COVID-19: the science of how we got here and where we are headed

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SARS-CoV-2

- Spike (S) protein binds to angiotensin-converting enzyme 2 (ACE2) on the membranes of lung alveolar cells, upper airway epithelial cells and glandular cells of the GI tract.
Routes of transmission

• SARS-CoV-2 spread by three routes:
  • Respiratory droplets spread (≥5μ)
  • Aerosol (airborne) spread (<5μ)
  • Fomite (surface) transmission

• Droplet spread is far and away the most common

• Target = respiratory epithelial cells with ACE2 receptor (including conjunctivae)

• Number of droplets exhaled depends on force of exhalation
  • Breathing 50-5,000 droplets (=200-1000 viral particles/min for influenza)
  • 10x increase when speaking
  • 30,000 droplets when sneezing (=2M viral particles)
Natural history of SARS-CoV-2 infection

- **Presymptomatic phase** (0-3 days):
  - No symptoms
  - Not infectious

- **Virologic phase** (4-7 days):
  - First week:
    - Fever, cough, fatigue, myalgia, loss of taste and smell. Diarrhea
  - Infectious but waning

- **Immunopathologic phase** (8-15 days):
  - Second week:
    - Respiratory distress, pneumonia, need for ICU admission and mechanical ventilation
    - May be infectious to 20 days

40% of patients develop no symptoms during course of illness
Spectrum of severity of illness from SARS-CoV-2 infection

- **Asymptomatic**: No dyspnoea, SOB or abnormal chest imaging, SpO2 ≥94%. 40%
- **Mildly symptomatic**: Evidence of lower respiratory track disease on exam or imaging, SpO2≥94%. 30%
- **Moderate COVID-19**: SpO2<94% on room air, RR>30/min, lung infiltrates, PaO2/FiO2 <300 mm Hg. 15%
- **Severe illness**: Respiratory failure, septic shock, multiorgan system dysfunction. 10%
- **Critical illness**: 5%
## Predictors of COVID-19 progression

<table>
<thead>
<tr>
<th>Strongest predictors</th>
<th>Mixed evidence</th>
<th>More data needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Asthma</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>Cerebrovascular disease</td>
<td>Neurologic conditions</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Hypertension</td>
<td>HIV</td>
</tr>
<tr>
<td>COPD</td>
<td>Pregnancy</td>
<td>Bone marrow transplant</td>
</tr>
<tr>
<td>Cardiovascular disease (CAD, CHR)</td>
<td>Immunosuppressive medications</td>
<td>Other immune deficiencies</td>
</tr>
<tr>
<td>Diabetes mellitus, type 2</td>
<td></td>
<td>Inherited metabolic disorders</td>
</tr>
<tr>
<td>Obesity (BMI &gt;30)</td>
<td></td>
<td>Diabetes mellitus, type 1</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>Thalassemia</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td></td>
<td>Overweight (BMI 25-29)</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td></td>
<td>Other chronic lung conditions</td>
</tr>
</tbody>
</table>
Persistence of neutralizing antibodies

• 18 HCWs neutralizing antibody seropositive at baseline
  • 8 (42%) had persistent antibody 2 months later
    • 6 (75%) of 8 symptomatic HCWs persistently seropositive
    • 2 (25%) of 8 asymptomatic HCWs persistently seropositive
    • P=0.35 by Fisher’s exact test
• Take home message, 58% of seropositive HCWs “lost” neutralizing antibody within two months

Pre-existing neutralizing antibody associated protection in outbreak on a U.S. fishing vessel

- 120 of 122 crew members consented to testing pre-voyage
- 103 (86%) attack rate
- 3 of 3 crew members with pre-existing neutralizing antibody to RDC did not become infected

<table>
<thead>
<tr>
<th>On boat</th>
<th>Infected</th>
<th>Not infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutralizing Ab (+)</td>
<td>0</td>
<td>103</td>
</tr>
<tr>
<td>Neutralizing Ab (-)</td>
<td>3</td>
<td>14</td>
</tr>
</tbody>
</table>

p=0.0024

Is reinfection possible?

