COREB
mission nationale
Coordination Opérationnelle
Risque Epidémique et Biologique

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REACTing
research & action
targeting emerging infectious diseases

https://reacting.inserm.fr/

# Scientific update on COVID-19

**Updated on 3 August 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

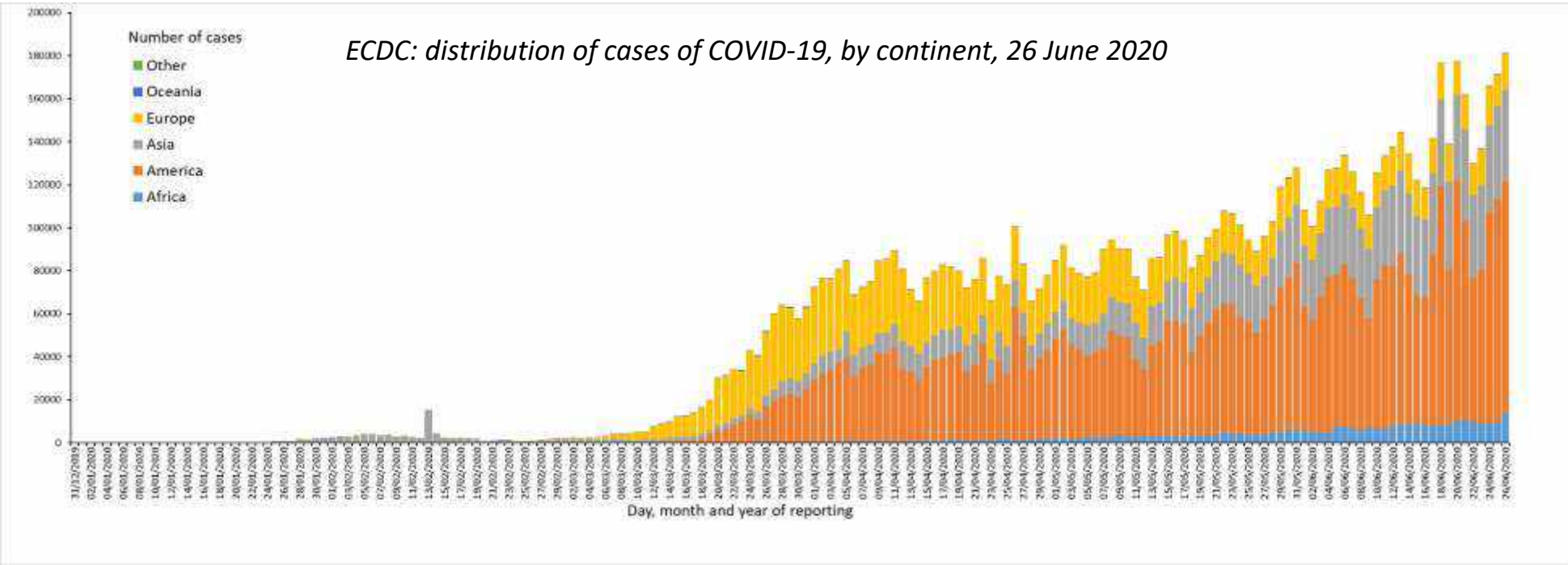
# EPIDEMIOLOGY

**Questions:**

- **What is the situation in the Word? In France?**
- **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



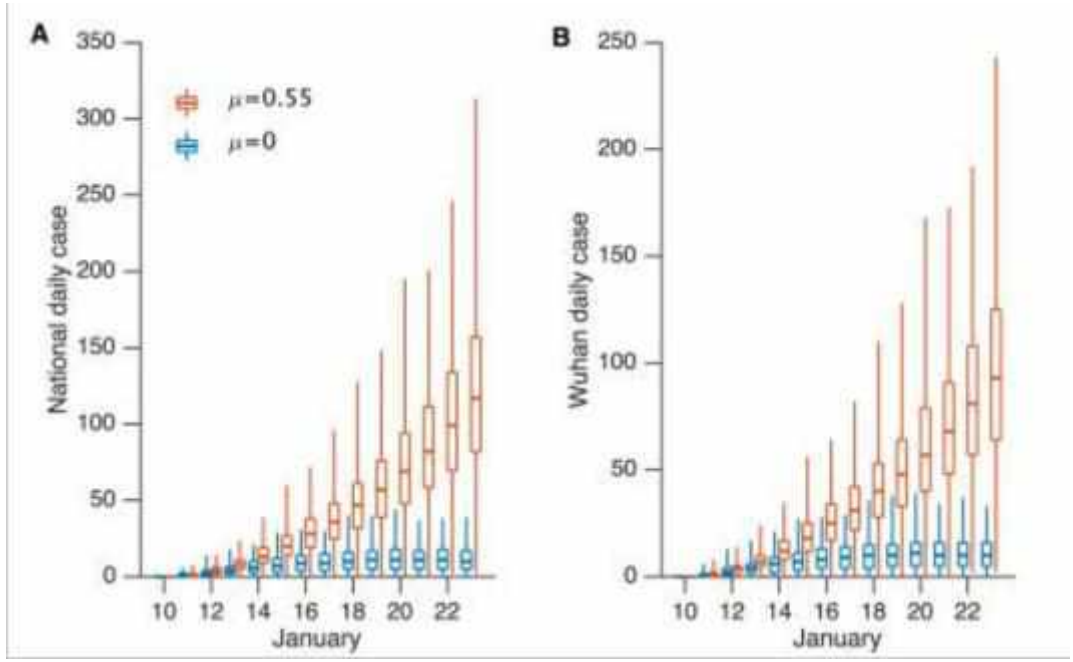

*ECDC: distribution of cases of COVID-19, by continent, 26 June 2020*

# 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 somes parameters*
*μ=factor applied to transmission rate due to undocumented infected persons*




- Very high rate of undocumented infection
- Contagious undocumented infection facilitated the spread of SARS-CoV-2
- **Dissemination by undocumented infection**
- Reduction of undocumented infection → decrease the growth and the spread of infection

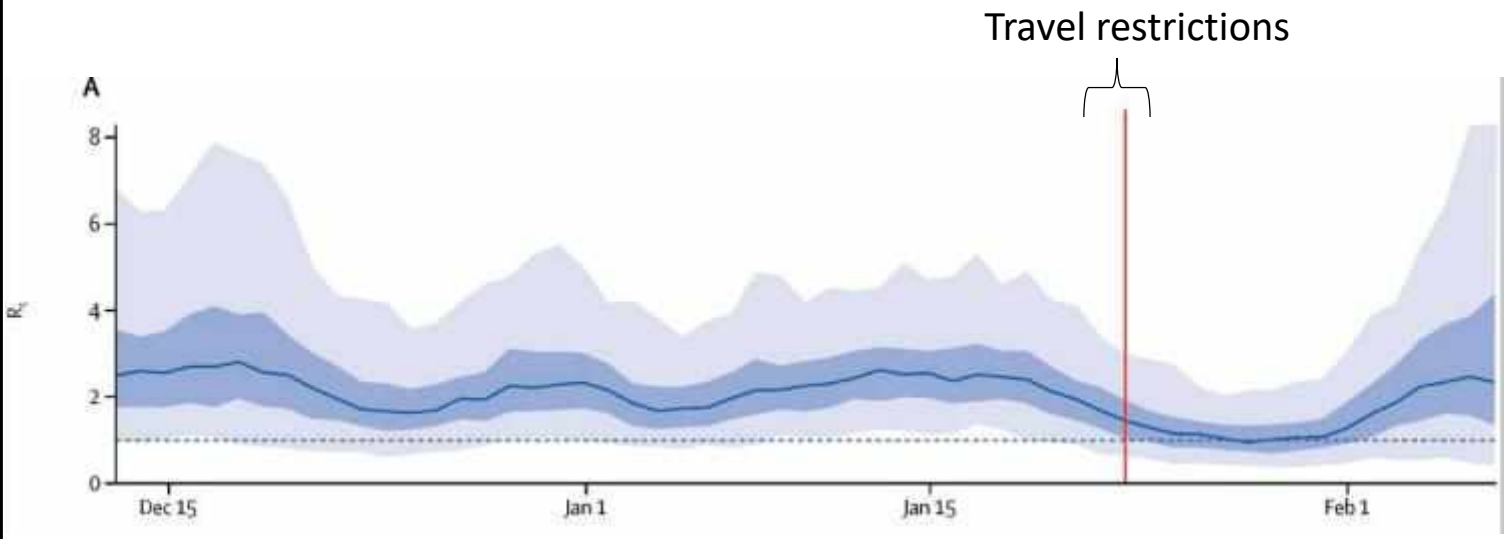
**The actual rates of asymptomatic transmission aren't yet know**
**This question must be answered quickly**

Chan JF *et al. Lancet.* Feb 2020

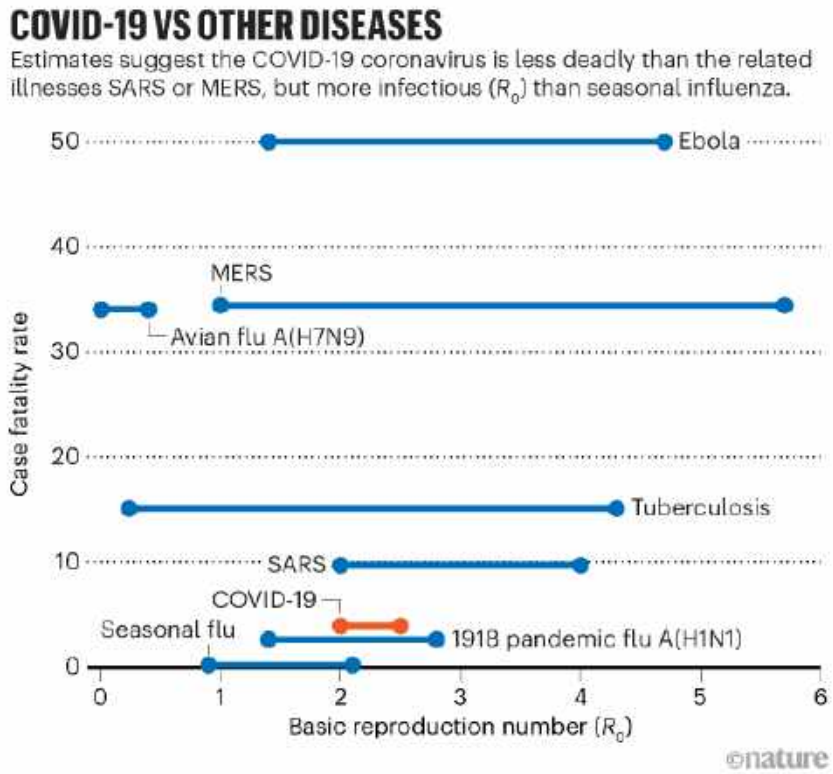
Li R et *al Science.* May 2020

# EPIDEMIOLOGY

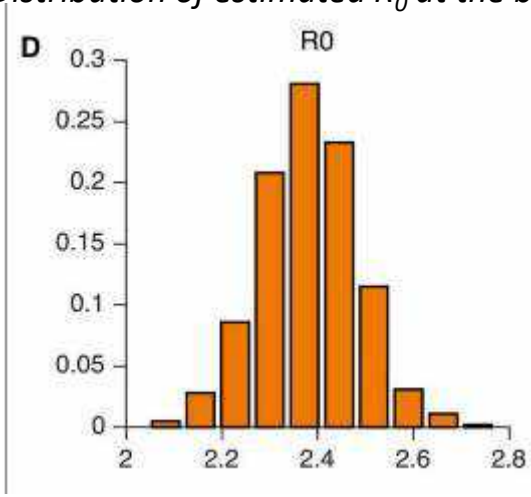
- Basic reproduction number **($R_0$)**: 2,2 to 6.4
- $R_0$ depends on
  - Geographic location
  - Stage of outbreak
  - Inclusion only nosocomial versus general transmission
- Doubling time : 2.9 to 7.3 days




*Estimated $R_t$ over time*




*Distribution of estimated $R_0$ at the begining of epidemic*

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Kucharski AJ et *al*. *Lancet Infect Dis.* Mar 2020

Callaway E et *al Nature.* Mar 2020

Li R et *al Science.* May 2020

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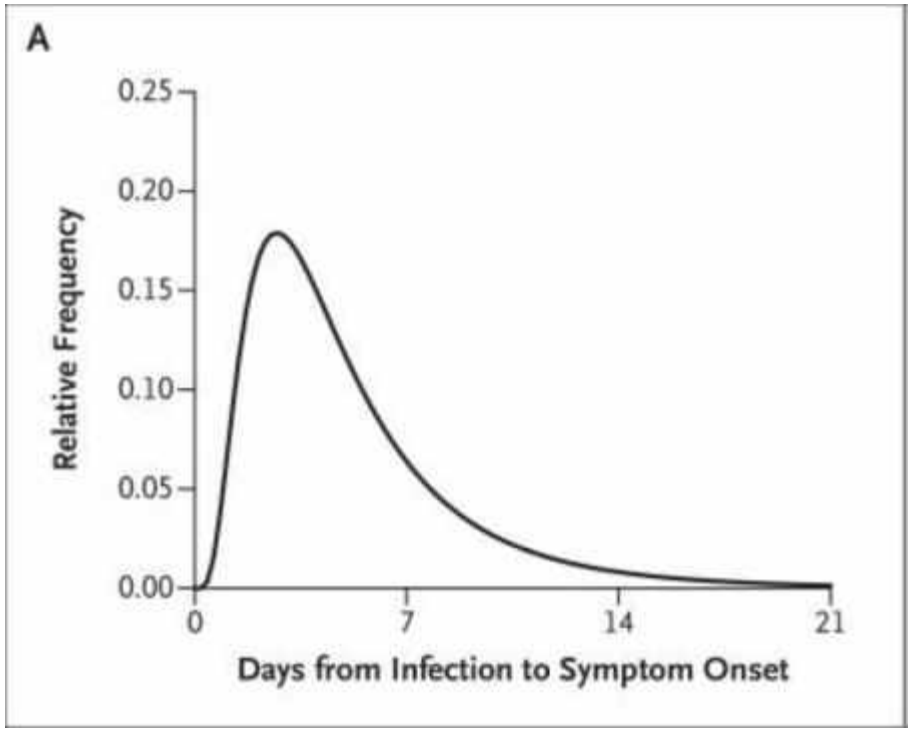
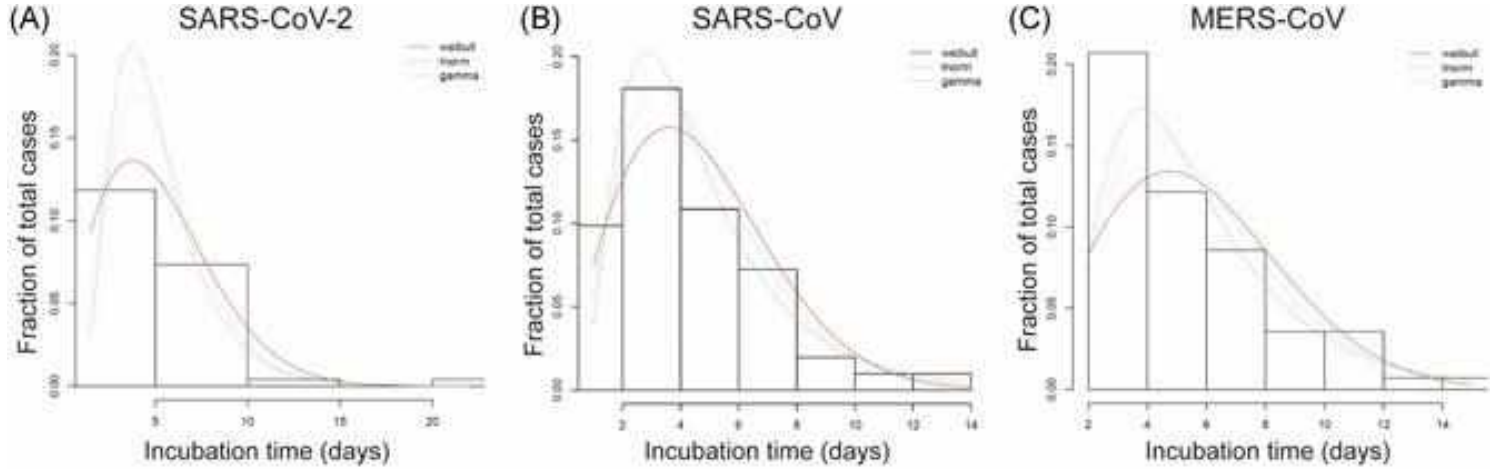
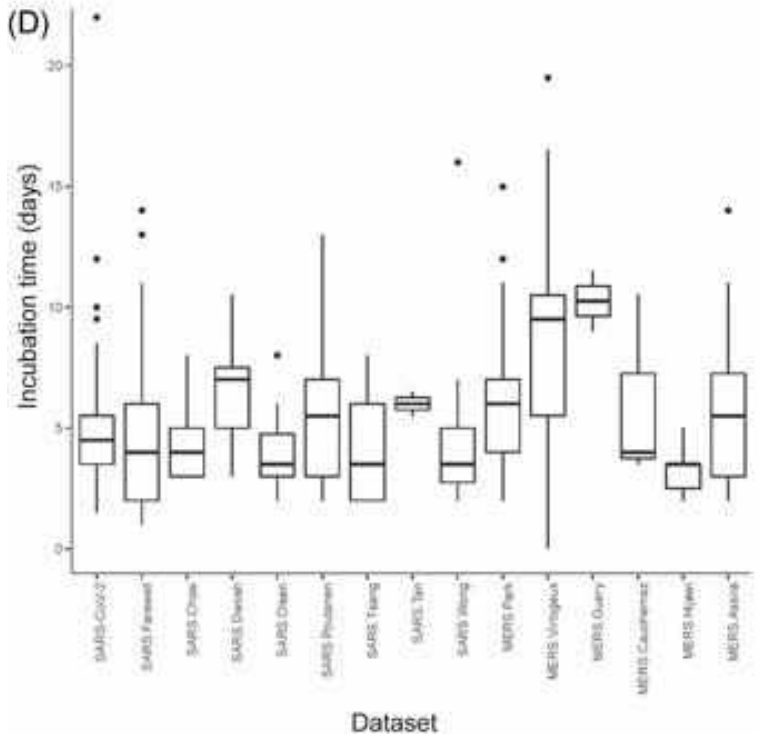
# EPIDEMIOLOGY

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



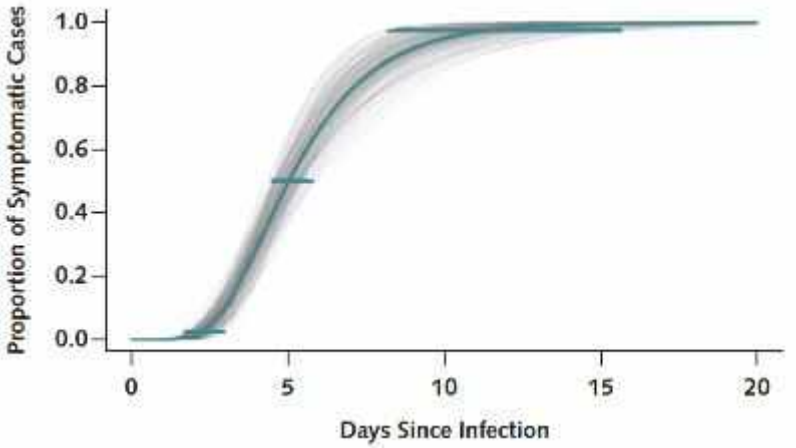




(E)

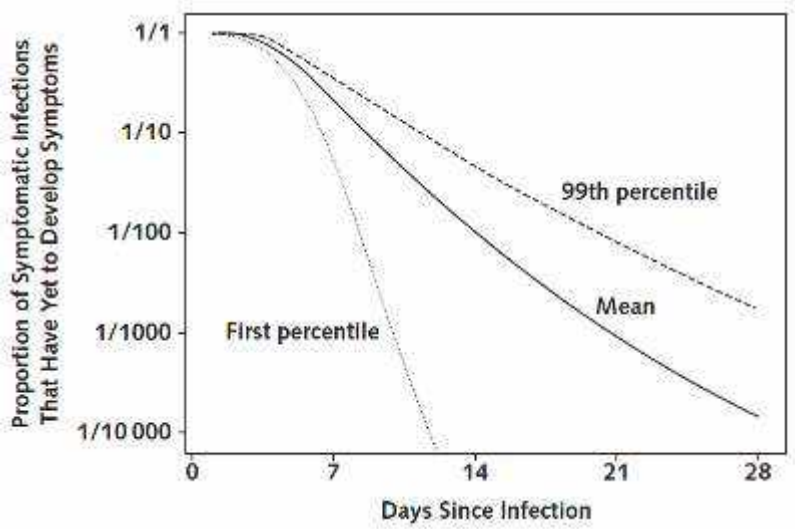
| | Incubation time (days) |
|---|---|
| SARS-CoV-2 | 4.9 (95% CI 4.4-5.5) |
| SARS-CoV | 4.7 (95% CI 4.3-5.1) |
| MERS-CoV | 5.8 (95% CI 5.0-6.5) |

# EPIDEMIOLOGY

- 185 cases of confirmed COVID-19 – before 24 Feb
- 24 countries – 89% had recent history of travel to Wuhan
- Median incubation period: 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: 5,5 days [4,4 – 7,0]
  - 95% range spanning from 2,1 to 14,7 days




- High risk = 1 to 100 chance of infection after exposure
- After 14 d → we would not missed a symptomatic infection amoung high risk persons




| 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

# Impact of social distancing measures

- 1356 UK participants who recorded 3849 contacts
- ⇩ Mean number of physical and non-physical contacts per person to 2.8 [1 – 4]
- 57,6% of contact occurred at home

Impact on **$R_0$**:

- Under physical distancing: 0,62 [0,37 – 0,89]
- Under physical contact only: 0,37 [0,51 – 0,32]

→ Physical distancing will lead to a decline of case

**Behavioral monitoring can give a rapid insight into transmission of COVID-19**

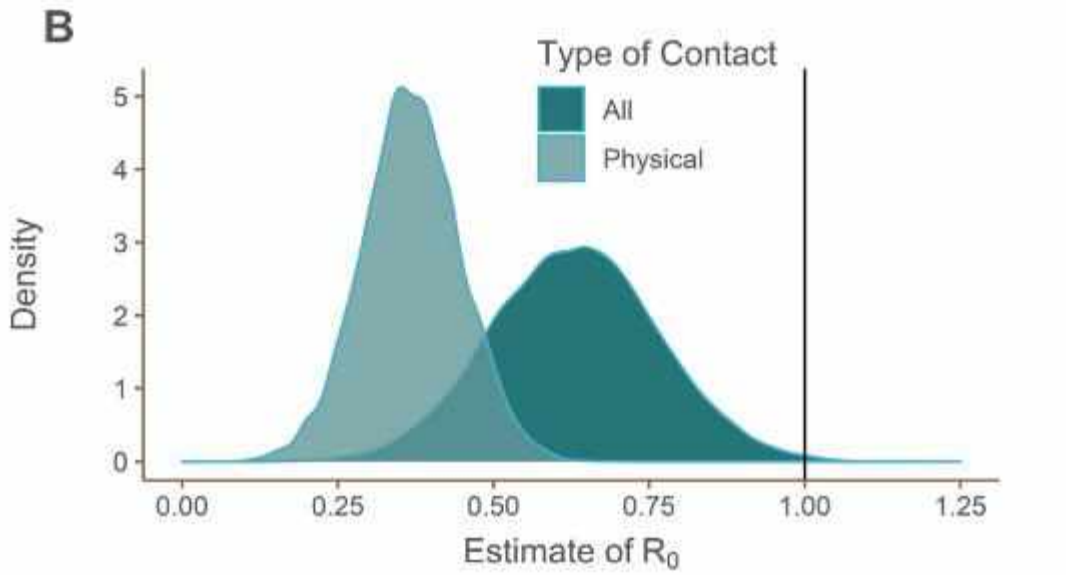
**Limits**

Survey → selection bias

Overestimate the impact of the measures

No evaluation of hand washing

Transmissibility is equal across age groups




Jarvis CI et *al. BMC Med.* May 2020

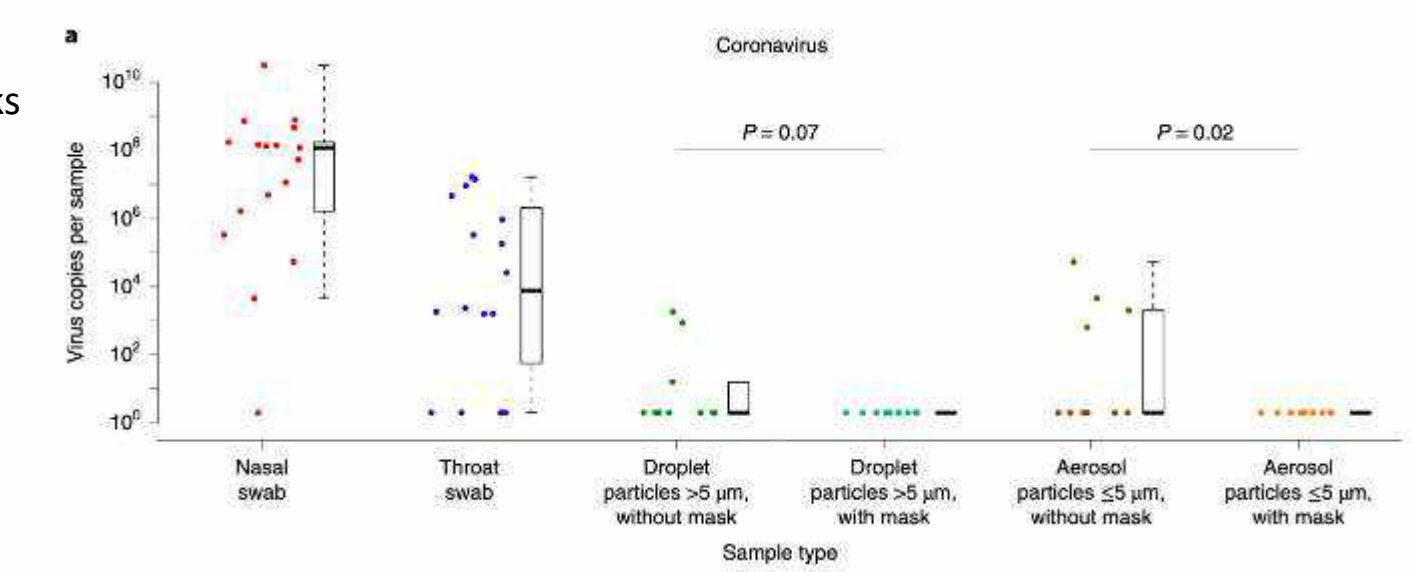
# Efficacy of face masks

- 246 participants
  - 122 without face masks and 124 with face masks
  - 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 reduce the transmission of COVID-19**




**Limits**

- Human coronavirus, not SARS-CoV-2
- Large proportion of undetectable viral shedding
- Not confirm the infectivity of coronavirus detect

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.

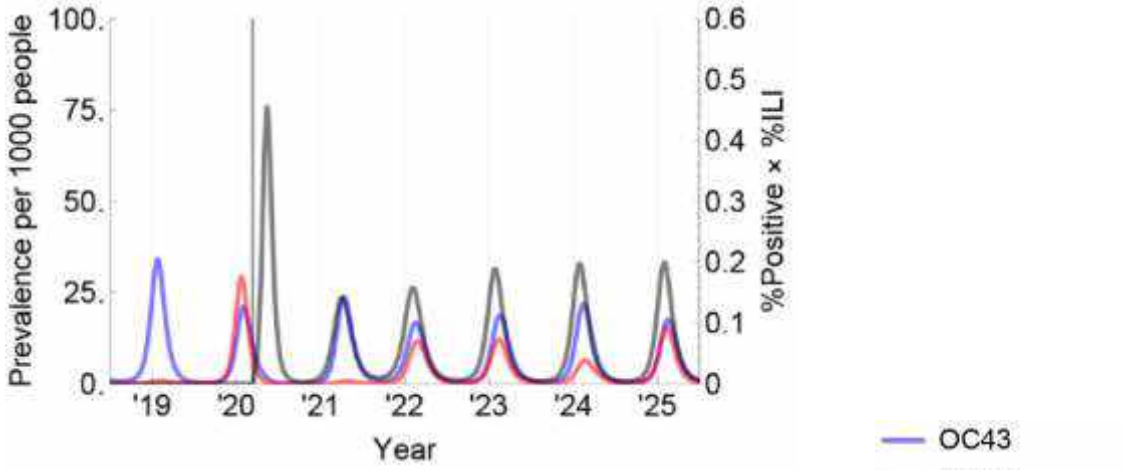
Used estimates of seasonality, immunity, and cross-immunity for betacoronaviruses (OC43 & HKU1)

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

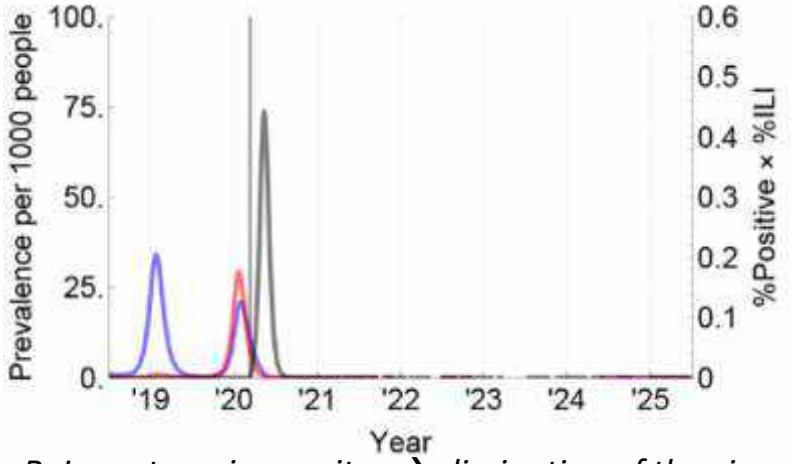
- Degree of season variation in transmission
- Duration of immunity
- Degree of cross-immunity between SARS-CoV-2 and other coronaviruses
- Intensity and timing of control measures

**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

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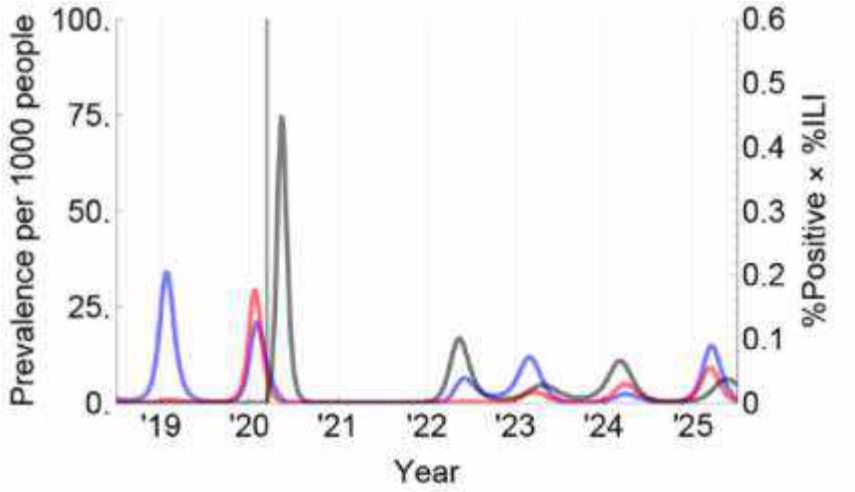
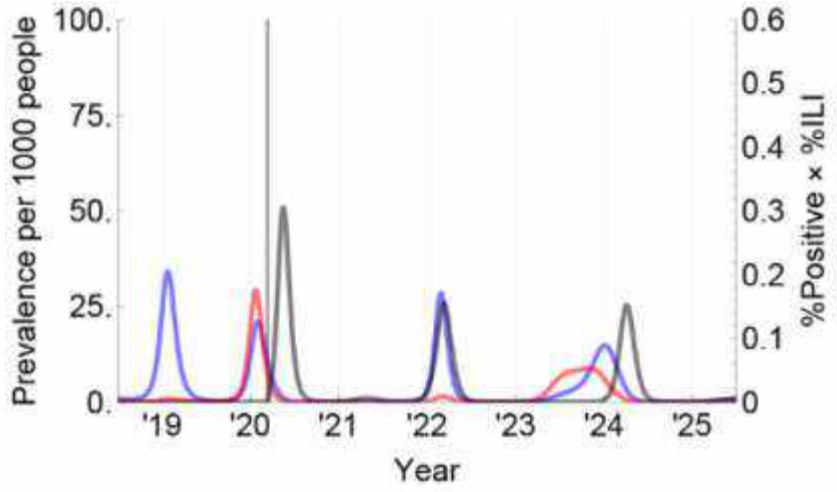
# Projection- Transmission dynamics

*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

Kissler SM et *al. Science.* Apr 2020

# EPIDEMIOLOGY

1. What is the situation in the Word? In France?

- More than 8 million of confirmed cases in the Word and 500 000 global deaths
- In France, more than 150 000 confirmed cases and 30 000 deaths

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

- Incubation period in adults and children: 2 to 14 days with a median of 5 days
- The basic reproductive number varies between 2 to 6

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

- Person to person transmission
- Route of transmission: droplet, direct contact, possible aerosol
- Unanswered question on transmission through children

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

- Face mask reduce the transmission of SARS-CoV-2
- Transmission of viruses is lower with physical distancing of 1 meter or more

