% CI) |
|---|---|---|---|---|
| **Overall (primary analysis)** | | | | |
| General community | 3623/32 980 571 | 0·33% | 1 (ref) | 1 (ref) |
| Front-line health-care worker | 1922/1 454 701 | 3·96% | 11·61 (10·93–12·33) | 3·40 (3·37–3·43) |

**Front-line health-care workers positive test risk increased 12 fold (HRa: 11,61)**.

The difference is not related to testing eligibility
→ *(HR model with inverse probability weighting for predictors of testing)*

Compared with the general community, health-care workers initially free of symptoms had an increase risk of predicted COVID-19 (HRa: 2,05) which was higher in the UK than in the USA (2,09 vs 1,31; $p$<0,0001)

# Risk of COVID-19: health-care workers & general community

**POST-HOC ANALYSIS**

| | Adequate PPE | Reused PPE | Inadequate PPE |
|---|---|---|---|
| **Overall** | | | |
| Event/person-days | 592/332 901 | 146/80 728 | 157/60 916 |
| Unadjusted hazard ratio (95% CI) | 1 (ref) | 1·46 (1·21–1·76) | 1·32 (1·10–1·57) |
| Multivariate-adjusted hazard ratio (95% CI) | 1 (ref) | 1·46 (1·21–1·76) | 1·31 (1·10–1·56) |
| **No exposure to patients with COVID-19** | | | |
| Event/person-days | 186/227 654 | 19/37 599 | 48/35 159 |
| Unadjusted hazard ratio (95% CI) | 1 (ref) | 0·96 (0·60–1·55) | 1·53 (1·11–2·11) |
| Multivariate-adjusted hazard ratio (95% CI) | 1 (ref) | 0·95 (0·59–1·54) | 1·52 (1·10–2·09) |
| **Exposure to patients with suspected COVID-19** | | | |
| Event/person-days | 126/54 676 | 36/19 378 | 26/14 083 |
| Unadjusted hazard ratio (95% CI) | 2·40 (1·91–3·02) | 3·23 (2·24–4·66) | 1·87 (1·24–2·83) |
| Multivariate-adjusted hazard ratio (95% CI) | 2·39 (1·90–3·00) | 3·20 (2·22–4·61) | 1·83 (1·21–2·78) |
| **Exposure to patients with documented COVID-19** | | | |
| Event/person-days | 280/50 571 | 91/23 751 | 83/11 675 |
| Unadjusted hazard ratio (95% CI) | 4·93 (4·07–5·97) | 5·12 (3·94–6·64) | 5·95 (4·57–7·76) |
| Multivariate-adjusted hazard ratio (95% CI) | 4·83 (3·99–5·85) | 5·06 (3·90–6·57) | 5·91 (4·53–7·71) |

Health-care workers with inadequate or reused PPE had an increased risk for COVID-19 after multivariable adjustment

Sufficient availability of PPE, quality of PPE, or both reduce the risk of COVID-19.

PPE reuse → self-contamination during repeated application

**Increased risk for SARS-CoV-2 infection among health-care workers compared with the general community.**

Adequate allocation of PPE is important
Need to ensure proper use of PPE and adherence to other infection control measures.

**Limits**:

- Details for some exposures were shortened (eg, type of PPE)
- Self-report (risk factor & primary outcome)
- Selection bias (not a random sampling)



*PPE= Personal Protective Equipment*

Nguyen LH et *al. Lancet Public Health.* Jul 2020

# Real-world network – COVID-19 control strategies

- Non-pharmaceutical interventions are central to reducing SARS-CoV-2 transmission
- Epidemic model that simulates COVID-19 outbreaks across a real-work network
  - Assess the impact of a range of testing and contact tracing strategies
  - Simulate physical distancing strategies
  - Quantify interaction among physical distancing, contact tracing & testing affects outbreak dynamics
- Uses a publicly dataset on human social interactions

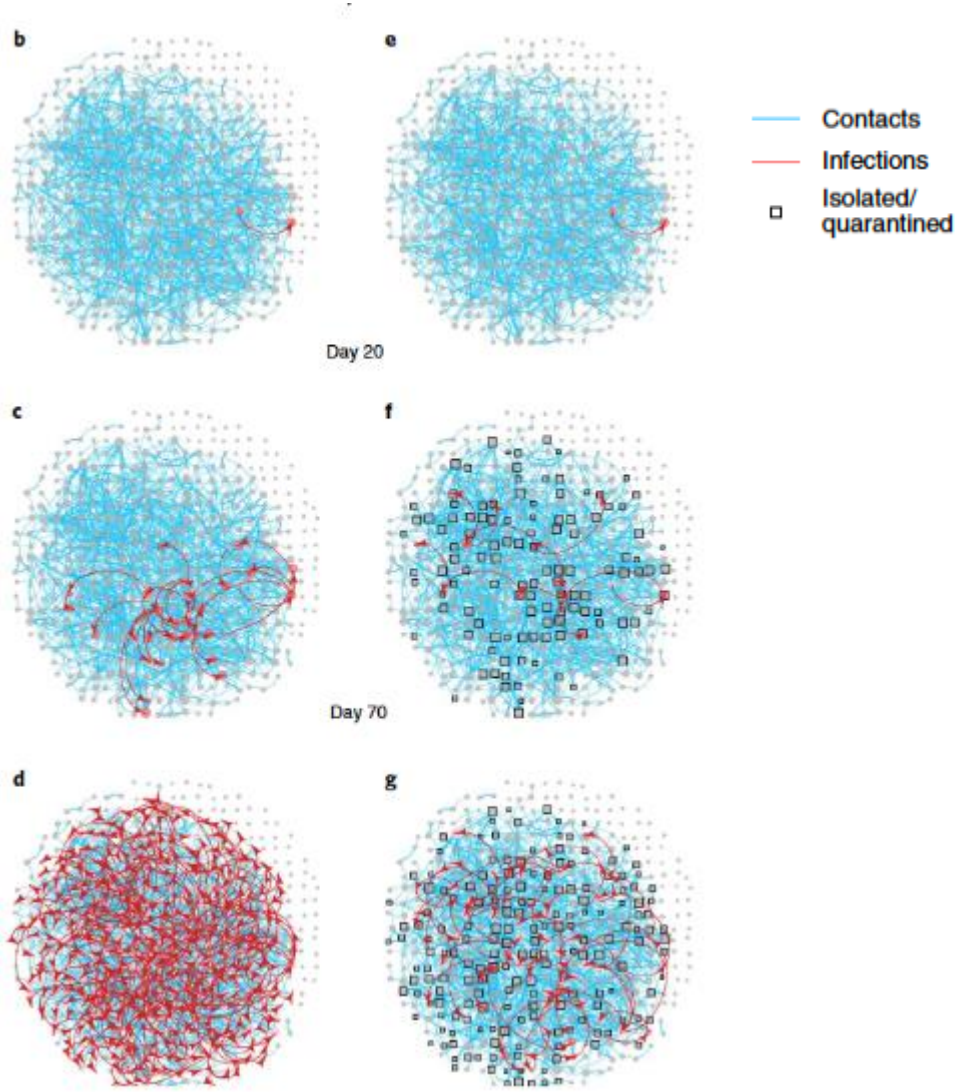


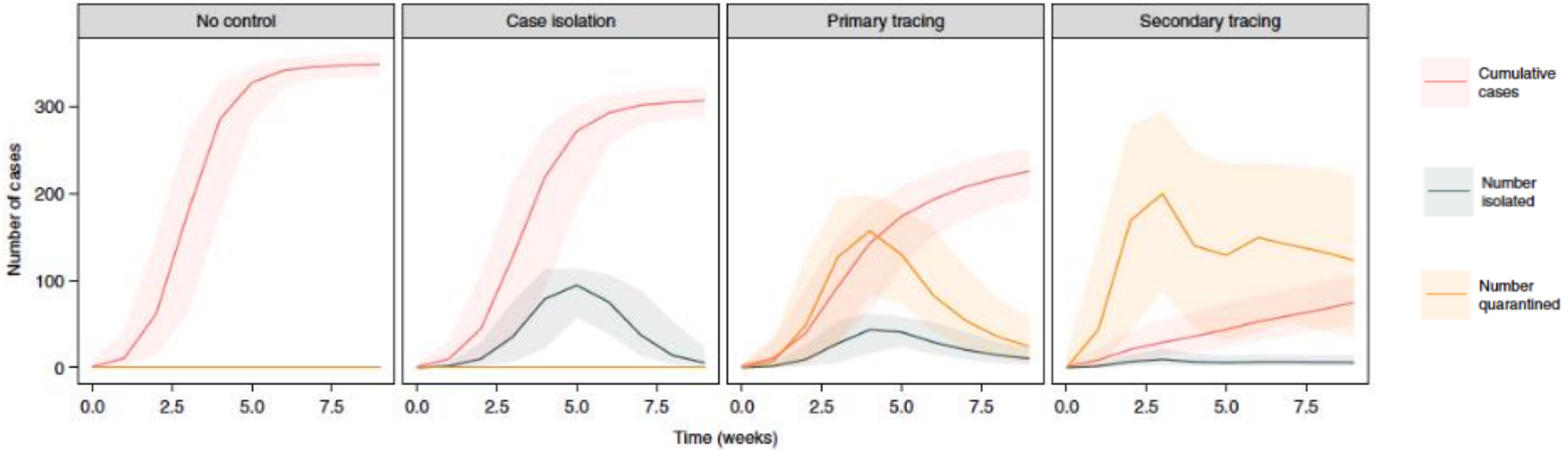

***Illustration of the Haslemere network with epidemic simulation predictions***.
*b–d: Progression of the COVID-19 epidemic under the no-intervention*
*e-g: under secondary contact tracing scenarios.*

Firth JA et *al. Nature Med.* Aug 2020

# Real-world network – COVID-19 control strategies

- From a single infected individual:
  - Uncontrolled outbreak: 75% of the population infected 70 days after the first simulated infection
  - Case isolation: 66% of the population infected
  - Primary tracing: 48% infected
  - Secondary contact tracing: 16% infected after 70 days

Very high proportion of quarantined individuals




***Epidemic model predictions of outbreak size & number of people isolated or quarantined***

*Cumulative number of cases, number of people isolated and number of people quarantined*

Firth JA et *al. Nature Med.* Aug 2020

# Real-world network – COVID-19 control strategies

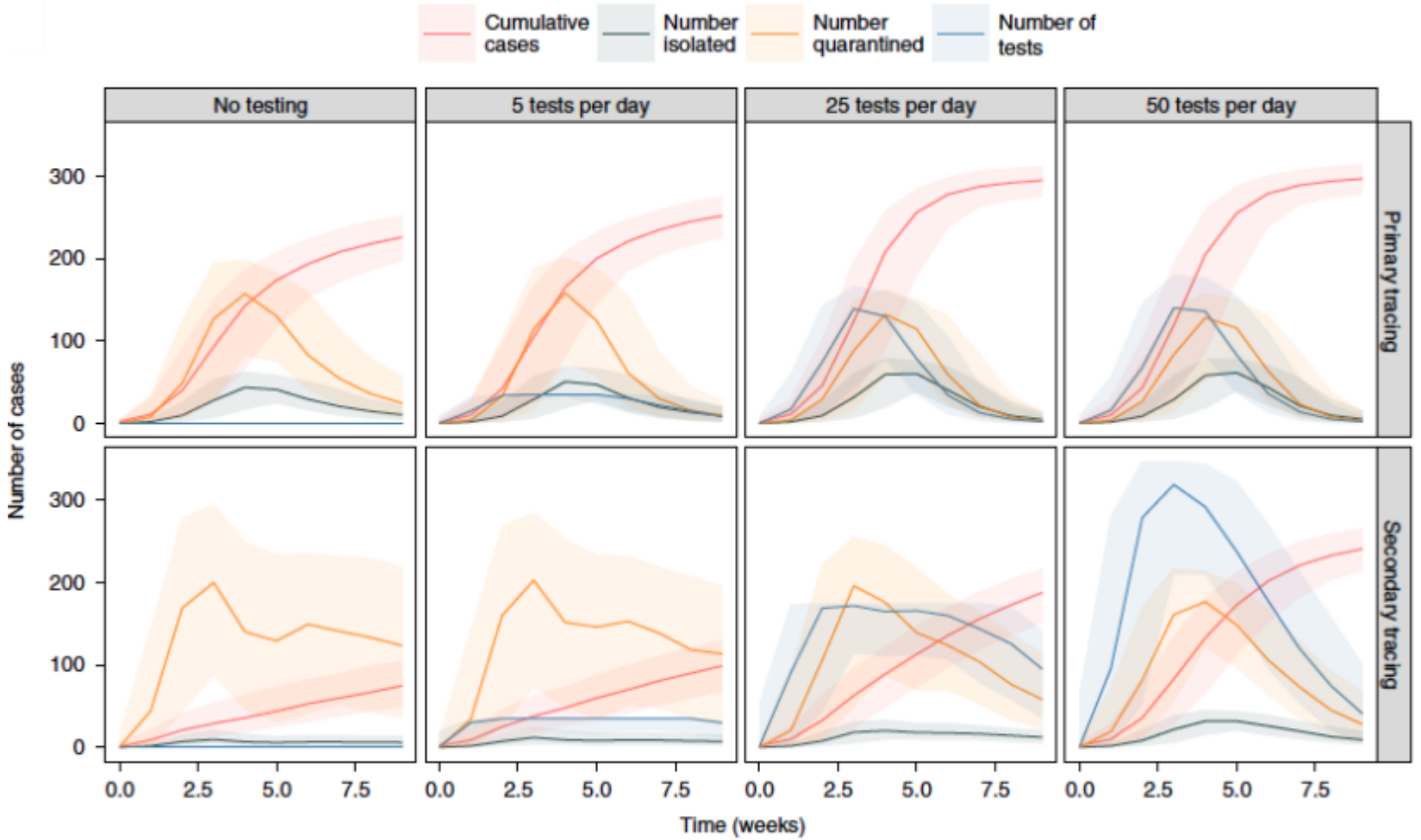
- Increasing the testing capacity → increases in outbreak size, especially under secondary contact tracing

- Number of quarantined individuals can be reduced through mass testing

**Contact tracing & quarantine strategy:**

→ Might be more effective than « local lockdown » strategy when contact rates are high

→ Would be most efficient when combined with other control measures such as physical distancing

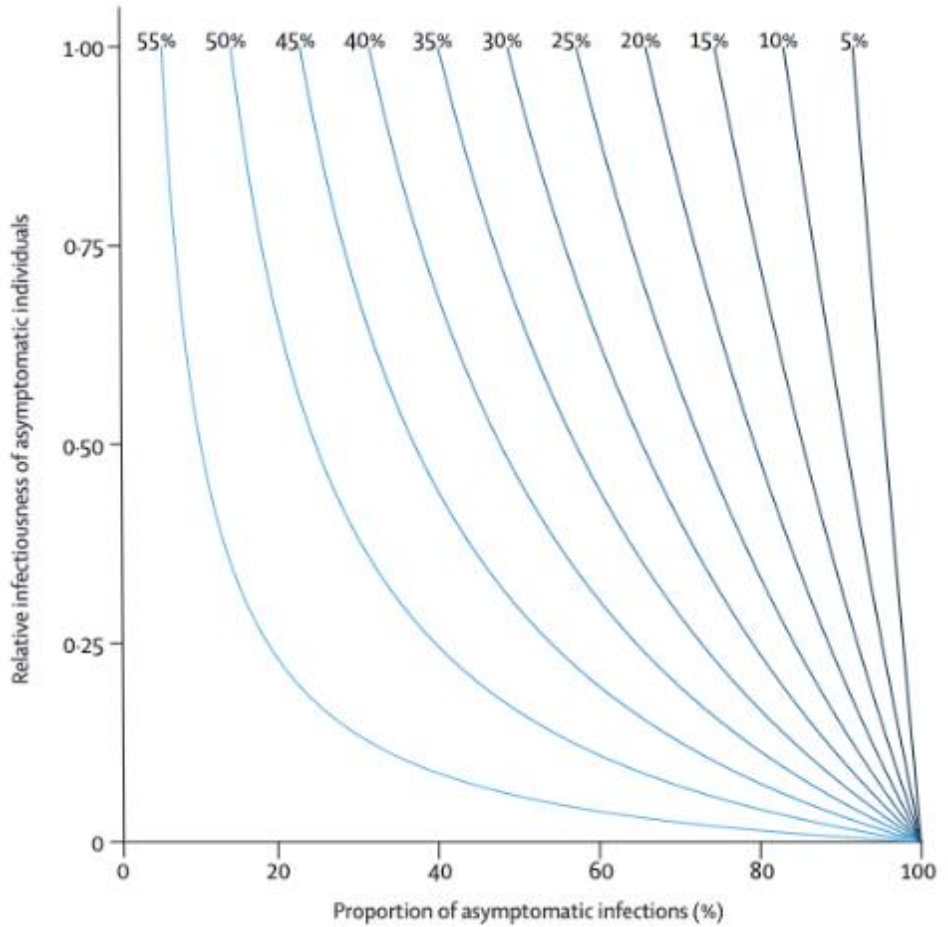



***Epidemic model predictions of how testing affect outbreak and qurantine dynamics***

Firth JA et *al. Nature Med.* Aug 2020

# Testing strategies for COVID-19 control

- Mathematical model of SARS-CoV-2 transmission based on:
  - Infectiousness: proportion of infection that are asymptomatic and their infectiousness
  - PCR test sensitivity over time since infection
- Evaluate
  - The impact of self-isolation following either a positive test result or symptom onset
  - The impact of quarantine of contacts of laboratory confirmed cases
- Percentage of reduction in *R* = expected effectiveness of different testing strategies
- Based on literature: 33% of infections are asymptomatic which have a relative infectiousness off about 50%
- If self-isolation was 100% effective + all individuals with symptoms compatible with COVID-19 self-isolated → reduction in *R* of 47%; $CI_{95\%}$ [32 – 55]
  - Play an important role in prevention of SARS-CoV-2 transmission
  - No single strategy will reduce *R* below 1

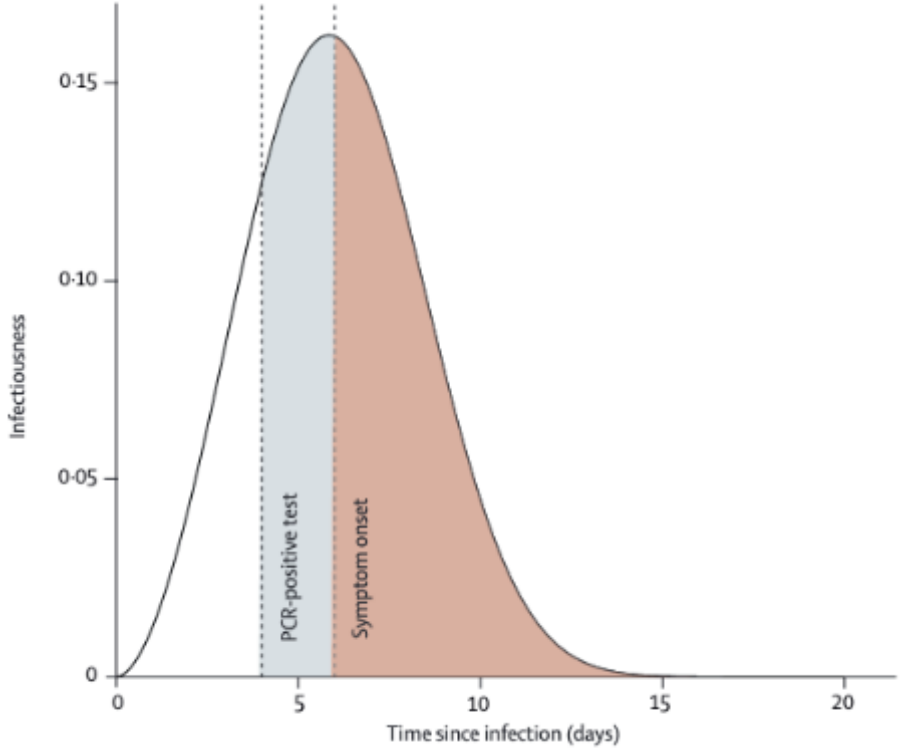



*Percentage of reduction in R by self-isolation following onset of symptoms as a function of the proportion of infections that are asymptomatic*

Grassly N C et *al. Lancet Infect Dis.* Aug 2020

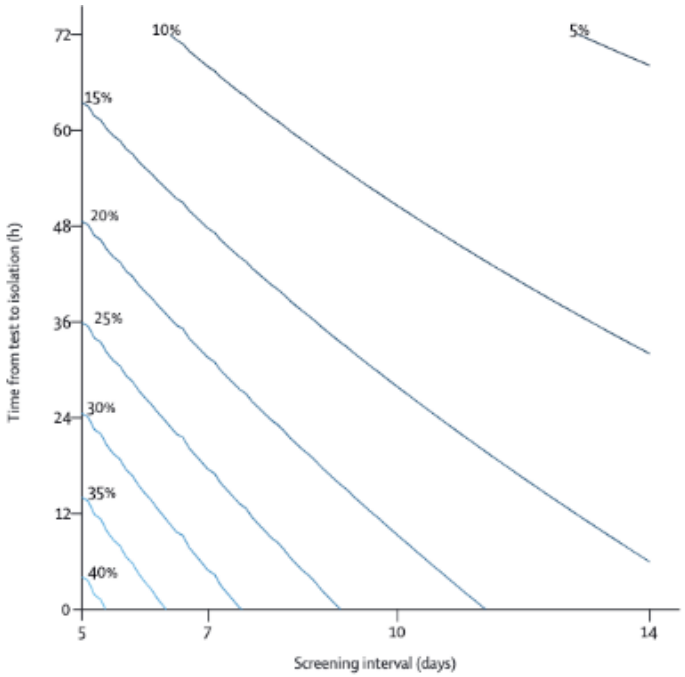
# Testing strategies for COVID-19 control

- Self-isolation following onset symptoms of COVID-19: reduction of their contribution to SARS-CoV-2 transmission




*Detection of presymptomatic SARS-CoV-2 infection and subsequent reduction in transmission through self-isolation after a positive PCR test*

- PCR testing of symptomatic individuals → reduces the number of individuals needing self-isolate BUT would reduce the effectiveness of self-isolation ( false negative)
- Regular PCR testing, irrespective of symptoms, could reduce transmission
  - Depends on the frequency of testing – timeliness of results – sensitivity of the test




*Additional percentage reduction in the R by a policy of repeated PCR testing*

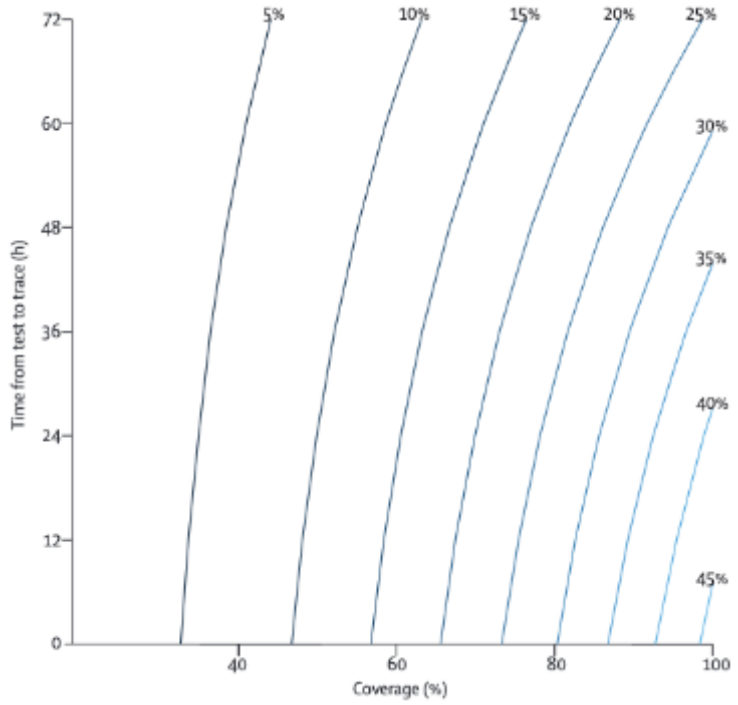
Grassly N C et *al. Lancet Infect Dis.* Aug 2020

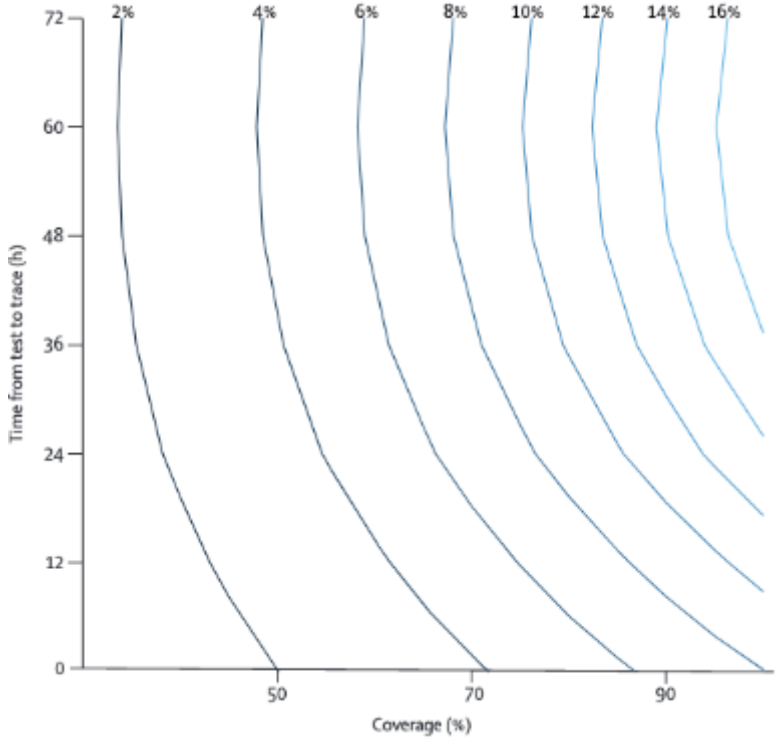
# Testing strategies for COVID-19 control

- Test-and-trace strategy: Isolating the contact of symptomatic SARS-CoV-2 positive individuals
  - Dependent on:
    - Proportion of symptomatic who are tested
    - Success of tracing their contact
    - Timeless of obtaining test results & identifying & quarantine them

- Test-trace-test strategy: testing contact & only those who tested positive put into isolation
  - Effectiveness is lower than a test-trace strategy
  - High probability of false negative

*Test-and-trace strategies*




*Test-trace-test strategies*

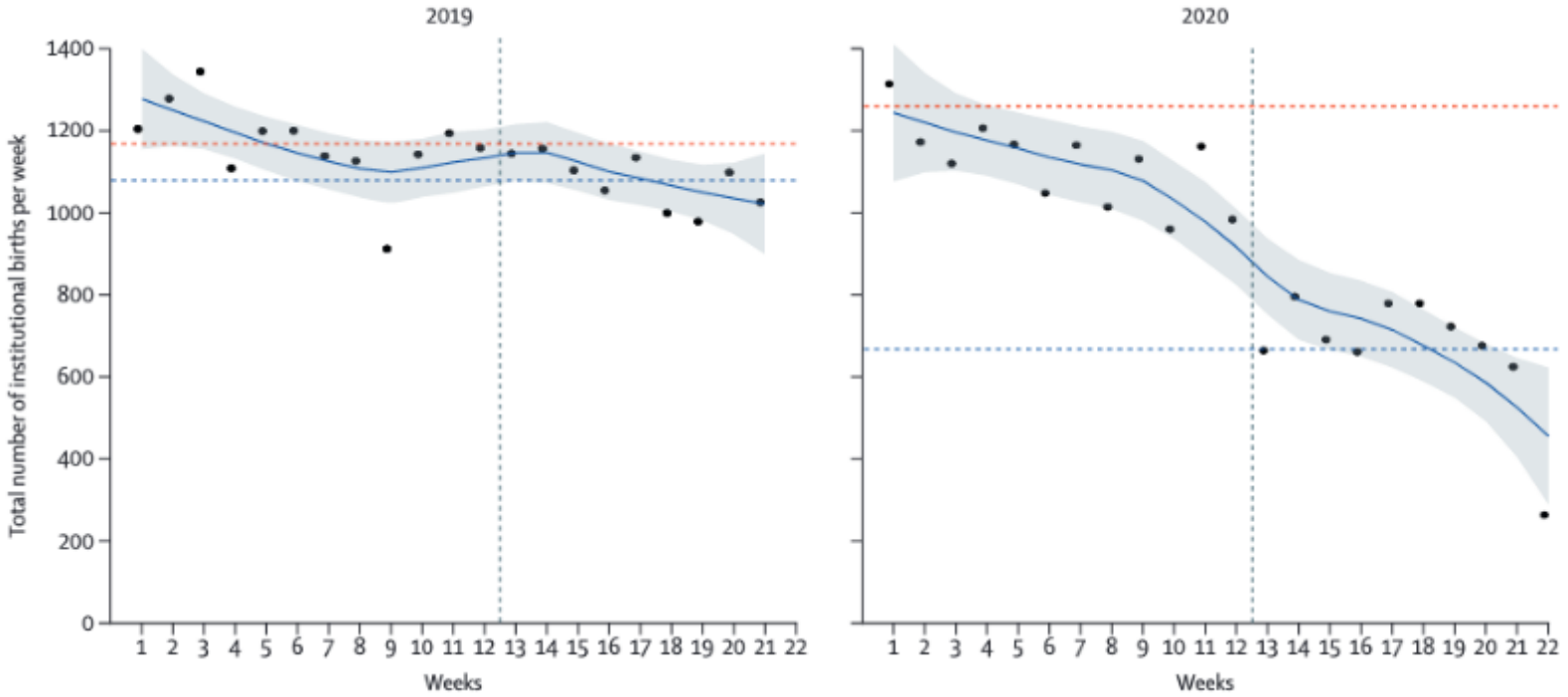
Grassly N C et *al. Lancet Infect Dis.* Aug 2020

# Impact of COVID-19 pandemic response - Nepal

Prospective – observational study in 9 health institutions in Nepal

Data over a period of 5 months: 12,5 weeks before lockdown and 9,5 weeks during lockdown

Women > 22 weeks of gestations + fetal heart sound was heard at the time of admission : 21 763 enrolled & 20 354 gave birth in the hospital




*Weekly institutional births for the first 22 weeks of 2019 & 2020*

<u>Institutional birth</u>:

- Substantial decrease – especially after week 12,5
- Reduction during lockdown was 7,4%
- **Total decrease of 52,4% by the end of lockdown**

Ashish KC et *al. Lancet Glob Health.* Aug 2020

# Impact of COVID-19 pandemic response - Nepal

| | Before lockdown | During lockdown | *P value* |
|---|---|---|---|
| **Institutional stillbirth** (per 1000 total births) | 14 | 21 | 0,0002 |
| **Intitutional neonatal mortality** (per 1000 livebirths) | 13 | 40 | 0,0022 |
| Intrapartum fetal heart rate monitoring (%) | 56,8 | 43,4 | <0,0001 |
| Skin to skin contact with the mother's chest (%) | 13,0 | 26,2 | <0,0001 |
| Health workers wash hand during childbirth (%) | 28,6 | 41,1 | <0,0001 |

| | Preterm birth rate | | Institutional stillbirth, rate per 1000 total births | | Institutional neonatal mortality rate, per 1000 livebirths | |
|---|---|---|---|---|---|---|
| | Estimate (95% CI) | p value | Estimate (95% CI) | p value | Estimate (95% CI) | p value |
| **Adjusted effect, β** | | | | | | |
| Baseline risk (risk before lockdown) | 0·14 (0·11–0·17) | <0·0001 | 3 (2–7) | <0·0001 | 0·9 (0·1–8) | <0·0001 |
| Risk ratio during lockdown *vs* before lockdown | 1·30 (1·20–1·40) | <0·0001 | 1·46 (1·13–1·89) | 0·0042 | 3·15 (1·47–6·74) | 0·0037 |

- These results raise questions on policies regarding strict lockdown in LMIC
- Pandemic lockdown jeopardize the progress that has been made in the past in Nepal
- Urgent need to protect access to high quality intrapartum care and prevent excess death

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

Ashish KC et *al. Lancet Glob Health.* Aug 2020

REACTing research & action targeting emerging infectious diseases

# EPIDEMIOLOGY (October 12th 2020)

**1. What is the situation in the World?**

- More than 30 millions of confirmed cases in the World and 1 million global deaths

**2. What is the incubation period & $R_0$?**

- The median incubation period is 5 days with an initial basic reproductive number between 2 to 6 before control measures
- Presymptomatic transmission: 44% - Infectiousness decline quickly within 7 days.

**3. What do we know about the risk of transmission & the mode of transmission?**

- Person to person transmission – transmission seems to be more effective in adolescents than in adults
- Route of transmission: droplet, direct contact, possible aerosol
- Increased risk for SARS-CoV-2 infection among health-care workers compared with the general community.
- Most close contact exposures were to private or public gathering

**4. What is the impact of the different measures taken by countries?**

- Face masks reduce the transmission of respiratory viruses
- Transmission of viruses is lower with physical distancing of 1 meter or more
- Pandemic lockdown can have an important impact on the access to the health system in some countries

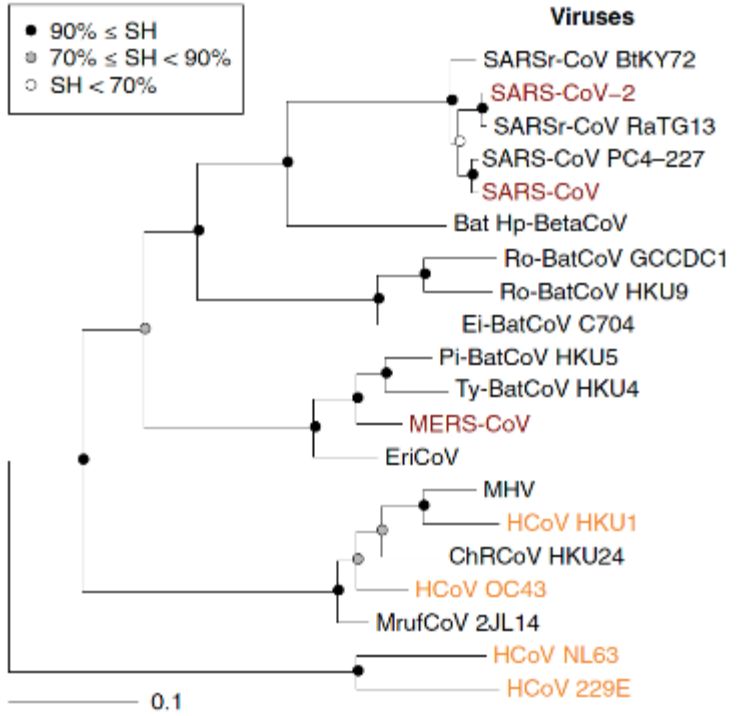
# VIROLOGY

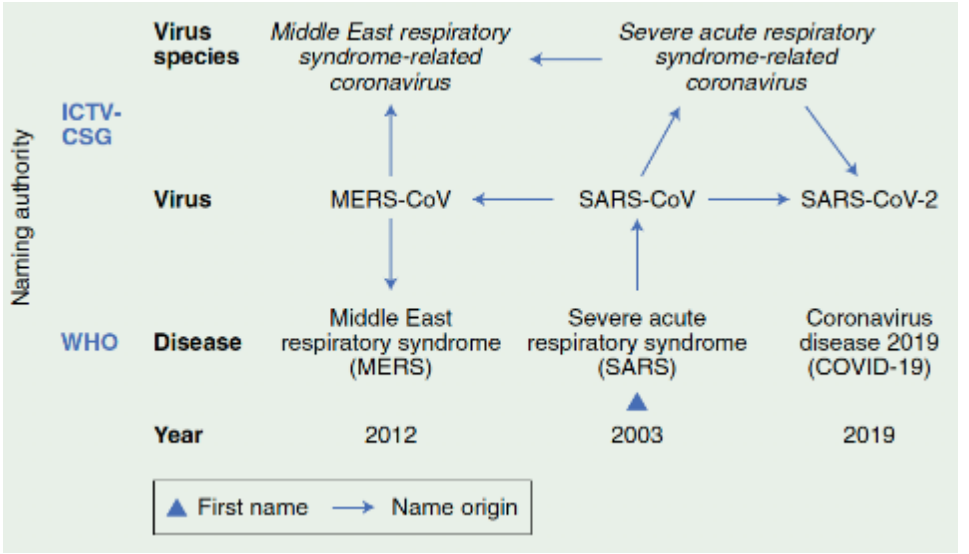
**Questions:**

- Which type of virus is SARS-CoV-2?
- What is the stability and viability of SARS-CoV-2?
- What do we know about viral load and shedding according to different samples?
- What is the description of the immune responses in infected patients?
- Alternative to the nasopharyngeal swab for SARS-CoV-2 detection?

# SARS-CoV-2

- Part of family of enveloped positive-strand RNA viruses (*coronaviridae*)
- Belongs to the *betacoronavirus genus*
  - 98% similarity with bat coronavirus RaTG13
  - 79% genetic similarity with SARS-CoV
- <u>7 coronaviruses known to infect humans</u>
  - 4 coronavirus infect mainly the upper respiratory tract
    - HCoV HKU1 – OC43 – NL63 – 229E
  - 3 coronavirus can replicated in lower respiratory tract and cause pneumonia with high case fatality rates
    - SARS-CoV = Case Fatality Rate (CFR) of 10% (2002 – 2003)
    - MERS-CoV = CFR of 37% (2012 - )
    - SARS-CoV-2 = CFR unknown (2019 - )




Coronaviridae Study Group *Nat Microbiol.* Apr 2020

# Stability of SARS-CoV-2

**IN VITRO**

Outcome: positive viral culture

Surface stability

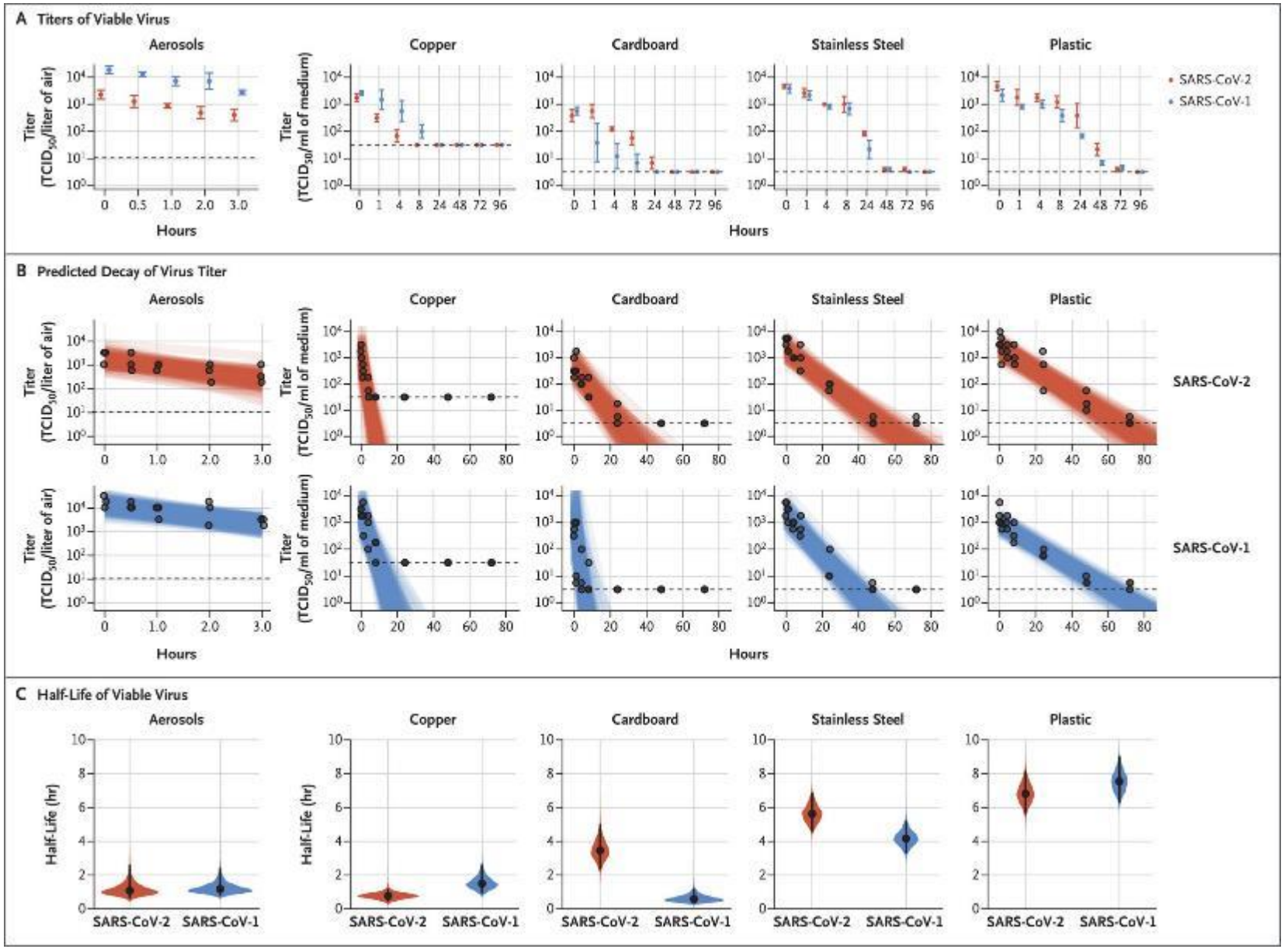
- Plastic and stainless steel: **72 hours**
- Cardboard: **24 h**
- Copper: **4 hours**

Viable in aerosol: **3 hours**

Half-life in aerosol:

- **1.1 to 1.2-h [0.64 – 2.24]**

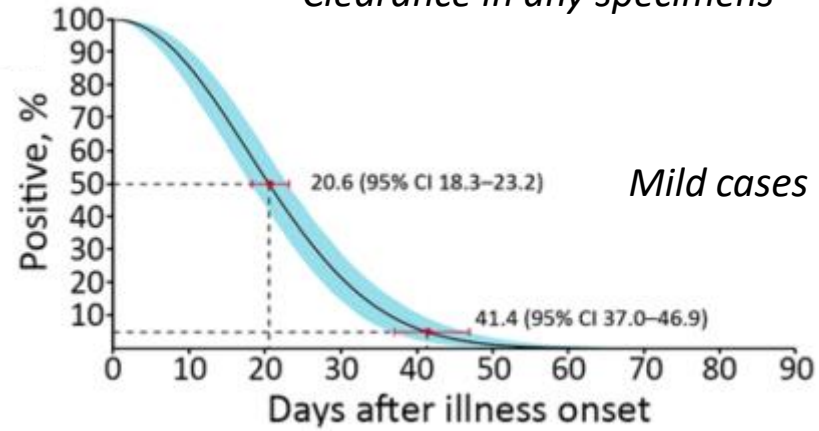
Aerosol transmission is possible in experimental conditions




Van Doremalen N *et al. NEJM.* Apr 2020

# Persistence of virus RNA

*Clearance in any specimens*




*Mild cases*

<u>49 patients with 490 specimens</u> → 171 specimens positive for SARS-CoV-2 RNA

Frequency and duration of detectable SARS-CoV-2 RNA in body fluids?

Weibull model → time loss of SARS-CoV-2 RNA detection

<u>Time to loss detection</u>

- Time to loss detection was longer for NP swabs and feces
- Significant differences for mild cases among specimens

**Prolonged persistence of SARS-CoV-2 RNA detection in hospitalized patient**

→ Does not imply the existence of infectious virus particles

→ Still a need for preventive measures?

