COVID-19: Diagnostic and Therapeutic Strategies

Prof. Dr. Hortense Slevogt

Berlin/ Istanbul, May 28th, 2020
May 28th, 2020

The Johns Hopkins University COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) provides real-time data on the global spread of COVID-19. The dashboard includes information on confirmed cases, deaths, and recoveries worldwide. The data is updated regularly to reflect the latest information from various sources. The dashboard is a valuable resource for monitoring the pandemic and understanding its impact on different regions globally.
Case-Fatality Ratio (CFR):

The proportion of deaths from a certain disease compared to the total number of people diagnosed with the disease for a certain period of time.

Case-Fatality Ratio is dependent on:

- Tests performed and test capacities in the reporting countries
- Quality of the surveillance systems for reporting COVID-19 cases and deaths
- Availability of an efficient health care system
Case fatality rate of the ongoing COVID-19 pandemic, May 26, 2020

The Case Fatality Rate (CFR) is the ratio between confirmed deaths and confirmed cases. During an outbreak of a pandemic the CFR is a poor measure of the mortality risk of the disease. We explain this in detail at OurWorldInData.org/Coronavirus.

Source: European CDC – Situation Update Worldwide – Last updated 26th May, 11:00 (London time)
Note: Only countries with more than 100 confirmed cases are included.

OurWorldInData.org/coronavirus • CC BY
May 28th, 2020

<table>
<thead>
<tr>
<th>Country, Other</th>
<th>Total Cases</th>
<th>New Cases</th>
<th>New Deaths</th>
<th>New Deaths</th>
<th>Total Deaths</th>
<th>Total Recovered</th>
<th>Active Cases</th>
<th>Serious, Critical</th>
<th>Tot Cases/1M pop</th>
<th>Deaths/1M pop</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>5,813,004</td>
<td>+28,401</td>
<td></td>
<td></td>
<td>357,789</td>
<td>2,514,866</td>
<td>2,940,229</td>
<td>52,935</td>
<td>746</td>
<td>45.9</td>
<td></td>
</tr>
<tr>
<td>1 USA</td>
<td>1,745,911</td>
<td>+108</td>
<td></td>
<td></td>
<td>102,114</td>
<td>490,151</td>
<td>1,153,646</td>
<td>17,166</td>
<td>5,277</td>
<td>309</td>
<td>330,822,304</td>
</tr>
<tr>
<td>2 Brazil</td>
<td>414,661</td>
<td></td>
<td></td>
<td></td>
<td>25,697</td>
<td>166,407</td>
<td>222,317</td>
<td>8,318</td>
<td>1,952</td>
<td>121</td>
<td>212,418,030</td>
</tr>
<tr>
<td>3 Russia</td>
<td>379,051</td>
<td>+8,371</td>
<td></td>
<td></td>
<td>4,142</td>
<td>150,993</td>
<td>223,916</td>
<td>2,300</td>
<td>2,598</td>
<td>28</td>
<td>145,928,826</td>
</tr>
<tr>
<td>4 Spain</td>
<td>283,849</td>
<td></td>
<td></td>
<td></td>
<td>27,118</td>
<td>196,958</td>
<td>59,773</td>
<td>854</td>
<td>6,071</td>
<td>580</td>
<td>46,763,147</td>
</tr>
<tr>
<td>5 UK</td>
<td>267,240</td>
<td></td>
<td></td>
<td></td>
<td>37,460</td>
<td>N/A</td>
<td>N/A</td>
<td>1,559</td>
<td>3,939</td>
<td>552</td>
<td>67,852,992</td>
</tr>
<tr>
<td>6 Italy</td>
<td>231,139</td>
<td></td>
<td></td>
<td></td>
<td>33,072</td>
<td>147,101</td>
<td>50,966</td>
<td>505</td>
<td>3,822</td>
<td>547</td>
<td>60,469,746</td>
</tr>
<tr>
<td>7 France</td>
<td>182,913</td>
<td></td>
<td></td>
<td></td>
<td>28,596</td>
<td>66,584</td>
<td>87,733</td>
<td>1,501</td>
<td>2,803</td>
<td>438</td>
<td>65,260,368</td>
</tr>
<tr>
<td>8 Germany</td>
<td>181,895</td>
<td></td>
<td></td>
<td></td>
<td>8,533</td>
<td>163,200</td>
<td>10,162</td>
<td>763</td>
<td>2,172</td>
<td>102</td>
<td>83,759,426</td>
</tr>
<tr>
<td>9 Turkey</td>
<td>159,797</td>
<td></td>
<td></td>
<td></td>
<td>4,431</td>
<td>122,793</td>
<td>32,573</td>
<td>723</td>
<td>1,897</td>
<td>53</td>
<td>84,252,379</td>
</tr>
<tr>
<td>10 India</td>
<td>158,897</td>
<td>+811</td>
<td></td>
<td></td>
<td>4,540</td>
<td>67,901</td>
<td>86,456</td>
<td>8,944</td>
<td>115</td>
<td>3</td>
<td>1,378,715,135</td>
</tr>
<tr>
<td>11 Iran</td>
<td>143,849</td>
<td>+2,258</td>
<td></td>
<td></td>
<td>7,627</td>
<td>112,988</td>
<td>23,234</td>
<td>2,543</td>
<td>1,715</td>
<td>91</td>
<td>83,889,077</td>
</tr>
<tr>
<td>12 Peru</td>
<td>135,905</td>
<td></td>
<td></td>
<td></td>
<td>3,983</td>
<td>56,169</td>
<td>75,753</td>
<td>926</td>
<td>4,127</td>
<td>121</td>
<td>32,927,196</td>
</tr>
<tr>
<td>13 Canada</td>
<td>87,519</td>
<td></td>
<td></td>
<td></td>
<td>6,765</td>
<td>46,164</td>
<td>34,590</td>
<td>502</td>
<td>2,321</td>
<td>179</td>
<td>37,710,897</td>
</tr>
<tr>
<td>14 China</td>
<td>82,005</td>
<td></td>
<td></td>
<td></td>
<td>4,834</td>
<td>70,208</td>
<td>73</td>
<td>1</td>
<td>52</td>
<td>4</td>
<td>130,222,778</td>
</tr>
</tbody>
</table>