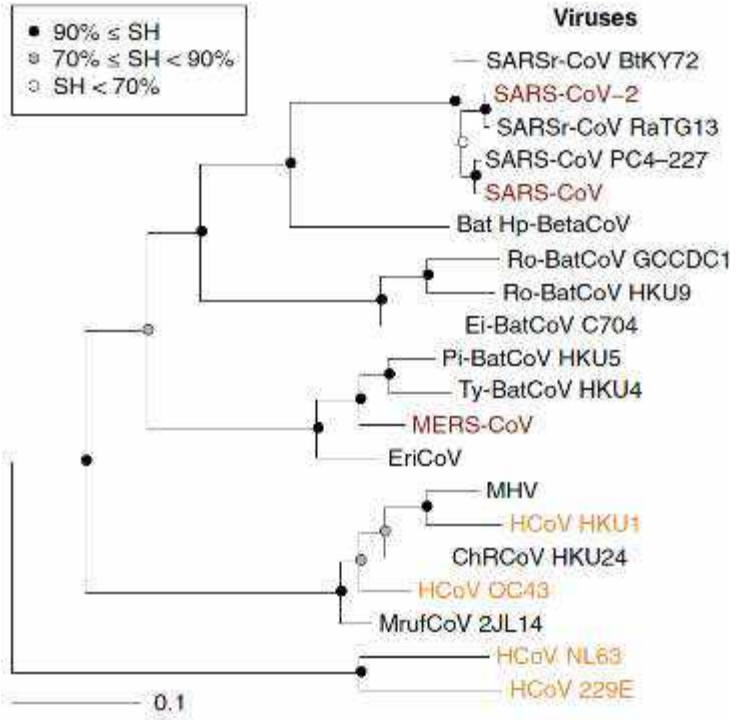
# VIROLOGY

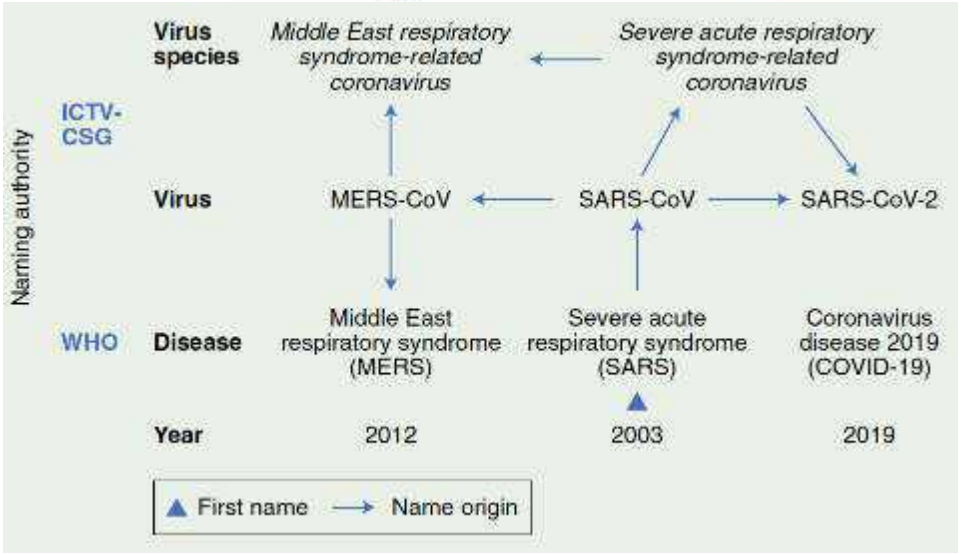
**Question**

- **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?**

# SARS-CoV-2

- Part a 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 coronavirus known to infect humans</u>
  - 4 coronavirus infect only the upper respiratory tract
    - HCoV HKU1 – OC43 – NL63 – 229E
  - 3 coronavirus can replicated in lower respiratory tract and cause pneumonia
    - 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

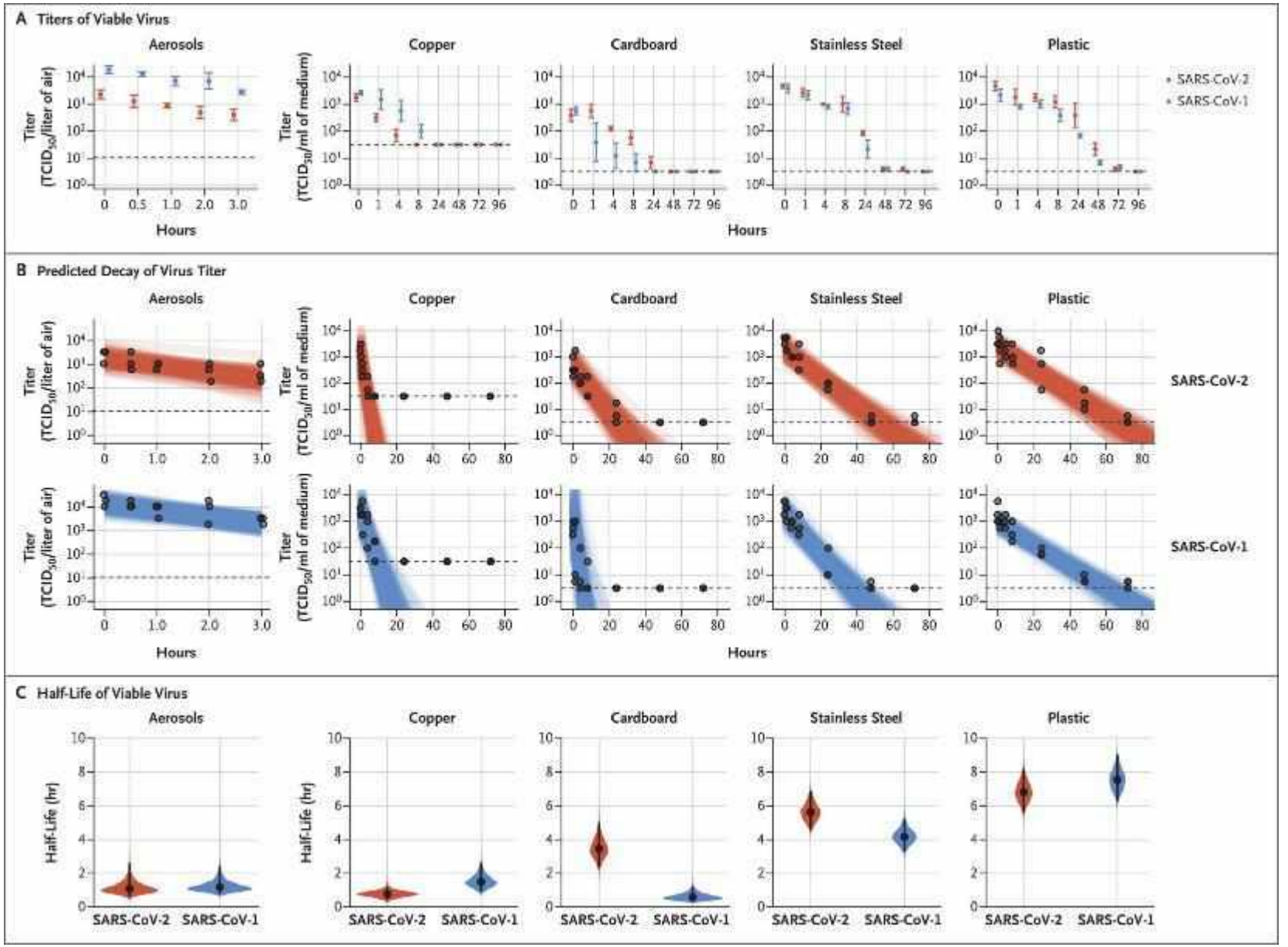
- Plastic and stainless steel: **72 hours**
- Cardboard: **24 h**
- Copper: **4 hours**

Viable in aerosol: **3 hours**

Half-life in aerosol:

- **1.1 to 1.2-h [0.64 – 2.24]**

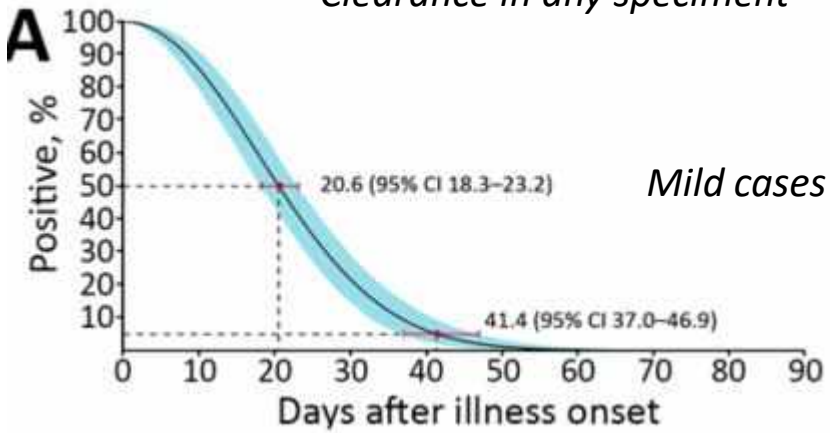
Aerosol transmission is possible in experimental conditions




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

# Persistence of virus RNA

*Clearance in any speciment*




*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**

→ Not imply the existence of infectious virus particules

→ Still 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

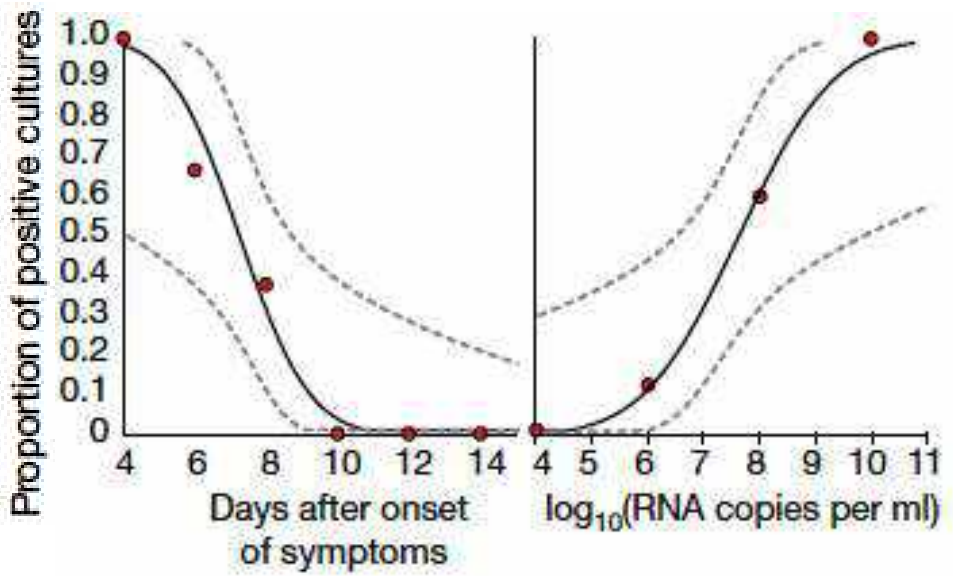
*Data are presented in days after illness onset*

| | 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

Virus isolation success based on probit distributions




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

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

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

Wölfel R *et al. Nature.* May 2020

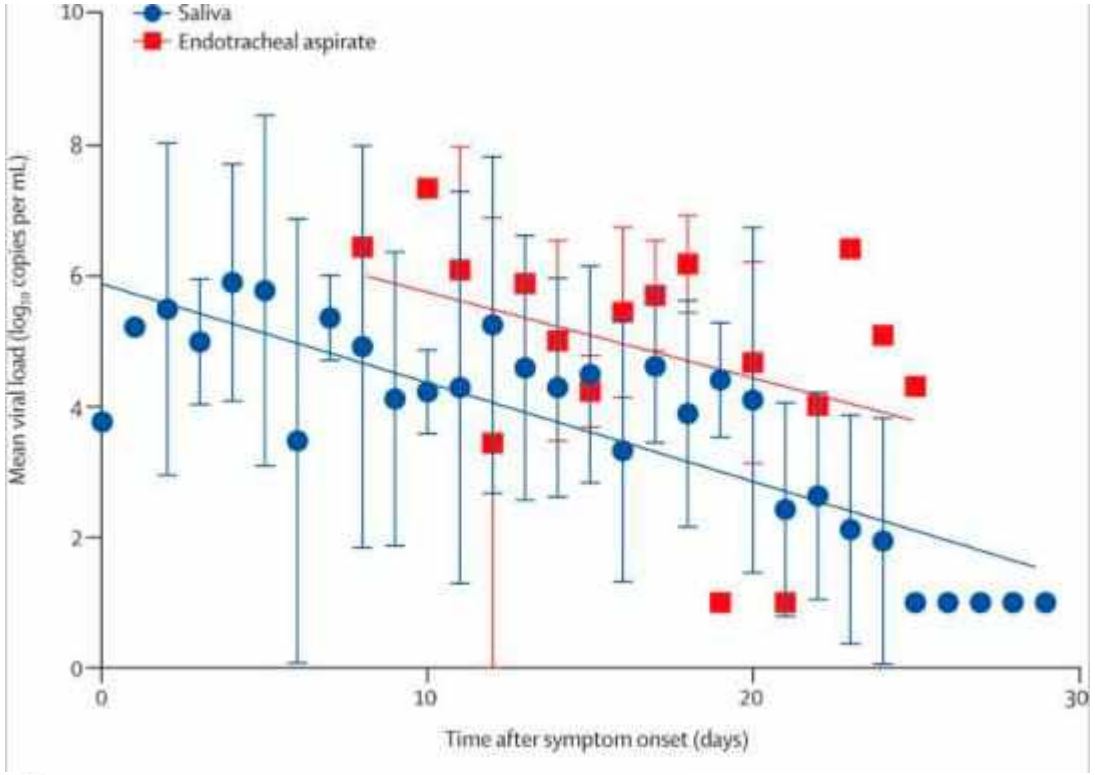
# Viral load

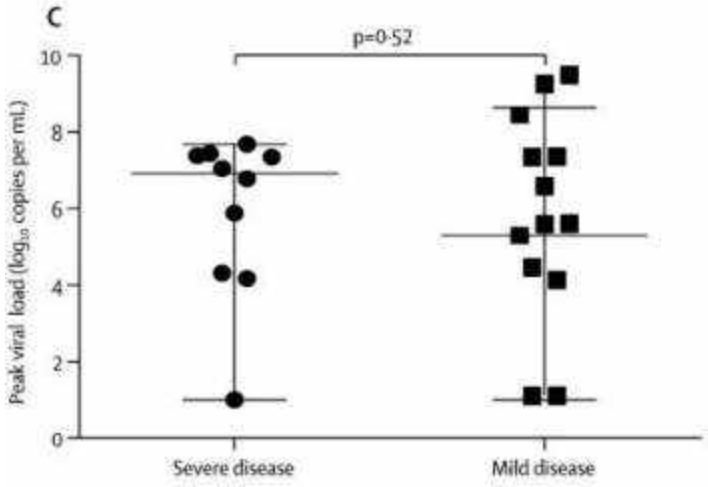
23 patients (median age: 62y) in Hong Kong → 173 respiratory specimens

- Morning saliva samples
- Endotracheal aspirate (intubated patients)

<u>Viral load:</u>

- Median: 5,2 $log_{10}$ copies per mL (IQR 4,1–7,0)
- Saliva viral load: higher during first week and declined
- Endotracheal aspirate viral load: non-significant decline
- 7 patients had viral RNA detect 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

**<u>Limit</u>**: a relatively low number of cases

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

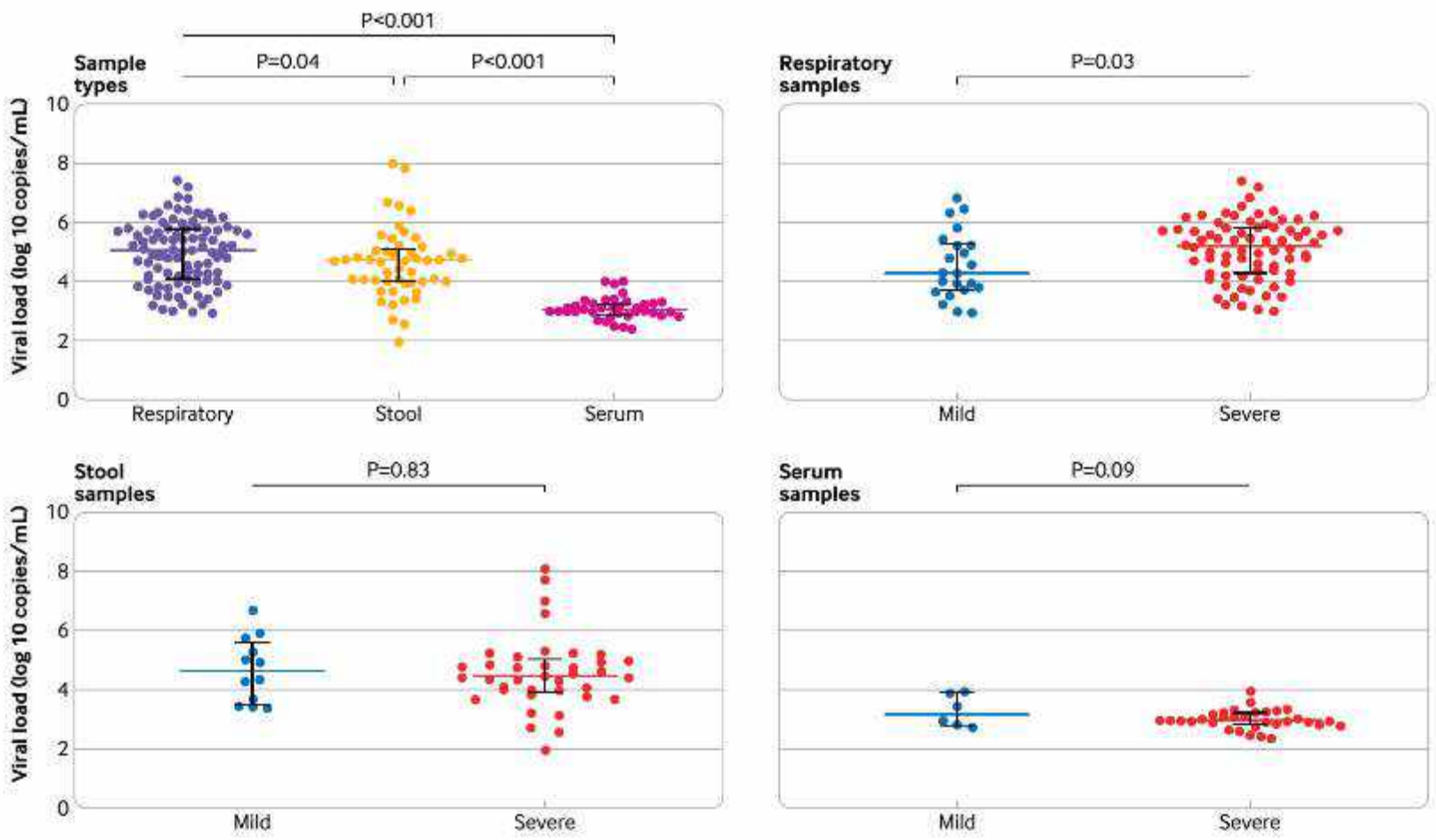
# Viral load

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 & fibrobronchoscopy brush biopsy

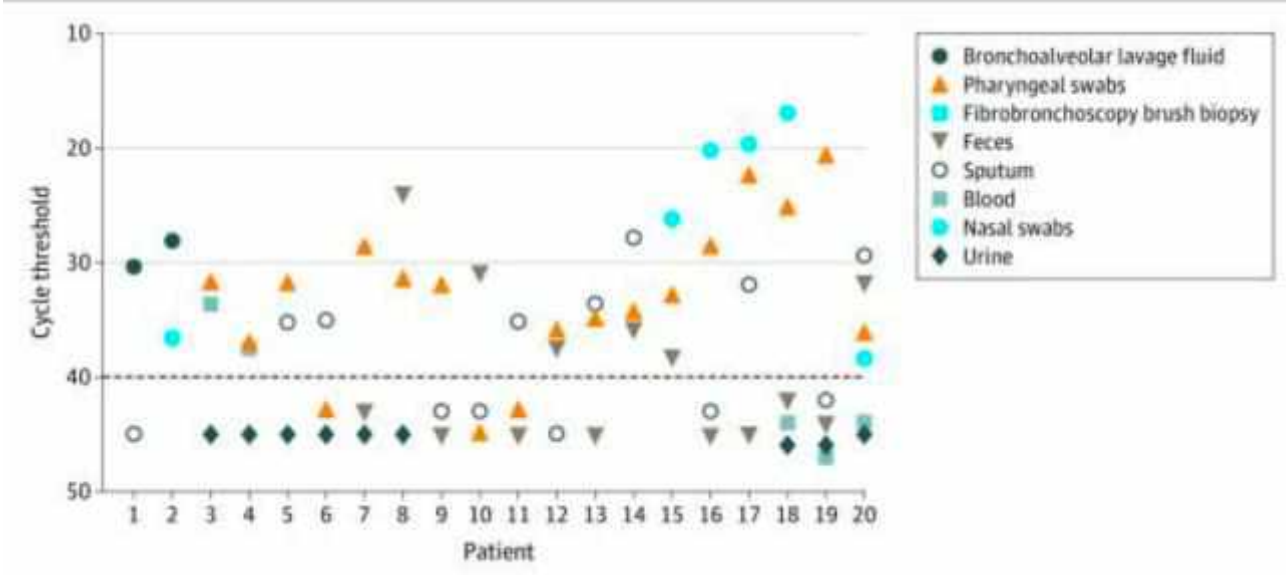
Cycle threshold: indicator of the copy number of SARS-CoV-2 RNA

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

<u>Positive rates:</u>

- Highest positive rates → bronchoalevolar 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 should differ according to the typology of patients and disease stages.

Wang W et *al. JAMA*. Mar 2020

# Dynamic in viral shedding

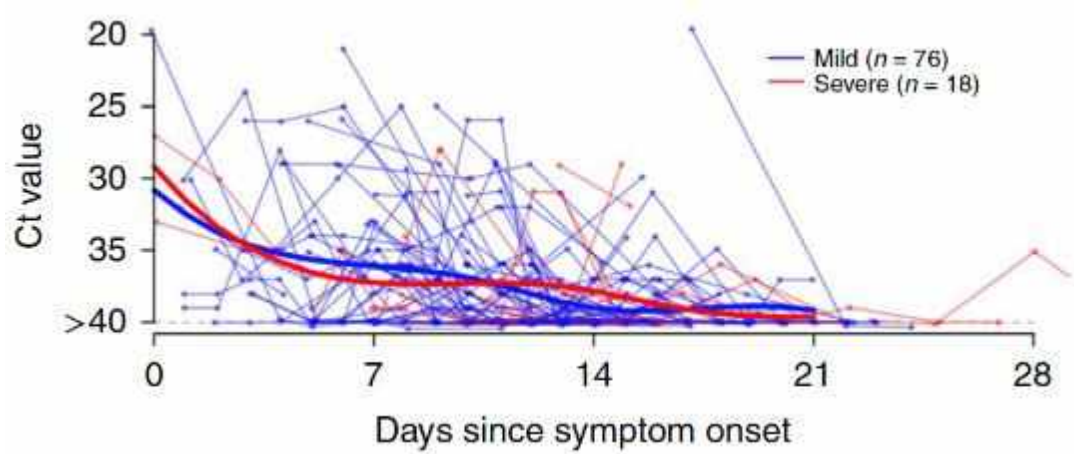
94 symptomatic patients → <u>414 throat swabs</u> from symptoms onset up to 32 days after

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

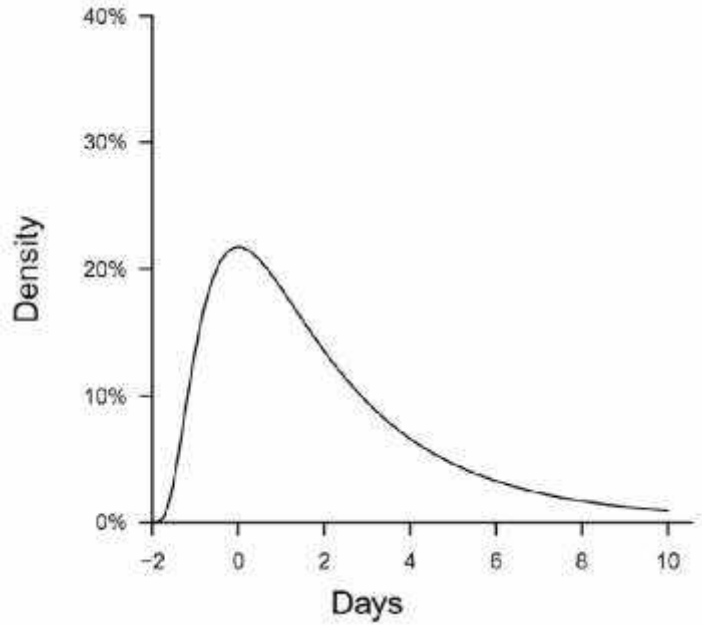
**<u>Dynamic in viral shedding</u>**

- High viral load soon after symptoms onset
- Decrease gradually after symptoms onset
- **No difference in viral loads across sex, age groups, disease severity**

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




*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 decrease  over time

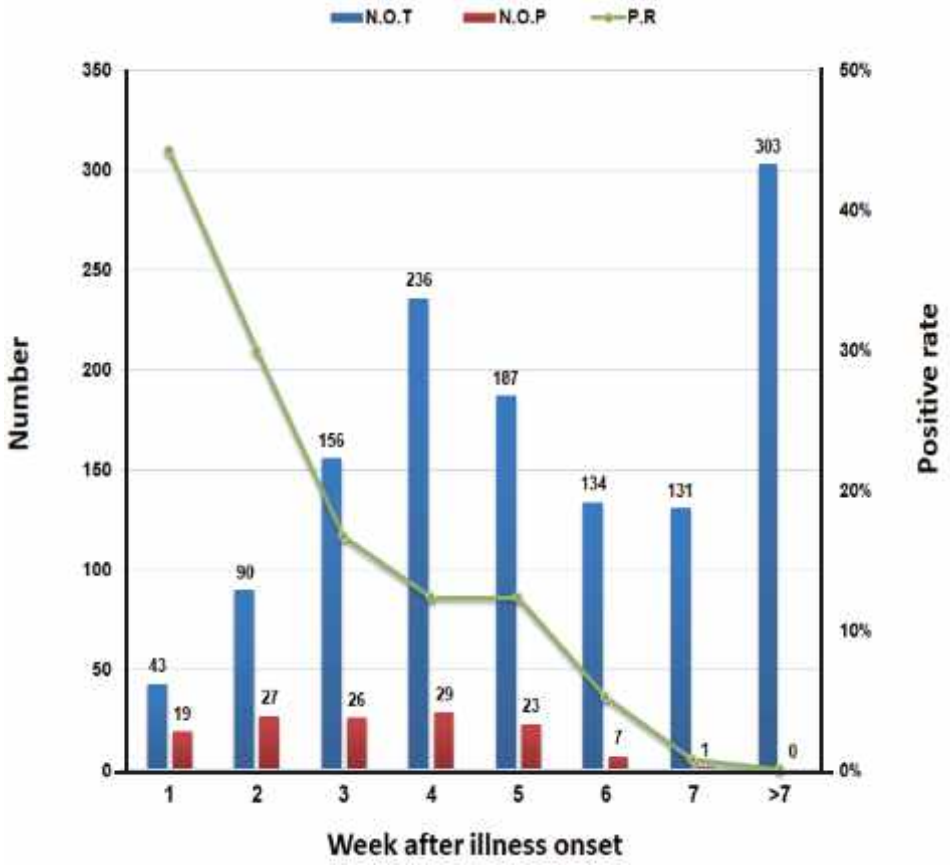
<u>517 pairs (respiratory + rectal samples) from the 80 patients positive in rectal swabs</u>

- 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

<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

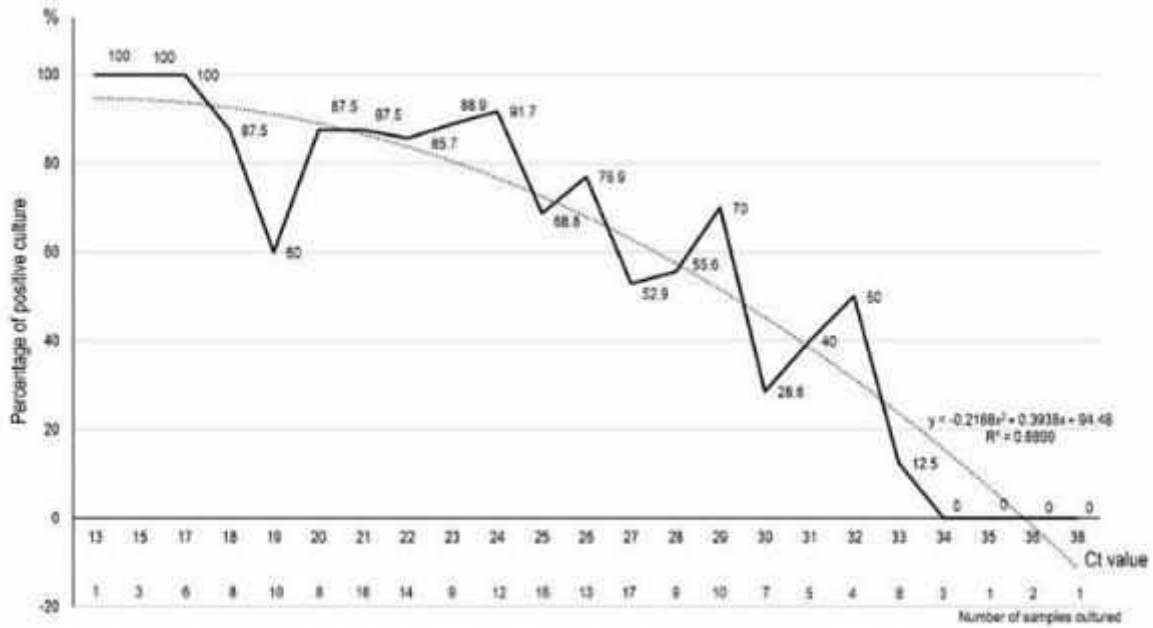
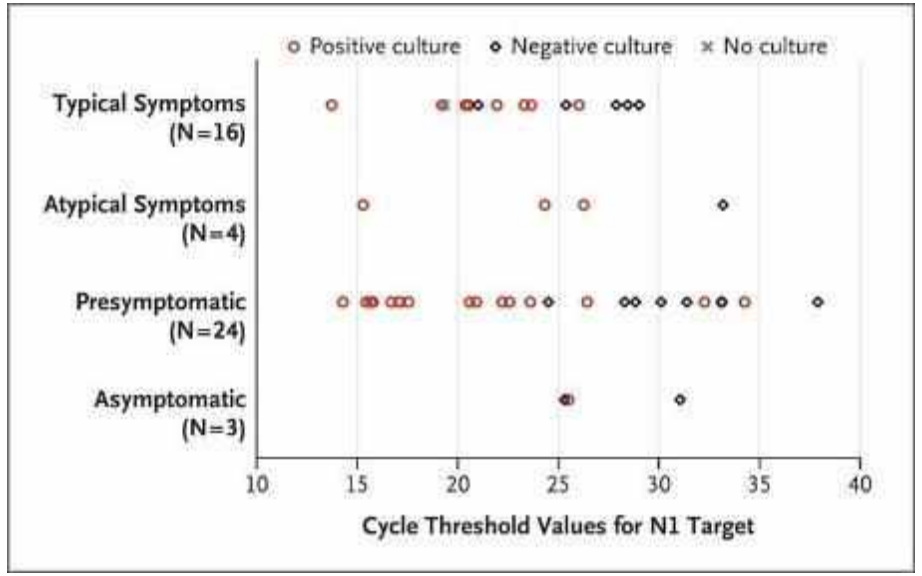
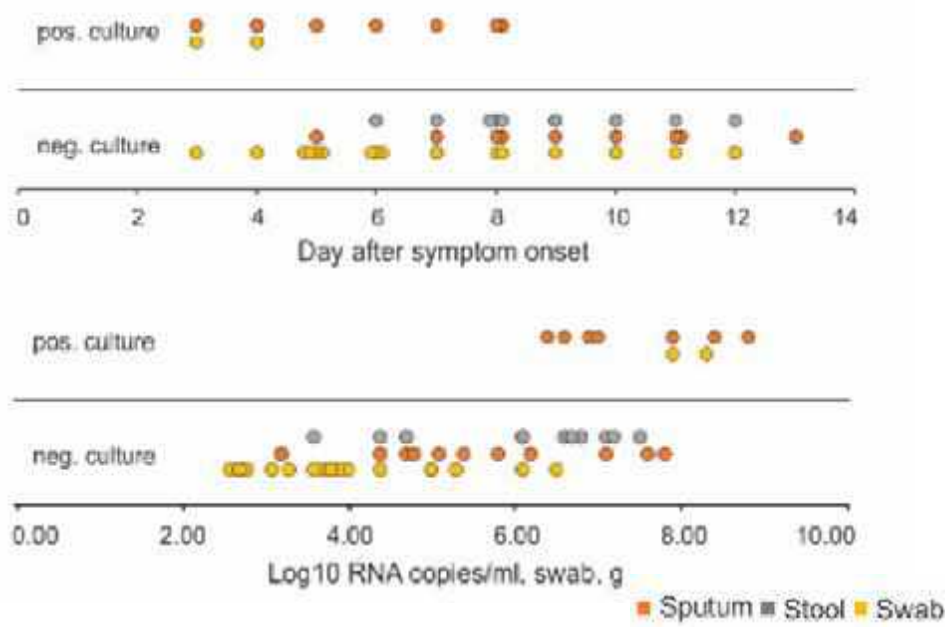
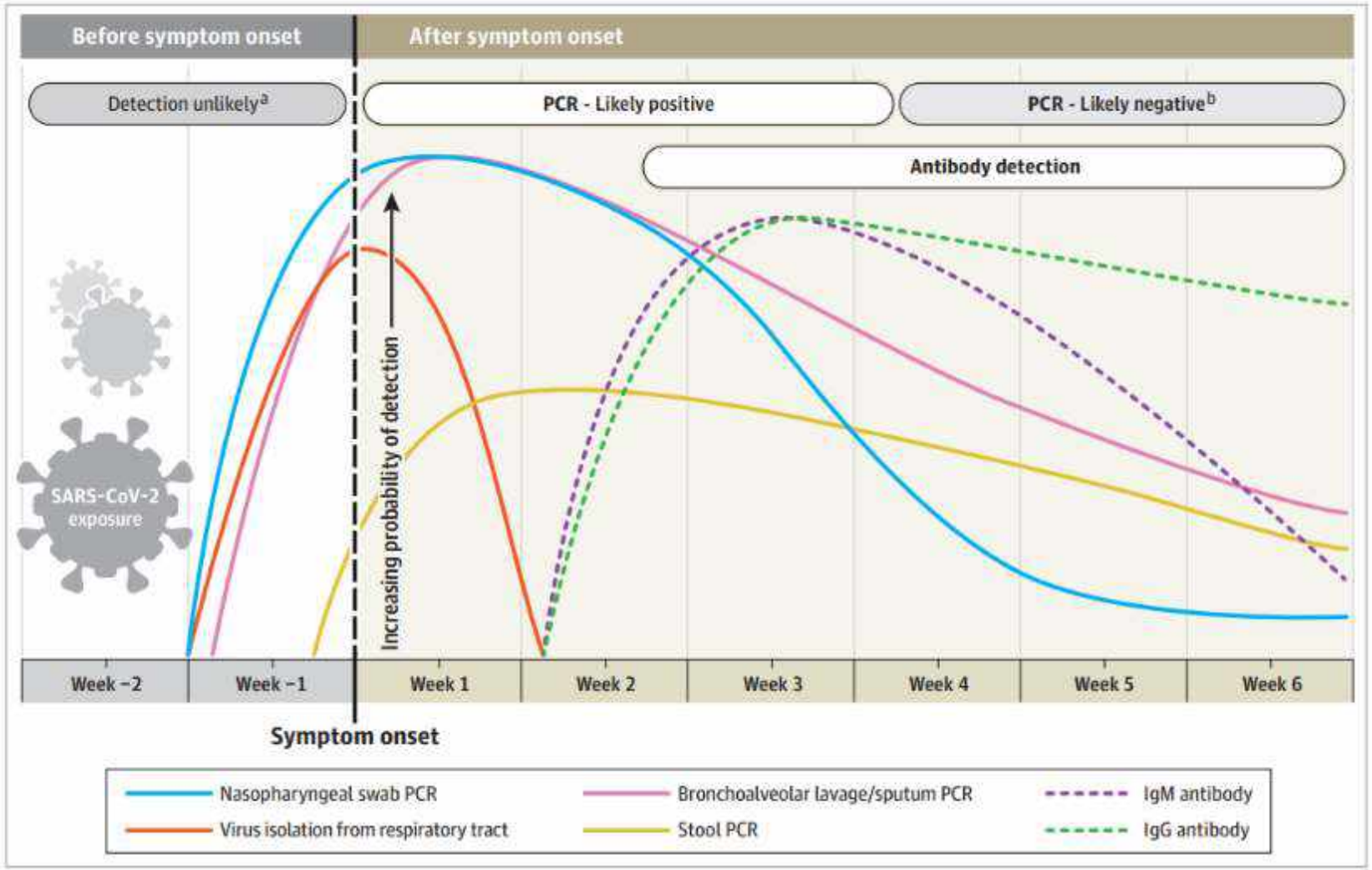