**<u>Limits</u>**

- Existence of infectious particles?
- Virus isolation and tests of specimen's infectivity
- not conducted
- Unspecified concentration of SARS-CoV-2 RNA
- May not be generalized to all population

*Data are presented in days after illness onset*

| | Mild cases, n = 43 | | Severe cases, n = 6 | |
|---|---|---|---|---|
| Specimens | Median (95% CI) | 95th percentile (95% CI) | Median (95% CI) | 95th percentile (95% CI) |
| Throat swab | 15.6 (11.8–20.7) | 32.8 (25.9–42.3) | 33.9 (24.2–47.3) | 53.9 (39.4–81.7) |
| Sputum | 20.0 (14.1–27.0) | 43.7 (33.6–60.4) | 30.9 (23.5–39.1) | 44.7 (36.3–58.0) |
| Nasopharyngeal swab | 22.7 (18.8–27.5) | 46.3 (39.0–55.2) | 33.5 (25.7–42.7) | 49.4 (38.4–68.5) |
| Feces | 24.5 (21.2–28.3) | 45.6 (40.0–52.8) | 32.5 (26.3–39.1) | 48.9 (41.3–59.7) |

Jiufeng S *et al. Emerg Infect Dis*. May 2020

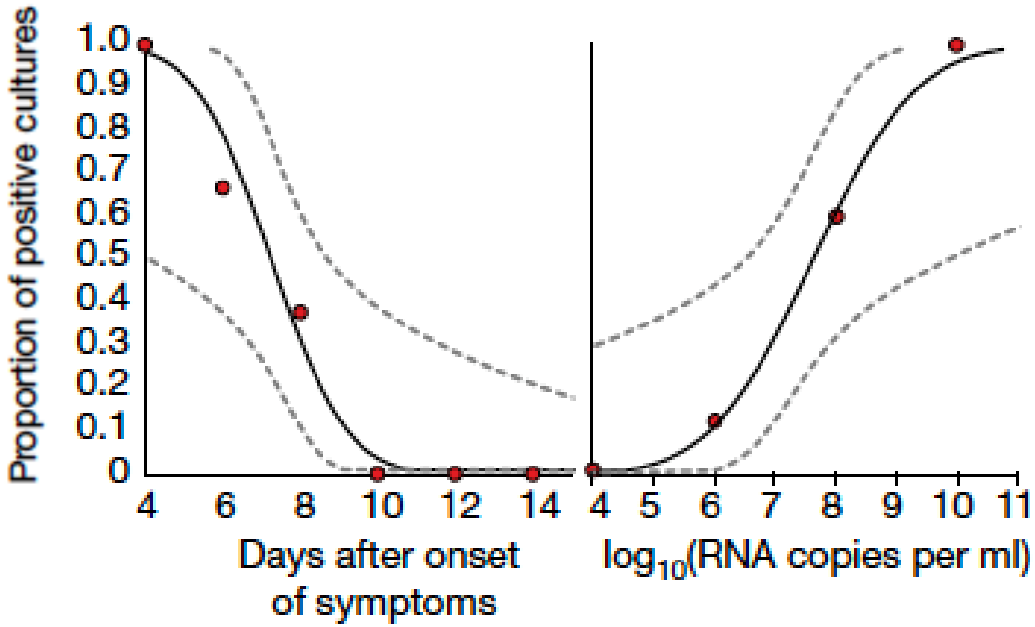
# Viability

9 patients (Munich) – Virological analysis & information on virus infectivity

- Active virus replication in tissues of the upper respiratory tract
- No indications of replication in the digestive system
- Infectious virus on swab or sputum samples but not from stool samples
- None of urine and serum samples tested positive for RNA for SARS-CoV-2
- The success of virus isolation also depend of viral load

- **No isolates of the virus were obtained from samples taken after day 8 in spite of ongoing high viral loads.**

*Virus isolation success based on probit distributions*




Wölfel R *et al. Nature.* May 2020

# Viral load

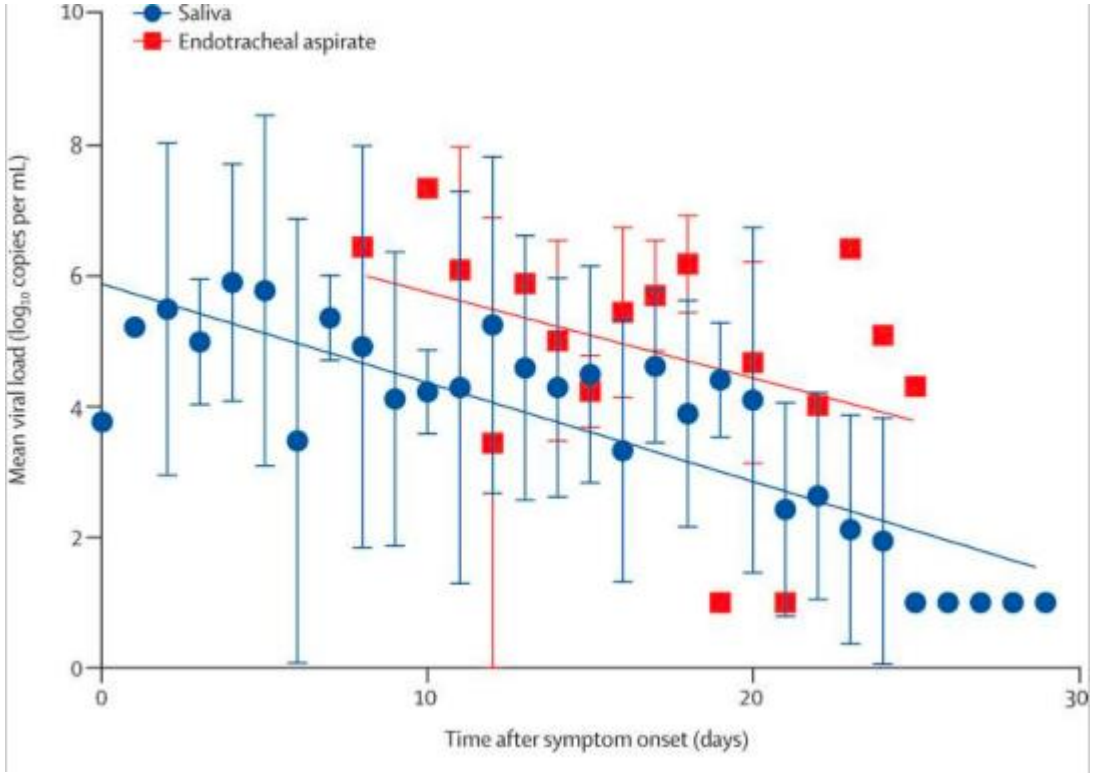
23 patients (median age: 62y) in Hong Kong → 173 respiratory specimens

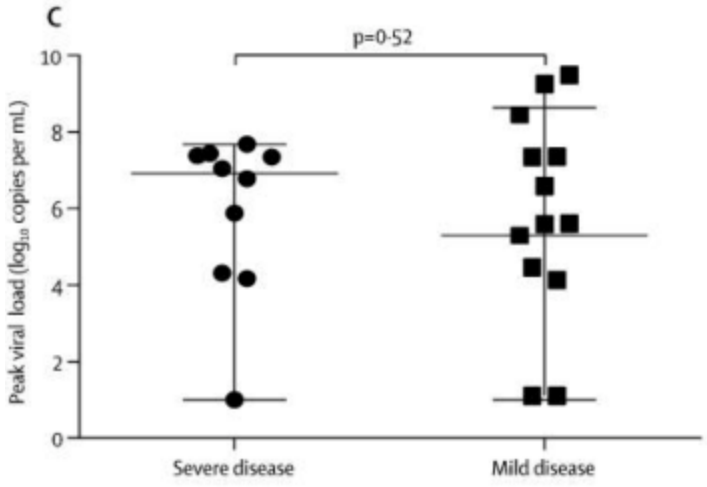
- Morning saliva samples
- Endotracheal aspirate (intubated patients)

Viral load:

- Median: 5,2 $log_{10}$ copies per mL (IQR 4,1–7,0)
- Saliva viral load: higher during first week and declining after this point
- Endotracheal aspirate viral load: non-significant decline during the first weeks
- 7 patients had viral RNA detected 20 days after symptoms
- No association between prolonged detection and severity
- Older age was correlated with higher viral load
- No difference between mild and severe cases

**Limit**: low number of cases




To KK et *al. Lancet Infec Dis*. May 2020

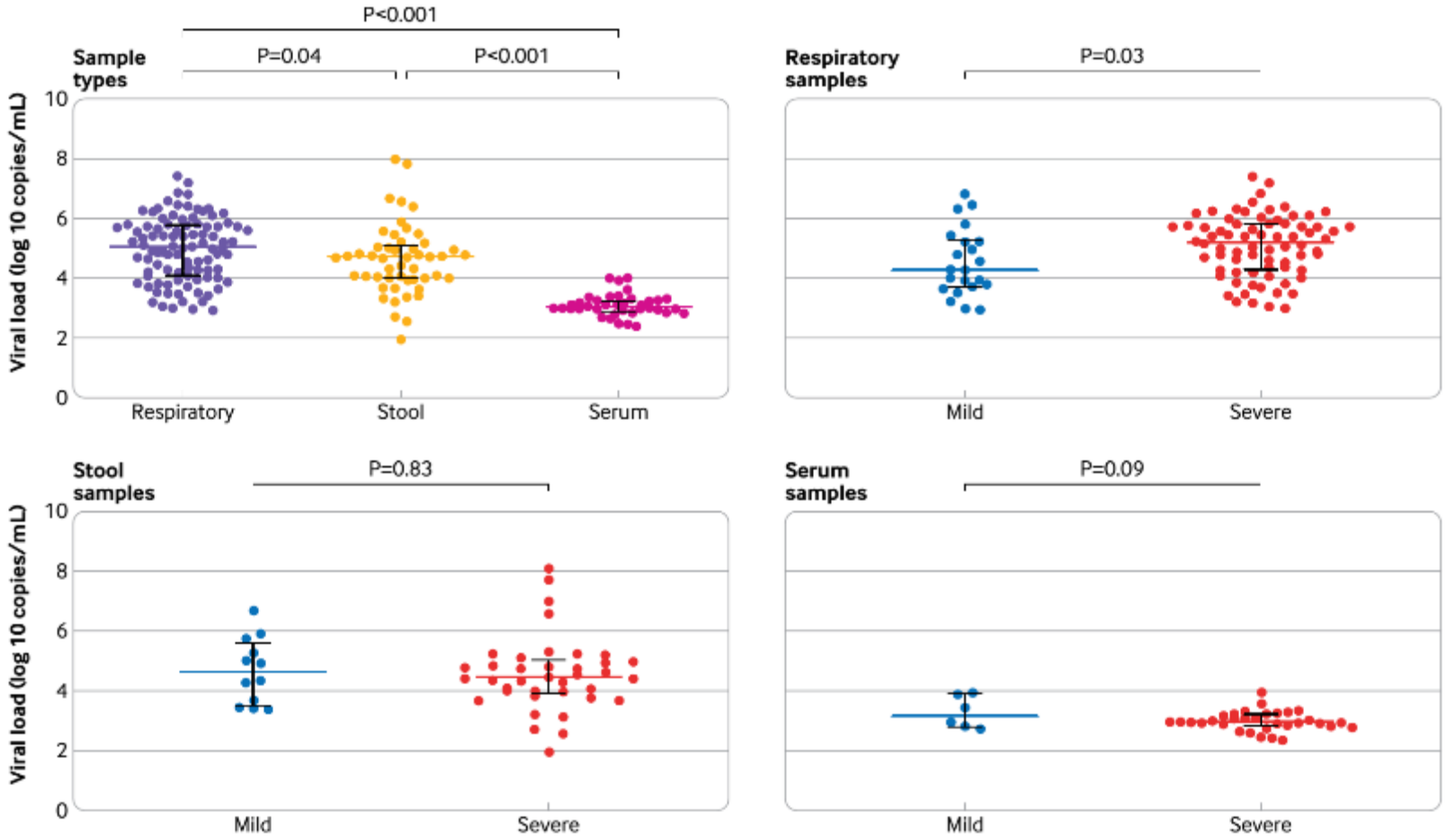
# Viral load

96 patients (22 with mild disease and 74 with severe diseases) in China

Viral load:

- Duration of virus shedding in respiratory samples longer among severe patients (21 vs 14 days), also longer in patients >60 years old and male.
- 59% of patients with positive stool samples and presenting a longer viral shedding in stool than respiratory sample (22 vs 18 days).
- Viral load were slightly higher among severe cases.

**Limit**: a relatively low number of cases




To Zheng et *al. BMJ*. Apr 2020

# Viral load

205 patients (mean age: 44y) → 1070 respiratory specimens:

- Pharyngeal swabs, urine, sputum, blood, feces
- Bronchoalveolar lavage fluid & fibro bronchoscopy brush biopsy

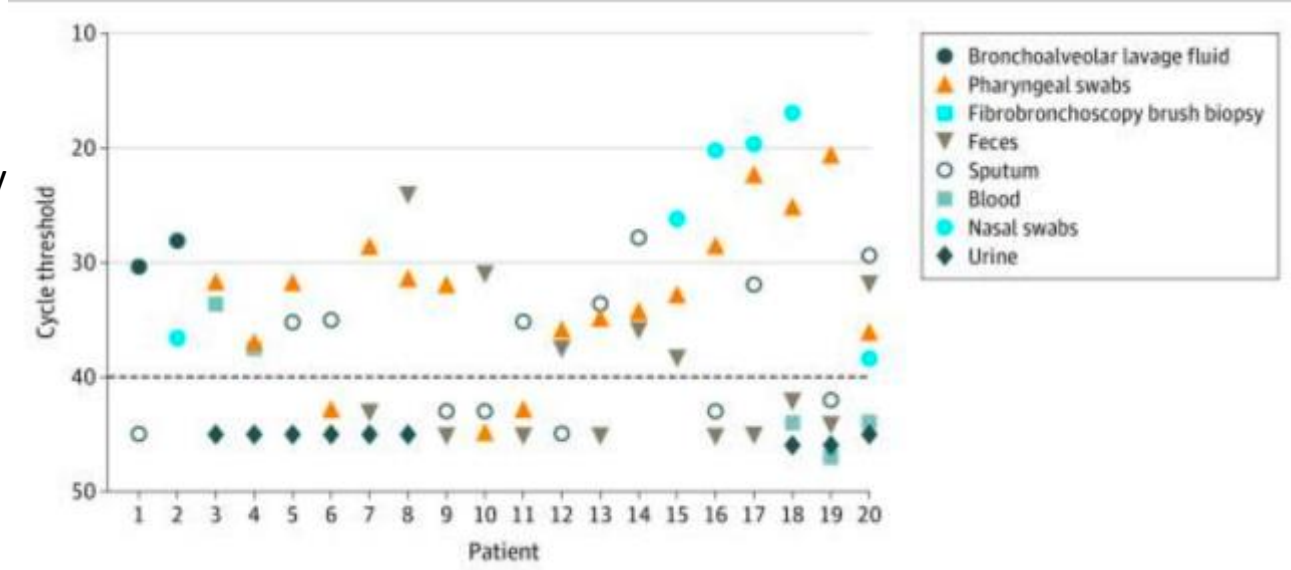
Cycle threshold: indicator of the copy number of SARS-CoV-2 RNA

Cycle threshold < 40 → positive for SARS-CoV-2 RNA

<u>Positive rates:</u>

- Highest positive rates → bronchoalveolar fluid (93%)
- Sputum (72%) – pharyngeal swabs (32%)
- Blood showed only 1% and urine 0%

- Mean cycle threshold for nasal swabs = 24,3 → higher viral load




→Testing of specimen from multiple sites
↑ sensitivity & ↓ false negative

**<u>Limit</u>**: this differ according to the typology of patients and disease stages.

Wang W et *al. JAMA*. Mar 2020

# Dynamic in viral shedding

94 symptomatic patients → <u>414 throat swabs</u> from symptoms onset up to 32 days after

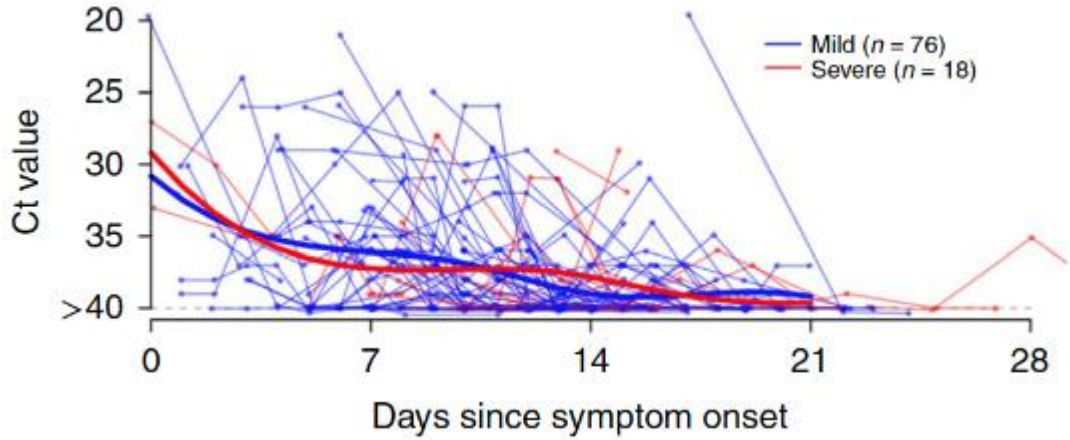
- Detection limit was Ct=40 (used to indicate negative samples)
- 50% were male
- Median age: 47 years
- No severe or critical patients

**<u>Dynamic in viral shedding</u>**

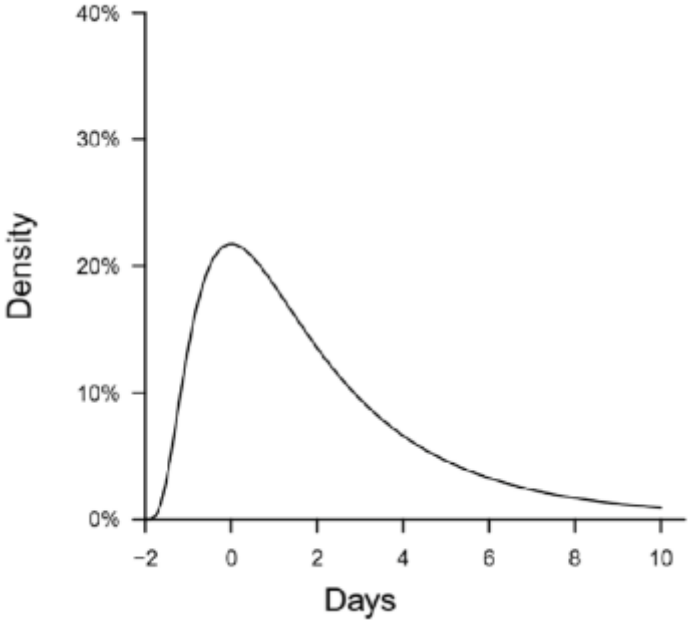
- Highest viral load soon after symptom onset
- Decreasing gradually after symptom onset
- **No difference in viral loads across sex, age groups, disease severity**

**Viral shedding may begin 2 to 3 days before first symptoms**

The estimated proportion **of presymptomatic transmission was 44%** ($CI_{95\%}$ [30–57%]). Infectiousness decline quickly within 7 days




*Viral load detected by RT–PCR in throat swabs from patients infected with SARS-CoV-2*




*Simulated serial intervals assuming infectiousness started 2 days before symptom onset*

He X et *al. Nat Med.* May 2020

# Oral & fecal viral shedding

401 patients → <u>1758 rectal swabs during 0 to 98 days after illness onset</u>

- 80 patients positive for SARS-CoV-2 in the rectal swabs
  - Pediatrics: positive rate of 56,7%
  - Adults: positive rate of 16,9%
- Positive rate decreases  over time

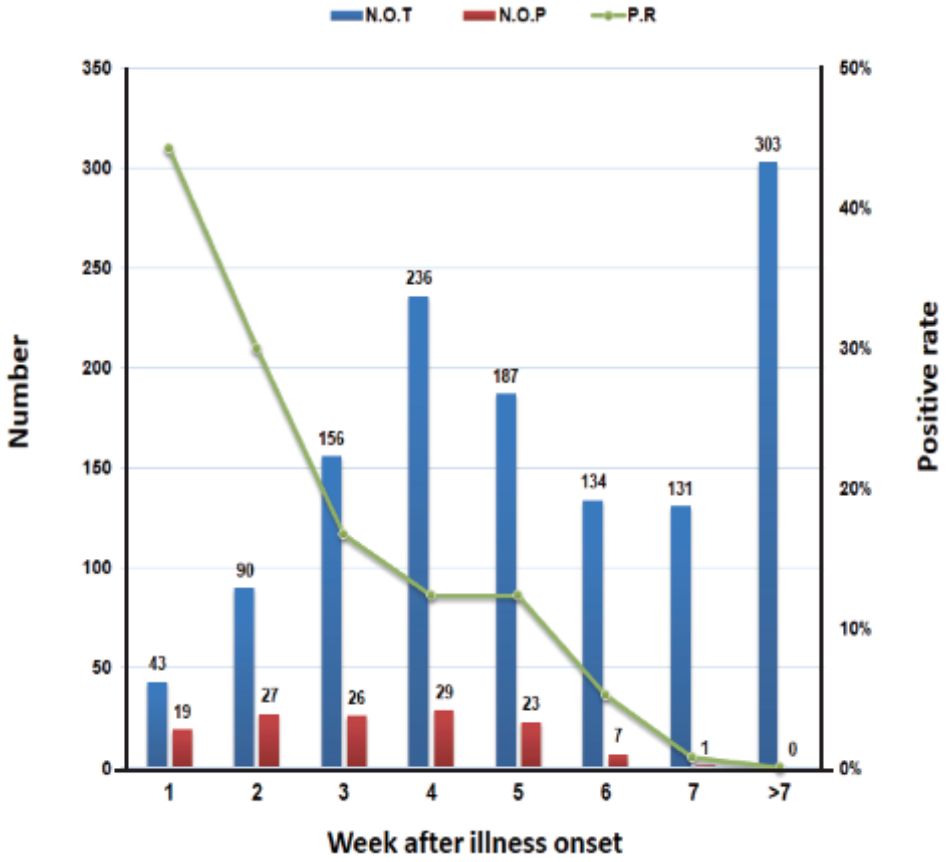
<u>517 pairs (respiratory + rectal samples) from the 80 patients positive in rectal swabs</u>

- 58 were double positive → coincidence rate increased during the disease progression
- 112 positive in rectal & negative in respiratory sample
- Higher viral load in rectal than respiratory samples

<u>Factors independently associated with the duration of fecal viral shedding</u>:

- Neutrophil level OR:1,55 $IC_{95\%}$[1,05 – 2,40]
- Interval between antiviral treatment and illness onset OR:1,17 $IC_{95\%}$[1,01 – 2,34]

*NOT: number of tested - NOP: number of positive - PR: positive rate*




→ Intestine = reservoir of SARS-CoV-2 RNA

The gastrointestinal viral reservoir is potentially a long-lasting fomite for SARS-CoV-2 transmission even for asymptomatic patients

→ **Still viable virus?**

Zhao F et *al. Gastroenterology.* May 2020

# Positivity of viral culture

Viral culture is only rarely positive for low viral load (Ct values above 25 to 30) and after 8 to 10 days after symptom onset

Viral culture is not positive for feces sample

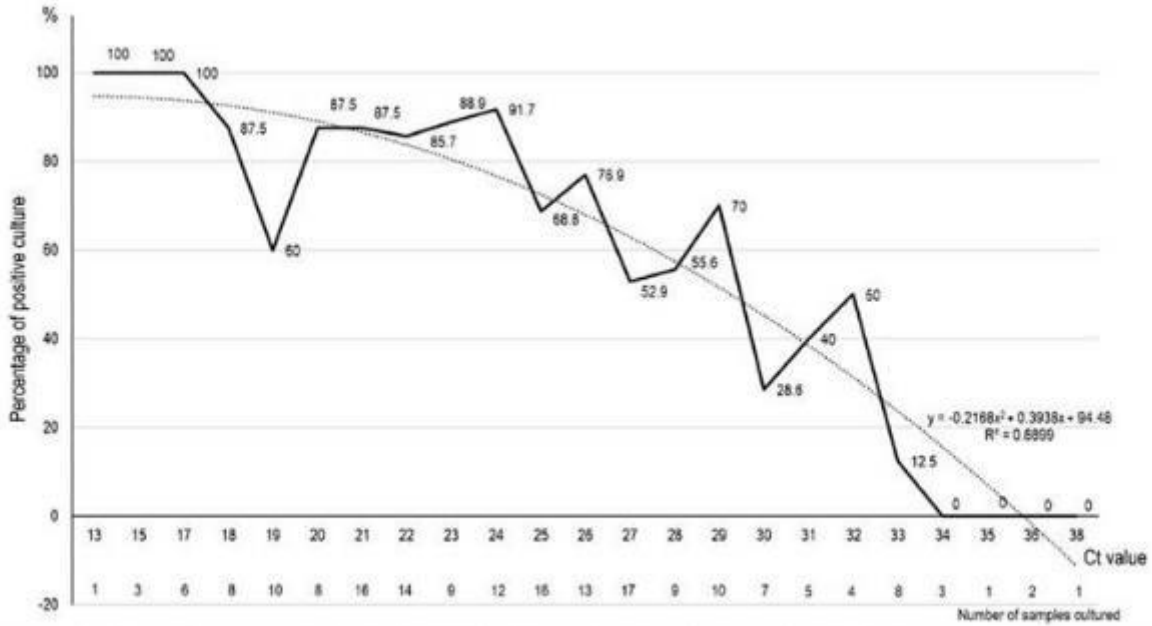
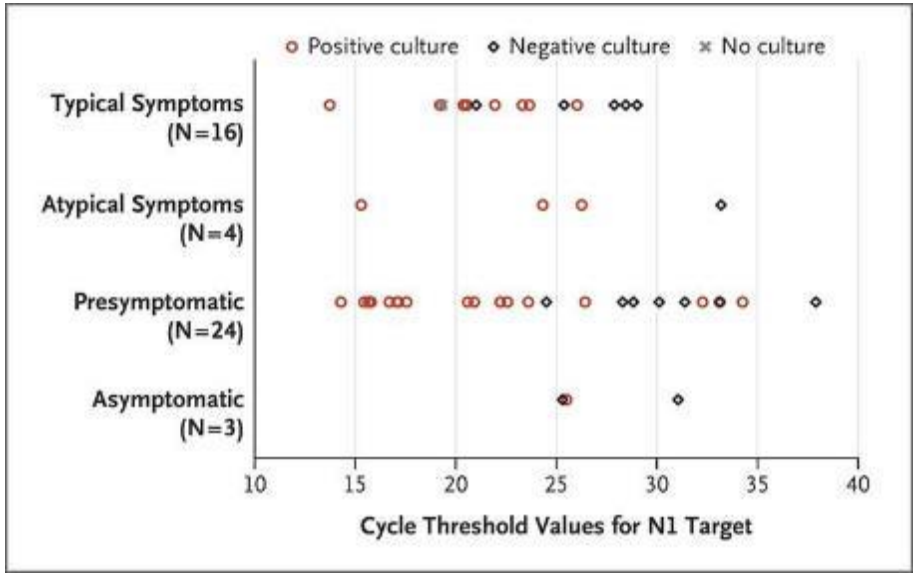
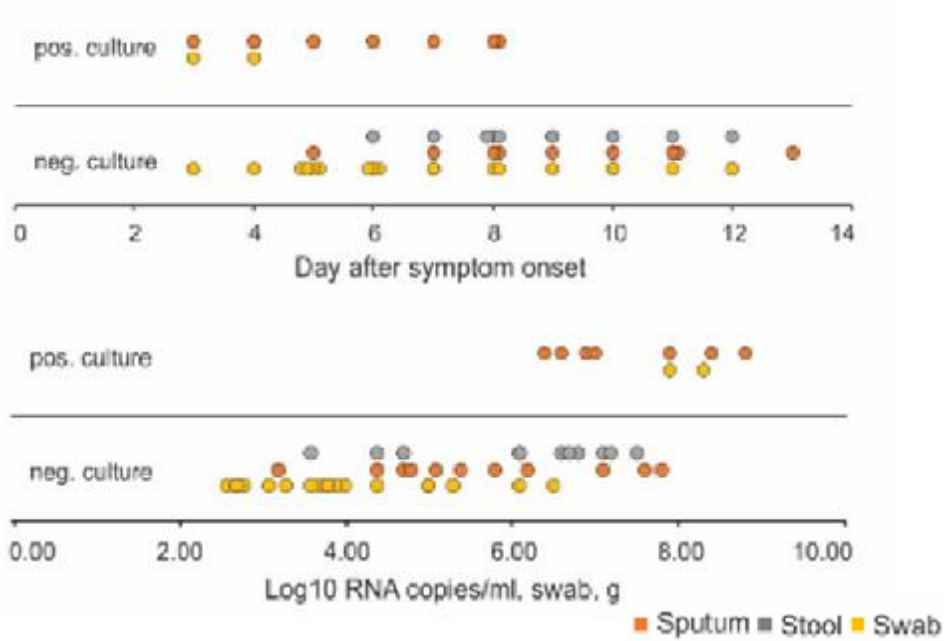
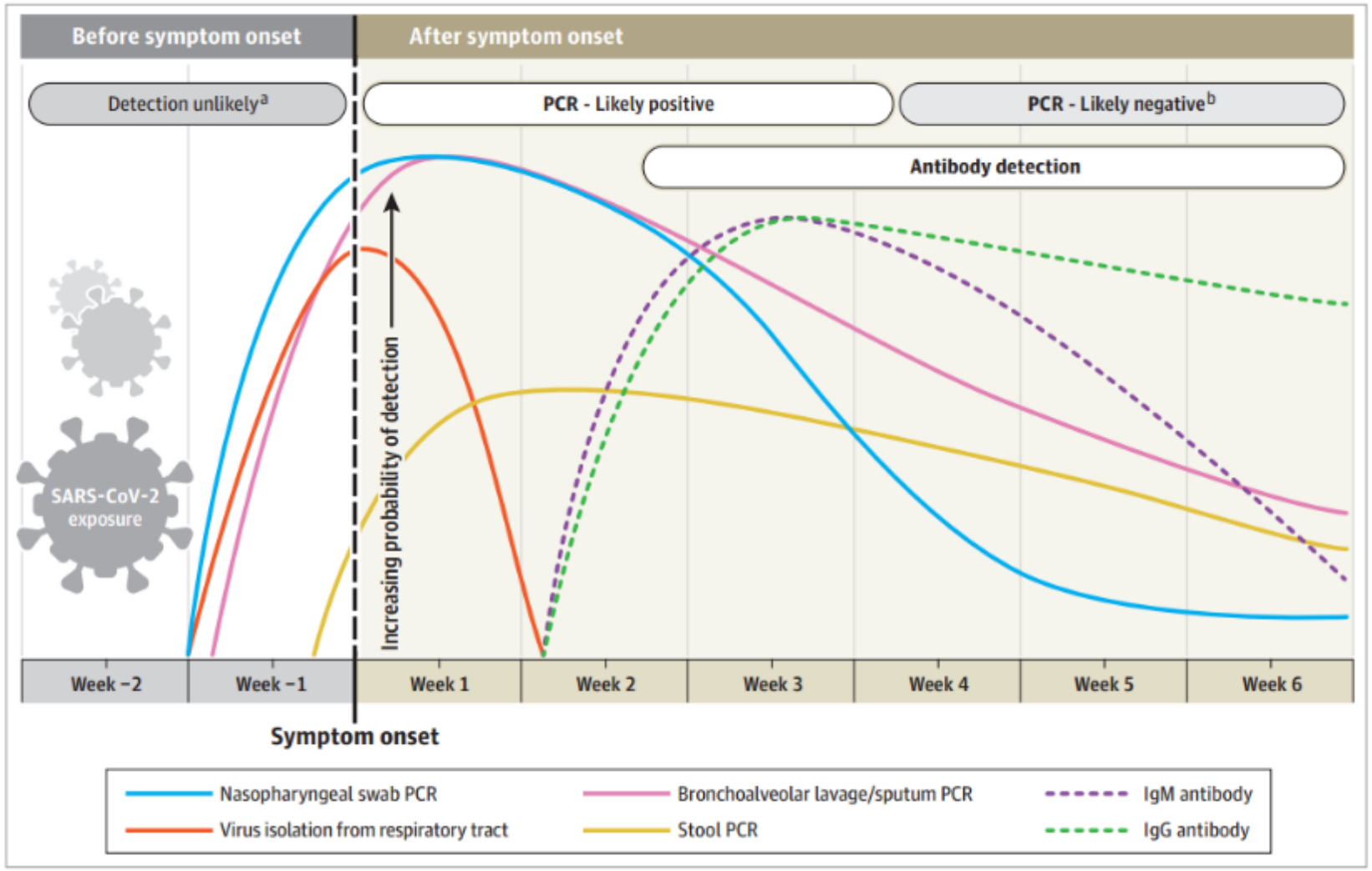



**Fig. 1** Percentage of positive viral culture of SARS-CoV-2 PCR-positive nasopharyngeal samples from Covid-19 patients, according to Ct value (plain line). The dashed curve indicates the polynomial regression curve



# SARS-CoV-2 detection




**Limit:** antibody response yet to be characterized among the various patients' populations

Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

# Immunological assessment

Cohort study of 178 confirmed SARS-CoV-2 infection

Asymptomatic infection = 20,8% (37/178 patients)

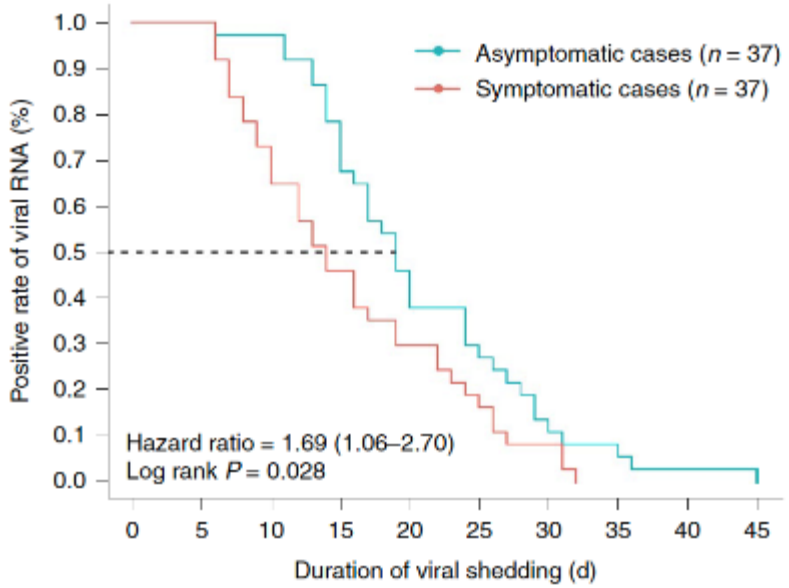
37 asymptomatic matched with 37 mild symptomatic patients

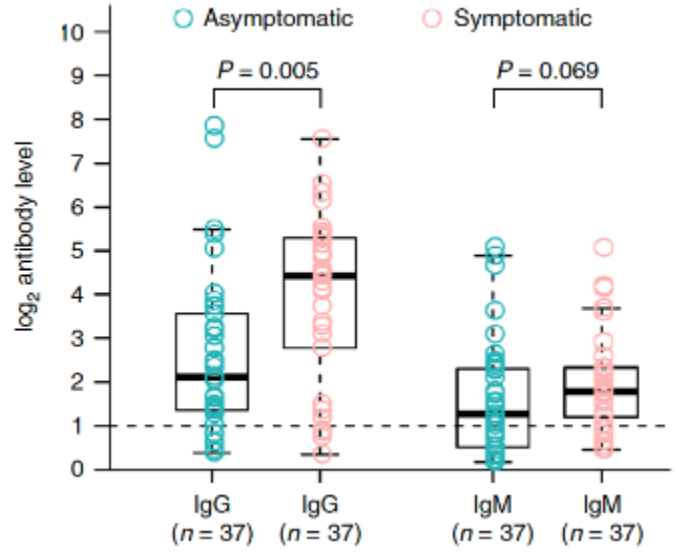
Viral shedding:

- Initial Ct value were similar in the two groups
- Asymptomatic group had a significantly longer duration of viral shedding (19 days versus 14 days; *p*=0.028)

IgG and IgM, 3 to 4 weeks after exposure (acute phase):

- IgG positivity rates similar between the two groups (81 and 84% of asymptomatic and symptomatic, respectively)
- IgG levels in the asymptomatic group (median S/CO, 3.4; IQR, 1.6–10.7) were lower than the symptomatic group (median S/CO, 20.5; IQR, 5.8–38.2; *p* = 0.005)
- IgM levels were similar in the two groups (62 and 78% of positivity of asymptomatic and symptomatic, respectively)




Long QX *et al. Nat Med.* Jun 2020

# Immunological assessment

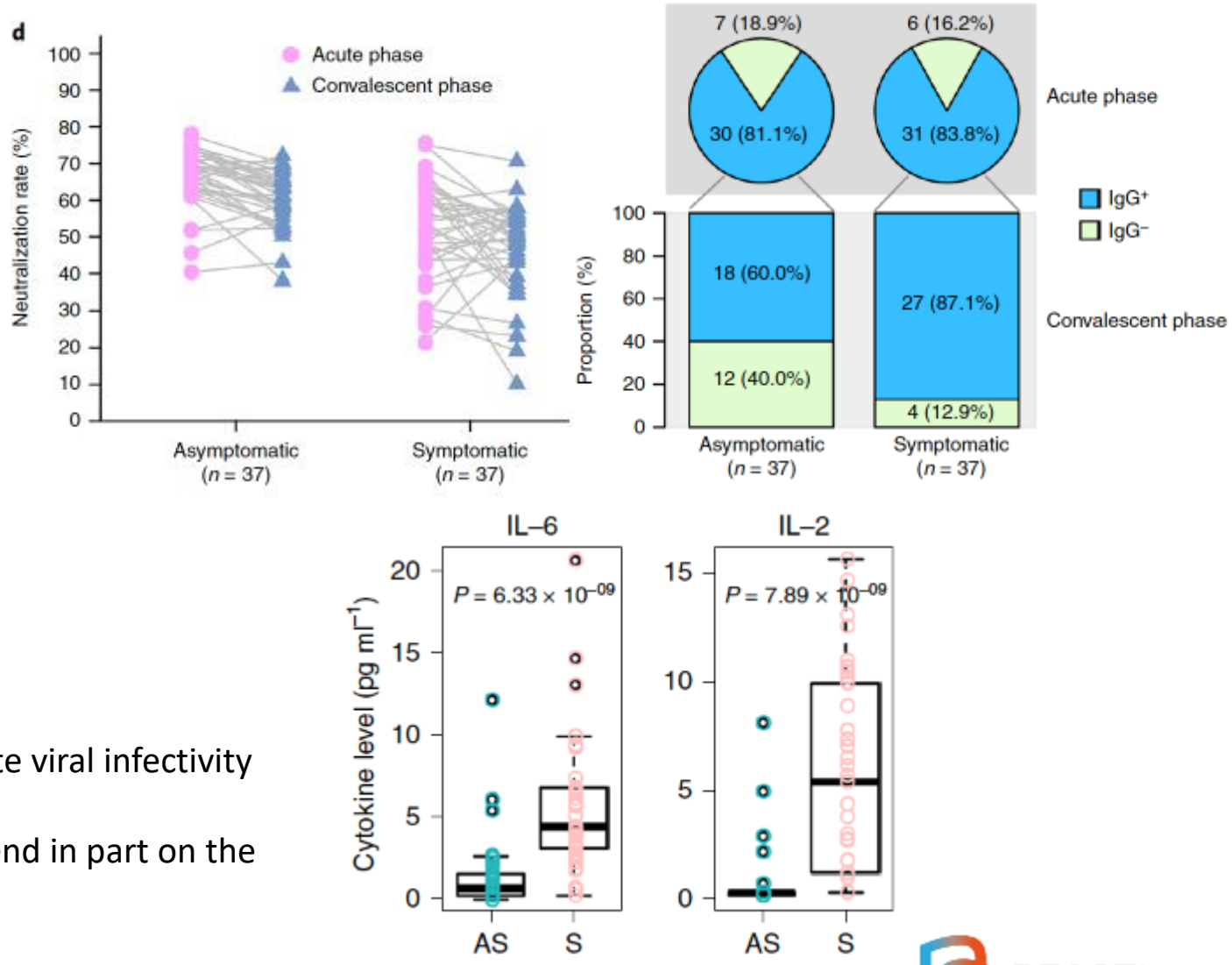
IgG and IgM, 8 weeks after exposure (convalescent phase)

- A decline of IgG is observed among >90% of patients
- 40% and 13% of asymptomatic individuals IgG+ at the acute phase became seronegative

Similar observations were made for neutralizing antibodies

Asymptomatic patients had a reduced inflammatory response with lower concentration of circulating cytokines and chemokines

The relatively low seroprevalence and its decrease within 2-3 months after infection highlights the potential limits of serology for diagnostic and the need of timely serosurvey




**Limits**

→Viral RNA shedding does not equate viral infectivity (not assessed in this study)

→Serological observations may depend in part on the commercial assay used

Long QX *et al. Nat Med.* Jun 2020

# SARS-CoV-2 salivary detection

Rapid and accurate diagnostic tests are essential for controlling the ongoing Covid-19 pandemic

70 patients hospitalized with COVID-19 (nasopharyngeal swabs).

