Early transmission, pandemic spread and severity of COVID-19

Basel Biometric Section - Aspects of COVID-19 pandemic, 3 June 2020

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Image: NIAID
Key questions for early outbreak response

1. What is the transmissibility (basic reproduction number $R_0$)

2. What is the disease severity (case fatality ratio)
Basic reproduction number $R_0$

To how many people does an infected person transmit the disease on average (no control interventions, no acquired immunity, no vaccine)?
$R_0$ and variation in secondary cases

$R_0 = 2$

Superspreading events

Steady transmission chains

Overdispersion parameter $k$
Simulating early outbreak trajectories in China

Strengths and limitations

The scarcity of available data, especially on case counts by date of disease onset as well as contact tracing, greatly limits the precision of our estimates and does not yet allow for reliable forecasts of epidemic spread. Case counts provided by local authorities in the early stage of an emerging epidemic are notoriously unreliable as reporting rates are unstable and vary with time. This is due to many factors such as the initial lack of proper diagnosis tools, the focus on the more severe cases or the overcrowding of hospitals. We avoided this surveillance bias by relying on an indirect estimate of epidemic size on January 18, based on cases identified in foreign countries before quarantine measures were implemented on January 23. This estimated range of epidemic size relies itself on several assumptions, including that all infected individuals who travelled from Wuhan to other countries have been detected. This caveat may lead to an underestimation of transmissibility, especially considering the recent reports about asymptomatic cases. Conversely, our results do not depend on any assumption about the existence of asymptomatic transmission, and only reflect the possible combinations of transmission events that lead to the situation on January 18.

Figure: Riou & Althaus (2020, Euro Surveill)
Estimated epidemiological parameters

Figure based on: Riou & Althaus (2020, Euro Surveill)

R0

Density

2.2 (90% HDI: 1.4-3.8)

Doubling time

Density

7.9 d (90% HDI: 3.9-17.0 d)

Control threshold

Density

55% (90% HDI: 29%-76%)
Comparison to MERS, SARS and influenza

Our analysis, while limited because of the scarcity of data, has two important strengths. Firstly, it is based on the simulation of a wide range of possibilities regarding epidemic parameters and allows for the full propagation on the final estimates of the many remaining uncertainties regarding 2019-nCoV and the situation in Wuhan: on the actual size of the epidemic, on the size of the initial zoonotic event at the wet market, on the date(s) of the initial animal-to-human transmission event(s) and on the generation time interval. As it accounts for all these uncertainties, our analysis provides a summary of the current state of knowledge about the human-to-human transmissibility of 2019-nCoV. Secondly, its focus on the possibility of superspreading events by using negative-binomial offspring distributions appears relevant in the context of emerging coronaviruses [7, 8]. While our estimate of $R_0$ remains imprecise, the simulations suggest that very low values $k < 0.1$ are less likely than higher values $> 0.1$ that correspond to a more homogeneous transmission pattern. However, values of $k$ in the range of 0.1–0.2 are still compatible with a small risk of occurrence of large superspreading events, especially impactful in hospital settings [15, 16].

Conclusions
Our analysis suggests that the early pattern of human-to-human transmission of 2019-nCoV is reminiscent of SARS-CoV emergence in 2002. International collaboration and coordination will be crucial in order to contain the spread of 2019-nCoV. At this stage, particular attention should be given to the prevention of possible rare but explosive superspreading events, while the establishment of sustained transmission chains from single cases cannot be ruled out. The previous experience with SARS-CoV has shown that established practices of infection control, such as early detection and isolation, contact tracing and the use of personal protective equipment, can stop such an epidemic. Given the existing uncertainty around the case fatality rate $F$.

Proportion of simulated epidemics that lead to a cumulative incidence between 1,000 and 9,700 of the 2019 novel coronavirus outbreak, China, on 18 January 2020

MERS: Middle East respiratory syndrome-related coronavirus; SARS: severe acute respiratory syndrome-related coronavirus.

This can be interpreted as the combinations of $R_0$ and $k$ values most compatible with the estimation of epidemic size before quarantine measures were put in place. As a comparison, we show the estimates of $R_0$ and $k$ for the early human-to-human transmission of SARS-CoV in Singapore and Beijing and of 1918 pandemic influenza [7, 9, 14].

Figure: Riou & Althaus (2020, Euro Surveill)
“We have therefore made the assessment that COVID-19 can be characterized as a pandemic.”

-WHO Director-General, 11 March 2020
Early-stage importation risk to Europe

Figure: Pullano et al. (2020, Euro Surveill)
Outbreak control by isolating cases and contacts

Figure: Hellewell et al. (2020, Lancet Glob Health)
“It’s just like the flu.”

