Scientific update on COVID-19

Updated on October 13th 2020


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

- EPIDEMIOLOGY
- VIROLOGY
- CLINICAL
- THERAPEUTIC

Color code

EPIDEMIOLOGY  VIROLOGY  CLINICAL  THERAPEUTIC
EPIDEMIOLOGY

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


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

Day, month and year of reporting
Epidemiology

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

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

- He and colleagues estimation (slide 35): 44% (CI$_{95\%}$ [30 – 57%]) of secondary cases were infected during the index cases’ presymptomatic stage
  Infectiousness was estimated to decline quickly within 7 days
Epidemiology

At beginning & before controls measures:

• Basic reproduction number ($R_0$): 2.2 to 6.4
• $R_0$ depends on
  o Geographic location
  o Stage of outbreak
• $R_e$ depends on
  o Control measures
• Doubling time: 2.9 to 7.3 days

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


Estimated $R_e$ over time

Travel restrictions

Li Q et al. NEJM. Mar 2020
Epidemiology

• 185 cases of confirmed COVID-19 – before Feb 24th
• 24 countries – 89% had recent history of travel to Wuhan
• Median incubation period (days) : 5.1 [4.5 – 5.8]
  o < 2.5% of infected persons will show symptoms within 2,2 days
  o 97.5% of symptomatic patients developing symptoms within 11.5 days
• Analysis specific for cases detected outside of China
  o Median incubation (days): 5.5 [4.4 – 7.0]
  o 95% range spanning from 2.1 to 14.7 days

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


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

<table>
<thead>
<tr>
<th>Monitoring Duration</th>
<th>Mean Estimated Number of Undetected Symptomatic Infections per 10,000 Monitored Persons (99th Percentile)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low Risk (1 in 10,000)</td>
</tr>
<tr>
<td>7d</td>
<td>0.2 (0.4)</td>
</tr>
<tr>
<td>14d</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>21d</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>28d</td>
<td>0.0 (0.0)</td>
</tr>
</tbody>
</table>

High risk = A 1-in-100 chances of developing a symptomatic infection after exposure
Distanciation measures to prevent transmission

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

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

16 countries & 6 continents
25,697 patients in the meta-analysis
Included COVID-19, SARS & MERS
Did not identify any randomized trials

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

<table>
<thead>
<tr>
<th>Physical distance</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effect (95% CI)</th>
<th>Difference</th>
<th>Certainty*</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 m vs &lt;1 m</td>
<td>aOR 0.18 (0.09 to 0.38) (95% CI 0.20 to 0.44)</td>
<td>Shorter distance, 12.8%</td>
<td>Further distance, 2.6% (1.3 to 5.3)</td>
<td>-10.2% (-11.5 to -7.5)</td>
</tr>
</tbody>
</table>

Face mask vs no face mask

<table>
<thead>
<tr>
<th>Face mask</th>
<th>No face mask</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effect (95% CI)</th>
<th>Difference</th>
<th>Certainty*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face mask</td>
<td>17.4%</td>
<td>aOR 0.15 (0.07 to 0.34) (95% CI 0.26 to 0.45)</td>
<td>No face mask, 3.1% (1.5 to 6.7)</td>
<td>-14.3% (-15.9 to -10.7)</td>
<td>Low</td>
</tr>
</tbody>
</table>

Eye protection (faceshield, goggles) vs no eye protection

<table>
<thead>
<tr>
<th>Eye protection</th>
<th>No eye protection</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effect (95% CI)</th>
<th>Difference</th>
<th>Certainty*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye protection</td>
<td>16.0%</td>
<td>Unadjusted RR 0.34 (0.22 to 0.52)</td>
<td>No eye protection, 5.5% (3.6 to 8.5)</td>
<td>-10.6% (-12.5 to -7.7)</td>
<td>Low</td>
</tr>
</tbody>
</table>

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

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

None of these interventions afforded complete protection from infection

Face masks’ effectiveness

• 246 participants
  o 122 without face masks and 124 with face masks
  o Provided exhaled breath samples

• 123 were infected by
  o HCoV (17), influenza (43) and rhinovirus (54)

• Test viral shedding
  o Nasal swab, throat swab
  o Respiratory droplet sample
  o Aerosol sample

• Detection of coronavirus
  o 30% (droplets) and 40% (aerosol) without mask
  o 0 %(droplet or aerosol) with mask

→ Aerosol transmission is possible
→ Face masks reduce coronavirus detection in aerosol (significantly) and respiratory droplet

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

Limits
• Human coronavirus, not SARS-CoV-2
• Large proportion of undetectable viral shedding
• Detected Coronavirus' infectivity not confirmed
Projection - Transmission dynamics

Model of SARS-CoV-2 transmission
Projected that recurrent wintertime outbreaks will probably occur after the initial outbreak
Used estimates of seasonality, immunity and cross-immunity for beta coronaviruses (OC43 & HKU1)
Post-pandemic transmission dynamics will depend on:
  o Degree of season variation in transmission
  o Duration of immunity
  o Degree of cross-immunity between SARS-CoV-2 and other coronaviruses
  o Intensity and timing of control measures

Presentation of different scenarios

Invasion scenario for SARS-CoV-2 in temperate regions

A: Short duration of immunity → annual outbreak
B: Long-term immunity → elimination of the virus

Kissler SM et al. Science. Apr 2020
Projection - Transmission dynamics

Invasion scenario for SARS-CoV-2 in temperate regions

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

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

Total incidence of COVID-19 illness over next years will depend on
• Regular circulation after the initial pandemic wave
• Duration of immunity that SARS-CoV-2 infection imparts
• Social distancing strategies
• Effective therapeutic
Comparison between (random sampling 1:2):

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

All were symptomatic

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

Interview by telephone:

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

Case-patients were more likely to have reported dining at restaurant (aOR: 2,4, IC95%: 1,5 – 3,8).

Analysis restricted to 225 participants:

- Dining at restaurant (aOR: 2,8, CI95%: 1,9 – 4,3)
- Going bar/coffee shop (aOR: 3,9, CI95%: 1,5 – 10,1)
Community and close contact exposures

Most close contact exposures were to family members

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

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

**Limits:**

- Ratio 1:2 could not be reached → unmatched analysis was performed
- Interview on behaviors one month before → memorization bias
- Participants were aware of their SARS-CoV-2 test results → could influence their responses
- At restaurant: not distinguish between outdoor and indoor
- In coffee shop/bar: not distinguish between venues or service delivery method
- Distanciation measures could not be accounted for restaurant & bar → extrapolate to other countries?
- No explanation about the result difference between dining at restaurant and going to coffee/bar in the full analysis?
COVID-19 & social and leisure activities

Description study of the outbreak in Spain

Transmission declined in early May 2020

Cases' number increased during June and mild July:

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

Social setting = 35% of all active outbreaks
- Family gathering or private party
- Leisure facility

Occupational setting = 20% of all active outbreaks
- Agriculture seasonal worker

New cases and cumulative incidence are currently increasing in all regions

Two main settings to target efforts:
- Social gatherings
- Workers in vulnerable situations
Infectiousness of children

A nationwide COVID-19 contact tracing program in South Korea

Index patient were eligible if they identified >1 contact.

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

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

- 10 592 household contacts \(\rightarrow 11.8\% \text{ (CI}_{95\%} [11.2\% - 12.4\%]) \) had COVID-19
  - with an index patient 10–19 years, 18.6\% \text{ (CI}_{95\%} [14.0\%–24.0\%]) \) of contacts had COVID-19
- 48 481 nonhousehold contacts \(\rightarrow 1.9\% \text{ (CI}_{95\%} [1.8\% - 2.0\%]) \) had COVID-19

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

<table>
<thead>
<tr>
<th>Index patient age, y</th>
<th>Household</th>
<th>No. contacts positive/</th>
<th>% Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. contacts traced</td>
<td>(95% CI)</td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>3/57</td>
<td>5.3 (1.3–13.7)</td>
<td></td>
</tr>
<tr>
<td>10–19</td>
<td>43/231</td>
<td>18.6 (14.0–24.0)</td>
<td></td>
</tr>
<tr>
<td>20–29</td>
<td>240/3,417</td>
<td>7.0 (6.2–7.9)</td>
<td></td>
</tr>
<tr>
<td>30–39</td>
<td>143/1,229</td>
<td>11.6 (9.9–13.5)</td>
<td></td>
</tr>
<tr>
<td>40–49</td>
<td>206/1,749</td>
<td>11.8 (10.3–13.4)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>300/2,045</td>
<td>14.7 (13.2–16.3)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>177/1,039</td>
<td>17.0 (14.8–19.4)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>86/477</td>
<td>16.0 (14.8–21.7)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>50/348</td>
<td>14.4 (11.8–18.4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1,248/10,592</td>
<td>11.8 (11.2–12.4)</td>
<td></td>
</tr>
</tbody>
</table>

Rates of coronavirus disease among household

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

\(\rightarrow\) Transmission potential in both children and adolescets,
\(\rightarrow\) Possibly more effective transmission in adolescents than in adults.
Risk of COVID-19: health-care workers & general community

Prospective – observational cohort study (UK & USA)
Data from the COVID Symptom Study smartphone application:
• Baseline demographic info
• Daily info on symptoms
• COVID-19 testing

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

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

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

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

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

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

POST-HOC ANALYSIS

<table>
<thead>
<tr>
<th>Event/person-days</th>
<th>Adequate PPE</th>
<th>Reused PPE</th>
<th>Inadequate PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>592/332 901</td>
<td>146/80 728</td>
<td>157/60 916</td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>1 (ref)</td>
<td>1.46 (1.21-1.76)</td>
<td>1.32 (1.10-1.57)</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1 (ref)</td>
<td>1.46 (1.21-1.76)</td>
<td>1.31 (1.10-1.56)</td>
</tr>
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</table>

No exposure to patients with COVID-19

<table>
<thead>
<tr>
<th>Event/person-days</th>
<th>Adequate PPE</th>
<th>Reused PPE</th>
<th>Inadequate PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No exposure to patients with COVID-19</td>
<td>186/227 654</td>
<td>19/37 599</td>
<td>48/35 159</td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>1 (ref)</td>
<td>0.96 (0.69-1.35)</td>
<td>1.53 (1.11-2.11)</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>1 (ref)</td>
<td>0.95 (0.69-1.35)</td>
<td>1.52 (1.10-2.09)</td>
</tr>
</tbody>
</table>

Exposure to patients with suspected COVID-19

<table>
<thead>
<tr>
<th>Event/person-days</th>
<th>Adequate PPE</th>
<th>Reused PPE</th>
<th>Inadequate PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to patients with suspected COVID-19</td>
<td>126/54 676</td>
<td>36/19 378</td>
<td>26/14 083</td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>2.40 (1.91-3.02)</td>
<td>3.23 (2.24-4.66)</td>
<td>1.87 (1.24-2.83)</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>2.39 (1.90-3.00)</td>
<td>3.20 (2.22-4.61)</td>
<td>1.83 (1.21-2.78)</td>
</tr>
</tbody>
</table>

Exposure to patients with documented COVID-19

<table>
<thead>
<tr>
<th>Event/person-days</th>
<th>Adequate PPE</th>
<th>Reused PPE</th>
<th>Inadequate PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to patients with documented COVID-19</td>
<td>280/59 571</td>
<td>91/23 751</td>
<td>83/11 675</td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>4.93 (4.07-6.97)</td>
<td>5.12 (3.94-6.64)</td>
<td>5.95 (4.57-7.76)</td>
</tr>
<tr>
<td>Multivariate-adjusted hazard ratio (95% CI)</td>
<td>4.83 (3.99-5.85)</td>
<td>5.06 (3.90-6.57)</td>
<td>5.91 (4.53-7.71)</td>
</tr>
</tbody>
</table>

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

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

PPE reuse → self-contamination during repeated application

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

Adequate allocation of PPE is important

Need to ensure proper use of PPE and adherence to other infection control measures.