Fig. 1 Percentage of positive viral culture of SARS-CoV-2 PCR-positive nasopharyngeal samples from Covid-19 patients, according to Ct value (plain line). The dashed curve indicates the polynomial regression curve



# 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)

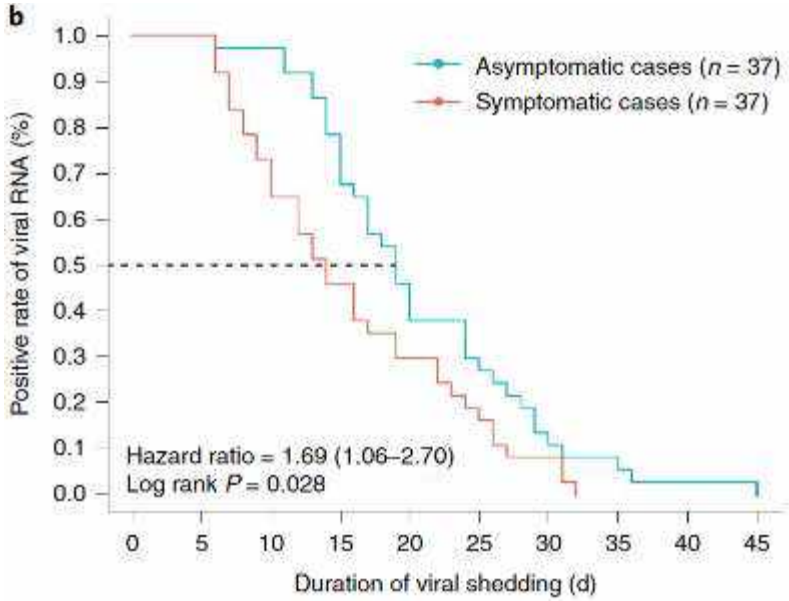
37 asymptomatic matched with 37 mild symptomatic patients

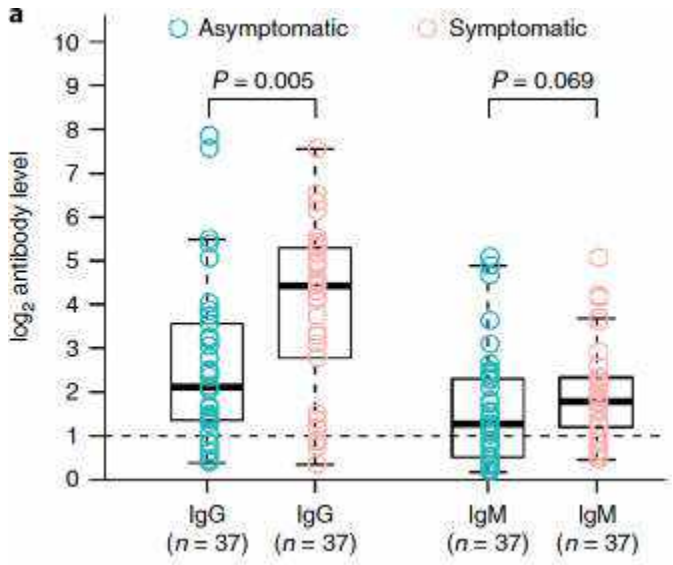
Viral shedding:

- Initial Ct value were similar in the two group
- 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

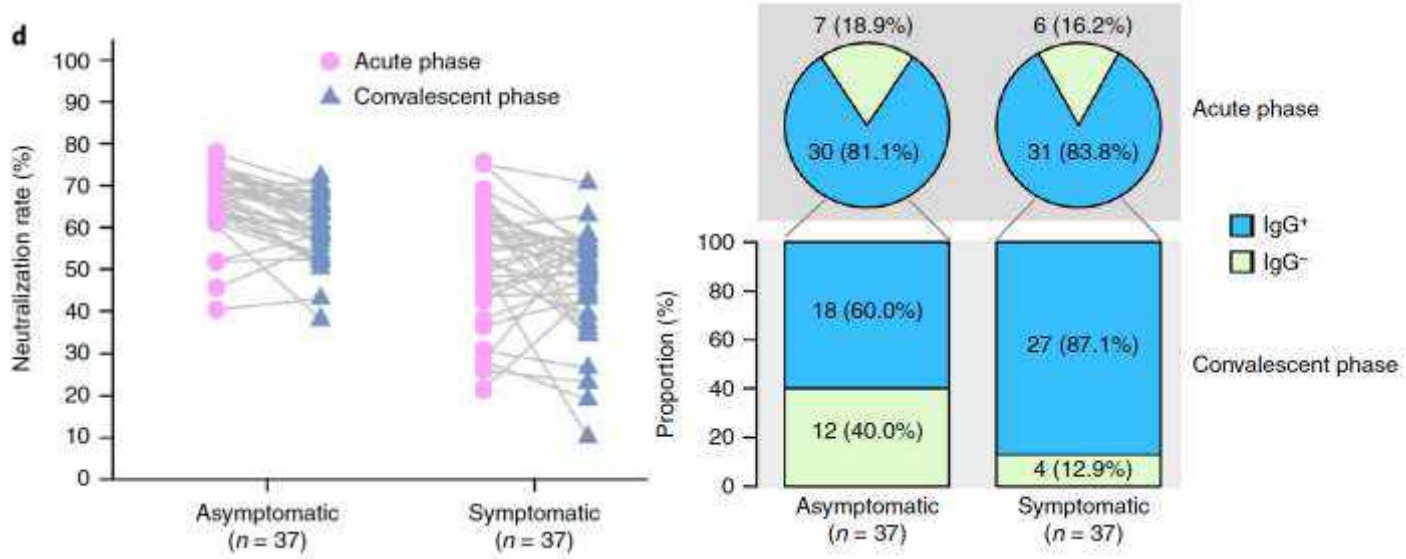
# Immunological assessment

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

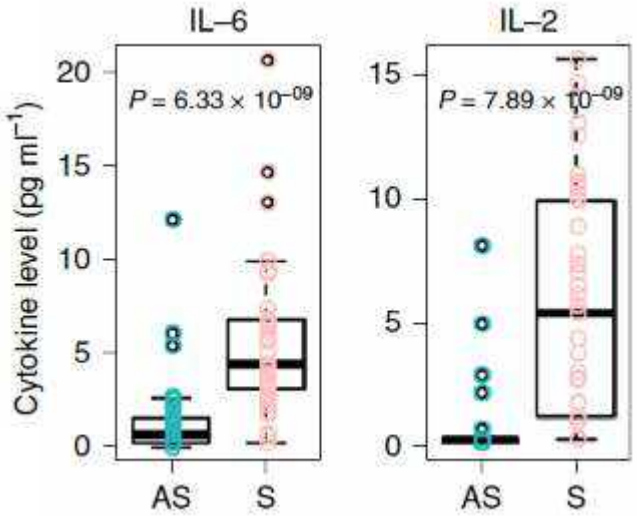
- A decline of IgG is observed among >90% of patients
- 40% and 13% of asymptomatic individuals IgG+ at the acute phase became seronegative

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 shadding does not equate viral infectivity (not assessed in this study)

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

Long QX *et al Nat Med.* Jun 2020

# VIROLOGY

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

- RNA viruses that belong to the *betacoronavirus* genus
- Similarity with SARS-CoV

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

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

- Highest positive rates of SARS-CoV-2 in bronchoalveolar fluid
- 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 but not well characterized
- Detection of viral RNA does not necessarily mean that infectious virus is present

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

# CLINICAL

**Question:**

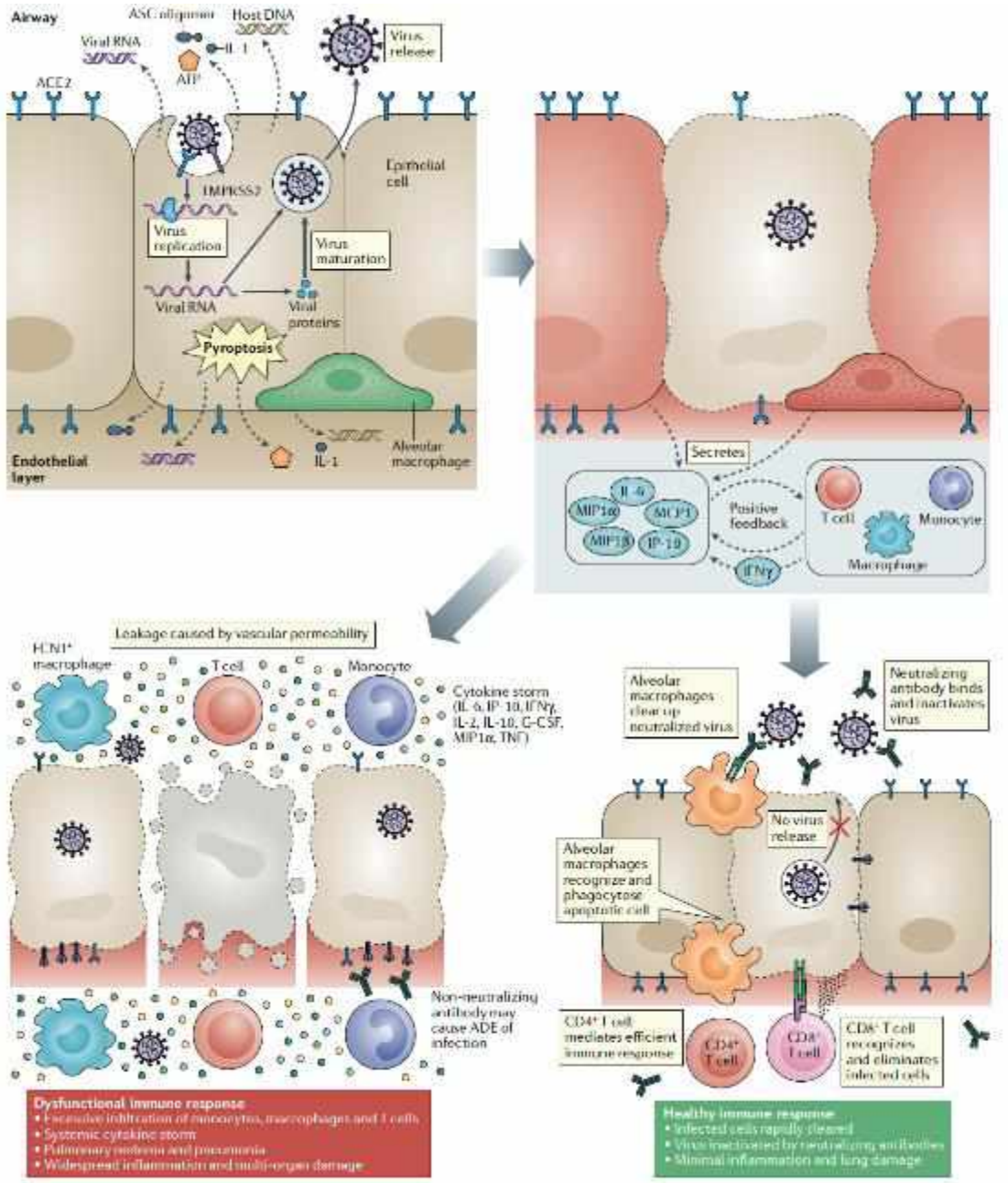
- **What is the mechanism of action of SARS-CoV-2?**
- **What is the clinical presentation of COVID-19 in adults and children?**
- **Is there multiple-organ damage?**

# Physiopathology

- **Binding** to host cell through ACE2 receptor by spike (S) protein
  - Lung, Kidney, Heart, Brain …
- **Fusion** of the viral envelope with cellular membranes (TMPRSS2)
- Virus **hijacks** the cells 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
  - Eliminated 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

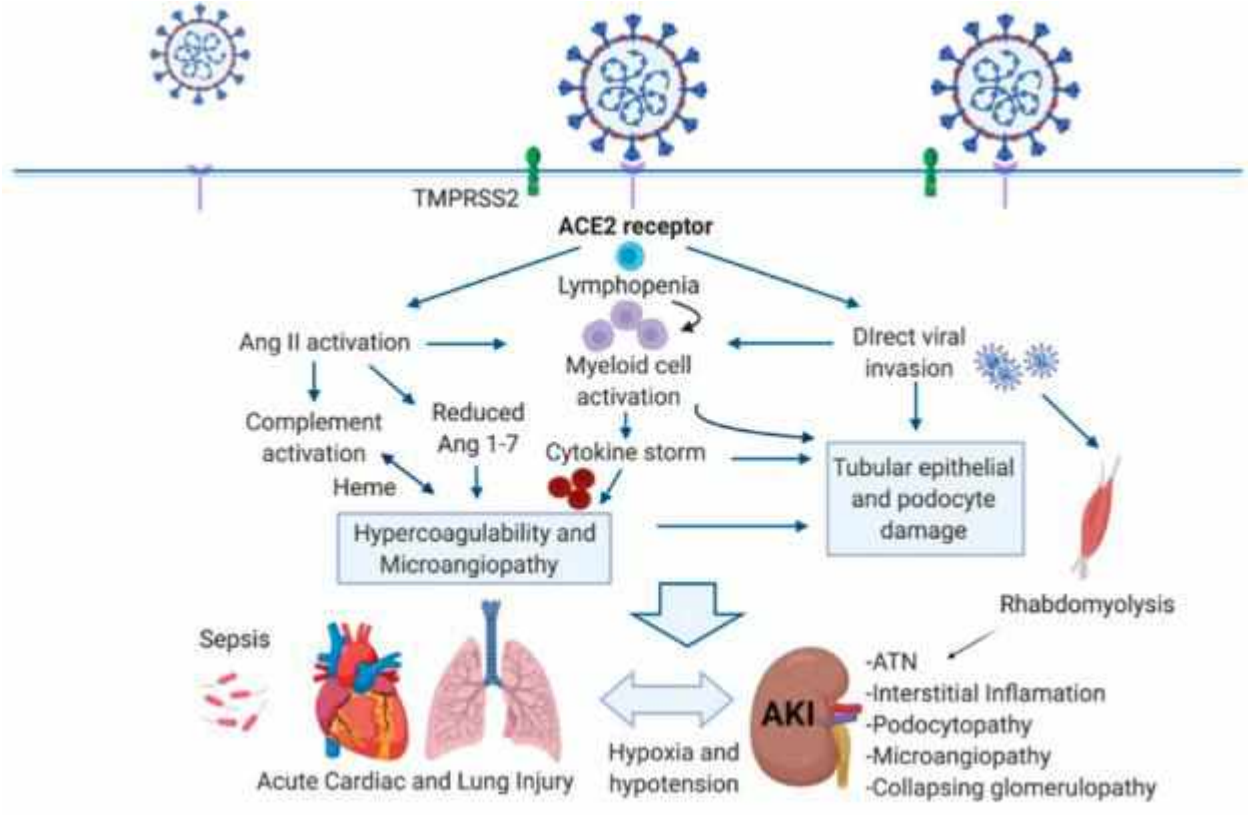



Tay MZ et *al. Nat review Immunol*. Apr 2020

# Physiopathology

- SARS-CoV-2 target ACE2 receptor and infected cells via « priming »
  - Angiotensine dysregulation
  - Activation of innate and adaptative immune pathway
  - Cytokine storm
  - coagulation pathway → hypercoagulation

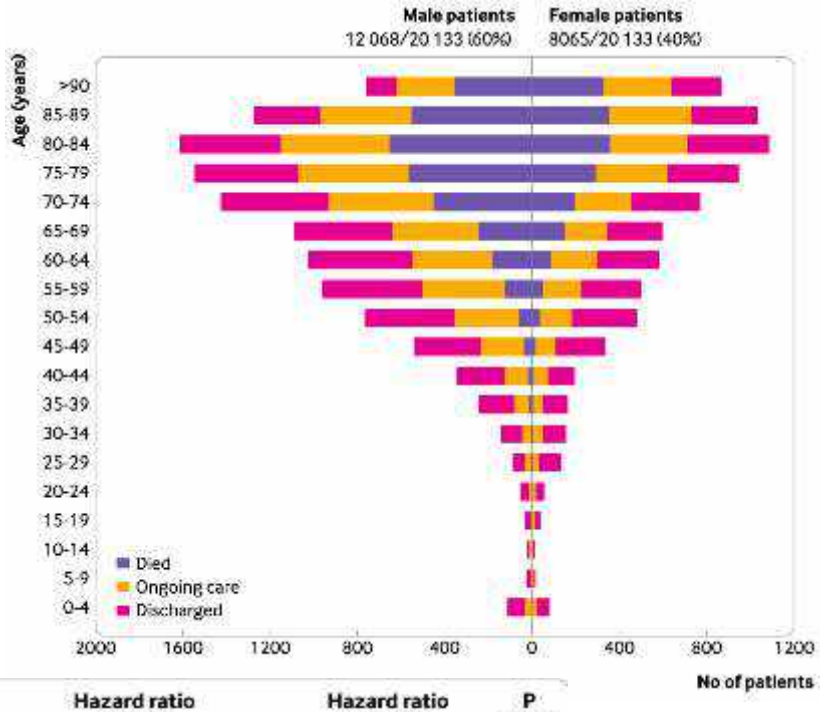
- Multi-organ damage
  - Kidney, heart, lungs, vessel, immune system ….

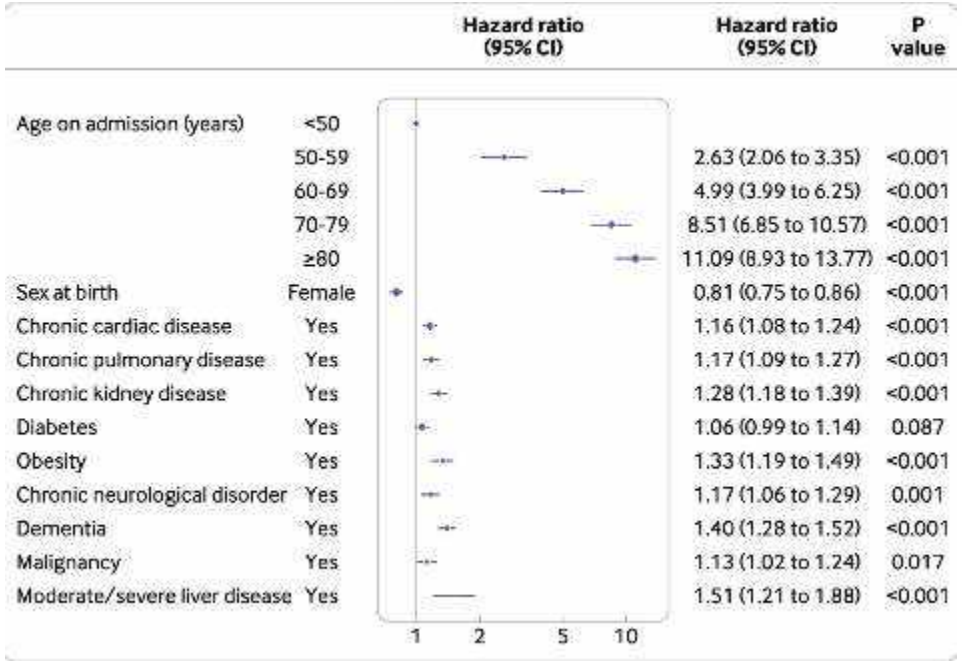



Battle D et *al. JASN*. May 2020

# Risk factor of mortality

- ISARIC WHO Clinical characterization protocol
- 208 acute care hospitals (England, Wales & Scotland)
- 20133 patients (6 February and 19 April 2020)
  - 8199 (41%) discharged alive
  - 5165 (26%) died
  - 6769 (34%) continued to receive care
- <u>Strong predictor of mortality in hospital</u>
  - Increasing age after adjusting for major comorbidity
- <u>Independent risk factor of hospital mortality</u>
  - Chronic disease
    - Cardiac, Pulmonary, Kidney, Neurological disorders
  - Obesity
  - Dementia
  - Malignancy
  - Liver disease




*N = 15194*
*Hazard = death*
*No of events: 3911*

Docherty AB *et al. BMJ.* May 2020

# 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
  - No modified by age – severity of clinical manifestation – course of Covid-19
  - No evidence of an indepent 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

# 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**

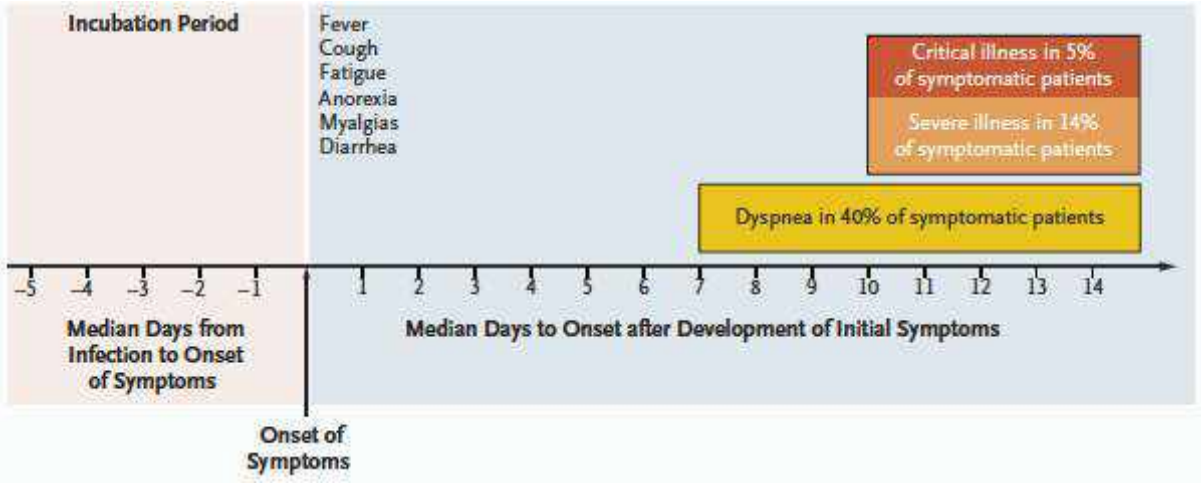
- Variation in the diagnostic characteristic for the Covid-19 testing method
- Multiple test for some patients
- Some patients may have been tested at other heath system
- May not reflect actual drug exposure
- Not account for socieconomic status, insurrance, …
- Additional unmeasured confunders

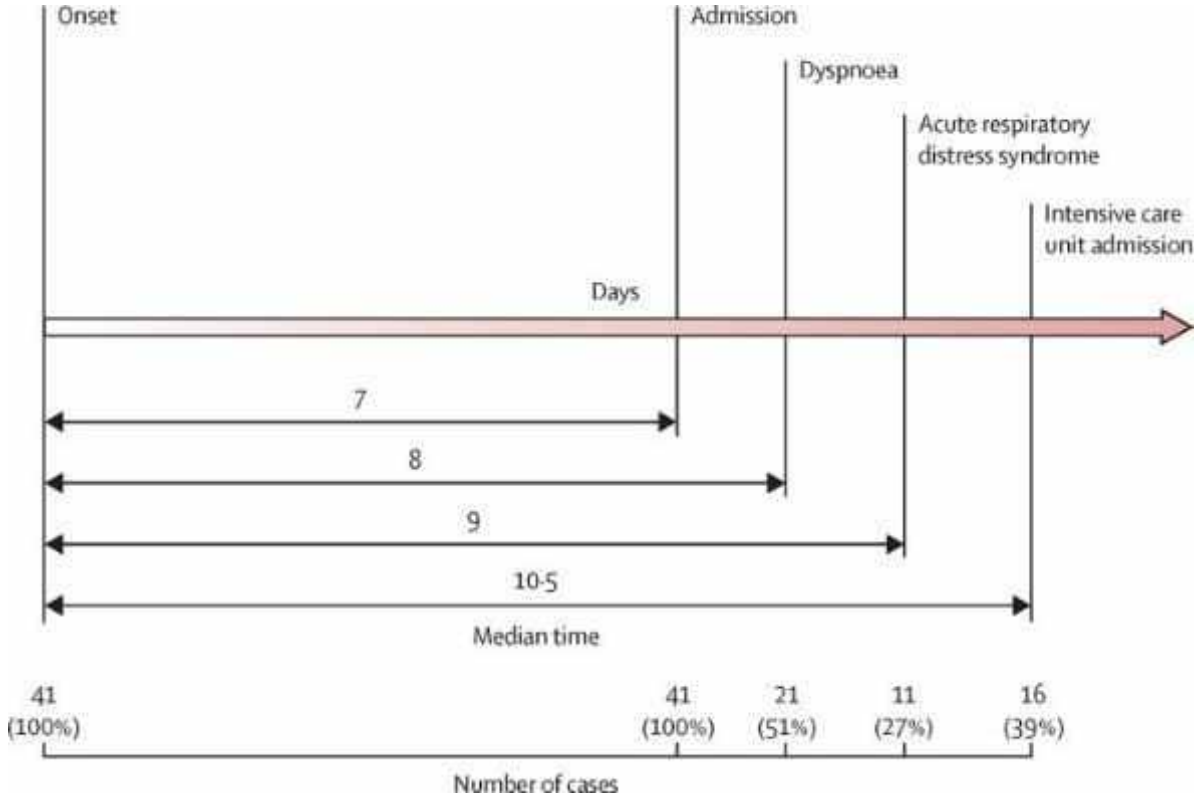
**→Rule out that the risk was higher among treated patients than among untreated patients**

# CLINICAL

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

- From onset of symptoms to first hospital admission
  - **7 days** [4.0–8.0]
- From illness onset to dyspnoea
  - **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

China, **1590 hospitalized** patients (13,4% of all cases reported in China)

Age (median): 48,9 years ± 16,3

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/athralgia: 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 %)

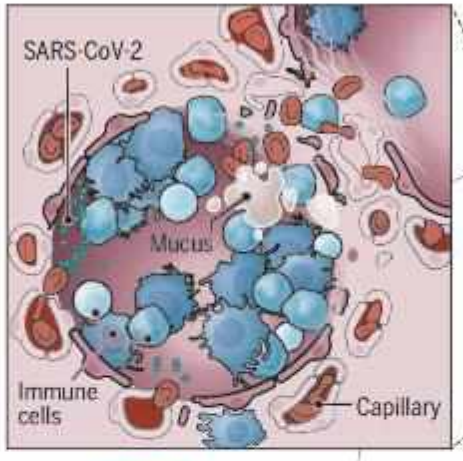
**Case fatality rate**: 50 (3,1 %)

# Organ damage

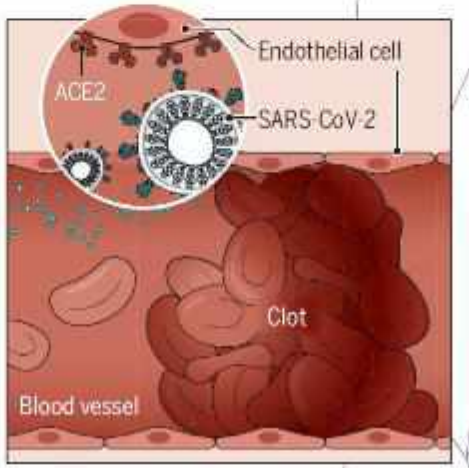
## An invader's impact

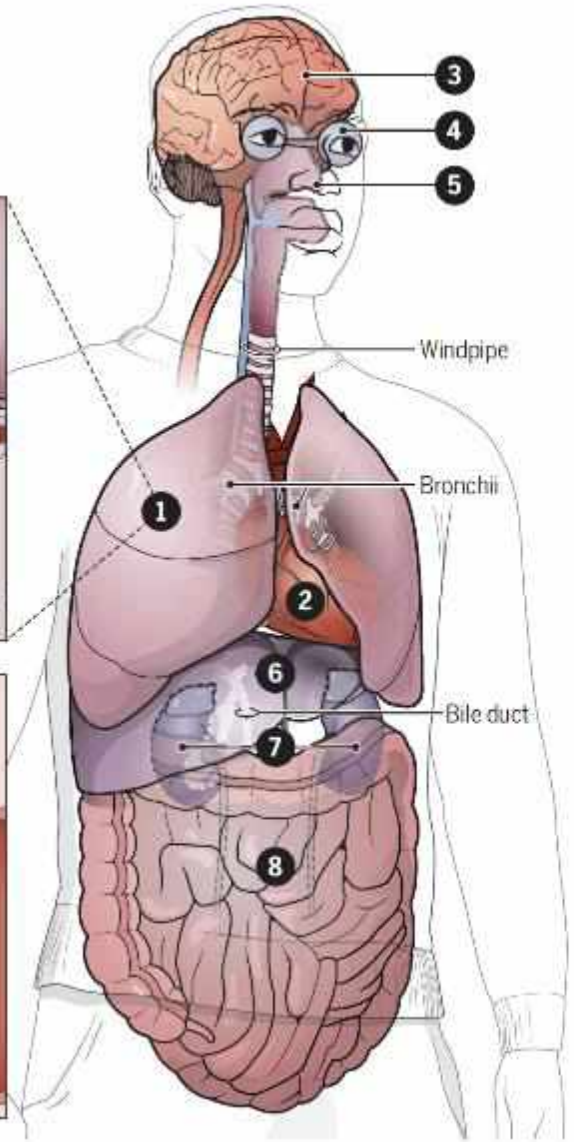
In serious cases, SARS-CoV-2 lands in the lungs and can do deep damage there. But the virus, or the body's response to it, can injure many other organs. Scientists are just beginning to probe the scope and nature of that harm.

