

Scientific update on COVID-19

Updated on April 19th 2021

Redaction committee

Boris Lacarra – *AP-HP Robert Debré*

F-Xavier Lescure – *Inserm, AP-HP Bichat, COREB*

Guillaume Mellon – *AP-HP Bichat, COREB*

Inmaculada Ortega Perez – *ANRS/Maladies infectieuses émergentes*

Eric D'Ortenzio – *ANRS/Maladies infectieuses émergentes, Inserm, AP-HP*

Erica Telford – *Inserm*

Reviewing committee

Jean-Marc Chaplain – *CHU Rennes, COREB*

Flavie Chatel – *COREB*

Hélène Coignard – *HCL, COREB*

Dominique Costagliola – *Inserm*

Marie-Paule Kieny – *Inserm*

Quentin Le Hingrat – *Inserm, AP-HP Bichat*

Jean-Christophe Lucet – *Inserm, AP-HP Bichat*

Claire Madelaine – *ANRS/Maladies infectieuses émergentes*

Matthieu Mahevas – *Inserm, AP-HP Henri-Mondor*

Emmanuelle Vidal Petiot – *Inserm, AP-HP Bichat*

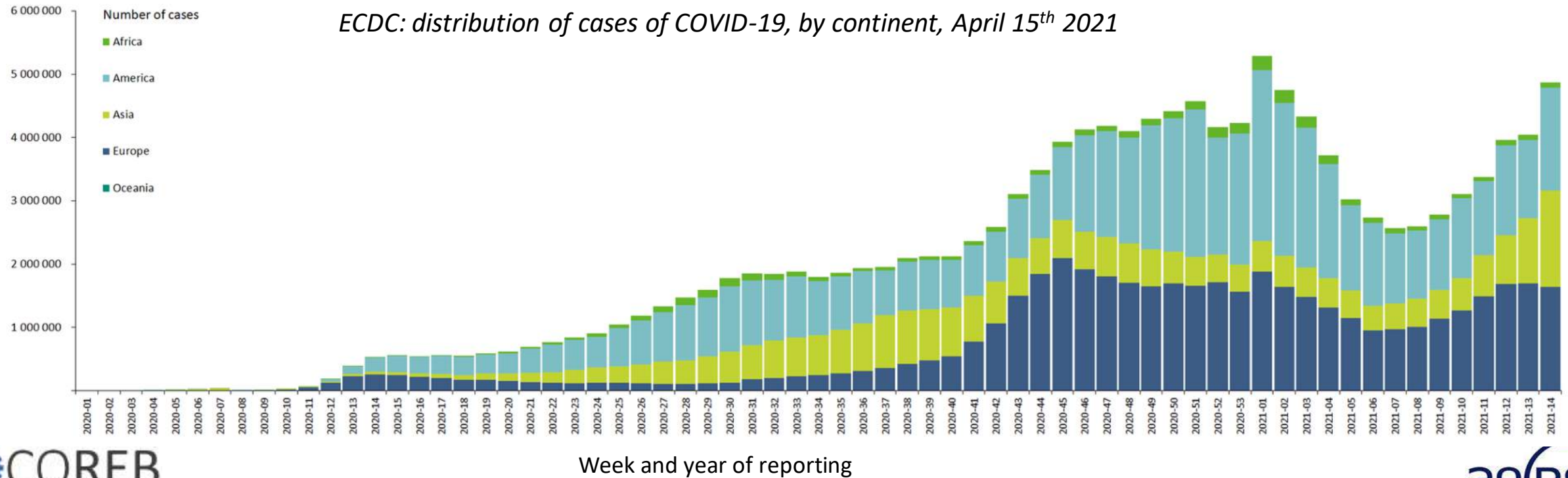
Benoit Visseaux – *Inserm, AP-HP Bichat*

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?