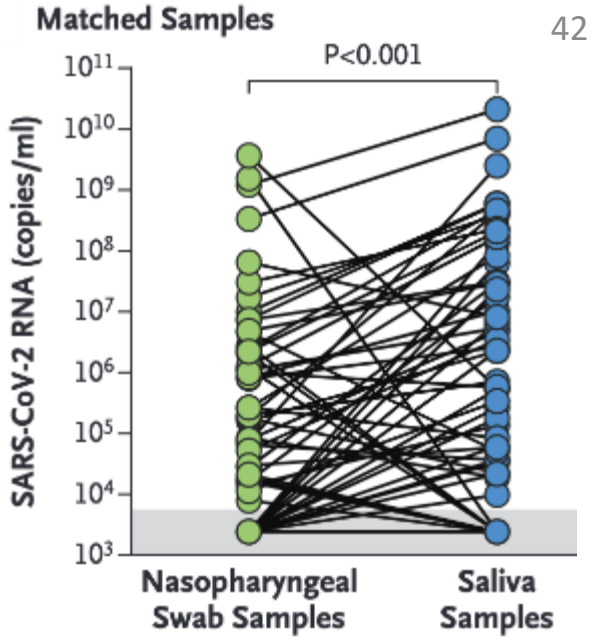
Additional samples (saliva specimens collected by the patients themselves + nasopharyngeal swabs collected by health care workers)

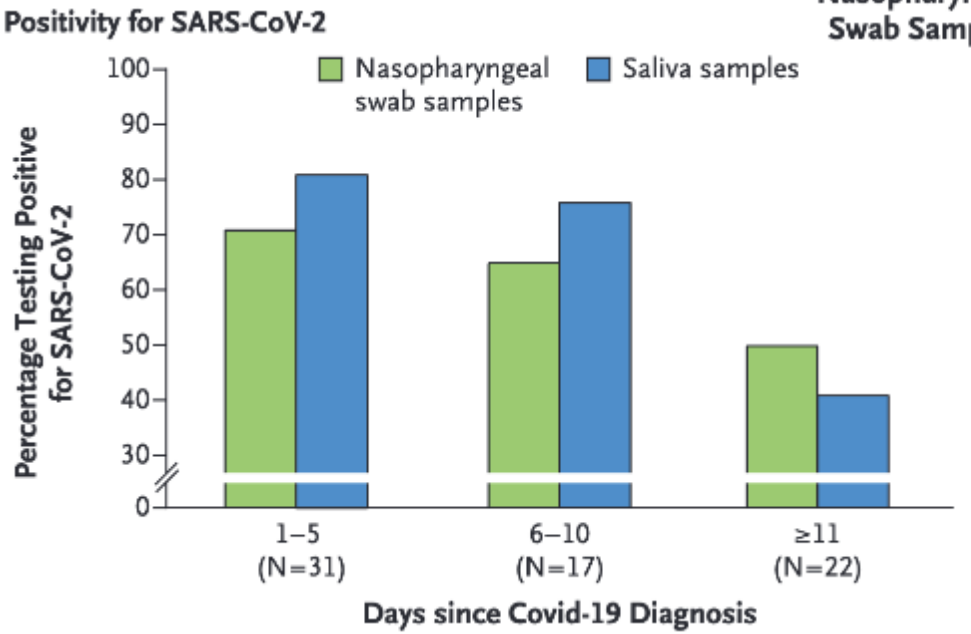
Detected more RNA copies in the saliva specimens than nasopharyngeal swabs (mean log copies per millilitre, 5.58 versus 4,93)

Higher percentage of saliva samples than nasopharyngeal swab samples were positive

Saliva specimens and nasopharyngeal swab specimens have at least similar sensitivity in the detection of SARS-CoV-2 during the course of hospitalization

**Limits:** hospitalized patients, nasopharyngeal samples presented an unusually low sensitivity (≈70% for earlier samples) in this study




**Saliva specimens could be effective in COVID-19 diagnosis, but needs to be confirmed for outpatients**

Wyllies AL *et al. NEJM.* Aug 2020

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REACTing research & action targeting emerging infectious diseases

# Salivary detection of SARS-CoV-2 in asymptomatic subjects

Mass screening study – 1924 asymptomatic subjects:

- Close contact white clinically confirmed COVID-19 patients (CT cohort, *n= 161*)
- Asymptomatic travelers arriving at Tokyo & Kansai (AQ cohort, *n= 1763*)

Saliva sample (self-collected) & NPS sample (medical officers)

Comparison between paired samples

<u>Estimated prevalence</u>:

- CT cohort: 29,6%, $CI_{90\%}$[23,8 – 35,8%]
- AQ cohort: 0,3%, $CI_{90\%}$[0,1 – 0,6%]
- The true concordance probability was:
  0,998, $CI_{90\%}$[0,996 – 0,999%] in AQ cohort
- Viral load was equivalent between NPS and saliva samples (Kendall's coefficient of concordance = 0,87)

*Diagnostic results of nasopharyngeal swab (NPS) and saliva test*

**Contact-tracing cohort (n=161)**

| | saliva | |
|---|---|---|
| NPS | positive | negative |
| positive | 38 | 3 |
| negative | 6 | 114 |

**Airport Quarantine cohort (n=1,763)**

| | saliva | |
|---|---|---|
| NPS | positive | negative |
| positive | 4 | 1 |
| negative | 0 | 1758 |

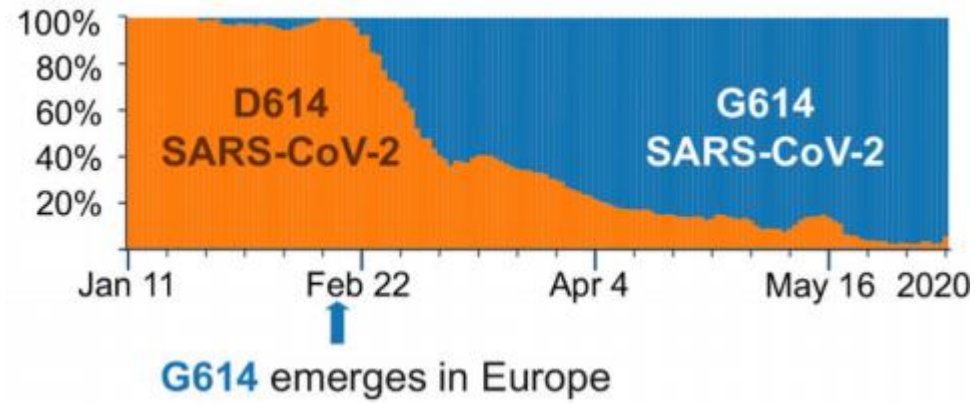
| | Sensitivity | Specificity |
|---|---|---|
| NPS | 86% , $CI_{90\%}$[77 – 93%] | 99,93%, $CI_{90\%}$[99,77 – 99,99%] |
| Saliva | 92% , $CI_{90\%}$[83 – 97%] | 99,96%, $CI_{90\%}$[99,85 – 100,00%] |

→ **Equivalent utility with similar sensitivity and specificity,**
→ **Self-collected saliva has significant advantages over NPS sampling,**
→ **Saliva may be a reliable alternative in detecting SARS-CoV-2 in asymptomatic**
→ **Limit:** the number of positive patients in the QC does not provide a strong evaluation of the saliva sensitivity in this population

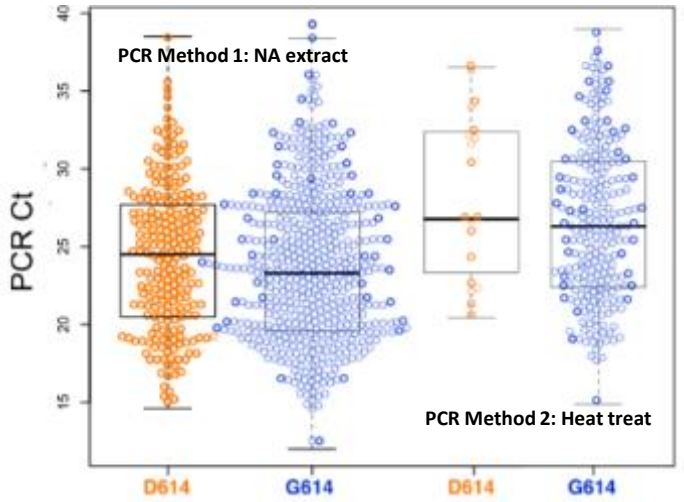
# Changes in SARS-CoV-2 Spike

SARS-CoV-2 variant with Spike G614 has replaced D614 as the dominant pandemic form:

- Spike D614G amino acid change is caused by an A-to-G nucleotide mutation at position 23,403 in the Wuhan reference strain

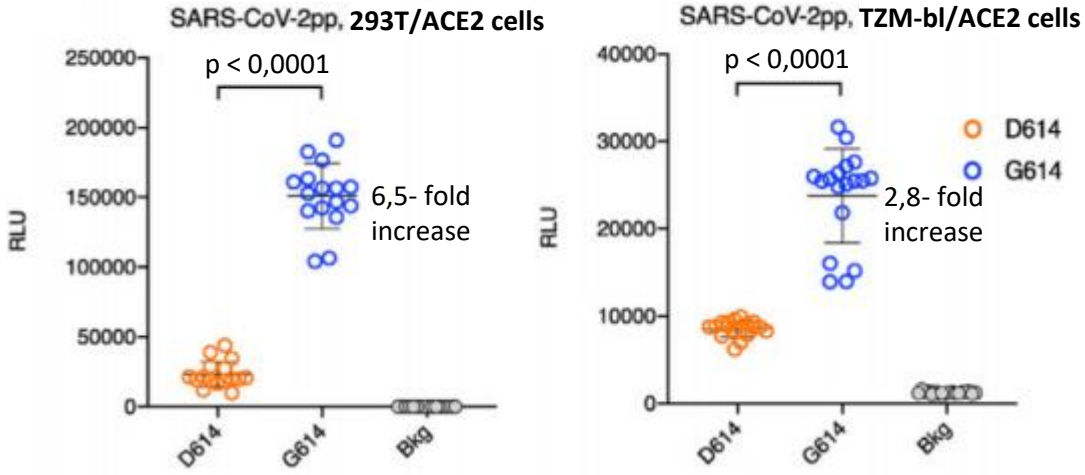



<u>G614 Is Associated with Potentially Higher Viral Loads in COVID-19 Patients but not with disease severity:</u>




- G614 is associated with a lower cycle threshold (Ct) required for detection (higher viral loads)

<u>Recombinant lentiviruses pseudo typed with the G614 Spike more infectious than corresponding D614 S-pseudo typed viruses</u>




**Limits:** this mutation is not single (*e.g.* associated to P314L in ORF1b) and represents the vast majority of cases in France among non-travelers since the very beginning of the outbreak

Korbert B *et al. Cell.* Aug 2020

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# VIROLOGY (October 12th 2020)

**1. Which type of virus is SARS-CoV-2?**

- RNA viruses that belong to the *betacoronavirus* genus

**2. What is the stability and viability of SARS-CoV-2?**

- Stability is similar to that of SARS-CoV-1 under experimental circumstances tested
- Aerosol and fomite transmission of SARS-CoV-2 is plausible
- Some mutations have been selected since the beginning of the outbreak, but without proven clinical impact to date

**3. What do we know about viral load and shedding according to different samples?**

- Highest positive rates of SARS-CoV-2 in bronchoalveolar fluid among severe patients
- No influence of sex, age and disease severity on viral loads, has been observed
- Viral shedding may begin 2 to 3 days before first symptoms
- Detection of viral RNA does not necessarily mean that infectious virus is present, especially for low viral loads and >8 days from symptoms onset

**4. What is the description of the immune responses in infected patients?**

- IgG levels and neutralizing antibodies start to decrease within 2-3 months after infection

**5. Alternative to the nasopharyngeal swab for SARS-CoV-2 detection?**

- Saliva sample might be a good alternative to the NPS with several advantages, but asymptomatic populations are poorly characterized

# CLINICAL

**Questions:**

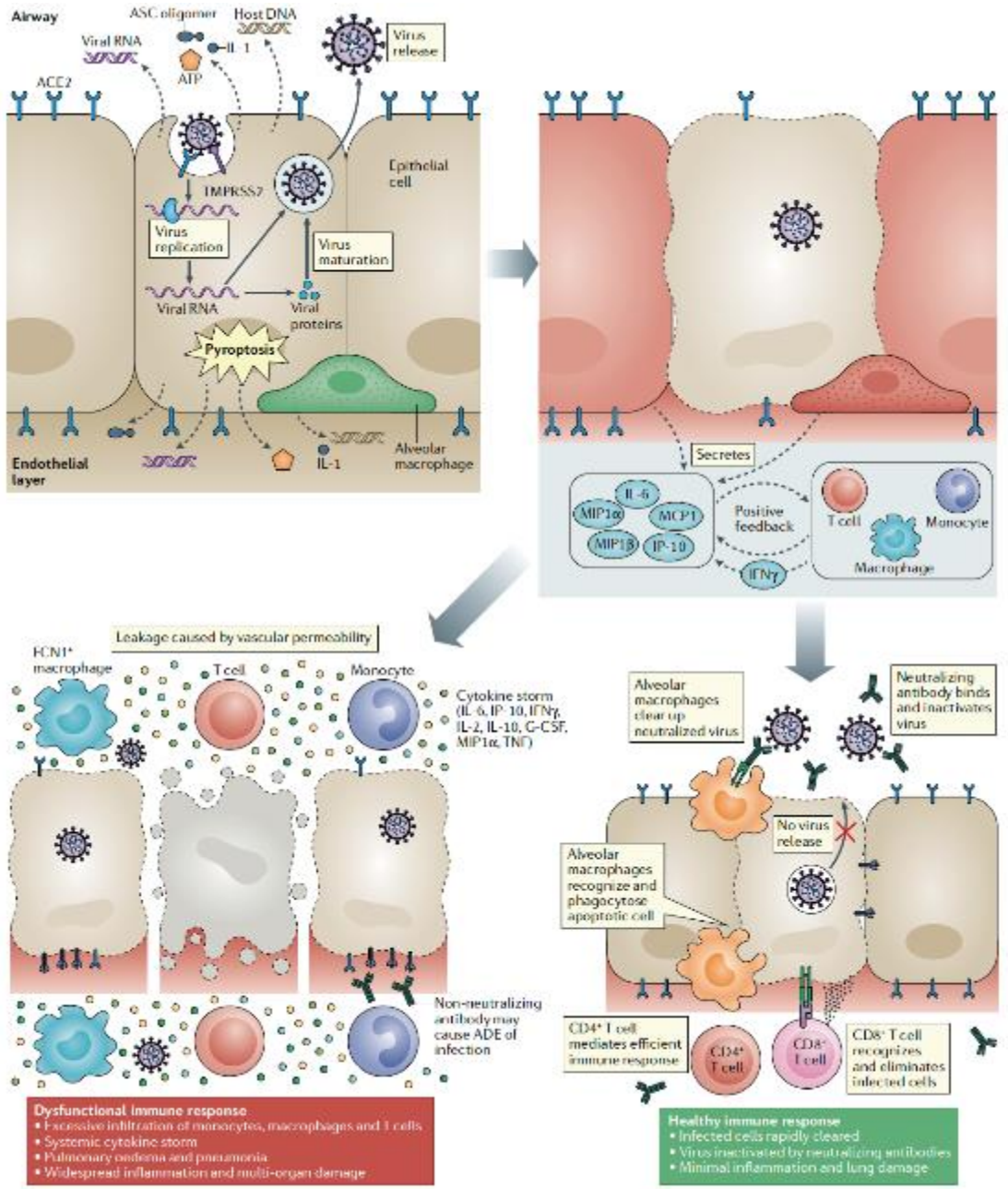
- What is the mechanism of action of SARS-CoV-2? Cell immunity?
- What is the clinical presentation of COVID-19 in adults and children?
- Is there multiple-organ damage?

# Physiopathology

- **Binding** to host cell through ACE2 receptor by spike (S) protein
  - Lung, Kidney, Heart, Brain …
- **Fusion** of the viral envelope with cellular membrane (TMPRSS2)
- Virus **hijacks** the cell machinery
- Host cell → **pyroptosis** and release damage-associated molecular
  - ATP, nucleic acid, ASC oligomer …
- **Inflammatory response**
  - Pro-inflammatory cytokines & chemokines: IL-6, IP-10, MCP1 …
- Attract other cells (monocytes, macrophage, T cells …)
  - Pro-inflammatory feedback loop
  - Eliminates the infected cells before the virus spreads

**BUT sometimes** (10 to 15 days after symptom onset)

- Accumulation of immune cells
  - **Cytokine storm**
  - Lung damage and multi-organ damage

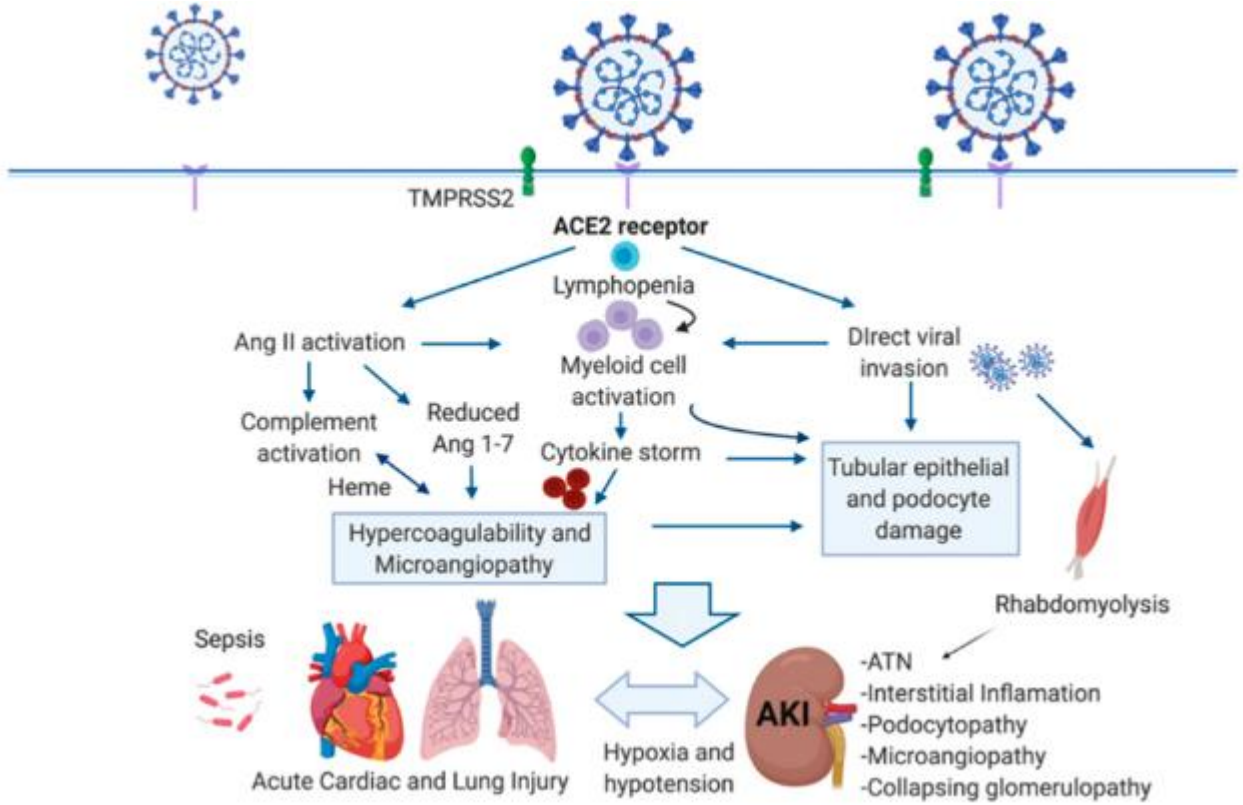



Tay MZ et *al. Nat review Immunol*. Apr 2020

# Physiopathology

- SARS-CoV-2 targets ACE2 receptor and infected cells via « priming »
  - Renin- Angiotensin system dysregulation
  - Activation of innate and adaptative immune pathways
  - Cytokine storm
  - coagulation pathway → hypercoagulation

- Multi-organ damage
  - Kidney, heart, lungs, vessel, immune system ….



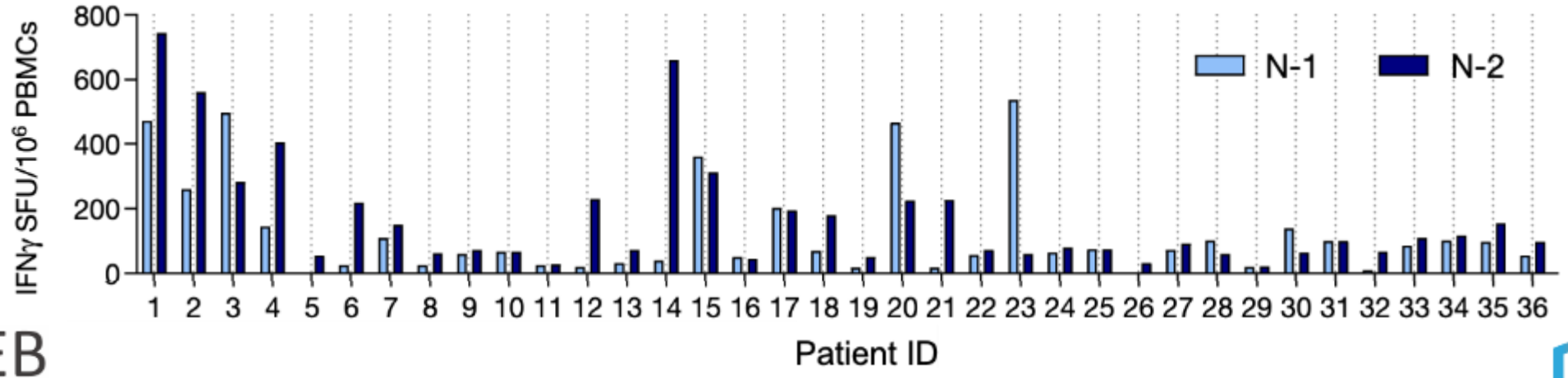

Battle D et *al. JASN*. May 2020

# SARS-CoV-2 specific T cell immunity

SARS-CoV2 specific T cells in patients with COVID-19

- 36 individuals after recovery from mild to severe COVID-19.
- T cell response against selected structural (N) and non-structural proteins (NSP7, NSP13 & ORF1).
- Use of an unbiased method with overlapping peptides.
- Peripherical blood mononuclear cell (PBMC) of the 36 patients were stimulated for 18h with the different peptides pools.

- **In 36 out of 36 individuals, found specific T cell that recognized multiple regions of the N-protein (IFNγ spot)**




Le Bert N et *al. Nature*. Jul 2020

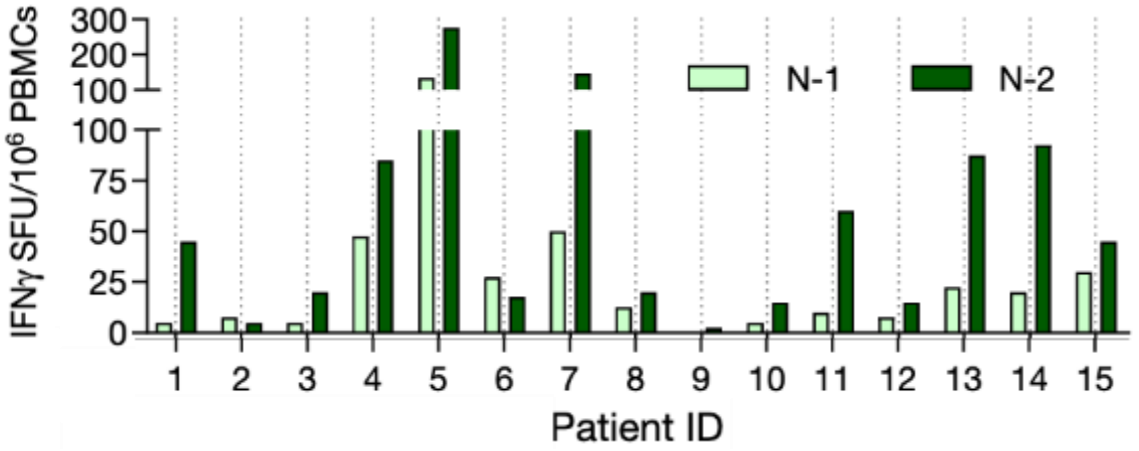
# SARS-CoV-2 specific T cell immunity

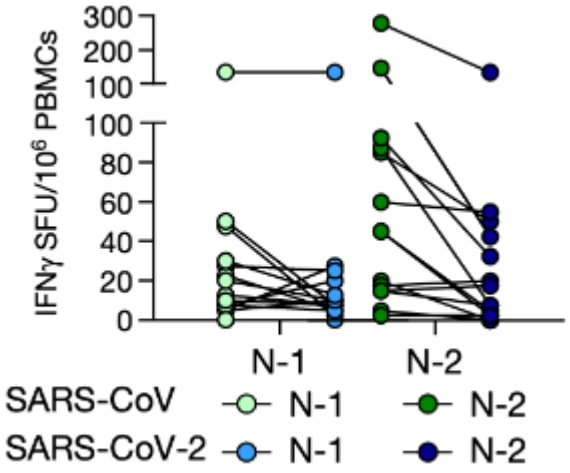
SARS-CoV2 specific T cells in patients with SARS

- Patients who recovered from SARS have T cells that are specific to epitopes within different SARS-CoV proteins.
- Collected PBMCs 17 years after SARS-CoV infection from 15 individuals.
- **17 years after infection, IFNγ responses to SARS-CoV peptides were still present.**
- These T cells displayed robust cross-reactivity to the N protein of SARS-CoV-2.
- SARS-CoV-2 N-specific T cells are part of the T cell repertoire of individuals with a history of SARS-CoV infection and these T cells are able to robustly expand after encountering N peptides of SARS-CoV-2.

**→ Supporting the notion that patients with COVID-19 will develop long-term T cell immunity.**

*PBMCs isolated from 15 individuals who recovered from SARS 17 years ago were stimulated with SARS-CoV*




*PBMCs of 15 individuals who recovered from SARS were stimulated in parallel with peptide pools covering the N proteins of SARS-CoV and SARS-CoV-2, and the frequency of IFNγ-producing cells is shown.*

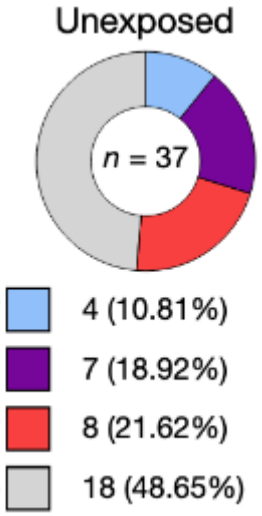
Le Bert N et *al. Nature*. Jul 2020

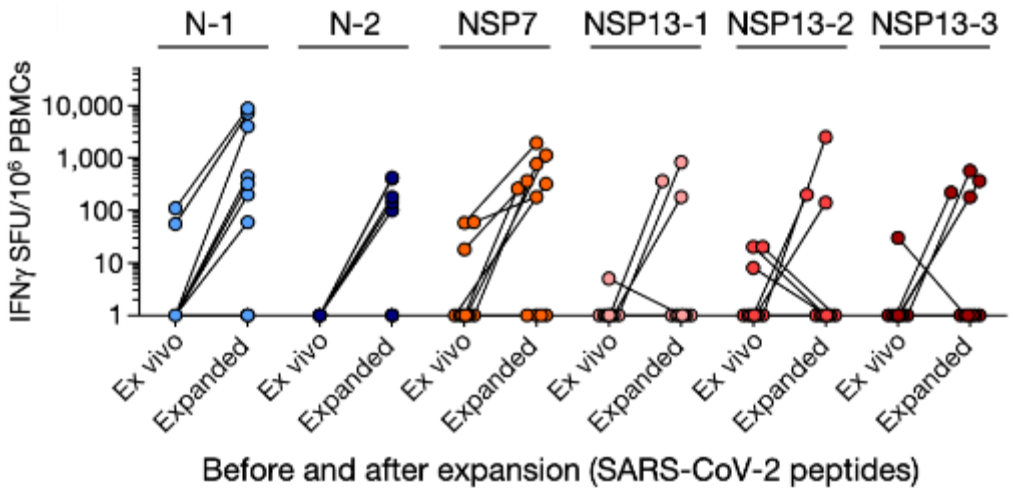
# SARS-CoV-2 specific T cell immunity

SARS-CoV2 specific T cells in unexposed donors

- 37 donors: not exposed to SARS-CoV and SARS-CoV-2
- **Detection of SARS-CoV-2-specific IFNγ responses in 19 out of 37 unexposed donor.**
- The unexposed group showed a mixed response to the N protein or to NSP7 and NSP13.
- These SARS-CoV-2-reactive cells from unexposed donors had the capacity to expand after stimulation with SARS-CoV-2-specific peptides.

*The percentage of individuals with N-specific responses*




**→ Infection with betacoronaviruses induces multi-specific and long lasting T cell immunity against the structural N protein.**

Le Bert N et *al. Nature*. Jul 2020

# Antibody response to SARS-CoV-2

Cohort of 149 cases and contacts: 111 with SAR-CoV-2 PCR positive + 46 close contacts.

Free of symptoms at least 14 days at the time of sample collection.

→ Convalescent plasma samples

- Binding to SARS-CoV-2 RBD and trimetric S protein?

IgG response: 78% showed anti-RBD and 70% anti-S

IgM response: 15% showed anti-RBD and 34% anti-S

Anti-RBD IgG levels → moderately correlated with age and severity

- Neutralizing activities? → the half-maximal neutralizing titer ($NT_{50}$)

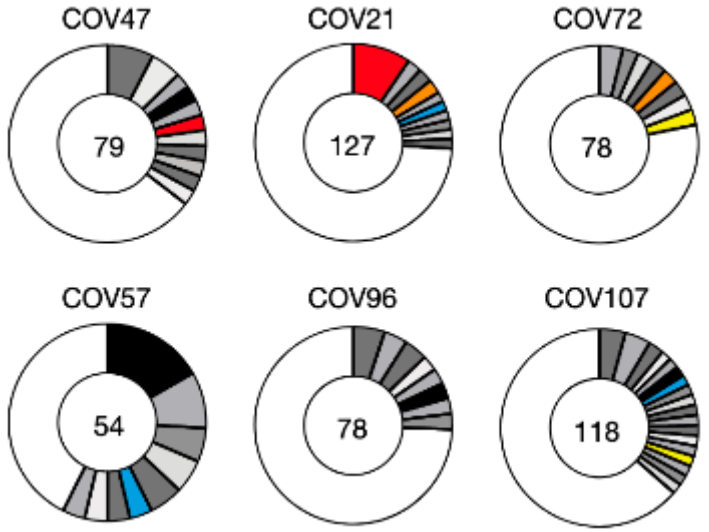
**Generally low**: $NT_{50}$<50 in 33% of samples and < 1000 in 79%

- Nature of the antibodies elicited by SARS-CoV-2 infection?

Expanded clones of viral antigen-binding B cells in all tested individuals convalescent after COVID-19.

95% of the antibodies tested bound to SARS-CoV-2 RBD with an average $EC_{50}$ of 6,9 ng/ml

*The distribution of antibody sequences from six individuals The number in the inner circle indicates the number of sequences analyzed for the individual denoted above the circle. White indicates sequences isolated only once, and grey or colored pie slices are proportional to the number of clonally related sequences.*



# Antibody response to SARS-CoV-2

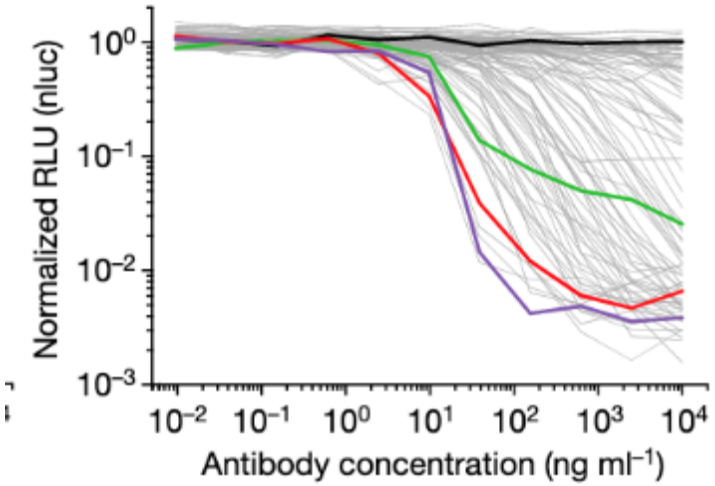
- <u>Do monoclonal antibodies have neutralizing activity?</u>

Among 89 RBD-binding antibodies tested, we found 52 that neutralized SARS-CoV-2 pseudovirus with IC50 values ranging from 3 to 709 ng/ml.

Potent neutralizing antibodies found irrespective of the $NT_{50}$ values.

→ Even individuals with modest plasma neutralizing activity have rare IgG memory B cells that produce potent SARS-CoV-2-neutralizing antibodies.

*The normalized relative luminescence values for cell lysates of 293TACE2 cells 48 h after infection with SARS-CoV-2 pseudovirus in the presence of increasing concentrations of monoclonal antibodies.*




**Plasma neutralizing activity is low in most convalescent individuals**

**Recurrent anti-SARS-CoV-2 RBD antibodies with potent neutralizing activity can be found in all individuals.**

**A vaccine designed to elicit such antibodies could be broadly effective.**

# Auto-antibodies & type I IFN & COVID-19

**Neutralizing auto-Abs against type I IFN could lead to life-threatening COVID-19 pneumoniae?**

987 patients hospitalized for life-threatening COVID-19

663 patients asymptomatic or mildly symptomatic (COVID-19)

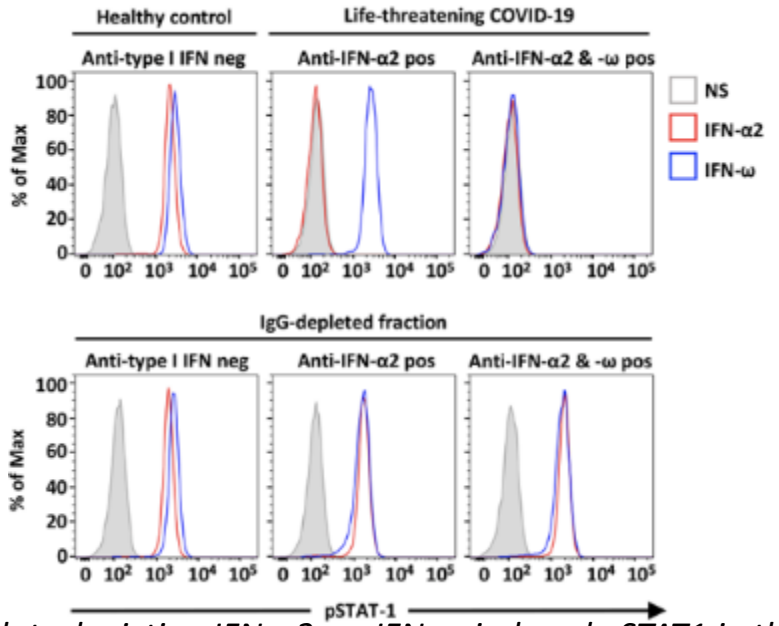
1227 healthy controls

<u>Auto-antibodies against IFN-α2 and/or IFN-ω</u>?

- 135 of 987 critically ill patients had IgG auto-Abs against at least one type I IFN.

<u>Auto-Abs neutralize IFN-α2 and/or IFN-ω in vitro</u>?

- 101 of 987 life-threatening COVID-19 had neutralizing IgG auto-Abs against at least one type I IFN:
  - 51% against IFN-α2 and IFN-ω,
  - 36% against IFN-α2 only,
  - 13% against IFN-ω only.
- Auto-Abs detected in only 4 of 1227 controls and none of 663 asymptomatic or mild-symptomatic patients.




*FACS plots depicting IFN-α2- or IFN-ω-induced pSTAT1 in the presence of 10% healthy control or anti-IFN-α2/ω- auto-Abs-containing patient plasma (top panel) or an IgG-depleted plasma fraction (bottom panel).*

IgG depletion from patients with auto-Abs restored normal pSTAT1 induction after IFN-α2 and IFN-ω stimulation.

# Auto-antibodies & type I IFN & COVID-19

Auto-Abs against all IFN-α subtypes?

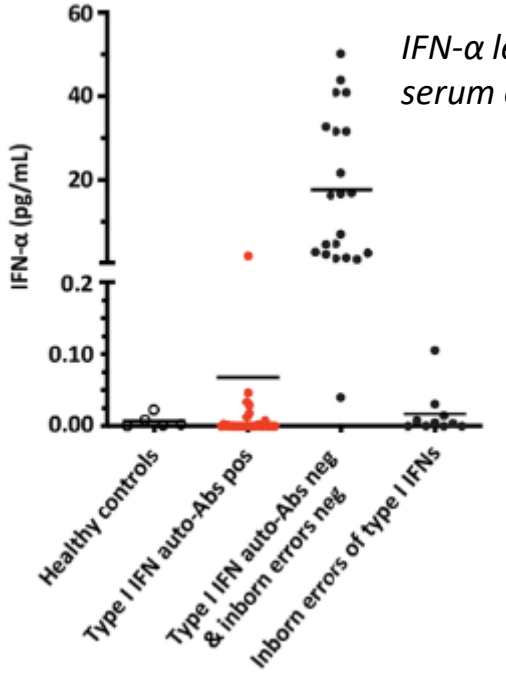
- All patients (22) with neutralizing auto-Abs against IFN-α2 had auto-Abs against all 13 IFN-α subtypes
- **Early treatment with IFN-α is unlikely to be beneficial**

Auto-Abs against IFN-β?

- 1,9% of the patients had auto-Abs against IFN-β
- All were severe COVID-19
- **Treatment with injected or nebulized IFN-β may have beneficial effects**

In vitro and in vivo?

- In patients with neutralizing auto-Abs against IFN-α2, the baseline levels of type I IFN-dependent transcripts were low,
- Neutralizing in vitro & in vivo
- Suggesting a pre-existing or concomitant biological impact in vivo




*IFN-α levels in the plasma or serum of patients.*

→ **Auto-Abs against type I IFNs are a cause of severe SARS-CoV-2 infection.**

→ Provides an explanation for the major sex bias in severe COVID-19 and the increase in risk with age

→ Clinical and therapeutic implications

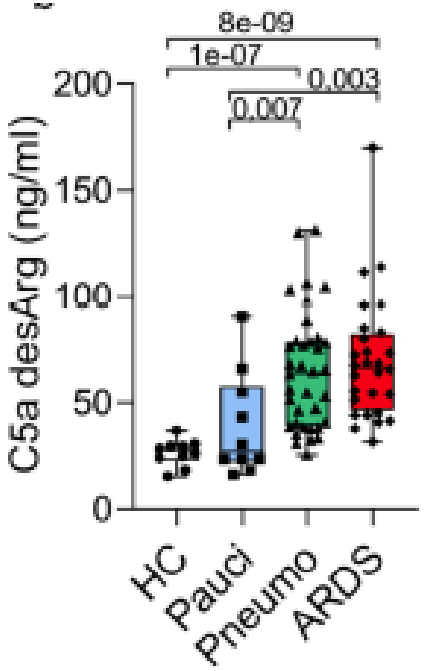
# C5a-C5aR1 axis & COVID-19

C5a anaphylatoxin and its receptor C5aR1 play a key role in the initiation and maintenance of inflammatory response

- Recruiting and activating neutrophils and monocytes

82 individuals: 10 healthy control, 10 paucisymptomatic COVID-19, 34 with pneumonia & 28 with ARDS due to SARS-CoV-2.

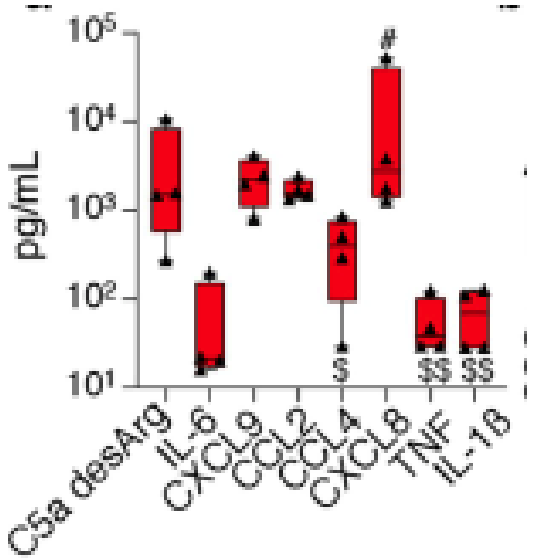
*Concentration of C5a desArg in plasma*




An increase in plasma C5a levels proportional to COVID-19 severity.

Increased systemic and local complement pathway activities on the peripheral blood.

*C5a is detected in lung sample from COVID-19 patients*




**Saliva specimens could be effective in the diagnosis of COVID-19**

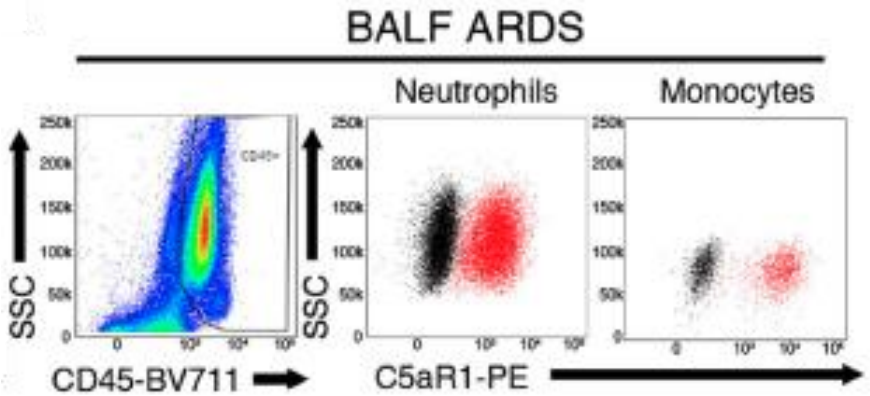
Carvelli J *et al Nature.* Jul 2020

# C5a-C5aR1 axis & COVID-19

C5a production leads to the chemo-attraction and activation of myeloid cells in the lung → release of inflammatory cytokines.

Possible that the vasculitis associated with severe COVID-19 is linked to the production of C5a.

*$CD45^+$ immune cell infiltration in BALF*
*C5a-R1 expression (red)*




Neutrophils and monocytes in BALF expressed C5aR1.

Potential therapeutic strategy → C5a-C5aR1 axis blockade.

Avdoralimab = mAb against C5aR1.

*In vitro*:

- inhibited C5a-induced neutrophil activation,
- Inhibited the C5a-induced migration of neutrophils.

*In mice*:

- Mice received an intranasal instillation of recombinant human C5a → developed ALI.
- Avdoralimab prevented albumin release in BALF
- Avdoralimab inhibited the increase in IL-6, TNF and CCL2.
- Avdoralimab inhibited ALI in mice

**CR5a-C5aR1 axis blockade might be used to prevent the excessive lung inflammation and endothelialitis associated with ARDS in COVID-19 patients**

# Risk factors of mortality

Nationwide cohort of all Danish individuals tested for SARS-CoV-2
The study cohort was linked to the Danish administrative and health registrie

<u>11 122 cases with PCR positive:</u> 80% were community-managed & 20% were hospitalized (whereas 2,8% in an ICU)

**30 days all cause of mortality = 5,2%**

<u>Risk factors of death</u>:

**Sex:**

- adjusted for age and number of co-morbidities, ORs = 2,1;$CI_{95\%}$ [1.7–2.6] for men

**Age:**

- 70 – 79 years: OR= 15; $CI_{95\%}$ [9– 26]
- 80-89 years: OR= 30; $CI_{95\%}$ [17–52]
- >90 years: OR= 90; $CI_{95\%}$ [50–162]

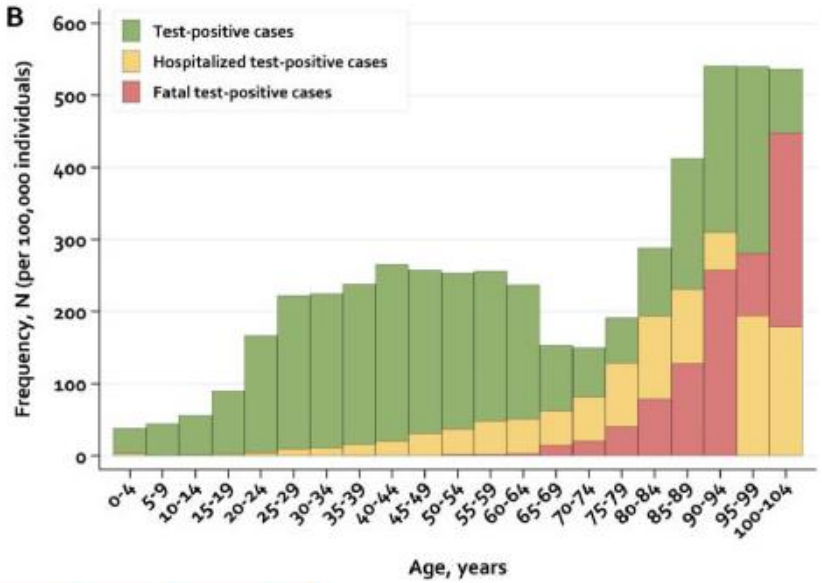
**Number of co-morbidities:**

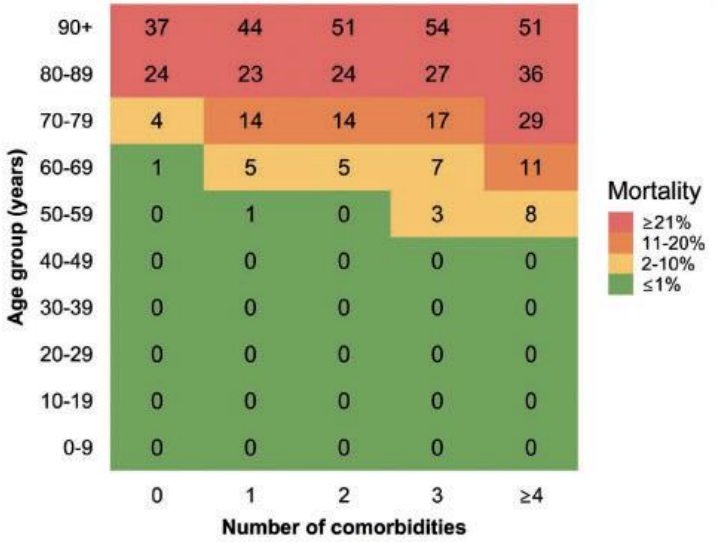
- OR=5.2; $CI_{95\%}$ [3.4–8.0], for cases with at least four co-morbidities
- 79% of deaths had at least two co-morbidities

**Chronic diseases:**

- Ischemic heart disease & hypertension → ORs 1,1 to 1,3
- Major psychiatric disorders & organ transplantation → ORs 2,5 to 3,2

*The proportion of hospitalized and fatal SARS-CoV-2 cases per 100 000 individuals relative to the total Danish population within each age group*




*Proportion of patients dying among SARS-CoV-2 PCR-positive cases within different subgroups of age and number of comorbidities*

# Antihypertensive drugs & COVID-19

- Observational study
- Lombardy Region in Italy - data extracted from the registry
- February 21 to March 11
- Patient older than 40 years
- 6272 cases matched to 30759 controls (on age, sex & municipality residence)
- Use of antihypertensive drugs
  - ARBs 22,2% among cases and 19,2% among controls
  - ACE inhibitors 23,9% among cases and 21,4% among controls

- **Neither ARBs nor ACE inhibitors had a significant association with risk of COVID-19**
  - Risk similar for women and men
  - Not modified by age – severity of clinical manifestation – course of COVID-19
  - No evidence of an independent relationship between RAAS blockers and the susceptibility to COVID-19

**Table 3. Odds Ratios for Covid-19 Associated with Use of Antihypertensive Drugs Dispensed as Monotherapy or Combination Therapy.**

| Variable | Odds Ratio for Covid-19 (95% CI)* | |
|---|---|---|
| | Unadjusted | Adjusted |
| No use during 2019 | 1.00 (reference) | 1.00 (reference) |
| Use only as monotherapy | 1.39 (1.28–1.51) | 1.03 (0.90–1.18) |
| Use as combination therapy | 1.60 (1.50–1.72) | 0.99 (0.90–1.09) |

* Shown are odds ratios for Covid-19 associated with drug use. Nonuse was considered as the reference. Estimates were obtained by fitting conditional logistic-regression models. Both unadjusted estimates and estimates that were fully adjusted for drugs and coexisting conditions are shown.