**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 of follow up: 18days [5 – 43]

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

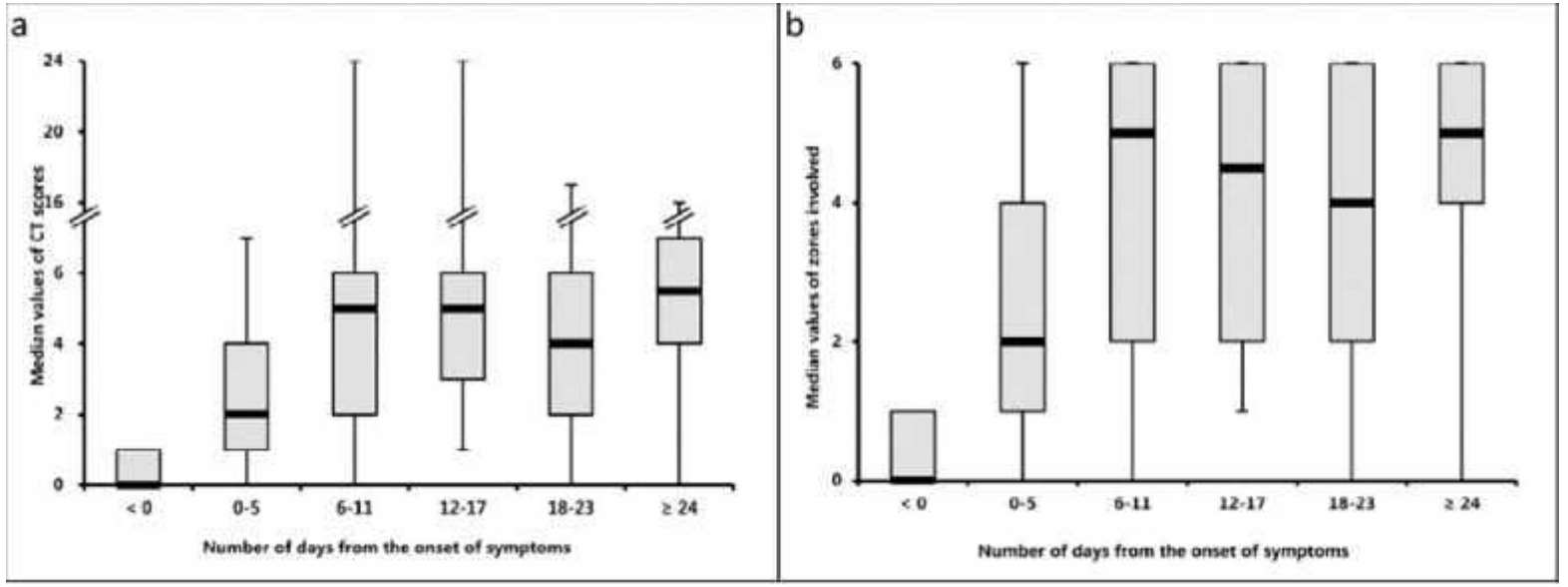
→ Each lung divided into 3 zones

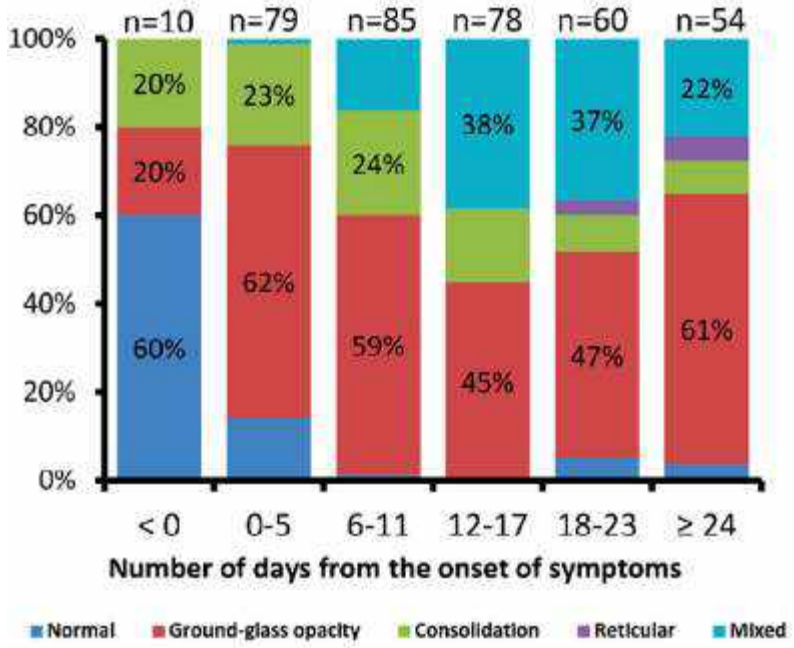
→ Overall CT score (max = 24)

<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 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)



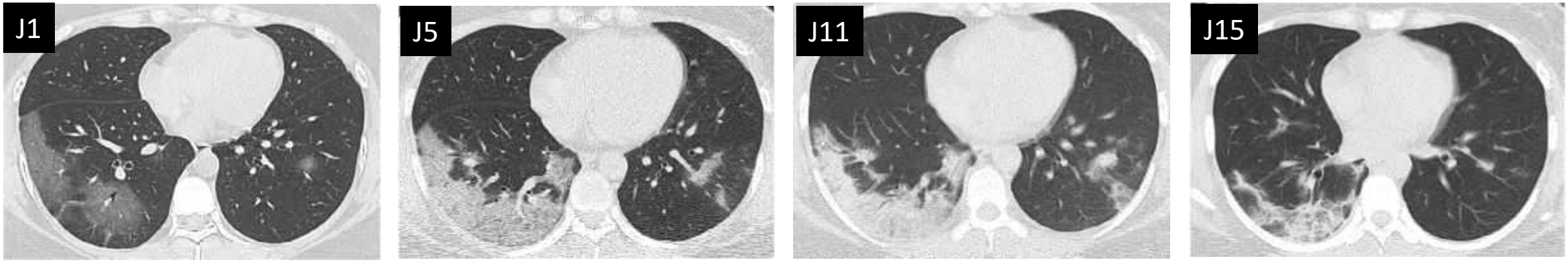

**→Bilateral GGO is the most commonly manifestation**

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

Wang Y *et al. Radiology*. Mar 2020

# Radiology

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



# Heart & COVID-19

**Acute myocarditis**

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

**Acute myocardial infarction**

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

**Acute heart failure**

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

**Dysrhythmias**

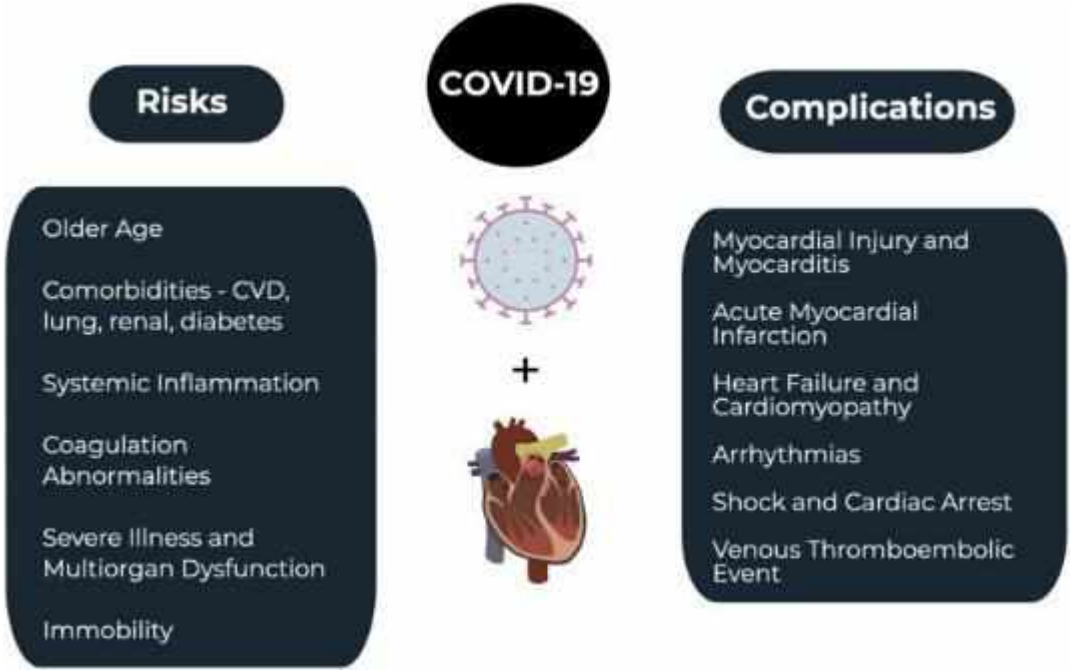
- 17% of hospitalized and 44% of ICU patients
- Hypoxia, inflammatory, abnormal metabolism

**Venous thromboembolic event**

- Increase 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

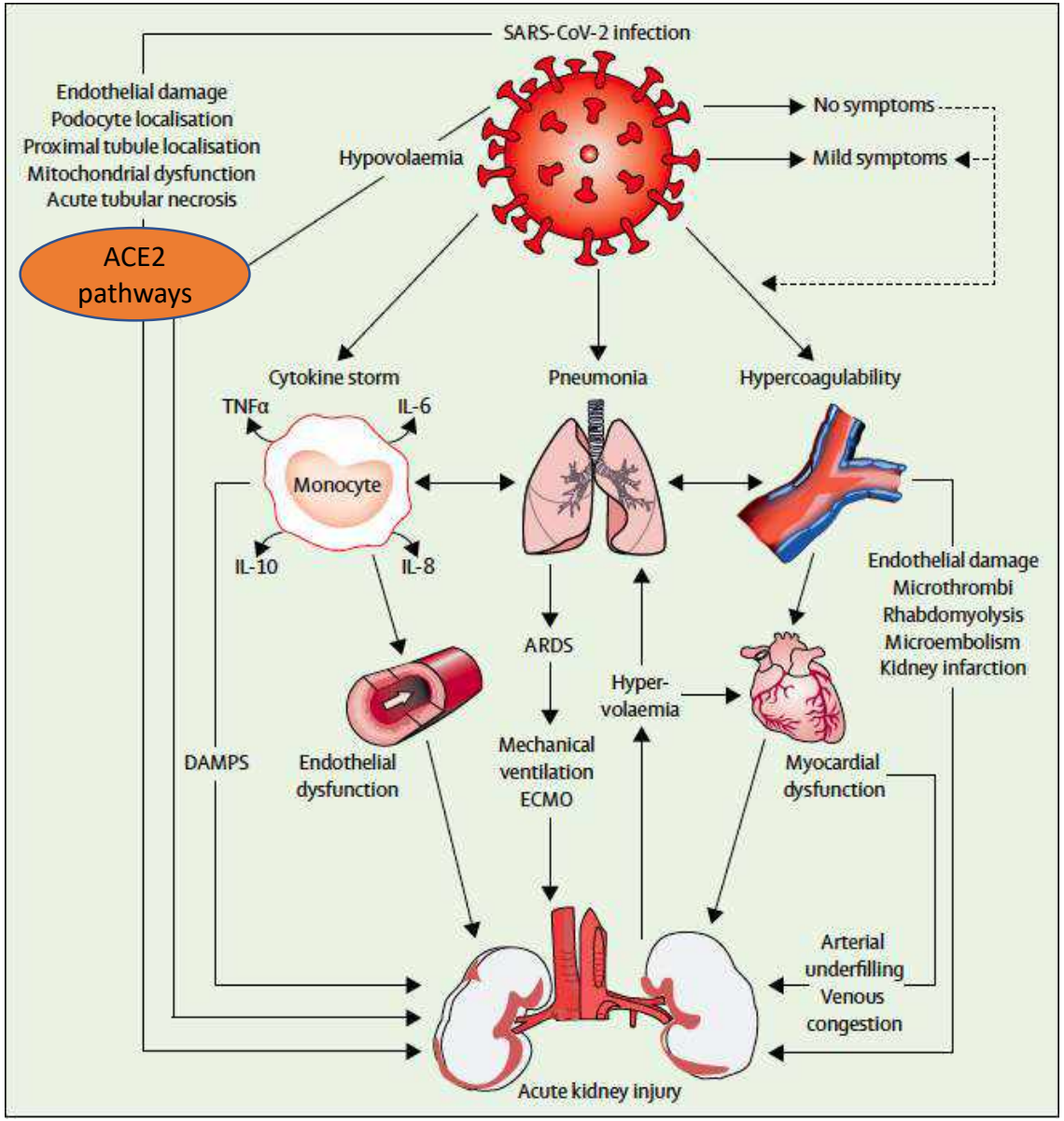
**Introduction**

- > 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)?
- Assocation between markers of kidney injury and death?

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

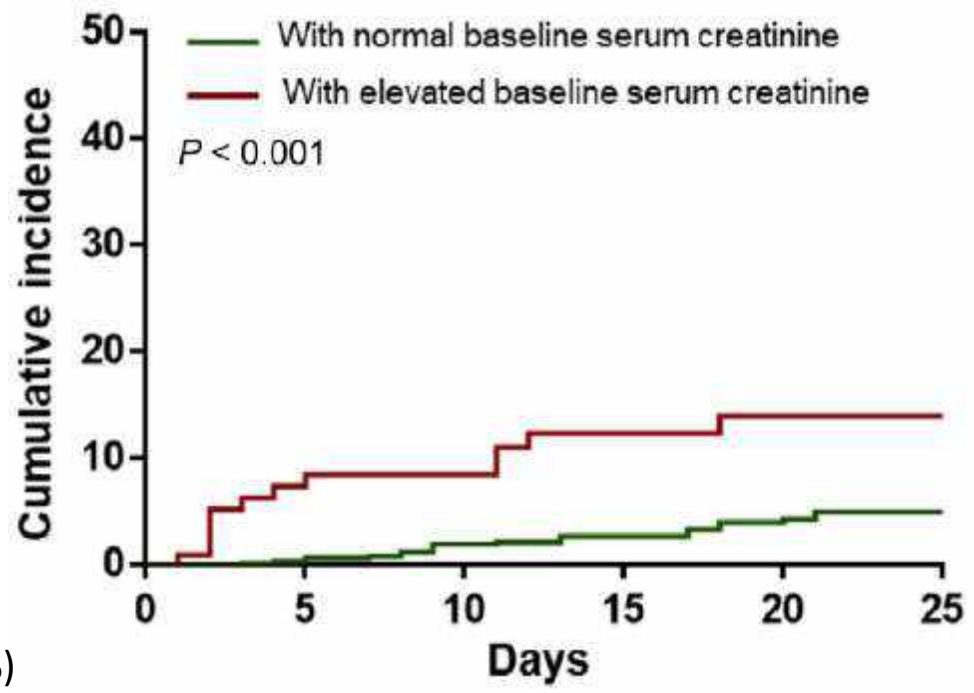
Kidney injury (**at admission**)

- 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)

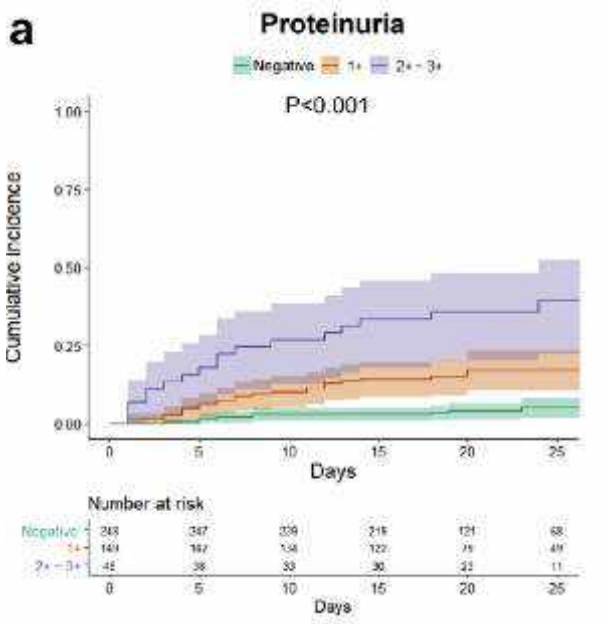
*Cumulative incidence of AKI subgrouped by baseline serum creatine*

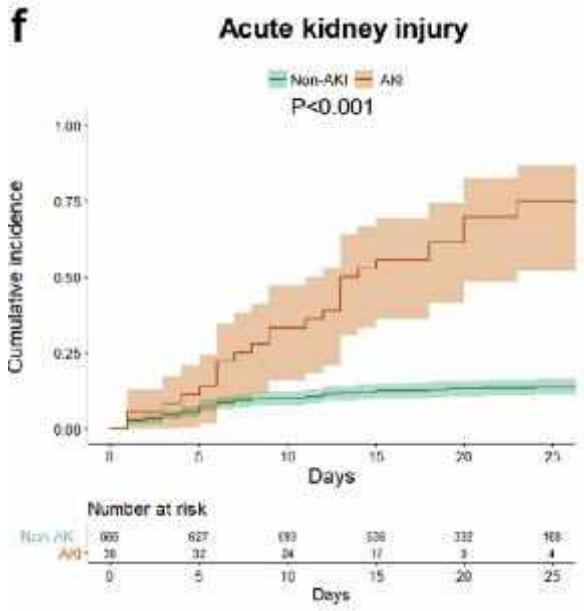



Cheng Y et *al. Kidney Int*. May 2020

# Kidney & COVID-19

**Kidney abnormalities → ↑ in hospital death**

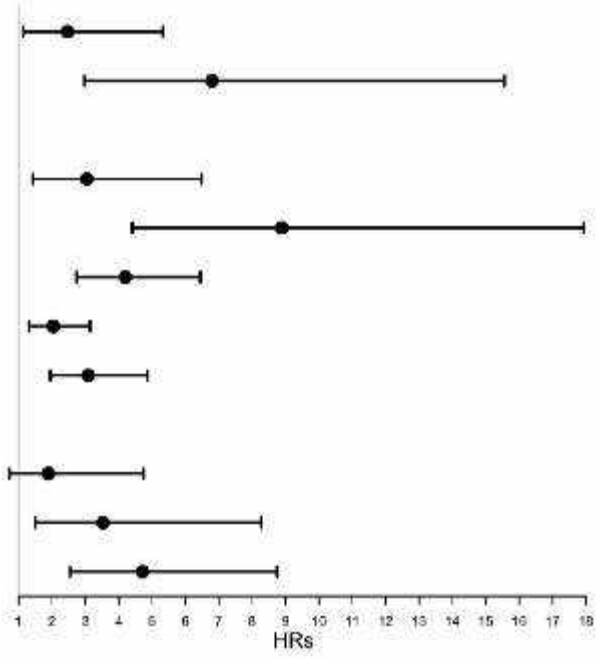



*Cumulative incidence for in-hospital death*

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 in patient hospitalized with COVID-19

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

→ Impact on long-term outcomes?

# Neuropsychiatric & COVID-19

Online network of secure rapid-response case report notification portals (CoroNerve plateforms)
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>

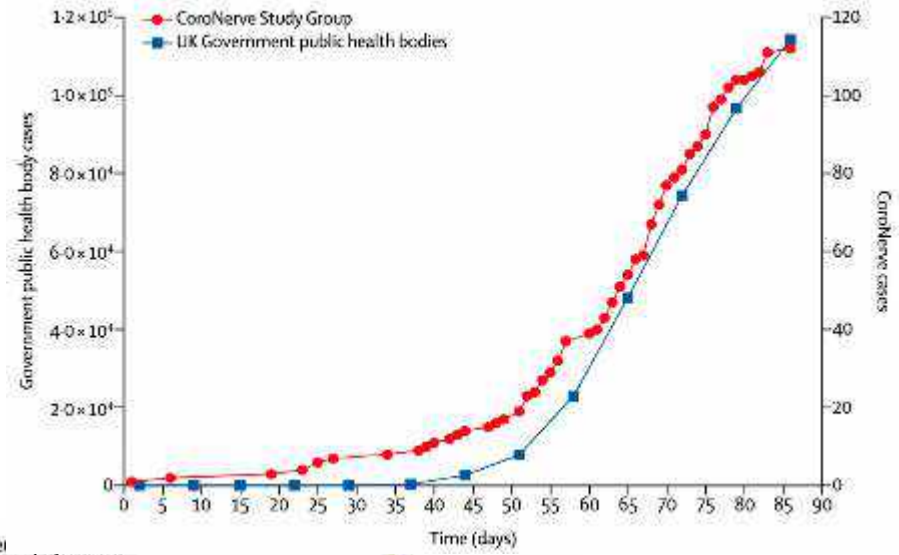
- **Cerebrovascular event** = 77 cases
  - Ischaemic stroke / intracerebral haemorrhage
- **Altered mental status** = 39 cases
  - Encephalopathy /encephalitis / primary psychiatric diagnoses / …
- **Peripheral neurology** = 6 cases
- **Other neurological disorders** = 3 cases

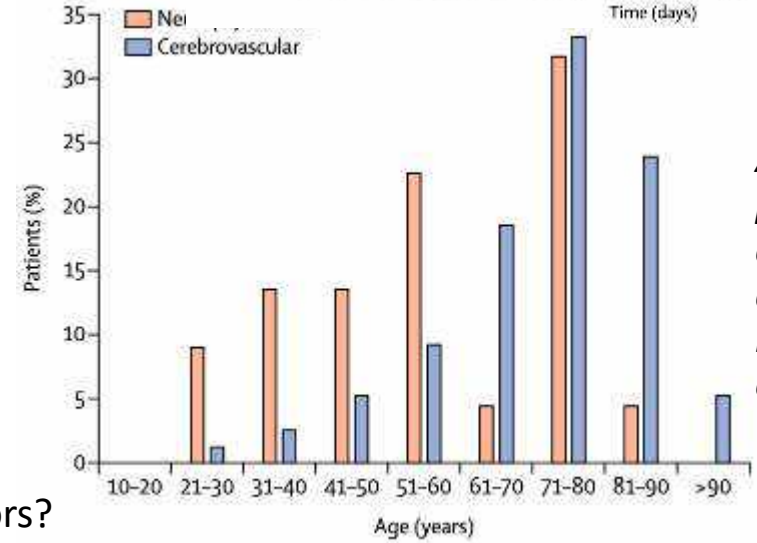
Acute alteration in mental status were overrepresented in young

→Cerebrovascular events in COVID-19 → vasculopathy

→Viral neurotropism? Host immune responses? Genetic factors?

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

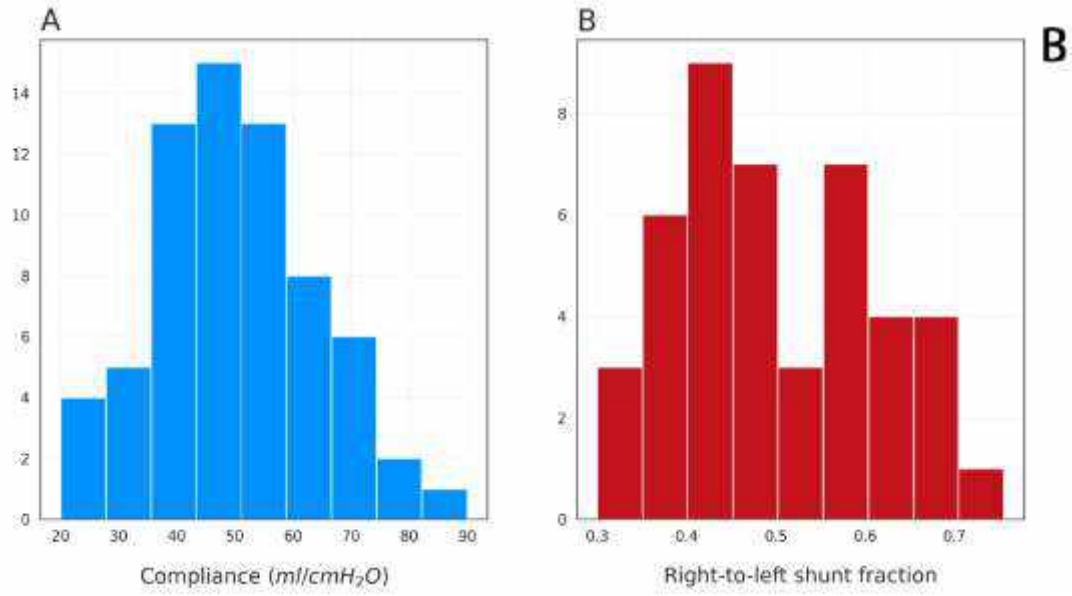


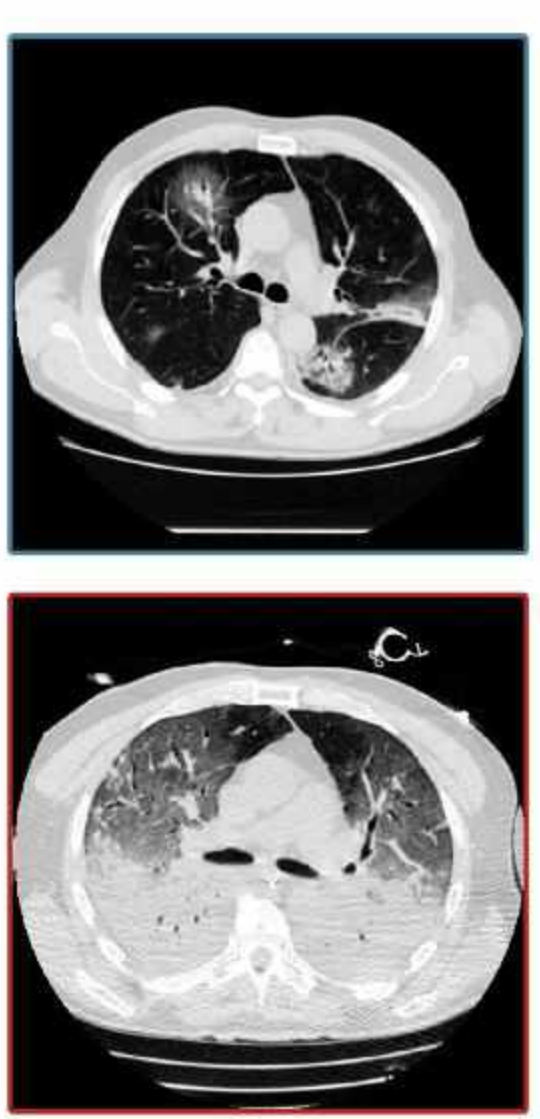




*Age distribution of patients – case definitions for cerebrovascular and neuropsychiatric events*

# ARDS & COVID-19 ?

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




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

**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

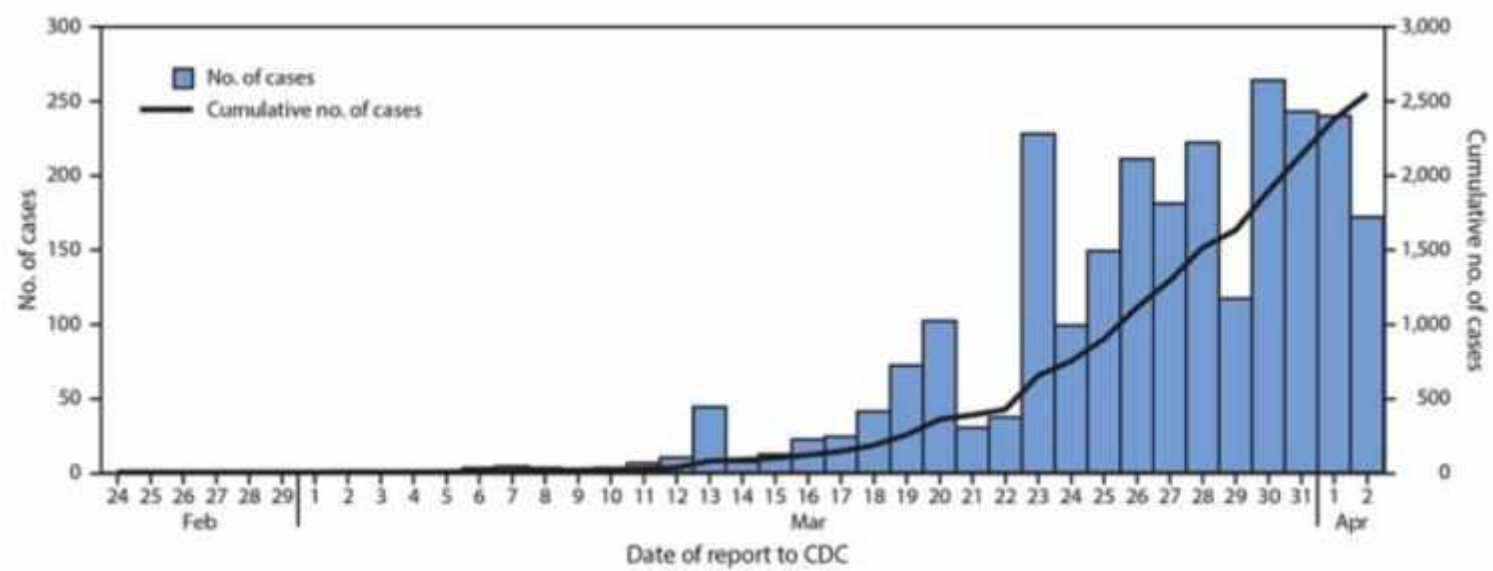
- Increase oedema → decrease gas volume
  - **Vt = 6ml/kg → DV<14cm$H_2O$**
- Recruitability is high
  - **PEP>12cm$H_2O$** (carefully)
- High lung weight → bilateral condensations
  - **Prone position**

# 2549 children in USA

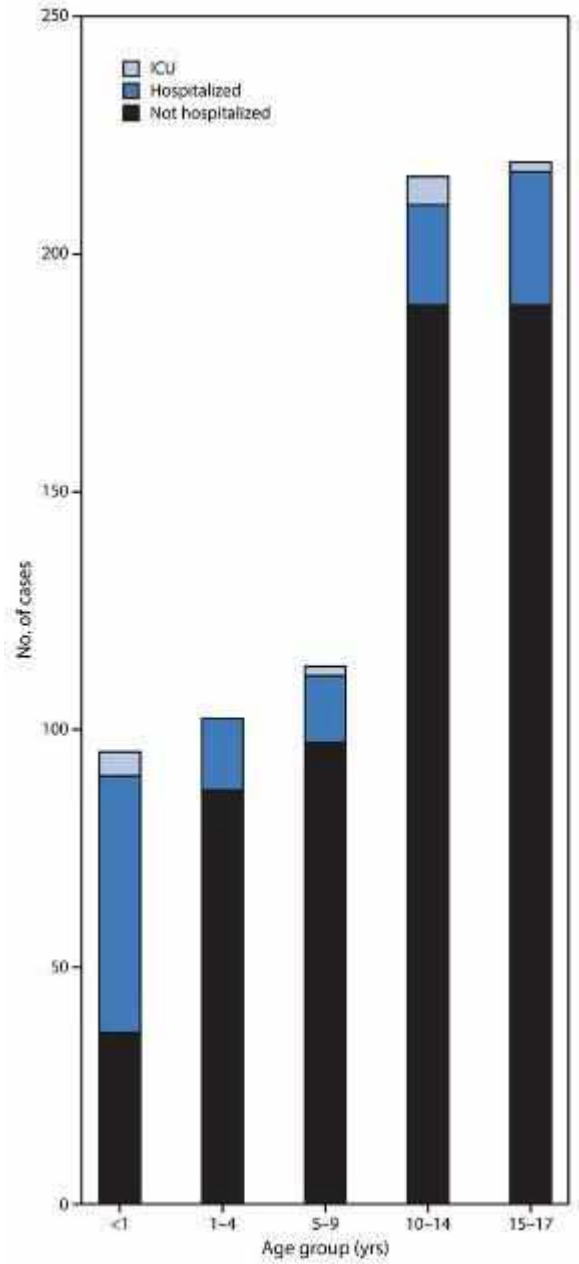
- Age (median): 11 years [0 – 17]
- Male: 57 %
- Exposure to a COVID-19 patients: 91% (household / community)

- **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

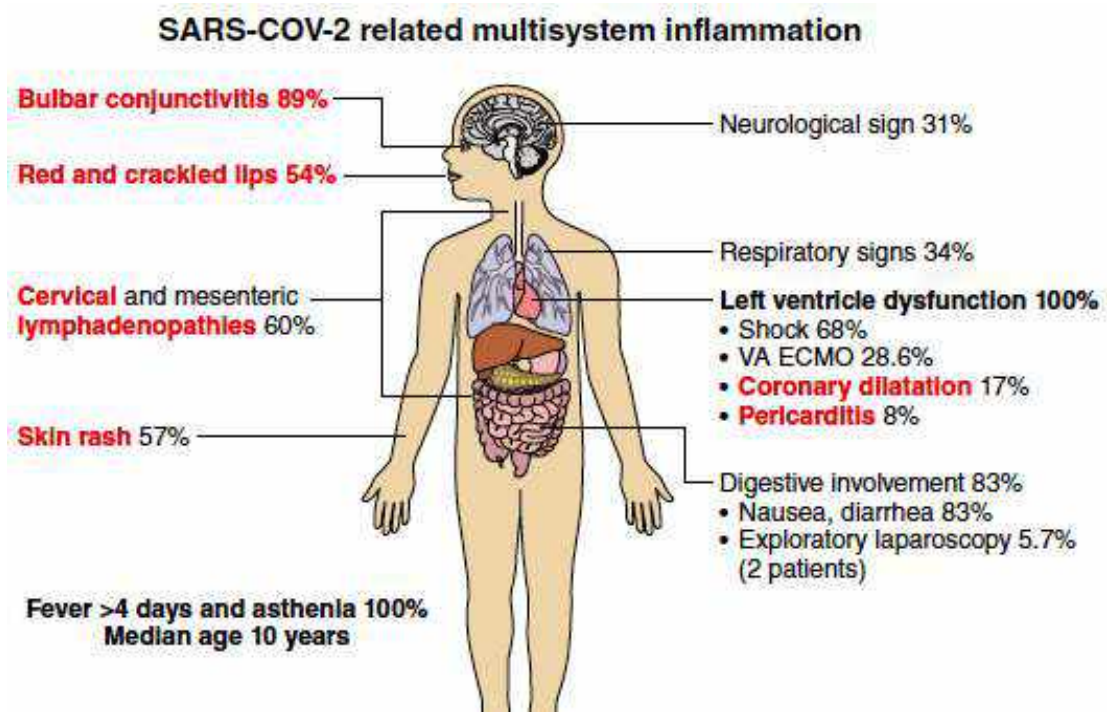
- **Observation of a large number of children hospitalized for cardiogenic shock potentially associated with SARS-CoV-2**
- Retrospective cohort – 2 countries (France & Switzerland) – 14 centers
- 35 children - Age (median): 10 years [2 – 16] – 51% were male
- 88% were positive for SARS-CoV-2 (nasopharyngeal 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 recommandation 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

# Pediatric inflammatory multisystem syndrome

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

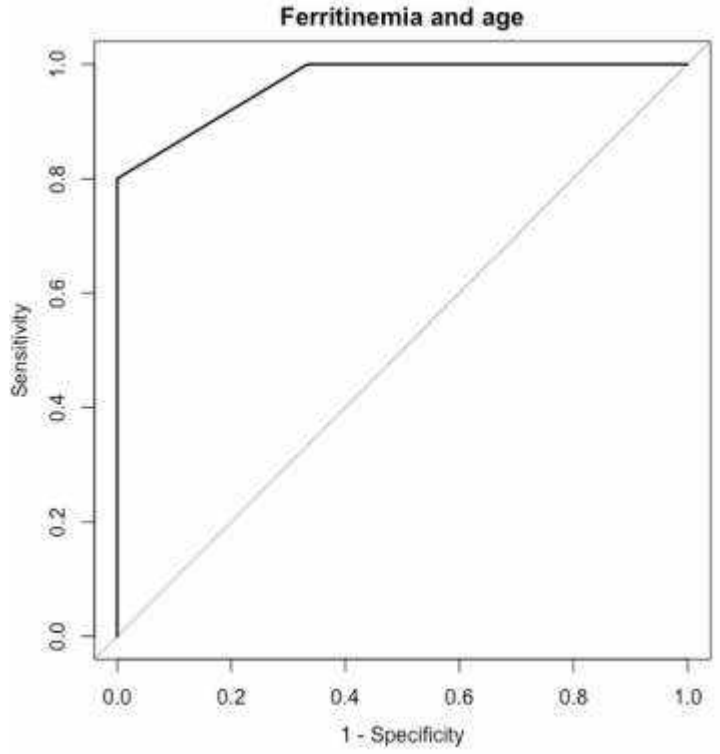
Compared with a historical cohort of «classical KD» (→ 220 patients)

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

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

<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 frquency 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

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

- Uses ACE2 receptor to enter the cell
- Activation of innate and adaptative immune pathway
- Can produce a cytokine storm → multiple-organ damage

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

- Most person are asymptomatic or mild symptomatic
- Independent risk factor of mortality: age – obesity – chronic disease
- Children are less represented than adult and have less severe or critical form of the disease
- New onset syndrome in children: *Pediatric Inflammatory Multisystem Syndrome*

3. Is there multiple-organ damage?

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

# THERAPEUTIC

**Questions:**

- What are the main drugs under study?
- Does exist drugs EMA or FDA approved for COVID-19 treatment?
- What are the types of vaccines in clinical evaluation?