Limits:

• Details for some exposures were shortened (e.g., type of PPE)
• Self-report (risk factor & primary outcome)
• Selection bias (not a random sampling)
Real-world network – COVID-19 control strategies

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

*Illustration of the Haslemere network with epidemic simulation predictions.*

b–d: Progression of the COVID-19 epidemic under the no-intervention scenarios.
e–g: under secondary contact tracing scenarios.
Real-world network – COVID-19 control strategies

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

Very high proportion of quarantined individuals

Epidemic model predictions of outbreak size & number of people isolated or quarantined
Cumulative number of cases, number of people isolated and number of people quarantined
Real-world network – COVID-19 control strategies

- Increasing the testing capacity → increases in outbreak size, especially under secondary contact tracing
- Number of quarantined individuals can be reduced through mass testing

Contact tracing & quarantine strategy:
- Might be more effective than « local lockdown » strategy when contact rates are high
- Would be most efficient when combined with other control measures such as physical distancing

Epidemic model predictions of how testing affect outbreak and quarantine dynamics
Testing strategies for COVID-19 control

• Mathematical model of SARS-CoV-2 transmission based on:
  o Infectiousness: proportion of infection that are asymptomatic and their infectiousness
  o PCR test sensitivity over time since infection

• Evaluate
  o The impact of self-isolation following either a positive test result or symptom onset
  o The impact of quarantine of contacts of laboratory confirmed cases

• Percentage of reduction in \( R \) = expected effectiveness of different testing strategies

• Based on literature: 33% of infections are asymptomatic which have a relative infectiousness of about 50%

• If self-isolation was 100% effective + all individuals with symptoms compatible with COVID-19 self-isolated \( \rightarrow \) reduction in \( R \) of 47%; CI \( 95\% [32 – 55] \)
  • Play an important role in prevention of SARS-CoV-2 transmission
  • No single strategy will reduce \( R \) below 1

Percentage of reduction in \( R \) by self-isolation following onset of symptoms as a function of the proportion of infections that are asymptomatic
Testing strategies for COVID-19 control

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

- PCR testing of symptomatic individuals → reduces the number of individuals needing self-isolate BUT would reduce the effectiveness of self-isolation (false negative)

- Regular PCR testing, irrespective of symptoms, could reduce transmission
  - Depends on the frequency of testing – timeliness of results – sensitivity of the test

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

Additional percentage reduction in the R by a policy of repeated PCR testing
Testing strategies for COVID-19 control

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

- **Test-trace-test strategy**: testing contact & only those who tested positive put into isolation
  - Effectiveness is lower than a test-trace strategy
  - High probability of false negative
Impact of COVID-19 pandemic response - Nepal

Prospective – observational study in 9 health institutions in Nepal

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

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

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

Institutional birth:
- Substantial decrease – especially after week 12.5
- Reduction during lockdown was 7.4%
- Total decrease of 52.4% by the end of lockdown
**Impact of COVID-19 pandemic response - Nepal**

<table>
<thead>
<tr>
<th></th>
<th>Before lockdown</th>
<th>During lockdown</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Institutional stillbirth</strong> (per 1000 total births)</td>
<td>14</td>
<td>21</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Intitutional neonatal mortality</strong> (per 1000 livebirths)</td>
<td>13</td>
<td>40</td>
<td>0.0022</td>
</tr>
<tr>
<td>Intrapartum fetal heart rate monitoring (%)</td>
<td>56.8</td>
<td>43.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skin to skin contact with the mother’s chest (%)</td>
<td>13.0</td>
<td>26.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Health workers wash hand during childbirth (%)</td>
<td>28.6</td>
<td>41.1</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adjusted effect, β</th>
<th>Preterm birth rate</th>
<th>Institutional stillbirth, rate per 1000 total births</th>
<th>Institutional neonatal mortality rate, per 1000 livebirths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline risk (risk before lockdown)</td>
<td>0.14 (0.11–0.17)</td>
<td>3 (2–7)</td>
<td>0.9 (0.1–8)</td>
</tr>
<tr>
<td>Risk ratio during lockdown vs before lockdown</td>
<td>1.30 (1.20–1.40)</td>
<td>1.46 (1.13–1.89)</td>
<td>3.15 (1.47–6.74)</td>
</tr>
</tbody>
</table>

- These results raise questions on policies regarding strict lockdown in LMIC
- Pandemic lockdown jeopardize the progress that has been made in the past in Nepal
- Urgent need to protect access to high quality intrapartum care and prevent excess death
1. What is the situation in the World?
- More than 30 millions of confirmed cases in the World and 1 million global deaths

2. What is the incubation period & $R_0$?
- The median incubation period is 5 days with an initial basic reproductive number between 2 to 6 before control measures
- Presymptomatic transmission: 44% - Infectiousness decline quickly within 7 days.

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

4. What is the impact of the different measures taken by countries?
- Face masks reduce the transmission of respiratory viruses
- Transmission of viruses is lower with physical distancing of 1 meter or more
- Pandemic lockdown can have an important impact on the access to the health system in some countries
Questions:
- Which type of virus is SARS-CoV-2?
- What is the stability and viability of SARS-CoV-2?
- What do we know about viral load and shedding according to different samples?
- What is the description of the immune responses in infected patients?
- Alternative to the nasopharyngeal swab for SARS-CoV-2 detection?
SARS-CoV-2

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

49 patients with 490 specimens → 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

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

Prolonged persistence of SARS-CoV-2 RNA detection in hospitalized patient
→ Does not imply the existence of infectious virus particles
→ Still a need for preventive measures?

Mild cases, n = 43

<table>
<thead>
<tr>
<th>Specimens</th>
<th>Median (95% CI)</th>
<th>95th percentile (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Throat swab</td>
<td>15.8 (11.8–20.7)</td>
<td>32.8 (25.9–62.9)</td>
</tr>
<tr>
<td>Sputum</td>
<td>20.0 (14.1–27.0)</td>
<td>43.7 (33.6–60.4)</td>
</tr>
<tr>
<td>Nasopharyngeal swab</td>
<td>22.7 (18.8–27.5)</td>
<td>46.3 (39.0–55.2)</td>
</tr>
<tr>
<td>Feces</td>
<td>24.8 (21.2–29.3)</td>
<td>45.6 (40.0–52.8)</td>
</tr>
</tbody>
</table>

Severe cases, n = 6

<table>
<thead>
<tr>
<th>Specimens</th>
<th>Median (95% CI)</th>
<th>95th percentile (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>33.9 (24.2–47.2)</td>
<td>58.9 (39.4–81.7)</td>
</tr>
<tr>
<td></td>
<td>30.9 (23.5–39.1)</td>
<td>44.7 (36.3–58.0)</td>
</tr>
<tr>
<td></td>
<td>33.5 (25.7–42.7)</td>
<td>49.4 (38.4–68.5)</td>
</tr>
<tr>
<td></td>
<td>32.5 (26.3–39.1)</td>
<td>48.9 (41.3–59.7)</td>
</tr>
</tbody>
</table>

Limits
• Existence of infectious particles?
• Virus isolation and tests of specimen’s infectivity
• Not conducted
• Unspecified concentration of SARS-CoV-2 RNA
• May not be generalized to all population
9 patients (Munich) – Virological analysis & information on virus infectivity

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

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

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

- Morning saliva samples
- Endotracheal aspirate (intubated patients)

**Viral load:**

- Median: 5.2 log$_{10}$ copies per mL (IQR 4.1–7.0)
- Saliva viral load: higher during first week and declining after this point
- Endotracheal aspirate viral load: non-significant decline during the first weeks
- 7 patients had viral RNA detected 20 days after symptoms
- No association between prolonged detection and severity
- Older age was correlated with higher viral load
- No difference between mild and severe cases

**Limit:** low number of cases
Viral load

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

Viral load:

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

Limit: a relatively low number of cases

To Zheng et al. BMJ. Apr 2020
Viral load

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

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

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

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

Positive rates:

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

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

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

Limit: this differ according to the typology of patients and disease stages.

Wang W et al. JAMA. Mar 2020
Dynamic in viral shedding

94 symptomatic patients → 414 throat swabs 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

Dynamic in viral shedding

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

Viral shedding may begin 2 to 3 days before first symptoms

The estimated proportion of presymptomatic transmission was 44% (CI95% [30–57%]). Infectiousness decline quickly within 7 days

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

Simulated serial intervals assuming infectiousness started 2 days before symptom onset
Oral & fecal viral shedding

401 patients → 1758 rectal swabs during 0 to 98 days after illness onset

- 80 patients positive for SARS-CoV-2 in the rectal swabs
  - Pediatrics: positive rate of 56.7%
  - Adults: positive rate of 16.9%
- Positive rate decreases over time

517 pairs (respiratory + rectal samples) from the 80 patients positive in rectal swabs

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

Factors independently associated with the duration of fecal viral shedding:
- Neutrophil level OR:1.55 IC\textsubscript{95%}[1.05 – 2.40]
- Interval between antiviral treatment and illness onset OR:1.17 IC\textsubscript{95%}[1.01 – 2.34]

→ 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?
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.
SARS-CoV-2 detection

Limit: antibody response yet to be characterized among the various patients’ populations
Immunological assessment

Cohort study of 178 confirmed SARS-CoV-2 infection

Asymptomatic infection = 20.8% (37/178 patients)

37 asymptomatic matched with 37 mild symptomatic patients

Viral shedding:

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

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

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

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

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

Similar observations were made for neutralizing antibodies

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

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

**Limits**

-> Viral RNA shedding does not equate viral infectivity (not assessed in this study)
-> Serological observations may depend in part on the commercial assay used
SARS-CoV-2 salivary detection

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

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

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

Detected more RNA copies in the saliva specimens than nasopharyngeal swabs (mean log copies per millilitre, 5.58 versus 4.93)

Higher percentage of saliva samples than nasopharyngeal swab samples were positive

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

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

Saliva specimens could be effective in COVID-19 diagnosis, but needs to be confirmed for outpatients
Salivary detection of SARS-CoV-2 in asymptomatic subjects

Mass screening study – 1924 asymptomatic subjects:
• Close contact white clinically confirmed COVID-19 patients (CT cohort, n= 161)
• Asymptomatic travelers arriving at Tokyo & Kansai (AQ cohort, n= 1763)

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

Comparison between paired samples

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

Diagnostic results of nasopharyngeal swab (NPS) and saliva test

<table>
<thead>
<tr>
<th>Contact-tracing cohort (n=161)</th>
<th>Airport Quarantine cohort (n=1,763)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPS</td>
<td>saliva</td>
</tr>
<tr>
<td>positive</td>
<td>negative</td>
</tr>
<tr>
<td>positive</td>
<td>38</td>
</tr>
<tr>
<td>negative</td>
<td>6</td>
</tr>
</tbody>
</table>

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

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

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

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

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

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

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

Recombinant lentiviruses pseudo typed with the G614 Spike more infectious than corresponding D614 S-pseudo typed viruses.
1. Which type of virus is SARS-CoV-2?
- RNA viruses that belong to the *betacoronavirus* genus

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

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

4. What is the description of the immune responses in infected patients?
- IgG levels and neutralizing antibodies start to decrease within 2-3 months after infection

5. Alternative to the nasopharyngeal swab for SARS-CoV-2 detection?
- Saliva sample might be a good alternative to the NPS with several advantages, but asymptomatic populations are poorly characterized
CLINICAL

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

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

**BUT sometimes** (10 to 15 days after symptom onset)
- Accumulation of immune cells
  - **Cytokine storm**
  - Lung damage and multi-organ damage
Physiopathology

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

• Multi-organ damage
  o Kidney, heart, lungs, vessel, immune system ....
SARS-CoV-2 specific T cell immunity

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

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

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

![Graph showing IFNγ spot levels for different patient IDs]
SARS-CoV-2 specific T cell immunity

SARS-CoV2 specific T cells in patients with SARS

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

→ Supporting the notion that patients with COVID-19 will develop long-term T cell immunity.
SARS-CoV-2 specific T cell immunity

SARS-CoV2 specific T cells in unexposed donors

• 37 donors: not exposed to SARS-CoV and SARS-CoV-2

• Detection of SARS-CoV-2-specific IFNγ responses in 19 out of 37 unexposed donor.