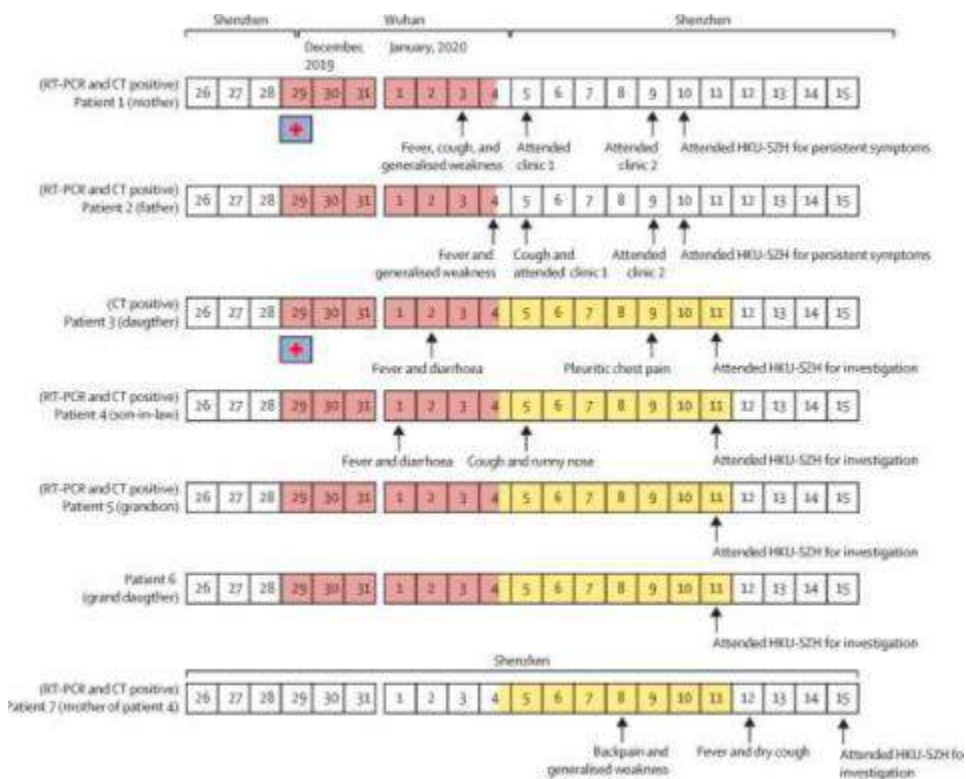
Situation update

- **Santé publique France:** <https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/infection-a-coronavirus/articles/infection-au-nouveau-coronavirus-sars-cov-2-covid-19-france-et-monde>
- **Johns Hopkins University:** <https://reliefweb.int/report/world/coronavirus-covid-19-global-cases-johns-hopkins-csse>
- **OMS:** <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/>
- **ECDC :** <https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases>