# COVID-19 Treatment

- More data from clinical trials are needed
- **Food and Drug Administration** (FDA) : remdesivir received emergency use authorization for the treatment of hospitalized COVID-19 patients with severe disease (May 1st)
- **European Medicines Agency** (EMA) : marketing authorization in the European Union under the invented name Veklury (July 3rd)
- **Classes of treatment**

**Anti viral effect**

- (Hydroxy)chloroquine
- Lopinavir/ritonavir
- Remdesivir

**Immunomodulatory effect**

- Corticosteroids
- IL R antagonist
- **Monoclonal antibody**

**Passive immunity**

- Convalescent plasma

**Vaccine**

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https://www.fda.gov/media/137564/download
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines-covid-19#remdesivir-section

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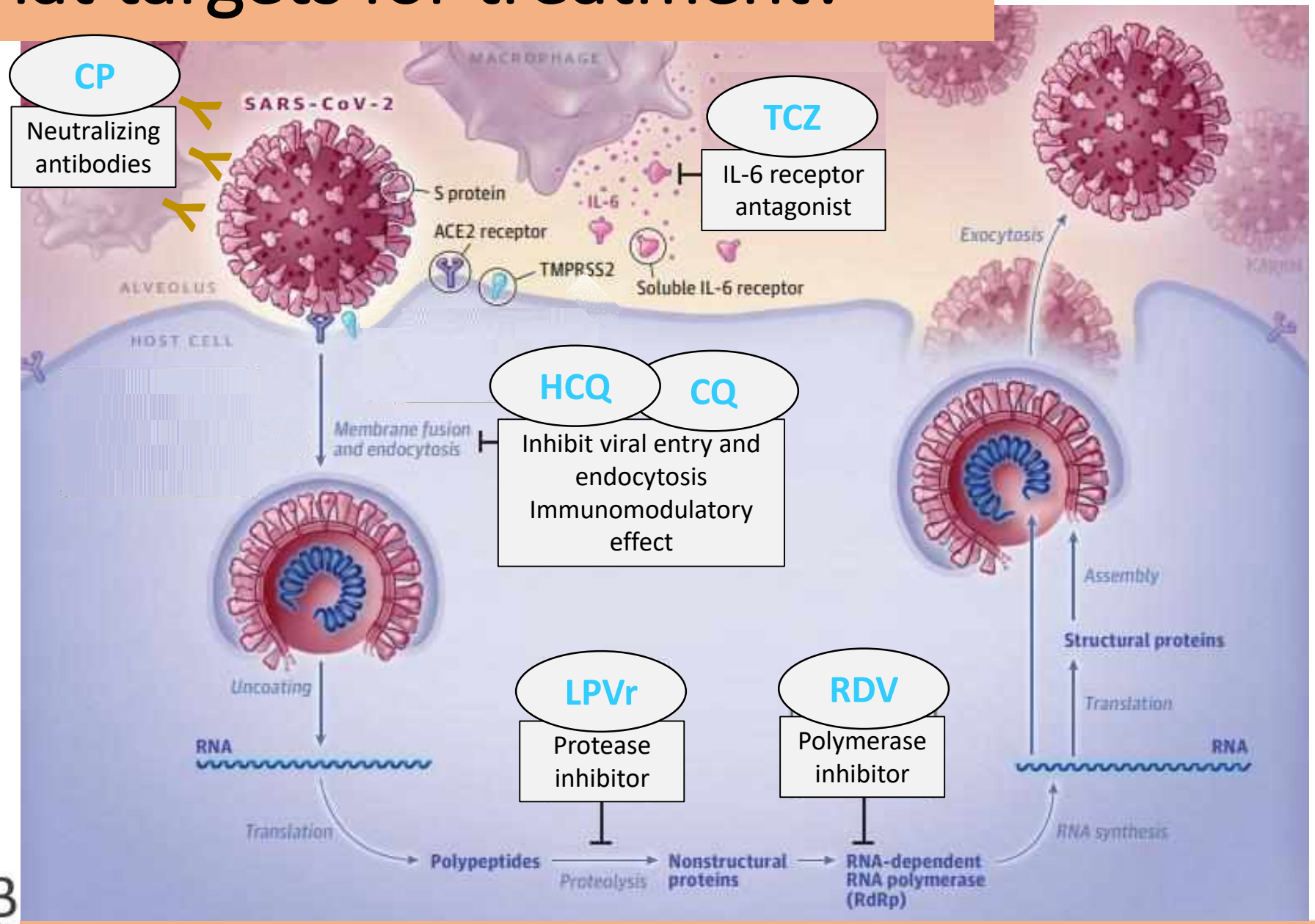
# What targets for treatment?




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

Sanders JM *et al. JAMA.* May 2020

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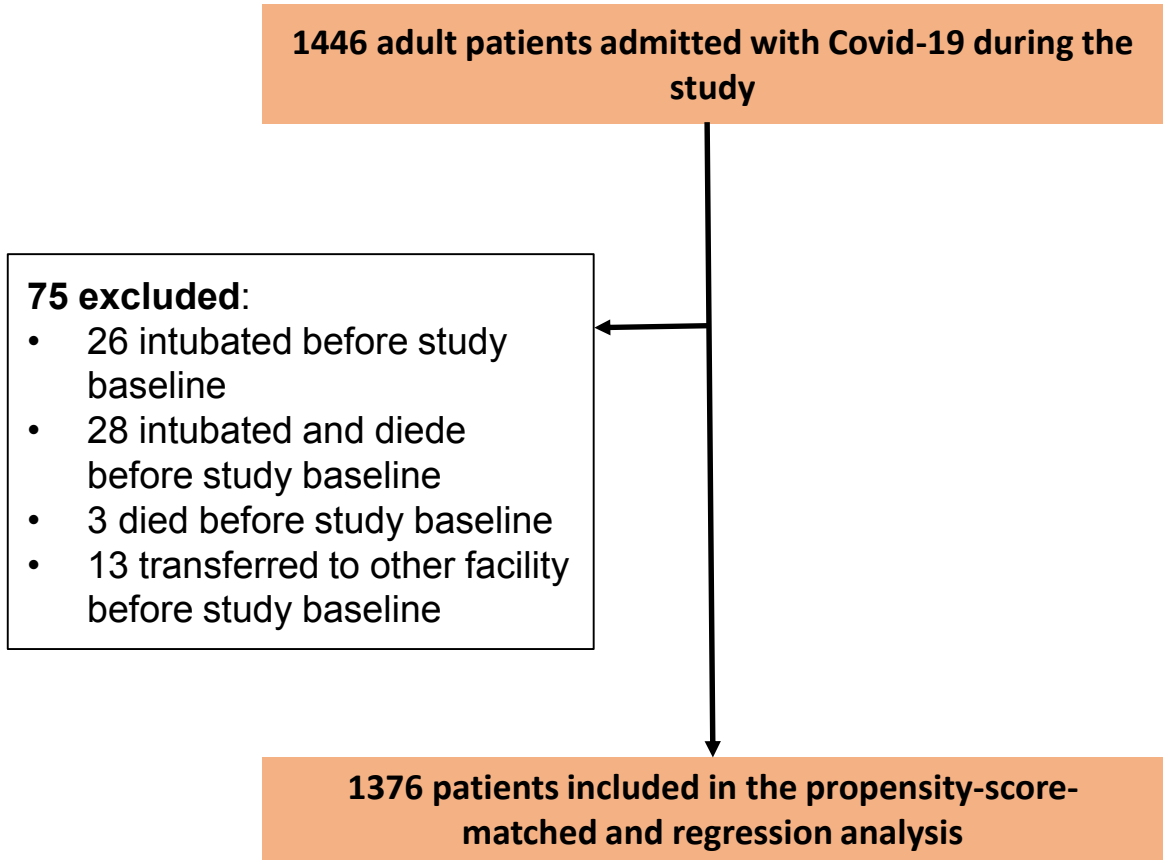
Anti viral effect

# Hydroxychloroquine (HCQ)

- Observational, not randomized, academic study, USA
- **Inclusion criteria** : positive SARS-CoV-2 RT PCR, moderate-to-severe respiratory illness, resting SpO2 < 94% (ambient air)
- **Exclusion criteria:** patient receiving RDV
- **Primary outcome**: time from study baseline to intubation or death
- 1376 patients; **811** (58.9%) **HCQ group** *vs.* **565 no HCQ group** (41.1%)




Geleris J *et al. NEJM.* Mar 2020

Anti viral effect

# Hydroxychloroquine (HCQ)

| | Unmatched patients | | Propensity score matched patients | |
|---|---|---|---|---|
| **Characteristics** | **HCQ (N=811)** | **No HCQ (N=565)** | **HCQ (N=811)** | **No HCQ (N=274)** |
| Age ≥ 60 yr – no (%) | 514 (63,4) | 318 (63) | 514 (63,4) | 177 (63,6) |
| Female sex – no (%) | 337 (41,6) | 258 (45,7) | 337 (41,6) | 113 (41,2) |
| BMI ≥ 25 – no (%) | 494 (60,9) | 310 (54,8) | 609 (75) | 214 (78) |
| **Coexisting conditions** | | | | |
| Diabetes – no (%) | 301 (37,1) | 190 (33,6) | 301 (37,1) | 94 (34,3) |
| Hypertension– no (%) | 398 (49,1) | 38 § (6,7) | 398 (49,1) | 146 (53,3) |
| Cancer – no (%) | 109 (13,4) | 67 (11,9) | 109 (13,4) | 35 (12,8) |
| **Vital signs** | | | | |
| Respiratory rate breaths/min – median (IQR) | 20 (18-22) | 18 (18-20) | 20 (18-22) | 19,5 (18-22) |

§ Typographical error that was not discovered in the proofs before publication, and confirmed by the corresponding author. The correct number is 278 (49.2%)

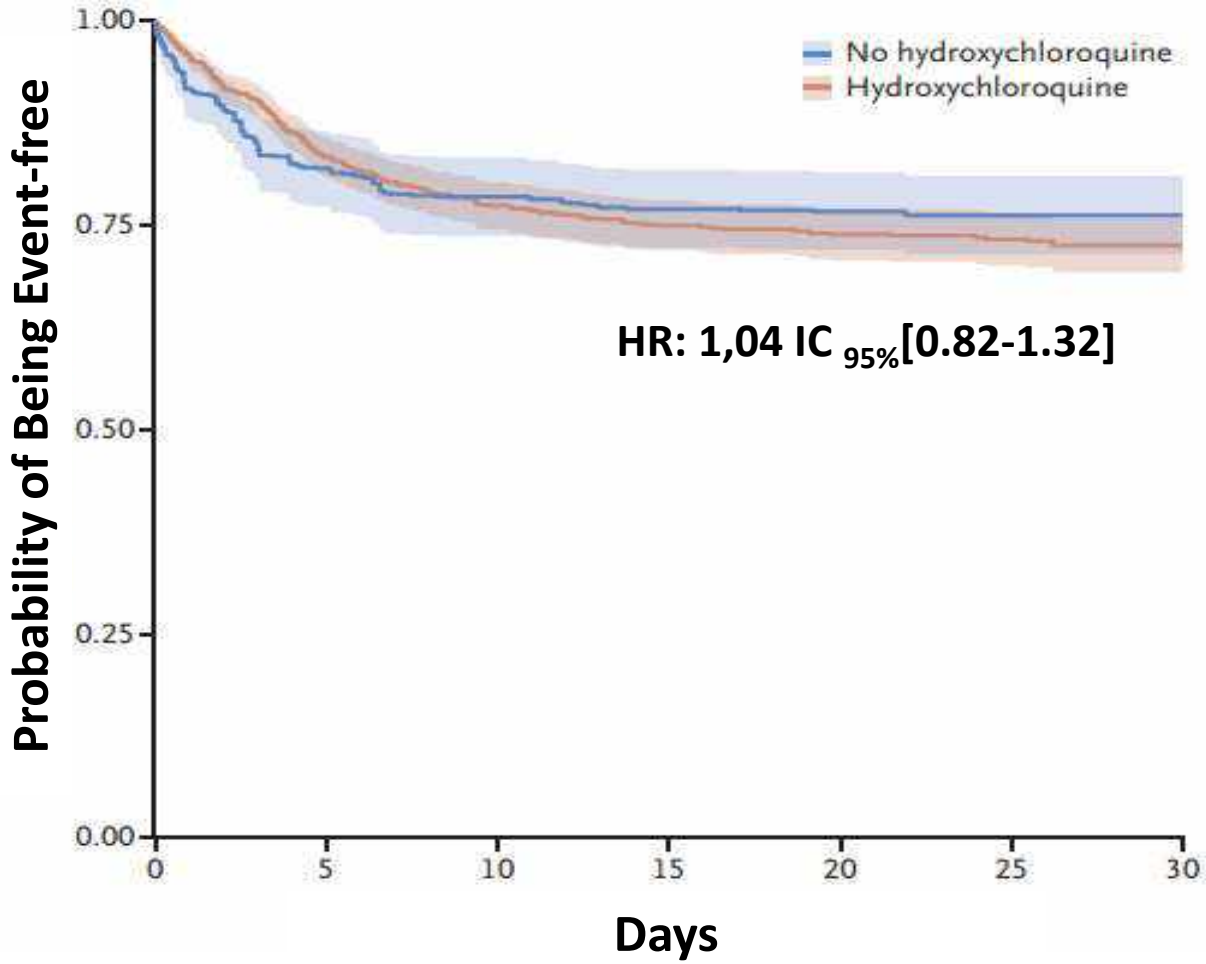
Geleris J *et al. NEJM.* Mar 2020

Anti viral effect

# Hydroxychloroquine (HCQ)

- **Time from study baseline to intubation or death**;
  - HCQ group 262/811 (32.3%),
  - no HCQ group 84/565 (14.9%);
  - no significant association between,
  - HR: 1.04 $CI_{95\%}$[0.82-1.32]

- **Limits:** observational study, not blind, no randomization, monocentric, selection of participants into the study heterogeneous for time when participants received HCQ, disease severity different between the two groups, short follow-up, data could be inaccurate or missing




Geleris J *et al. NEJM.* Mar 2020

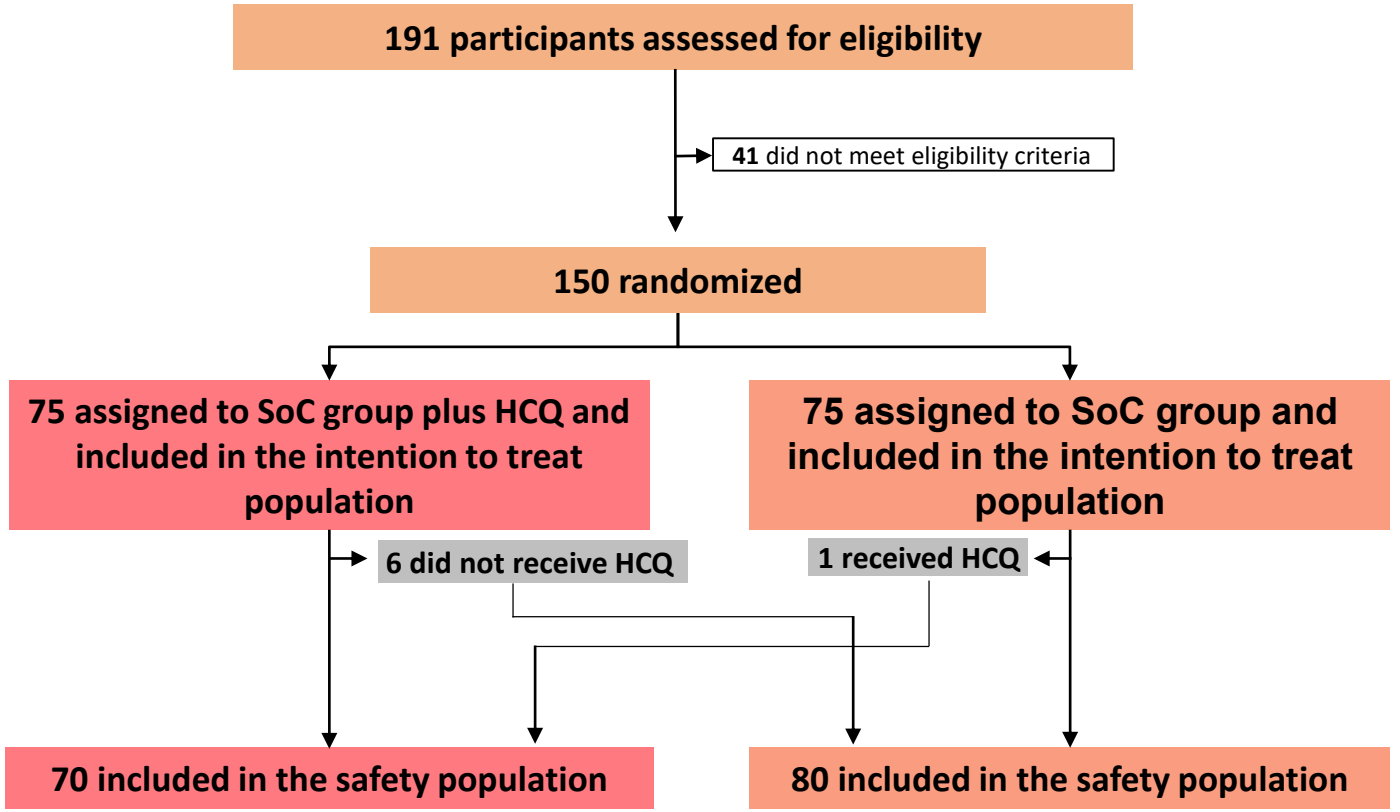
Anti viral effect

# Hydroxychloroquine (HCQ)

- Randomized, controlled, multicenter, open label, academic study, China
- **Inclusion criteria** : age ≥ 18yo, positive RT PCR SARS-CoV-2, mild (mild symptoms, no pneumonia on imaging) and moderate (fever, cough, sputum production, pneumonia on imaging) presentations

NB: pneumonia on computed tomography of the chest was not mandatory for inclusion

- **Exclusion criteria:** severe pneumonia defined as the presence of SpO2 < 94% (room air) or $PaO_2/FiO_2$ ratio of 300 or lower
- ITT, 150 hospitalized patients (148 mild to moderate); **75** HCQ + SoC *vs.* **75** SoC




SoC: standard of care

Tang W *et al. BMJ.* May 2020

Anti viral effect

# Hydroxychloroquine (HCQ)

- **Primary outcome**: D28 negative conversion of SARS-CoV-2 (two consecutive reports of a negative result for SARS-CoV-2 at least 24 hours apart)

- **Secondary outcome (one of them)**: D28 alleviation of clinical symptoms

| Characteristics | SoC + HCQ (N=75) | SoC (N=75) | Total (N=150) |
|---|---|---|---|
| Age, year – mean (SD) | 48 (14,1) | 44,1 (15) | 46,1 (14,7) |
| Male sex – no (%) | 42 (56) | 40 (53) | 82 (55) |
| BMI – mean (SD) | 23,9 (3,24) n=74 | 23,2 (3) n=71 | 23,5 (3,2) n=145 |
| **Coexisting conditions** | | | |
| Diabetes – no (%) | 12 (16) | 9 (12) | 21 (14) |
| Hypertension– no (%) | 6 (8) | 3 (4) | 9 (6) |
| Others – no (%) | 21 (28) | 10 (13) | 31 (21) |
| **Disease severity** | | | |
| Mild – no (%) | 15 (20) | 7 (9) | 22 (15) |
| Moderate – no (%) | 59 (79) | 67 (89) | 126 (84) |
| Severe – no (%) | 1 (1) | 1 (1) | 2 (1) |

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SoC: standard of care

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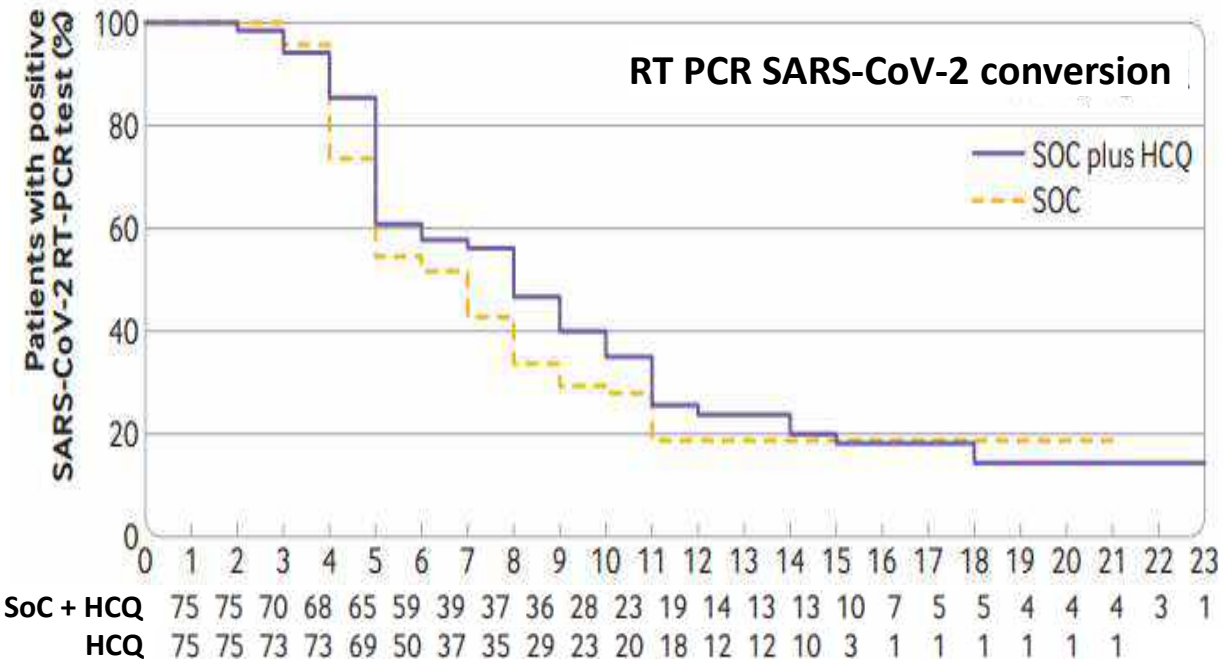
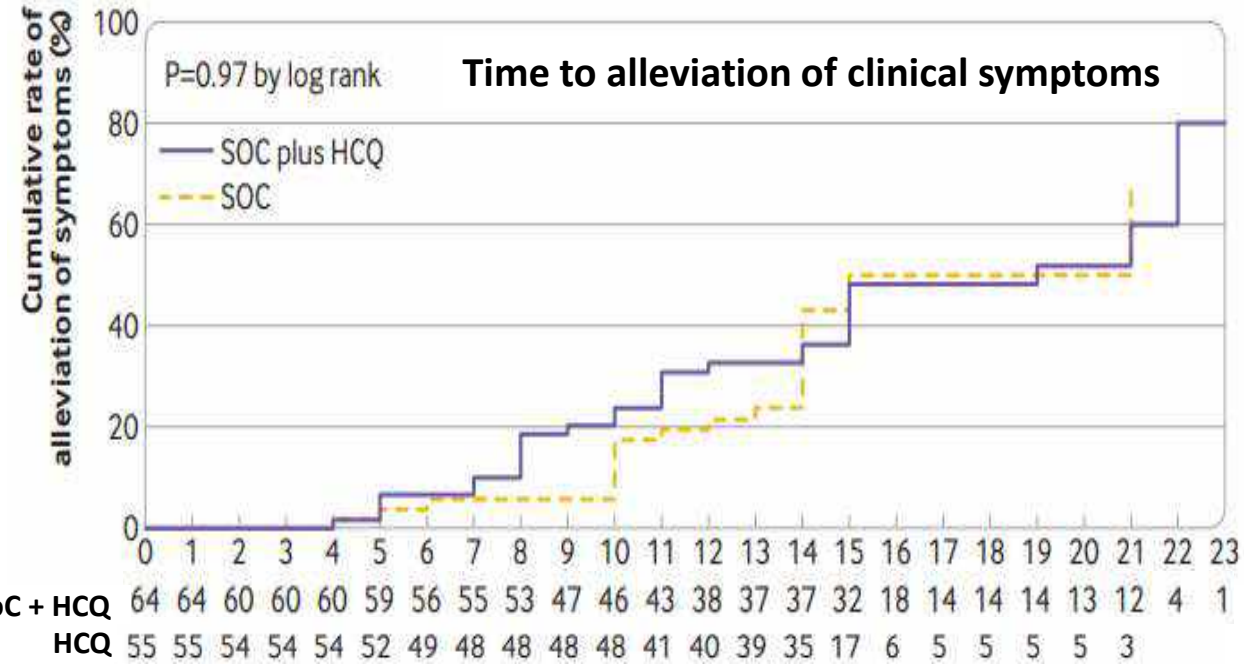
Anti viral effect

# Hydroxychloroquine (HCQ)

- **D28 negative SARS-CoV-2 conversion**: HCQ + SoC: 85.4%, $IC_{95\%}$[73.8% - 93.8%] *vs.* SoC: 81.3%, $IC_{95\%}$[71.2%-89.6%] : **no difference**

- **D28 probability of alleviation of symptoms**: HCQ + SoC: 59.9%, $IC_{95\%}$[45.0%-75.3%] *vs.* SoC: 66.6%, $IC_{95\%}$[35.5%-90.9%] : **similar**




SoC: standard of care

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Anti viral effect

# Hydroxychloroquine (HCQ)

| Adverse events | SoC + HCQ (N=70) | SoC (N=80) |
|---|---|---|
| **Any adverse events – no (%)** | 21 (30) | 7 (9) |
| **Serious adverse events – no (%)** | 2 (3) | 0 |
| Disease progression | 1 (1) | 0 |
| Upper respiratory tract infection | 1 (1) | 0 |
| **Non serious adverse events – no (%)** | 19 (27) | 7 (9) |
| Diarrhea | 7 (10) | 0 |
| Vomiting | 2 (3) | 0 |
| Nausea | 1 (1) | 0 |
| Sinus bradycardia | 1 (1) | 0 |

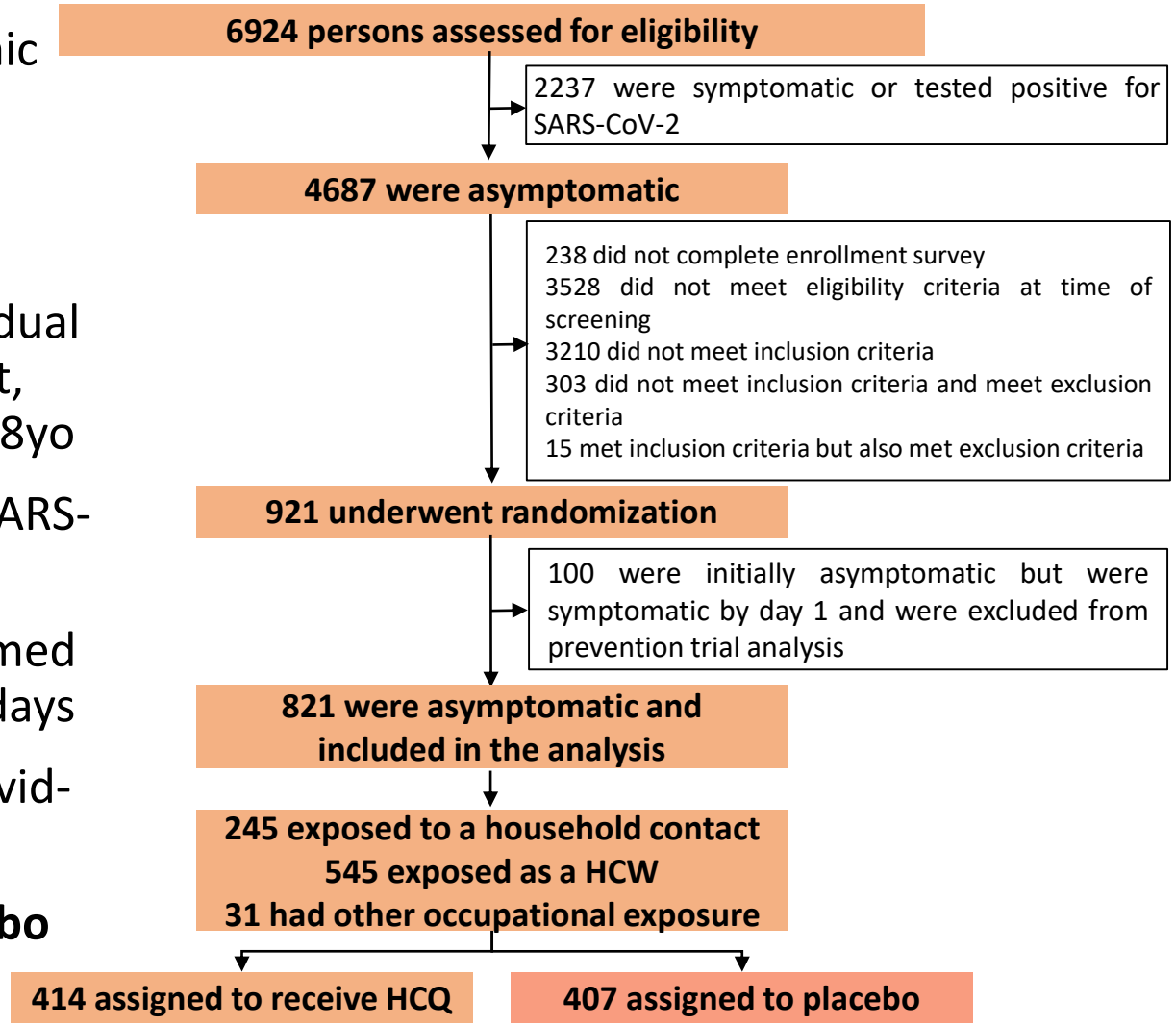
- **Limits:** trial stopped early, secondary endpoint (results on clinical improvement) changed during the study, secondary outcome forecast in the protocol but not didn't appear on the trial registration list, sample size had not been reached as expected, primary outcome not clinically relevant, no link between clinical presentation and viral load, patients whose clinical presentation were getting worse had lower VL

Anti viral effect

# Hydroxychloroquine (HCQ)

Post exposure prophylaxis

- Randomized, double-blind, placebo-controlled, academic study, USA
- **Post exposure prophylaxis** evaluation with HCQ after COVID-19 exposure
- **Inclusion criteria**: Exposure to a known COVID-19 individual (laboratory confirmed) within 3 days (household contact, HCW, occupational exposures), not hospitalized, age ≥ 18yo
- **Exclusion criteria**: COVID-19 symptoms or PCR proven SARS-CoV-2 infection
- **Primary outcome**: incidence of either laboratory confirmed Covid-19 or illness compatible with Covid-19 within 14 days
- **Secondary outcome**: incidence of hospitalization for Covid-19 or death, side effects
- 821 asymptomatic participants; **HCQ** group (414), **placebo** group (407)