• 33-year-old man in Hong Kong
  • Two diagnoses of SARS-CoV-2 infection 4.5 months apart (first mild, second asymptomatic)
  • Second infection was acquired in Europe
  • On genetic analysis, the strains from the first and second infection do not match – indicates new infection rather than prolonged viral shedding

• Two additional cases from Europe reported on August 25
  • One older patient from the Netherlands with a weakened immune system, the other a Belgian woman who was infected with mild symptoms in March and again in June

• One additional case from Nevada on August 28
  • 25-year-old man reinfected 62 days later, more symptomatic the second time

• Implications
  • Immunity wanes after 4 months?

Super spreading events – point source exposures

- Review of nine point-source SARS-CoV-2 exposures
- Overall secondary attack rate 35% (95% confidence interval, 27-44%) (varied from 21%-100%)
- Suggests transmission is driven by relatively small number of high-risk, close contacts

<table>
<thead>
<tr>
<th>Location</th>
<th>Date of exposure</th>
<th>Setting</th>
<th>Number at gathering (excluding primary case)</th>
<th>Subsequently infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harbin, Heilongjiang, China</td>
<td>Jan 24, 2020</td>
<td>Meal (home)</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Shuangyashan, Heilongjiang, China</td>
<td>Jan 24, 2020</td>
<td>Meal (home)</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Hangzhou, Zhejiang, China</td>
<td>Jan 17, 2020</td>
<td>Meal (unknown location)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Nanjing, Jiangsu, China</td>
<td>Jan 23, 2020</td>
<td>Meal (unknown location)</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Nanjing, Jiangsu, China</td>
<td>Jan 24, 2020</td>
<td>Meal (restaurant)</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Enshi, Hubei, China</td>
<td>Unknown</td>
<td>Meal (unknown location)</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Enshi, Hubei, China</td>
<td>Unknown</td>
<td>Meal (unknown location)</td>
<td>47</td>
<td>10</td>
</tr>
<tr>
<td>Haute-Savoie, France</td>
<td>Jan 24-28, 2020</td>
<td>Chalet</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Hong Kong</td>
<td>Unknown</td>
<td>Meal (home)</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

Full details are provided in the appendix.

Table: Summary of severe acute respiratory syndrome coronavirus 2 transmission events where the numbers of people exposed and subsequently infected were known, assuming a single primary case, by location

Source of SARS-CoV-2 infection by time, Hong Kong

Models of super spreading

Goyal A, Reeves DB, Cardozo-Ojeda EF, Schiffer JT, Mayer BT. Wrong person, place, and time: viral load and contact network structure predict SARS-CoV-s transmission and super-spreading events. medRxiv 2020 Aug 7 [Preprint].

Fig 3. SARS-CoV-2 transmission probability as a function of shedding. A. Optimal infectious dose (ID) response curve (infection risk = \( P_i \)) and transmission dose (TD) response curve (transmission risk = \( P_t \)) curves for SARS-CoV-2. Transmission probability is a product of two probabilities, contagiousness and infectiousness. B-D. Three simulated viral shedding curves. Heat maps represent risk of transmission at each shedding timepoint given an exposed contact with an uninfected person at that time.
COVID cases by country and WHO region, worldwide, 2020

- 50,913,451 cases
- 1,242,263 deaths
- 35,323,467 recovered

Leading countries
- United States 10.11M
- India 8.59M
- Brazil 5.68M
- France 1.86M
- Russia 1.78M
- Spain 1.38M
- Argentina 1.25M
- United Kingdom 1.22M
- Colombia 1.15M
- Italy 1.00M
Figure 2. COVID-19 cases per million population reported in the last seven days by countries, territories and areas, 26 October through 1 November 2020**

Cases reported in the last 7 days (per 1 million population)
- < 101
- 101 - 500
- 501 - 1,000
- > 1,000
- No cases reported in the last 7 days
- No reported cases

Map Production: WHO Health Emergencies Programme

**See data, table and figure notes**
COVID-19 cases and deaths, United States, 2020

• Cases continue to rise explosively across much of the country, and rise will likely accelerate as people move indoors for winter
• Rapidly increasing everywhere but the CA, HI, NH, ME, VT
• Largest number of cases in past 7 days
  • ND, SD, IA, WI, NE, WY, MN, MT, IL, UT per capita
  • IL, TX, WI, CA, FL, MI, OH, MN, IN, IA absolute cases
  • With surge, TX has passed CA as having the most cases since beginning of the pandemic

