Scientific update on COVID-19

Updated on April 19th 2021
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EPIDEMIOLOGY

Questions:
- What is the situation in worldwide?
- What is the incubation period & $R_0$ of SARS-CoV-2?
- What is the impact of non-pharmaceutical interventions on $R$?
- What do we know about the risk of transmission & modes of transmission?
- What is the impact of the different measures taken by countries?
Situation update


ECDC: distribution of cases of COVID-19, by continent, April 15th 2021
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\textsubscript{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
  - Geographic location
  - Stage of outbreak
- $R_e$ depends on
  - Control measures
- Doubling time: 2.9 to 7.3 days

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

$R_t$: median daily reproduction number

$R_e$: estimated daily reproduction number


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

| Monitoring Duration | Low Risk (1 in 10 000) | Medium Risk (1 in 1000) | High Risk (1 in 100) | Infected (1 in 1)
<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>7 d</td>
<td>0.2 (0.4)</td>
<td>2.1 (3.6)</td>
<td>21.2 (36.5)</td>
<td>2120.6 (3638.5)</td>
</tr>
<tr>
<td>14 d</td>
<td>0.0 (0.0)</td>
<td>0.1 (0.5)</td>
<td>0.1 (2.0)</td>
<td>100.9 (481.7)</td>
</tr>
<tr>
<td>21 d</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.1)</td>
<td>0.0 (2.2)</td>
<td>9.5 (62.5)</td>
</tr>
<tr>
<td>28 d</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (2.2)</td>
<td>1.4 (17.8)</td>
</tr>
</tbody>
</table>

High risk = A 1-in-100 chances of developing a symptomatic infection after exposure

Non pharmaceutical interventions and $R$

Temporal association between introducing and lifting non-pharmaceutical interventions (NPIs) and levels of SARS-CoV-2 transmission ($R$)?

Modelling study – data from 131 countries:
- On country-level estimate $R$ from the EpiForecast project
- On country-specific policies on NPIs from the OxCGRT

Jan 1 to July 20, 2020

Definitions:
- Phase: a time period when all of the eight NPIs remained the same
- $R_{dayi}$ as the $R$ of the $i$th day of that phase (i.e., since the NPI status changed) and defined $R_{day0}$ as the $R$ of the last day of its previous phase
- $R$ ratio between $R_{dayi}$ and $R_{day0}$ as a measure of the degree of association of introducing and lifting an NPI with the transmission of SARS-CoV-2
- Modelled the $R$ ratio using a log-linear regression

790 phases from 131 countries
- Median duration of phase 11 days

The NPIs
- Stay at home and restriction on internal movements were the most common,
- Closure schools and public events ban were the two first NPIs introduced,
- Stay at home and closure of public transport were the two last NPIs introduced.

Decreasing trend over time in $R$ ratio was found in the first 14 days after introducing NPIs
Non pharmaceutical interventions and $R$

Greatest increase in $R$ ratio:
- Relaxation of school closure:
  - On day 7, $1.05$ (CI$_{95\%}$: $0.96–1.14$)
  - On day 14, $1.18$ (CI$_{95\%}$: $1.02–1.36$)
- Relaxation of a ban on gatherings of $>10$
  - On day 28, $1.25$ (CI$_{95\%}$: $1.03–1.51$)

Time in days needed to reach 60% of its maximum effect:
- Median of 8 days following the introduction
- Median of 17 days following its relaxation

Greatest reduction in $R$:

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Day 7</th>
<th>Day 14</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>School and workplace closure plus ban on public events and gatherings of more than ten people plus internal movement limits plus stay at home requirement</td>
<td>$0.65$ ($0.54–0.78$)</td>
<td>$0.58$ ($0.42–0.78$)</td>
<td>$0.48$ ($0.32–0.71$)</td>
</tr>
</tbody>
</table>

Introducing NPIs were associated with reductions in $R$ of 3–24% on day 28 after their introduction.

Lifting NPIs were associated with increases in $R$ of 11-25% on day 28 after their relaxation.

Effects not immediate & time required to reach certain levels of effect differed by NPI.

Several limits:

- Base on control policy rather than on actual population behavior → use of personal hygiene / behavioral change.
- Compliance with these NPIs was not examine.
- Data on national levels only → vary among different parts of a country.
- Heterogeneity across different countries → findings no sensitive to the removal of different lists of countries.
- Not consider the role of underlying seasonality or meteorological factors.
- The $R$ estimate was subject to the specification of parameters.
- Change over time in contact/tracing or testing or case definition.
- Innate limitation of $R$ as measure of transmission.