**Limits**

- Change in strategy to test for coronavirus during study
- Information on drug use is limited to prescription
- Exposure to antihypertensive drug not available after December 2019
- Control group included persons with COVID-19
- Unmeasured confounders

Mancia G. *et al. NEJM.* May 2020

# Antihypertensive drugs & COVID-19

- Observational study
- New-York University - Use of the NYU Langone Health
- March 1 to April 15, 2020
- All patients with Covid-19 test results recorded
- Extracted from the chart (preceding 18 months)
  - Medical history
  - Medication data
- For a given medication, used a propensity-score models that adjusted for multiple variable
- 12594 patients
  - 5894 COVID-19+
  - 4357 history of hypertension → 2573 COVID-19+
- **No association with any medication studied of**
  - **Risk of severe COVID-19**
  - **Increased likelihood of a positive test**

**Table 3. Likelihood of Severe Covid-19, According to Treatment with Various Antihypertensive Agents, in Propensity-Score–Matched Patients with a Positive Test for Covid-19, with Hypertension and Overall.***

| Medication | Matched Patients with Hypertension | | | All Matched Patients | | |
|---|---|---|---|---|---|---|
| | Severe Covid-19 in Patients Treated with Medication | Severe Covid-19 in Patients Not Treated with Medication | Median Difference (95% CI) | Severe Covid-19 in Patients Treated with Medication | Severe Covid-19 in Patients Not Treated with Medication | Median Difference (95% CI) |
| | *no./total no. (%)* | | *percentage points* | *no./total no. (%)* | | *percentage points* |
| ACE inhibitor | 139/584 (23.8) | 158/583 (27.1) | −3.3 (−8.2 to 1.7) | 150/627 (23.9) | 169/653 (25.9) | −1.9 (−6.6 to 2.8) |
| ARB | 161/629 (25.6) | 156/612 (25.5) | 0.1 (−4.8 to 4.9) | 162/664 (24.4) | 165/639 (25.8) | −1.4 (−6.1 to 3.3) |
| ACE inhibitor or ARB | 252/1019 (24.7) | 249/986 (25.3) | −0.5 (−4.3 to 3.2) | 275/1110 (24.8) | 274/1101 (24.9) | −0.1 (−3.7 to 3.5) |
| Beta-blocker | 210/792 (26.5) | 231/829 (27.9) | −1.4 (−5.7 to 3.0) | 230/912 (25.2) | 250/976 (25.6) | −0.4 (−4.3 to 3.6) |
| Calcium-channel blocker | 253/950 (26.6) | 207/930 (22.3) | 4.4 (0.5 to 8.2) | 263/992 (26.5) | 235/976 (24.1) | 2.4 (−1.4 to 6.2) |
| Thiazide diuretic | 116/515 (22.5) | 114/520 (21.9) | 0.6 (−4.5 to 5.7) | 120/549 (21.9) | 149/590 (25.3) | −3.4 (−8.3 to 1.6) |

* Severe Covid-19 was defined as admission to the intensive care unit, the use of noninvasive or invasive mechanical ventilation, or death.

**Limits**

- Variation in the diagnostic characteristic for the COVID-19 testing method
- Multiple tests for some patients
- Some patients may have been tested at other heath systems
- May not reflect actual drug exposure
- Not account for socioeconomic status, insurance, …
- Additional unmeasured confounders

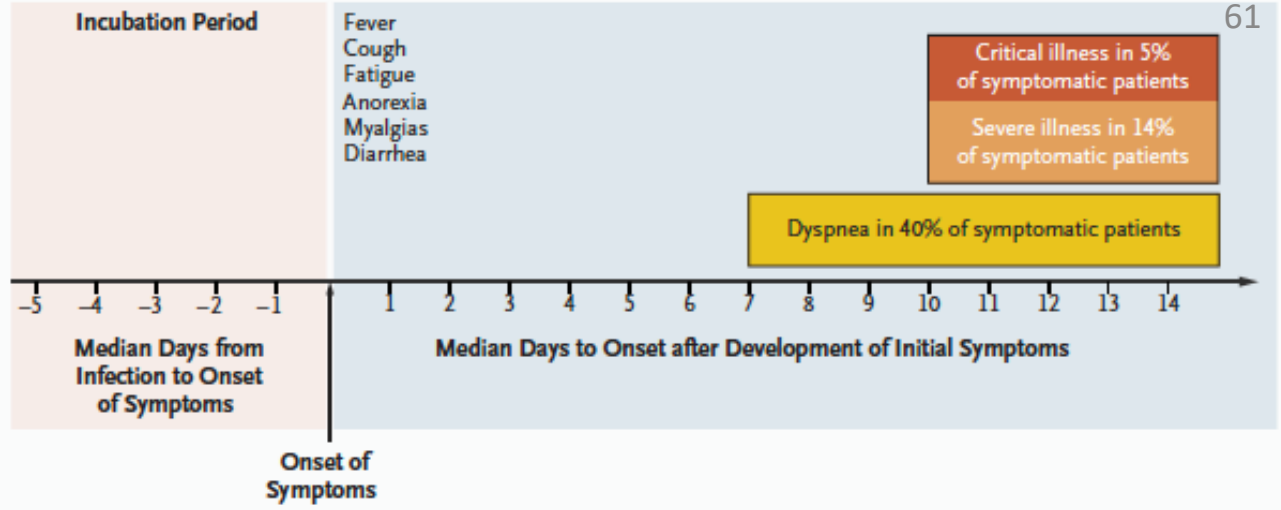
**→Rule out that the risk was higher among treated patients than among untreated patients**

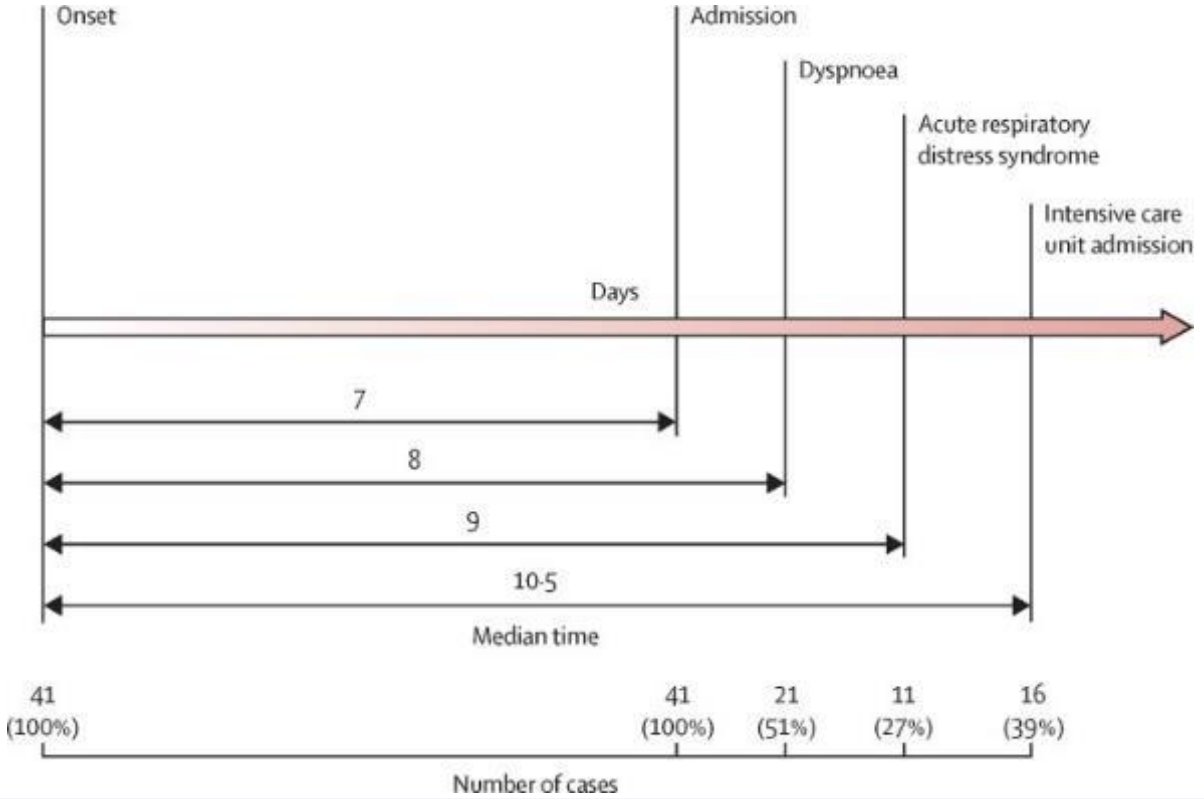
Reynolds HR. *et al. NEJM.* May 2020

# Clinical features

**Median time** (41 patients admitted to hospital)

- From onset of symptoms to first hospital admission
  - **7 days** [4,0–8,0]
- From illness onset to dyspnea
  - **8 days** [5,0–13,0]
- To ARDS
  - **9 days** [8,0–14,0]
- To ICU admission
  - **10,5 days**
- To mechanical ventilation
  - **10,5 days** [7,0–14,0]




Huang C *et al. Lancet*. Feb 2020

Berlin DA. *et al. NEJM*. May 2020

# Clinical features

China, **1 590 hospitalized** patients (13,4% of all cases reported in China)

Age (median): 48,9 ± 16,3 years

Male: 904 (57,3 %)

**Comorbidities**

- Hypertension: 16,9 %
- Diabetes: 8,2 %
- CHD: 3,7 %
- Cerebrovascular disease: 1,9 %
- COPD: 1,5 %
- Chronic kidney disease: 1,3 %
- Malignancy: 1,1 %

**Symptoms**

- Fever: 88 %
- Cough: >70 %
- Fatigue: 42,8 %
- Shortness of breath: 20,8 %
- Myalgia/arthralgia: 17,5 %
- Pharyngalgia: 14,7 %
- Headache: 15,4 %
- Chill: 12,2 %
- Nausea/vomiting: 5,8 %
- Diarrhea: 4,2 %

**Abnormal chest CT**: 1130 (71,1 %)

**Outcomes**

- Critical illness: 131 (8,24 %)
- ICU admission: 99 (6,23 %)
- Mechanical ventilation: 50 (3,1 %)

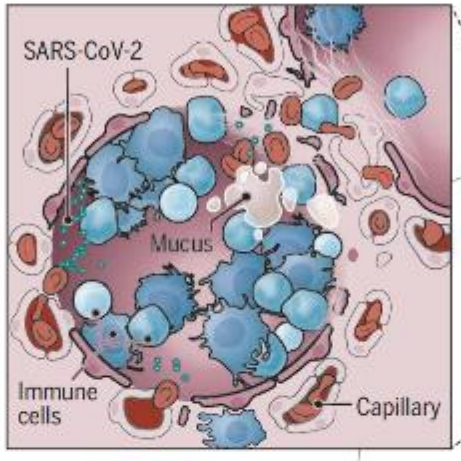
**Case fatality rate**: 50 (3,1 %)

# Organ damage

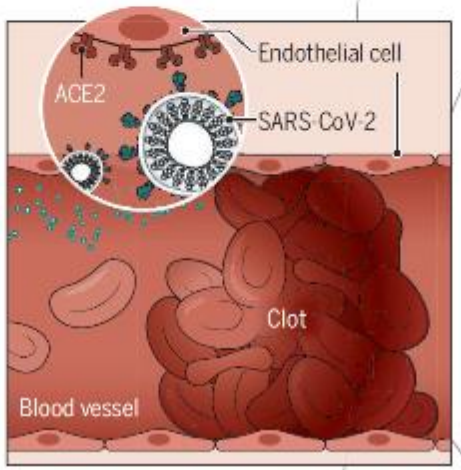
## An invader's impact

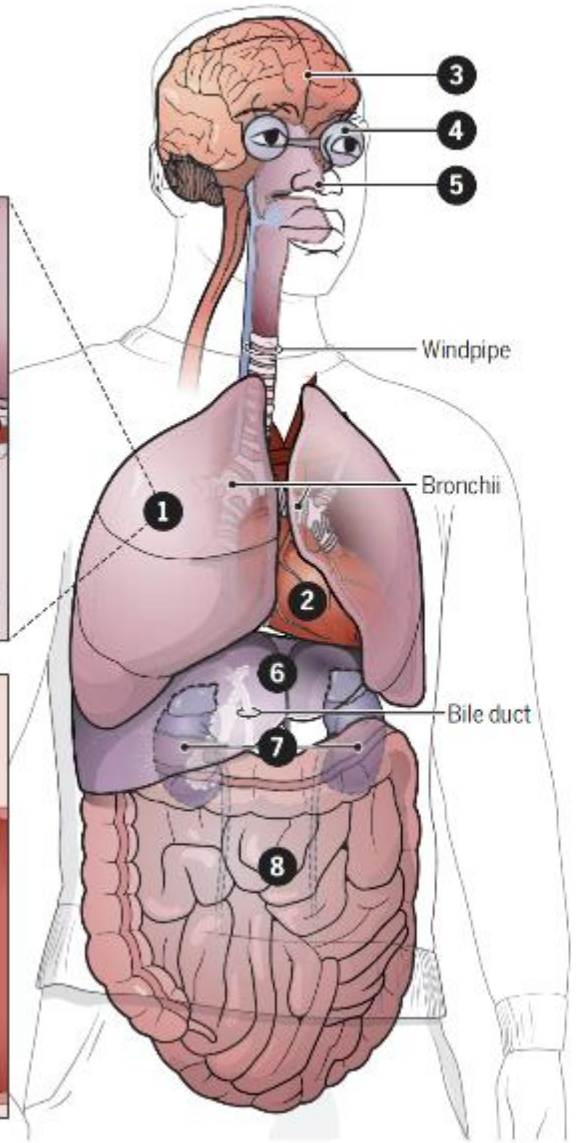
In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body's response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm.

**1 Lungs**
A cross section shows immune cells crowding an inflamed alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fevers rise, and breathing becomes labored.




**2 Heart and blood vessels**
The virus (teal) enters cells, likely including those lining blood vessels, by binding to angiotensin-converting enzyme 2 (ACE2) receptors on the cell surface. Infection can also promote blood clots, heart attacks, and cardiac inflammation.




**3 Brain**
Some COVID-19 patients have strokes, seizures, confusion, and brain inflammation. Doctors are trying to understand which are directly caused by the virus.

**4 Eyes**
Conjunctivitis, inflammation of the membrane that lines the front of the eye and inner eyelid, is more common in the sickest patients.

**5 Nose**
Some patients lose their sense of smell. Scientists speculate that the virus may move up the nose's nerve endings and damage cells.

**6 Liver**
Up to half of hospitalized patients have enzyme levels that signal a struggling liver. An immune system in overdrive and drugs given to fight the virus may be causing the damage.

**7 Kidneys**
Kidney damage is common in severe cases and makes death more likely. The virus may attack the kidneys directly, or kidney failure may be part of whole-body events like plummeting blood pressure.

**8 Intestines**
Patient reports and biopsy data suggest the virus can infect the lower gastrointestinal tract, which is rich in ACE2 receptors. Some 20% or more of patients have diarrhea.

Wadman M *et al. Science*. Apr 2020

# Radiology

Monocentric – from 16 January to 17 February

90 patients - Median follow up: 18 days [5 – 43]

<u>CT interpretation</u> (366 CT scan)

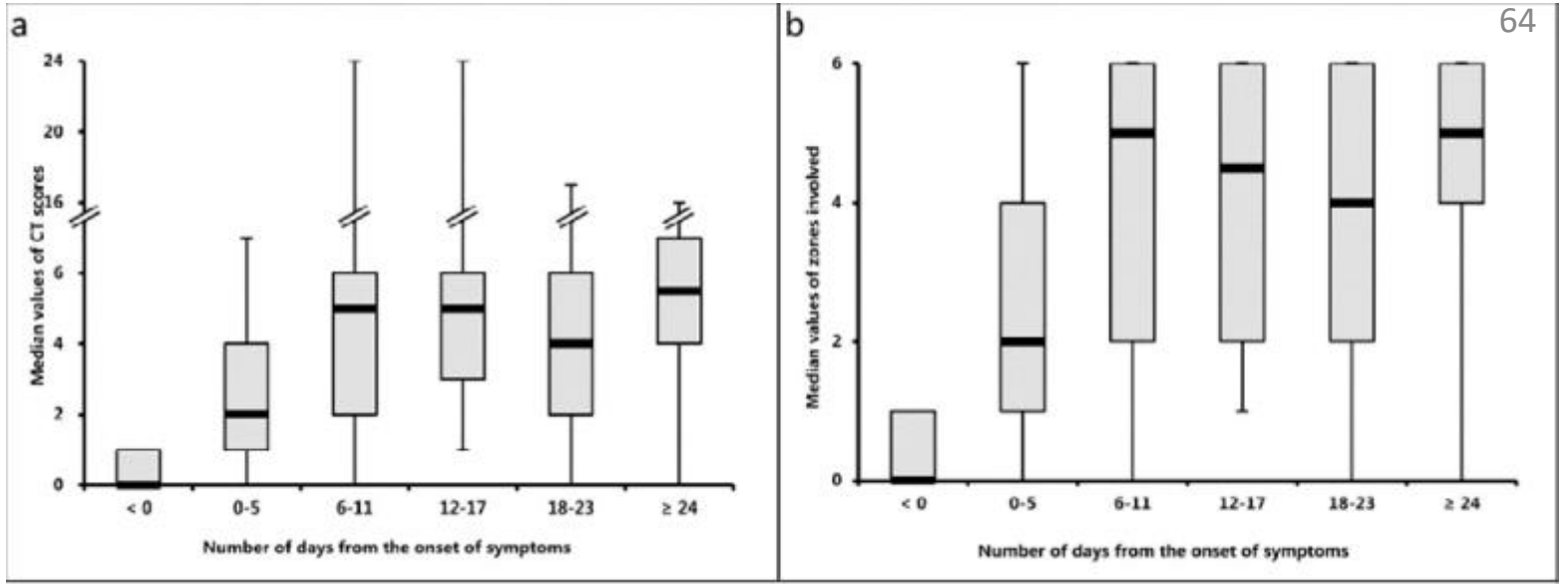
→ Each lung divided into 3 zones

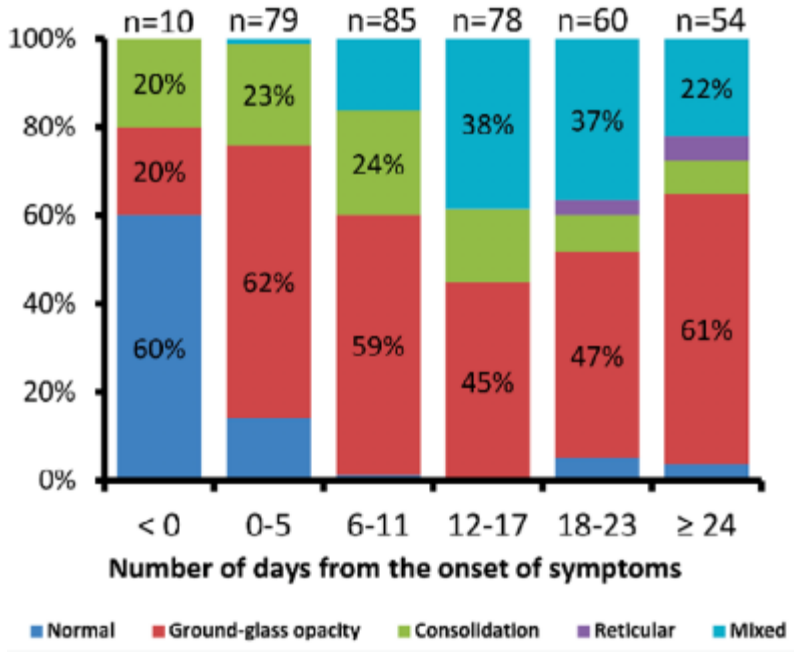
→ Overall CT score (max = 24)

<u>Results</u>

- Increase median values of CT score with time
- Peak levels of lung involvement: 6-11d from symptom onset
- Ground glass opacity (GGO) is the most common finding
- More diverse manifestations around 6-11d and after
- Sensitivity of CT for SARS-CoV-2 increase over time
- At discharge: 64% still had abnormalities

<u>Limitations :</u> No subgroup analysis (mild and severe)



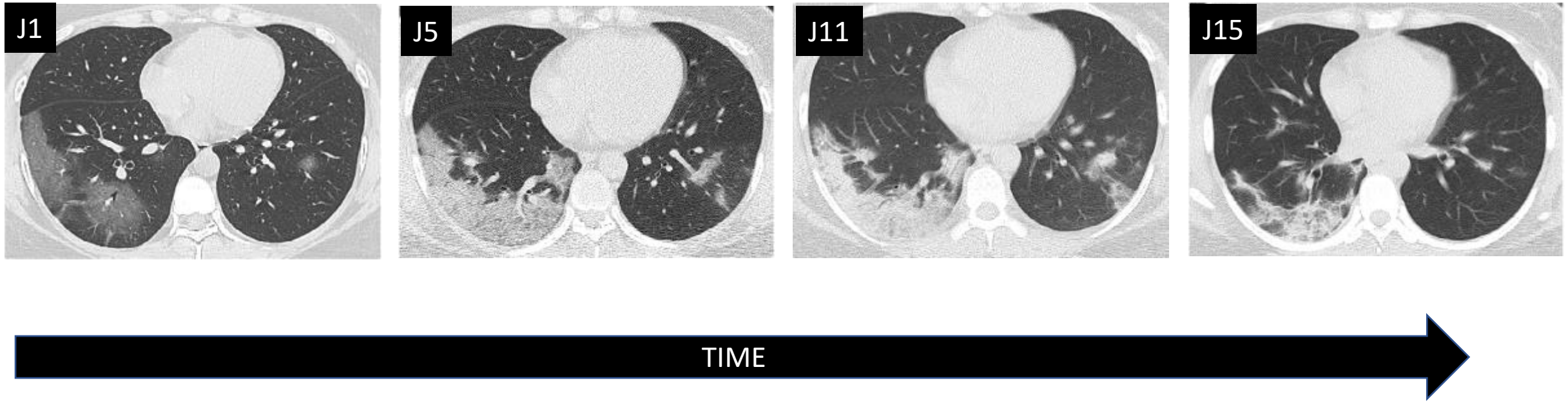

**→Bilateral GGO is the most common manifestation**

**→Rapid extension and specific pattern of evolution**

Wang Y *et al. Radiology*. Mar 2020

# Radiology

Ground glass opacity in a 35-year-old woman with COVID-19 pneumonia






Wang Y *et al. Radiology*. Mar 2020

# Heart & COVID-19

**Acute myocarditis**

- 7 – 17% of hospitalized patients
- 22 – 31% patients admitted in ICU
- 7% of COVID-19 related deaths

**Acute myocardial infarction**

- Viral illness → increase the risk
- Inflammation + hypercoagulability → increased risk

**Acute heart failure**

- 20-25% of patients in their initial presentation
- Increased risk of mortality
- New cardiomyopathy or exacerbation?

**Dysrhythmias**

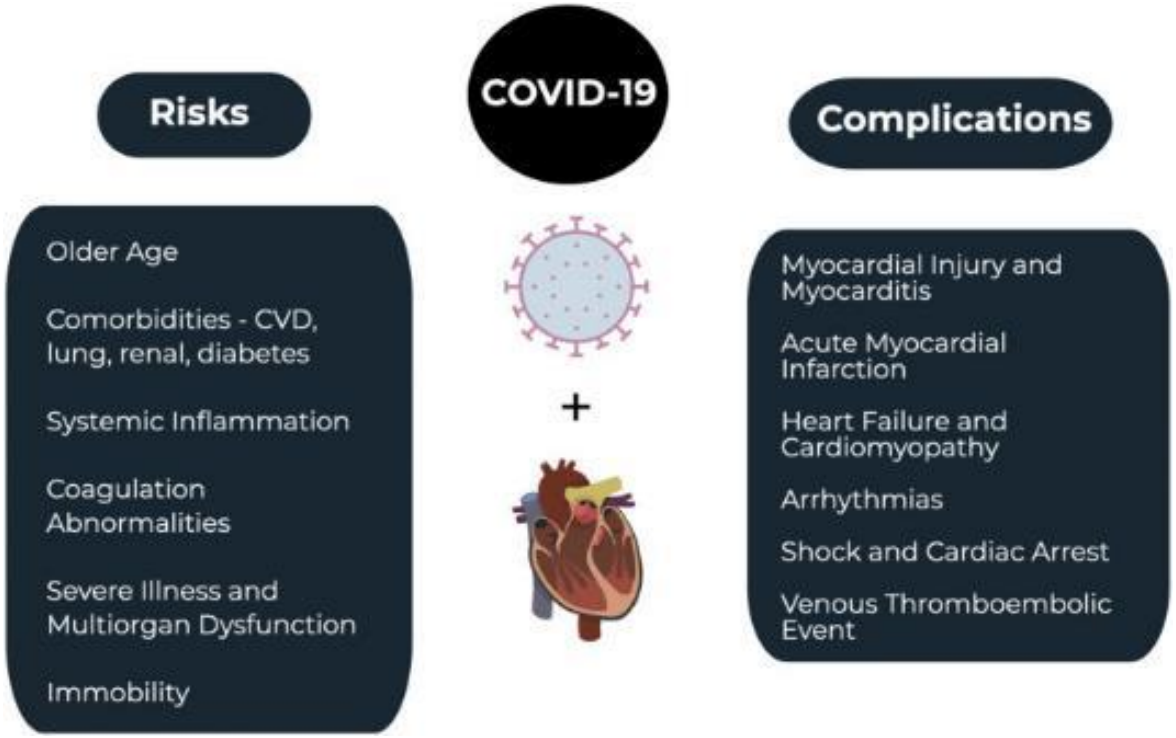
- 17% of hospitalized and 44% of ICU patients
- Hypoxia, inflammatory, abnormal metabolism

**Venous thromboembolic event**

- Increased risk
- Inflammation, organ dysfunction, abnormal coagulation
- 16-17% of pulmonary embolism

ECG and echocardiographic abnormalities

- Correlated with worse outcomes






Long B et *al. Am J Emerg Med*. Apr 2020

# Kidney & COVID-19

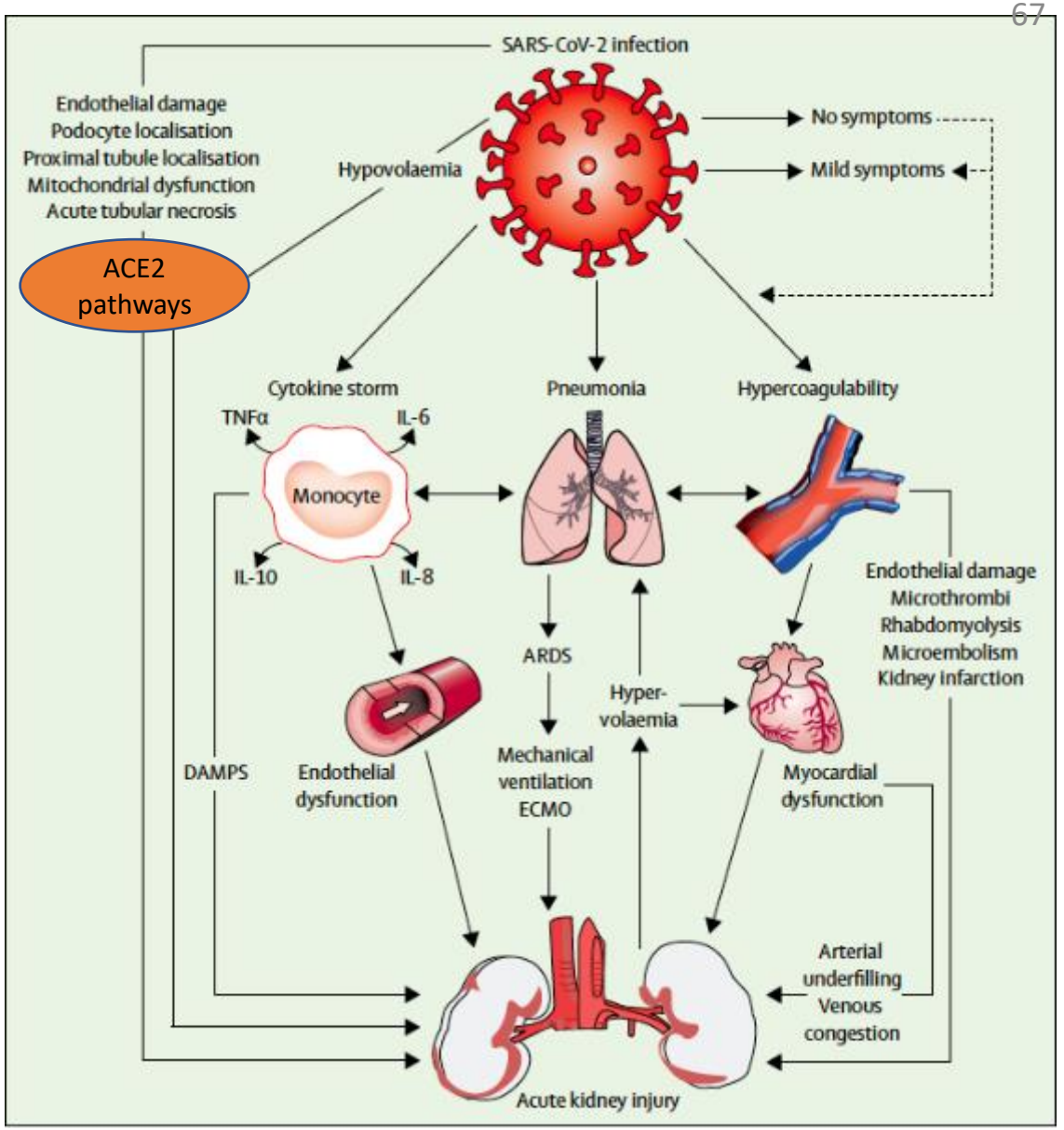
**Introduction**

- > 40% cases of COVID-19 have abnormal proteinuria at hospital admission
- Patients admitted to ICU with COVID-19:
  - 20 to 40% have an AKI
  - 20% require renal replacement therapy (RRT)

**Pathophysiology → multifactorial with predisposing factors**

**Management**

- Implementation of KDIGO guidelines
- Restore normal volume status
- Reduce the risk of
  - Pulmonary oedema
  - Right ventricular overload
  - Congestion
- Application of lung-protective ventilation
- RRT
  - Volume overload ± refractory hypoxemia
  - Right jugular vein
  - Anticoagulation protocols: LMWH or UFH




Ronco.C et *al. Lancet Respir Med*. May 2020

# Kidney & COVID-19

Prospective cohort – 1 hospital in China – **701 patients**

- Prevalence of acute kidney injury (AKI)?
- Association between markers of kidney injury and death?

Age (median): 63 years with 52,4% male
Illness onset to admission: 10 days

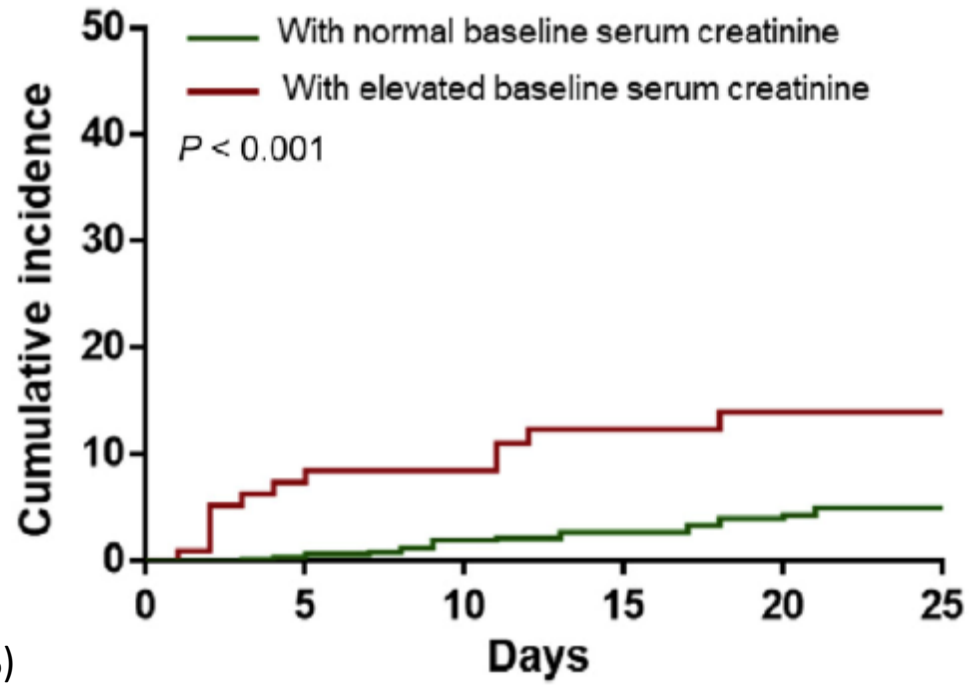
Kidney injury (**at admission**)

- Elevated serum creatinine (SC) at admission 14,4%
- Elevated BUN at admission 13,1%
- GFR<60 ml/min/1,73m$^2$ for 13,1%
- Proteinuria (43,9%) & hematuria (26,7%)

AKI and hospital death

- Prevalence of AKI: 5,1% - higher in patients with elevated SC at admission(11,9%)
- In hospital death: 16,1%
  - 33,7% in patient with elevated SC at admission vs 13,2% others (p<0,05)

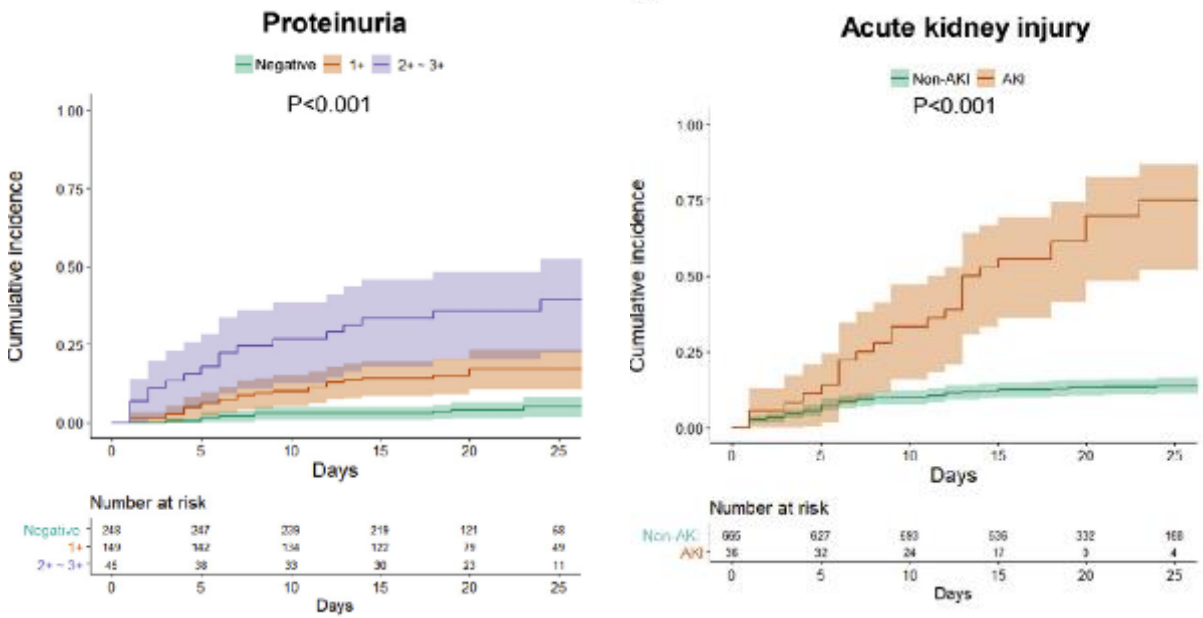
*Cumulative incidence of AKI subgrouped by baseline serum creatine*




Cheng Y et *al. Kidney Int*. May 2020

# Kidney & COVID-19

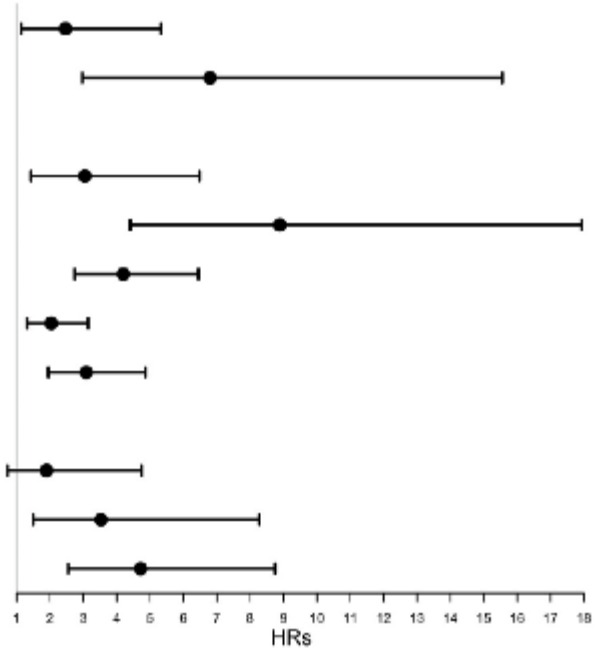
**Kidney abnormalities → ↑ in hospital death**




*Cumulative incidence for in-hospital death*

After adjusting

| Variables | HRs | 95% CI |
|---|---|---|
| Proteinuria | | |
| 1+ | 2.47 | 1.15–5.33 |
| 2+ ~ 3+ | 6.80 | 2.97–15.56 |
| Hematuria | | |
| 1+ | 3.05 | 1.43–6.49 |
| 2+ ~ 3+ | 8.89 | 4.41–17.94 |
| Elevated baseline blood urea nitrogen | 4.20 | 2.74–6.45 |
| Elevated baseline serum creatinine | 2.04 | 1.32–3.15 |
| Peak serum creatinine > 133 μmol/l | 3.09 | 1.95–4.87 |
| Acute kidney injury | | |
| Stage 1 | 1.90 | 0.76–4.75 |
| Stage 2 | 3.53 | 1.50–8.27 |
| Stage 3 | 4.72 | 2.55–8.75 |




→ High prevalence of kidney disease among hospitalized patients with COVID-19

→ Association between kidney involvement and poor outcome
→ Early detection and effective intervention of kidney involvement

→ Impact on long-term outcomes?

# Neuropsychiatric disorders & COVID-19

Online network of secure rapid-response case report notification portals (CoroNerve platforms)
From April 2 to April 26, 2020 in the UK
**153 unique cases** (correlated with the national case identification data)

- 114 = confirmed SARS-CoV-2 infection
- 6 = probable SARS-CoV-2 infection
- 5 = possible SARS-CoV-2 infection
- 28 excluded because missing data

<u>4 clinical syndromes associated with COVID-19</u>

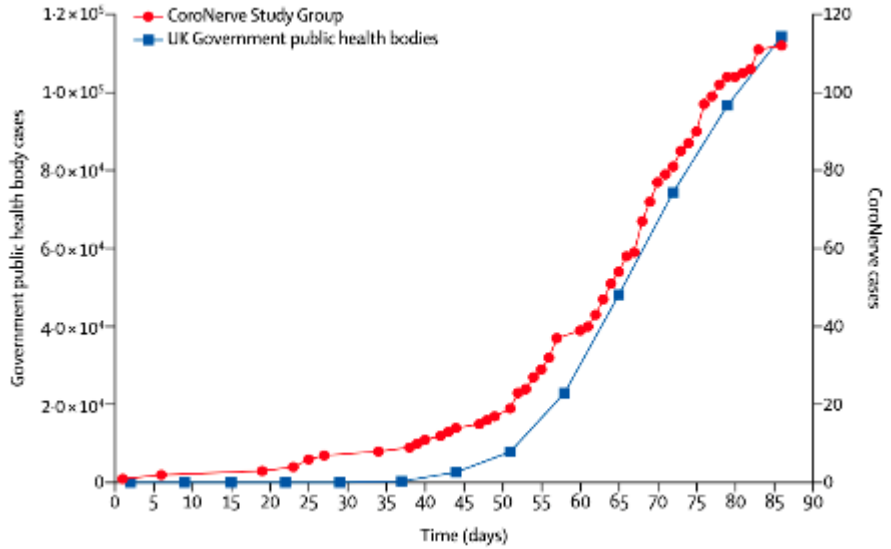
- **Cerebrovascular event** = 77 cases
  - Ischemic stroke / intracerebral hemorrhage
- **Altered mental status** = 39 cases
  - Encephalopathy /encephalitis / primary psychiatric diagnoses / …
- **Peripheral neurology** = 6 cases
- **Other neurological disorders** = 3 cases

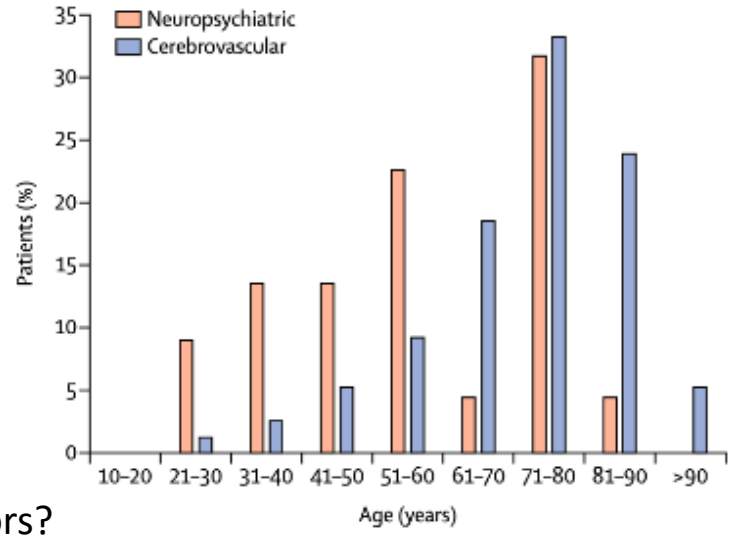
Acute alteration in mental status were overrepresented in young patients

→Cerebrovascular events in COVID-19 → vasculopathy

→Viral neurotropism? Host immune responses? Genetic factors?