10,191,200 total cases
130,553 on Nov 9

238,776 total deaths
745 on Nov 9
COVID-19 cases by day at three peaks, United States, 2020
COVID-19 cases and deaths by day, California, 2020

Most new cases in past 7 days: Los Angeles, San Bernardino, San Diego, Riverside, Orange, Sacramento, Santa Clara, Fresno, Alameda, Kern

Most new cases per capita: Alpine, Mono, Kings, Shasta, Modoc, Trinity, San Bernardino, Imperial, San Luis Obispo, Napa

982,666 cases +8,085 on Nov 9

18,004 deaths +29 on Nov 9
Hospitalized COVID-19 patients by date and level of care, California, 2020
$R_e$ and test positivity for SARS-CoV-2 infection, California, 2020

As of November 9, 2020
SARS-CoV-2 infections by county, California, November 10, 2020

1. Los Angeles
   13,159 cases in last 7 days

2. San Bernardino
   3,534

3. San Diego
   3,161

4. Riverside
   2,700

5. Orange
   2,265

6. Sacramento
   1,521

7. Santa Clara
   1,470

8. Fresno
   1,006

9. Alameda
   906

10. Kern
    904
<table>
<thead>
<tr>
<th>County</th>
<th>Total deaths</th>
<th>Total cases</th>
<th>New cases curve</th>
<th>Weekly change in new cases</th>
<th>Cases/10^5/d*</th>
<th>R_0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santa Clara</td>
<td>433</td>
<td>26,747</td>
<td>193 (March 11)</td>
<td>356 (Nov 9) +36%</td>
<td>3.2</td>
<td>1.04</td>
</tr>
<tr>
<td>Alameda</td>
<td>475</td>
<td>25,001</td>
<td>122 (March 11)</td>
<td>175 (Nov 9) +26%</td>
<td>3.2</td>
<td>0.99</td>
</tr>
<tr>
<td>Contra Costa</td>
<td>253</td>
<td>20,166</td>
<td>109 (March 11)</td>
<td>202 (Nov 9) +36%</td>
<td>4.8</td>
<td>1.07</td>
</tr>
<tr>
<td>San Francisco</td>
<td>151</td>
<td>13,081</td>
<td>73 (March 11)</td>
<td>162 (Nov 9) +46%</td>
<td>1.7</td>
<td>0.98</td>
</tr>
<tr>
<td>San Mateo</td>
<td>162</td>
<td>11,937</td>
<td>63 (March 11)</td>
<td>143 (Nov 9) +48%</td>
<td>2.9</td>
<td>1.02</td>
</tr>
<tr>
<td>Sonoma</td>
<td>146</td>
<td>10,424</td>
<td>80 (March 11)</td>
<td>188 (Nov 9) +50%</td>
<td>11.1</td>
<td>1.01</td>
</tr>
<tr>
<td>Solano</td>
<td>79</td>
<td>8,366</td>
<td>72 (March 11)</td>
<td>150 (Nov 9) +43%</td>
<td>6.5</td>
<td>1.03</td>
</tr>
<tr>
<td>Marin</td>
<td>128</td>
<td>7,270</td>
<td>14 (March 11)</td>
<td>29 (Nov 9) +43%</td>
<td>2.6</td>
<td>1.03</td>
</tr>
<tr>
<td>Napa</td>
<td>15</td>
<td>2,299</td>
<td>23 (March 11)</td>
<td>76 (Nov 9) +90%</td>
<td>3.1</td>
<td>0.96</td>
</tr>
</tbody>
</table>

*Adjusted for testing rate, 7-day lag

Proportion positive range from 0.9% in San Francisco to 5.2% in Sonoma

125,291 total cases +1,342 on Nov 9

1,842 total deaths +3 on Nov 9
Latest Estimate of R-effective is:

0.98

Spread of COVID-19 is likely stable

Download County R-eff Trends

NOTE: Some counties do not have sufficient case numbers in order for modelers to estimate R-effective.
Infectious disease deaths, United States, 1900-1996

Two strategic goals

- Limit new cases by decreasing $R_e$, the effective reproductive number
- Flatten and prolong the outbreak to (1) assure adequacy of health care resources and (2) buy time for antivirals and eventually vaccine

What interventions do we have available?