Total Tests

15,877,027
47,993
330,822,304

Tests/1M pop

47,993
1M pop

Population

330,822,304
Case-Fatality Rate is dependent on:

- Tests performed/Test capacities in the reporting countries
- Quality of the surveillance systems for reporting COVID-19 cases and deaths

Increasing tests in number and capacity in Germany over time between March 16th and Mai 18th, 2020

<table>
<thead>
<tr>
<th>Kalenderwoche 2020</th>
<th>KW 11</th>
<th>KW 12</th>
<th>KW 13</th>
<th>KW 14</th>
<th>KW 15</th>
<th>KW 16</th>
<th>KW 17</th>
<th>KW 18</th>
<th>KW 19</th>
<th>KW 20</th>
<th>KW 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anzahl übermittelnde Labore</td>
<td>28</td>
<td>93</td>
<td>111</td>
<td>113</td>
<td>132</td>
<td>112</td>
<td>126</td>
<td>133</td>
<td>137</td>
<td>134</td>
<td>136</td>
</tr>
<tr>
<td>Testkapazität pro Tag</td>
<td>7.115</td>
<td>31.010</td>
<td>64.725</td>
<td>103.515</td>
<td>116.655</td>
<td>123.304</td>
<td>136.064</td>
<td>141.815</td>
<td>153.698</td>
<td>157.150</td>
<td>159.418</td>
</tr>
<tr>
<td>Neu ab KW 15: wöchentliche Kapazität anhand von Wochenarbeitstagen</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>730.156</td>
<td>818.426</td>
<td>860.494</td>
<td>964.962</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.038.223</td>
<td>1.050.676</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Tab. 2 | Testkapazitäten der übermittelnden Labore pro Tag und Kalenderwoche (19.5.2020, 12.00 Uhr)
SARS-CoV-2: Diagnostic Strategies

- Detection of virus specific RNA by PCR
- Detection of virus specific antibodies generated by the host by ELISA
- Detection of SARS-CoV-2 typical infiltrations the Computertomography
SARS-CoV-2

Antibody Detection

PCR

The SARS-CoV-2 PCR test from the combined nasal and throat swab

Method: PCR (Polymerase Chain Reaction)
- Method for amplifying minute amounts of DNA
- A piece of DNA can be copied as often as desired and thus be detected

Diagnostic of acute Covid-19 Infections
The PCR tests of patients hospitalized with clinically diagnosed COVID-19 are not always PCR positive:

Results: RT-PCR test results of pharyngeal swab specimens variable and unstable. Combination with clinical based methods often needed in hospitalized patients.