Authors: “The decisions to reintroduce and relax restrictions should be informed by various factors, including the capacity and resilience of the health-care system, and might be best made at provincial or district rather than national levels.”
Distancing 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>Measurements</th>
<th>Studies and participants</th>
<th>Relative effect (95% CI)</th>
<th>Anticipated absolute effect (95% CI); eg, chance of viral infection or transmission</th>
<th>Difference (95% CI)</th>
<th>Certainty*</th>
<th>What happens (standardised GRADE terminology)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical</td>
<td>Nine adjusted studies (n=7782); 29 unadjusted studies (n=10738)</td>
<td>aOR 0.18 (0.09 to 0.38); unadjusted RR 0.30 (95% CI 0.20 to 0.44)</td>
<td>Shorter distance; 12.8%; Further distance, 2.6% (1.3 to 5.3)</td>
<td>-10.2% (-11.5 to -7.5)</td>
<td>Moderate</td>
<td>A physical distance of more than 1 m probably results in a large reduction in virus infection; for every 1 m further away in distancing, the relative effect might increase 2-02 times.</td>
</tr>
<tr>
<td>Face mask vs no face mask</td>
<td>Ten adjusted studies (n=2647); 79 unadjusted studies (n=10570)</td>
<td>aOR 0.45 (0.07 to 0.34); unadjusted RR 0.34 (95% CI 0.26 to 0.45)</td>
<td>No face mask, 17.4%; Face mask, 3.1% (1.5 to 6.7)</td>
<td>-14.3% (-15.9 to -10.7)</td>
<td>Low</td>
<td>Medical or surgical face masks might result in a large reduction in virus infection; N95 respirators might be associated with a larger reduction in risk compared with surgical or similar masks.</td>
</tr>
<tr>
<td>Eye protection (faceshield, goggles) vs no eye protection</td>
<td>13 unadjusted studies (n=3713)</td>
<td>Unadjusted RR 0.34 (0.22 to 0.57);</td>
<td>No eye protection, 16.0%; Eye protection, 5.5% (1.6 to 8.5)</td>
<td>-10.6% (-12.5 to -7.7)</td>
<td>Low</td>
<td>Eye protection might result in a large reduction in virus infection.</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 when evaluated in isolation

Face masks’ effectiveness in respiratory viruses

- 246 participants
  - 122 without face masks and 124 with face masks
  - Provided exhaled breath samples
- 123 were infected by
  - HCoV (17), influenza (43) and rhinovirus (54)
- Test viral shedding
  - Nasal swab, throat swab
  - Respiratory droplet sample
  - Aerosol sample
- Detection of coronavirus
  - 30% (droplets) and 40% (aerosol) without mask
  - 0% (droplet or aerosol) with mask
  - Aerosol transmission is possible
  - Face masks reduce coronavirus detection in aerosol (significantly) and respiratory droplet
- Face masks 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
Face masks’ effectiveness in COVID-19

Event study that examined the effect over different period

- state executive orders or directives signed by governors that mandate use
- Fifteen states + Washington D.C.
- March 31 and May 22, 2020

Estimated the effects of face cover mandates on the daily county-level COVID-19 growth rate.

Significant decline in daily COVID-19 growth rate after the mandating of face covers in public

- Increasing over time after the orders were signed

No evidence of declines in daily COVID-19 growth rates with employee-only mandates

**Limits:**
- Unable to measure the compliance with the mandate
- Examine only confirmed COVID-19 cases
- Other existing social distancing measures
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 $\rightarrow$ annual outbreak

B: Long-term immunity $\rightarrow$ elimination of the virus

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
Community and close contact exposures

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 2nd: 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