• The unexposed group showed a mixed response to the N protein or to NSP7 and NSP13.

• These SARS-CoV-2-reactive cells from unexposed donors had the capacity to expand after stimulation with SARS-CoV-2-specific peptides.

→ Infection with betacoronaviruses induces multi-specific and long lasting T cell immunity against the structural N protein.
Antibody response to SARS-CoV-2

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

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

→ Convalescent plasma samples
  - Binding to SARS-CoV-2 RBD and trimetric S protein?
    IgG response: 78% showed anti-RBD and 70% anti-S
    IgM response: 15% showed anti-RBD and 34% anti-S
  - Anti-RBD IgG levels → moderately correlated with age and severity
    - Neutralizing activities? → the half-maximal neutralizing titer (NT_{50})
  - Generally low: NT_{50}<50 in 33% of samples and < 1000 in 79%
  - Nature of the antibodies elicited by SARS-CoV-2 infection?
    Expanded clones of viral antigen-binding B cells in all tested individuals convalescent after COVID-19.

95% of the antibodies tested bound to SARS-CoV-2 RBD with an average EC_{50} of 6.9 ng/ml.

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

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

Potent neutralizing antibodies found irrespective of the NT50 values.

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

Plasma neutralizing activity is low in most convalescent individuals

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

A vaccine designed to elicit such antibodies could be broadly effective.
Auto-antibodies & type I IFN & COVID-19

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

987 patients hospitalized for life-threatening COVID-19
663 patients asymptomatic or mildly symptomatic (COVID-19)
1227 healthy controls

Auto-antibodies against IFN-α2 and/or IFN-ω?

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

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

• 101 of 987 life-threatening COVID-19 had neutralizing IgG auto-Abs against at least one type I IFN:
  • 51% against IFN-α2 and IFN-ω,
  • 36% against IFN-α2 only,
  • 13% against IFN-ω only.

• Auto-Abs detected in only 4 of 1227 controls and none of 663 asymptomatic or mild-symptomatic patients.

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

FACS plots depicting IFN-α2- or IFN-ω-induced pSTAT1 in the presence of 10% healthy control or anti-IFN-α2/ω- auto-Abs-containing patient plasma (top panel) or an IgG-depleted plasma fraction (bottom panel).
Auto-antibodies & type I IFN & COVID-19

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

Auto-Abs against IFN-β?
- 1.9% of the patients had auto-Abs against IFN-β
- All were severe COVID-19
- Treatment with injected or nebulized IFN-β may have beneficial effects

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

→ Auto-Abs against type I IFNs are a cause of severe SARS-CoV-2 infection.
→ Provides an explanation for the major sex bias in severe COVID-19 and the increase in risk with age
→ Clinical and therapeutic implications
C5a-C5aR1 axis & COVID-19

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

- Recruiting and activating neutrophils and monocytes

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

Concentration of C5a desArg in plasma

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

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

C5a is detected in lung sample from COVID-19 patients

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

C5a-C5aR1 axis & COVID-19

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

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

Potential therapeutic strategy → C5a-C5aR1 axis blockade.

Avdoralimab = mAb against C5aR1.

In vitro:
- Inhibited C5a-induced neutrophil activation,
- Inhibited the C5a-induced migration of neutrophils.

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

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

Neutrophils and monocytes in BALF expressed C5aR1.
**Risk factors of mortality**

Nationwide cohort of all Danish individuals tested for SARS-CoV-2

The study cohort was linked to the Danish administrative and health registries.

11 122 cases with PCR positive: 80% were community-managed & 20% were hospitalized (whereas 2.8% in an ICU)

30 days all cause of mortality = 5.2%

**Risk factors of death:**

**Sex:**
- adjusted for age and number of co-morbidities, ORs = 2.1; CI$_{95\%}$ [1.7–2.6] for men

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

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

**Chronic diseases:**
- Ischemic heart disease & hypertension → ORs 1.1 to 1.3
- Major psychiatric disorders & organ transplantation → ORs 2.5 to 3,2

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

Proportion of patients dying among SARS-CoV-2 PCR-positive cases within different subgroups of age and number of comorbidities.
Antihypertensive drugs & COVID-19

- Observational study
- Lombardy Region in Italy - data extracted from the registry
- February 21 to March 11
- Patient older than 40 years
- 6272 cases matched to 30759 controls (on age, sex & municipality residence)
- Use of antihypertensive drugs
  - ARBs 22.2% among cases and 19.2% among controls
  - ACE inhibitors 23.9% among cases and 21.4% among controls
- Neither ARBs nor ACE inhibitors had a significant association with risk of COVID-19
  - Risk similar for women and men
  - Not modified by age – severity of clinical manifestation – course of COVID-19
  - No evidence of an independent relationship between RAAS blockers and the susceptibility to COVID-19

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

Mancia G. et al. NEJM. May 2020
## Antihypertensive drugs & COVID-19

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

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

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

### 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. (*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Matched Patients with Hypertension</th>
<th>Severe Covid-19 in Patients Treated with Medication</th>
<th>Severe Covid-19 in Patients Not Treated with Medication</th>
<th>Median Difference (95% CI)</th>
<th>Percentage Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor</td>
<td>139 (23.8)</td>
<td>156 (27.1)</td>
<td>-3.3 (-8.3 to 1.7)</td>
<td>150 (21.9)</td>
<td>169 (25.9)</td>
</tr>
<tr>
<td>ARB</td>
<td>161 (25.6)</td>
<td>156 (25.5)</td>
<td>-0.1 (-6.4 to 6.6)</td>
<td>162 (24.3)</td>
<td>165 (24.8)</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>152 (25.3)</td>
<td>145 (25.2)</td>
<td>-1.3 (-7.0 to 4.3)</td>
<td>225 (31.3)</td>
<td>274 (38.5)</td>
</tr>
<tr>
<td>Calcium-channel blocker</td>
<td>211 (35.2)</td>
<td>211 (35.3)</td>
<td>-0.1 (-6.3 to 6.2)</td>
<td>210 (31.2)</td>
<td>210 (31.2)</td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>116 (22.5)</td>
<td>114 (21.9)</td>
<td>-0.6 (-4.5 to 3.7)</td>
<td>120 (17.8)</td>
<td>149 (23.9)</td>
</tr>
</tbody>
</table>

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

Median time (41 patients admitted to hospital)

- From onset of symptoms to first hospital admission
  - 7 days [4.0–8.0]
- From illness onset to dyspnea
  - 8 days [5.0–13.0]
- To ARDS
  - 9 days [8.0–14.0]
- To ICU admission
  - 10.5 days
- To mechanical ventilation
  - 10.5 days [7.0–14.0]
Clinical features

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

Age (median): 48,9 ± 16,3 years
Male: 904 (57,3 %)

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

Symptoms
- Fever: 88 %
- Cough: >70 %
- Fatigue: 42,8 %
- Shortness of breath: 20,8 %
- Myalgia/arthralgia: 17,5 %

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

Abnormal chest CT: 1130 (71,1 %)

Case fatality rate: 50 (3,1 %)
Organ damage

An invader’s impact
In serious cases, SARS-CoV-2 invades 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 infected alveolus, or air sac, whose walls break down during attack by the virus, diminishing oxygen uptake. Patients cough, fever rise, and breathing becomes labored.

2 Heart and blood vessels
The virus (blue) 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 a 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.
Monocentric – from 16 January to 17 February
90 patients - Median follow up: 18 days [5 – 43]
CT interpretation (366 CT scan)
→ Each lung divided into 3 zones
→ Overall CT score (max = 24)

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

Limitations: No subgroup analysis (mild and severe)

→ Bilateral GGO is the most common manifestation
→ Rapid extension and specific pattern of evolution
Ground glass opacity in a 35-year-old woman with COVID-19 pneumonia
Heart & COVID-19

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

**Acute myocardial infarction**
- Viral illness → increase the risk
- Inflammation + hypercoagulability → increased risk

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

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

**Venous thromboembolic event**
- Increased risk
- Inflammation, organ dysfunction, abnormal coagulation
- 16-17% of pulmonary embolism

**ECG and echocardiographic abnormalities**
- Correlated with worse outcomes
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

Kidney & COVID-19

Prospective cohort – 1 hospital in China – 701 patients
- Prevalence of acute kidney injury (AKI)?
- Association between markers of kidney injury and death?

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

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

AKI and hospital death
- Prevalence of AKI: 5,1% - higher in patients with elevated SC at admission(11,9%)
- In hospital death: 16,1%
  - 33,7% in patient with elevated SC at admission vs 13,2% others (p<0.05)
Kidney abnormalities → ↑ in hospital death

- Proteinuria
  - 1+ → HR: 2.47, 95% CI: 1.15–5.33
  - 2+ → 3+ → HR: 6.80, 95% CI: 2.97–16.06
- Hematuria
  - 1+ → HR: 3.05, 95% CI: 1.43–6.49
  - 2+ → 3+ → HR: 8.89, 95% CI: 4.41–17.84
- Elevated baseline blood urea nitrogen → HR: 4.20, 95% CI: 2.74–6.45
- Elevated baseline serum creatinine → HR: 2.04, 95% CI: 1.32–3.15
- Peak serum creatinine > 133 umol/l → HR: 3.09, 95% CI: 1.55–6.87

Acute Kidney Injury
- Stage 1 → HR: 1.90, 95% CI: 0.76–4.75
- Stage 2 → HR: 3.63, 95% CI: 1.60–8.27
- Stage 3 → HR: 4.72, 95% CI: 2.66–8.75

- High prevalence of kidney disease among hospitalized patients with COVID-19
- Association between kidney involvement and poor outcome
- Early detection and effective intervention of kidney involvement
- Impact on long-term outcomes?
Neuropsychiatric disorders & COVID-19

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

From April 2 to April 26, 2020 in the UK

153 unique cases (correlated with the national case identification data)

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

4 clinical syndromes associated with COVID-19

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

Acute alteration in mental status were overrepresented in young patients

- Cerebrovascular events in COVID-19 → vasculopathy
- Viral neurotropism? Host immune responses? Genetic factors?
ARDS & COVID-19

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

Type «L»: Low elastance
- Gas volume nearly normal
  - $V_t \approx 7-8 \text{ ml/kg} \rightarrow DV<14 \text{cmH}_2\text{O}$
- Recruitability is low
  - $\text{PEP}<12 \text{cmH}_2\text{O}$
- Loss of hypoxic pulmonary vasoconstriction
- Ventilation/perfusion mismatch $\rightarrow$ hypoxemia
- Low lung weight $\rightarrow$ ground glass densities

Type «H»: High elastance (10 – 30%)
Evolution of the COVID-19 injury attributable to P-SILI
- Increase oedema $\rightarrow$ decrease gas volume
  - $V_t = 6\text{ml/kg} \rightarrow DV<14\text{cmH}_2\text{O}$
- Recruitability is high
  - $\text{PEP}>12\text{cmH}_2\text{O}$ (carefully)
- High lung weight $\rightarrow$ bilateral condensations
  - Prone position

CT scan
A: spontaneous breathing
B: mechanical ventilation

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

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

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

Treatment (no recommendation for the moment)
- 62% had invasive respiratory support
- 28% needed VA-ECMO

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

→ Understanding the immune mechanisms of this disease is a priority

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

Cohort of Kawa-COVID-19

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

Kawa-COVID-19 versus historical cohort

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

Factor prognostic for the development of severe disease
- Age > 5 years
- Ferritinaemia >1400 µg/L
1. What is the mechanism of action of SARS-CoV-2? Cell immunity?
- Uses ACE2 receptor to enter the cell and can produce a cytokine storm
- Activation of innate and adaptative immune pathways
- Induces long lasting T cell immunity against the structural N protein
- Recurrent anti-SARS-CoV-2 RBD antibodies with potent neutralizing activity can be found in all individuals
- Auto-Abs against type I IFNs are a cause of severe SARS-CoV-2 infection

2. What is the clinical presentation of COVID-19 in adults and children?
- Most persons are asymptomatic or mildly symptomatic
- Independent risk factors of mortality: age – obesity – chronic disease
- Children are less represented than adults and have less severe or critical forms of the disease

3. Is there multiple-organ damage?
- Predominantly lung damage → prognostic of the disease
- Several cases of heart & kidney damage
Questions:
- What drug showed clinical efficacy?
- What drugs did not show proven benefits?
- What are the types of vaccines in clinical evaluation?
COVID-19 Treatment

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

Classes of treatment

- Anti viral effect: Remdesivir, (Hydroxy)chloroquine, Lopinavir/ritonavir
- Immunomodulatory effect: Corticosteroids
- Passive immunity: Convalescent plasma, Monoclonal antibody
What targets for treatment?