Boulware DR *et al. NEJM.* May 2020

Anti viral effect

# Hydroxychloroquine (HCQ)

Post exposure prophylaxis

| Characteristics | HCQ (N=414) | Placebo (N=407) |
|---|---|---|
| Age, median (IQR) – yr | 41 (33-51) | 40 (32-50) |
| Female sex – no (%) | 218 (52,7) | 206 (50,6) |
| Weight, median (IQR) – kg | 75 (64-86) | 76 (64-91) |
| Health Care worker – no (%) | 275 (66,4) | 270 (66,3) |
| High-risk exposure – no (%) | 365 (88,2) | 354 (87) |
| No PPE worn – no (%) | 258 (62,3) | 237 (58,2) |
| **Coexisting conditions** | | |
| Diabetes – no (%) | 12 (2,9) | 16 (3,9) |
| Hypertension– no (%) | 51 (12,3) | 48 (11,8) |
| Asthma – no (%) | 31 (7,5) | 31 (7,6) |

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Boulware DR *et al. NEJM.* May 2020

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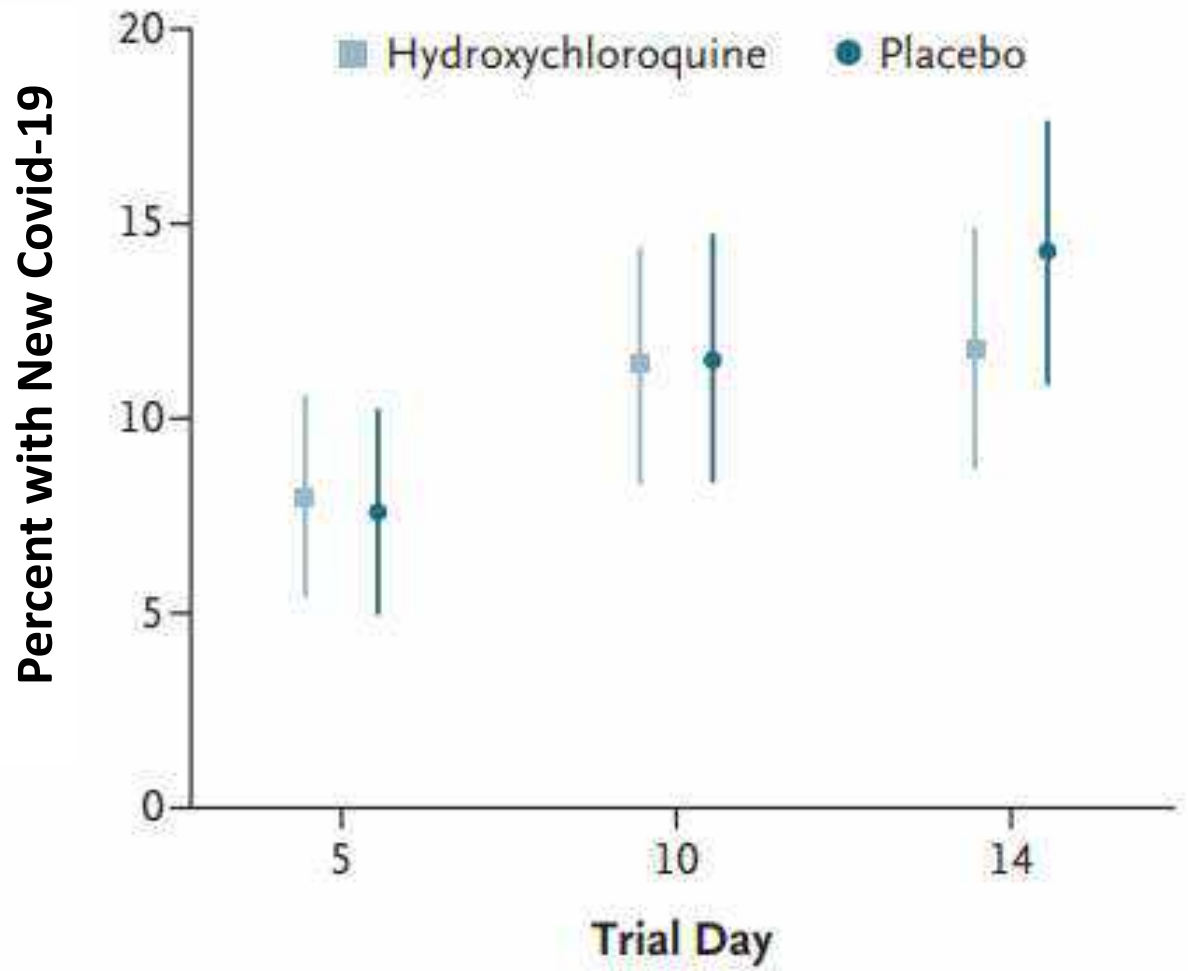
Anti viral effect

# Hydroxychloroquine (HCQ)

Post exposure prophylaxis

- **Laboratory-confirmed or illness compatible COVID-19**: HCQ group 49/414 (11,8%) *vs.* placebo group 58/407 (14,3%): no significant difference (p=0,35)
- Two hospitalization reported (one in each group), no arrhythmias nor deaths occurred
- **Side effects**: **HCQ** group 140/349 (40,1%) (nausea, diarrhea) *vs.* **placebo** group 59/351 (16,8%): significant difference (p<0,001)

- **Limits**: eligibility criteria changed during the study, young and healthy study population, no assessment of asymptomatic infection, no serology available before inclusion




Boulware DR *et al. NEJM.* May 2020

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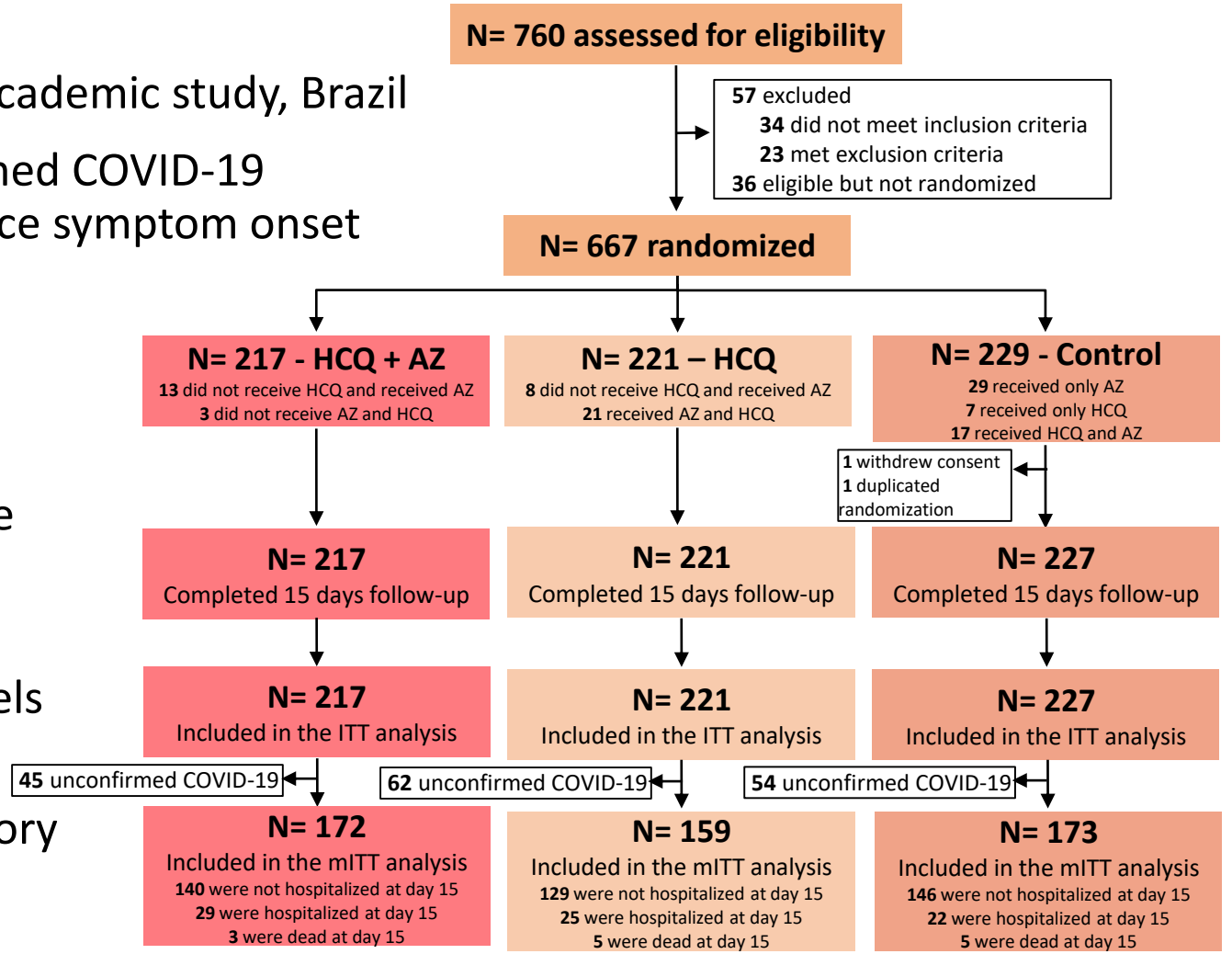
Anti viral effect

# Hydroxychloroquine (HCQ)

- Multicenter, randomized, open-label, controlled, academic study, Brazil
- **Inclusion criteria:** age ≥ 18yo, hospitalized, confirmed COVID-19 (positive RT PCR SARS-CoV-2), 14 or fewer days since symptom onset
- **Exclusion criteria:** supplemental oxygen (rate ≥ 4L/min by nasal cannula or level ≥ 40% by Venturi mask, high-flow nasal cannula or invasive or noninvasive ventilation); previous use of CQ, HCQ, AZ, macrolide > 24 hours before enrollment; severe ventricular tachycardia history, ECG findings with (QTc) ≥ 480 msec
- **Main outcome** clinical status at 15 days (seven levels ordinal scale)
- **Other outcomes**: Days alive and free from respiratory support, duration of hospital stay, and others

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AZ: azithromycine – CQ: chloroquine – QTc: corrected QT interval

Cavalcanti *et al*. *NEJM.* Jul 2020

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Anti viral effect

# Hydroxychloroquine (HCQ)

| Characteristics | HCQ + AZ (N=217) | HCQ (N=221) | Control (N=227) | Total (N=665) |
|---|---|---|---|---|
| Age, year – mean (SD) | 49,6 (14,2) | 51,3 (14,5) | 49,9 (15,1) | 50,3 (14,6) |
| Male sex – no (%) | 123 (56,7) | 142 (64,3) | 123 (54,2) | 388 (58,3) |
| **Coexisting conditions** | | | | |
| Diabetes – no (%) | 40 (18,4) | 47 (21,3) | 40 (17,6) | 127 (19,1) |
| Hypertension– no (%) | 81 (37,3) | 94 (42,5) | 83 (36,6) | 258 (38,8) |
| Obesity – no (%) | 29 (13,4) | 37 (16,7) | 37 (16,3) | 103 (15,5) |
| **Score** on ordinal scale | | | | |
| 3. Hospitalized, not receiving supplemental $O_2$ – no (%) | 125 (57.6) | 132 (59.7) | 130 (57.3) | 387 (58.2) |
| 4. Hospitalized, receiving supplemental $O_2$ – no (%) | 92 (42.4) | 89 (40.3) | 97 (42.7) | 278 (41.8) |
| Median time from symptom onset to randomization (IQR) — days | 7 (5-9) | 7 (5-8) | 7 (4-9) | 7 (5-9) |

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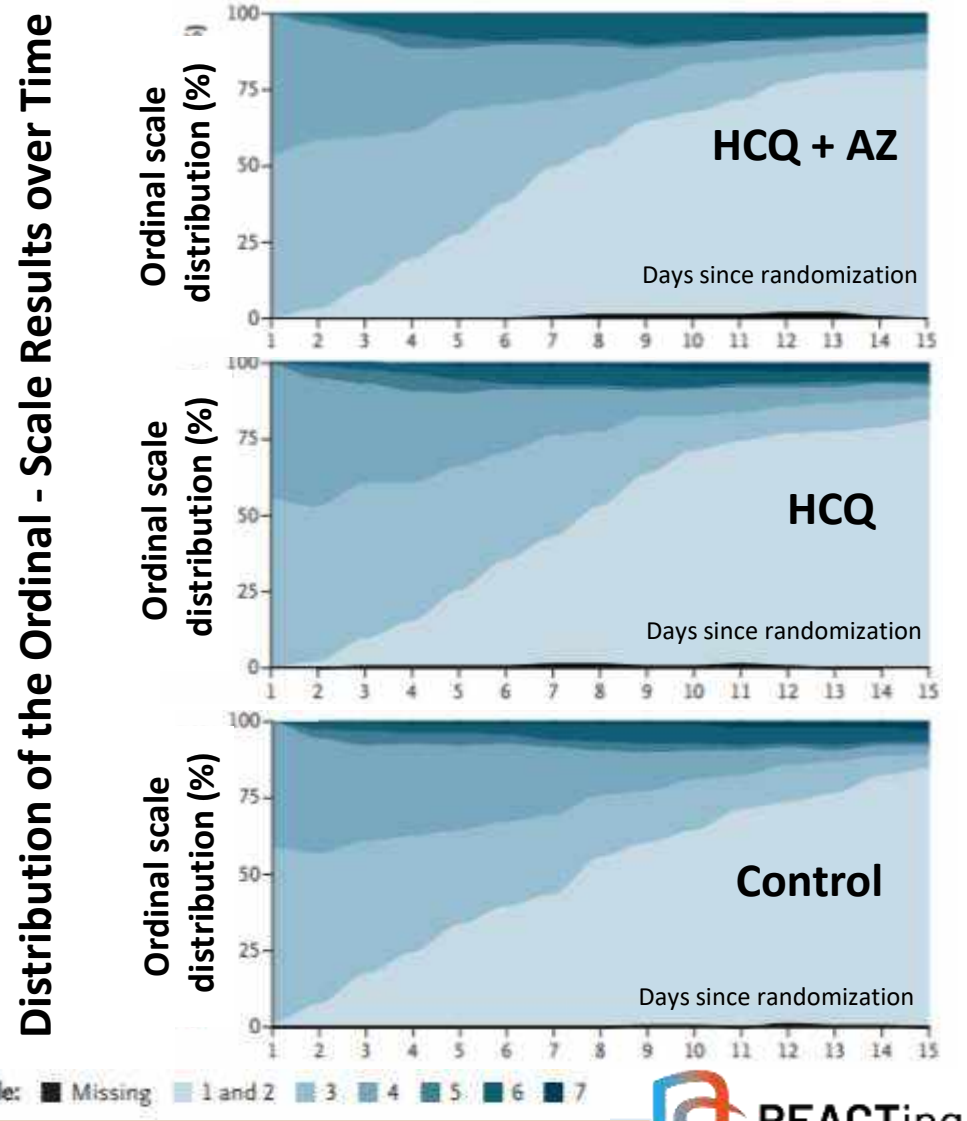
Anti viral effect

# Hydroxychloroquine (HCQ)

- **Clinical status at 15 days** : no significant between-group differences (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])
- **Days alive and free from respiratory support** : no between-group differences; 11,1±4,9 in HCQ + AZ group, 11,2±4,9 in HCQ group, 11,1±4,9 in control group
- **Duration of hospital stay** : no between-group differences; 10,3±8,4 in HCQ + AZ group, 9,6±6,5 in HCQ group, 9,5±7,2 in control group
- **Limits** : not blinded study, protocol deviations reported, participants received HCQ + AZ before be enrolled, participants have been included up to 14 days after the beginning of symptoms




CQ: chloroquine – AZ: azithromycine

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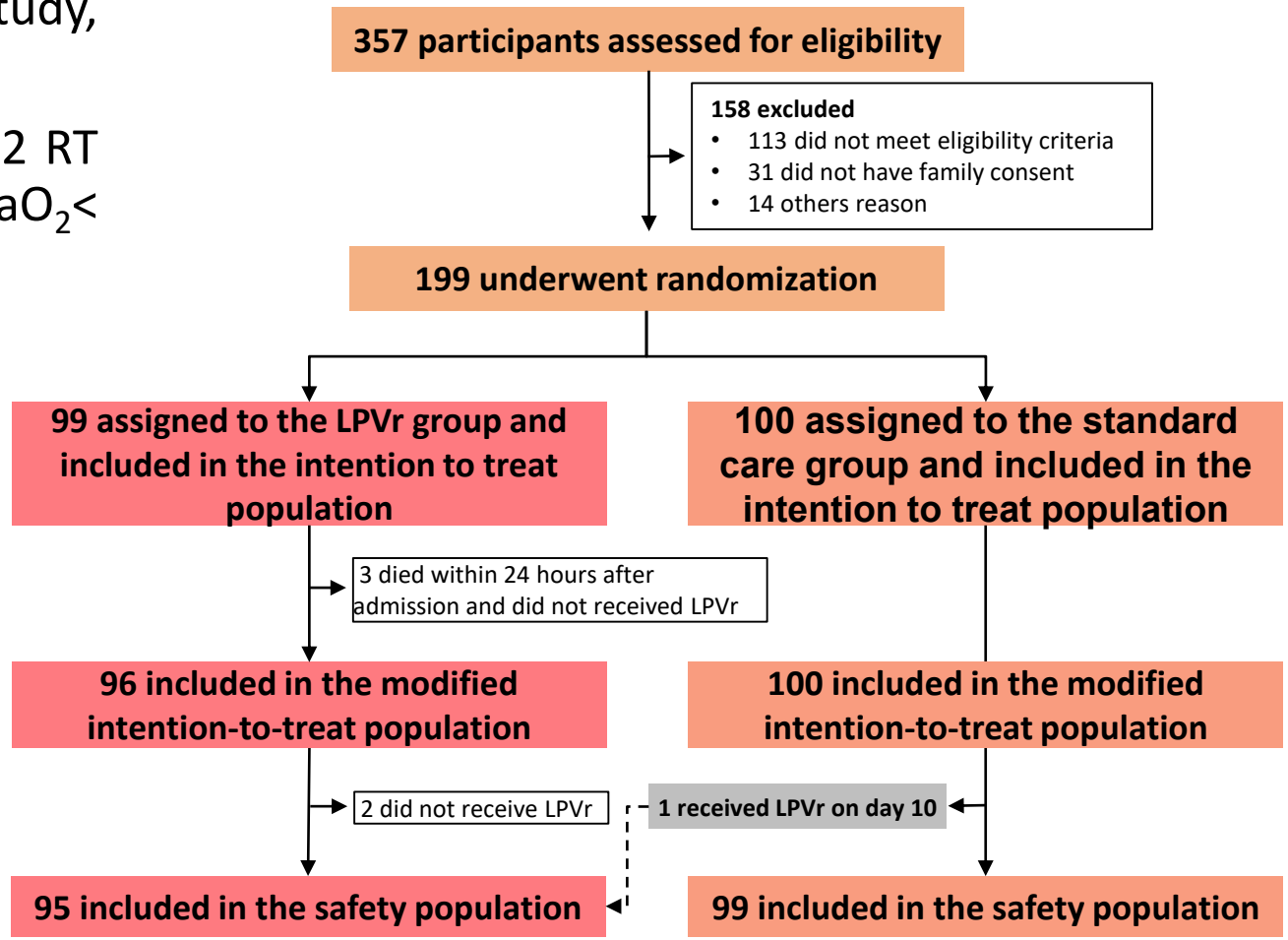
Anti viral effect

# Lopinavir/ritonavir (LPVr)

- Randomized, controlled, open-label, academic study, China
- **Inclusion criteria:** age ≥ 18yo, positive SARS-CoV-2 RT PCR, pneumonia confirmed by chest Imaging, $SaO_2$< 94% (room air) or $PaO_2/FiO_2$ ≤ 300 mmHg
- **Exclusion criteria:** pregnant women, LPVr allergy/hypersensitivity, liver disease, HIV infection
- **Primary outcome:** time to clinical improvement
- **Secondary outcome (one of them);** viral RNA detection
- 199 serious ill hospitalized adults patients; **94** received **LPVr**, **99 standard care group** (1:1)

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Anti viral effect

# Lopinavir/ritonavir (LPVr)

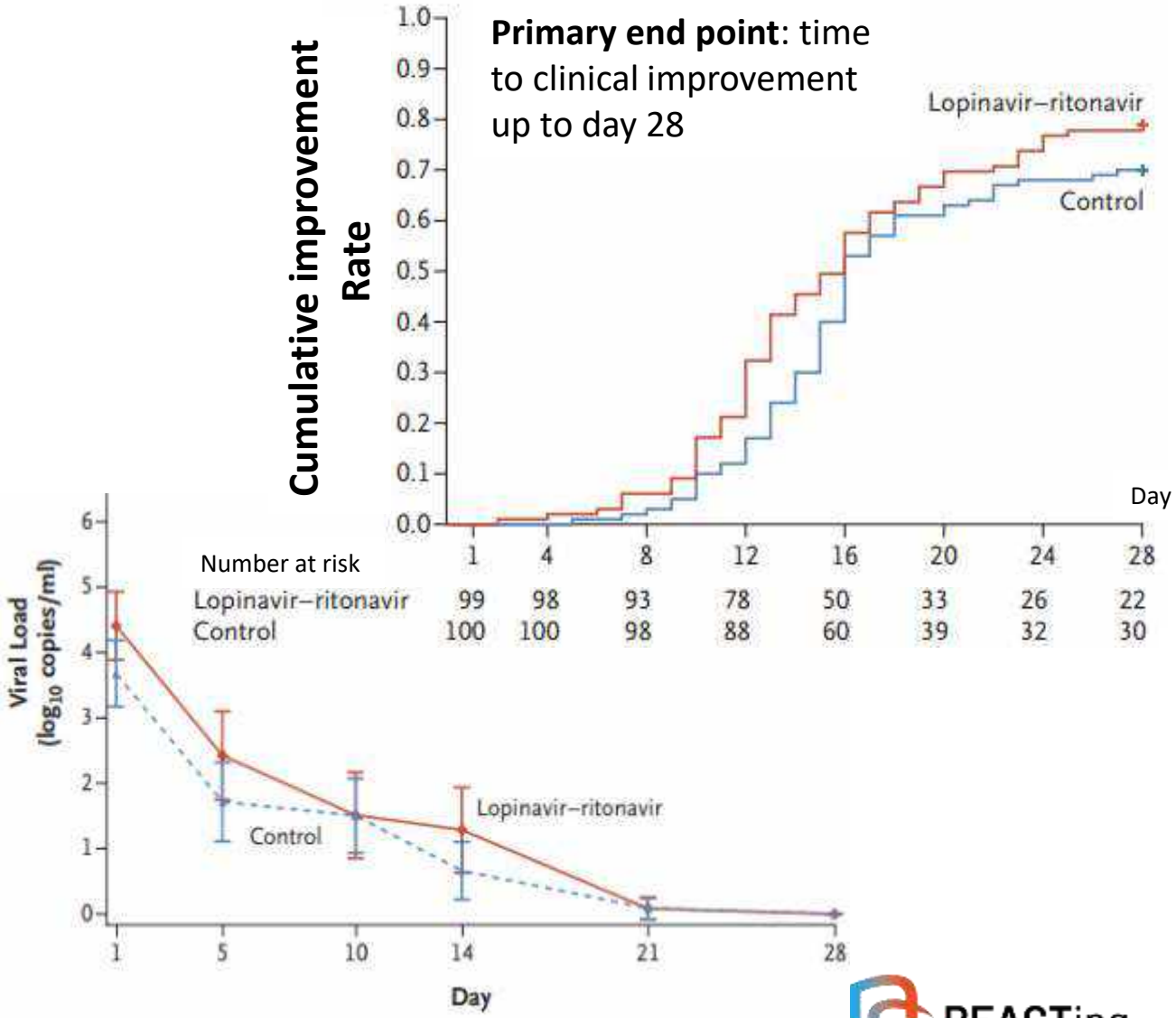
| Characteristics | Total (N=199) | LPVr (N=99) | SoC (N=100) |
|---|---|---|---|
| Age, median (IQR) - yr | 58 (49-68) | 58 (50-68) | 58 (48-68) |
| Male sex – no (%) | 120 (60,3) | 61 (61,6) | 59 (59) |
| **Coexisting conditions** | | | |
| Diabetes – no (%) | 23 (11,6) | 10 (10,1) | 13 (13) |
| Cardiovascular disease | 13 (6,5) | 5 (5,1) | 8 (8) |
| Cancer – no (%) | 6 (3) | 5 (5,1) | 1 (1) |
| **Vital sign** | | | |
| Respiratory rate > 24/min – no (%) | 37 (18,8) | 21 (21,6) | 16 (16) |

Anti viral effect

# Lopinavir/ritonavir (LPVr)

- LPVr group: <u>not associated</u> with a difference in time to clinical improvement, HR:1,31 $CI_{95\%}$[0,95:1,80]
- **Day 28 mortality** : similar in two groups, 19.2% (LPVr) *vs.* 25.0% (SoC); difference, −5.8 percentage points; $CI_{95\%}$[-17,3:5,7]
- Difference of mortality between two groups seems to be numerically greater among patients treated within 12 days after the onset symptoms
- **RNA load or RNA detectability** : no reduction LPVr group compared with standard care group
- 14% LPVr group unable full 14-day administration (gastrointestinal adverse events)
- **<u>Limits :</u>** higher throat viral loads in the LPVr group, positive virus RNA detection (throat swabs) on D14 and D28, but no data about virus infectiousness (no virus isolation performed)

**Primary end point**: time to clinical improvement up to day 28

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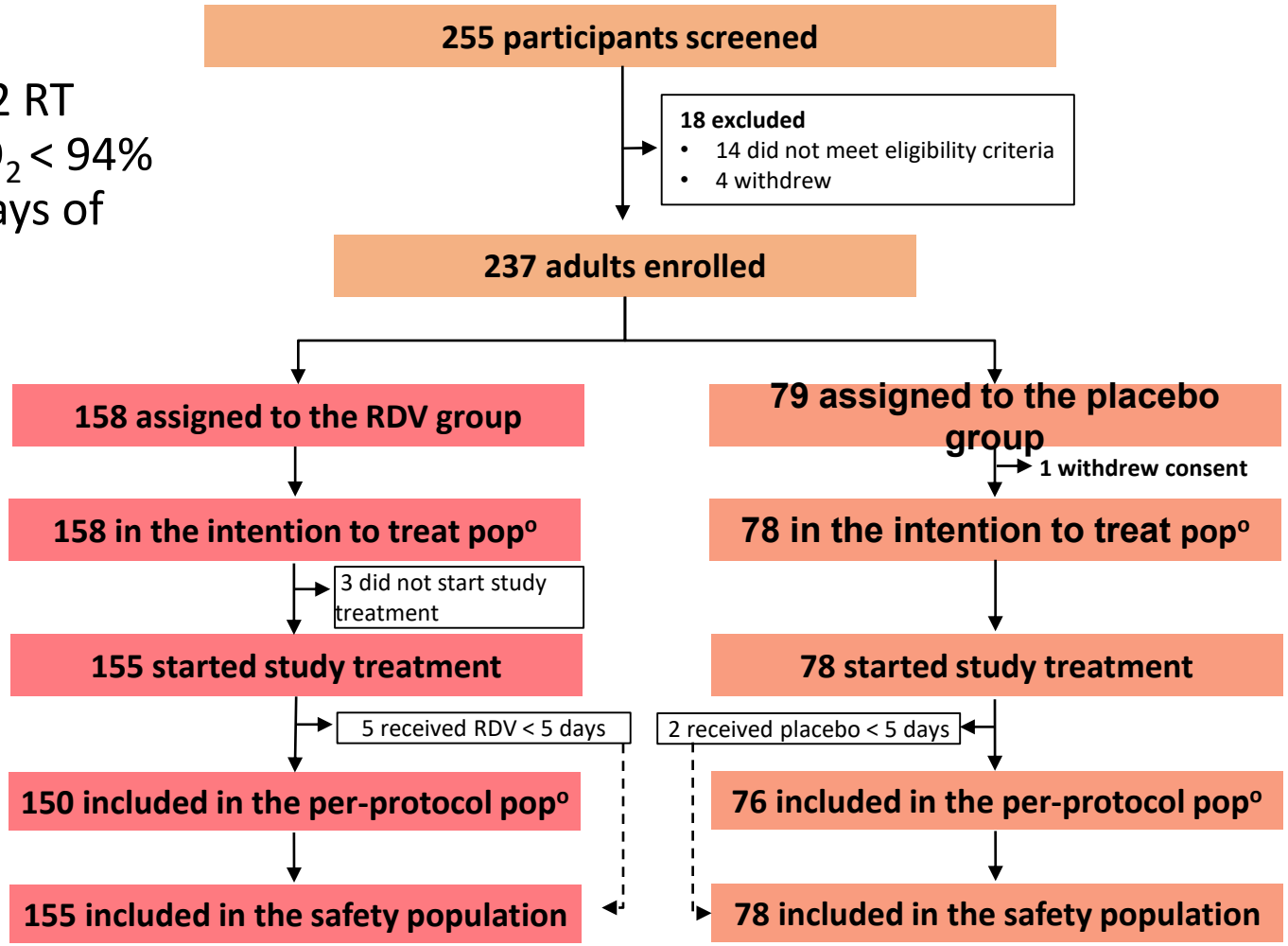
Anti viral effect

# Remdesivir (RDV)

- 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

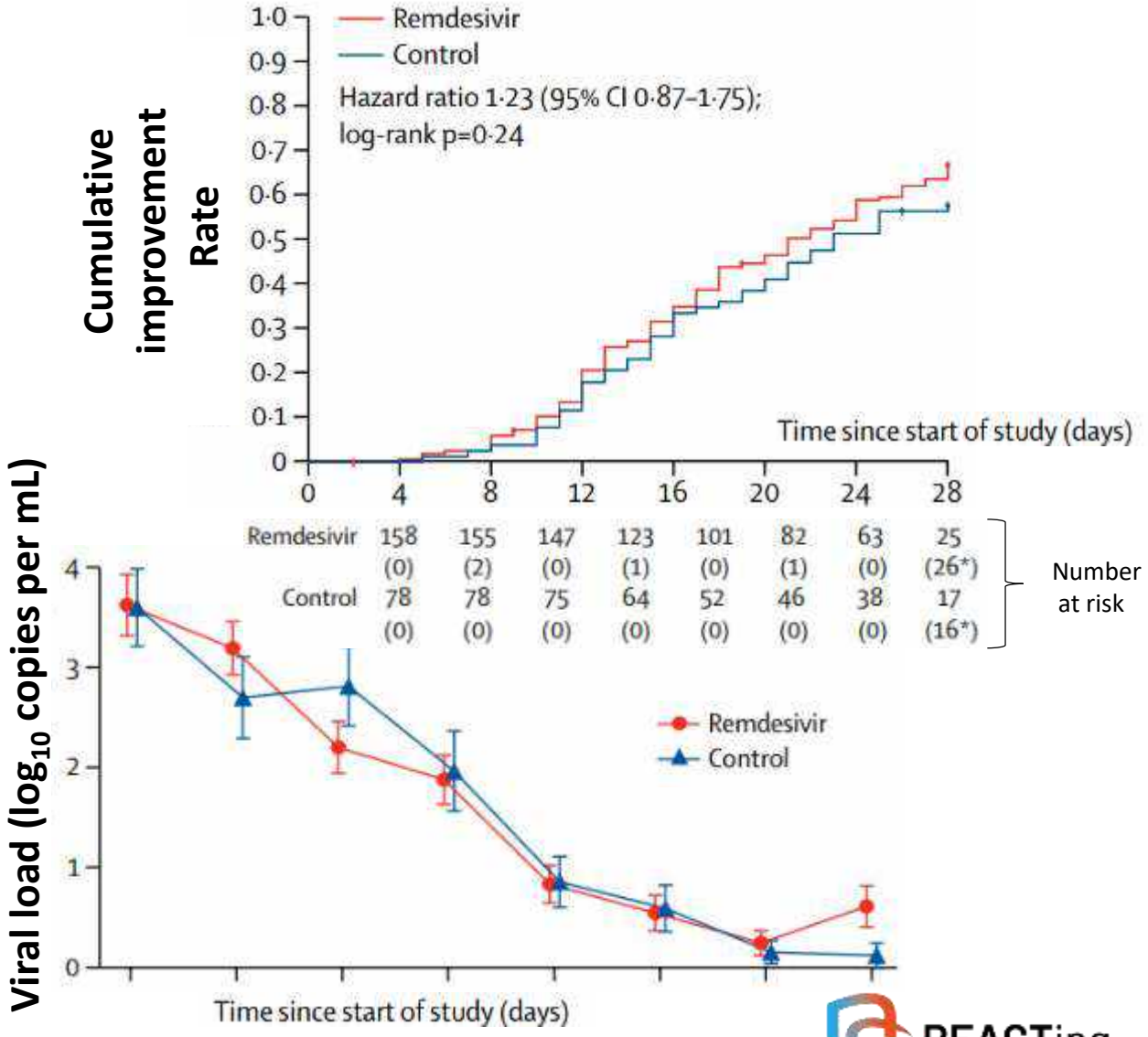
# Remdesivir (RDV)

| 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)

- **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)