### Table: Outbreaks and Cases by Setting

<table>
<thead>
<tr>
<th>Setting</th>
<th>Total</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outbreaks</td>
<td>Cases</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Healthcare facility</td>
<td>20</td>
<td>3.0</td>
</tr>
<tr>
<td>Long-term care facility</td>
<td>59</td>
<td>8.8</td>
</tr>
<tr>
<td>Vulnerable social group</td>
<td>44</td>
<td>6.5</td>
</tr>
<tr>
<td>Family - different households</td>
<td>65</td>
<td>9.7</td>
</tr>
<tr>
<td>Occupational</td>
<td>146</td>
<td>21.7</td>
</tr>
<tr>
<td>Slaughterhouse/meat plant</td>
<td>19</td>
<td>NA</td>
</tr>
<tr>
<td>Agriculture seasonal worker</td>
<td>45</td>
<td>1,022</td>
</tr>
<tr>
<td>Other/not specified</td>
<td>82</td>
<td>NA</td>
</tr>
<tr>
<td>Social</td>
<td>206</td>
<td>30.6</td>
</tr>
<tr>
<td>Organised event/public space</td>
<td>31</td>
<td>NA</td>
</tr>
<tr>
<td>Family/friends reunion or private party</td>
<td>120</td>
<td>NA</td>
</tr>
<tr>
<td>Leisure facility (restaurant, bar, club...)</td>
<td>35</td>
<td>NA</td>
</tr>
<tr>
<td>Other/not specified</td>
<td>20</td>
<td>NA</td>
</tr>
<tr>
<td>Mixed</td>
<td>111</td>
<td>16.5</td>
</tr>
<tr>
<td>Other</td>
<td>22</td>
<td>3.3</td>
</tr>
<tr>
<td>Total</td>
<td>673</td>
<td>100</td>
</tr>
</tbody>
</table>

COVID-19 & community – Infection modelling

SEIR model tracking infection trajectories of census block cluster (CBG) and the points of interest (POIs) where infections likely occurred

Based on mobility data (1 March – 2 May 2020) from 10 metropolitan areas in the US.

- The magnitude of mobility reduction was as important as its timing
- The majority of the predicted infections occurred at a small fraction of superspreader POIs. Certain categories of POIs (especially full-service restaurants) contributed far more to infections
- Reducing maximum occupancy substantially reduced risk of infection without sharply reducing overall mobility – Non-linear relationship between number of infections and number of visits
- Demographic disparities in infections:
  - CBGs in the bottom decile for income had a substantially higher likelihood of being infected
  - Lower-income CBGs saw smaller reductions in mobility during restrictions
  - The predicted transmission rates at POIs frequented by individuals from lower-income CBGs tended to be higher than rates for those from higher-income (i.e., smaller and more crowded places)

Infection predictions and demographic disparities must be taken into account in reopening strategies
Household transmission of SARS-CoV-2

Modelling study on 27,101 households – Wuhan (Dec 2, 2019 – April 18, 2020)
- 29,578 primary cases
- 57,581 household contacts – 10,367 secondary cases, 29,658 test-negative contacts
- Household: group of family members or close relatives who did not necessarily live at the same address. Median size: 3 people.

- Clinical severity: Secondary cases were clinically less severe than primary cases – asymptomatic cases 4.2% vs. 1.9%; severe or critical cases 13.9% vs. 19.2%
- Pathogenicity: 84% (95% CI 81.6–86.1) of secondary cases developed symptoms after infection
  - Young adults (20–39y) were more likely to develop symptoms than ≥60y (78.8% vs. 87.5%)
  - Pathogenicity of infection in children and adolescent resembled that of adults ≥40y, although the latter were more likely to show severe or critical symptoms
  - Pathogenicity and severity did not differ between sexes

- More infections were reported in densely populated districts. Secondary attack rate were spatially more even distributed.
Household transmission of SARS-CoV-2

Secondary attack rate
- Overall secondary attack rate was 16.0% (95% CI, 15.7-16.3)
- The smaller the household size, the higher the secondary attack rate – 27%(26.3-27.9) in a household of 2, 8.0%(7.2-8.9) in a household of >6
- Secondary attack rate (SAI) and odd of infection (OI) increased with age of the household contact:
  - ≥60yo – most susceptible age group; SAI ~25% - Reference
  - Individuals ≤20yo – 66-84% less susceptible than reference
  - Adults 20-59yo – 31-49% less susceptible than reference
  - Toddlers 2-5yo – least susceptible group; SAI 2.7%(2.1-3.5), OI 0.15(0.12-0.19). Infants 0-1yo were more susceptible than toddlers: SAI 6.1%(3.5-9.7), OI 0.32(0.21-0.50)

Infectivity
- Asymptomatically infected individuals were associated with ~80% lower infectivity than symptomatic ones after symptoms onset
  - Asymptomatic primary case: SAI 2.0%(1.3-2.9), OI 0.34
  - Mild or moderate primary case: SAI 15.8%(15.5-16.2), OI 1 (Ref)
  - Severe or critical primary case: SAI 18.5%(17.7-19.2), OI 1.01
- Presymptomatic period was more infectious than the symptomatic period
- Cases younger than 20yo were more likely to infect others than cases older than 60yo