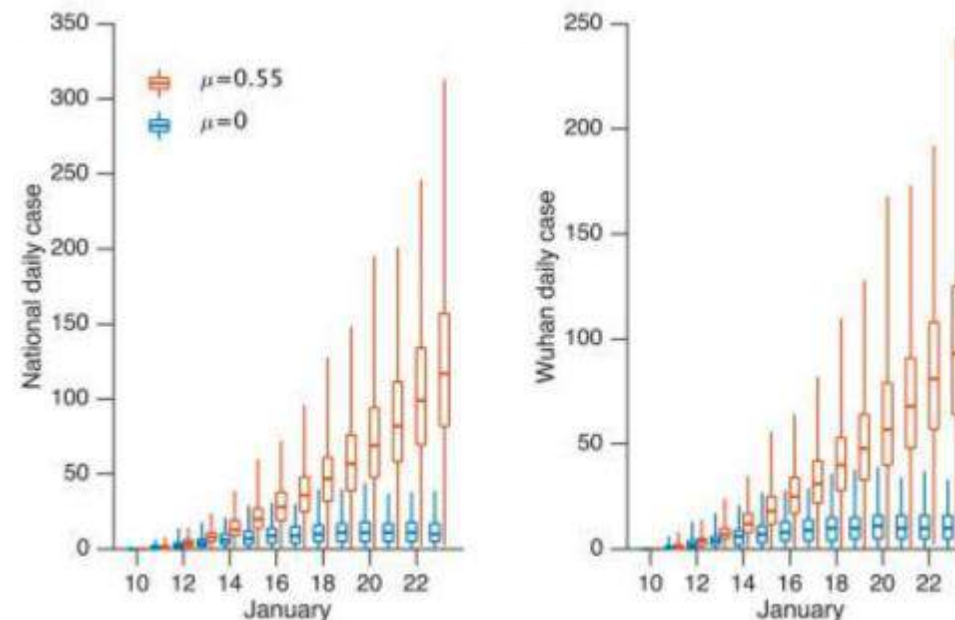
Epidemiology

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



Chronology of symptom onset of the family cluster

Daily documented cases – simulation generated using some parameters μ -factor applied to transmission rate due to undocumented infected persons

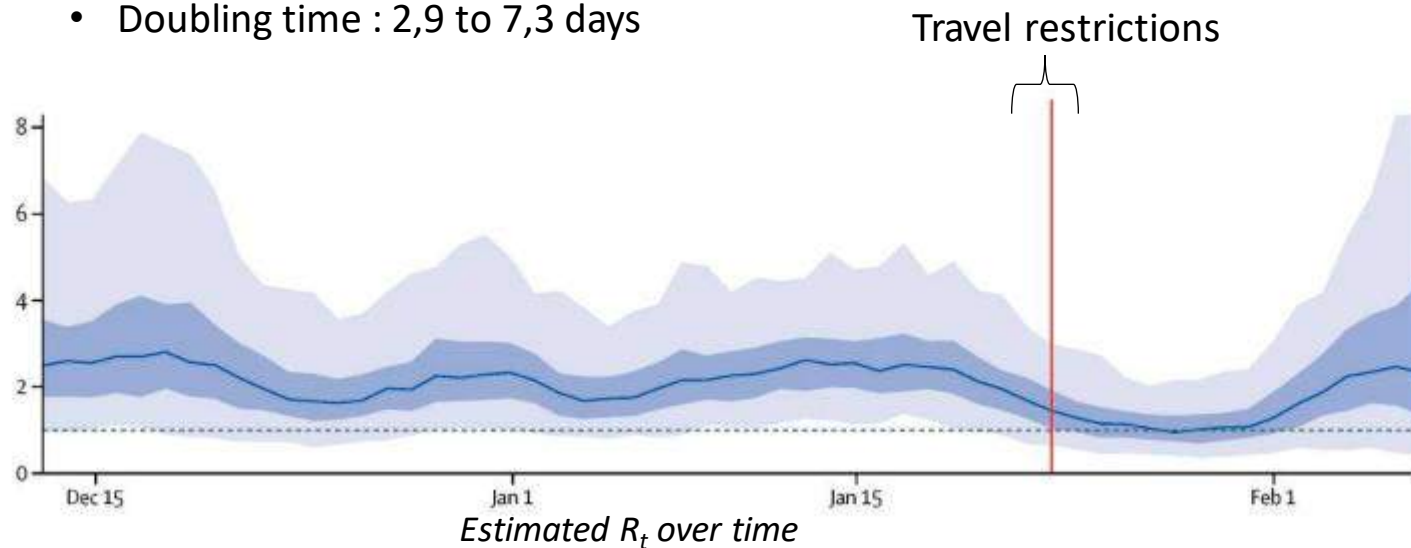


- Very high rate of undocumented infection
 - **Dissemination by undocumented infection** (asymptomatic, presymptomatic...)
 - He and colleagues estimation (slide 35): 44% (CI_{95%} [30 – 57%]) of secondary cases were infected during the index cases' presymptomatic stage
- Infectiousness was estimated to decline quickly within 7 days