*Temporal distribution for cases notified to the CoroNerve Study group*



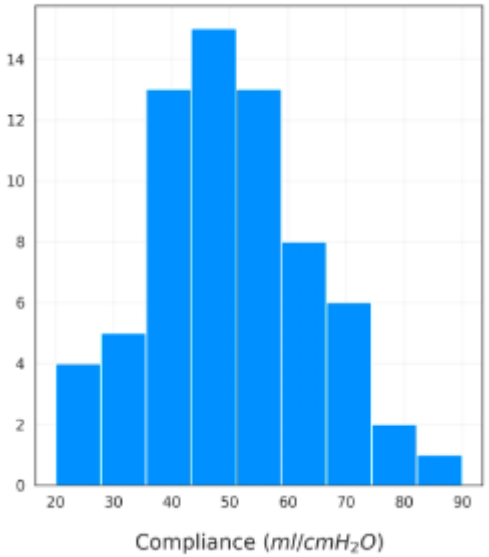



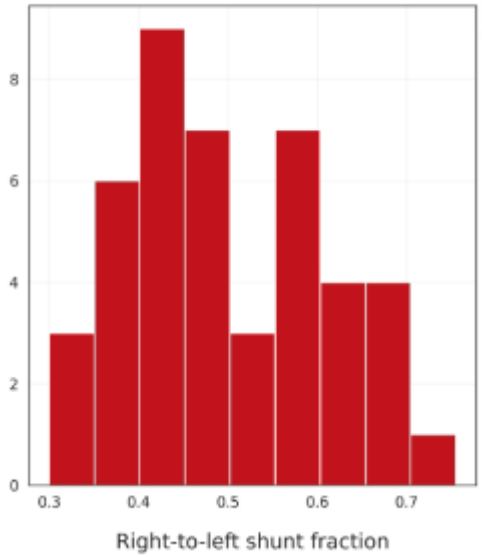

*Age distribution of patients – case definitions for cerebrovascular and neuropsychiatric events*

Varatharaj A et *al. Lancet Psychiatry*. June 2020

# ARDS & COVID-19

- Atypical form of ARDS
- Dissociation in more than 50%:
  - Well preserved lung mechanics
  - Severity of hypoxemia




**2 types of phenotypes**

**Type «L»: *Low elastance***

- Gas volume nearly normal
  - **Vt 7-8 ml/kg → DV<14cm$H_2O$**
- Recruitability is low
  - **PEP<12cm$H_2O$**
- Loss of hypoxic pulmonary vasoconstriction
- Ventilation/perfusion mismatch → hypoxemia
- Low lung weight → ground glass densities

**Type «H»: *High elastance*** *(10 – 30%)*

Evolution of the COVID-19 injury attributable to P-SILI

- Increase oedema → decrease gas volume
  - **Vt = 6ml/kg → DV<14cm$H_2O$**
- Recruitability is high
  - **PEP>12cm$H_2O$** (carefully)
- High lung weight → bilateral condensations
  - **Prone position**

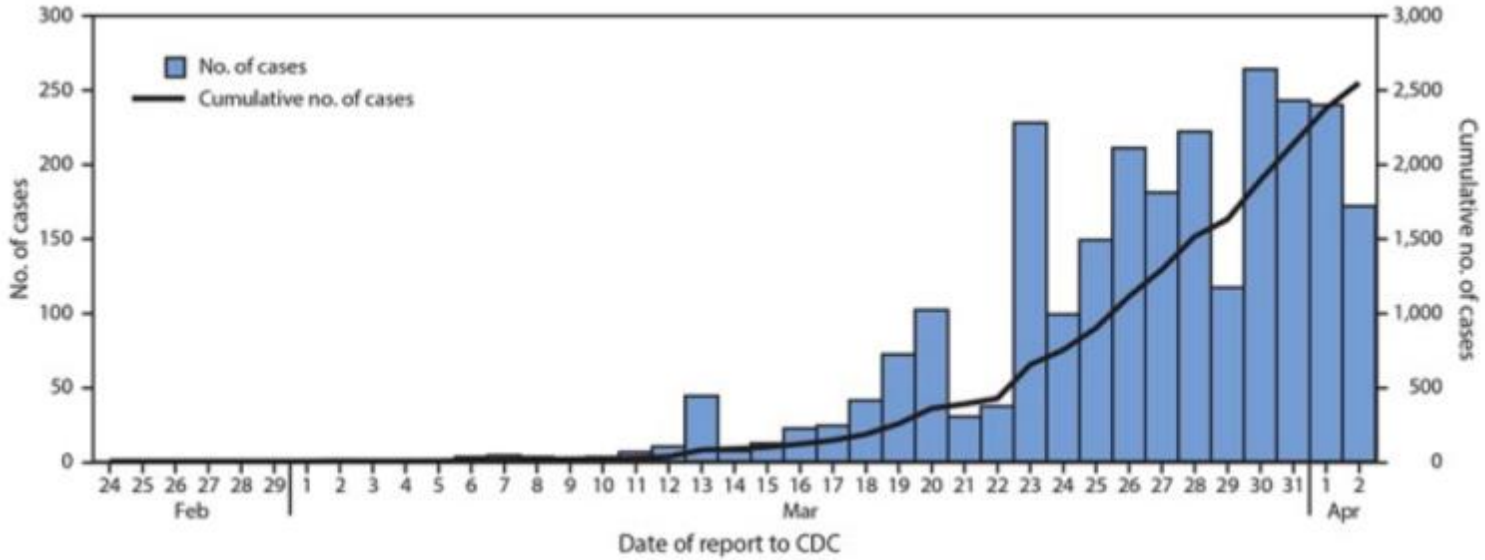
*CT scan*
*A: spontaneous breathing*
*B: mechanical ventilation*

# 2549 children in USA

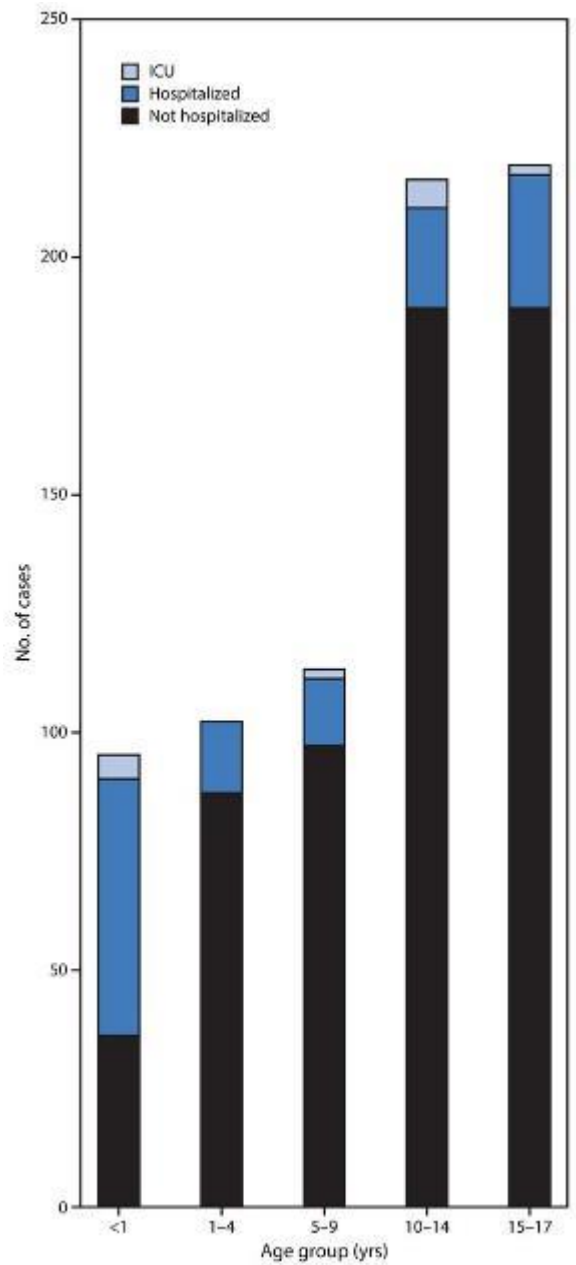
- Age (median): 11 years [0 – 17]
- Male: 57 %
- Exposure to a COVID-19 patients: 91% (household / community)

- **Symptoms** (on 291 cases)
  - Fever: 56%
  - Cough: 54%
  - Dyspnea: 13%
  - Diarrhea: 13%
  - Nausea/vomiting: 11%
  - Abdominal pain: 5,8%
  - …

- **Outcomes** (on 745 cases)
  - Hospitalized: 147
  - ICU admission: 15
- **Case fatality rate**: 0,1%




*Children aged <18 years, by date reported to CDC*




CDC COVID19 Response Team *MMWR*. Apr 2020

# Pediatric inflammatory multisystem syndrome

**Observation of a large number of children hospitalized for cardiogenic shock potentially associated with SARS-CoV-2**

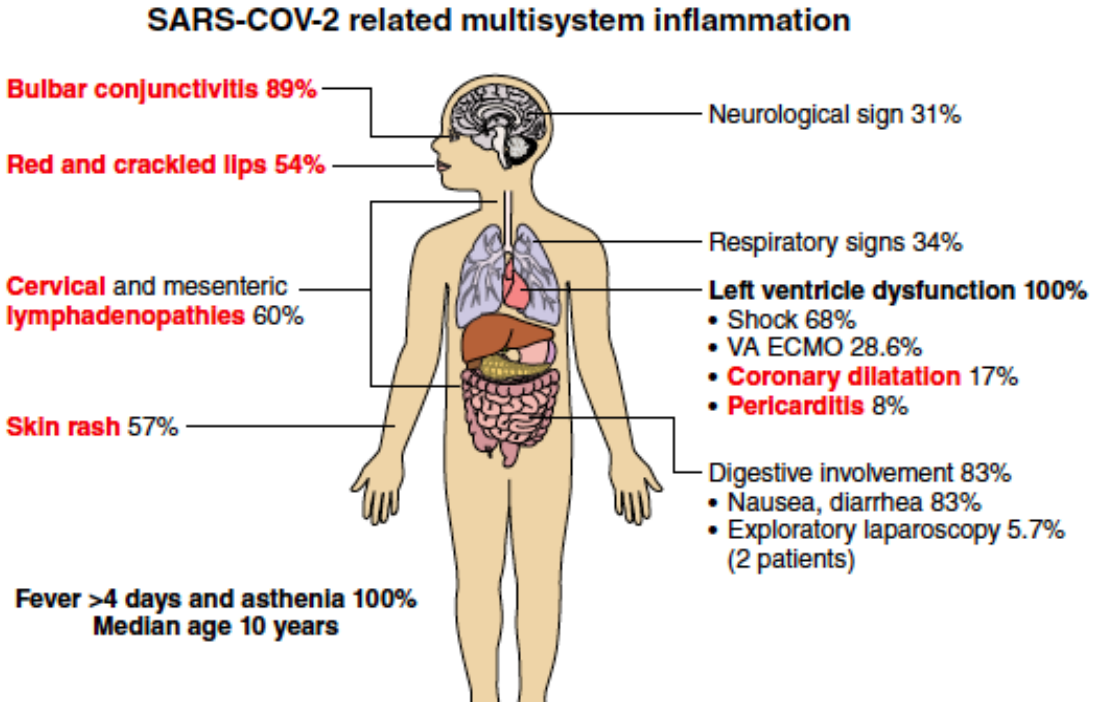
- Retrospective cohort – 2 countries (France & Switzerland) – 14 centers
- 35 children - Age (median): 10 years [2 – 16] – 51% were male
- 88% were positive for SARS-CoV-2 (nasopharyngeal swabs or serology)

Evolution

- 71% had total recovery left ventricular ejection fraction at day 7
- Time to full recovery = 2 days [2 – 5]

Treatment (no recommendation for the moment)

- 62% had invasive respiratory support
- 28% needed VA-ECMO




New disease related to SARS-CoV-2? No precise arguments
Shares some similarities with KD

→ Understanding the immune mechanisms of this disease is a priority

**Differences with Kawasaki disease**

- Older (median age: 8 to 10y)
- Incomplete forms of KD
- Limited number of coronary artery dilatation

Belhadjer Z et *al. Circulation*. May 2020

# Pediatric inflammatory multisystem syndrome

Cohort of patients with KD in Paris region associated with SARS-CoV-2 (→ 16 patients)

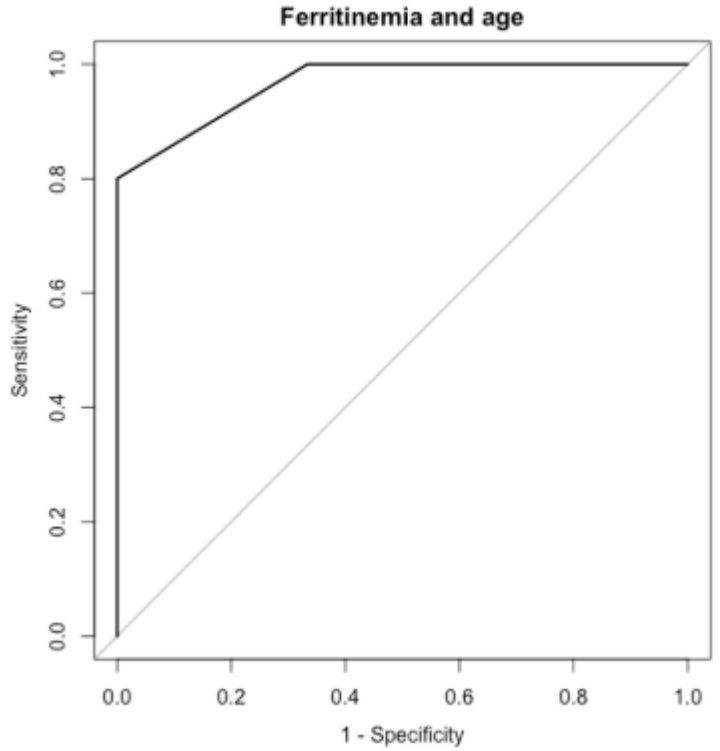
Compared with a historical cohort of «classical KD» (→ 220 patients)

<u>Cohort of Kawa-COVID-19</u>

- Median age = 10 y IQR [4,7 – 12,5]
- Median time from the onset of KD to hospitalization was 5 days
- RT PCR all site positive: 69% (11 cases)
- Cardiac ultrasound was abnormal in 11 patients
- No death – all are in remission

<u>Kawa-COVID-19 versus historical cohort</u>

- Older 10 vs 2 years (*p<0,0001*)
- Lower platelet count (*p<0,0001*)
- Lower lymphocyte counts (*p<0,0001*)
- Higher frequency of cardiac involvement: myocarditis & pericarditis




*ROC curve of the severity score*

<u>Factor prognostic for the development of severe disease</u>

- **Age > 5 years**
- **Ferritinaemia >1400 µg/L**

# CLINICAL (October 12th 2020)

**1.What is the mechanism of action of SARS-CoV-2? Cell immunity?**

- Uses ACE2 receptor to enter the cell and can produce a cytokine storm
- Activation of innate and adaptative immune pathways
- Induces long lasting T cell immunity against the structural N protein
- Recurrent anti-SARS-CoV-2 RBD antibodies with potent neutralizing activity can be found in all individuals
- Auto-Abs against type I IFNs are a cause of severe SARS-CoV-2 infection

**2. What is the clinical presentation of COVID-19 in adults and children?**

- Most persons are asymptomatic or mildly symptomatic
- Independent risk factors of mortality: age – obesity – chronic disease
- Children are less represented than adults and have less severe or critical forms of the disease

**3. Is there multiple-organ damage?**

- Predominantly lung damage → prognostic of the disease
- Several cases of heart & kidney damage

# THERAPEUTIC

**Questions:**

- What drug showed clinical efficacy?
- What drugs did not show proven benefits?
- What are the types of vaccines in clinical evaluation?

# COVID-19 Treatment

- **Dexamethasone** is the first drug to show life-saving efficacy in patients infected with COVID-19
- More data from clinical trials are needed

## Classes of treatment

### Anti viral effect

- Remdesivir
- ~~(Hydroxy)chloroquine~~
- ~~Lopinavir/ritonavir~~

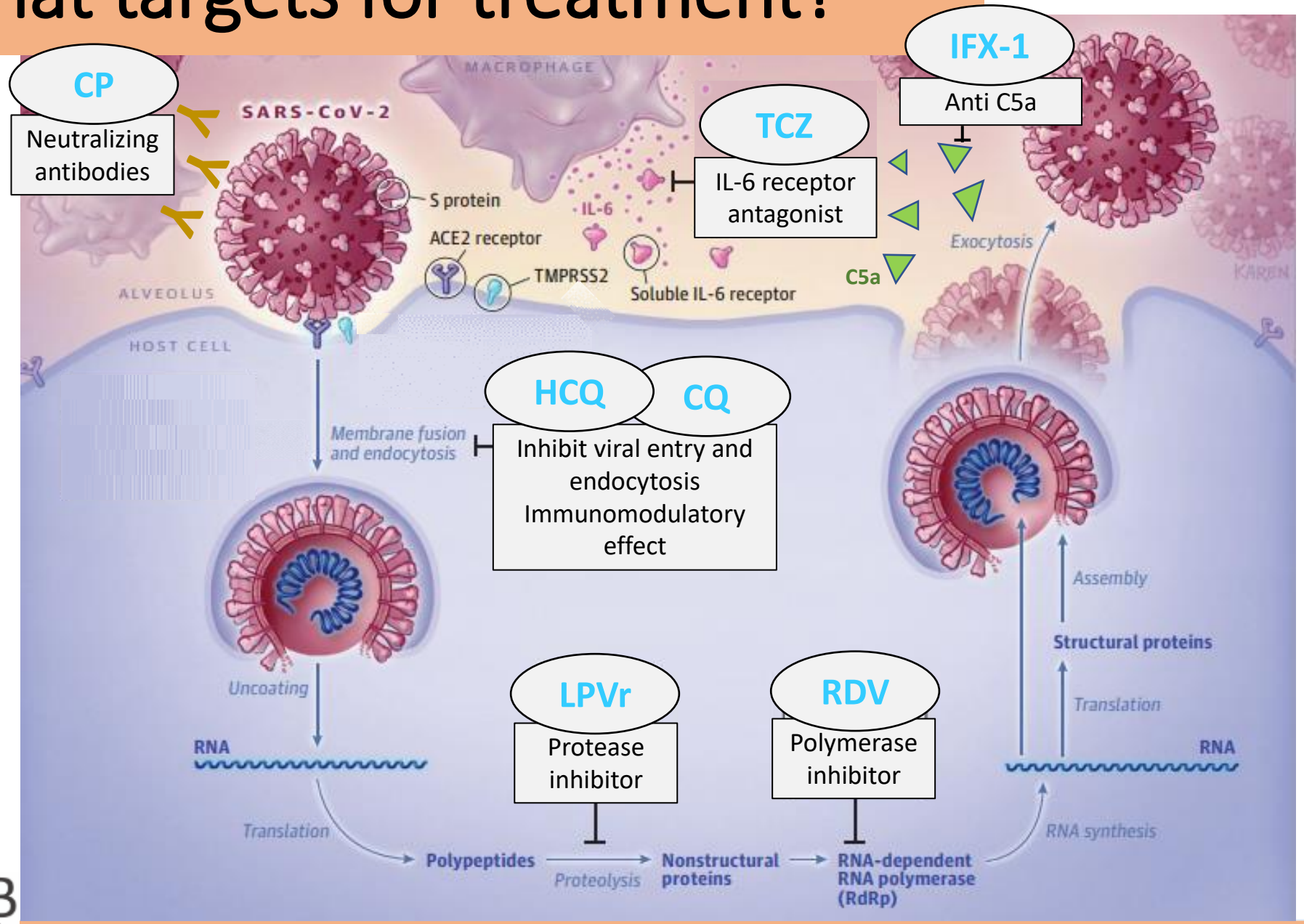
### Immunomodulatory effect

- Corticosteroids
- Monoclonal antibody

### Passive immunity

- Convalescent plasma

# What targets for treatment?




**CT:** corticosteroids
**CP**: convalescent plasma
**CQ:** chloroquine
**HCQ**: hydroxychloroquine
**IFX-1:** vilobelimab
**LPVr**: lopinavir/ritonavir
**RDV**: remdesivir
**TCZ**: tocilizumab

Sanders JM *et al. JAMA.* May 2020

Anti viral effect

# Hydroxychloroquine (HCQ)

| 1st Author | Design | Groups | Participants | Primary outcome | Main results (Primary outcome) |
|---|---|---|---|---|---|
| Boulware | Randomized, double-blind, placebo-controlled | HCQ *vs* placebo (**Post exposure prophylaxis, Not Hospitalized**) | N= 821 Exposed to a known COVID-19 individual | Incidence of either laboratory confirmed COVID-19 or illness compatible with COVID-19 within 14 days | HCQ group: 49/414 (11,8%) *vs.* placebo group: 58/407 (14,3%); p=0,35 |
| Geleris | Observational, not randomized | HCQ *vs.* no HCQ (**Hospitalized**) | N= 1376 Moderate-to-severe respiratory illness | Time from study baseline to intubation or death | HR: 1.04 $CI_{95\%}$[0,82-1,32] |
| Tang | Randomized, controlled, multicenter, open label | HCQ + SoC *vs.* SoC (**Hospitalized**) | N= 150 Mild to moderate or severe disease | D28 negative conversion of SARS-CoV-2 | HCQ + SoC: 85,4%, $IC_{95\%}$[73,8% - 93,8%] *vs.* SoC: 81,3%, $IC_{95\%}$[71,2%-89,6%] |

No virological data on some studies.

No proven benefits

AZ: azithromycin – ED: emergency department – HCW: health care worker – HCQ: hydroxychloroquine

Anti viral effect

# Hydroxychloroquine (HCQ)

| 1st Author | Design | Groups | Participants | Primary outcome | Main results (Primary outcome) |
|---|---|---|---|---|---|
| Abella | Randomized, double-blind, placebo-controlled | HCQ *vs* placebo (**HCWs, pre-exposure prophylaxis**) | N=130 Hospital HCW (ED and COVID-19 units) | Incidence of SARS-CoV-2 infection | Early termination of the study HCQ group: 4/64 (6,3%) *vs.* placebo group: 4/61 (6,6%); p > 0,99 |
| Cavalcanti | Multicenter, randomized, open-label, controlled | HCQ + AZ *vs.* SoC, HCQ *vs.* SoC, HCQ + AZ *vs.* HCQ (**Hospitalized**) | N= 667 No supplemental $O_2$ or a maximum of 4 L/min supplemental | D15 clinical status (seven-level ordinal scale) | HCQ + AZ *vs.* control: OR: 0,99 $IC_{95\%}$ [0,57-1,73]; HCQ *vs.* control: OR: 1,21 $IC_{95\%}$ [0,69-2,11]; HCQ + AZ *vs.* HCQ: OR: 0,82 $IC_{95\%}$ [0,47-1,43] |
| RECOVERY | Randomized, controlled, open-label | HCQ *vs.* usual care (**Hospitalized**) | N= 4717 Not specified | D28 mortality | HCQ group: 421/1561 (27.0%) vs. usual care group: 790/3155 (25.0%) RR: 1.09; $IC_{95\%}$ [0,97-1,23]; p=0,15 |

No virological data on some studies.

No proven benefits

AZ: azithromycin – ED: emergency department – HCW: health care worker – HCQ: hydroxychloroquine

Cavalcanti *et al*. *NEJM.* Jul 2020 Abella BS *et al. JAMA Int Med.* Sep 2020
RECOVERY *NEJM.* Oct 2020

Anti viral effect

# Lopinavir/ritonavir (LPVr)

| 1st Author | Design | Groups | Participants | Primary outcome | Main results (Primary outcome) |
|---|---|---|---|---|---|
| Schoergenhofer | Experimental | One group (**non ICU Hospitalized**) | N= 8<br>Not specified | LPVr plasma concentration | LPV plasma concentration: approximately 2-fold higher than HIV patients receiving the same dose (7.1 µg/mL)<br>60 to 120-fold higher concentrations are required to reach the assumed LPV EC50 at trough levels |
| Cao | Randomized, controlled, open-label | LPVr *vs.* SoC (**Hospitalized**) | N= 199<br>$SaO_2 \leq 94\%$ or $PaO_2/FiO_2 < 300$ mm Hg | Time to clinical improvement | LPVr group **not associated** with a difference in time to clinical improvement<br>HR: 1,31 $CI_{95\%}$[0,95-1,80] |
| Zhang | Systematic review and meta-analysis | LPVr *vs.* control specified (**Hospitalized**) | N= 4 023<br>Not specified (meta-analysis) | Mortality rate and ARDS rate | ARDS: LPVr group 15,6% *vs.* control group 24,2%; p=0,49<br>Mortality rate: LPVr group 6,2% *vs* control group 5,5%; p=0,93 |
| RECOVERY | Randomized, controlled, open-label | LPVr + SoC *vs.* SoC (**Hospitalized**) | N=5 040<br>Not specified | 28-day all-cause mortality | LPVr + SoC group: 364/1616 (23%) *vs.* SoC group 767/3424 (22%); RR: 1,03 $CI_{95\%}$[0,91-1,17], p=0,60 |

LPVr : Lopinavir/ritonavir – SoC: Standard of Care

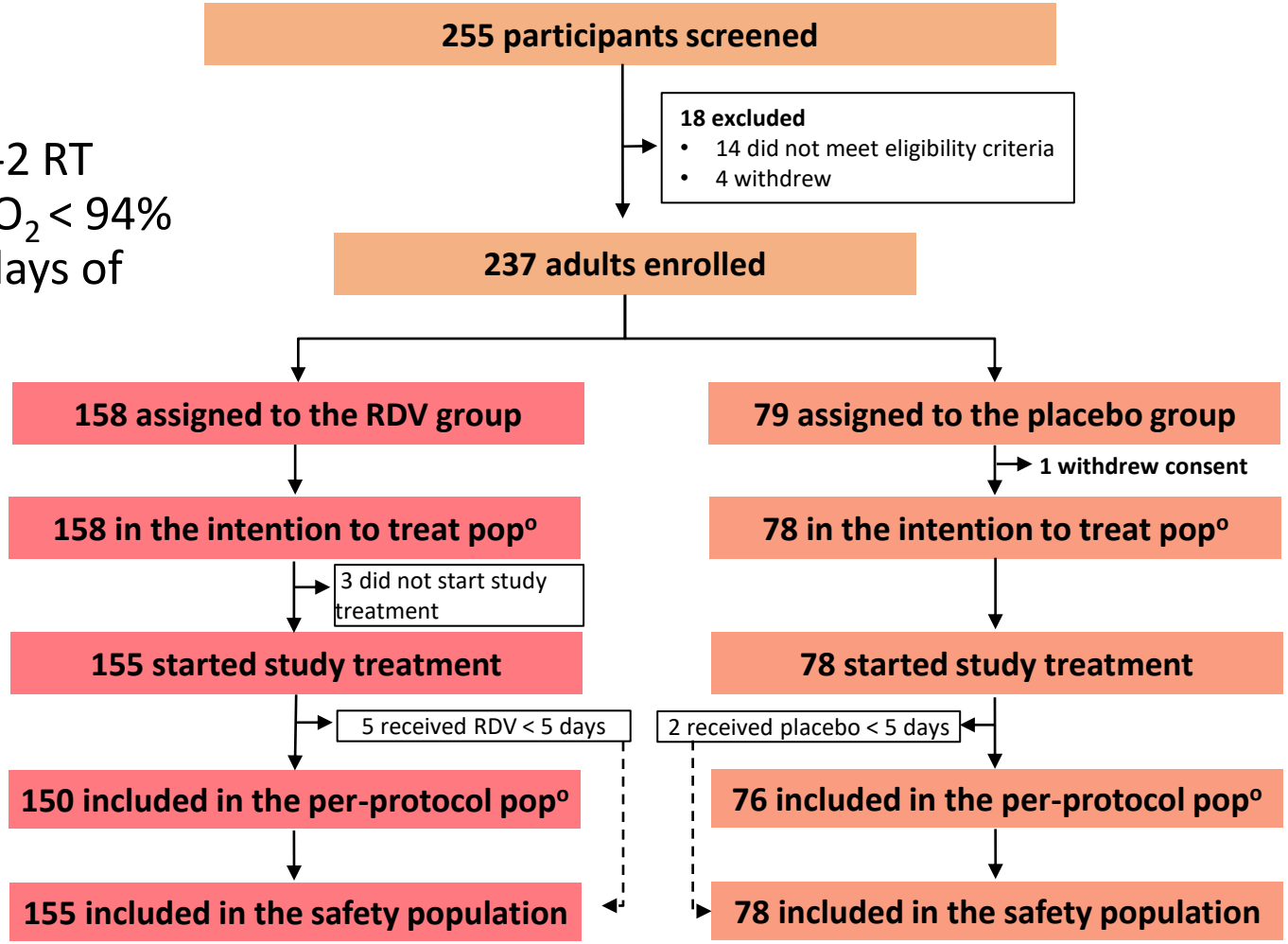
No virological data on some studies.

No proven benefits

Anti viral effect

# Remdesivir (RDV) - 1

- Randomized, double-blind, placebo-controlled, multicenter, academic study, China
- **Inclusion criteria:** age ≥ 18yo, positive SARS-CoV-2 RT PCR, pneumonia confirmed by chest Imaging, $SpO_2 < 94\%$ (room air) or $PaO_2/FiO_2 \leq 300$ mmHg, within 12 days of symptom onset
- **Exclusion criteria:** pregnant women, renal impairment, hepatic cirrhosis
- **Primary outcome**: time to clinical improvement within 28 days after randomization
- **Secondary outcome** : D28 mortality, SARS-CoV-2 viral load
- 237 eligible patients, 158 received **RDV**, 79 **placebo** (2:1)




Wang Y *et al*. *Lancet.* Apr 2020

Anti viral effect

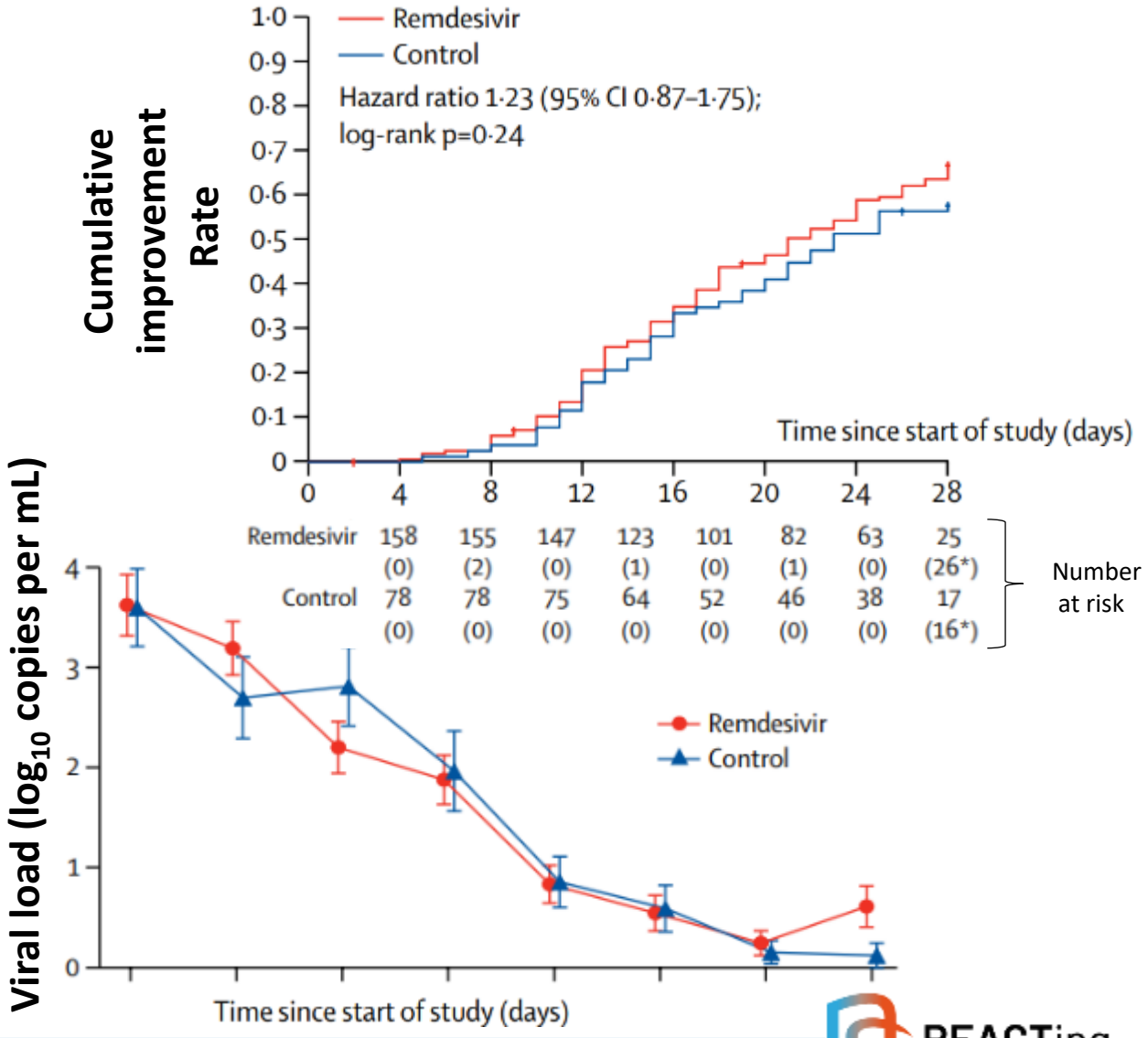
# Remdesivir (RDV) - 1

| Characteristics | RDV (N=158) | Placebo(N=78) |
|---|---|---|
| Age, median (IQR) – yr | 66 (57-73) | 64 (53-70) |
| Male sex – no (%) | 89 (56) | 51 (65) |
| **Coexisting conditions** | | |
| Diabetes – no (%) | 40 (25) | 16 (21) |
| Hypertension – no (%) | 72 (46) | 30 (38) |
| Coronary heart disease – no (%) | 15 (9) | 2 (3) |
| **Vital sign** | | |
| Respiratory rate > 24/min – no (%) | 36 (23) | 11 (14) |

Anti viral effect

# Remdesivir (RDV) - 1

- **Time to clinical improvement**: median 21,0 days [IQR 13,0–28,0] RDV group *vs.* 23,0 days [15,0–28,0] placebo group; no significant difference HR 1,23 $IC_{95\%}$[0,87-1,75]
- **D28 mortality**: 22/158 (14%) RDV group *vs.* 10/78 (13%) placebo group; **similar**
- **Viral load**: decreased over time similarly in both groups
- Adverse events: 102 (66%) RDV group *vs*. 50 (64%) placebo group
- **<u>Limits:</u>** target enrolment not reached; insufficient power to detect assumed differences in clinical outcomes, late treatment initiation (within 12 days of symptom onset), no virological data




Wang Y *et al*. *Lancet.* Apr 2020

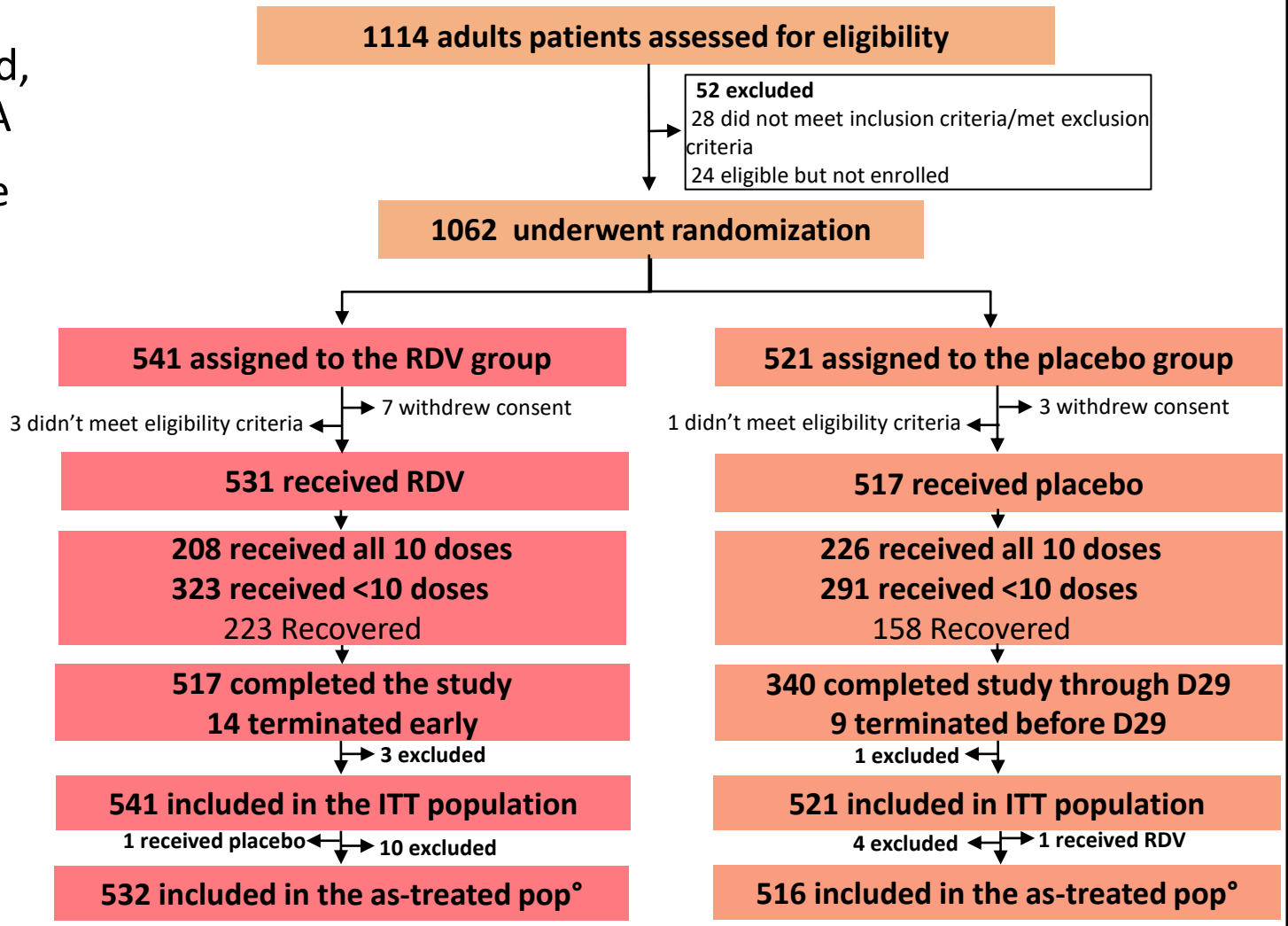
COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

REACTing research & action targeting emerging infectious diseases

Anti viral effect

# Remdesivir (RDV) - 2

- Randomized, double-blind, placebo-controlled, multicenter (73 centers), academic study, USA
- **Inclusion criteria**: SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, $SpO_2$ < 94% (room air) or requiring supplemental oxygen, mechanical ventilation, or ECMO
- **Exclusion criteria:** pregnant women, allergy to study product
- **Primary outcome**: time to recovery
- 1062 patients underwent randomization; 541 **RDV** group, 521 **placebo** group (1:1)




Beigel JH *et al*. *NEJM.* Oct 2020

Anti viral effect

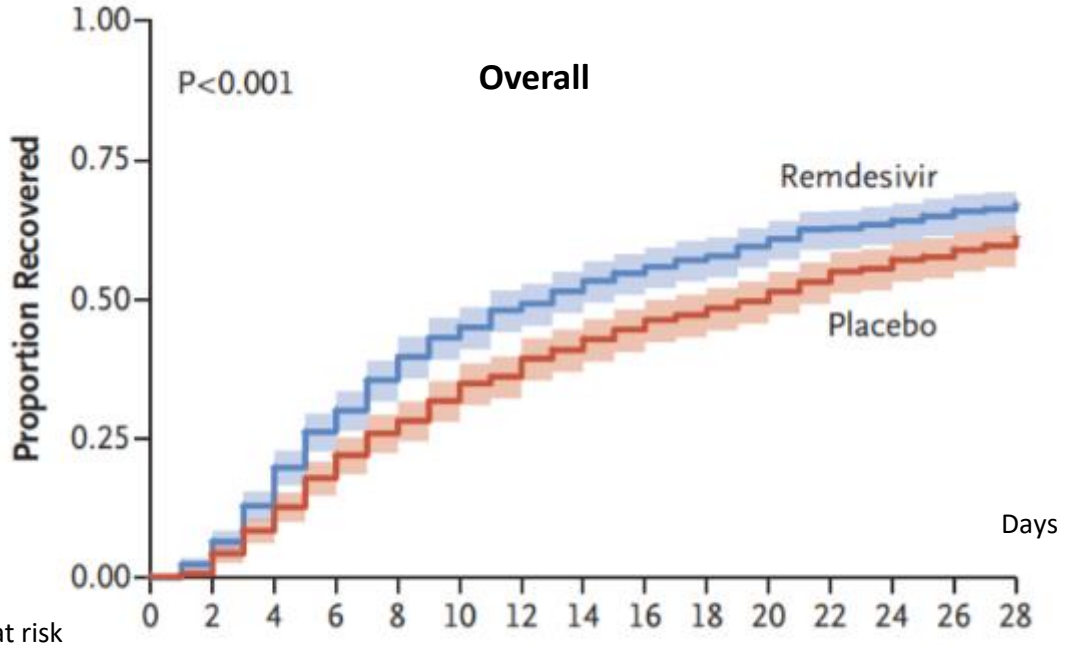
# Remdesivir (RDV) - 2

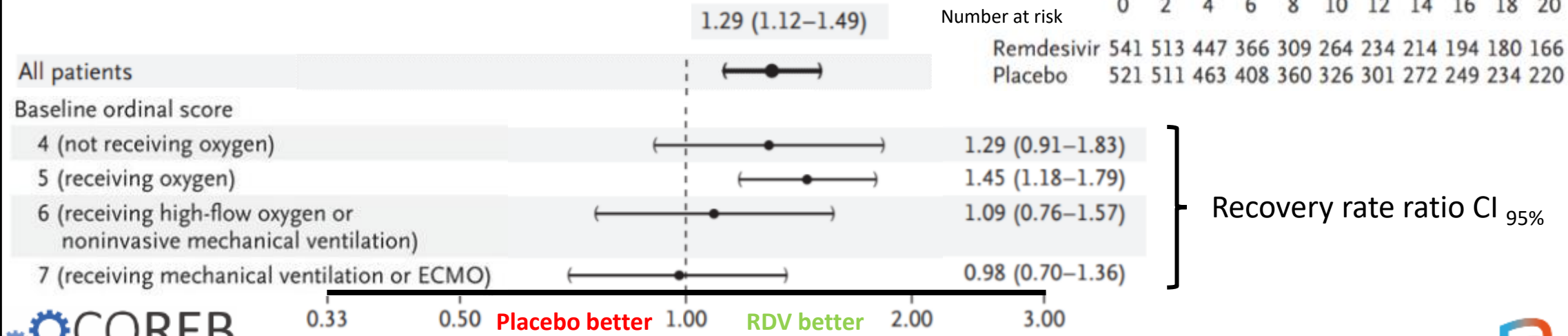
| Characteristics | All (N=1062) | RDV (N=541) | Placebo (N=521) |
|---|---|---|---|
| Age, mean (SD) – yo | 58,9 (15) | 58,6 (14,6) | 59,2 (15,4) |
| Male sex – no (%) | 684 (64,4) | 352 (65,1) | 332 (63,6) |
| **Co existing conditions** | | | |
| Type 2 Diabetes – no (%) | 322/1051 (30,6) | 164/532 (30,8) | 158/519 (30,4) |
| Hypertension – no (%) | 533/1051 (50,7) | 269/532 (50,6) | 264/519 (50,9) |
| Obesity – no (%) | 476/1049 (45,4) | 242/531 (45,6) | 234/518 (45,2) |
| **Score on ordinal scale** | | | |
| 4. Hospitalized, not requiring supplemental $O_2$, requiring ongoing medical care – no (%) | 133 (13,0) | 75 (13,9) | 63 (12,1) |
| 5. Hospitalized, requiring supplemental $O_2$ – no (%) | 435 (41,0) | 232 (41) | 203 (39,0) |
| 6. Hospitalized, receiving noninvasive ventilation or high flow $O_2$ device – no (%) | 193 (18,2) | 95 (17,6) | 98 (18,8) |
| 7. Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%) | 285 (26,8) | 131 (24,2) | 154 (29,6) |