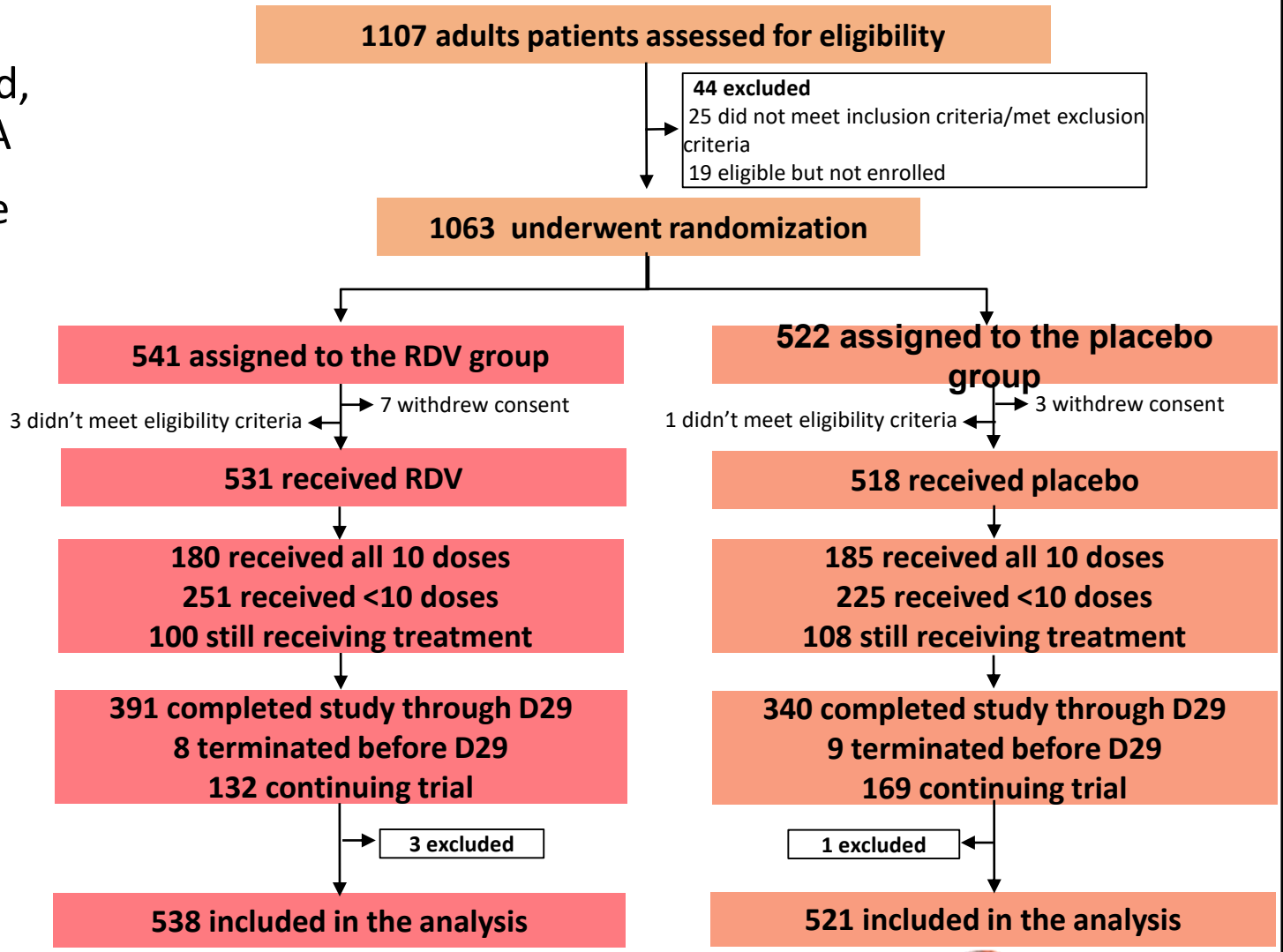



Wang Y *et al*. *Lancet.* Apr 2020

Anti viral effect

# Remdesivir (RDV)

- 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
- 1063 patients underwent randomization; 538 **RDV** group, 521 **placebo** group (1:1)

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Anti viral effect

# Remdesivir (RDV)

| Characteristics | All (N=1063) | RDV (N=541) | Placebo (N=522) |
|---|---|---|---|
| Age, mean (SD) - yo | 58,9 (15) | 58,6 (14,6) | 59,2 (15,4) |
| Male sex – no (%) | 684 (64,3) | 352 (65,1) | 332 (63,6) |
| **Co existing conditions** | | | |
| Type 2 Diabetes – no (%) | 275/927 (29,7) | 144/470 (30,6) | 131/457 (28,7) |
| Hypertension – no (%) | 460/928 (49,6) | 231/469 (49,3) | 229/459 (49,9) |
| Obesity – no (%) | 342/925 (37) | 177/469 (37,7) | 165/456 (36,2) |
| **Score** on ordinal scale | | | |
| 4. Hospitalized, not requiring supplemental $O_2$, requiring ongoing medical care – no (%) | 127 (11,9) | 67 (12,4) | 60 (11,5) |
| 5. Hospitalized, requiring supplemental $O_2$ – no (%) | 421 (39,6) | 222 (41) | 199 (38,1) |
| 6. Hospitalized, receiving noninvasive ventilation or high flow $O_2$ device – no (%) | 197 (18,5) | 98 (18,1) | 99 (19) |
| 7. Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%) | 272 (25,6) | 125 (23,1) | 147 (28,2) |

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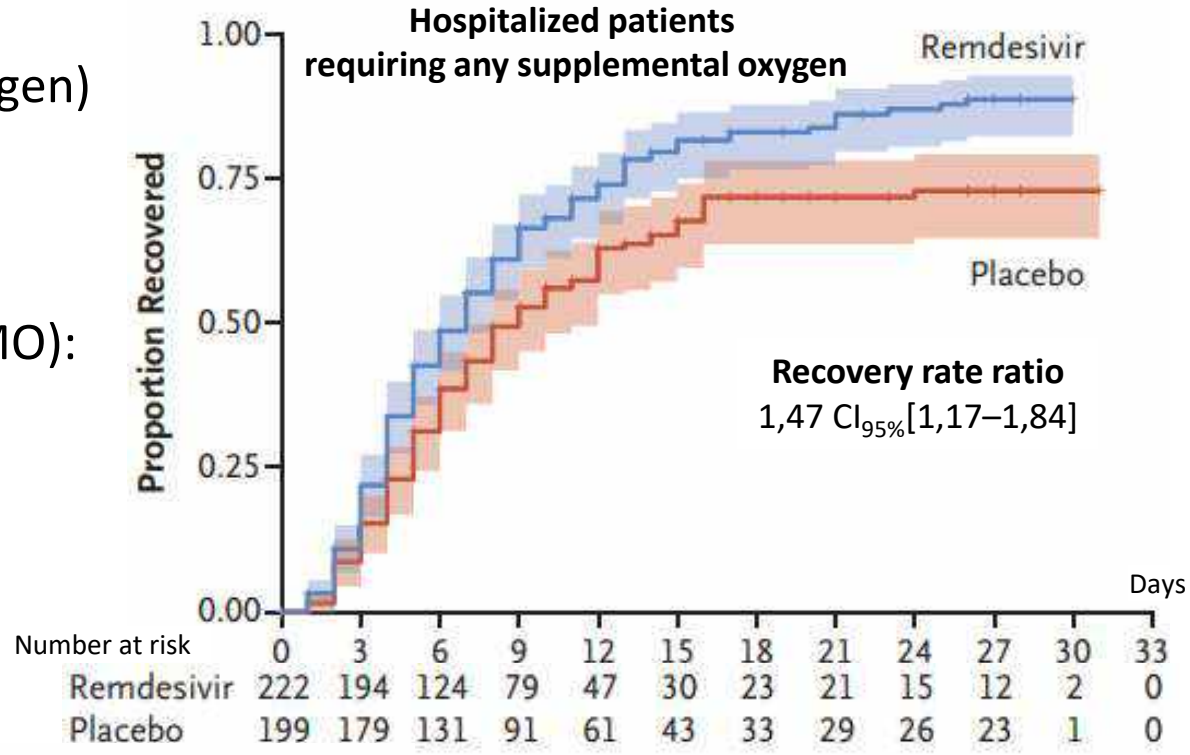
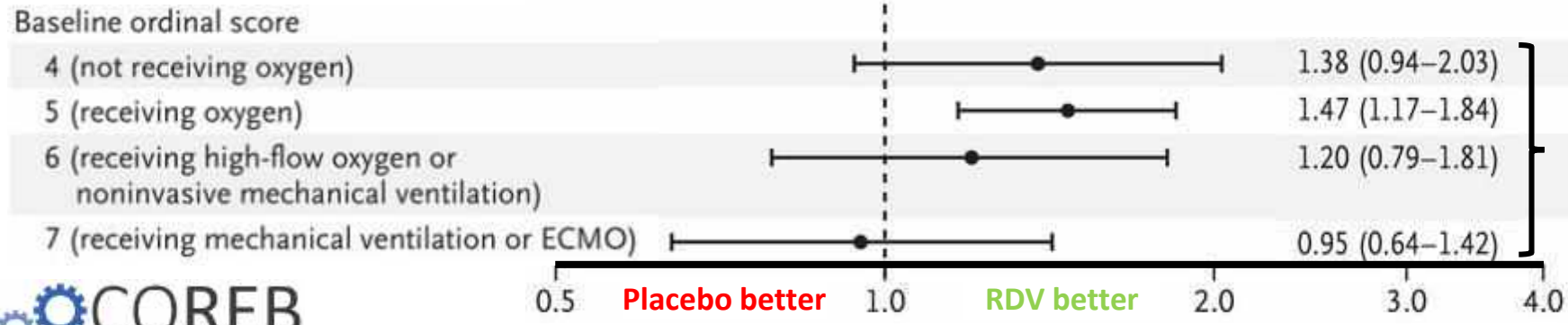
Anti viral effect

# Remdesivir (RDV)

- RDV group (hospitalized, requiring any supplemental oxygen) recovery rate ratio 1,47 $CI_{95\%}$[1,17-1,84]
- RDV group (hospitalized, not requiring supplemental $O_2$, requiring non invasive ventilation or use of high-flow $O_2$ devices, receiving invasive mechanical ventilation or ECMO): **no significant difference**
- Adverse events: 114 (21%) RDV *vs*. 141 (27%) placebo
- **Limits:** primary outcome changed during the study, preliminary results, uncompleted follow up

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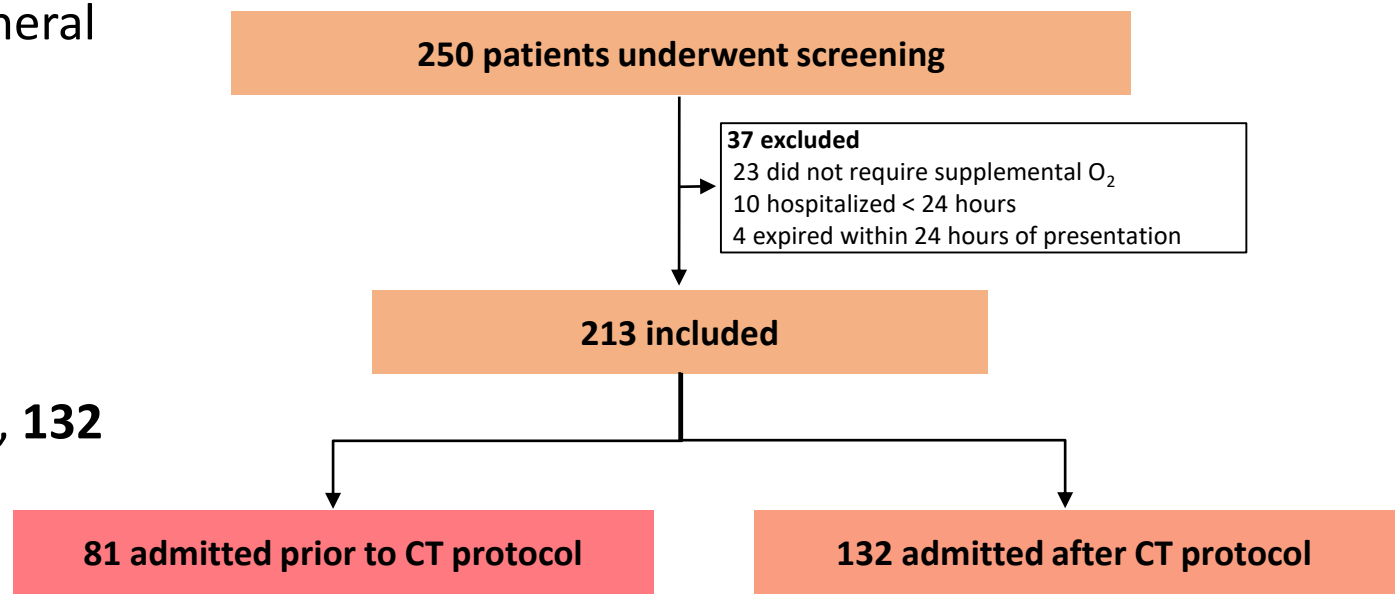
Immunomodulatory effect

# Corticosteroids (CT)

- Multi-center, quasi-experimental, academic study, USA
- **Inclusion criteria** : age ≥ 18yo, positive RT PCR SARS-CoV-2, radiographic bilateral pulmonary infiltrates, $O_2$ required (nasal cannula or high-flow nasal cannula (moderate COVID), mechanical ventilation (severe COVID))
- **Exclusion criteria**: subject transferred from an out-of-system hospital, or died within 24 hours of presentation to the ED, or admitted for less than 24 hours.
- **Primary outcome**: escalation to ICU from a general medical unit, progression to respiratory failure requiring mechanical ventilation after hospital admission, or in-hospital all-cause mortality
- **Secondary outcome**: one of them; length of hospital stay (LOS)
- 213 included participants; **81** (38%) **SoC group**, **132** (62%) **early corticosteroid group** (methylprednisolone)



Immunomodulatory effect

# Corticosteroids (CT)

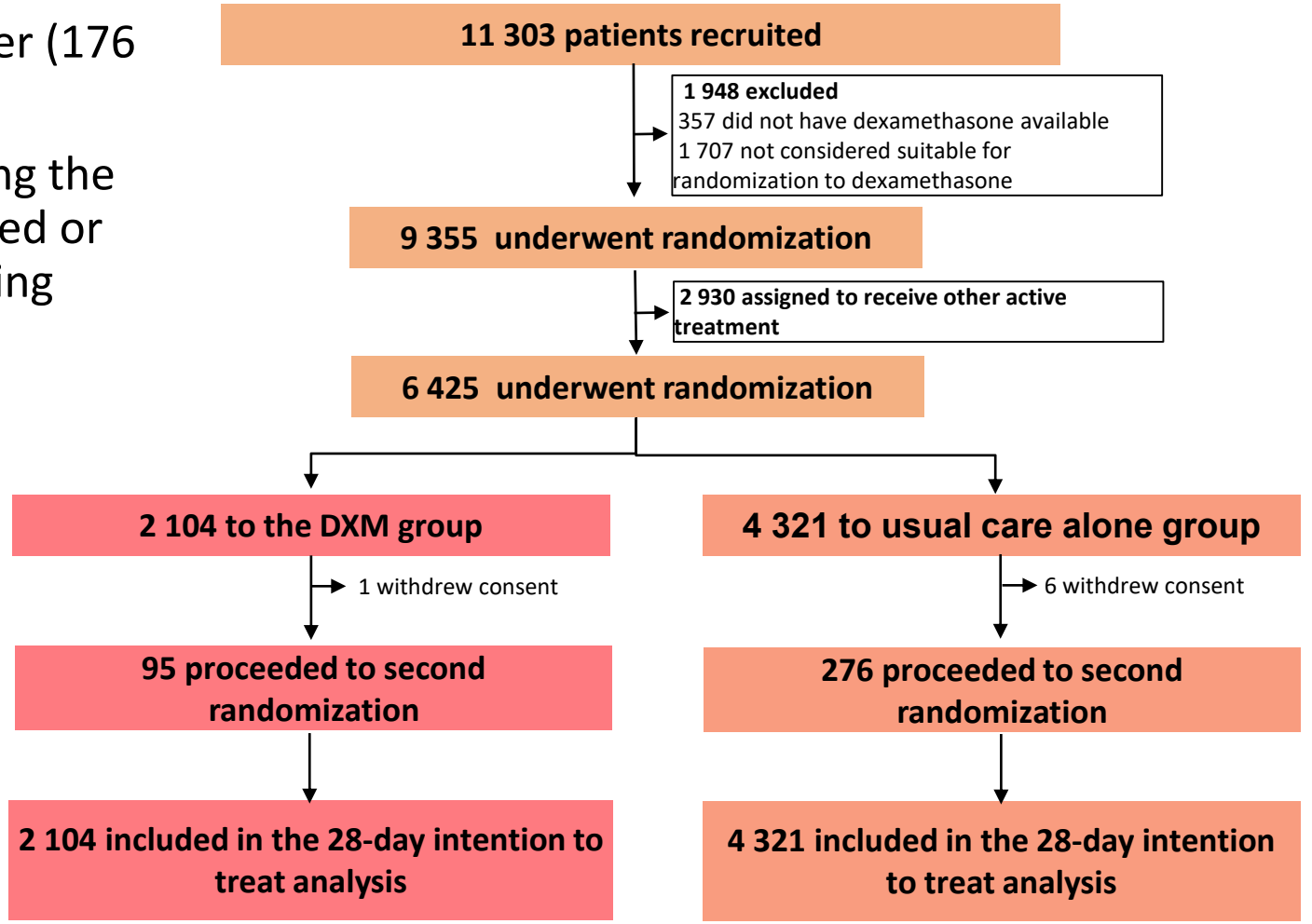
- **Escalation to ICU from a general medical unit**: SoC group 31 (44,3%) *vs.* CT group 32 (27,3%) OR: 0,47 $CI_{95\%}$[0,25-0,88], p= 0,017
- **Respiratory failure requiring mechanical ventilation**: SoC group 26 (36,6%) *vs.* CT group 26 (21,7%) OR: 0,47 $CI_{95\%}$[0,25-0,92], p= 0,025
- **In-hospital all-cause mortality**: SoC group 21 (26,3%) *vs.* CT group 18 (13,6%) OR: 0,45 $CI_{95\%}$[0,22-0,91], p= 0,024
- **Median hospital length of stay:** SoC group: 8 days IQR(5-14) *vs.* CT group 7 days IQR(3-7); p < 0,001
- **Limits**: pragmatic quasi-experimental design was used and there are some differences in the baseline

| Characteristics | Total (n=213) | SoC (n=81) | Early CT (n=132) |
|---|---|---|---|
| Age, median (IQR) - yr | 62 (51-62) | 64 (51,5-73,5) | 61 (51-72) |
| Male sex – no (%) | 109 (51,2) | 41 (50,6) | 68 (51,5) |
| Median BMI (IQR) – $kg/m^2$ | 32 (27,3-38,7) | 30 (25-39) | 33,2 (28,9-38,5) |
| **Co existing conditions** | | | |
| Diabetes – no (%) | 105 (49,3) | 37 (45,7) | 68 (51,5) |
| Hypertension – no (%) | 158 (74,2) | 62 (76,5) | 96 (72,7) |

Immunomodulatory effect

# Corticosteroids (CT)

- 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, 2104 DXM group** (2:1)




DXM: dexamethasone

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Immunomodulatory effect

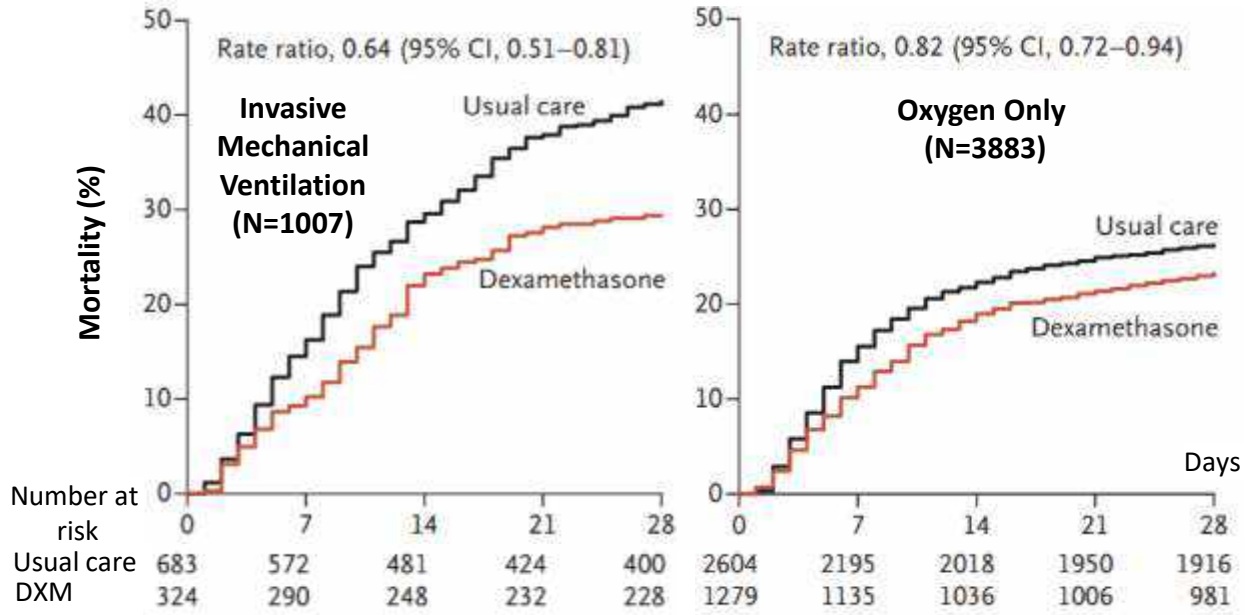
# Corticosteroids (CT)

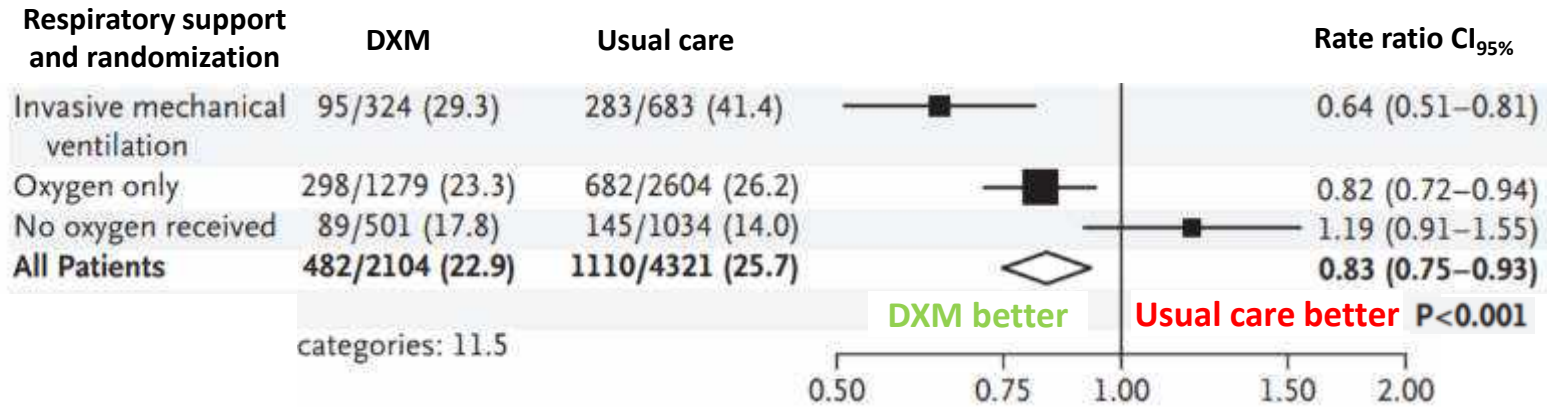
| | Treatment assignment | |
|---|---|---|
| **Characteristics** | **DXM (N=2104)** | **Usual care (N=4321)** |
| Age ≥ 70 yr – no (%) | 963 (45) | 1817 (42) |
| Female sex – no (%) | 766 (36) | 1572 (36) |
| **Coexisting conditions** | | |
| Diabetes – no (%) | 521 (25) | 1025 (24) |
| Heart disease – 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)

- **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]
- **Limits:** Preliminary report, patients without confirmed SARS-CoV-2 positive PCR included, age of inclusion changed during the study, absence of viral load follow-up

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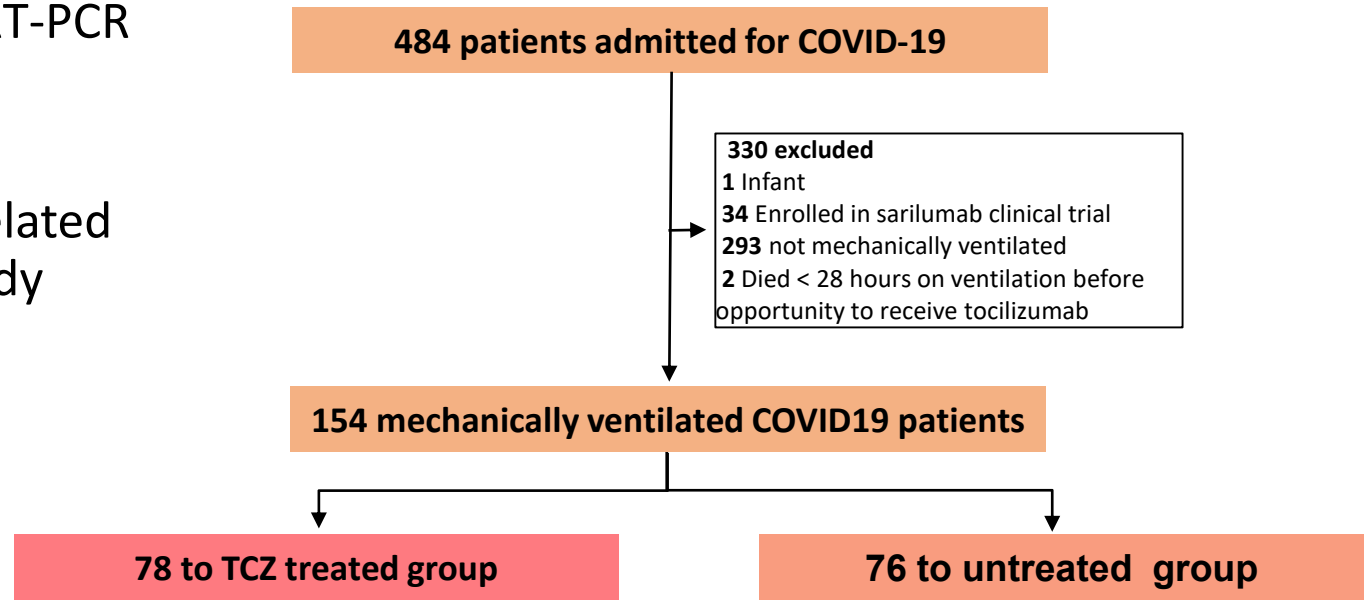
Immunomodulatory effect

# Tocilizumab (TCZ)

- 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

# Tocilizumab (TCZ)

| 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 |

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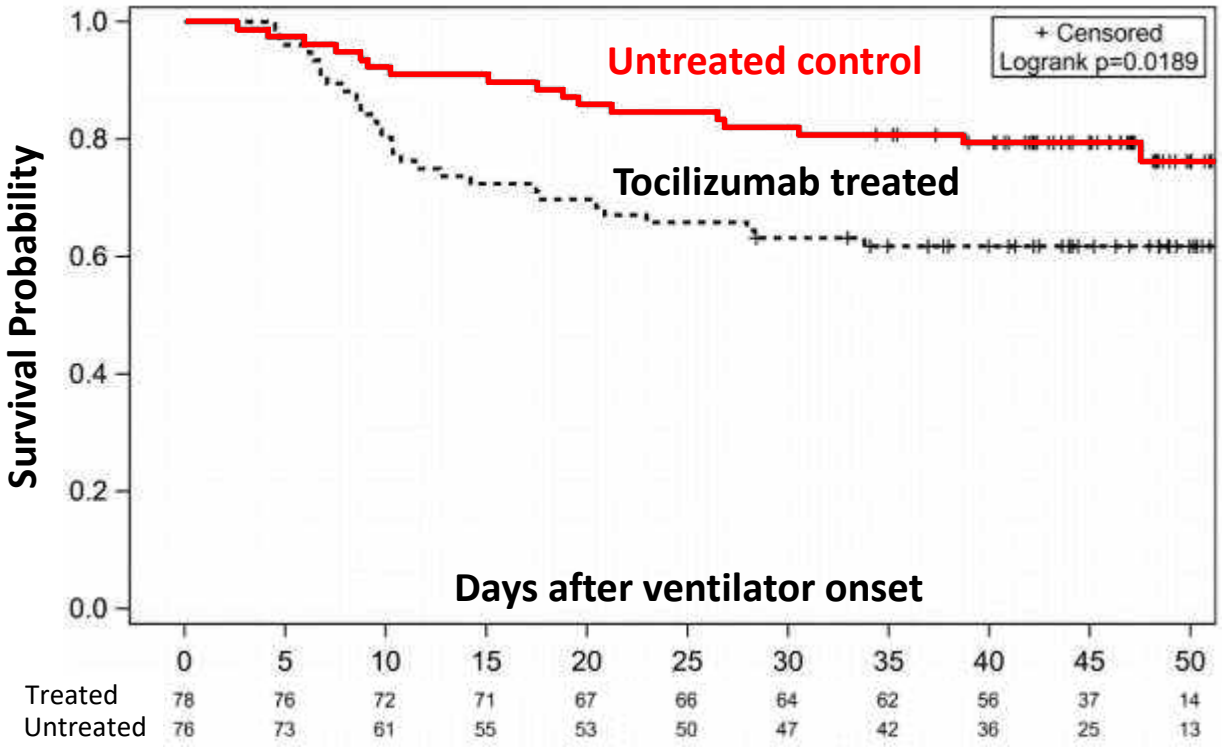
Immunomodulatory effect

# Tocilizumab (TCZ)

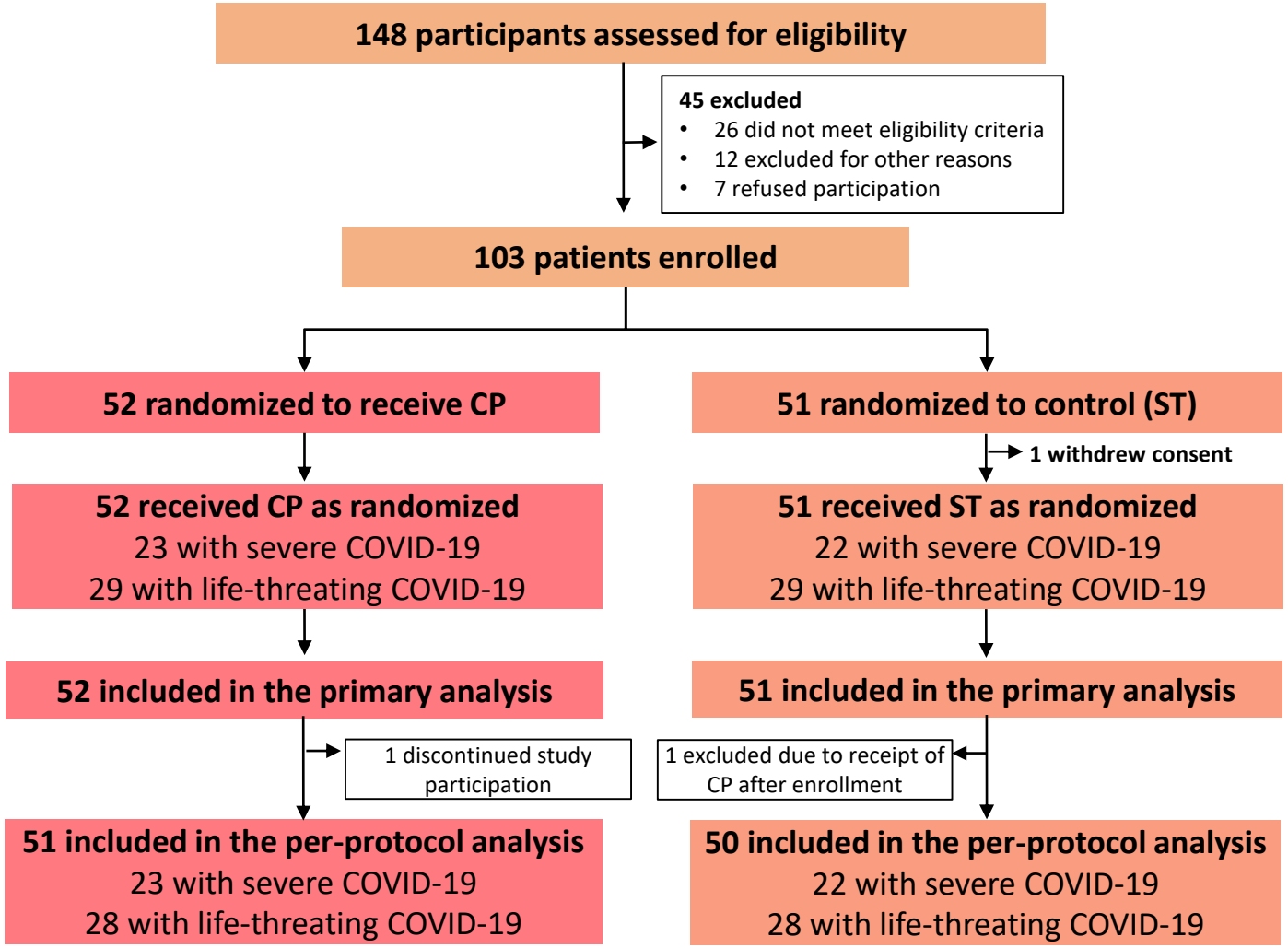
- **Survival probability after intubation**: higher among TCZ group *vs.* untreated group; hazard ratio 0,50 $CI_{95\%}$ [0,27-0,90]
- **Superinfections**: 42/78 (54%) TCZ group *vs.* 20/76 (26%) untreated group, p < 0,001
- **Patients with pneumonia**: 35/78 (45%) TCZ group *vs.* 15/76 (20%) untreated group, p < 0,001
- **Patients discharged alive (study period)**: 44/78 (56%) TCZ group *vs. 3*0/76 (40%) untreated group, p = 0,04
- **Limits:** not a randomized controlled trial, laboratories data were missing, no definition of severe cases nor super infections, only interested in patients mechanically ventilated