-Several ‘experts’
Case fatality in mainland China

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Confirmed Cases, N (%)</th>
<th>Deaths, N (%)</th>
<th>Case Fatality Rate, %</th>
<th>Observed Time, PD</th>
<th>Mortality, per 10 PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>44,672</td>
<td>1,023</td>
<td>2.3</td>
<td>661,609</td>
<td>0.015</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>416 (0.9)</td>
<td>-</td>
<td>-</td>
<td>4,383</td>
<td>-</td>
</tr>
<tr>
<td>10–19</td>
<td>549 (1.2)</td>
<td>1 (0.1)</td>
<td>0.2</td>
<td>6,625</td>
<td>0.002</td>
</tr>
<tr>
<td>20–29</td>
<td>3,619 (8.1)</td>
<td>7 (0.7)</td>
<td>0.2</td>
<td>53,953</td>
<td>0.001</td>
</tr>
<tr>
<td>30–39</td>
<td>7,600 (17.0)</td>
<td>18 (1.8)</td>
<td>0.2</td>
<td>114,550</td>
<td>0.002</td>
</tr>
<tr>
<td>40–49</td>
<td>8,571 (19.2)</td>
<td>38 (3.7)</td>
<td>0.4</td>
<td>128,448</td>
<td>0.003</td>
</tr>
<tr>
<td>50–59</td>
<td>10,008 (22.4)</td>
<td>130 (12.7)</td>
<td>1.3</td>
<td>151,059</td>
<td>0.009</td>
</tr>
<tr>
<td>60–69</td>
<td>8,583 (19.2)</td>
<td>309 (30.2)</td>
<td>3.6</td>
<td>128,088</td>
<td>0.024</td>
</tr>
<tr>
<td>70–79</td>
<td>3,918 (8.8)</td>
<td>312 (30.5)</td>
<td>8.0</td>
<td>55,832</td>
<td>0.056</td>
</tr>
<tr>
<td>≥80</td>
<td>1,408 (3.2)</td>
<td>208 (20.3)</td>
<td>14.8</td>
<td>18,671</td>
<td>0.111</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>22,981 (51.4)</td>
<td>653 (63.8)</td>
<td>2.8</td>
<td>342,063</td>
<td>0.019</td>
</tr>
<tr>
<td>Female</td>
<td>21,691 (48.6)</td>
<td>370 (36.2)</td>
<td>1.7</td>
<td>319,546</td>
<td>0.012</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Service industry</td>
<td>3,449 (7.7)</td>
<td>23 (2.2)</td>
<td>0.7</td>
<td>54,484</td>
<td>0.004</td>
</tr>
<tr>
<td>Farmer/laborer</td>
<td>9,811 (22.0)</td>
<td>139 (13.6)</td>
<td>1.4</td>
<td>137,992</td>
<td>0.010</td>
</tr>
<tr>
<td>Health worker</td>
<td>1,716 (3.8)</td>
<td>5 (0.5)</td>
<td>0.3</td>
<td>28,069</td>
<td>0.002</td>
</tr>
<tr>
<td>Retiree</td>
<td>9,193 (20.6)</td>
<td>472 (46.1)</td>
<td>5.1</td>
<td>137,118</td>
<td>0.034</td>
</tr>
<tr>
<td>Other/none</td>
<td>20,503 (45.9)</td>
<td>384 (37.5)</td>
<td>1.9</td>
<td>303,946</td>
<td>0.013</td>
</tr>
</tbody>
</table>
Challenges in assessing case fatality ratio

1. Under-ascertainment of mild cases ⇒ leads to overestimation

2. Right-censoring of cases with respect to delay from illness onset to death ⇒ leads to underestimation

Figure: Linton et al. (2020, J Clin Med)
Compartmental COVID-19 transmission model

Figure: Hauser et al. (2020, PLOS Med, in print)
COVID-19 epidemic in Switzerland

Figure S7: Data used to fit the model in Switzerland. (A) Reported confirmed cases of COVID-19. (B) Age distribution of the Chinese population compared to that of confirmed cases and of deaths due to COVID-19. (C) Reported deaths (D) Matrix representing the average number of daily contacts between each age class in Europe (POLYMOD)

Figure: Hauser et al. (2020, PLOS Med, in print)
Model fit to COVID-19 epidemic in Hubei, China

Our work has three important strengths. First, we use a mechanistic model for the transmission of, and the mortality associated with SARS-CoV-2 infection which directly translates the data-generating mechanisms leading to biased estimates. In Hubei, as the model captured most of the epidemic wave, the predicted number and timing of deaths until 11 February 2020, projected deaths after 11 February 2020 and overall deaths.

Strengths and limitations

Deaths per day

Cases per day

Total cases

Infected cases

Symptomatic cases

Reported cases

Projected deaths

Reported deaths

Total deaths

Figure: Hauser et al. (2020, PLOS Med, in print)
Adjusted infection fatality ratios in Hubei, China and six areas of Europe

Table 1: Model estimates of total infections of SARS-CoV-2 infection, total deaths, crude case fatality rate (CFR), symptomatic fatality rate (SFR) and infection fatality rate (IFR) by area.