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

<table>
<thead>
<tr>
<th>1st Author</th>
<th>Design</th>
<th>Groups</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boulware</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>HCQ vs placebo (Post exposure prophylaxis, Not Hospitalized)</td>
<td>N= 821 Exposed to a known COVID-19 individual</td>
<td>Incidence of either laboratory confirmed COVID-19 or illness compatible with COVID-19 within 14 days</td>
<td>HCQ group: 49/414 (11.8%) vs. placebo group: 58/407 (14.3%); p=0.35</td>
</tr>
<tr>
<td>Geleris</td>
<td>Observational, not randomized</td>
<td>HCQ vs. no HCQ (Hospitalized)</td>
<td>N= 1376 Moderate-to-severe respiratory illness</td>
<td>Time from study baseline to intubation or death</td>
<td>HR: 1.04 CI&lt;sub&gt;95%&lt;/sub&gt; [0.82-1.32]</td>
</tr>
<tr>
<td>Tang</td>
<td>Randomized, controlled, multicenter, open label</td>
<td>HCQ + SoC vs. SoC (Hospitalized)</td>
<td>N= 150 Mild to moderate or severe disease</td>
<td>D28 negative conversion of SARS-CoV-2</td>
<td>HCQ + SoC: 85.4%, IC&lt;sub&gt;95%&lt;/sub&gt; [73.8% - 93.8%] vs. SoC: 81.3%, IC&lt;sub&gt;95%&lt;/sub&gt; [71.2%-89.6%]</td>
</tr>
</tbody>
</table>

No virological data on some studies.

# Hydroxychloroquine (HCQ)

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<th>Main results (Primary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abella BS</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>HCQ vs placebo (HCWs, pre-exposure prophylaxis)</td>
<td>N=130 Hospital HCW (ED and COVID-19 units)</td>
<td>Incidence of SARS-CoV-2 infection</td>
<td>Early termination of the study HCQ group: 4/64 (6.3%) vs. placebo group: 4/61 (6.6%); p &gt; 0.99</td>
</tr>
<tr>
<td>Cavalcanti</td>
<td>Multicenter, randomized, open-label, controlled</td>
<td>HCQ + AZ vs. SoC, HCQ vs. SoC, HCQ + AZ vs. HCQ (Hospitalized)</td>
<td>N=667 No supplemental O₂ or a maximum of 4 L/min supplemental</td>
<td>D15 clinical status (seven-level ordinal scale)</td>
<td>HCQ + AZ vs. control: OR: 0.99 IC(<em>{95}%) [0.57-1.73]; HCQ vs. control: OR: 1.21 IC(</em>{95}%) [0.69-2.11]; HCQ + AZ vs. HCQ: OR: 0.82 IC(_{95}%) [0.47-1.43]</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>Randomized, controlled, open-label</td>
<td>HCQ vs. usual care (Hospitalized)</td>
<td>N=4717 Not specified</td>
<td>D28 mortality</td>
<td>HCQ group: 421/1561 (27.0%) vs. usual care group: 790/3155 (25.0%) RR: 1.09; IC(_{95}%) [0.97-1.23]; p=0.15</td>
</tr>
</tbody>
</table>

No virological data on some studies.

**AZ:** azithromycin – **ED:** emergency department – **HCW:** health care worker – **HCQ:** hydroxychloroquine
# Lopinavir/ritonavir (LPVr)

<table>
<thead>
<tr>
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<th>Design</th>
<th>Groups</th>
<th>Participants</th>
<th>Primary outcome</th>
<th>Main results (Primary outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoergenhofer</td>
<td>Experimental</td>
<td>One group (non ICU Hospitalized)</td>
<td>N= 8 Not specified</td>
<td>LPVr plasma concentration</td>
<td>LPV plasma concentration: approximately 2-fold higher than HIV patients receiving the same dose (7.1 µg/mL) 60 to 120-fold higher concentrations are required to reach the assumed LPV EC50 at trough levels</td>
</tr>
<tr>
<td>Cao</td>
<td>Randomized, controlled, open-label</td>
<td>LPVr vs. SoC (Hospitalized)</td>
<td>N= 199 SaO₂ ≤ 94% or PaO₂/FiO₂ &lt; 300 mm Hg</td>
<td>Time to clinical improvement</td>
<td>LPVr group not associated with a difference in time to clinical improvement HR: 1.31 CI95%[0.95-1.80]</td>
</tr>
<tr>
<td>Zhang</td>
<td>Systematic review and meta-analysis</td>
<td>LPVr vs. control specified (Hospitalized)</td>
<td>N= 4 023 Not specified (meta-analysis)</td>
<td>Mortality rate and ARDS rate</td>
<td>ARDS: LPVr group 15.6% vs. control group 24.2%; p=0.49 Mortality rate: LPVr group 6.2% vs control group 5.5%; p=0.93</td>
</tr>
<tr>
<td>RECOVERY</td>
<td>Randomized, controlled, open-label</td>
<td>LPVr + SoC vs. SoC (Hospitalized)</td>
<td>N=5 040 Not specified</td>
<td>28-day all-cause mortality</td>
<td>LPVr + SoC group: 364/1616 (23%) vs. SoC group 767/3424 (22%); RR: 1.03 Cl95%[0.91-1.17], p=0.60</td>
</tr>
</tbody>
</table>

LPVr : Lopinavir/ritonavir – SoC: Standard of Care

No virological data on some studies.
Remdesivir (RDV) - 1

- Randomized, double-blind, placebo-controlled, multicenter, academic study, China
- **Inclusion criteria:** age ≥ 18yo, positive SARS-CoV-2 RT PCR, pneumonia confirmed by chest Imaging, SpO₂ < 94% (room air) or PaO₂/FiO₂ ≤ 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)

**Study Details:**
- 255 participants screened
  - 18 excluded
    - 14 did not meet eligibility criteria
    - 4 withdrew
- 237 adults enrolled
- 158 assigned to the RDV group
  - 158 in the intention to treat pop
    - 3 did not start study treatment
- 79 assigned to the placebo group
  - 78 in the intention to treat pop
    - 1 withdrew consent
- 155 started study treatment
  - 150 included in the per-protocol pop
    - 5 received RDV < 5 days
- 78 started study treatment
  - 76 included in the per-protocol pop
    - 2 received placebo < 5 days
- 155 included in the safety population
  - 78 included in the safety population

**References:**
Wang Y et al. Lancet. Apr 2020
# Remdesivir (RDV) - 1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RDV (N=158)</th>
<th>Placebo(N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) – yr</td>
<td>66 (57-73)</td>
<td>64 (53-70)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>89 (56)</td>
<td>51 (65)</td>
</tr>
<tr>
<td><strong>Coexisting conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>40 (25)</td>
<td>16 (21)</td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>72 (46)</td>
<td>30 (38)</td>
</tr>
<tr>
<td>Coronary heart disease – no (%)</td>
<td>15 (9)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Vital sign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate &gt; 24/min – no (%)</td>
<td>36 (23)</td>
<td>11 (14)</td>
</tr>
</tbody>
</table>
Remdesivir (RDV) - 1

- **Time to clinical improvement**: median 21.0 days [IQR 13.0–28.0] RDV group vs. 23.0 days [15.0–28.0] placebo group; no significant difference HR 1.23 IC95%[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
- **Limits**: target enrolment not reached; insufficient power to detect assumed differences in clinical outcomes, late treatment initiation (within 12 days of symptom onset), no virological data

Wang Y et al. Lancet. Apr 2020
Remdesivir (RDV) - 2

- Randomized, double-blind, placebo-controlled, multicenter (73 centers), academic study, USA
- **Inclusion criteria:** SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, SpO₂ < 94% (room air) or requiring supplemental oxygen, mechanical ventilation, or ECMO
- **Exclusion criteria:** pregnant women, allergy to study product
- **Primary outcome:** time to recovery
- 1062 patients underwent randomization; 541 RDV group, 521 placebo group (1:1)

---

Anti viral effect

---

1114 adults patients assessed for eligibility

- 52 excluded
- 28 did not meet inclusion criteria/met exclusion criteria
- 24 eligible but not enrolled

1062 underwent randomization

- 541 assigned to the RDV group
  - 3 didn’t meet eligibility criteria
  - 7 withdrew consent
  - 531 received RDV
    - 208 received all 10 doses
    - 323 received <10 doses
      - 223 Recovered
    - 517 completed the study
      - 14 terminated early
    - 541 included in the ITT population
      - 1 received placebo
      - 10 excluded
    - 532 included in the as-treated pop°
- 521 assigned to the placebo group
  - 1 didn’t meet eligibility criteria
  - 3 withdrew consent
  - 517 received placebo
    - 226 received all 10 doses
    - 291 received <10 doses
      - 158 Recovered
    - 340 completed study through D29
      - 9 terminated before D29
    - 521 included in ITT population
      - 4 excluded
      - 1 received RDV
    - 516 included in the as-treated pop°

Beigel JH et al. NEJM. Oct 2020
## Remdesivir (RDV) - 2

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All (N=1062)</th>
<th>RDV (N=541)</th>
<th>Placebo (N=521)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD) – yo</strong></td>
<td>58,9 (15)</td>
<td>58,6 (14,6)</td>
<td>59,2 (15,4)</td>
</tr>
<tr>
<td><strong>Male sex – no (%)</strong></td>
<td>684 (64,4)</td>
<td>352 (65,1)</td>
<td>332 (63,6)</td>
</tr>
<tr>
<td><strong>Co existing conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 2 Diabetes – no (%)</td>
<td>322/1051 (30,6)</td>
<td>164/532 (30,8)</td>
<td>158/519 (30,4)</td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>533/1051 (50,7)</td>
<td>269/532 (50,6)</td>
<td>264/519 (50,9)</td>
</tr>
<tr>
<td>Obesity – no (%)</td>
<td>476/1049 (45,4)</td>
<td>242/531 (45,6)</td>
<td>234/518 (45,2)</td>
</tr>
<tr>
<td><strong>Score on ordinal scale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Hospitalized, not requiring supplemental O₂, requiring ongoing medical care – no (%)</td>
<td>133 (13,0)</td>
<td>75 (13,9)</td>
<td>63 (12,1)</td>
</tr>
<tr>
<td>5. Hospitalized, requiring supplemental O₂ – no (%)</td>
<td>435 (41,0)</td>
<td>232 (41)</td>
<td>203 (39,0)</td>
</tr>
<tr>
<td>6. Hospitalized, receiving noninvasive ventilation or high flow O₂ device – no (%)</td>
<td>193 (18,2)</td>
<td>95 (17,6)</td>
<td>98 (18,8)</td>
</tr>
<tr>
<td>7. Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%)</td>
<td>285 (26,8)</td>
<td>131 (24,2)</td>
<td>154 (29,6)</td>
</tr>
</tbody>
</table>
Remdesivir (RDV) - 2