- Individual-level interventions
  - Wearing masks
  - Social distancing
  - Staying home if ill
  - Hand hygiene

- Public health interventions
  - *Cordon sanitaire* and shelter-in-place
  - Case investigation and contact tracing, isolation and quarantine
  - Case finding (focused testing)
  - Increased ventilations (indoor spaces)
San Francisco and the 1918-19 influenza epidemic
Masks reduce airborne transmission

Infectious aerosol particles can be released during breathing and speaking by asymptomatic infected individuals. No masking maximizes exposure, whereas universal masking results in the least exposure.

Particle size ($\mu$m)

| 100 | 10  | 1   | 0.1 |

Infected, asymptomatic vs. Healthy

Maximum exposure

Minimum exposure

GRAPHIC: V. ALTOUNIAN/SCIENCE
Kimberly A. Prather et al. Science 2020;science.abc6197
Modeling benefit of universal masking post-shelter-in-place

Correlation between mask wearing most or all of the time in public and knowing someone with COVID-19 symptoms.
SARS-CoV-2 transmission dynamics, Wuhan, China, 2020

If $R_e$ is 3.54, herd immunity will lie at 72%

Bayesian inference of SIR model parameters from daily new cases of COVID-19 enables us to assess the impact of interventions. In Germany, three interventions (mild social distancing, strong social distancing, and contact ban) were enacted consecutively (circles). Colored lines depict the inferred models that include the impact of one, two, or three interventions (red, orange, or green, respectively, with individual data cutoff) or all available data until 21 April 2020 (blue). Forecasts (dashed lines) show how case numbers would have developed without the effects of the subsequent change points. Note the delay between intervention and first possible inference of parameters caused by the reporting delay and the necessary accumulation of evidence (gray arrows). Shaded areas indicate 50% and 95% Bayesian credible intervals.
Social Distancing Alters the Clinical Course of COVID-19 in Young Adults: A Comparative Cohort Study

CID study (June 2020) showed Switzerland soldiers when social distance OR masks established had 0% illness compared to 30% illness without these measures (cases in both)

- No social distancing OR masks (n=354) – 30% illness, 62% cases
- Social distancing OR masks (n=154) – 0% illness, 15% cases
# California’s Blueprint for a Safer Economy

**County risk level**

<table>
<thead>
<tr>
<th>New cases</th>
<th>positive tests</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WIDESPREAD</strong></td>
<td></td>
</tr>
<tr>
<td>More than 7</td>
<td>More than 8%</td>
</tr>
<tr>
<td>daily new cases (per 100k)</td>
<td>positive tests</td>
</tr>
<tr>
<td>Many non-essential indoor business operations are closed</td>
<td></td>
</tr>
</tbody>
</table>

| **SUBSTANTIAL** |                |
| 4 - 7           | 5 - 8%         |
| daily new cases (per 100k) | positive tests |
| Some non-essential indoor business operations are closed |

| **MODERATE**    |                |
| 1 - 3.9         | 2 - 4.9%       |
| daily new cases (per 100k) | positive tests |
| Some indoor business operations are open with modifications |

| **MINIMAL**     |                |
| Less than 1     | Less than 2%   |
| daily new cases (per 100k) | positive tests |
| Most indoor business operations are open with modifications |
Considerations in testing

- Type of test
  - Sensitivity, specificity
- Frequency of testing
- Turnaround time
  - Point-of-care testing
- Who collects the specimen?
  - Home collection

- Type of biologic fluid tested
  - Nasopharyngeal or oropharyngeal swab
  - Tracheal aspirate
  - Anterior nasal swab
  - Oral sulcus
  - Saliva