Anti viral effect

# Remdesivir (RDV) - 2

- **Time to recovery (median)**: RDV group: 10 days *vs.* placebo group: 15 days; recovery rate ratio 1,29 $CI_{95\%}$[1,12-1,49]
- **D29 mortality**: RDV group: 11,4% *vs.* placebo group: 15,2%; HR 0,73 $CI_{95\%}$[0,52-1,03]
- **Adverse events**: RDV group: 131/532 (24,6%) *vs.* placebo group: 163/516 (31,6%)
- **<u>Limits:</u>** primary outcome changed during the study, uncompleted follow up, no virological data



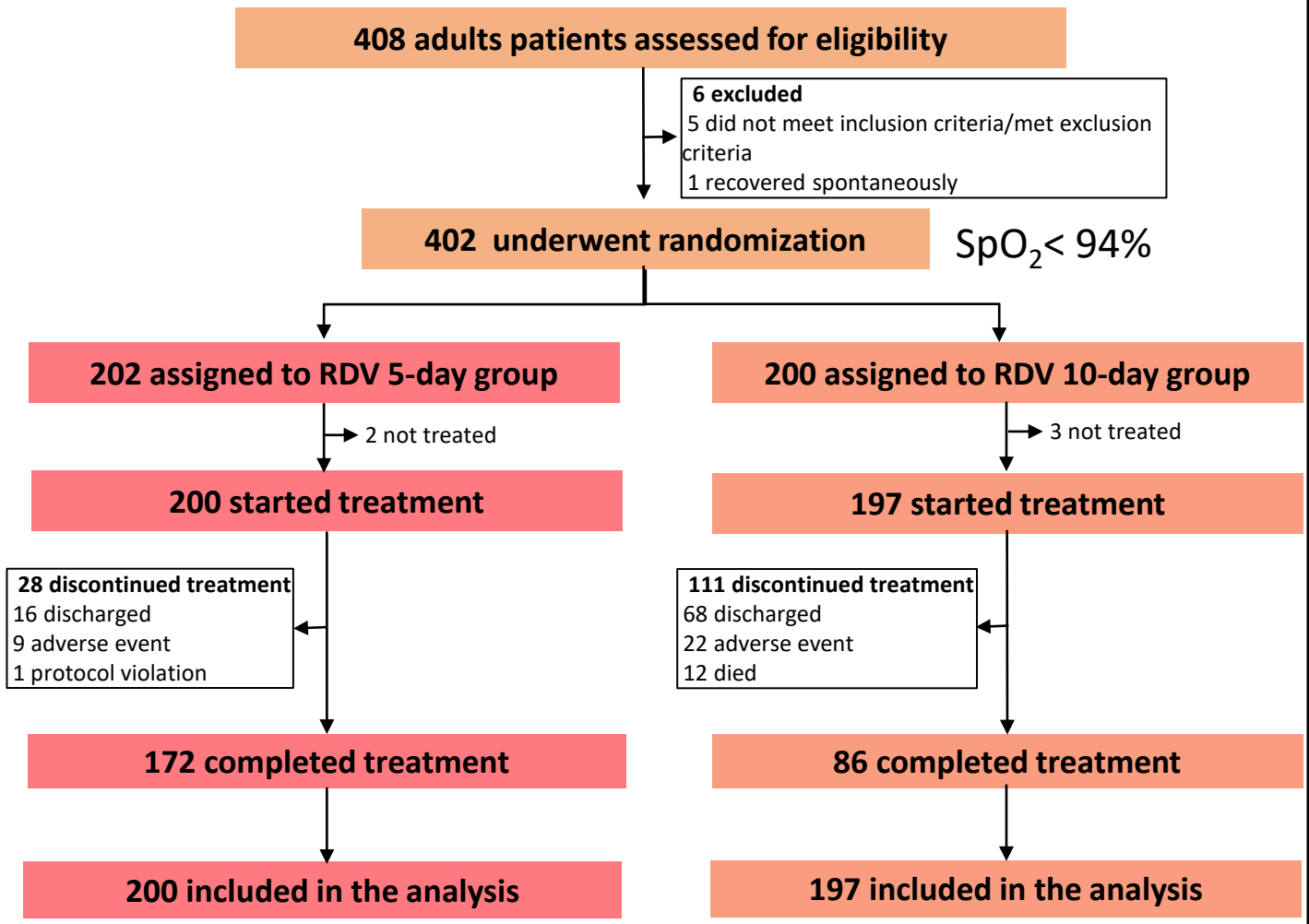




Beigel JH *et al*. *NEJM*. Oct 2020

Anti viral effect

# Remdesivir (RDV) - 3

- Open labelled, randomized, placebo-controlled, multicenter (55 centers), academic study, USA, Europe, Asia
- **Inclusion criteria**: age > 12 yo, SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, **$SpO_2$ < 94%** (room air) or requiring supplemental oxygen
- **Exclusion criteria:** mechanical ventilation, or ECMO, ALT or AST > 5 ULNR, creatine clearance < 50 mL/min/$m^2$
- **Primary outcome**: status assessed on day 14 on a 7-point ordinal scale
- 402 patients underwent randomization; 200 **5-day course** RDV group, 197 **10-day course** RDV group (1:1)




Goldman JD *et al*. *NEJM*. May 2020

Anti viral effect

# Remdesivir (RDV) - 3

| Characteristics | RDV 5 days (N=200) | RDV 10 days (N=197) |
|---|---|---|
| Age, median (IQR) – yo | 61 (50-69) | 62 (50-71) |
| Male sex – no (%) | 120 (60) | 133 (68) |
| **Co existing conditions** | | |
| Type 2 Diabetes – no (%) | 47 (24) | 42 (22) |
| Hypertension – no (%) | 100 (50) | 98 (50) |
| BMI, median (IQR) – $kg/m^2$ | 29 (25-34) | 29 (25-33) |
| **Score on ordinal scale** | | |
| 4. Hospitalized, not requiring $O_2$ – no (%) | 34 (17) | 21 (11) |
| 5. Hospitalized, requiring $O_2$ – no (%) | 113 (56) | 107 (54) |
| 6. Hospitalized, receiving noninvasive ventilation or high flow $O_2$ device – no (%) | 49 (24) | 60 (30) |
| 7. Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%) | 4 (2) | 9 (5) |

Anti viral effect

# Remdesivir (RDV) - 3

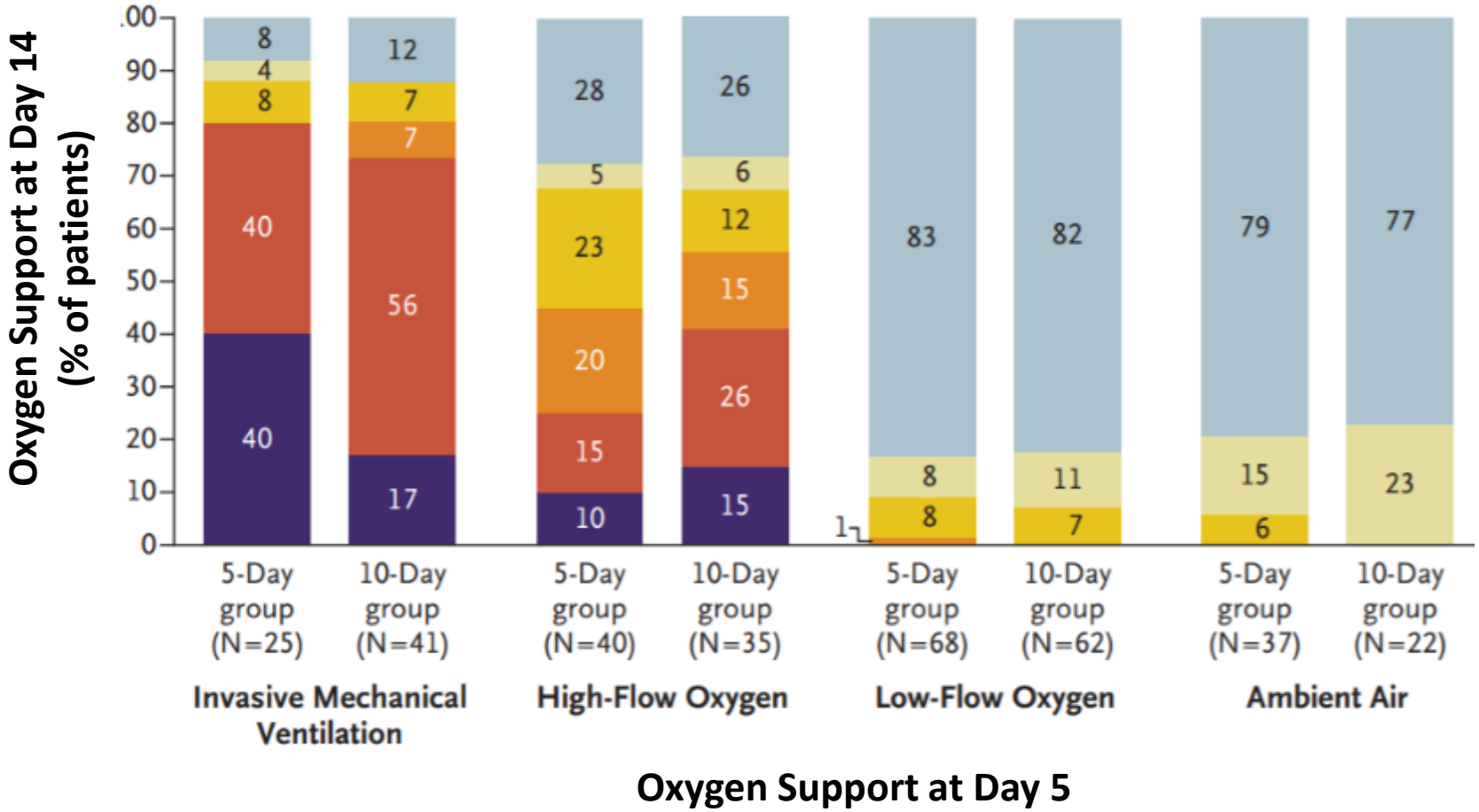
| Outcomes | 5-days (N=200) | 10-days (N=197) | Baseline-Adjusted Difference $_{95\%}$ CI |
|---|---|---|---|
| **Clinical status at day 14 on the 7-point ordinal scale - no (%)** | | | |
| Hospitalized, receiving invasive mechanical ventilation or ECMO | 16 (8) | 33 (17) | - |
| Hospitalized, receiving noninvasive ventilation or high flow $O_2$ device | 9 (4) | 10 (5) | - |
| Hospitalized, requiring $O_2$ | 19 (10) | 14 (7) | - |
| Hospitalized, not requiring $O_2$ | 9 (4) | 3 (2) | - |
| Not Hospitalized | 120 (60) | 103 (52) | - |
| Time to clinical improvement (median day of 50% cumulative incidence) | 10 | 11 | 0.79 (0,61-1,01) |
| **Recovery - no (%)** | | | |
| Day 7 | 71 (36) | 51 (26) | −6.0% (−14,8 to 2,7) |
| Day 14 | 129 (64) | 106 (54) | −6.3% (−15,4 to 2,8) |

Anti viral effect

# Remdesivir (RDV) - 3

- **D14 Clinical status:** No significant difference in efficacy between 5-day and 10-day courses of remdesivir

- **Limits:** lack of a randomized placebo control group; open-label design; no virological data



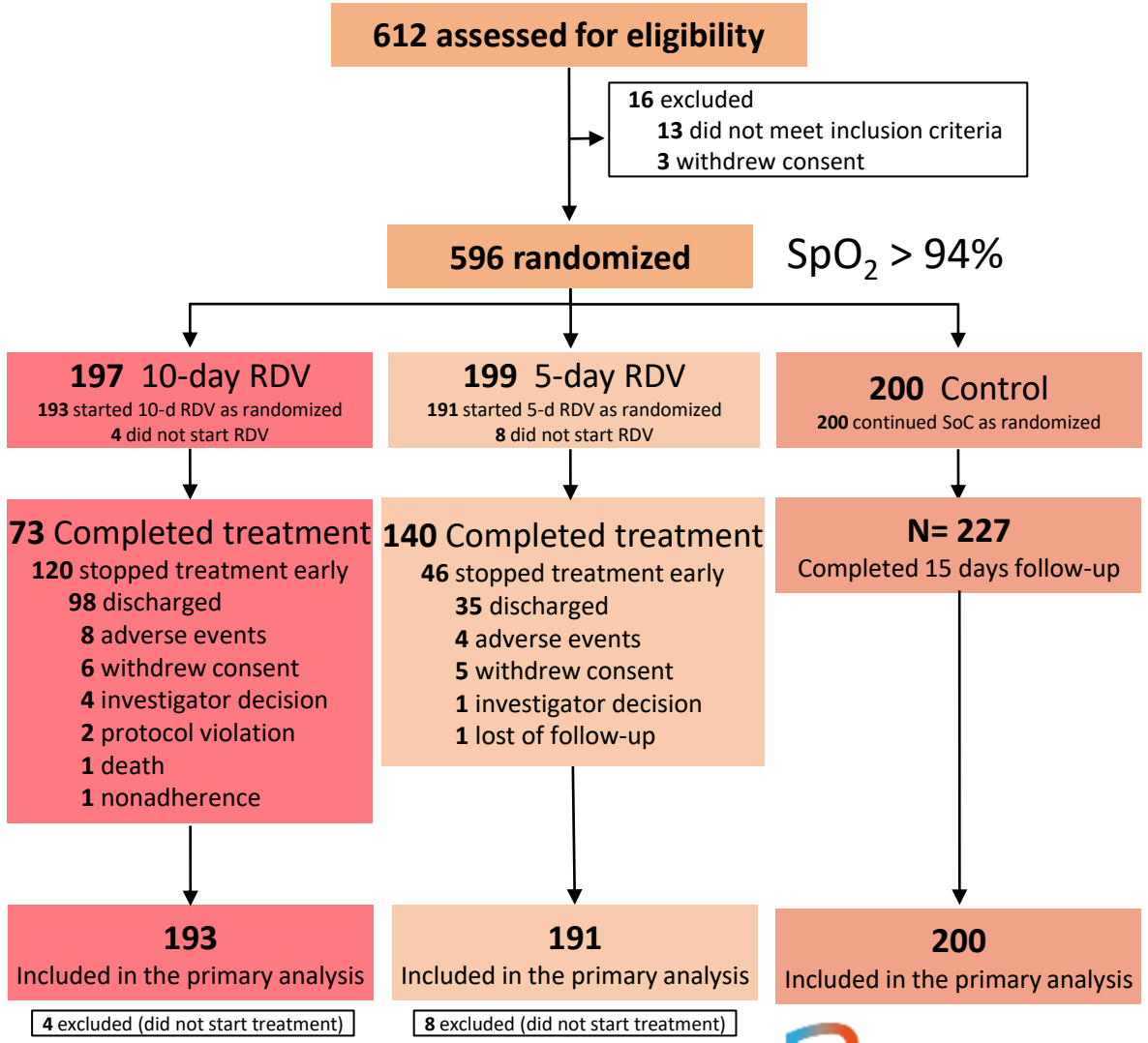

Discharge
Ambient air
Low-flow oxygen
High-flow oxygen
Invasive mechanical ventilation
Death

Goldman JD *et al*. *NEJM*. May 2020

Anti viral effect

# Remdesivir (RDV) - 4

- Randomized, open-label, placebo-controlled, multicenter (105 centers), academic study, USA, Europe, Asia
- **Inclusion criteria**: hospitalized patients, SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, **$SpO_2$ > 94%** (room air)
- **Exclusion criteria:** mechanical ventilation, or ECMO, ALT or AST > 5 ULNR, creatine clearance < 50 mL/min/$m^2$
- **Primary outcome**: clinical status assessed on the 7-point ordinal scale on study day 11
- 402 patients underwent randomization; 191 **5-day course** RDV group, 193 **10-day course** RDV group, 200 **control** group (1:1:1)




Spinner CD *et al*. *JAMA* Aug 2020

Anti viral effect

# Remdesivir (RDV) - 4

| Characteristics | 5-days (N=191) | 10-days (N=193) | SoC (N=200) |
|---|---|---|---|
| Age, median (IQR) – yo | 58 (48-66) | 56 (45-66) | 57 (45-66) |
| Male sex – no (%) | 114 (60) | 118 (61) | 125 (63) |
| **Co existing conditions** | | | |
| Diabetes – no (%) | 71 (37) | 85 (44) | 76 (38) |
| Hypertension – no (%) | 82 (43) | 85 (44) | 81 (41) |
| BMI, median (IQR) – $kg/m^2$ | 25 (24-30) | 28 (25-32) | 27 (24-31) |
| **Day 1 clinical status on 7-point scale** | | | |
| Hospitalized, not requiring $O_2$ – no (%) | 160 (84) | 163 (84) | 160 (80) |
| Hospitalized, requiring $O_2$ – no (%) | 29 (15) | 23 (12) | 36 (18) |
| Hospitalized, receiving noninvasive ventilation or high flow $O_2$ device – no (%) | 2 (1) | 1 (1) | 2 (1) |

Anti viral effect

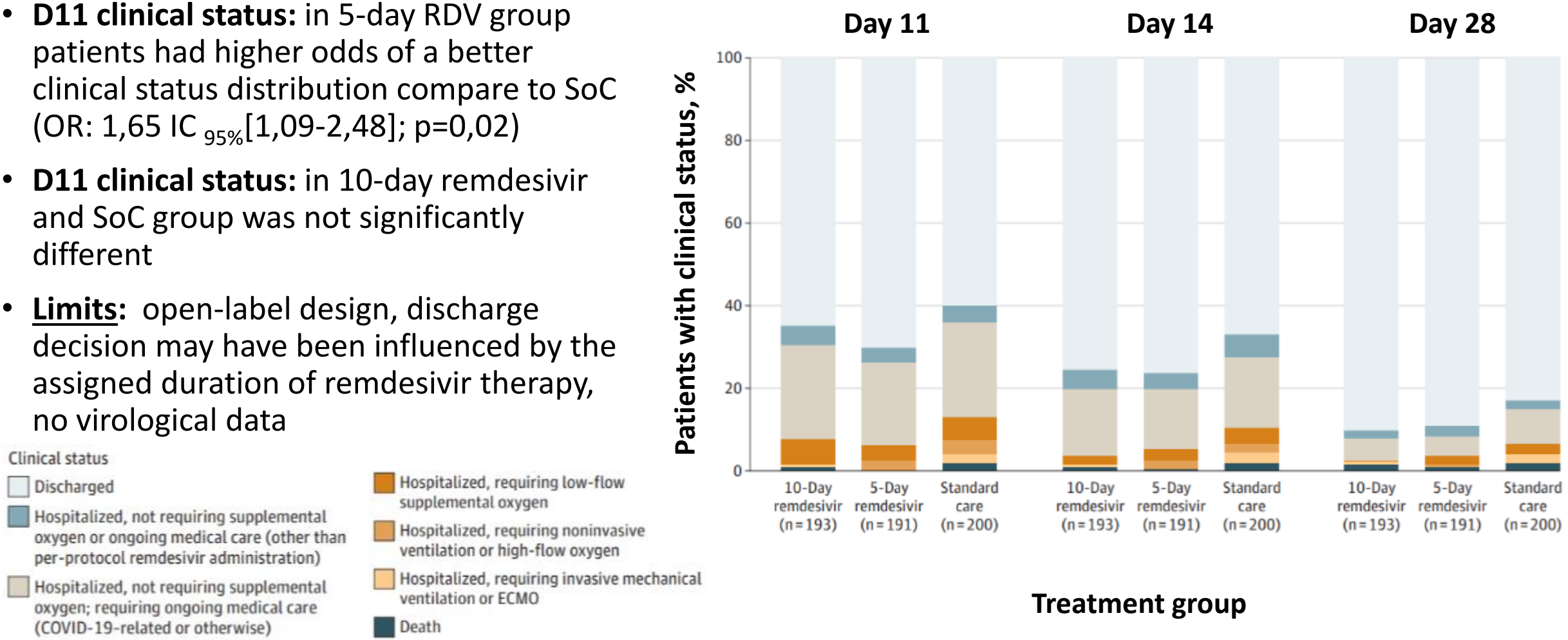
# Remdesivir (RDV) - 4

| Outcomes | 5-days (N=191) | 10-days (N=193) | SoC (N=200) |
|---|---|---|---|
| **Day 1 clinical status on 7-point scale** | | | |
| Not hospitalized – no (%) | 134 (70) | 125 (65) | 120 (60) |
| Hospitalized, not requiring $O_2$ – no (%) | 38 (20) | 44 (23) | 46 (23) |
| Hospitalized, requiring $O_2$ – no (%) | 7 (4) | 12 (6) | 11 (6) |
| Hospitalized, receiving noninvasive ventilation or high flow $O_2$ device – no (%) | 5 (3) | 0 | 7 (4) |
| Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%) | 0 | 1 (1) | 4 (2) |
| Death – no (%) | 0 | 2 (1) | 4 (2) |
| **Adverse events** | | | |
| Any adverse event – no (%) | 98 (51) | 113 (59) | 93 (47) |
| Any grade ≥ 3 adverse event – no (%) | 20 (10) | 24 (12) | 24 (12) |
| Any serious adverse event – no (%) | 9 (5) | 10 (5) | 18 (9) |

Anti viral effect

# Remdesivir (RDV) - 4

- **D11 clinical status:** in 5-day RDV group patients had higher odds of a better clinical status distribution compare to SoC (OR: 1,65 IC $_{95\%}$[1,09-2,48]; p=0,02)
- **D11 clinical status:** in 10-day remdesivir and SoC group was not significantly different
- **Limits:** open-label design, discharge decision may have been influenced by the assigned duration of remdesivir therapy, no virological data

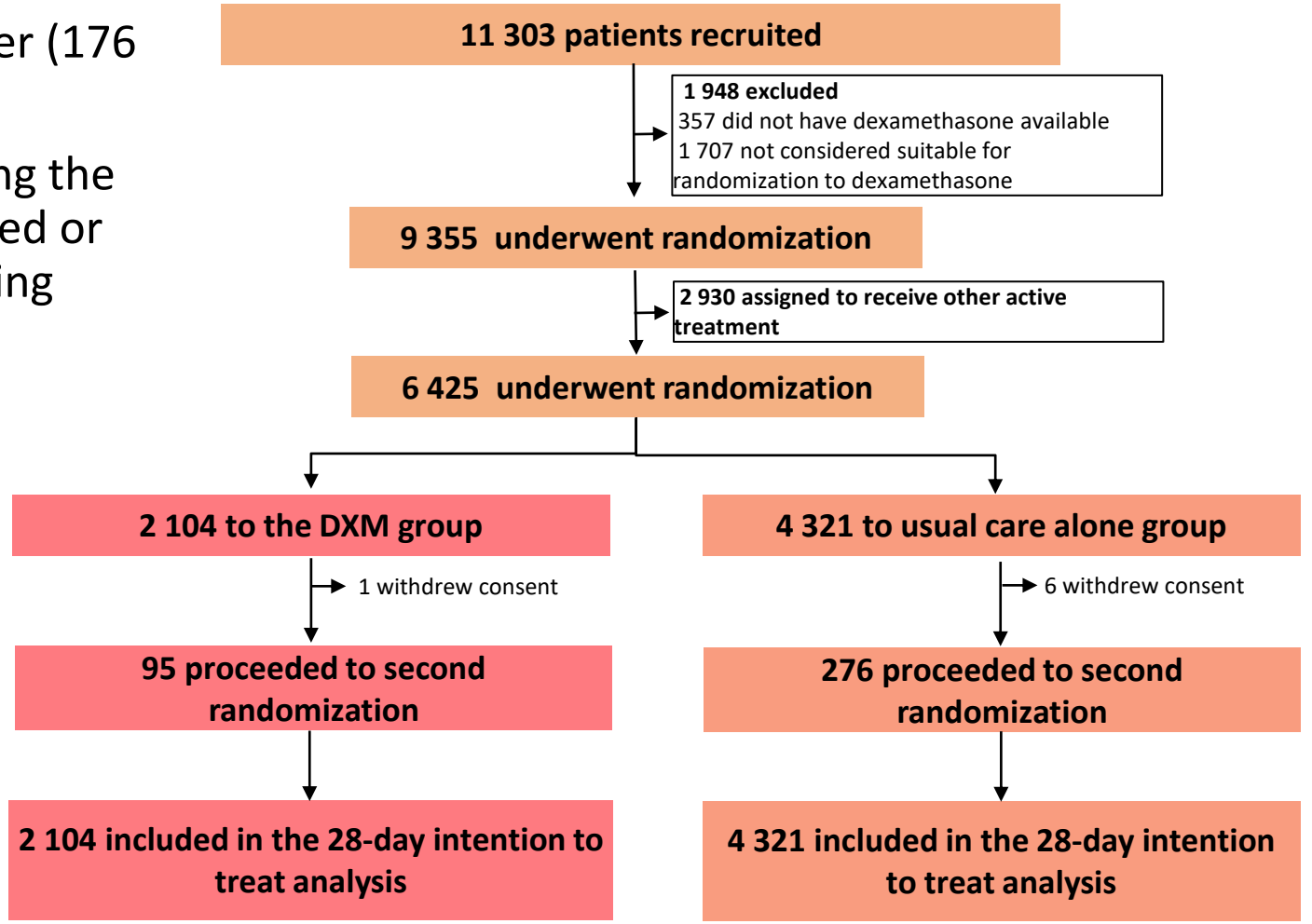



Spinner CD *et al*. *JAMA* Aug 2020

Immunomodulatory effect

# Corticosteroids (CT) - 1

- Randomized, controlled, open-label, multi center (176 hospitals), academic study, UK
- **Inclusion criteria** : age ≥ 9yo (age changed during the study)), SARS-CoV-2 infection (clinically suspected or laboratory confirmed), pregnant or breast-feeding women were eligible
- **Primary outcome**: all-cause mortality within 28 days after randomization
- **Secondary outcome**: time until discharge from hospital, invasive mechanical ventilation (including ECMO) or death (among patients not receiving invasive mechanical ventilation at randomization)
- 6 425 participants; **4 321 usual care alone group, 2 104 DXM group** (2:1)




DXM: dexamethasone

RECOVERY *collaborative group NEJM.* Jul 2020

Immunomodulatory effect

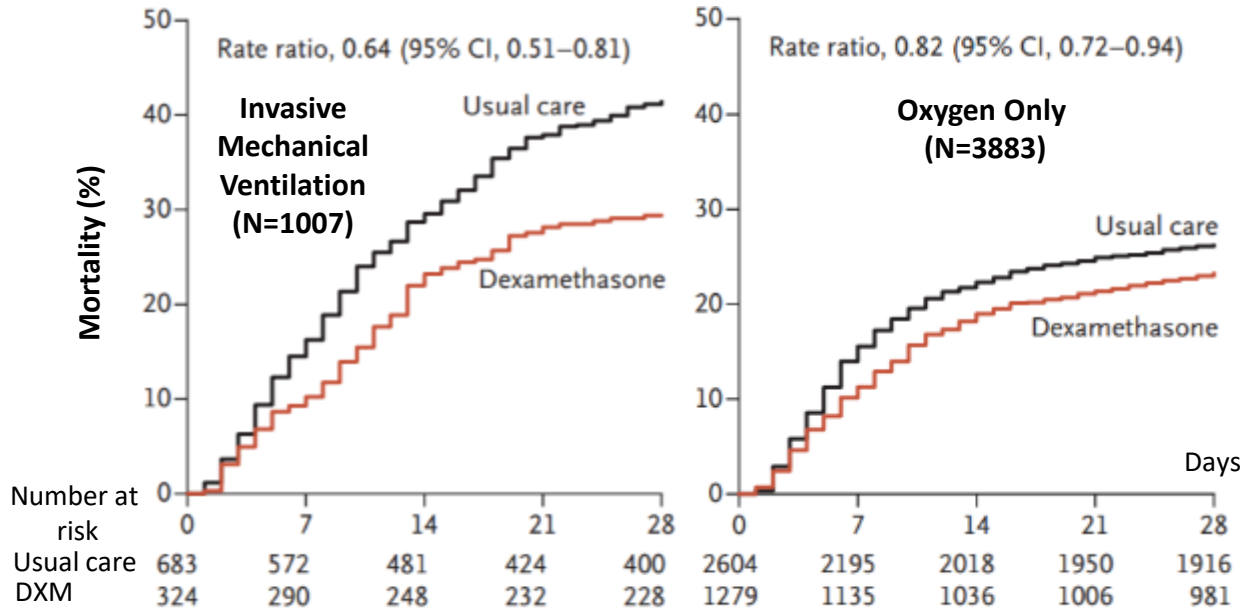
# Corticosteroids (CT) - 1

| | Treatment assignment | |
|---|---|---|
| **Characteristics** | **DXM (N=2 104)** | **Usual care (N=4 321)** |
| Age ≥ 70 yr – no (%) | 963 (45) | 1817 (42) |
| Female sex – no (%) | 766 (36) | 1572 (36) |
| **Coexisting conditions** | | |
| Diabetes – no (%) | 521 (25) | 1025 (24) |
| Heart disease – no (%) | 586 (49,1) | 1171 (27) |
| Chronic lung disease – no (%) | 415 (20) | 931 (22) |
| **SARS-CoV-2 test result** | | |
| Positive – no (%) | 20 (18-22) | 18 (18-20) |
| **Respiratory support received** | | |
| No oxygen – no (%) | 501 (24) | 1034 (24) |
| Oxygen only – no (%) | 1279 (61) | 2604 (60) |
| Invasive mechanical ventilation – no (%) | 324 (15) | 683 (16) |

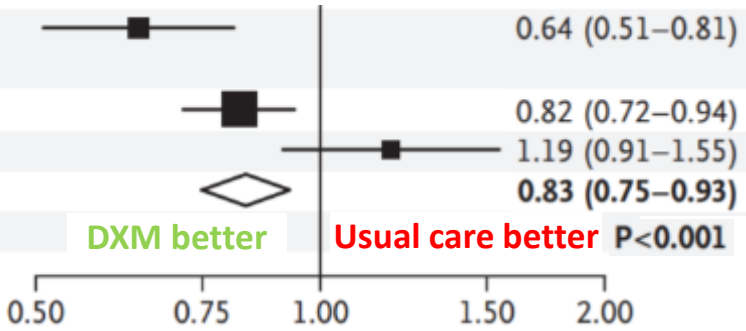
Immunomodulatory effect

# Corticosteroids (CT) - 1

- **Day 28 mortality**: 482/2104 (22,9%) DXM group *vs.* 1110/4321 (25,7%) usual care group, risk ratio 0,83 $CI_{95\%}$[0,75-0,93]
- **Discharged from hospital within 28 days**: 1413/2104 (67,2%) DXM group *vs.* 2745/4321 (63,5%) usual care group, risk ratio 1,10 $CI_{95\%}$[1,03-1,17]
- **Invasive mechanical ventilation or death**: 456/1780 (25,6%) DXM group *vs.* 994/3638 (27,3%) usual care group, risk ratio 0,92 $CI_{95\%}$[0,84-1,01]
- **<u>Limits</u>:** Preliminary report, patients without confirmed SARS-CoV-2 positive PCR included, age of inclusion changed during the study, absence of viral load follow-up




| Respiratory support and randomization | DXM | Usual care | Rate ratio $CI_{95\%}$ |
|---|---|---|---|
| Invasive mechanical ventilation | 95/324 (29.3) | 283/683 (41.4) | 0.64 (0.51–0.81) |
| Oxygen only | 298/1279 (23.3) | 682/2604 (26.2) | 0.82 (0.72–0.94) |
| No oxygen received | 89/501 (17.8) | 145/1034 (14.0) | 1.19 (0.91–1.55) |
| **All Patients** | **482/2104 (22.9)** | **1110/4321 (25.7)** | **0.83 (0.75–0.93)** |



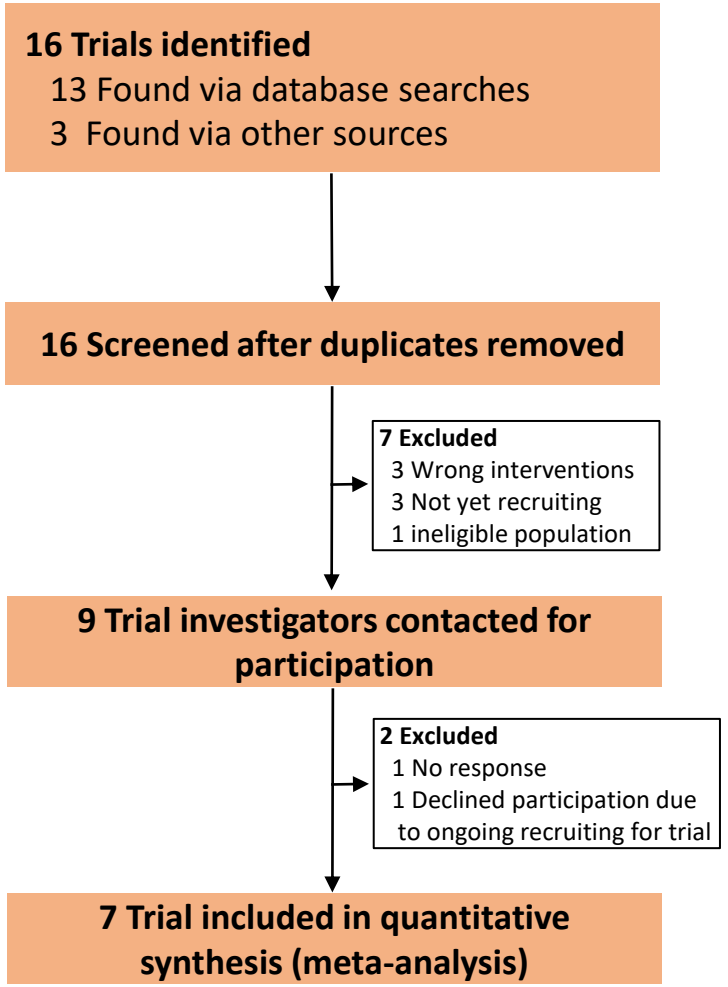

categories: 11.5

RECOVERY *collaborative group NEJM.* Jul 2020

Immunomodulatory effect

# Corticosteroids (CT) - 2

- Prospective Meta-analysis, academic study, WHO
- **Objective:** estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality
- **Primary outcome**: all-cause mortality at 28 days after randomization
- **Secondary outcome**: investigator-defined serious adverse events
- 1703 included participants; **678** (%) **corticosteroid group** (systemic dexamethasone, hydrocortisone, or methylprednisolone); **1025** (62%) **usual care or placebo group**



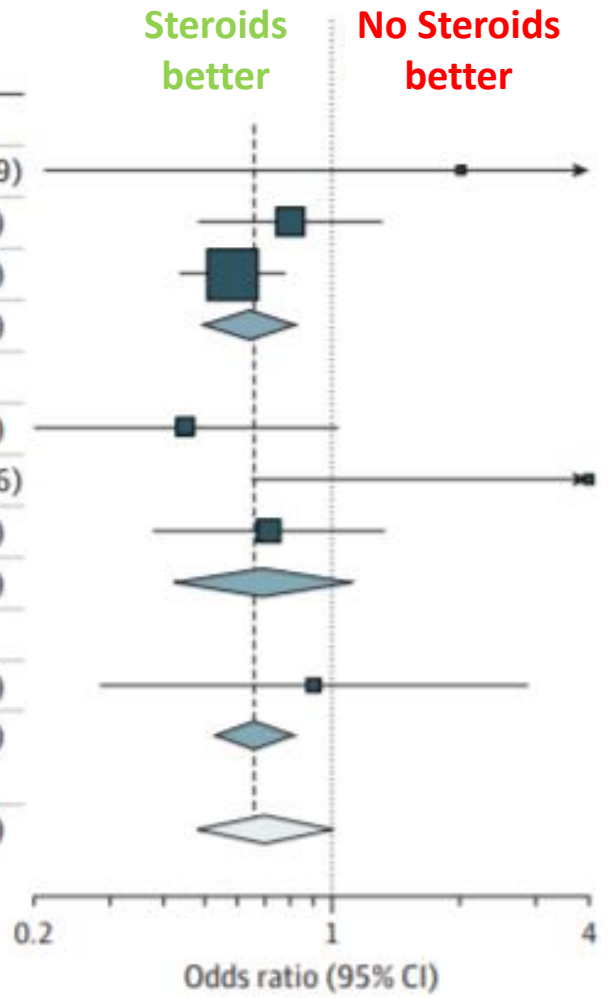

Sterne *et al. JAMA* Sep 2020

Immunomodulatory effect

# Corticosteroids (CT) - 2

- 222/678 deaths among patients randomized to corticosteroids group *vs.* 425/1025 deaths among patients randomized to usual care or placebo; OR: 0,66 $IC_{95\%}$ [0,53-0,82]; p < 0,001 fixed-effect meta-analysis)
- **Association with mortality**: **DXM**: 0,64 $IC_{95\%}$ [0,5-0,82]; p<0,001 (3 trials), **HC**: 0,69 $IC_{95\%}$ [0,43-1,12]; p=0,13 (3 trials), **mPred**: 0,91 $IC_{95\%}$ [0,29-2,87]; p=0,87 (1 trial)
- **Limits**: risk of selective reporting or of publication bias, missing outcome data, trials only recruited adults, effect of corticosteroids on children remains unclear

| Drug and trial | No. of deaths/total No. of patients: Steroids | No steroids | Odds ratio (95% CI) |
|---|---|---|---|
| Dexamethasone | | | |
| DEXA-COVID 19 | 2/7 | 2/12 | 2.00 (0.21-18.69) |
| CoDEX | 69/128 | 76/128 | 0.80 (0.49-1.31) |
| RECOVERY | 95/324 | 283/683 | 0.59 (0.44-0.78) |
| Subgroup fixed effect | 166/459 | 361/823 | 0.64 (0.50-0.82) |
| Hydrocortisone | | | |
| CAPE COVID | 1/75 | 20/73 | 0.46 (0.20-1.04) |
| COVID STEROID | 6/15 | 2/14 | 4.00 (0.65-24.66) |
| REMAP-CAP | 26/105 | 29/92 | 0.71 (0.38-1.33) |
| Subgroup fixed effect | 43/195 | 51/179 | 0.69 (0.43-1.12) |
| Methylprednisolone | | | |
| Steroids-SARI | 13/24 | 13/23 | 0.91 (0.29-2.87) |
| Overall (fixed effect) | 222/678 | 425/1025 | 0.66 (0.53-0.82) |
| *P* = .31 for heterogeneity | | | |
| Overall (random effects[a] | 222/678 | 425/1025 | 0.70 (0.48-1.01) |




DXM: dexamethasone – HC: hydrocortisone – mPred: methylprednisolone

Sterne *et al. JAMA* Sep 2020

Immunomodulatory effect

# Corticosteroids (CT) - 3

| Authors | CT | Patients | Design | Groups | Outcome | Main results (outcome) |
|---|---|---|---|---|---|---|
| Fadel R | **mPred** | N=213 Moderate to severe COVID-19 | Multi-center, quasi-experimental | mPred *vs.* no mPred | Escalation of care from ward to ICU | SoC group 31 (44,3%) *vs.* mPred group 32 (27,3%) OR: 0,47 $CI_{95\%}$[0,25-0,88], p= 0,017 |
| | | | | | New requirement for mechanical ventilation | SoC group 26 (36,6%) *vs.* CT group 26 (21,7%) OR: 0,47 $CI_{95\%}$[0,25-0,92], p= 0,025 |
| | | | | | Death | SoC group 21 (26,3%) *vs.* CT group 18 (13,6%) OR: 0,45 $CI_{95\%}$[0,22-0,91], p= 0,024 |
| Prado Jeronimo | **mPred** | N=416 Suspected COVID-19 hospitalized patients | Parallel, double-blind, placebo-controlled, randomized | mPred *vs.* placebo | D28 mortality | mPred group 72/194 (37,1%) *vs.* placebo group 76/199 (38,2%) HR: 0,924 $CI_{95\%}$[0,669-1,275], p= 0,629 |
| Nelson B | **mPred** | N=117 Requiring mechanical ventilation | Case-control study | mPred *vs.* control | D28 ventilator-free after admission | mPred group 6,2 *vs.* control group 3,14, p=0,044 |



mPred: methylprednisolone

Fadel R *et al. CID May* 2020

Prado Jeronimo *et al.* CID Aug 2020

Nelson B *et al.* CID Aug 2020

Immunomodulatory effect

# Corticosteroids (CT) - 4

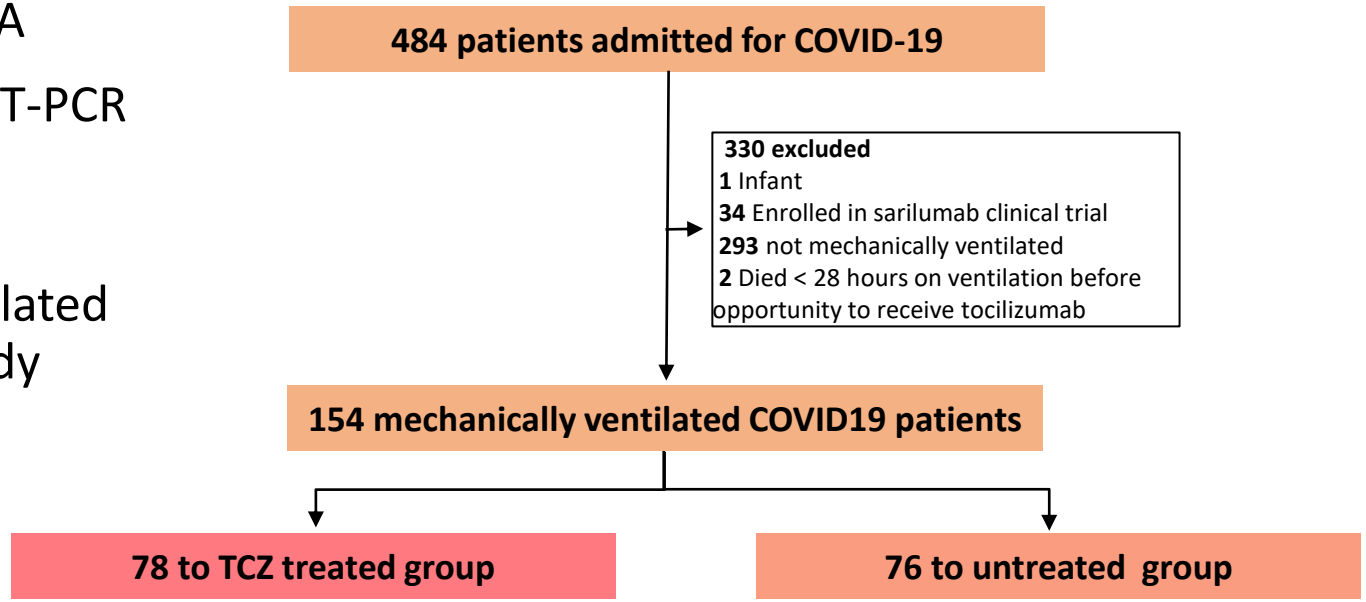
| Authors | CT | Patients | Design | Groups | Outcome | Main results (outcome) |
|---|---|---|---|---|---|---|
| Dequin PF | **HC** | N=149<br>Critically ill, acute respiratory failure | Multicenter randomized double-blind | HC *vs.* placebo | D21 treatment failure | **Study stopped early**<br>HC group 32/76 (42,1%) *vs.* placebo group 37/76 (50,7%)<br>p= 0,29 |
| Angus D | **HC** | N=384<br>Admitted in ICU for respiratory or cardiovascular organ support | Multicenter, openlabel trial | HC *vs.* placebo | D21 respiratory and cardiovascular organ support–free | **Study stopped early**<br>No treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions |
| | | | | | | |
| Tomazini BM | **DXM** | N= 299<br>Receiving mechanical ventilation | Multicenter, randomized, open-label | DXM + SoC *vs.* SoC | Ventilator-free days during the first 28 days | **Study interrupted**<br>DXM + SoC group 6,6 $IC_{95\%}$ [5-8,2] *vs.* SoC group 4,0 $IC_{95\%}$ [2,9-5,4], p= 0,04 |