- **Time to recovery (median)**: RDV group: 10 days vs. placebo group: 15 days; recovery rate ratio 1.29 CI$_{95%}$[1.12-1.49]
- **D29 mortality**: RDV group: 11.4% vs. placebo group: 15.2%; HR 0.73 CI$_{95%}$[0.52-1.03]
- **Adverse events**: RDV group: 131/532 (24.6%) vs. placebo group: 163/516 (31.6%)
- **Limits**: primary outcome changed during the study, uncompleted follow up, no virological data
Remdesivir (RDV) - 3

- Open labelled, randomized, placebo-controlled, multicenter (55 centers), academic study, USA, Europe, Asia
- **Inclusion criteria**: age > 12 yo, SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, SpO$_2$ < 94% (room air) or requiring supplemental oxygen
- **Exclusion criteria**: mechanical ventilation, or ECMO, ALT or AST > 5 ULNR, creatine clearance < 50 mL/min/m$^2$
- **Primary outcome**: status assessed on day 14 on a 7-point ordinal scale
- 402 patients underwent randomization; 200 5-day course RDV group, 197 10-day course RDV group (1:1)

408 adults patients assessed for eligibility
6 excluded
5 did not meet inclusion criteria/met exclusion criteria
1 recovered spontaneously

402 underwent randomization
SpO$_2$ < 94%

202 assigned to RDV 5-day group
2 not treated
28 discontinued treatment
16 discharged
9 adverse event
1 protocol violation
172 completed treatment
200 included in the analysis

200 assigned to RDV 10-day group
3 not treated
111 discontinued treatment
68 discharged
22 adverse event
12 died
86 completed treatment
197 included in the analysis

Goldman JD et al. NEJM. May 2020
### Remdesivir (RDV) - 3

#### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RDV 5 days (N=200)</th>
<th>RDV 10 days (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) – yo</td>
<td>61 (50-69)</td>
<td>62 (50-71)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>120 (60)</td>
<td>133 (68)</td>
</tr>
</tbody>
</table>

#### Co existing conditions

<table>
<thead>
<tr>
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<th>RDV 5 days (N=200)</th>
<th>RDV 10 days (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 Diabetes – no (%)</td>
<td>47 (24)</td>
<td>42 (22)</td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>100 (50)</td>
<td>98 (50)</td>
</tr>
<tr>
<td>BMI, median (IQR) – kg/m²</td>
<td>29 (25-34)</td>
<td>29 (25-33)</td>
</tr>
</tbody>
</table>

#### Score on ordinal scale

<table>
<thead>
<tr>
<th>Score on ordinal scale</th>
<th>RDV 5 days (N=200)</th>
<th>RDV 10 days (N=197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4. Hospitalized, not requiring O₂ – no (%)</td>
<td>34 (17)</td>
<td>21 (11)</td>
</tr>
<tr>
<td>5. Hospitalized, requiring O₂ – no (%)</td>
<td>113 (56)</td>
<td>107 (54)</td>
</tr>
<tr>
<td>6. Hospitalized, receiving noninvasive ventilation or high flow O₂ device – no (%)</td>
<td>49 (24)</td>
<td>60 (30)</td>
</tr>
<tr>
<td>7. Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%)</td>
<td>4 (2)</td>
<td>9 (5)</td>
</tr>
</tbody>
</table>
# Remdesivir (RDV) - 3

## Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>5-days (N=200)</th>
<th>10-days (N=197)</th>
<th>Baseline-Adjusted Difference 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical status at day 14 on the 7-point ordinal scale - no (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized, receiving invasive mechanical ventilation or ECMO</td>
<td>16 (8)</td>
<td>33 (17)</td>
<td>-</td>
</tr>
<tr>
<td>Hospitalized, receiving noninvasive ventilation or high flow O₂ device</td>
<td>9 (4)</td>
<td>10 (5)</td>
<td>-</td>
</tr>
<tr>
<td>Hospitalized, requiring O₂</td>
<td>19 (10)</td>
<td>14 (7)</td>
<td>-</td>
</tr>
<tr>
<td>Hospitalized, not requiring O₂</td>
<td>9 (4)</td>
<td>3 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Not Hospitalized</td>
<td>120 (60)</td>
<td>103 (52)</td>
<td>0.79 (0.61-1.01)</td>
</tr>
<tr>
<td><strong>Time to clinical improvement (median day of 50% cumulative incidence)</strong></td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td><strong>Recovery - no (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 7</td>
<td>71 (36)</td>
<td>51 (26)</td>
<td>−6.0% (−14.8 to 2.7)</td>
</tr>
<tr>
<td>Day 14</td>
<td>129 (64)</td>
<td>106 (54)</td>
<td>−6.3% (−15.4 to 2.8)</td>
</tr>
</tbody>
</table>

Goldman JD et al. NEJM. May 2020
Remdesivir (RDV) - 3

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

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

---

**Oxygen Support at Day 14** (% of patients)

- **Oxygen Support at Day 5**

---

Goldman JD *et al*. *NEJM*. May 2020
Remdesivir (RDV) - 4

- Randomized, open-label, placebo-controlled, multicenter (105 centers), academic study, USA, Europe, Asia

- **Inclusion criteria:** hospitalized patients, SARS-CoV-2 RT PCR positive patients, radiographic infiltrates, SpO$_2$ > 94% (room air)

- **Exclusion criteria:** mechanical ventilation, or ECMO, ALT or AST > 5 ULNR, creatine clearance < 50 mL/min/m$^2$

- **Primary outcome:** clinical status assessed on the 7-point ordinal scale on study day 11

- 402 patients underwent randomization; 191 **5-day course** RDV group, 193 **10-day course** RDV group, 200 **control** group (1:1:1)

---

612 assessed for eligibility

- 16 excluded
  - 13 did not meet inclusion criteria
  - 3 withdrew consent

596 randomized

- SpO$_2$ > 94%

- 197 10-day RDV
  - 193 started 10-d RDV as randomized
  - 4 did not start RDV

- 199 5-day RDV
  - 191 started 5-d RDV as randomized
  - 8 did not start RDV

- 200 Control
  - 200 continued SoC as randomized

73 Completed treatment

- 120 stopped treatment early
  - 98 discharged
  - 8 adverse events
  - 6 withdrew consent
  - 4 investigator decision
  - 2 protocol violation
  - 1 death
  - 1 nonadherence

140 Completed treatment

- 46 stopped treatment early
  - 35 discharged
  - 4 adverse events
  - 5 withdrew consent
  - 1 investigator decision
  - 1 lost of follow-up

N= 227

- Completed 15 days follow-up

- 193 Included in the primary analysis
  - 4 excluded (did not start treatment)

- 191 Included in the primary analysis
  - 8 excluded (did not start treatment)

- 200 Included in the primary analysis

---

*Spinner CD et al. JAMA Aug 2020*
### Remdesivir (RDV) - 4

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>5-days (N=191)</th>
<th>10-days (N=193)</th>
<th>SoC (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) – yo</td>
<td>58 (48-66)</td>
<td>56 (45-66)</td>
<td>57 (45-66)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>114 (60)</td>
<td>118 (61)</td>
<td>125 (63)</td>
</tr>
<tr>
<td><strong>Co existing conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>71 (37)</td>
<td>85 (44)</td>
<td>76 (38)</td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>82 (43)</td>
<td>85 (44)</td>
<td>81 (41)</td>
</tr>
<tr>
<td>BMI, median (IQR) – kg/m²</td>
<td>25 (24-30)</td>
<td>28 (25-32)</td>
<td>27 (24-31)</td>
</tr>
<tr>
<td><strong>Day 1 clinical status on 7-point scale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized, not requiring O₂ – no (%)</td>
<td>160 (84)</td>
<td>163 (84)</td>
<td>160 (80)</td>
</tr>
<tr>
<td>Hospitalized, requiring O₂ – no (%)</td>
<td>29 (15)</td>
<td>23 (12)</td>
<td>36 (18)</td>
</tr>
<tr>
<td>Hospitalized, receiving noninvasive ventilation or high flow O₂ device – no (%)</td>
<td>2 (1)</td>
<td>1 (1)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>
## Remdesivir (RDV) - 4

### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>5-days (N=191)</th>
<th>10-days (N=193)</th>
<th>SoC (N=200)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 1 clinical status on 7-point scale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not hospitalized – no (%)</td>
<td>134 (70)</td>
<td>125 (65)</td>
<td>120 (60)</td>
</tr>
<tr>
<td>Hospitalized, not requiring O&lt;sub&gt;2&lt;/sub&gt; – no (%)</td>
<td>38 (20)</td>
<td>44 (23)</td>
<td>46 (23)</td>
</tr>
<tr>
<td>Hospitalized, requiring O&lt;sub&gt;2&lt;/sub&gt; – no (%)</td>
<td>7 (4)</td>
<td>12 (6)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Hospitalized, receiving noninvasive ventilation or high flow O&lt;sub&gt;2&lt;/sub&gt; device – no (%)</td>
<td>5 (3)</td>
<td>0</td>
<td>7 (4)</td>
</tr>
<tr>
<td>Hospitalized, receiving invasive mechanical ventilation or ECMO – no (%)</td>
<td>0</td>
<td>1 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Death – no (%)</td>
<td>0</td>
<td>2 (1)</td>
<td>4 (2)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event – no (%)</td>
<td>98 (51)</td>
<td>113 (59)</td>
<td>93 (47)</td>
</tr>
<tr>
<td>Any grade ≥ 3 adverse event – no (%)</td>
<td>20 (10)</td>
<td>24 (12)</td>
<td>24 (12)</td>
</tr>
<tr>
<td>Any serious adverse event – no (%)</td>
<td>9 (5)</td>
<td>10 (5)</td>
<td>18 (9)</td>
</tr>
</tbody>
</table>
Remdesivir (RDV) - 4

- **D11 clinical status:** in 5-day RDV group patients had higher odds of a better clinical status distribution compare to SoC (OR: 1.65 IC _95%_[1.09-2.48]; p=0.02)
- **D11 clinical status:** in 10-day remdesivir and SoC group was not significantly different
- **Limits:** open-label design, discharge decision may have been influenced by the assigned duration of remdesivir therapy, no virological data
Corticosteroids (CT) - 1

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

11 303 patients recruited

<table>
<thead>
<tr>
<th>Patients</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 948</td>
<td>excluded</td>
</tr>
<tr>
<td>357</td>
<td>did not have dexamethasone available</td>
</tr>
<tr>
<td>1 707</td>
<td>not considered suitable for randomization to dexamethasone</td>
</tr>
</tbody>
</table>

9 355 underwent randomization

<table>
<thead>
<tr>
<th>Patients</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 930</td>
<td>assigned to receive other active treatment</td>
</tr>
</tbody>
</table>

6 425 underwent randomization

- 2 104 to the DXM group
  - 1 withdrew consent
  - 95 proceeded to second randomization
    - 2 104 included in the 28-day intention to treat analysis
- 4 321 to usual care alone group
  - 6 withdrew consent
  - 276 proceeded to second randomization
  - 4 321 included in the 28-day intention to treat analysis
## Corticosteroids (CT) - 1