→ Importance of isolating cases and quarantining households contacts outside of the home to prevent onward transmission within households

Limits:
- No protocol for laboratory testing – Asymptomatic infections could be underdetected even with universal testing of household contacts
- Epidemiologically linked households were merged – mixing pattern between households could be more complex than assumed
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 → 11.8% (CI95% [11.2% - 12.4%]) had COVID-19
  - with an index patient 10–19 years, 18.6% (CI95% [14.0%–24.0%]) of contacts had COVID-19
- 48 481 nonhousehold contacts → 1.9% (CI95% [1.8% - 2.0%]) had COVID-19

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

Rates of coronavirus disease among household

<table>
<thead>
<tr>
<th>Index patient age, y</th>
<th>No. contacts positive/ % Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. contacts traced</td>
</tr>
<tr>
<td>0–9</td>
<td>3/57</td>
</tr>
<tr>
<td>10–19</td>
<td>43/231</td>
</tr>
<tr>
<td>20–29</td>
<td>240/3,417</td>
</tr>
<tr>
<td>30–39</td>
<td>143/1,229</td>
</tr>
<tr>
<td>40–49</td>
<td>206/1,749</td>
</tr>
<tr>
<td>50–59</td>
<td>300/2,045</td>
</tr>
<tr>
<td>60–69</td>
<td>177/1,039</td>
</tr>
<tr>
<td>70–79</td>
<td>86/477</td>
</tr>
<tr>
<td>≥80</td>
<td>50/348</td>
</tr>
<tr>
<td>Total</td>
<td>1,248/10,592</td>
</tr>
</tbody>
</table>

Limits:

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

→ Transmission potential in both children and adolescents,
→ Possibly more effective transmission in adolescents than in adults.
Risk of COVID-19: health-care workers

Prospective observational study on staff at Oxford University Hospitals, UK, mid-March – 8th June 2021

- 636 Covi-19 patients admitted by June 8th
- 348/1498 (23%) symptomatic staff tested positive
- 10,034 asymptomatic staff tested at least once 9926 by PCR and 9958 by serology. 1128/10,034 (11.2%) tested positive

Risk factors for SARS-CoV-2 infection:

- 67/174 (38.5%) staff reporting household contact with a PCR-confirmed case tested positive, 1059/9858 (10.7%) without (p<0.001).

- 368/2165 (17.0%) staff reporting workplace contact without PPE with a known or suspected Covid-19 patient tested positive, 758/7867 (9.6%) not reporting similar exposure (p<0.001).

- Staff on wards caring for patients with Covid-19 were at higher risk of infection compared to non-Covid-19 facing wards. The proportion of staff tested positive in acute medicine (222/793, 28.0%) was greater than in the emergency department (41/344, 11.9%) and in the ICUs (44/448, 9.8%) – the difference might be due to different protection equipment.

- Based on occupational role, porters and cleaners were the category at higher risk.
Risk of COVID-19: health-care workers

Univariable (A) and multivariable (B) relationships between risk factors and staff infection with SARS-CoV-2.

Eyre DW, et al. eLife. Nov 2020
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></th>
<th>Adequate PPE</th>
<th>Reused PPE</th>
<th>Inadequate PPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event/person-days</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 (1.21-1.75)</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 (1.21-1.75)</td>
<td>1.31 (1.10-1.56)</td>
</tr>
<tr>
<td><strong>No exposure to patients with COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event/person-days</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 (0.60-1.55)</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 (0.59-1.54)</td>
<td>1.52 (1.10-2.09)</td>
</tr>
<tr>
<td><strong>Exposure to patients with suspected COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event/person-days</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 (2.22-4.51)</td>
<td>1.83 (1.21-2.78)</td>
</tr>
<tr>
<td><strong>Exposure to patients with documented COVID-19</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Event/person-days</td>
<td>289/90,571</td>
<td>91/37,571</td>
<td>83/11,675</td>
</tr>
<tr>
<td>Unadjusted hazard ratio (95% CI)</td>
<td>4.93 (4.07-5.97)</td>
<td>5.42 (3.94-6.64)</td>
<td>5.93 (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 (eg, 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
  - Assess the impact of a range of testing and contact tracing strategies
  - Simulate physical distancing strategies
  - 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:
  - Infectiousness: proportion of infection that are asymptomatic and their infectiousness
  - PCR test sensitivity over time since infection