Passive immunity

# Convalescent plasma (CP)

- 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)

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Passive immunity

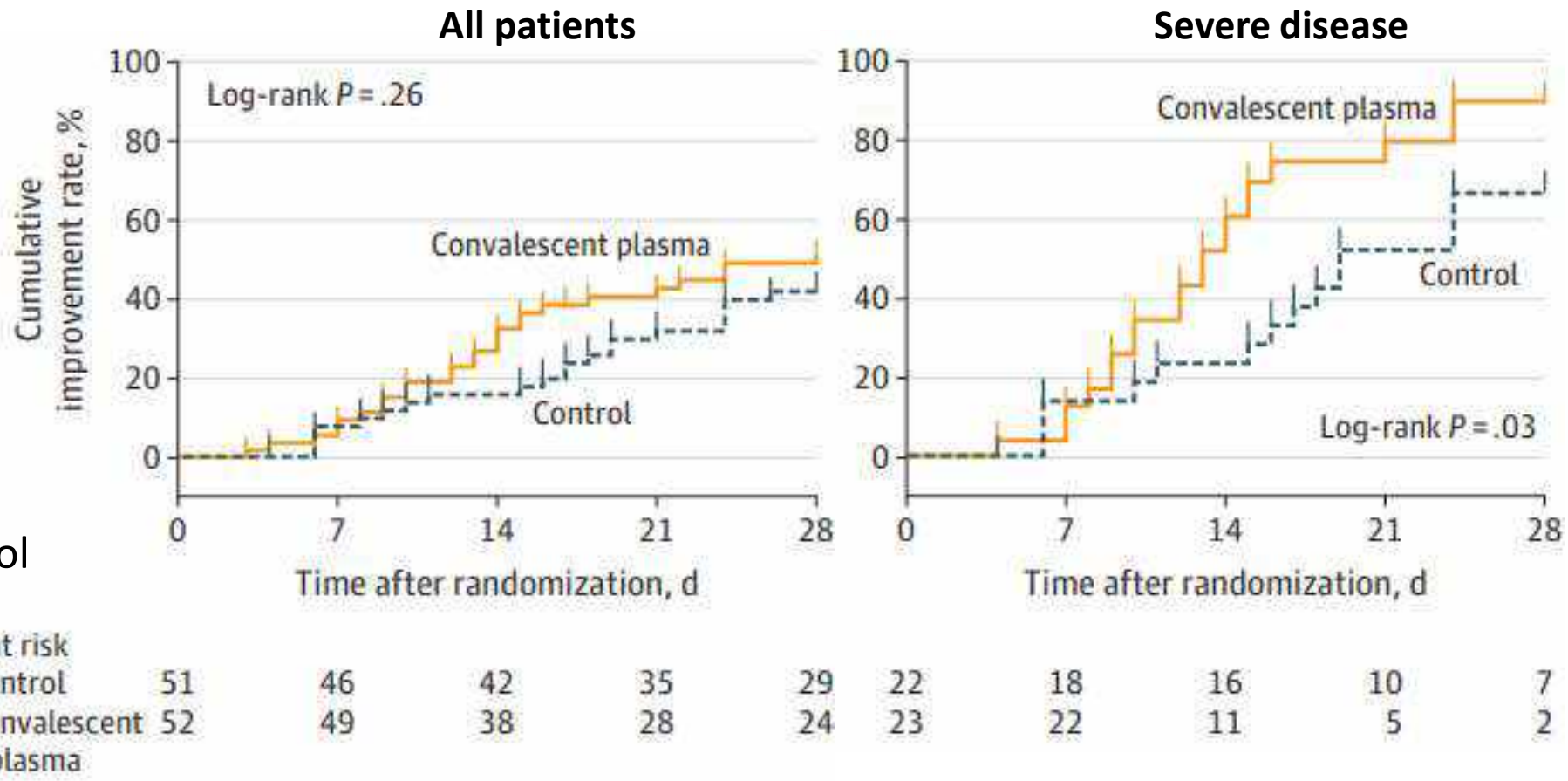
# Convalescent plasma (CP)

| 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)

- **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

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Passive immunity

# Convalescent plasma (CP)

- 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) |

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ST: standard treatment - CPP: COVID-19 convalescent plasma

Joyner M *et al. J Clin Invest* Jun 2020

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Passive immunity

# Convalescent plasma (CP)

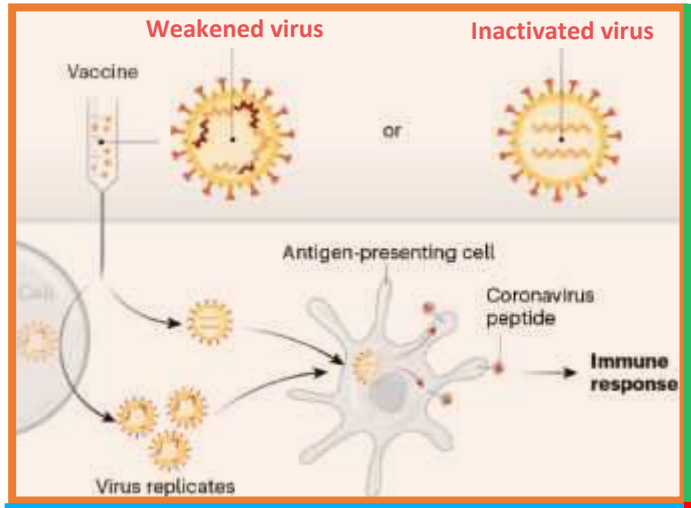
- **Incidence** of serious adverse events (SAEs) in the first four hours after transfusion: < 1% (n=36)
- **Related** SAEs: 3 severe allergic transfusion reactions, 4 deaths, 18 TACO&TRALI (2 definitely related to CP)
- **Seven-day mortality rate**: 14.9%

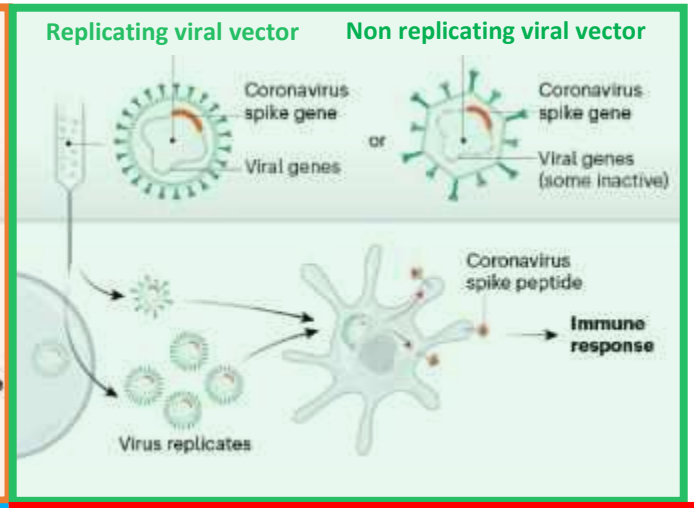
| Serious Adverse Evens (SAEs) Characteristics | Reported (n=36) | Related (n'=25) | Estimate ($_{95\%}$CI) |
|---|---|---|---|
| **Four hour reports** | | | |
| Mortality | 15 | 4 | 0,08% (0,03-0,21) |
| Transfusion-Associated Circulatory Overload (TACO) | 7 | 7 | 0,14% (0,07-0,29) |
| Transfusion-Related 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 ($_{95\%}$CI)** |
| Mortality | 602 | | 14,9% (13,8-16,0) |

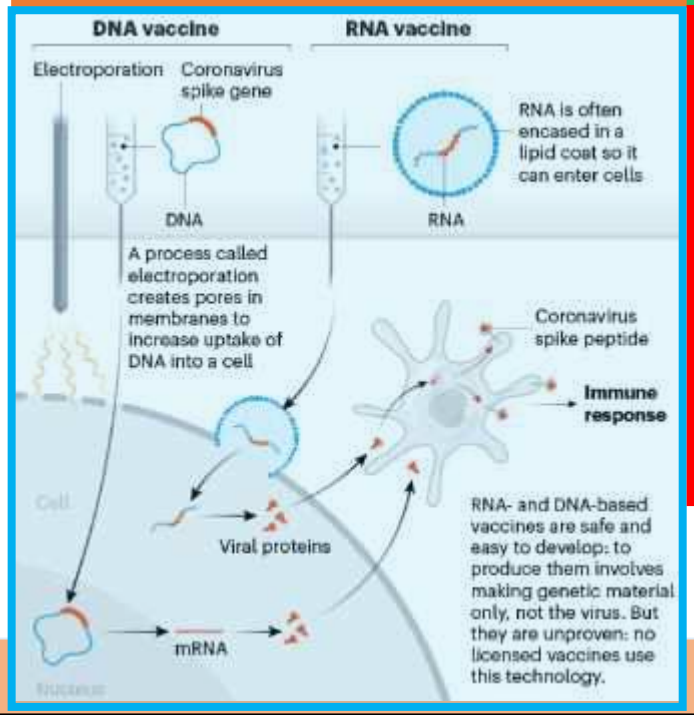
- **<u>Limits:</u>** lack of detailed training of study personnel and monitoring, criteria specific to hospitalized patients

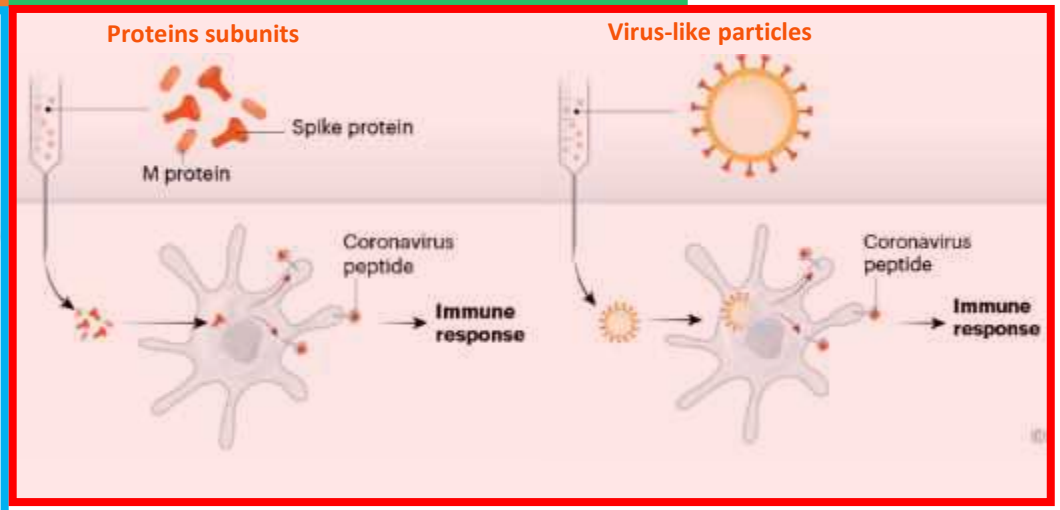
# Vaccine

- **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)



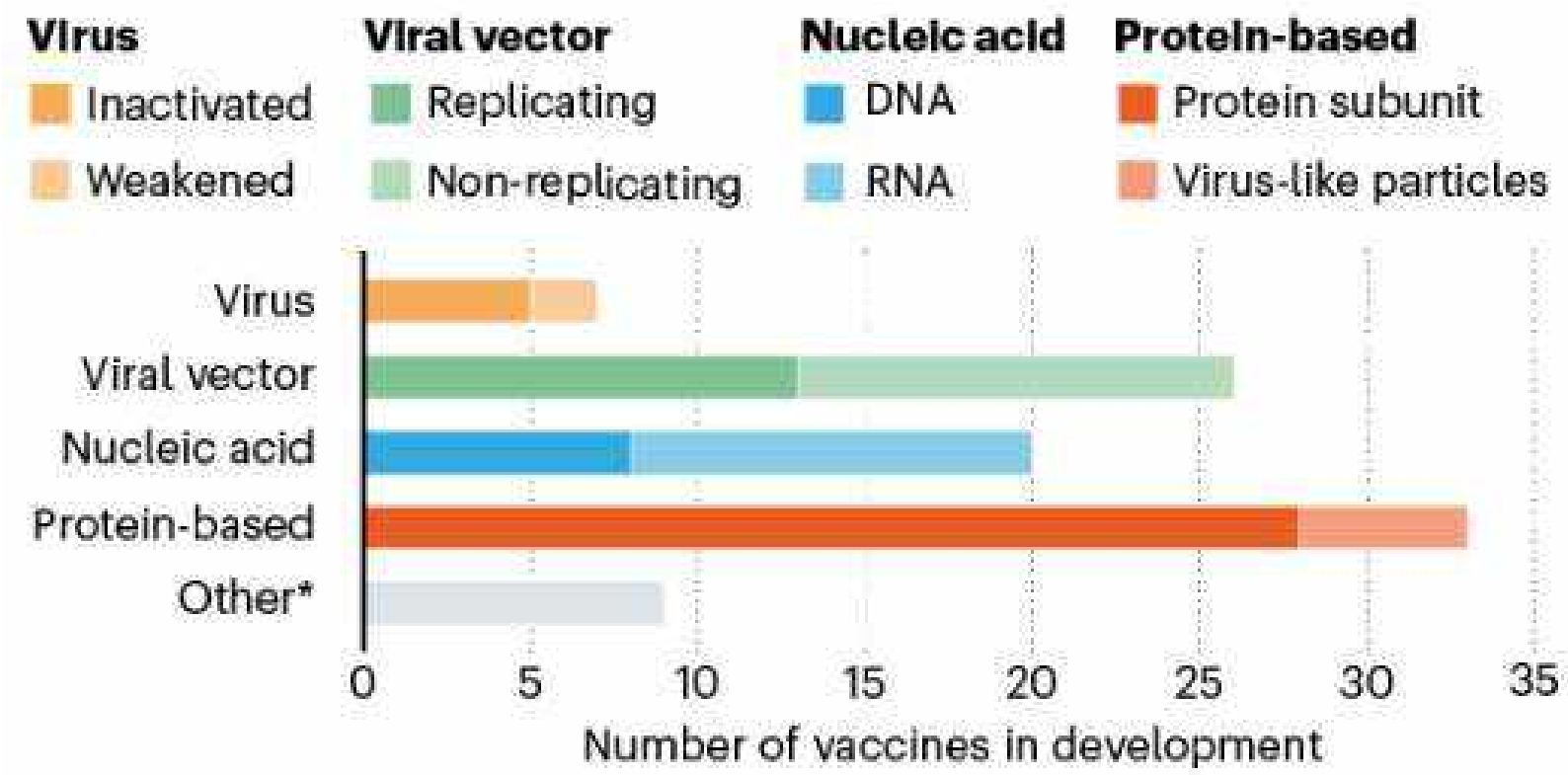




Callaway E *Nature.* Apr 2020

# Vaccine

- **R&D landscape**: WHO lists more than 139 candidates in preclinical development, 26 candidate vaccines in clinical evaluation (July 31st); update available at :

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




Thanh Le T *et al. Nat Rev Drug Discov*. May 2020

# Vaccine

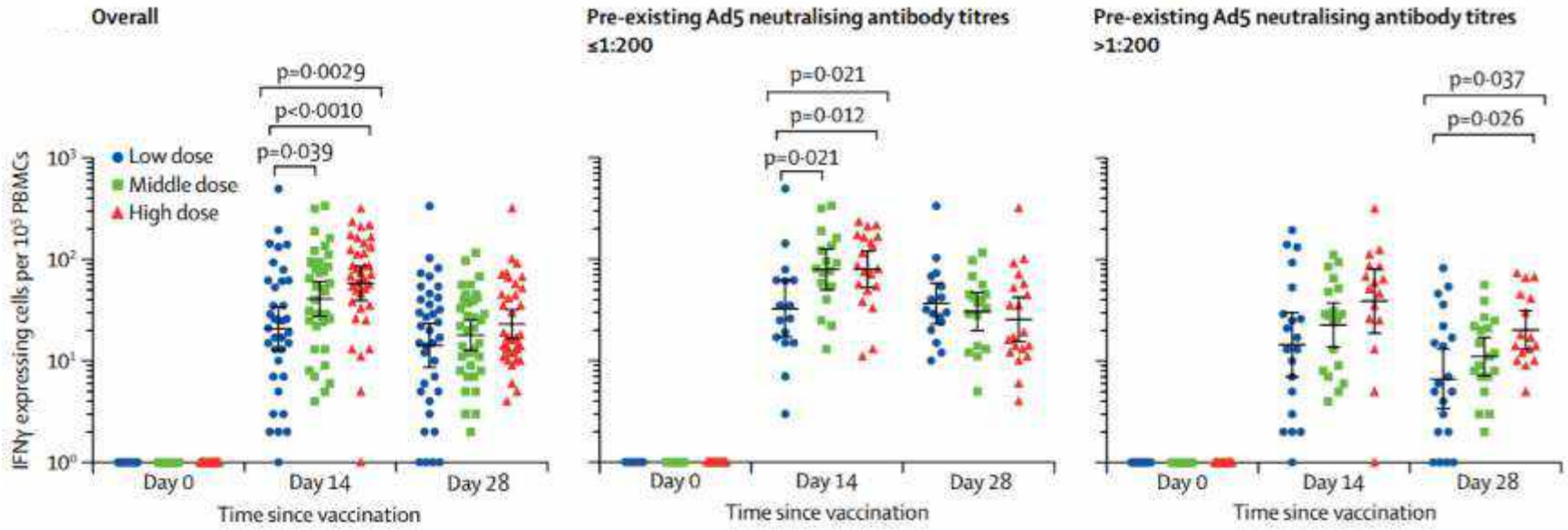
- Adenovirus type 5 vectored COVID-19 vaccine (Ad5-nCoV)
- Dose-escalation, single-center, open-label, non-randomized, **phase 1**, academic and industrial study, China
- **Inclusion criteria:** healthy adults aged between 18 and 60 years**,** negative results of serum specific IgM and IgG SARS-CoV-2 antibodies
- **Primary outcome**: adverse events in the 7 days post-vaccination
- 195 eligible individuals; 108 enrolled: low dose group (36), middle dose group (36), high dose group (36)

| | Low dose group (n=36) | Middle dose group (n=36) | High dose group (n=36) | Total (N=108) |
|---|---|---|---|---|
| **All adverse reactions within 0–7 days** | | | | |
| Any | 30 (83%) | 30 (83%) | 27 (75%) | 87 (81%) |
| Grade 3 | 2 (6%) | 2 (6%) | 6 (17%) | 10 (9%) |
| **Injection site adverse reactions within 0–7 days** | | | | |
| Pain | 17 (47%) | 20 (56%) | 21 (58%) | 58 (54%) |
| Induration | 2 (6%) | 1 (3%) | 1 (3%) | 4 (4%) |
| Redness | 2 (6%) | 1 (3%) | 1 (3%) | 4 (4%) |
| Swelling | 4 (11%) | 4 (11%) | 0 | 8 (7%) |
| Itch | 2 (6%) | 3 (8%) | 0 | 5 (5%) |
| Muscular weakness | 0 | 0 | 1 (3%) | 1 (1%) |
| **Systemic adverse reactions within 0–7 days** | | | | |
| Fever | 15 (42%) | 15 (42%) | 20 (56%) | 50 (46%) |
| Grade 3 fever | 2 (6%) | 2 (6%) | 5 (14%) | 9 (8%) |
| Headache | 14 (39%) | 11 (31%) | 17 (47%) | 42 (39%) |
| Fatigue | 17 (47%) | 14 (39%) | 16 (44%) | 47 (44%) |
| Grade 3 fatigue | 0 | 0 | 2 (6%) | 2 (2%) |
| Vomiting | 1 (3%) | 0 | 1 (3%) | 2 (2%) |
| Diarrhoea | 3 (8%) | 4 (11%) | 5 (14%) | 12 (11%) |
| Muscle pain | 7 (19%) | 3 (8%) | 8 (22%) | 18 (17%) |

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

# Vaccine

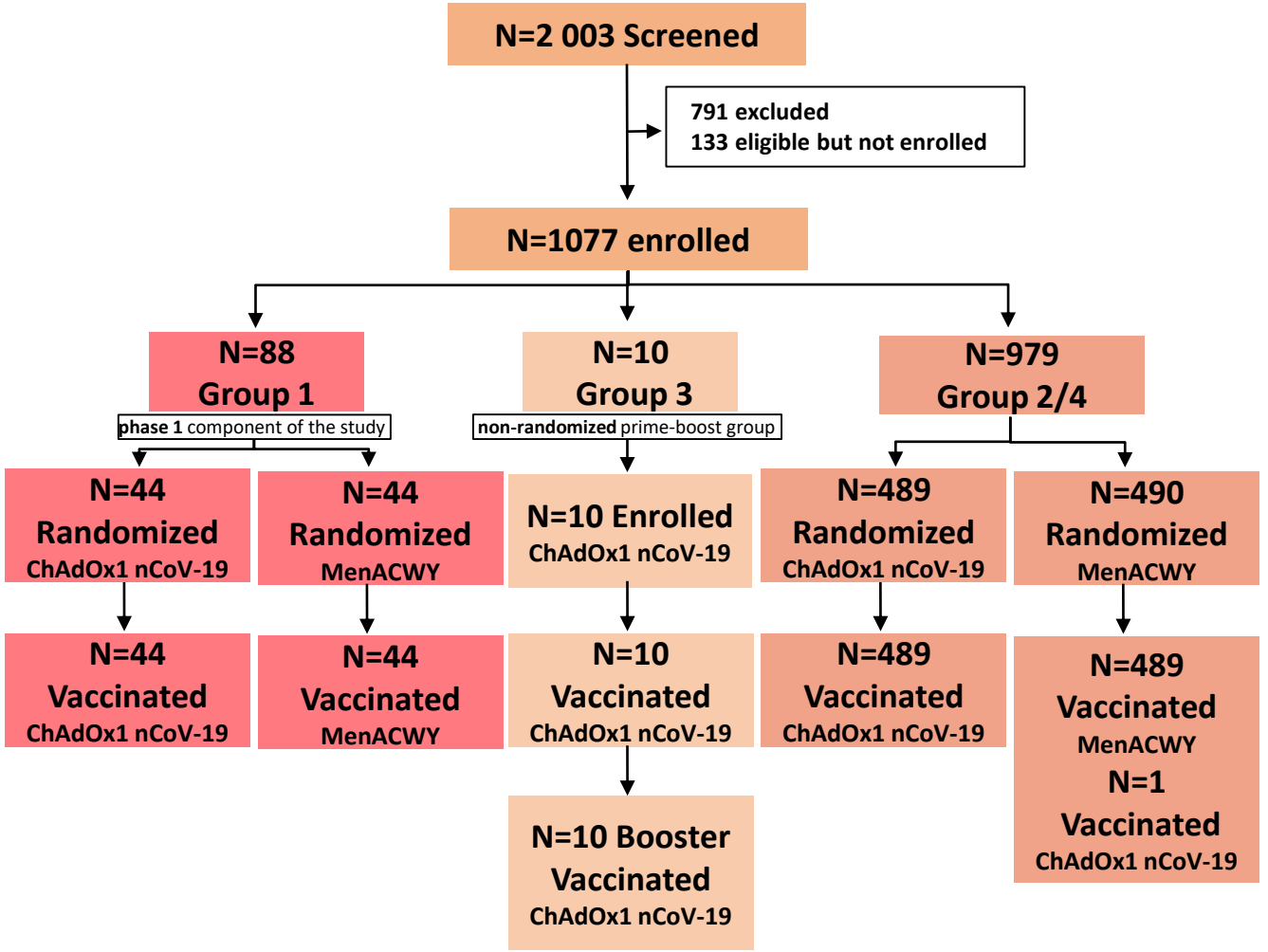
- **Adverse events in the 7 days post-vaccination** : 87/108 (81%) participants reported at least one adverse reaction (pain, fever, fatigue, headache). No significant difference in the overall across the 3 treatment groups
- Strength: first-inhuman clinical trial of a novel Ad5 vectored COVID-19 Vaccine, measured the neutralizing antibody responses induced by vaccination
- **Limits:** phase 1 trial, open label, mono center, not randomized, small size of population study, short duration of follow-up, no measure of vaccine efficacy, self reported side effects, ADE risk not assessed




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

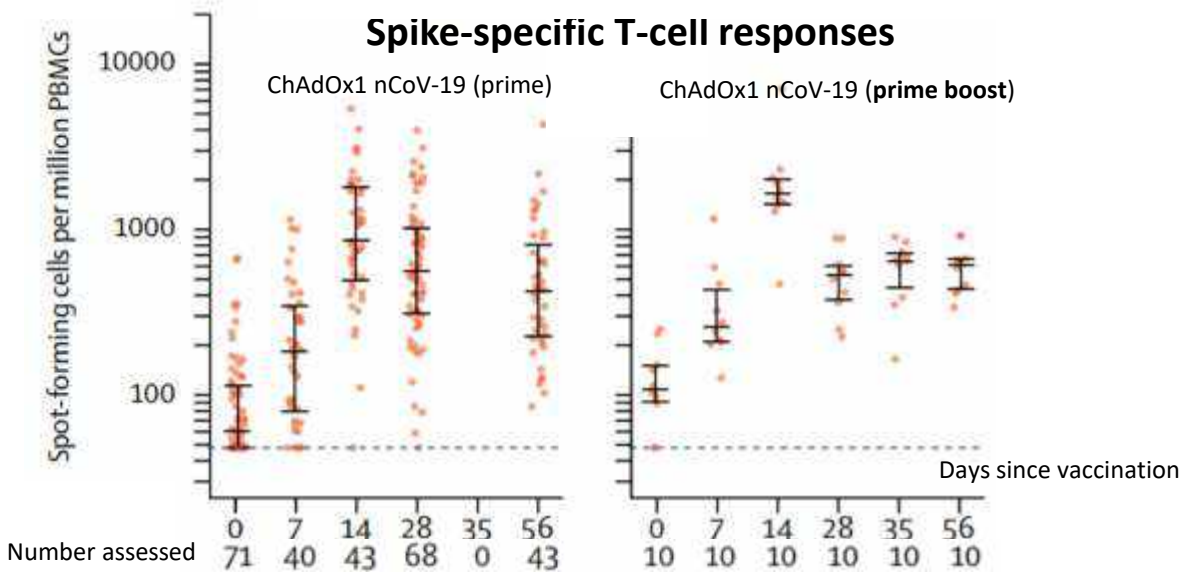
# Vaccine

- Phase **1/2**, participant-blinded, multicenter, randomized controlled, academic study, UK
- **Inclusion criteria:** healthy adult, aged 18–55 years
- **Exclusion criteria:** history of laboratory confirmed SARS-CoV-2 infection, higher risk for SARS-CoV-2 exposure pre-enrolment; new onset of fever, cough, shortness of breath, and anosmia or ageusia since Feb 1, 2020
- **Main outcome** : safety of the vaccine; occurrence of serious adverse events
- **Other outcomes**: reactogenicity, ChAdOx1 nCoV-19 immunogenicity profiles, efficacy against hospital-attended COVID-19, death, seroconversion against non-spike proteins



# Vaccine

- **Safety of the vaccine**: no severe adverse events in ChAdOx1 nCoV-19 group, reactions (pain, feeling feverish, chills, muscle ache, headache malaise) more common in ChAdOx1 nCoV-19 group, reduced with paracetamol (prophylactic)
- **Reactogenicity**: ChAdOx1 nCoV-19 group, spike-specific T-cell responses peaked on day 14 (median 856, IQR [493–1802]




| Characteristics | ChAdOx1 N=543 | MenACWYN=534 |
|---|---|---|
| Age, median [IQR] - yr | 34 [28;43] | 36 [28;45] |
| Female sex – no (%) | 265 (49) | 271 (51) |
| BMI (kg/m²), median [IQR] | 24 [22;27] | 24 [22;27] |
| Non-smoker– no (%) | 495 (91) | 485 (91) |
| Non-drinker– no (%) | 89 (16) | 60 (11) |

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Folegatti *et al*. *Lancet*. Jul 2020

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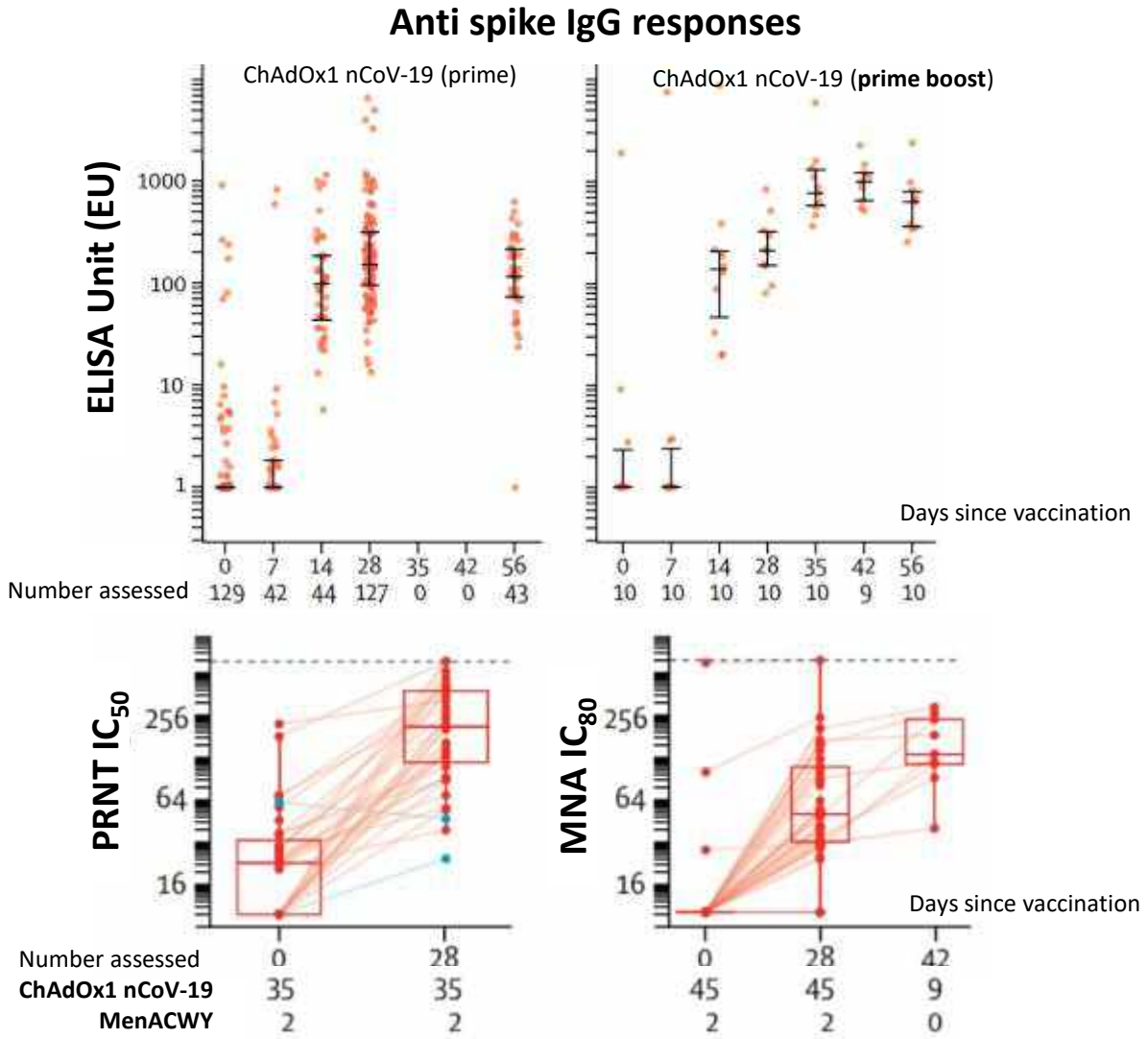
# Vaccine

- **ChAdOx1 nCoV-19 immunogenicity profiles:** Anti-spike IgG responses rose by day 28 (median 157 EU, [96–317], boosted after a 2nd dose (639 EU, 360–792)
- **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
- **Limitations:** short follow-up reported, small number of participants in the prime-boost group, single-blinded design




MNA: microneutralisation assay - PRNT: plaque reduction neutralisation test

Folegatti *et al*. *Lancet*. Jul 2020

# THERAPEUTIC

- **What are the main drugs under study?**
  - Antiviral effect: (Hydroxy)chloroquine, Lopinavir/ritonavir, Remdesivir
  - Immunomodulatory effect: Corticosteroids, Monoclonal antibodies (interleukin receptors antagonist)
  - Passive immunity: Convalescent plasma
- **Does exist drugs EMA or FDA approved for COVID-19 treatment?**
  - Remdesivir has been authorized for marketing authorization in the European Union under the invented name Veklury (July 3rd)
  - Remdesivir received from the FDA an emergency use authorization for the treatment of hospitalized COVID-19 patients with severe disease
- **What are the types of vaccines in clinical evaluation**
  - 26 candidates vaccines are in clinical evaluation
  - Using one of these eight technologies: virus (inactivated, weakened), viral vector (replicating, non replicating), nucleic acid (DNA, RNA), protein based (protein subunit, virus like particles

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