Li Y et al J med Virol 2020
Results: Active pharyngeal viral shedding can be detected in the first week of symptoms later in the disease SARS-CoV-2 can be detected in the lower respiratory tract

Wölfel R et al. Nature 2020
Serological Test Systems:

- IgM, IgA, IgG antibodies specifically detecting SARS-CoV-2
- Detection between 7 and 11 days postexposure to the virus

Serologic testing may (!) facilitate

- Contact tracing
- Serologic surveillance at the local, regional, state, and national levels
- Identification of those who have already had the virus
- Can possibly be used diagnostically to test viral RNA-negative individuals presenting late in their illness

Patel R et al, Mbio 2020
Serological Test Systems:

Problems:

- Reliable detection of a specific antibody response targeting distinct SARS-CoV-2 in all infected patients: Unknown
- Differences in antibody response between mild and severe cases: Possible
- Duration of detectable antibodies: Unknown
- Protective effect of the antibodies: Unknown

To KKW et al. Lancet Infectious Diseases 2020
# Tests for SARS-CoV-2/COVID-19 and Potential Uses

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Measure</th>
<th>Value</th>
<th>Beneficiary</th>
</tr>
</thead>
</table>
| Nucleic acid amplification test for viral RNA (nasopharyngeal swab, oropharyngeal swab, sputum, bronchoalveolar lavage fluid, others) | Current infection with SARS-CoV-2          | • Inform individual of infection status so they can anticipate course of illness and take action to prevent transmission  
• Inform patient management and actions needed to prevent transmission  
• Inform actions needed to prevent transmission | • Individual  
• Healthcare or long-term care facility  
• Public health |
| Antibody detection           | Past exposure to SARS-CoV-2               | • Detect susceptible individuals (antibody negative) and those previously infected  
• Identify individuals with neutralizing antibodies  
• Facilitate contact tracing and surveillance | • Identify those potentially immune to SARS-CoV-2 (if tests can detect protective immunity, individuals could be returned to work)  
• Healthcare facilities: Experimental therapy  
• Public health |

Robin Patel et al. mBio 2020; doi:10.1128/mBio.00722-20
The COVID-19 Patient: Course of disease and therapeutic strategies

Therapeutic concepts
- Inhibition of virus entry into the cell and virus replication
- Specific strengthening of the body's own defence against viral infections
- Inhibition of the excessive inflammatory reaction in severe courses
Prerequisite for the development of a therapy against SARS-CoV-2

- Efficacy against SARS-CoV-2 proven in the laboratory
- Meaningful hypothesis of effectiveness
- Quickly available
- Tolerable side effects
- Approval already exists for other indications in humans
- Experience with the drug
Concept I: SARS-CoV-2: Inhibition of the entry into the human cell

- Production of the isolated ACE2 receptor of the human cell, which the virus uses for invasion. This soluble receptor will then be given to the patient to protect the cells for the viral infection (studies are ongoing)

- Specific antibodies against SARS-CoV-2 are isolated from the blood of reconvalescent patients and given to the patient during the disease (research in progress)

- The plasma of convalescent patients known to contain antibodies is used to treat patients with severe infections
Convalescent plasma treatment of severe COVID-19: A matched control study

Convalescent plasma recipients were more likely to remain the same or have improvements in their supplemental oxygen requirements by post-transfusion day 14.

- Demonstrated improved survival, compared to control patients.
- Improved survival for non-intubated patients, but not for intubated patients.
- FAZIT: Improving effect detectable after one week, not in severe cases.

Figure 1. Comparison of oxygen requirements between Day 14 versus Day 0.

39 Patients: (Moderate and severe disease)
Concept I: SARS-CoV-2: Inhibition of virus replication

- Remdesivir
- Lopinavir/Ritonavir (Kaletra)
- Chloroquin/Hydroxychloroquin
Conclusions

- Remdesivir was superior to placebo in shortening the time to recovery in adults hospitalized with Covid-19
- Only slight statistically and not significant survival benefit, with a 14-day mortality rate (7.1% versus 11.9%)
Registerstudy:
Multinational registry analysis of the use of hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19. The registry comprised data from 671 hospitals in six continents.

Increased risk of death
CONCLUSIONS: In hospitalized adult patients with severe Covid-19, no benefit was observed with lopinavir–ritonavir treatment beyond standard care.

(...) need to evaluate antivirals with other therapeutic agents to continue to improve clinical outcomes for patients with COVID-19.
Concept II: Immunomodulation

- Support of the body's own virus-specific immune therapy
  - Interferon beta (studies are ongoing)
- Reduction of the excessive inflammatory reaction
  - Tociluzimab, etc. (studies are ongoing)
Combination therapy:
Lopinavir/ Ritonavir + Interferon beta + Ribavirin

127 participants (mild and moderate disease):

Conclusion: Early triple antiviral therapy was safe and superior to lopinavir–ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19.
COVID-19: Consequences for patients with other diseases and their willingness to take health risks

May 2020: Shown are data from the Kaiser Permanente Northern California health system.
Thank you for your attention!
Danke für die Aufmerksamkeit!
İlginiz için teşekkür ederim!
hortense.slevogt@med.uni-jena.de