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

- Percentage of reduction in $R = \text{expected effectiveness of different testing strategies}$

- Based on literature: 33% of infections are asymptomatic which have a relative infectiousness off 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

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

- 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


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
    - Timelessness 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></td>
<td>14</td>
<td>21</td>
<td>0.0002</td>
</tr>
<tr>
<td>(per 1000 total births)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Intitutional neonatal mortality</strong></td>
<td>13</td>
<td>40</td>
<td>0.0022</td>
</tr>
<tr>
<td>(per 1000 livebirths)</td>
<td></td>
<td></td>
<td></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>

- 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
Impact of COVID-19 pandemic response – Manaus, Brazil

Estimate of the proportion of the population in Manaus with IgG antibodies to SARS-CoV-2 using a sample of blood donation.

- Prevalence of SARS-CoV-2 IgG peaked at 52.5% in June, then seroconversion caused it to lower to 25.8% in October.
- Cumulative incidence after adjusting for seroconversion: 66.2% in July and 76.0% in October.
- These results can be extrapolated to the 16-69yo population in Manaus. Possible confounders: donors have higher socio-economic profiles and higher health awareness; symptomatic donors were deferred.

SARS-CoV-2 antibody prevalence estimates in Manaus adjusted with different methods
Impact of COVID-19 pandemic response – Manaus, Brazil

- Manaus was expected to be above the theoretical herd immunity threshold (67%) given a R0 of 3
- Unexpected abrupt increase of COVID-19 hospital admissions in January 2021 (3431 in Jan 1-19 2021 vs. 552 in Dec 1-19 2020)

4 possible scenarios:

1. SARS-CoV-2 attack rate was overestimated
2. Immunity against infection had already begun to wane by December 2020
3. New SARS-CoV-2 mineages evade immunity from previous infections (B.1.1.7 and P.1 circulating in Brazil)
4. New lineages have higher inherent transmissibility than previous ones

Effect of the first wave on all-cause mortality

Knowledge of the total effect on mortality is needed:
• The true public health effect of the pandemic
• The policy response

→ Application of 16 Bayesian models to vital statistics data to estimate the all-cause mortality effect of the pandemic for 21 industrialized countries

Countries: From Europe and the Pacific
• Total population in 2020 > 4 million
• Up-to-date weekly data on all-cause mortality through May 2020
• Time series of data went back at least to 2015

Weekly number of death from any cause from January 2020 through May 2020

Deaths in all countries started to diverge to higher levels in March (e.g. in 4 countries)

From mild-February through end of May 2020, an estimated 206,000 more people died in these 21 countries than would have been expected had the pandemic not occurred

The turquoise-shaded areas show the predictions of how many deaths would have been expected from mid-February had the COVID-19 pandemic not occurred
Effect of the first wave on all-cause mortality

Posterior probability = the inherent uncertainty in how many deaths would have occurred in the absence of the pandemic

The largest rise in mortality was most likely to be in England & Wales followed by Spain and Italy.

For the 21 countries:
- The number of excess deaths from all-causes was 23% (7–38%) higher than the number of deaths assigned to COVID-19 as underlying cause of death.
- The difference between all-cause excess and COVID-19 deaths was largest in Spain and Italy.
- The number of excess deaths for all causes, excess deaths per 100,000 people and relative increase in deaths were similar between men and women in most countries.

4 groups:
- (1): Countries that have avoided a detectable rise
- (2-3): Countries which experienced a low-to-medium effect of the pandemic on overall deaths
- (4): Countries which experienced the highest mortality toll (Belgium, Italy, Scotland, Spain and England and Wales)
Effect of the first wave on all-cause mortality

Death returned to levels that would expected without the pandemic in April (e.g. France & Spain).

But remained above the levels expected in others (e.g. UK & Sweden)

**Limits:**
- No data on underlying cause of death
- Not access data for several other countries
- No data on total mortality by socio-demographic status
- No explanation for the observed difference among countries
- Difference between health care system → comparaison?