Immunomodulatory effect

Monoclonal antibody

# Tocilizumab (TCZ) - 1

- **TCZ**: anti-interleukin-6 receptor monoclonal antibody
- Single center, observational, academic study, USA
- **Inclusion criteria** : severe pneumonia, positive RT-PCR SARS-CoV-2 test, required invasive mechanical ventilation
- **Exclusion criteria** : age<16yo, intubated for unrelated COVID-19 conditions, enrolled for sarilumab study
- **Primary outcome**: survival probability after intubation
- **Secondary outcome**: status at day 28 on a 6-level ordinal scale of illness severity*
- 154 participants; **76 untreated group, 78 TCZ treated group** (1:1)




*(1) discharged alive, (2) hospitalized/off ventilator without superinfection, (3) hospitalized/off ventilator with superinfection, (4) hospitalized/mechanically ventilated without superinfection, (5) hospitalized/mechanically ventilated with superinfection, (6) deceased

Immunomodulatory effect

Monoclonal antibody

# Tocilizumab (TCZ) - 1

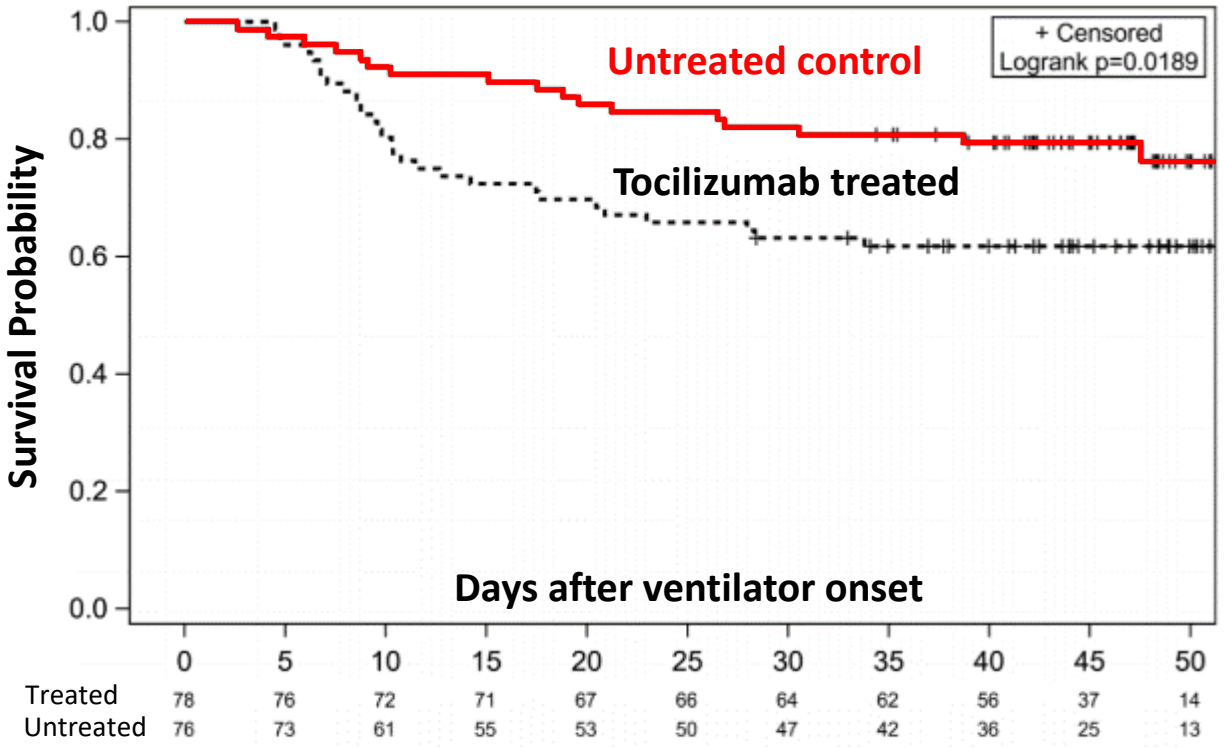
| Characteristics | Overall (N=154) | TCZ (N=78) | Untreated (N=76) | P value |
|---|---|---|---|---|
| Age (y) – mean (SD) | 58 (14,9) | 55 (14,9) | 60 (14,5) | 0,05 |
| Female sex – no (%) | 52 (41,6) | 25 (32) | 27 (36) | 0,65 |
| BMI (kg/m²) – no (%) | 34,1 (9,5) | 34,7 (10,1) | 33,4 (8,8) | 0,40 |
| **Coexisting conditions** | | | | |
| Diabetes – no (%) | 25 (16) | 10 (13) | 15 (20) | 0,24 |
| Hypertension – no (%) | 102 (66) | 50 (64) | 52 (68) | 0,57 |
| Chronic kidney disease – no (%) | 64 (42) | 27 (35) | 37 (49) | 0,99 |
| **Values at intubation time** | | | | |
| PaO2/FiO2 (n=80) – median (IQR) | 165 (136,5 – 231.5) | 155 (129,0 – 188,0) | 198 (163,0 – 240,0) | 0,001 |
| **Fatality rate** | | | | |
| 14-day case fatality rate – no (%) | - | 7 (9) | 20 (26) | 0,005 |
| 28-day case fatality rate – no (%) | - | 14 (18) | 27 (36) | 0,01 |

Immunomodulatory effect

Monoclonal antibody

# Tocilizumab (TCZ) - 1

- **Survival probability after intubation**: higher among TCZ group *vs.* untreated group; hazard ratio 0,50 $CI_{95\%}$ [0,27-0,90]
- **Superinfections**: 42/78 (54%) TCZ group *vs.* 20/76 (26%) untreated group, p < 0,001
- **Patients with pneumonia**: 35/78 (45%) TCZ group *vs.* 15/76 (20%) untreated group, p < 0,001
- **Patients discharged alive (study period)**: 44/78 (56%) TCZ group *vs.* 30/76 (40%) untreated group, p = 0,04
- **<u>Limits</u>:** not a randomized controlled trial, laboratories data were missing, no definition of severe cases nor super infections, only interested in patients mechanically ventilated



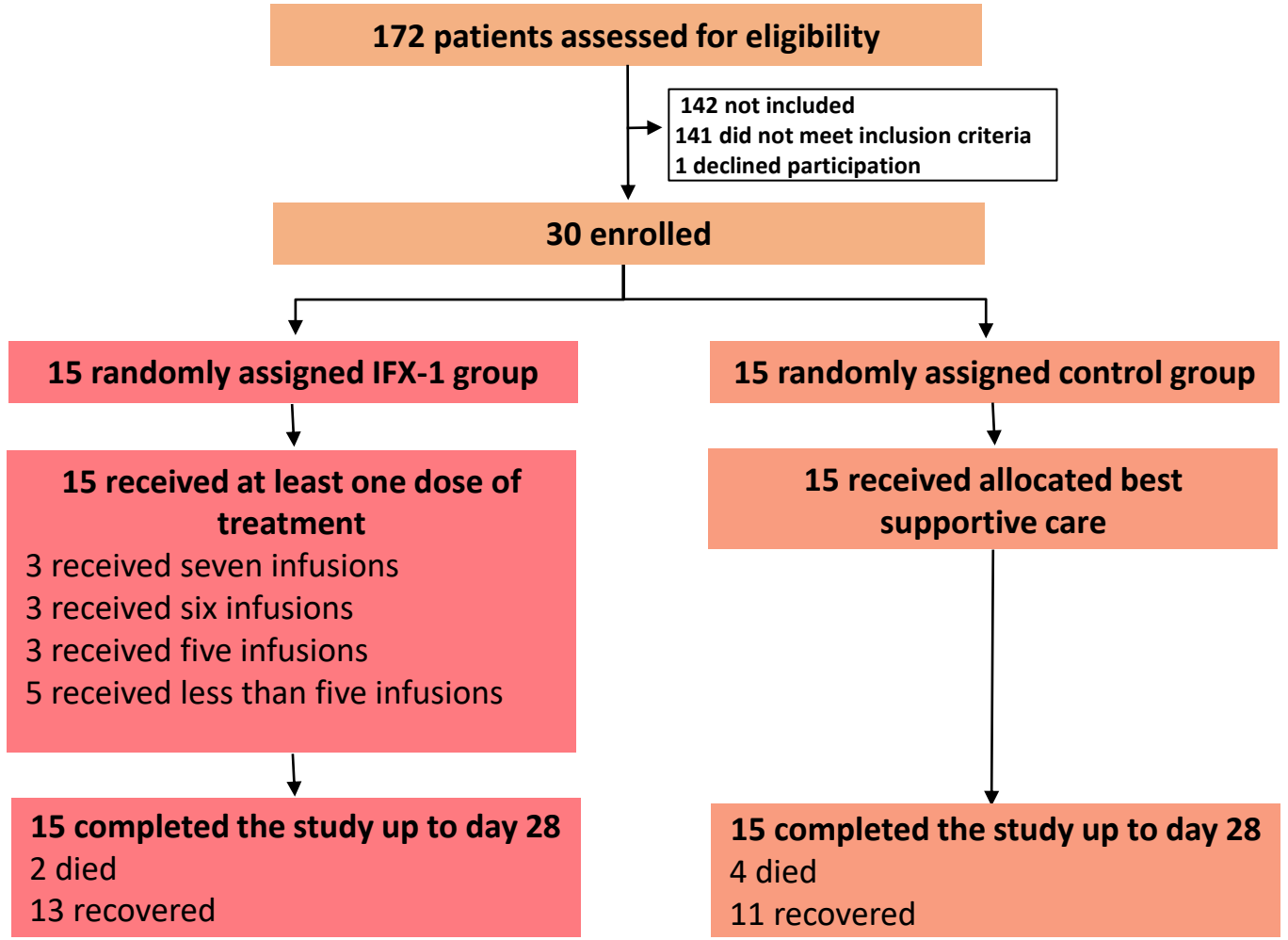

Somers EC *et al. CID.* Jul 2020

Immunomodulatory effect

Monoclonal antibody

# Vilobelimab (IFX-1) - 1

- **IFX-1**: anti-complement C5a monoclonal antibody
- Exploratory, open label, randomized, phase 2, multicenter, academic study, Netherlands
- **Inclusion criteria** : age ≥ 18yo, severe pneumonia ($PaO_2/FiO_2$ between [100-250] mmHg), positive RT-PCR SARS-CoV-2 test, requiring non-invasive or invasive ventilation
- **Primary outcome**: Day 5 $PaO_2/FiO_2$ percentage change from the baseline
- **Secondary outcome**: Day 28 mortality
- 30 participants; **15 control group, 15 IFX 1 treated group** (1:1)

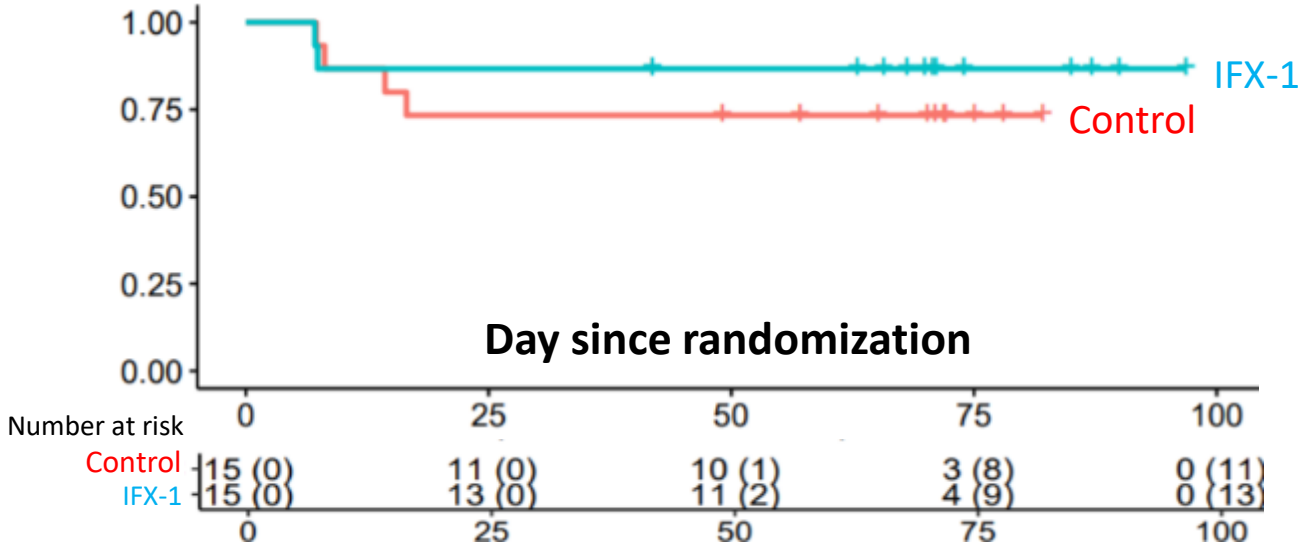


Immunomodulatory effect

Monoclonal antibody

# Vilobelimab (IFX-1) - 1

- **Day 5 $PaO_2/FiO_2$ percentage change**: no differences; IFX-1 group (17%) *vs*. control group (41%); difference –24% $CI_{95\%}$ [–58-9], p=0,15
- **D28 mortality**: IFX-1 group 13%; $CI_{95\%}$[0-31] *vs*. control group 27 %; $CI_{95\%}$[7-49]; HR=0,65 $CI_{95\%}$[0,1-4,14]



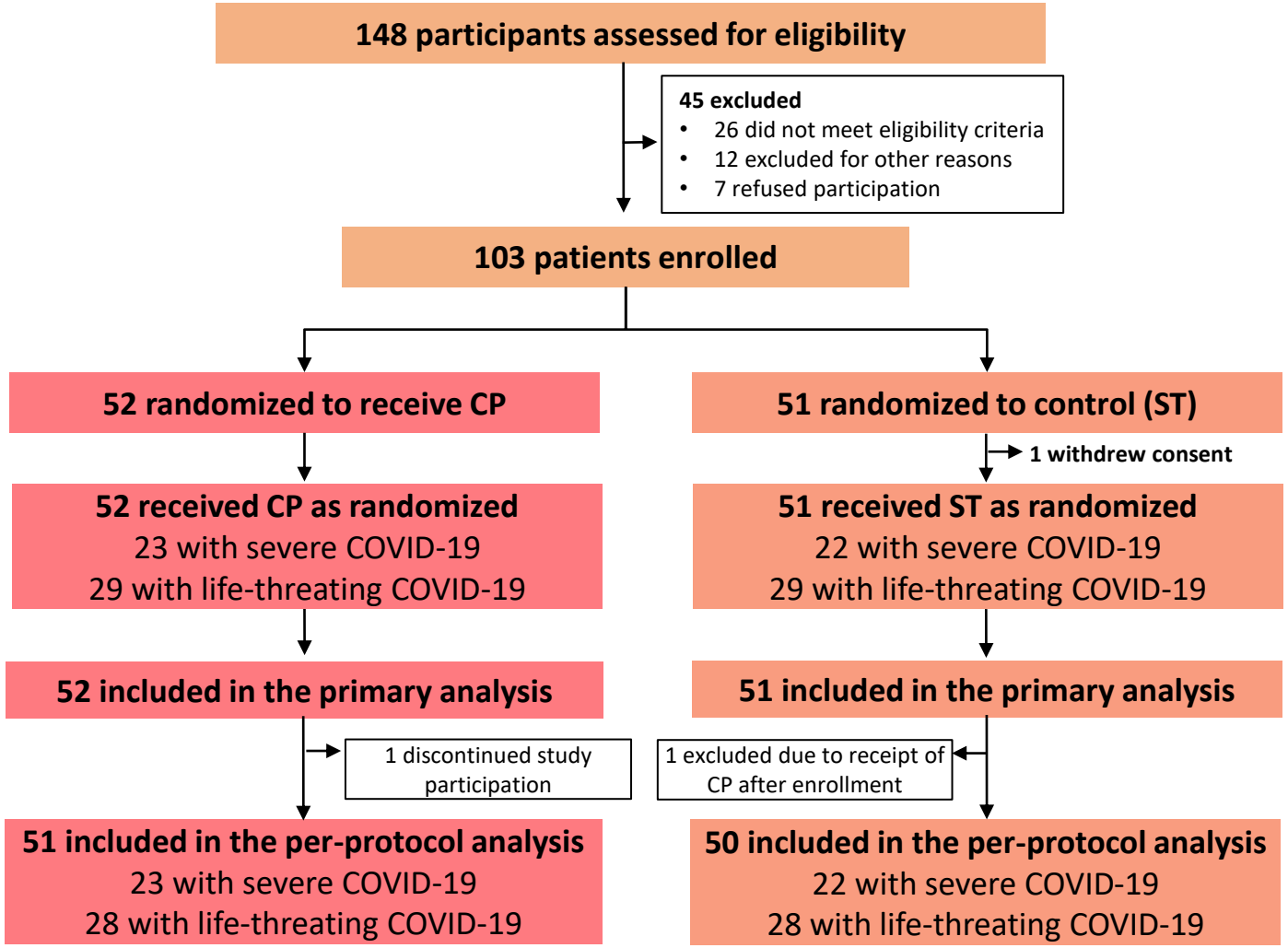

- **Limits**: patient heterogeneity, open label study

| Characteristics | IFX-1 (N=15) | Control (N=15) |
|---|---|---|
| Age, mean (SD) - yr | 58 (9) | 63 (8) |
| Male sex – no (%) | 11 (73) | 11 (73) |
| **Coexisting conditions** | | |
| Hypertension – no (%) | 6 (40) | 3 (20) |
| Diabetes – no (%) | 4 (27) | 4 (27) |
| Obesity – no (%) | 2 (13) | 4 (27) |
| **Respiratory support** | | |
| Intubated at randomization – no (%) | 8 (53) | 10 (67) |
| Oxygen mask – no (%) | 6 (40) | 2 (13) |
| Nasal cannula – no (%) | 1(7) | 3 (20) |

Passive immunity

# Convalescent plasma (CP) - 1

- Open-label, multicenter, randomized, academic study, China
- **Inclusion criteria:** age ≥ 18yo, chest imaging pneumonia confirmed, positive SARS-CoV-2 RT PCR, hospital admission, severe pneumonia (≥30 breaths/min, SpO2 ≤ 94% (room air) or $PaO_2/FiO_2 \leq 300$)
- **Main outcome**: time to clinical improvement within 28 days
- **Other outcomes**: D28 mortality, time to discharge, SARS-CoV-2 PCR rate results turned negative
- **CP + SoC group**: 52 patients *vs.* **SoC group (control)**: 51 patients (1:1)




Ling Li *et al. JAMA.* Jun 2020

Passive immunity

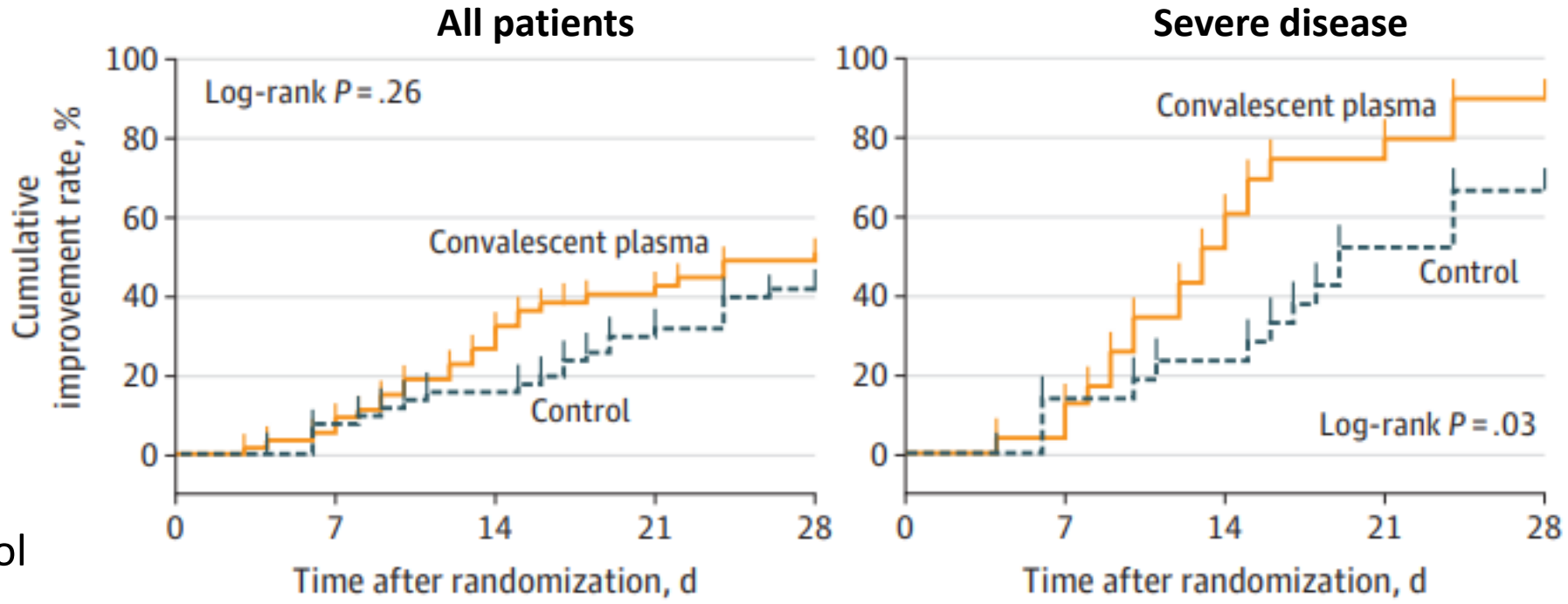
# Convalescent plasma (CP) - 1

| Characteristics | CP group (N=52) | Control group (N=51) |
|---|---|---|
| Age, median (IQR) – yr | 70 (62-80) | 69 (63-76) |
| Male sex – no (%) | 27 (51,9) | 33 (64,7) |
| **Co existing conditions** | | |
| Diabetes – no (%) | 9 (17,3) | 12 (23,5) |
| Hypertension – no (%) | 29 (55,8) | 27 (52,9) |
| Cardiovascular disease – no (%) | 14 (26,9) | 12 (23,5) |
| Cerebrovascular disease – no (%) | 11 (21,2) | 7 (13,7) |
| Cancer – no (%) | 3 (5,8) | 0 |
| **Vital sign** | | |
| Respiratory rate > 24/min – no (%) | 11/52 (21,2) | 7/49 (14,3) |

Passive immunity

# Convalescent plasma (CP) - 1

- **Time to clinical improvement within 28 days (all patient):** 51,9% (27/52) CP group *vs.* 43,1% (22/51) control group, HR: 1,40 CI $_{95\%}$[0,79-2,49]; p = 0,26
- **Time to clinical improvement within 28 days (severe disease):** 91.3% (21/23) CP group *vs.* 68.2% (15/22) control group, HR: 2,15 CI $_{95\%}$[1,07-4,32]; p = 0,03




- **Limits:** small number of participants, CP administrated late, SoC not protocolized, did not reached recruitment targets; 103 participants enrolled rather than 200 initially expected

Ling Li *et al. JAMA.* Jun 2020

Passive immunity

# Convalescent plasma (CP) - 2

- Multi centric, open label, academic study, USA
- **Inclusion criteria:** age ≥ 18yo, hospitalized, laboratory confirmed SARS-CoV-2 infection, high risk of progression to severe or life-threatening COVID-19 (dyspnea, ≥30 breaths/min, SpO2 ≤ 93%, lung infiltrates >50% within 24-28 hours of enrollment, respiratory failure, septic shock, multiple organ dysfunction, failure)
- **Main Outcomes** : determine the safety of transfusion of COVID-19 CP (incidence and relatedness of serious adverse events including death)
- **Convalescent plasma:** from COVID-19 survivor, symptoms free for at least 14 days, administrated intravenously, volume range from 200 cc to 500cc

| Characteristics | N=5 000 |
|---|---|
| Age, median (range) – yr | 62,3 (18,5-97,8) |
| Male sex – no (%) | 3 153 (63,1) |
| **Clinical Status** | |
| Current severe or life-threating COVID-19 – no (%) | 4 051 (81,0) |
| High risk of severe COVID-19 – no (%) | 949 (19,0) |
| ICU admission – no (%) | 3 316 (66,3) |
| **Clinical symptoms** | |
| Respiratory failure – no (%) | 2 912 (71,9) |
| Dyspnea – no (%) | 2 550 (62,9) |
| Blood oxygen saturation ≤ 93% – no (%) | 2 519 (62,2) |
| Respiratory frequency ≥ 30/min – no (%) | 1 546 (38,2) |
| $PaO_2/FiO_2 < 300$ | 1 365 (33,7) |
| Septic shock | 600 (14,8) |

Passive immunity

# Convalescent plasma (CP) - 2

- **Incidence** of serious adverse events (SAEs) in the first four hours after transfusion: < 1% (N=36)
- **Related** SAEs: 3 severe allergic transfusion reactions, 4 deaths, 18 TACO&TRALI (2 definitely related to CP)
- **Seven-day mortality rate**: 14,9%
- **Limits:** lack of detailed training of study personnel and monitoring, criteria specific to hospitalized patients

| Serious Adverse Evens (SAEs) Characteristics | Reported (N=36) | Related (N=25) | Estimate ($CI_{95\%}$) |
|---|---|---|---|
| **Four hour reports** | | | |
| Mortality | 15 | 4 | 0,08% (0,03-0,21) |
| Transfusion-Associated Circulatory Overload (TACO) | 7 | 7 | 0,14% (0,07-0,29) |
| Transfusion-Related Acute Lung Injury (TRALI) | 11 | 11 | 0,22% (0,12-0,39) |
| Severe allergic transfusion reaction | 3 | 3 | 0,06% (0,02-0,18) |
| **Seven day reports** | **Reported** | | **Estimate ($CI_{95\%}$)** |
| Mortality | 602 | | 14,9% (13,8-16,0) |

Passive immunity

# Convalescent plasma (CP) - 3

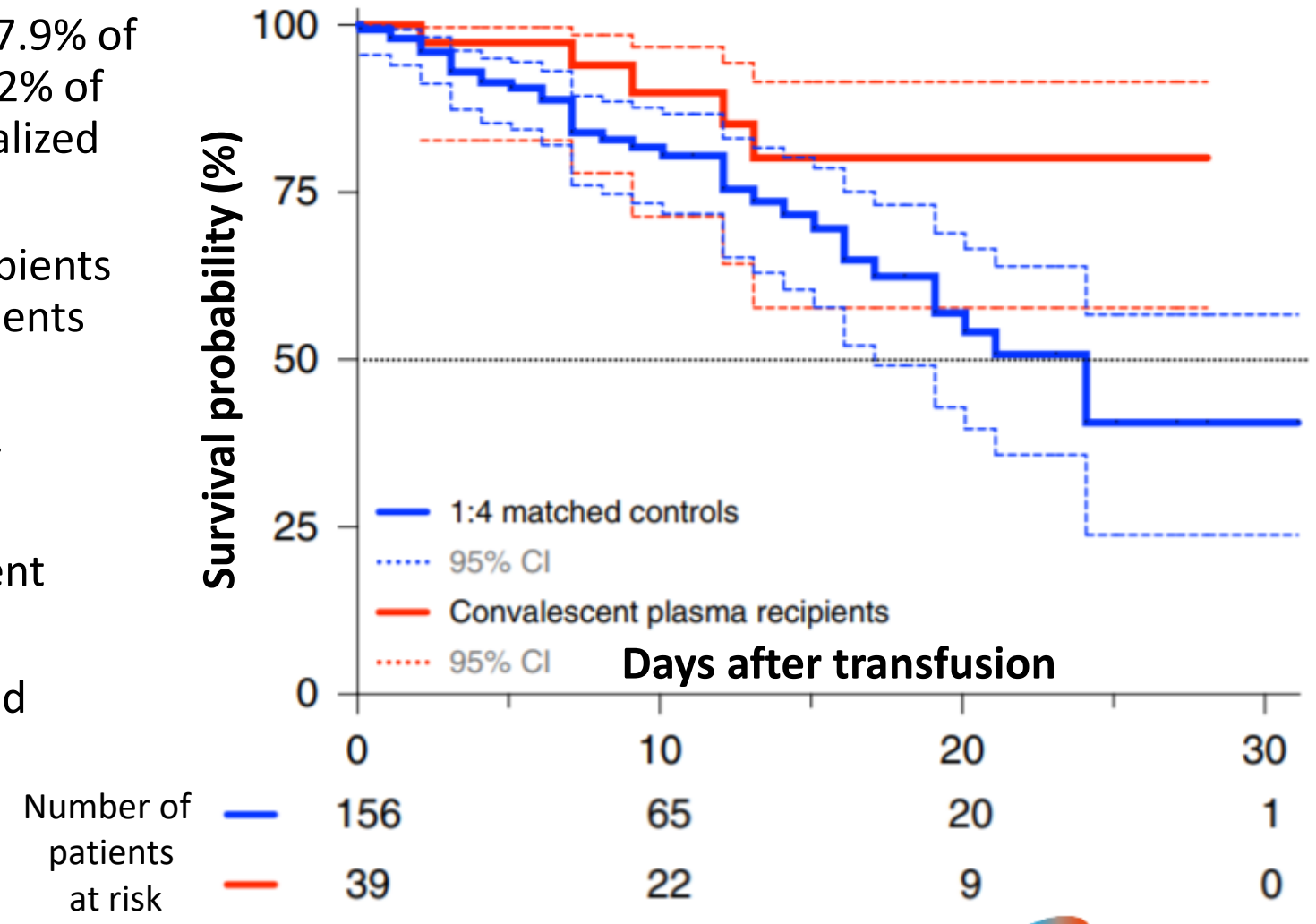
- Retrospective, propensity score-matched case-control study, academic study, USA
- **Inclusion criteria:** laboratory confirmed COVID-19, severe (dyspnea, respiratory frequency ≥ 30/min, $SpO_2$ ≤ 93%, $PaO_2/FiO_2$ < 300 mm Hg, and/or lung infiltrates > 50% within 24 to 48 hours) or immediately life-threatening (respiratory failure, septic shock, and/or multiple organ dysfunction or failure) COVID-19,
- **Main outcome** : D14 oxygen requirement
- **Other outcomes**: death, discharge alive, survival probability
- **Convalescent plasma group**: 39 patients *vs.* **Control group** : 156 patients (1:4)

| Characteristics | CP group (N=39) |
|---|---|
| Age, mean (SD) – yr | 55 (13) |
| Male sex – no (%) | 25 (64) |
| BMI, mean (SD) – kg/m² | 31,7 (6) |
| **Co existing conditions** | |
| Diabetes – no (%) | 8 (21) |
| Current or former smoker – no (%) | 29 (55,8) |
| Cancer – no (%) | 2 (5) |
| **Vital sign** | |
| Respiratory rate ≥ 20/min – no (%) | 28 (72) |
| Heart rate > 100/min – no (%) | 22 (56) |

Passive immunity

# Convalescent plasma (CP) - 3

- **D14 oxygen requirements**: worsened in 17.9% of convalescent plasma recipients versus 28.2% of propensity score matched controls hospitalized with COVID-19
- **Death**: 12,8% of convalescent plasma recipients and 24,4% of the 1:4 matched control patients
- **Discharged alive:** of convalescent plasma recipients and 71,8% and 66,7% of the 1:4 matched control patients
- **Survival probability**: greater in convalescent plasma recipients than controls
- **Limits:** small sample size, not a randomized controlled trial

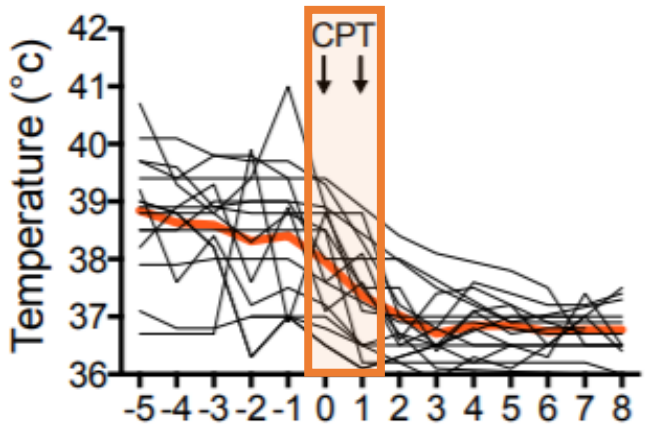


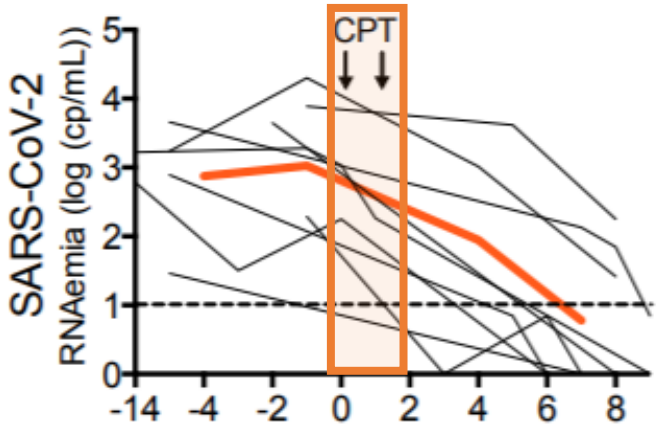

Liu S.T.H *et al. Nature Medicine.* Jun 2020

Passive immunity

# Convalescent plasma (CP) - 4

- Observational, multicenter, academic study, France
- **Inclusion criteria:** B-cell immunodeficiency with prolonged COVID-19 symptoms, positive SARS-CoV-2 RT-PCR from respiratory samples, no SARS-CoV-2 seroconversion
- 17 patients treated with 4 units of COVID-19 convalescent plasma



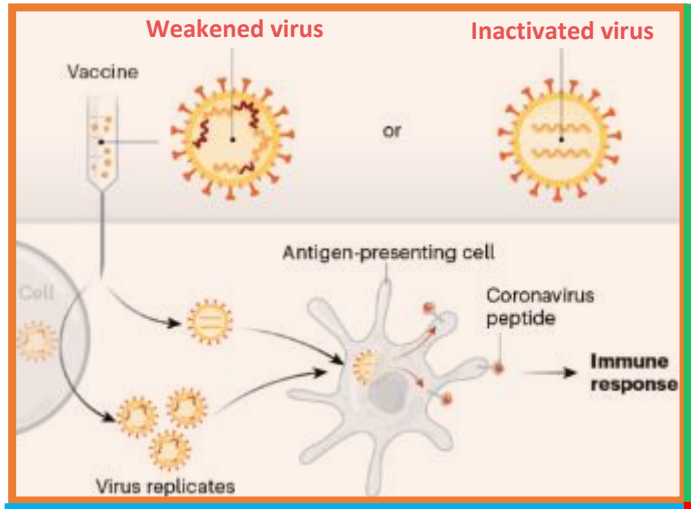



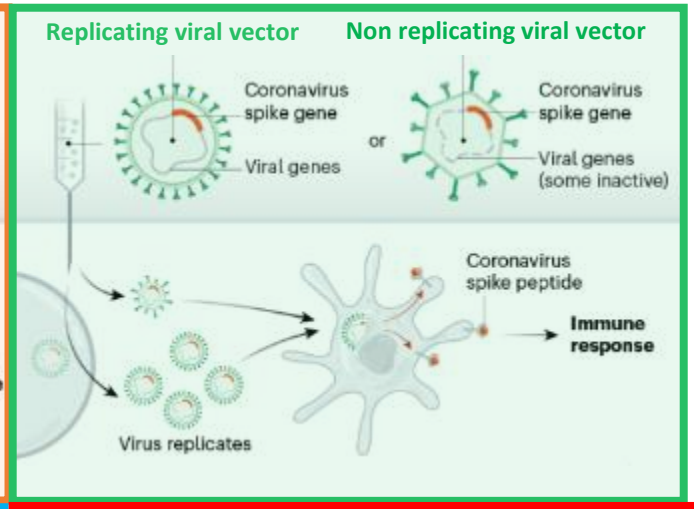

| Characteristics (N=17) | | CP |
|---|---|---|
| Age, median [range] - yr | | 58 [35-77] |
| Male sex – no (%) | | 12 (71) |
| Hematological malignancies | | 15 (88) |
| Non - Hematological malignancies | | 2 (12) |
| COVID -19 severity (WHO score), n (%) | 4 – no (%) | 5 (29) |
| | 5-6 – no (%) | 10 (59) |
| | 7 – no (%) | 2 (12) |
| Time between COVID -19 symptoms onset and CPT (days), median [range] | | 56 [7-83] |
| Time for oxygen weaning after CPT (days), median [range] | | 5 [1-45] |
| Overall survival, n (%) | | 16 (94) |

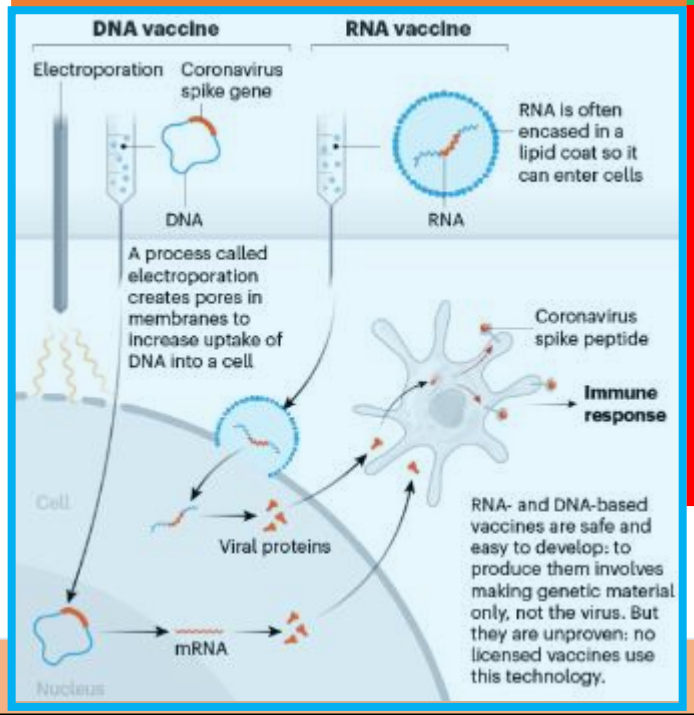
- **Clinical symptoms**: 16/17 patients experienced amelioration of SARS-CoV-2 within 48 hours CP
- **SARS-CoV-2 RNAemia**: 9/9 patients witnessed a decreased below sensitivity threshold

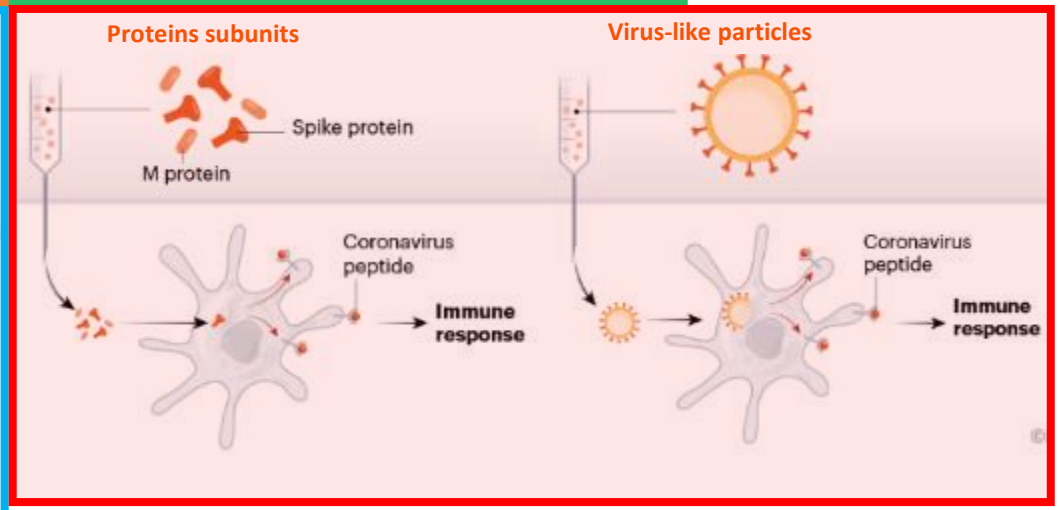
# Vaccine

- **Vaccines aims**: expose the immune system to an antigen that won't cause disease, provoke an immune response (able to block/kill the virus)
- **Eight types of vaccines**:
  - virus (inactivated, weakened),
  - viral vector (replicating, non replicating)
  - nucleic acid (DNA, RNA)
  - protein based (protein subunit, virus like particles)



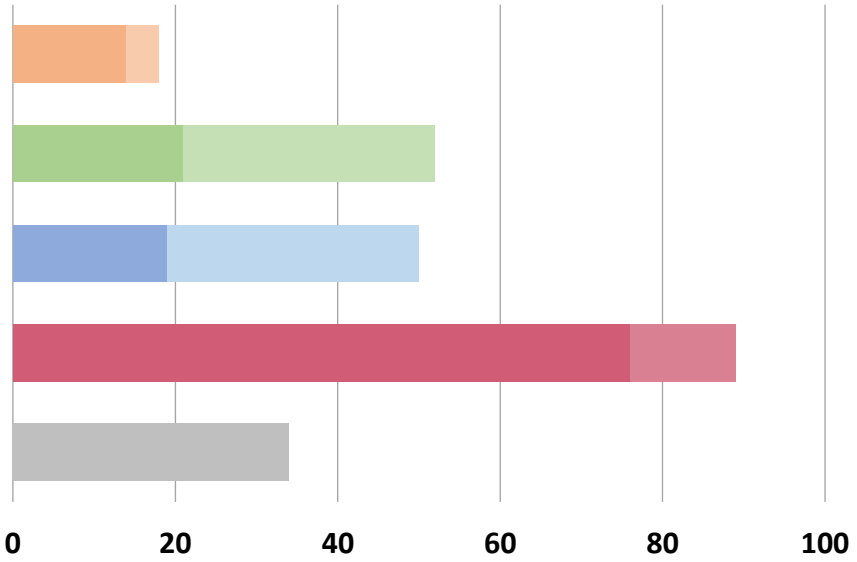

Callaway E. *Nature.* Apr 2020

# Vaccine

- **R&D landscape**: WHO lists more than 151 candidates in preclinical development, 42 candidate vaccines in clinical evaluation (October 2nd); update available at :

  https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

| | | Preclinical | Phase I | Phase I/II | Phase II | Phase II/III | Phase III | Licensed |
|---|---|---|---|---|---|---|---|---|
| VIRUS | Inactivated | 7 | 1 | 3 | | | 3 | |
| | Weakened | 4 | | | | | | |
| VIRAL VECTOR | Replicating | 17 | 4 | 1 | | | | |
| | Non replicating | 25 | 2 | | | | 4 | |
| NUCLEIC ACID | DNA | 14 | 1 | 4 | | | | |
| | RNA | 25 | 2 | 2 | 1 | 1 | 1 | |
| PROTEIN BASED | Protein subunit | 62 | 8 | 4 | 1 | | 1 | |
| | Virus-like Particles | 13 | 1 | 1 | | | | |
| Other/unknown | | 32 | 3 | | | | | |




*2 non replicating viral vector and 3 inactivated vaccines already approved for early or limited use (approved by Chinese or Russian medicines agencies before Phase III results)*