### Treatment assignment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>DXM (N=2 104)</th>
<th>Usual care (N=4 321)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age ≥ 70 yr – no (%)</strong></td>
<td>963 (45)</td>
<td>1817 (42)</td>
</tr>
<tr>
<td><strong>Female sex – no (%)</strong></td>
<td>766 (36)</td>
<td>1572 (36)</td>
</tr>
<tr>
<td><strong>Coexisting conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>521 (25)</td>
<td>1025 (24)</td>
</tr>
<tr>
<td>Heart disease – no (%)</td>
<td>586 (49.1)</td>
<td>1171 (27)</td>
</tr>
<tr>
<td>Chronic lung disease – no (%)</td>
<td>415 (20)</td>
<td>931 (22)</td>
</tr>
<tr>
<td><strong>SARS-CoV-2 test result</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive – no (%)</td>
<td>20 (18-22)</td>
<td>18 (18-20)</td>
</tr>
<tr>
<td><strong>Respiratory support received</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No oxygen – no (%)</td>
<td>501 (24)</td>
<td>1034 (24)</td>
</tr>
<tr>
<td>Oxygen only – no (%)</td>
<td>1279 (61)</td>
<td>2604 (60)</td>
</tr>
<tr>
<td>Invasive mechanical ventilation – no (%)</td>
<td>324 (15)</td>
<td>683 (16)</td>
</tr>
</tbody>
</table>
Corticosteroids (CT) - 1

- **Day 28 mortality:** 482/2104 (22.9%) DXM group vs. 1110/4321 (25.7%) usual care group, risk ratio 0.83 CI$_{95\%}$[0.75-0.93]
- **Discharged from hospital within 28 days:** 1413/2104 (67.2%) DXM group vs. 2745/4321 (63.5%) usual care group, risk ratio 1.10 CI$_{95\%}$[1.03-1.17]
- **Invasive mechanical ventilation or death:** 456/1780 (25.6%) DXM group vs. 994/3638 (27.3%) usual care group, risk ratio 0.92 CI$_{95\%}$[0.84-1.01]
- **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
Corticosteroids (CT) - 2

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

16 Trials identified
13 Found via database searches
3 Found via other sources

16 Screened after duplicates removed

7 Excluded
3 Wrong interventions
3 Not yet recruiting
1 ineligible population

9 Trial investigators contacted for participation

2 Excluded
1 No response
1 Declined participation due to ongoing recruiting for trial

7 Trial included in quantitative synthesis (meta-analysis)

Sterne et al. JAMA Sep 2020
Corticosteroids (CT) - 2

- 222/678 deaths among patients randomized to corticosteroids group vs. 425/1025 deaths among patients randomized to usual care or placebo; OR: 0.66 IC$_{95%}$[0.53-0.82]; p < 0.001 fixed-effect meta-analysis

- **Association with mortality:** DXM: 0.64 IC$_{95%}$[0.5-0.82]; p<0.001 (3 trials), HC: 0.69 IC$_{95%}$[0.43-1.12]; p=0.13 (3 trials), mPred: 0.91 IC$_{95%}$[0.29-2.87]; p=0.87 (1 trial)

- **Limits:** risk of selective reporting or of publication bias, missing outcome data, trials only recruited adults, effect of corticosteroids on children remains unclear

Sterne et al. JAMA Sep 2020

DXM: dexamethasone – HC: hydrocortisone – mPred: methylprednisolone

No Steroids better
Steroids better
**Corticosteroids (CT) - 3**

<table>
<thead>
<tr>
<th>Authors</th>
<th>CT</th>
<th>Patients</th>
<th>Design</th>
<th>Groups</th>
<th>Outcome</th>
<th>Main results (outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fadel R</td>
<td>mPred</td>
<td>N=213 Moderate to severe COVID-19</td>
<td>Multi-center, quasi-experimental</td>
<td>mPred vs. no mPred</td>
<td>Escalation of care from ward to ICU</td>
<td>SoC group 31 (44.3%) vs. mPred group 32 (27.3%) OR: 0.47 CI.&lt;sub&gt;95%=[0.25-0.88], p= 0.017</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>New requirement for mechanical ventilation</td>
<td>SoC group 26 (36.6%) vs. CT group 26 (21.7%) OR: 0.47 CI.&lt;sub&gt;95%=[0.25-0.92], p= 0.025</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Death</td>
<td>SoC group 21 (26.3%) vs. CT group 18 (13.6%) OR: 0.45 CI.&lt;sub&gt;95%=[0.22-0.91], p= 0.024</td>
</tr>
<tr>
<td>Prado Jeronimo</td>
<td>mPred</td>
<td>N=416 Suspected COVID-19 hospitalized patients</td>
<td>Parallel, double-blind, placebo-controlled, randomized</td>
<td>mPred vs. placebo</td>
<td>D28 mortality</td>
<td>mPred group 72/194 (37.1%) vs. placebo group 76/199 (38.2%) HR: 0.924 CI.&lt;sub&gt;95%=[0.669-1.275], p= 0.629</td>
</tr>
<tr>
<td>Nelson B</td>
<td>mPred</td>
<td>N=117 Requiring mechanical ventilation</td>
<td>Case-control study</td>
<td>mPred vs. control</td>
<td>D28 ventilator-free after admission</td>
<td>mPred group 6.2 vs. control group 3.14, p=0.044</td>
</tr>
</tbody>
</table>

mPred: methylprednisolone

## Corticosteroids (CT) - 4

<table>
<thead>
<tr>
<th>Authors</th>
<th>CT</th>
<th>Patients</th>
<th>Design</th>
<th>Groups</th>
<th>Outcome</th>
<th>Main results (outcome)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dequin PF</td>
<td>HC</td>
<td>N=149 Critically ill, acute respiratory failure</td>
<td>Multicenter randomized double-blind</td>
<td>HC vs. placebo</td>
<td>D21 treatment failure</td>
<td>Study stopped early&lt;br&gt;HC group 32/76 (42,1%) vs. placebo group 37/76 (50,7%)&lt;br&gt;p = 0,29</td>
</tr>
<tr>
<td>Angus D</td>
<td>HC</td>
<td>N=384 Admitted in ICU for respiratory or cardiovascular organ support</td>
<td>Multicenter, openlabel trial</td>
<td>HC vs. placebo</td>
<td>D21 respiratory and cardiovascular organ support–free</td>
<td>Study stopped early&lt;br&gt;No treatment strategy met prespecified criteria for statistical superiority, precluding definitive conclusions</td>
</tr>
<tr>
<td>Tomazini BM</td>
<td>DXM</td>
<td>N= 299 Receiving mechanical ventilation</td>
<td>Multicenter, randomized, open-label</td>
<td>DXM + SoC vs. SoC</td>
<td>Ventilator-free days during the first 28 days</td>
<td>Study interrupted&lt;br&gt;DXM + SoC group 6,6 IC95% [5-8,2] vs. SoC group 4,0&lt;br&gt;IC95% [2,9-5,4], p = 0,04</td>
</tr>
</tbody>
</table>

DXM: dexamethasone – HC: hydrocortisone

Tomazini BM et al. JAMA Sep 2020
Dequin PF et al. JAMA Sep 2020
Angus DC et al. JAMA Sep 2020
Tocilizumab (TCZ) - 1

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

484 patients admitted for COVID-19

330 excluded
1 Infant
34 Enrolled in sarilumab clinical trial
293 not mechanically ventilated
2 Died < 28 hours on ventilation before opportunity to receive tocilizumab

154 mechanically ventilated COVID19 patients

78 to TCZ treated group
76 to untreated group

*(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
## Tocilizumab (TCZ) - 1

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (N=154)</th>
<th>TCZ (N=78)</th>
<th>Untreated (N=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) – mean (SD)</td>
<td>58 (14,9)</td>
<td>55 (14,9)</td>
<td>60 (14,5)</td>
<td>0,05</td>
</tr>
<tr>
<td>Female sex – no (%)</td>
<td>52 (41,6)</td>
<td>25 (32)</td>
<td>27 (36)</td>
<td>0,65</td>
</tr>
<tr>
<td>BMI (kg/m²) – no (%)</td>
<td>34,1 (9,5)</td>
<td>34,7 (10,1)</td>
<td>33,4 (8,8)</td>
<td>0,40</td>
</tr>
</tbody>
</table>

**Coexisting conditions**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Overall (N=154)</th>
<th>TCZ (N=78)</th>
<th>Untreated (N=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes – no (%)</td>
<td>25 (16)</td>
<td>10 (13)</td>
<td>15 (20)</td>
<td>0,24</td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>102 (66)</td>
<td>50 (64)</td>
<td>52 (68)</td>
<td>0,57</td>
</tr>
<tr>
<td>Chronic kidney disease – no (%)</td>
<td>64 (42)</td>
<td>27 (35)</td>
<td>37 (49)</td>
<td>0,99</td>
</tr>
</tbody>
</table>

**Values at intubation time**

<table>
<thead>
<tr>
<th>Value</th>
<th>Overall (N=154)</th>
<th>TCZ (N=78)</th>
<th>Untreated (N=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PaO2/FiO2 (n=80) – median (IQR)</td>
<td>165 (136,5 – 231.5)</td>
<td>155 (129,0 – 188,0)</td>
<td>198 (163,0 – 240,0)</td>
<td>0,001</td>
</tr>
</tbody>
</table>

**Fatality rate**

<table>
<thead>
<tr>
<th>Case fatality rate – no (%)</th>
<th>Overall (N=154)</th>
<th>TCZ (N=78)</th>
<th>Untreated (N=76)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>14-day</td>
<td>-</td>
<td>7 (9)</td>
<td>20 (26)</td>
<td>0,005</td>
</tr>
<tr>
<td>28-day</td>
<td>-</td>
<td>14 (18)</td>
<td>27 (36)</td>
<td>0,01</td>
</tr>
</tbody>
</table>
• **Survival probability after intubation:** higher among TCZ group vs. untreated group; hazard ratio 0.50 CI\(_{95%}\) [0.27-0.90]

• **Superinfections:** 42/78 (54%) TCZ group vs. 20/76 (26%) untreated group, \(p < 0.001\)

• **Patients with pneumonia:** 35/78 (45%) TCZ group vs. 15/76 (20%) untreated group, \(p < 0.001\)

• **Patients discharged alive (study period):** 44/78 (56%) TCZ group vs. 30/76 (40%) untreated group, \(p = 0.04\)

• **Limits:** not a randomized controlled trial, laboratories data were missing, no definition of severe cases nor super infections, only interested in patients mechanically ventilated
Vilobelimab (IFX-1) - 1

- **IFX-1**: anti-complement C5a monoclonal antibody
- Exploratory, open label, randomized, phase 2, multicenter, academic study, Netherlands
- **Inclusion criteria**: age ≥ 18yo, severe pneumonia (PaO₂/FiO₂ between [100-250] mmHg), positive RT-PCR SARS-CoV-2 test, requiring non-invasive or invasive ventilation
- **Primary outcome**: Day 5 PaO₂/FiO₂ percentage change from the baseline
- **Secondary outcome**: Day 28 mortality
- 30 participants; 15 control group, 15 IFX 1 treated group (1:1)

172 patients assessed for eligibility
142 not included
141 did not meet inclusion criteria
1 declined participation
30 enrolled

15 randomly assigned IFX-1 group
15 received at least one dose of treatment
3 received seven infusions
3 received six infusions
3 received five infusions
5 received less than five infusions
15 completed the study up to day 28
2 died
13 recovered

15 randomly assigned control group
15 received allocated best supportive care
15 completed the study up to day 28
4 died
11 recovered
Vilolbelimab (IFX-1) - 1

- **Immunomodulatory effect**
  - **Day 5 PaO₂/FiO₂ percentage change**: no differences; IFX-1 group (17%) vs. control group (41%); difference –24% CI \(_{95\%} [-58-9]\), p=0,15
  - **D28 mortality**: IFX-1 group 13%; CI \(_{95\%}[0-31]\) vs. control group 27%; CI \(_{95\%}[7-49]\); HR=0,65 CI \(_{95\%}[0,1-4,14]\)

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

---

**Characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>IFX-1 (N=15)</th>
<th>Control (N=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) - yr</td>
<td>58 (9)</td>
<td>63 (8)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>11 (73)</td>
<td>11 (73)</td>
</tr>
<tr>
<td>Coexisting conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>6 (40)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>4 (27)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Obesity – no (%)</td>
<td>2 (13)</td>
<td>4 (27)</td>
</tr>
<tr>
<td>Respiratory support</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intubated at randomization – no (%)</td>
<td>8 (53)</td>
<td>10 (67)</td>
</tr>
<tr>
<td>Oxygen mask – no (%)</td>
<td>6 (40)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Nasal cannula – no (%)</td>
<td>1(7)</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>
Convalescent plasma (CP) - 1