<table>
<thead>
<tr>
<th>Area (limit date)</th>
<th>Estimated total infections</th>
<th>Estimated total deaths</th>
<th>CFR</th>
<th>SFR</th>
<th>IFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hubei, China (11 February)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Baseline</td>
<td>83,300 (73,000-98,600)</td>
<td>2,450 (2,230-2,700)</td>
<td>2.4% (2.1-2.8)</td>
<td>3.7% (3.2-4.2)</td>
<td>2.9% (2.4-3.5)</td>
</tr>
<tr>
<td>- After correction</td>
<td>138,000 (120,000-162,000)</td>
<td>3,430 (3,120-3,760)</td>
<td>2.1% (1.8-2.4)</td>
<td>3.1% (2.7-3.5)</td>
<td>2.5% (2.1-2.9)</td>
</tr>
<tr>
<td>- With lower susceptibility of children</td>
<td>74,100 (63,600-86,700)</td>
<td>2,440 (2,230-2,710)</td>
<td>2.4% (2.1-2.8)</td>
<td>4.1% (3.6-4.7)</td>
<td>3.3% (2.7-4.0)</td>
</tr>
<tr>
<td>Austria (14 April)</td>
<td>69,100 (56,500-82,700)</td>
<td>731 (623-867)</td>
<td>3.0% (2.4-3.7)</td>
<td>1.3% (1.1-1.6)</td>
<td>1.1% (0.8-1.3)</td>
</tr>
<tr>
<td>Baden-Württemberg, Germany (16 April)</td>
<td>212,000 (188,000-247,000)</td>
<td>1,580 (1,060-2,710)</td>
<td>3.3% (2.1-5.7)</td>
<td>0.9% (0.6-1.6)</td>
<td>0.7% (0.5-1.3)</td>
</tr>
<tr>
<td>Bavaria, Germany (16 April)</td>
<td>257,000 (228,000-296,000)</td>
<td>1,940 (1,420-2,720)</td>
<td>3.3% (2.4-4.9)</td>
<td>0.9% (0.7-1.3)</td>
<td>0.8% (0.5-1.1)</td>
</tr>
<tr>
<td>Lombardy, Italy (25 April)</td>
<td>1,150,000 (1,010,000-1,350,000)</td>
<td>15,700 (13,900-17,600)</td>
<td>18.2% (15.7-21.0)</td>
<td>1.7% (1.5-2.0)</td>
<td>1.4% (1.1-1.6)</td>
</tr>
<tr>
<td>Spain (16 April)</td>
<td>2,650,000 (2,360,000-3,090,000)</td>
<td>27,800 (25,400-30,500)</td>
<td>11.1% (9.9-12.5)</td>
<td>1.3% (1.2-1.5)</td>
<td>1.0% (0.9-1.2)</td>
</tr>
<tr>
<td>Switzerland (23 April)</td>
<td>308,000 (248,000-383,000)</td>
<td>1,520 (1,380-1,690)</td>
<td>4.1% (3.4-5.1)</td>
<td>0.6% (0.5-0.8)</td>
<td>0.5% (0.4-0.6)</td>
</tr>
</tbody>
</table>

Table: Hauser et al. (2020, PLOS Med, in print)
Report 4: Severity of 2019-novel coronavirus (nCoV)

(Download Report 4)

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Summary Report 4

We present case fatality ratio (CFR) estimates for three strata of COVID-19 (previously termed 2019-nCoV) infections. For cases detected in Hubei, we estimate the CFR to be 18% (95% credible interval: 11%-81%). For cases detected in travellers outside mainland China, we obtain central estimates of the CFR in the range 1.2-5.6% depending on the statistical methods, with substantial uncertainty around these central values. Using estimates of underlying infection prevalence in Wuhan at the end of January derived from testing of passengers on repatriation flights to Japan and Germany, we adjusted the estimates of CFR from either the early epidemic in Hubei Province, or from cases reported outside mainland China, to obtain estimates of the overall CFR in all infections (asymptomatic or symptomatic) of approximately 1% (95% confidence interval 0.5%-4%). It is important to note that the differences in these estimates does not reflect underlying differences in disease severity between countries. CFRs seen in individual countries will vary depending on the sensitivity of different surveillance systems to detect cases of differing levels of severity and the clinical care offered to severely ill cases. All CFR estimates should be viewed cautiously at the current time as the sensitivity of surveillance of both deaths and cases in mainland China is unclear. Furthermore, all estimates rely on limited data on the typical time intervals from symptom onset to death or recovery which influences the CFR estimates.

Source: https://www.imperial.ac.uk/mrc-global-infectious-disease-analysis
Summary

• Transmission: $R_0$ around 2 - 3

• Variation in secondary cases: Between SARS and influenza

• Control: More than 75% of cases need to be isolated for successful control

• Severity: Infection fatality ratio of 0.5%-1.5% in different areas of Europe

• Open questions: Seasonality, immunity, endemicity