- Pooling vs. no pooling
## Selected diagnostic tests for SARS-CoV-2

<table>
<thead>
<tr>
<th></th>
<th>Molecular tests</th>
<th>Antigen tests</th>
<th>Antibody tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Real-time polymerase chain reaction</td>
<td>Loop-mediated isothermal amplification (LAMP)</td>
<td></td>
</tr>
<tr>
<td>What it detects</td>
<td>RNA (quantitative – cycle threshold)</td>
<td>RNA (qualitative)</td>
<td>Viral proteins</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IgG, IgM to spike protein or nucleocapsid</td>
</tr>
<tr>
<td>When it turns positive</td>
<td>3 days post exposure</td>
<td>3 days post exposure</td>
<td>3 days post exposure</td>
</tr>
<tr>
<td></td>
<td>4-8 hours</td>
<td>&lt;30 minutes</td>
<td>15 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hours</td>
</tr>
<tr>
<td>Time to result</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensitivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Lower</td>
<td>Lower</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
High frequency testing with low analytic sensitivity versus low-frequency testing with high analytic sensitivity

Herd immunity

• Proportion of the population that needs to have durable immunity before viral spread stops

Herd immunity (%) = (Re - 1)/Re

• So, if Re = 3, herd immunity = 67%
• From a variety of outbreaks, herd immunity lies probably between 60 and 80%
SARS-CoV-2 phase 3 vaccines in trials

- Nucleic acid vaccines
- Inactivated virus vaccines
- Live attenuated vaccines
- Protein or peptide subunit vaccines
- Viral-vectored vaccines

Progress is vaccines

- Pfizer and BioNTech announced yesterday that interim analysis of their mRNA vaccine BNT162b2 showed 90% efficacy in preventing infection at 7 days after the second dose
- No serious safety concerns
- 43,538 participants, 94 cases to date (need to accumulate 164 for trial to end)
- Likely to be in a position to apply for FDA emergency approval in mid-December
- Issues
  - Vaccine storage and distribution (-70°C)
  - Limited doses available in 2020 – who gets vaccinated first?
  - How well does it work in those most at risk of severe disease?
Daily infections and testing

**Estimated infections** are the number of people we estimate are infected with COVID-19 each day, including those not tested.

![Graph showing daily infections over time](image-url)
371,509 COVID-19 deaths
based on Current projection scenario by January 1, 2021

Total deaths

To see results within this country, select a subnational location

Scenario

Observed (smoothed)  Current projection  Mandates easing  Universal masks

All deaths specific to COVID-19 patients.
What does the future hold?

- Now until the Spring
  - Vaccine(s) not widely available
  - Use only for highest risk populations
  - Well into third wave of infection in the late Fall-Winter
    - Colleges and universities
    - High schools and middle schools
  - Continued need for masks, social distancing, etc.
  - Reopening businesses will depend on local epidemiology and politics
  - Low mortality?

- Spring through late Summer
  - Vaccine(s) go out to general public
  - Variable uptake of vaccine due to vaccine hesitancy, refusal
  - Whether transmission can be sustained depends on vaccine coverage, vaccine efficacy, mass crowd events with super spreading, mask wearing, etc.
What does the future hold

• Likely will need to have vaccination levels in excess of 60-70% to achieve herd immunity
  • Add 10% on top of estimate to account for 90% vaccine efficacy
• If it’s <<60%, we may end up with a two-tiered system of people who have been vaccinated or have been recently tested and are uninfected (green) versus those who haven’t (red)
• We will likely still need masks and social distancing
Happy (and safe) Thanksgiving

• Risk factors for transmission
  • Community levels of COVID-19
  • Indoors vs. outdoors
  • Duration of the gathering
  • Number of participants
  • Where participants are traveling from
  • Behaviors of attendees prior to gathering
  • Behaviors of attendees during the gathering

• Traveling for the holidays
  • Testing and quarantine

• Some additional tips
  • Wear masks and maintain social distance as much as possible
  • Separate tables for separate bubbles
  • Prepare plates in the kitchen rather than passing food or serving it on a buffet
  • Shop online and have food delivered
  • Don’t cook the stuffing inside the turkey!!!
  • Clean cutting boards between poultry and foods that will be eaten raw