- Open-label, multicenter, randomized, academic study, China
- **Inclusion criteria**: age ≥ 18yo, chest imaging pneumonia confirmed, positive SARS-CoV-2 RT PCR, hospital admission, severe pneumonia (≥30 breaths/min, SpO2 ≤ 94% (room air) or PaO2/FiO2 ≤ 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)

148 participants assessed for eligibility

- 103 patients enrolled

52 randomized to receive CP | 51 randomized to control (ST)

52 received CP as randomized
23 with severe COVID-19
29 with life-threatening COVID-19

51 received ST as randomized
22 with severe COVID-19
29 with life-threatening COVID-19

52 included in the primary analysis

1 discontinued study participation

51 included in the primary analysis

1 excluded due to receipt of CP after enrollment

51 included in the per-protocol analysis
23 with severe COVID-19
28 with life-threatening COVID-19

50 included in the per-protocol analysis
22 with severe COVID-19
28 with life-threatening COVID-19

Ling Li et al. JAMA. Jun 2020
### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CP group (N=52)</th>
<th>Control group (N=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR) – yr</td>
<td>70 (62-80)</td>
<td>69 (63-76)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>27 (51,9)</td>
<td>33 (64,7)</td>
</tr>
<tr>
<td><strong>Co existing conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes – no (%)</td>
<td>9 (17,3)</td>
<td>12 (23,5)</td>
</tr>
<tr>
<td>Hypertension – no (%)</td>
<td>29 (55,8)</td>
<td>27 (52,9)</td>
</tr>
<tr>
<td>Cardiovascular disease – no (%)</td>
<td>14 (26,9)</td>
<td>12 (23,5)</td>
</tr>
<tr>
<td>Cerebrovascular disease – no (%)</td>
<td>11 (21,2)</td>
<td>7 (13,7)</td>
</tr>
<tr>
<td>Cancer – no (%)</td>
<td>3 (5,8)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Vital sign</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory rate &gt; 24/min – no (%)</td>
<td>11/52 (21,2)</td>
<td>7/49 (14,3)</td>
</tr>
</tbody>
</table>
Convalescent plasma (CP) - 1

- **Time to clinical improvement within 28 days (all patients):** 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 reach recruitment targets; 103 participants enrolled rather than 200 initially expected
Convalescent plasma (CP) - 2

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

### Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=5 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range) – yr</td>
<td>62,3 (18,5-97,8)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>3 153 (63,1)</td>
</tr>
</tbody>
</table>

### Clinical Status

<table>
<thead>
<tr>
<th>Clinical Status</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current severe or life-threatening COVID-19 – no (%)</td>
<td>4 051 (81,0)</td>
</tr>
<tr>
<td>High risk of severe COVID-19 – no (%)</td>
<td>949 (19,0)</td>
</tr>
<tr>
<td>ICU admission – no (%)</td>
<td>3 316 (66,3)</td>
</tr>
</tbody>
</table>

### Clinical symptoms

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory failure – no (%)</td>
<td>2 912 (71,9)</td>
</tr>
<tr>
<td>Dyspnea – no (%)</td>
<td>2 550 (62,9)</td>
</tr>
<tr>
<td>Blood oxygen saturation ≤ 93% – no (%)</td>
<td>2 519 (62,2)</td>
</tr>
<tr>
<td>Respiratory frequency ≥ 30/min – no (%)</td>
<td>1 546 (38,2)</td>
</tr>
<tr>
<td>PaO2/FiO2 &lt; 300</td>
<td>1 365 (33,7)</td>
</tr>
<tr>
<td>Septic shock</td>
<td>600 (14,8)</td>
</tr>
</tbody>
</table>
Convalescent plasma (CP) - 2

- **Incidence** of serious adverse events (SAEs) in the first four hours after transfusion: < 1% (N=36)
- **Related** SAEs: 3 severe allergic transfusion reactions, 4 deaths, 18 TACO&TRALI (2 definitely related to CP)
- **Seven-day mortality rate**: 14.9%
- **Limits**: lack of detailed training of study personnel and monitoring, criteria specific to hospitalized patients

### Serious Adverse Evens (SAEs) Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Reported (N=36)</th>
<th>Related (N=25)</th>
<th>Estimate (CI&lt;sub&gt;95%&lt;/sub&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Four hour reports</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>15</td>
<td>4</td>
<td>0.08% (0.03-0.21)</td>
</tr>
<tr>
<td>Transfusion-Associated Circulatory Overload (TACO)</td>
<td>7</td>
<td>7</td>
<td>0.14% (0.07-0.29)</td>
</tr>
<tr>
<td>Transfusion-Related Acute Lung Injury (TRALI)</td>
<td>11</td>
<td>11</td>
<td>0.22% (0.12-0.39)</td>
</tr>
<tr>
<td>Severe allergic transfusion reaction</td>
<td>3</td>
<td>3</td>
<td>0.06% (0.02-0.18)</td>
</tr>
<tr>
<td><strong>Seven day reports</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>602</td>
<td></td>
<td>14.9% (13.8-16.0)</td>
</tr>
</tbody>
</table>

Passive immunity

Convalescent plasma (CP) - 3

- Retrospective, propensity score-matched case-control study, academic study, USA
- **Inclusion criteria:** laboratory confirmed COVID-19, severe (dyspnea, respiratory frequency ≥ 30/min, SpO₂ ≤ 93%, PaO₂/FiO₂ < 300 mm Hg, and/or lung infiltrates > 50% within 24 to 48 hours) or immediately life-threatening (respiratory failure, septic shock, and/or multiple organ dysfunction or failure) COVID-19,
- **Main outcome:** D14 oxygen requirement
- **Other outcomes:** death, discharge alive, survival probability
- **Convalescent plasma group:** 39 patients vs. **Control group**: 156 patients (1:4)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CP group (N=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD) – yr</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Male sex – no (%)</td>
<td>25 (64)</td>
</tr>
<tr>
<td>BMI, mean (SD) – kg/m²</td>
<td>31,7 (6)</td>
</tr>
</tbody>
</table>

**Co existing conditions**

- Diabetes – no (%) 8 (21)
- Current or former smoker – no (%) 29 (55.8)
- Cancer – no (%) 2 (5)

**Vital sign**

- Respiratory rate ≥ 20/min – no (%) 28 (72)
- Heart rate > 100/min – no (%) 22 (56)
Convalescent plasma (CP) - 3

- **D14 oxygen requirements**: worsened in 17.9% of convalescent plasma recipients versus 28.2% of propensity score matched controls hospitalized with COVID-19
- **Death**: 12.8% of convalescent plasma recipients and 24.4% of the 1:4 matched control patients
- **Discharged alive**: of convalescent plasma recipients and 71.8% and 66.7% of the 1:4 matched control patients
- **Survival probability**: greater in convalescent plasma recipients than controls
- **Limits**: small sample size, not a randomized controlled trial
Convalescent plasma (CP) - 4

• Observational, multicenter, academic study, France

• **Inclusion criteria:** B-cell immunodeficiency with prolonged COVID-19 symptoms, positive SARS-CoV-2 RT-PCR from respiratory samples, no SARS-CoV-2 seroconversion

• 17 patients treated with 4 units of COVID-19 convalescent plasma

• **Clinical symptoms:** 16/17 patients experienced amelioration of SARS-CoV-2 within 48 hours CP

• **SARS-CoV-2 RNAemia:** 9/9 patients witnessed a decreased below sensitivity threshold

---

### Characteristics (N=17)

<table>
<thead>
<tr>
<th>Age, median [range] - yr</th>
<th>58 [35-77]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex – no (%)</td>
<td>12 (71)</td>
</tr>
<tr>
<td>Hematological malignancies</td>
<td>15 (88)</td>
</tr>
<tr>
<td>Non - Hematological malignancies</td>
<td>2 (12)</td>
</tr>
<tr>
<td>COVID -19 severity (WHO score), n (%)</td>
<td></td>
</tr>
<tr>
<td>4 – no (%)</td>
<td>5 (29)</td>
</tr>
<tr>
<td>5-6 – no (%)</td>
<td>10 (59)</td>
</tr>
<tr>
<td>7 – no (%)</td>
<td>2 (12)</td>
</tr>
<tr>
<td>Time between COVID -19 symptoms onset and CPT (days), median [range]</td>
<td>56 [7-83]</td>
</tr>
<tr>
<td>Time for oxygen weaning after CPT (days), median [range]</td>
<td>5 [1-45]</td>
</tr>
<tr>
<td>Overall survival, n (%)</td>
<td>16 (94)</td>
</tr>
</tbody>
</table>
• **Vaccines aims**: expose the immune system to an antigen that won’t cause disease, provoke an immune response (able to block/kill the virus)

• **Eight types of vaccines**:
  - **virus** (inactivated, weakened),
  - **viral vector** (replicating, non replicating)
  - **nucleic acid** (DNA, RNA)
  - **protein based** (protein subunit, virus like particles)

Callaway E. *Nature*. Apr 2020
Vaccine

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

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

<table>
<thead>
<tr>
<th>Category</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase I/II</th>
<th>Phase II</th>
<th>Phase II/III</th>
<th>Phase III</th>
<th>Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>VIRUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivated</td>
<td>7</td>
<td>1</td>
<td>3</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weakened</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>VIRAL VECTOR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Replicating</td>
<td>17</td>
<td>4</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non replicating</td>
<td>25</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NUCLEIC ACID</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA</td>
<td>14</td>
<td>1</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA</td>
<td>25</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td><strong>PROTEIN BASED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein subunit</td>
<td>62</td>
<td>8</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virus-like Particles</td>
<td>13</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>32</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Adapted from LSHTM COVID19 vaccine tracker [https://vac.lshtm.shinyapps.io/ncov_vaccine_landscape/](https://vac.lshtm.shinyapps.io/ncov_vaccine_landscape/)
### Phase III COVID-19 Vaccines (Sep 30th 2020)

<table>
<thead>
<tr>
<th>Developer</th>
<th>Vaccine Platform</th>
<th>Description</th>
</tr>
</thead>
</table>
| BioNTech – Pfizer – Fosun Pharma | RNA | BNT162b2*: Lipid nanoparticle-formulated, nucleoside modified mRNA vaccine encoding full-length spike (S) protein  
*Phase I published data refers to candidate BNT162b1 using RBD as antigen (Ugur S et al Nature, Sep 2020). The company has decided to proceed to Phase II/III trials with BNT162b2 candidate who displayed reactogenicity in vaccinated adults. |
| Moderna – NIAID | RNA | mRNA-1273: Lipid nanoparticle-encapsulated, mRNA vaccine encoding pre-fusion spike (S) protein |
| CanSino Biologicals Inc – Beijing Institute of Biotechnology | Non replicating viral vector | Ad5-nCoV: Replication-deficient Ad5 vector containing optimised full-length spike (S) protein |
| Gamaleya Research Institute | Non replicating viral vector | Sputnik V: Recombinant Ad26 (prime) and recombinant Ad5 (boost) viruses expressing the gene for spike (S) protein |
| Janssen Pharmaceutical Companies – Beth Israel Deaconess Medical Center | Non replicating viral vector | Ad26COV-S1: Recombinant adenovirus vaccine (Ad26) incorporating SARS-CoV-2 full stabilized Spike (S) protein |
| University of Oxford – AstraZeneca | Non replicating viral vector | ChAdOx1 nCoV-19: Replication-deficient simian adenovirus vector containing codon-optimised spike (S) protein |
| Novavax | Protein subunit | NVX-COV2373: Recombinant nanoparticle vaccine consisting of full-length spike (S) protein, with or without Matrix-M1 adjuvant |
| Sinovac – Institut Butantan | Inactivated | CoronaVac: β-propiolactone inactivated vaccine administered with aluminium hydroxide adjuvant |
| Beijing Institute of Biological Products – Sinophram | Inactivated | BBIBP-CorV: β-propiolactone inactivated vaccine administered with aluminium hydroxide adjuvant |
| Wuhan Institute of Biological products– Sinopharm | Inactivated | SARS-CoV-2 Vaccine: β-propiolactone inactivated vaccine adsorbed to 0.5-mg aluminum |
mRNA 1273