# Phase III COVID-19 Vaccines (Sep 30th 2020)

*Approved for limited use* | *Phase I/II data available (peer reviewed)* | *Phase I/II data available (pre-print)*

| Developer | Vaccine Platform | Description |
|---|---|---|
| BioNTech – Pfizer – Fosun Pharma | RNA | **BNT162b2*:** Lipid nanoparticle-formulated, nucleoside **modified mRNA** vaccine encoding **full-length spike (S) protein**<br>** Phase I published data refers to candidate BNT162b1 using RBD as antigen (Ugur S et al Nature, Sep 2020) . The company has decided to proceed to Phase II/III trials with BNT162b2 candidate who displayed reactogenicity in vaccinated adults.* |
| Moderna – NIAID | RNA | **mRNA-1273:** Lipid nanoparticle encapsulated, mRNA vaccine encoding **pre fusion spike (S) protein** |
| CanSino Biologicals Inc – Beijing Institute of Biotechnology | Non replicating viral vector | **Ad5-nCoV:** Replication-deficient **Ad5** vector containing optimised **full-length spike (S) protein** |
| Gamaleya Research Institute | Non replicating viral vector | **Sputnik V:** Recombinant **Ad26 (prime**) and recombinant **Ad5 (boost)** viruses expressing the gene for **spike (S) protein** |
| Janssen Pharmaceutical Companies – Beth Israel Deaconness Medical Center | Non replicating viral vector | **Ad26COVS1:** Recombinant adenovirus vaccine **(Ad26)** incorporating SARS-CoV-2 full stabilized **Spike (S)** protein |
| University of Oxford – AstraZeneca | Non replicating viral vector | **ChAdOx1 nCoV-19:** Replication-deficient **simian adenovirus** vector containing **codon-optimised spike (S) protein** |
| Novavax | Protein subunit | **NVX-COV2373:** Recombinant **nanoparticle** vaccine consisting of **full-length spike (S) protein**, with or without **Matrix-M1 adjuvant** |
| Sinovac – Institut Butantan | Inactivated | **CoronaVac: β-propiolactone inactivated** vaccine adiministered with **aluminium hydroxide adjuvant** |
| Beijing Institute of Biological Products – Sinophram | Inactivated | **BBIBP-CorV**: **β-propiolactone i**nactivated vaccine adiministered with **aluminium hydroxide adjuvant** |
| Wuhan Institute of Biological products– Sinopharm | Inactivated | **SARS-CoV-2 Vaccine: β-propiolactone inactivated** vaccine adsorbed to 0.5-mg **aluminum** |

mRNA vaccine

# mRNA 1273

## Moderna-NIH

**Phase I: NCT04283461**

| | |
|---|---|
| **Study Design** | Phase I open-label, non-randomised, dose-finding trial |
| **Age range** | 18 – 55 |
| **Nb of participants** | 45 |
| **Nb of doses/route** | 2 (days 1/29)-IM |
| **Vaccine groups** | 25 µg (n = 15)<br>100 µg (n = 15)<br>250 µg (n = 15) |
| **SAE** | None |
| **Local AE** | Injection site pain *(67–100% at ds1, 77–100% at ds 2)* |
| **Systemic AE** | Headache *(20–47% at ds1, 23–100% at ds2)*, myalgia *(7–27% at ds1, 23–93% at ds2)*, chills *(8–86% at ds2)*, fatigue *(27–33% at ds1, 39–80% at ds2)*, fever *(0–57% at ds2)*, nausea *(0–47% at ds 2)* |

## IMMUNOGENICITY 1/2

**1. GMHI* assay to spike protein in trial participants.**

**Assay:** ELISA
**Units:** Geometric mean titre (95% CI)

| Time Point | 25-µg Group | | 100-µg Group | | 250-µg Group | | Convalescent Serum | |
|---|---|---|---|---|---|---|---|---|
| | *no.* | *GMT (95% CI)* | *no.* | *GMT (95% CI)* | *no.* | *GMT (95% CI)* | *no.* | *GMT (95% CI)* |
| ELISA anti–S-2P | | | | | | | 38 | 142,140 (81,543–247,768) |
| Day 1 | 15 | 116 (72–187) | 15 | 131 (65–266) | 15 | 178 (81–392) | | |
| Day 15† | 15 | 32,261 (18,723–55,587) | 15 | 86,291 (56,403–132,016) | 15 | 163,449 (102,155–261,520) | | |
| Day 29 | 15 | 40,227 (29,094–55,621) | 15 | 109,209 (79,050–150,874) | 14 | 213,526 (128,832–353,896) | | |
| Day 36 | 13 | 391,018 (267,402–571,780) | 15 | 781,399 (606,247–1,007,156) | 14 | 1,261,975 (973,972–1,635,140) | | |
| Day 43 | 13 | 379,764 (281,597–512,152) | 14 | 811,119 (656,336–1,002,404) | 14 | 994,629 (806,189–1,227,115) | | |
| Day 57 | 13 | 299,751 (206,071–436,020) | 14 | 782,719 (619,310–989,244) | 13 | 1,192,154 (924,878–1,536,669) | | |

Binding antibody IgG geometric mean titers (GMTs) to S protein: **seroconversion in all participants by day 15.**

A recent study shows that mRNA 1273 vaccine induces specific IgG responses and NAbs in adults older than 70 years of age. *(Anderson EJ, NEJM 2020)*

mRNA vaccine

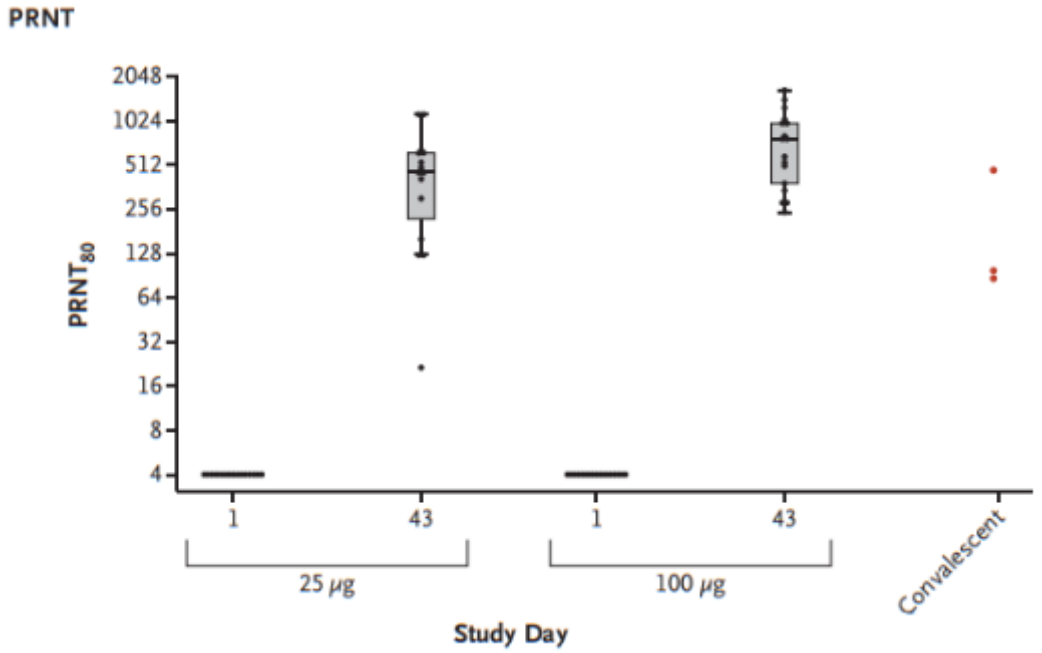
# mRNA 1273

## IMMUNOGENICITY 2/2

### 2. Neutralizing responses

**Assay:** Plaque-reduction neutralization test (80% inhibitory dilution)
**Units:** Geometric mean response, ID80 (95% CI)

At day 43, **wild-type virus–neutralizing activity capable of reducing SARS-CoV-2 infectivity by 80%** or more ($PRNT_{80}$) detected in all participants, with geometric mean $PRNT_{80}$ responses of 339.7 (95% CI, 184.0 to 627.1) in the 25-µg group and 654.3 (95% CI, 460.1 to 930.5) in the 100-µg group




**3. Cellular responses:** 25-µg and 100-µg doses elicit CD4 T-cell responses **biased toward expression of Th1** cytokines (TNFα > IL2> IFNγ).

Adenoviral vector vaccine

# Ad5-nCoV

## CaSino BIO

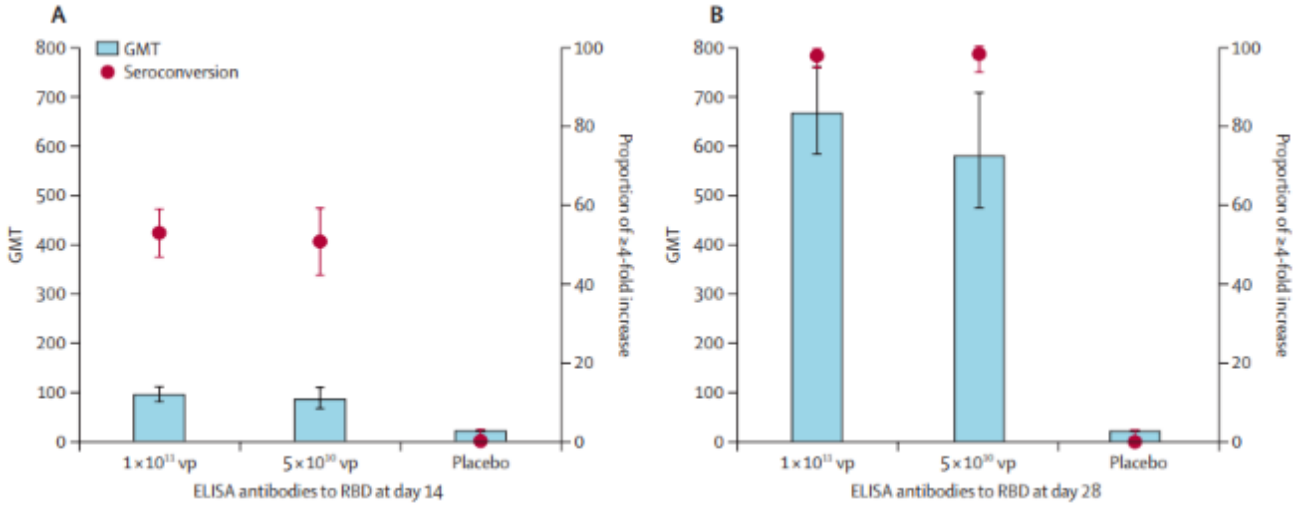
**Phase I:** NCT04313127
**Phase II:** NCT04341389

| | |
|---|---|
| **Study Design** | Phase I open-label, non-randomized, dose-finding trial<br>Phase II randomized controlled, dose-finding trial |
| **Age range** | Phase I: 18 – 60; Phase II>18 |
| **Nb of participants** | Phase I: 108; Phase II: 508 |
| **Nb of doses/route** | 1–IM |
| **Vaccine groups** | Phase I:<br>Low dose: $5 \times 10^{10}$ vp (n = 36)<br>Medium dose: $1 \times 10^{11}$ vp (n = 36)<br>High dose: $1.5 \times 10^{11}$ vp (n = 36)<br>Phase II:<br>Low (n=129) and medium (n=253)<br>**Control group:** placebo (N=126) |
| **SAE** | None |
| **Local AE** | Injection site pain *(Ph I: 47–58%; Ph II: 56 – 57%)* |
| **Systemic AE** | Fever *(Ph I: 42–56%; Ph II: 16-32% )*, fatigue *(Ph I: 39–47%; Ph II: 34-42%)*, headache *(Ph I: 31–47%; Ph II: 28-29%)* |

## IMMUNOGENICITY 1/2 *(data corresponding to Phase II trial)*

### 1. RBD-specific ELISA antibody responses induced by the Ad5-NCoV vaccine

**Assay:** ELISA
**Units:** Geometric mean titre (95% CI)




**Anti-RBD IgG** responses detected **from day 14**. At day 28, the specific IgGs peaked at 656·5 (575·2–749·2) at the low dose group and 571·0 (467·6–697·3) at the high dose group. **Seroconversion** on 96% (95% CI 93–98) within the low dose group and 97% (95% CI 92–99) at the high dose group

*Zhu FC* et al. *Lancet*. Jul 2020

Adenoviral vector vaccine

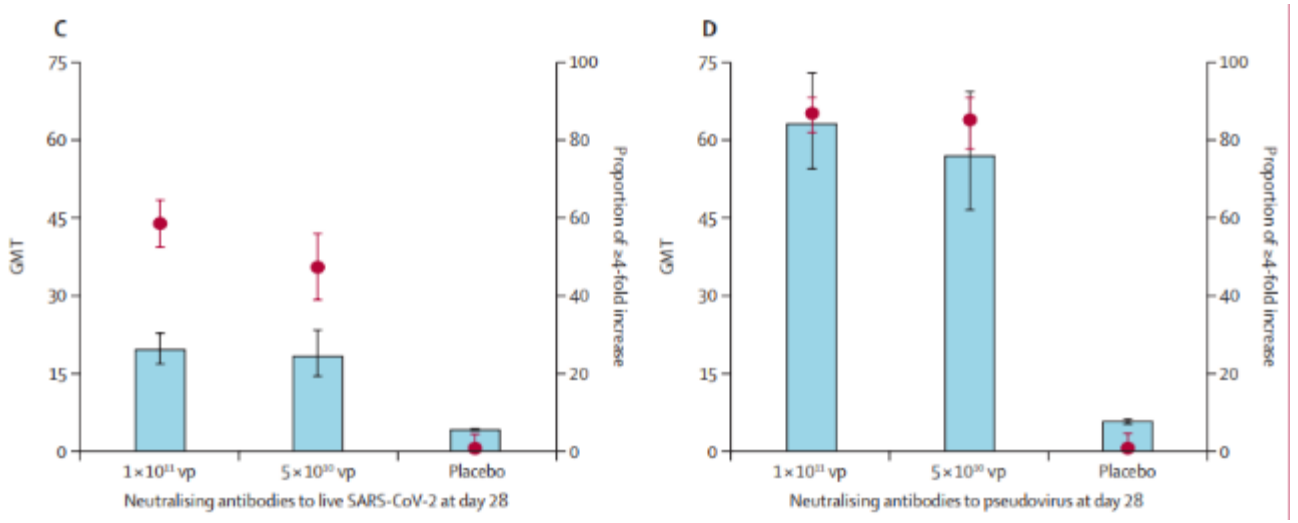
# Ad5-nCoV

## IMMUNOGENICITY 2/2 *(data corresponding to Phase II trial)*

### 2. Neutralizing responses

**Assay:** SARS-CoV-2 virus neutralization test
**Units:** Geometric mean titer (95% CI)

**Significant neutralizing antibody responses** to live SARS-CoV-2, with GMTs of 19·5 (95% CI 16·8–22·7) and 18·3 (14·4–23·3) (low *vs* high dose groups) at day 28 post vaccination.




| Pre-existing adenovirus type-5 neutralising antibody | | | |
|---|---|---|---|
| ≤1:200, titre | 127 (50%) | 54 (42%) | 61 (48%) |
| >1:200, titre | 126 (50%) | 75 (58%) | 65 (52%) |

***Ad5 pre-existing immunity did not prevent neutralization titers***

### 3. Induction of T cell mediated responses

Adenoviral vector vaccine

# Sputnik V

**Gamaleya Research Institute**

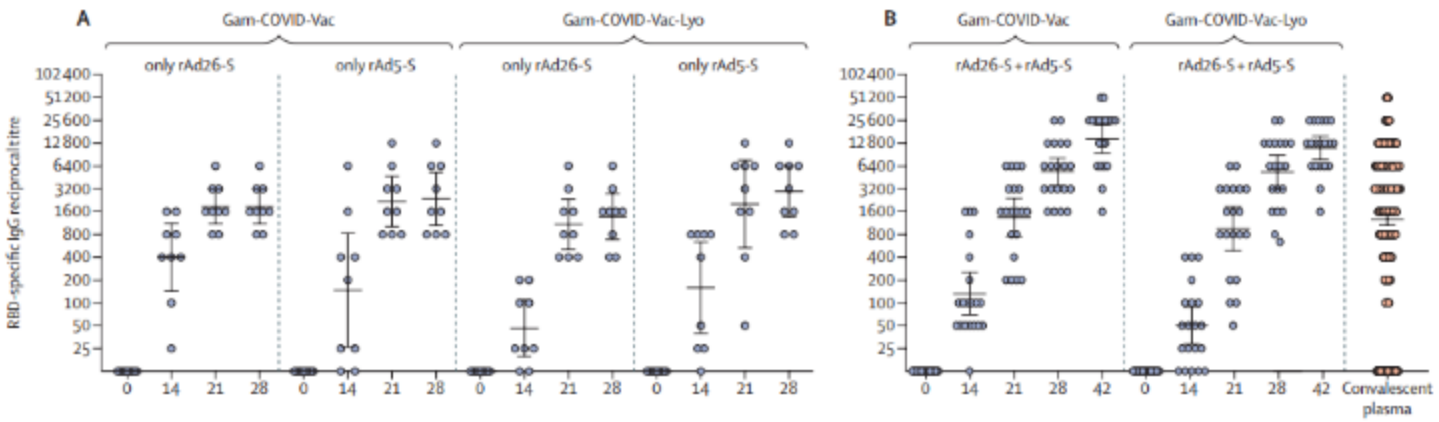
**Phase I/II:** NCT04436471 *(frozen product)*
NCT04437875 *(lyo product)*

| | |
|---|---|
| **Study Design** | Phase I/II open-label, non-randomised trial |
| **Age range** | 18 – 60 |
| **Nb of participants** | 76 |
| **Nb of doses/route** | 1 (day 0) or 2 (rAd26 on day 0, rAd5 on day 21) -IM |
| **Vaccine groups** | Frozen 1 x $10^{11}$ rAd26 (n = 9)<br>Frozen 1 x $10^{11}$ rAd5 (n = 9)<br>Frozen $10^{11}$ rAd26/$10^{11}$ rAd5 (n = 20)<br>Lyo 1 x $10^{11}$ rAd26 (n = 9)<br>Lyo 1 x $10^{11}$ rAd5 (n = 9)<br>Lyo $10^{11}$ rAd26/$10^{11}$ rAd5 (n = 20) |
| **SAE** | None |
| **Local AE** | Injection site pain *(40–78%)* |
| **Systemic AE** | Changes in laboratory variables *(67–100%),* hyperthermia *(11–100%),* headache *(25–67%),* asthenia *(0–55%),* muscle or joint pain *(11–33%),* subjective heartbeat palpitation *(0–33%)* |

## IMMUNOGENICITY 1/2

### 1. SARS-CoV-2 RBD-specific IgGs

**Assay:** ELISA
**Units:** Geometric mean titre (95% CI)




**Anti-RBD IgG** responses detected **from day 14** for both products and in all vaccine administration schemes . At **day 21** RBD-specific IgGs were detected in **100% of vaccinated** participants. ([GMT] 1629 with the frozen formulation and 951 with the lyophilized one). **Heterologous boosting** with rAd5-S led to an **increase in SARS-CoV-2 RBD specific IgG** titres; 7 days after boost.

Moderna:

*Logunov DY* et al *Lancet.* Sep 2020

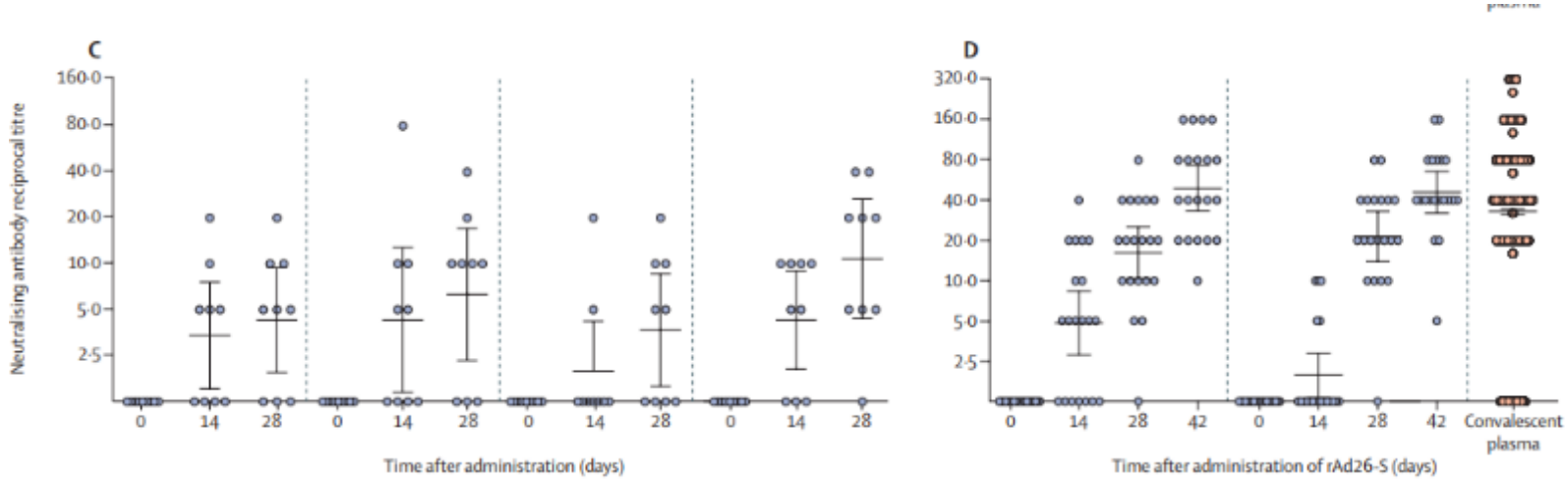
Adenoviral vector vaccine

# Sputnik V

## IMMUNOGENICITY 2/2

### 2. Neutralizing responses

**Assay:** Microneutralisation assay (50% inhibitory dilution, Vero E6 cells)
**Units:** Geometric mean titre, ID50 (95% CI)




Administration of **both rAd26-S and rAd5-2** led to production of **neutralizing antibodies in 100% of participants**, whereas administration of only rAd26-S led to a lower seroconversion rate

**3. T cell response:** induction of **CD4+** and **CD8+** cells and an increase in the concentration of **interferon-γ secretion**

Adenoviral vector vaccine

# ChAdOx1 nCoV-19

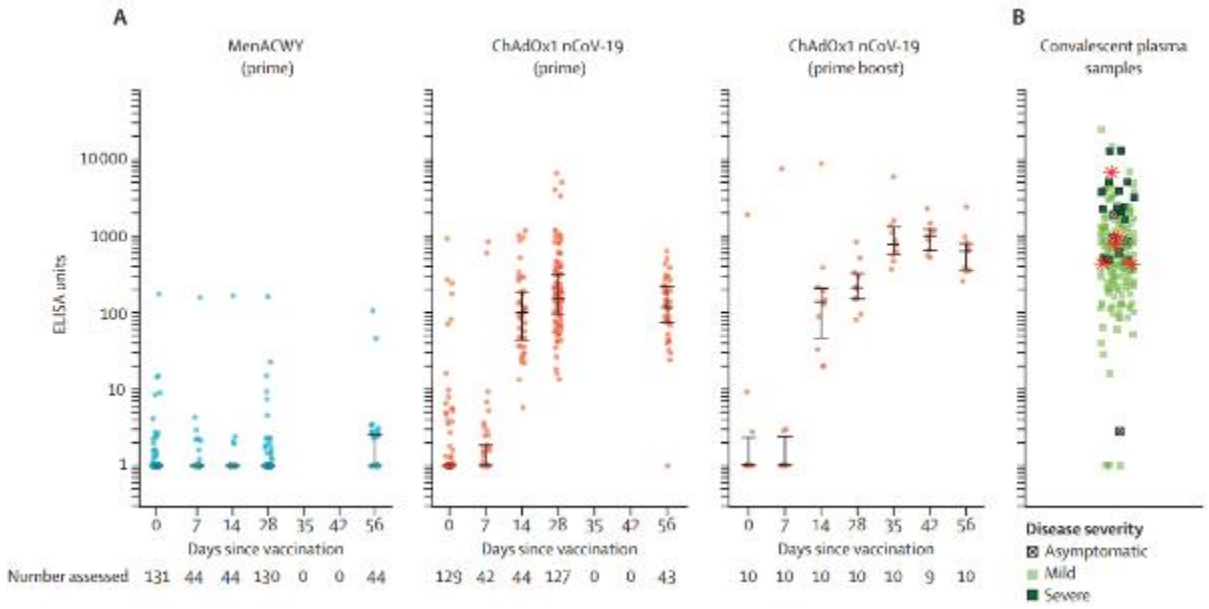
## AstraZeneca-Oxford University Phase I: NCT04324606

| | |
|---|---|
| **Study Design** | Phase I/II randomised controlled trial |
| **Age range** | 18 – 55 |
| **Nb of participants** | 1077 |
| **Nb of doses/route** | 1 (day 0) or 2 (days 0/28)- IM |
| **Vaccine groups** | 1 dose at 5 × $10^{10}$ viral particles (n = 543)<br>2 doses at 5 × $10^{10}$ viral particles (n = 10; non-randomised)<br>**Control group:** MenACWY (n = 534) |
| **SAE** | None* *(Ph III trial suspended and resumed in Sep 2020 due to 2 cases of tranverse myelitis among participants, found not to be related to vaccination)* |
| **Local AE** | **Without prophylactic paracetamol**: tenderness *(83%),* injection site pain *(67%),* warmth *(25%).* **With prophylactic paracetamol:** tenderness *(77%),* injection site pain *(50%).* |
| **Systemic AE** | **Without prophylactic paracetamol:** fatigue *(70%),* headache *(68%),* malaise *(61%),* chills *(56%),* feverish *(51%),* joint pain *(31%),* nausea *(25%).* **With prophylactic paracetamol**: fatigue *(71%),* headache *(61%),* malaise *(48%),* feverish *(36%),* joint pain *(29%),* chills *(27%),* nausea *(25%).* |

## IMMUNOGENICITY 1/2

1. **SARS-CoV-2 IgG response by standardized ELISA to spike protein in trial participants. Comparison with PCR confirmed COVID19 cases**

**Assay:** ELISA
**Units:** Median ELISA units (IQR)




**Anti-spike IgG** responses **rose by day 28** (median 157 EU, [96–317], boosted after a 2nd dose (639 EU, 360–792)

*Folegatti PM* et al *Lancet.* Aug 2020

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

REACTing research & action targeting emerging infectious diseases

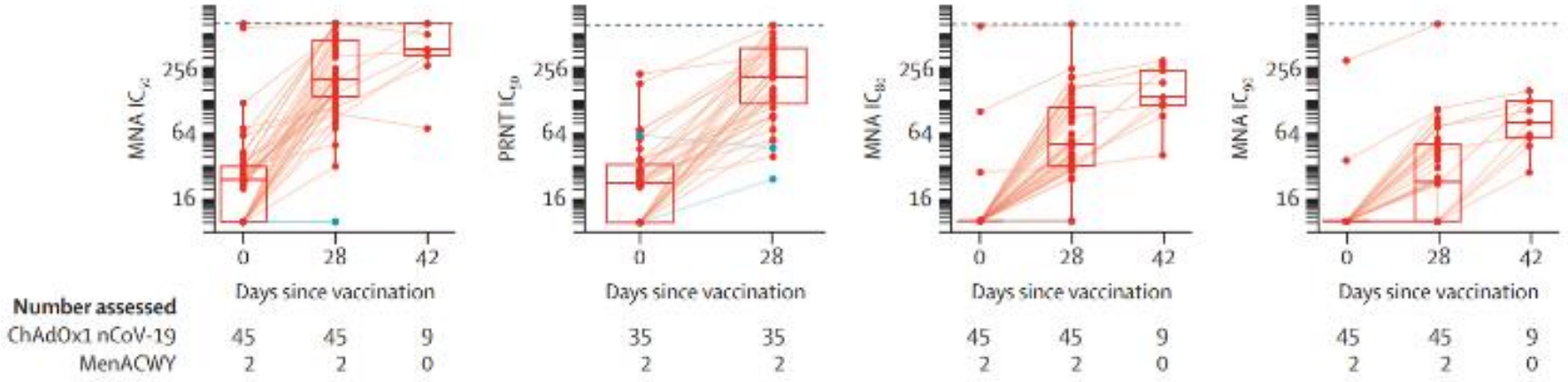
Adenoviral vector vaccine

# ChAdOx1 nCoV-19

## IMMUNOGENICITY 2/2

### 2. Live SARS-CoV-2 neutralization assays (PHE PRNT50) and microneutralisation assays (PHE MNA)

**Assay:** Plaque-reduction neutralisation test (50% inhibitory dilution)/ Microneutralisation assay (80% inhibitory dilution)
**Units:** Median titre, ID50 (IQR)




**Neutralizing antibody responses:** detected in 32 (91%) of 35 participants after a single dose when measured ($MNA_{80}$) and in 35 (100%) participants when measured in $PRNT_{50}$. After a booster dose, all participants had neutralizing activity (nine of nine in $MNA_{80}$ at day 42)

### 3. Induction of T cell responses and increase of IFN-γ expression

Protein Subunit vaccine

# NVX-COV-2373

## NOVAVAX

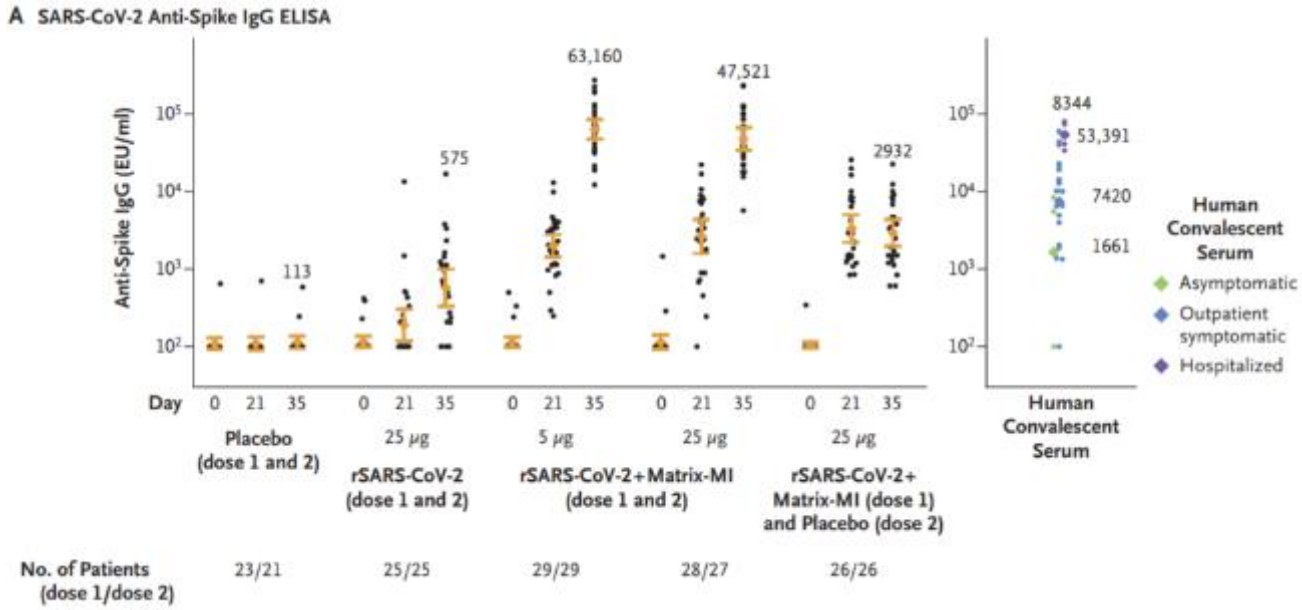
**Phase I:** [NCT04368988]

| | |
|---|---|
| **Study Design** | Phase I randomised controlled, dose-finding trial |
| **Age range** | 18 – 59 |
| **Nb of participants** | 131 |
| **Nb of doses/route** | 1 (day 0) or 2 (days 0/21) - IM |
| **Vaccine groups** | 2 x 25 µg (n = 25)<br>2 x 5 µg + 50 µg Matrix-M1 (n = 28)<br>2 x 25 µg + 50 µg Matrix-M1 (n = 28)<br>1 x 25 µg + 50 µg Matrix-M1 (n = 25)<br>2 x 5 µg and 2 x 25 µg included 3 sentinel participants who were vaccinated in an open-label manner and observed for reactogenicity<br>**Control group:** 0.9% saline placebo (n = 25) |
| **SAE** | None |
| **Local AE** | Tenderness *(20–65% at ds1, 12–81% at ds2)*, injection site pain *(24–54% at ds1, 8–63% at ds 2)* |
| **Systemic AE** | Headache *(23–40% at dose 1, 28–58% at dose 2),* muscle pain/myalgia *(12–32% at dose 1, 8–54% at dose 2)*, fatigue *(16–40% at dose 1, 12–50% at dose 2)*, malaise *(4–28% at dose 1, 8–38% at dose 2),* joint pain *(4–27% at dose 2)* |

## IMMUNOGENICITY 1/2

### 1. SARS-CoV-2 Anti-Spike IgGs

**Assay:** ELISA
**Units:** Geometric mean titre (95% CI)




**By day 21** after 1st vaccination, **IgG specific responses** occurred for all adjuvant regimens (**10-fold of non adjuvant).** IgGs concentrations **further increased after 2nd dose** vaccination (day 29 and day 35)

*Keech C* et al. *NEJM.* Sep 2020

Protein Subunit vaccine

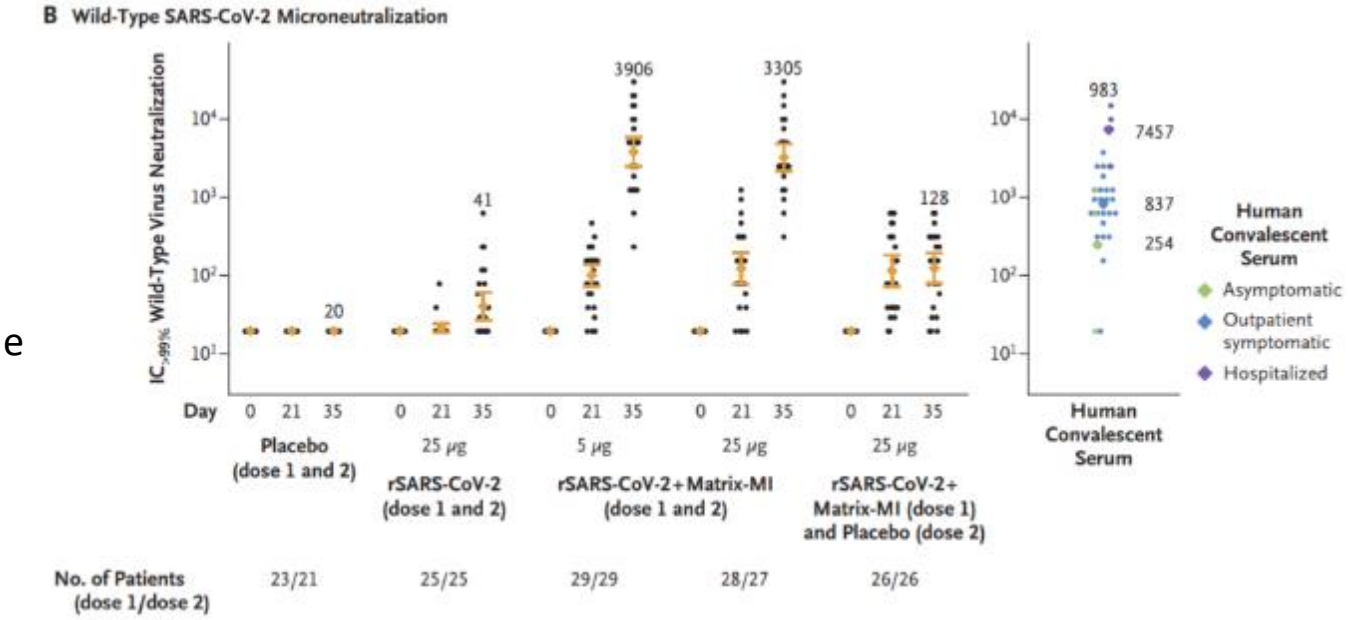
# NVX-COV-2373

## IMMUNOGENICITY 2/2

### 2. Neutralizing responses

**Assay:** Microneutralisation assay (99% inhibitory dilution, Vero E6 cells)
**Units:** Geometric mean titre, ID99 (95% CI)

**Two doses of adjuvant vaccine** induced an increase on the concentration of neutralizing antibodies more than **100 times greater** than single vaccinations without adjuvant.




**3. Induction of T-cell responses:** antigen-specific induction of CD4+ T-cell responses A strong bias toward this Th1 phenotype observed

Inactivated vaccine

# SARS-CoV-2 Vaccine

## Wuhan Institute of Biological products

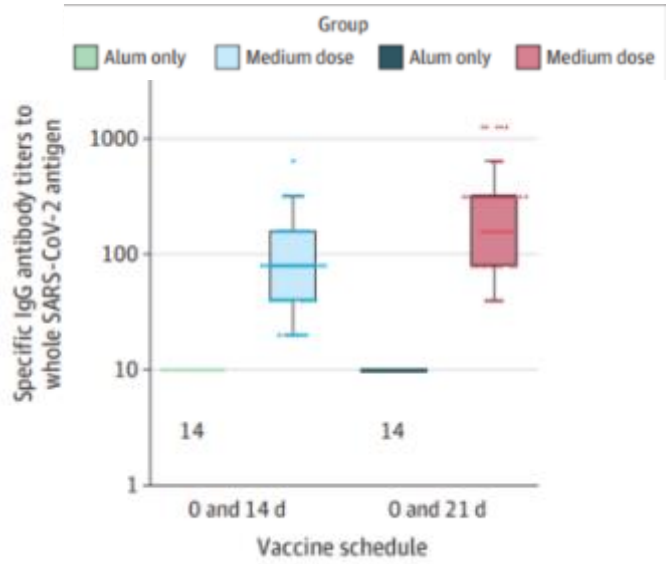
**Phase I and II:** ChiCTR2000031809

| | |
|---|---|
| **Study Design** | Phase I: randomised controlled dose-finding trial<br>Phase II: randomised controlled trial |
| **Age range** | 18 – 59 |
| **Nb of participants** | Phase I: 96 Phase II: 224 |
| **Nb of doses/route** | Phase I: 3 (days 0/28/56) – IM<br>Phase II: 2 (days 0/14 or 0/21) -IM |
| **Vaccine groups** | Phase I :<br>I2.5 µg (n = 24)<br>5 µg (n = 24)<br>10 µg (n = 24)<br>**Control group:** Placebo of aluminum hydroxide (n = 24)<br>Phase II:<br>5 µg at d0/14 or d0/21 (n = 84 each group)<br>**Control group:** Placebo of aluminum hydroxide, d0/14 (n = 28) or d0/21 (n = 28) |
| **SAE** | None |
| **Local AE** | Phase I: Injection site pain (4–25% combining across doses)<br>Phase II: None at ≥25% prevalence |
| **Systemic AE** | Phase I and Phase II: None at ≥25% prevalence |

## IMMUNOGENICITY1/2 *(Phase II data)*

### 1. Specific IgG antibody responses to whole SARS-CoV-2 antigen

**Assay:** ELISA
**Units:** Geometric mean titre (95% CI)




The GMTs of specific IgGs antibody was 74 (95% CI, 56-97) in the group vaccinated on d0 and d14 and 215 (95% CI, 157-296) in the group vaccinated on d0 and d21. Seroconversion was noted in all participants receiving injections on d0 and d21

*Xia S* et al. *JAMA*. Sep 2020

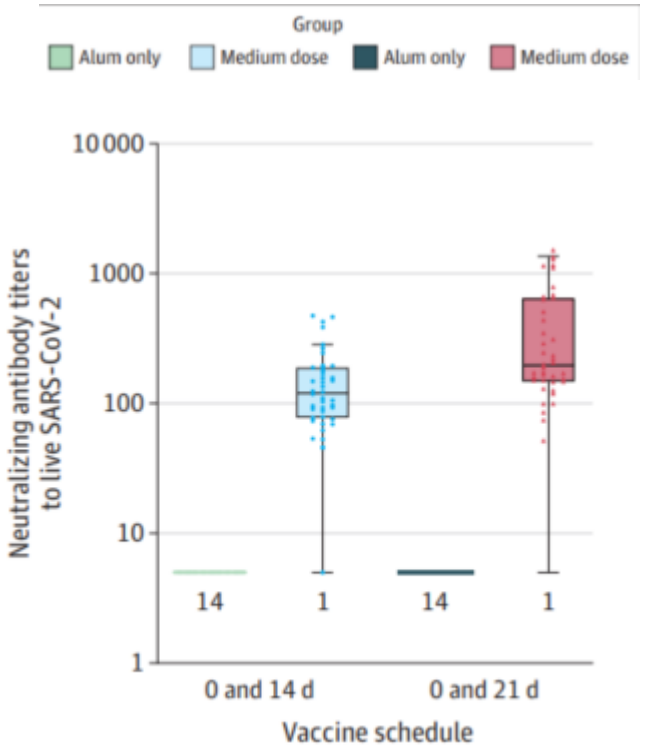
Inactivated vaccine

# SARS-CoV-2 Vaccine

## IMMUNOGENICITY 2/2 *(Phase II data)*

### 2. Neutralizing antibodies to live SARS-CoV-2

**Assay:** Plaque-reduction neutralisation test (50% inhibitory dilution, Vero E6 cells)
**Units:** Geometric mean titre, ID50 (95% CI)




The geometric mean titer (GMT) of neutralizing antibody was 121 (95% CI, 95-154) in the group vaccinated on d0 and 14 and 247 (95% CI, 176-345) in other group. Seroconversion was noted in 97.6% of the vaccinated patients (none in the alum-only group)

*Xia S* et al. *JAMA.* Sep 2020

# Vaccine Summary results

| Vaccine & Developer | Phase III regimen | Specific IgG titers (14 - 28 days after 2nd dose) *as per Phase I or II published results* | NAb titers (14 - 28 days after 2nd dose) *as per Phase I or II published results* |
|---|---|---|---|
| **BNT162b2**<br>BioNTech – Pfizer – Fosun Pharma | 2 doses (d1 and d22)<br>30µg/dose | Non published yet-preprint | |
| **mRNA-1273**<br>Moderna – NIAID | 2 doses (d1 and d29)<br>100µg/dose | 782 719 GMT<br>*Test: ELISA anti S IgG* | 654.3 GMT<br>*Test: $PRNT_{80}$* |
| **Ad5-nCoV**<br>CanSino Biologicals Inc –Beijing Institute of Biotechnology | 1 dose<br>$5x10^{10}$ vp | 571.0 GMT<br>*Test: ELISA anti RBD IgG* | 18.3 GMT<br>*Test: WT virus neutralization* |
| **SputnikV**<br>Gamaleya Research Institute | d1 0,5 mL rAd26<br>d21 0,5 mL rAd5 | 14 703 GMT<br>*Test: ELISA anti RBD IgG* | 49.25 GMT<br>*Test: $MNA_{50}$* |
| **Ad26COVS1**<br>Janssen Pharmaceutical Companies<br>Beth Israel Deaconness Medical Center | 1 dose<br>$1x10^{11}$ vp | Non published yet-preprint | |
| **ChAdOx1 nCoV-19**<br>University of Oxford – AstraZeneca | 2 doses (d1 and d29)<br>$5x10^{10}$ vp | 639 EU<br>*Test: ELISA anti S IgG* | 136 MT<br>*Test: $MNA_{80}$* |
| **NVX COV2373**<br>Novavax | 2 doses (d0 and d28)<br>25µg+Matrix M/ dose | 47 521 GMEU<br>*Test: ELISA anti S IgG* | 3305 GMT<br>*Test: $MNA_{99}$* |
| **CoronaVac**<br>Sinovac – Institut Butantan | 2 doses (d1 and d14) | Non published yet-preprint | |
| **BBIBP-CorV**<br>Beijing Inst. Biological Products –Sinophram | 2 doses (d0 and d21) | Non published yet-preprint | |
| **SARS-CoV-2 Vaccine**<br>Wuhan Inst. Biological products– Sinopharm | 2 doses (d0 and d21) | 215 GMT<br>*Test: ELISA anti S IgG* | 247 GMT<br>*Test: $PRNT_{50}$* |

**NOTE:**

**COMPARISONS SHOULD NOT BE MADE AS ASSAYS ARE NOT STANDARDIZED**

# THERAPEUTIC (October 12th 2020)

**1. What drug showed clinical efficacy?**

- Dexamethasone is the first drug to show life-saving efficacy in patients infected with COVID-19

**2. What drugs did not show proven benefits?**

- No proven benefits have been reported with (hydroxy)chloroquine nor lopinavir/ritonavir treatment

**3. What are the types of vaccines in clinical evaluation**

- 40 candidates vaccines are in an ongoing clinical evaluation
- Published Phase I/II data suggests that vaccine candidates on trial are immunogenic and mostly well tolerated in young adults
- Induced titers of NAb are variable depending on the vaccine candidate
- No data on ADE risk on humans nor virus clearance in upper respiratory tract after human vaccination has been published yet
- 10 vaccines are already in Phase III for efficacy evaluation

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