→ The heterogeneous mortality effects of the COVID-19 pandemic reflect differences in how well countries have managed the pandemic and the resilience and preparedness of the health and social care system.
COVID-19 versus seasonal influenza

National retrospective cohort study (France, PMSI)
All patients hospitalised from:
- COVID-19: March 1 to April 30, 2020 → 89 530 patients
- Influenza: Dec 1, 2018 and Feb 28, 2019 → 45 819 patients

1. Characteristics

<table>
<thead>
<tr>
<th></th>
<th>COVID-19</th>
<th>Seasonal Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>53 %</td>
<td>48,3 %</td>
</tr>
<tr>
<td>Age, mean, years</td>
<td>65</td>
<td>59</td>
</tr>
<tr>
<td>Obese or overweight</td>
<td>20,9 %</td>
<td>11,5 %</td>
</tr>
<tr>
<td>Hypertension</td>
<td>33,1 %</td>
<td>28,2 %</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19 %</td>
<td>16 %</td>
</tr>
<tr>
<td>Heart failure</td>
<td>8 %</td>
<td>13,7 %</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>1,6 %</td>
<td>4 %</td>
</tr>
</tbody>
</table>

2. Outcomes

<table>
<thead>
<tr>
<th></th>
<th>COVID-19</th>
<th>Seasonal Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute respiratory failure</td>
<td>27,2 %</td>
<td>17,4 %</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>3,4 %</td>
<td>0,9 %</td>
</tr>
<tr>
<td>Septic shock</td>
<td>2,8 %</td>
<td>2 %</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0,6 %</td>
<td>1,1 %</td>
</tr>
<tr>
<td>Admission ICU</td>
<td>16,3 %</td>
<td>10,8 %</td>
</tr>
<tr>
<td>Invasive mechanical ventilation (ICU patients)</td>
<td>71,5 %</td>
<td>61 %</td>
</tr>
<tr>
<td>In-hospital death</td>
<td>16,9 %</td>
<td>5,8 %</td>
</tr>
<tr>
<td>Chronic respiratory disease</td>
<td>1,6 %</td>
<td>4 %</td>
</tr>
</tbody>
</table>
Mean length of stay in ICU:
- COVID-19: 15 days
- Seasonal influenza: 8 days

A quarter of patients with COVID-19 remained in the ICU for more than 3 weeks.

Patients with COVID-19 were twice as likely to receive invasive mechanical ventilation.

In-hospital mortality for COVID-19 was nearly three-times higher than for seasonal influenza,

Age-standardised mortality ratio of 2.82 (COVID-19)
Protection against reinfection with SARS-CoV-2

Infection with SARS-CoV-2 confers protection towards subsequent reinfection?

Population level observational study (Denmark)

Analysed infection rates during the second surge of the COVID-19 epidemic, by comparison of infection rates between individuals with positive and negative PCR tests during the first surge

- 533,381 people were tested (1 surge)
  - 11,727 were positive (2.20%)
- Exclusion: 610 + 7432 (death)
- 525,339 remained in follow-up

  11,068 positive during 1st surge

  72 (0.65%) positive during 2nd surge

  16,819 (3.27%) positive during 2nd surge

Protection against repeat infection after previous SARS-CoV-2 infection was 80.5% (95% CI 75.4–84.5)

Protection against reinfection with SARS-CoV-2

Does SARS-CoV-2 infection confer protection towards subsequent reinfection?

The daily rate of infection during the second surge was 5.35 positive tests per 100 000 people among those who had previously tested positive versus 27.06 per 100 000 people among those who previously tested negative.

The adjusted RR of infection was 0.195 (95% CI 0.155–0.246) among those who previously tested positive compared with those who had previously only tested negative.

No evidence of differences in the estimates of protection against repeat infection by sex, nor any evidence was found that protection against repeated infection was waning after 6 months of follow-up.

Individuals aged 65 years and older had less than 50% protection against repeat SARS-CoV-2 infection.

Vaccination of previously infected individuals should be done because natural protection cannot be relied on.

**Limits:**
- No correlation between symptoms with protection against repeat infection
- Misclassifications of reinfection might have occurred
- Variant were not yet established in Denmark during the period
1. What is the incubation period & R₀?
   - 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.

2. What is the impact of non-pharmaceutical intervention on R?
   - Introducing and lifting NPIs were associated with reductions and increases of R, respectively, with no immediate effect

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, plausible 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
   - In-hospital mortality for COVID-19 was nearly three-times higher than for seasonal influenza

4. What is the impact of the different measures taken by countries?
   - Face masks reduce the transmission of respiratory viruses and probably of SARS-CoV-2
   - Pandemic lockdown can have an important impact on the access to the health system in some countries
   - The number of excess deaths from all-causes was 23% (7–38%) higher than the number of deaths assigned to COVID-19


References


References


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