IMMUNOGENICITY 1/2

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

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

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

<table>
<thead>
<tr>
<th>Time Point</th>
<th>25-μg Group</th>
<th>100-μg Group</th>
<th>250-μg Group</th>
<th>Convalescent Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no.</td>
<td>GMT (95% CI)</td>
<td>no.</td>
<td>GMT (95% CI)</td>
</tr>
<tr>
<td>Day 1</td>
<td>15</td>
<td>316 (72–187)</td>
<td>15</td>
<td>133 (65–266)</td>
</tr>
<tr>
<td>Day 15†</td>
<td>15</td>
<td>12,261 (1,000–555,000)</td>
<td>15</td>
<td>86,291 (54,000–132,000)</td>
</tr>
<tr>
<td>Day 26</td>
<td>15</td>
<td>391,018 (267,422–571,99)</td>
<td>15</td>
<td>78,199 (606,247–1,007,356)</td>
</tr>
<tr>
<td>Day 41</td>
<td>15</td>
<td>107,764 (21,597–531,152)</td>
<td>14</td>
<td>81,119 (65,314–1,002,400)</td>
</tr>
<tr>
<td>Day 57</td>
<td>13</td>
<td>209,751 (205,071–430,020)</td>
<td>14</td>
<td>782,719 (519,310–1,536,669)</td>
</tr>
</tbody>
</table>

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

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

*GMHI: Geometric mean humoral immunogenicity assay

ModernaNiH Phase I: [NCT04283461](https://clinicaltrials.gov/ct2/show/NCT04283461)
mRNA 1273

IMMUNOGENICITY 2/2

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

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

3. Cellular responses: 25-μg and 100-μg doses elicit CD4 T-cell responses biased toward expression of Th1 cytokines (TNFα > IL2 > IFNγ).
Ad5-nCoV

**CaSino BIO**

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

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

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

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

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

   ![ELISA antibody responses](image)

   **Anti-RBD IgG responses detected from day 14.** At day 28, the specific IgGs peaked at 656.5 (575.2–749.2) at the low dose group and 571.0 (467.6–697.3) at the high dose group. **Seroconversion** on 96% (95% CI 93–98) within the low dose group and 97% (95% CI 92–99) at the high dose group.
Ad5-nCoV

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

2. Neutralizing responses

**Assay:** SARS-CoV-2 virus neutralization test

**Units:** Geometric mean titer (95% CI)

Significant neutralizing antibody responses to live SARS-CoV-2, with GMTs of 19.5 (95% CI 16.8–22.7) and 18.3 (14.4–23.3) (low vs high dose groups) at day 28 post vaccination.

<table>
<thead>
<tr>
<th>Pre-existing adenovirus type-5 neutralising antibody</th>
<th>Low (50%)</th>
<th>High (48%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1:200, titre</td>
<td>127 (50%)</td>
<td>54 (42%)</td>
</tr>
<tr>
<td>&gt;1:200, titre</td>
<td>128 (50%)</td>
<td>75 (58%)</td>
</tr>
</tbody>
</table>

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

3. Induction of T cell mediated responses
**Gamaleya Research Institute**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Phase I/II open-label, non-randomised trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range</td>
<td>18 – 60</td>
</tr>
<tr>
<td>Nb of participants</td>
<td>76</td>
</tr>
<tr>
<td>Nb of doses/route</td>
<td>1 (day 0) or 2 (rAd26 on day 0, rAd5 on day 21) - IM</td>
</tr>
</tbody>
</table>

**Vaccine groups**
- **Frozen**
  - 1 x $10^{11}$ rAd26 (n = 9)
  - 1 x $10^{11}$ rAd5 (n = 9)
  - 10 x $10^{11}$ rAd26/10 x $10^{11}$ rAd5 (n = 20)
- **Lyo**
  - 1 x $10^{11}$ rAd26 (n = 9)
  - 1 x $10^{11}$ rAd5 (n = 9)
  - 10 x $10^{11}$ rAd26/10 x $10^{11}$ rAd5 (n = 20)

**SAE**
- None

**Local AE**
- Injection site pain (40–78%)

**Systemic AE**
- Changes in laboratory variables (67–100%), hyperthermia (11–100%), headache (25–67%), asthenia (0–55%), muscle or joint pain (11–33%), subjective heartbeat palpitation (0–33%)

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**IMMUNOGENICITY 1/2**

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

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

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

IMMUNOGENICITY 2/2

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

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

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

Logunov DY et al Lancet. Sep 2020
**ChAdOx1 nCoV-19**

**AstraZeneca-Oxford University**  
**Phase I:** [NCT04324606](https://clinicaltrials.gov/ct2/show/NCT04324606)

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

**IMMUNOGENICITY 1/2**

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

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

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

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

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

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

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

**Study Design**
Phase I randomised controlled, dose-finding trial

**Age range**
18 – 59

**Nb of participants**
131

**Nb of doses/route**
1 (day 0) or 2 (days 0/21) - IM

**Vaccine groups**
- 2 x 25 μg (n = 25)
- 2 x 5 μg + 50 μg Matrix-M1 (n = 28)
- 2 x 25 μg + 50 μg Matrix-M1 (n = 28)
- 1 x 25 μg + 50 μg Matrix-M1 (n = 25)
- 2 x 5 μg and 2 x 25 μg included 3 sentinel participants who were vaccinated in an open-label manner and observed for reactogenicity

**Control group:** 0.9% saline placebo (n = 25)

**SAE**
None

**Local AE**
Tenderness (20–65% at ds1, 12–81% at ds2), injection site pain (24–54% at ds1, 8–63% at ds 2)

**Systemic AE**
Headache (23–40% at dose 1, 28–58% at dose 2), muscle pain/myalgia (12–32% at dose 1, 8–54% at dose 2), fatigue (16–40% at dose 1, 12–50% at dose 2), malaise (4–28% at dose 1, 8–38% at dose 2), joint pain (4–27% at dose 2)

**IMMUNOGENICITY 1/2**

1. **SARS-CoV-2 Anti-Spike IgGs**
   - **Assay:** ELISA
   - **Units:** Geometric mean titre (95% CI)

   ![ELISA Graph](image)

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

**Keech C et al. NEJM. Sep 2020**
IMMUNOGENICITY 2/2

2. Neutralizing responses

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

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

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

**SARS-CoV-2 Vaccine**

**Wuhan Institute of Biological products**

**Study Design**
- Phase I: randomised controlled dose-finding trial
- Phase II: randomised controlled trial

**Age range**
18 – 59

**Nb of participants**
- Phase I: 96
- Phase II: 224

**Nb of doses/route**
- Phase I: 3 (days 0/28/56) – IM
- Phase II: 2 (days 0/14 or 0/21) -IM

**Vaccine groups**
- **Phase I:**
  - I2.5 μg (n = 24)
  - 5 μg (n = 24)
  - 10 μg (n = 24)
- **Control group:** Placebo of aluminum hydroxide (n = 24)
- **Phase II:**
  - 5 μg at d0/14 or d0/21 (n = 84 each group)
- **Control group:** Placebo of aluminum hydroxide, d0/14 (n = 28) or d0/21 (n = 28)

**SAE**
None

**Local AE**
- Phase I: Injection site pain (4–25% combining across doses)
- Phase II: None at ≥25% prevalence

**Systemic AE**
- Phase I and Phase II: None at ≥25% prevalence

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

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

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

   ![Graph showing specific IgG antibody titers to whole SARS-CoV-2 antigen](image)

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

_Xia S et al. JAMA. Sep 2020_
SARS-CoV-2 Vaccine

IMMUNOGENICITY 2/2 *(Phase II data)*

2. Neutralizing antibodies to live SARS-CoV-2

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

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

<table>
<thead>
<tr>
<th>Vaccine &amp; Developer</th>
<th>Phase III regimen</th>
<th>Specific IgG titers (14 - 28 days after 2nd dose) as per Phase I or II published results</th>
<th>NAb titers (14 - 28 days after 2nd dose) as per Phase I or II published results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BNT162b2 BioNTech – Pfizer – Fosun Pharma</td>
<td>2 doses (d1 and d22) 30µg/dose</td>
<td>Non published yet-preprint</td>
<td></td>
</tr>
<tr>
<td>mRNA-1273 Moderna – NIAID</td>
<td>2 doses (d1 and d29) 100µg/dose</td>
<td>782 719 GMT Test: ELISA anti S IgG</td>
<td>654.3 GMT Test: PRNT&lt;sub&gt;80&lt;/sub&gt;</td>
</tr>
<tr>
<td>Ad5-nCoV CanSino Biologicals Inc – Beijing Institute of Biotechnology</td>
<td>1 dose 5x10&lt;sup&gt;10&lt;/sup&gt; vp</td>
<td>571.0 GMT Test: ELISA anti RBD IgG</td>
<td>18.3 GMT Test: WT virus neutralization</td>
</tr>
<tr>
<td>SputnikV Gamaleya Research Institute</td>
<td>d1 0,5 mL rAd26 d21 0,5 mL rAd5</td>
<td>14 703 GMT Test: ELISA anti RBD IgG</td>
<td>49.25 GMT Test: MNA&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
<tr>
<td>Ad26COVS1 Janssen Pharmaceutical Companies Beth Israel Deaconness Medical Center</td>
<td>1 dose 1x10&lt;sup&gt;11&lt;/sup&gt; vp</td>
<td>Non published yet-preprint</td>
<td></td>
</tr>
<tr>
<td>ChAdOx1 nCoV-19 University of Oxford – AstraZeneca</td>
<td>2 doses (d1 and d29) 5x10&lt;sup&gt;10&lt;/sup&gt; vp</td>
<td>639 EU Test: ELISA anti S IgG</td>
<td>136 MT Test: MNA&lt;sub&gt;40&lt;/sub&gt;</td>
</tr>
<tr>
<td>NVX COV2373 Novavax</td>
<td>2 doses (d0 and d28) 25µg+Matrix M/ dose</td>
<td>47 521 GMEU Test: ELISA anti S IgG</td>
<td>3305 GMT Test: MNA&lt;sub&gt;99&lt;/sub&gt;</td>
</tr>
<tr>
<td>CoronaVac Sinovac – Institut Butantan</td>
<td>2 doses (d1 and d14)</td>
<td>Non published yet-preprint</td>
<td></td>
</tr>
<tr>
<td>BBIBP-CorV Beijing Inst. Biological Products – Sinopharm</td>
<td>2 doses (d0 and d21)</td>
<td>Non published yet-preprint</td>
<td></td>
</tr>
<tr>
<td>SARS-CoV-2 Vaccine Wuhan Inst. Biological products – Sinopharm</td>
<td>2 doses (d0 and d21)</td>
<td>215 GMT Test: ELISA anti S IgG</td>
<td>247 GMT Test: PRNT&lt;sub&gt;50&lt;/sub&gt;</td>
</tr>
</tbody>
</table>

**NOTE:** COMPARISONS SHOULD NOT BE MADE AS ASSAYS ARE NOT STANDARDIZED
1. What drug showed clinical efficacy?
   - Dexamethasone is the first drug to show life-saving efficacy in patients infected with COVID-19

2. What drugs did not show proven benefits?
   - No proven benefits have been reported with (hydroxy)chloroquine nor lopinavir/ritonavir treatment

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