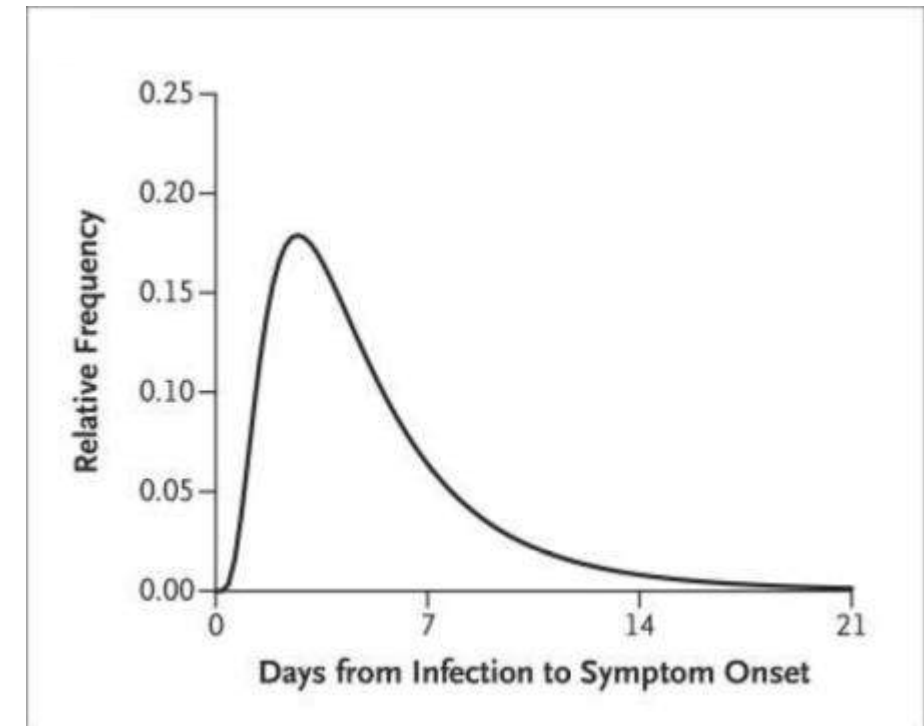
Epidemiology

At beginning & before controls measures:

- Basic reproduction number (R_0): 2,2 to 6,4
- R_0 depends on
 - Geographic location
 - Stage of outbreak
- R_e depends on
 - Control measures
- Doubling time : 2,9 to 7,3 days



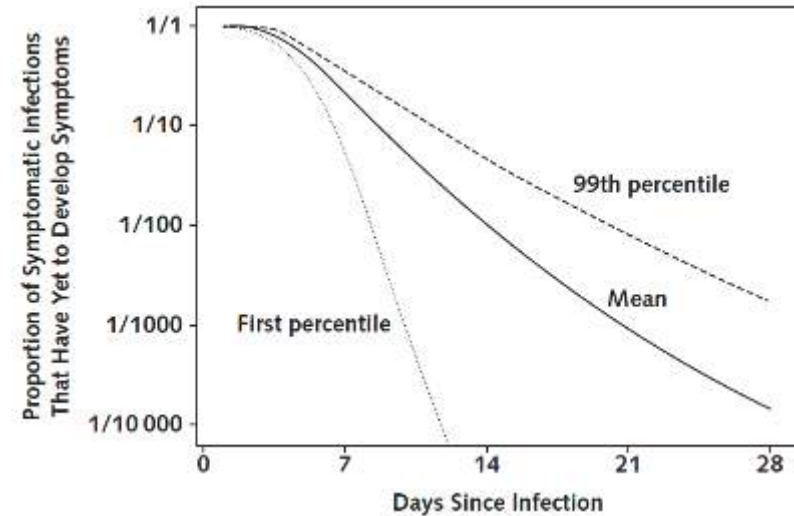
- Incubation period SARS-CoV-2
 - Median: 5 days
 - 2 to 14 days



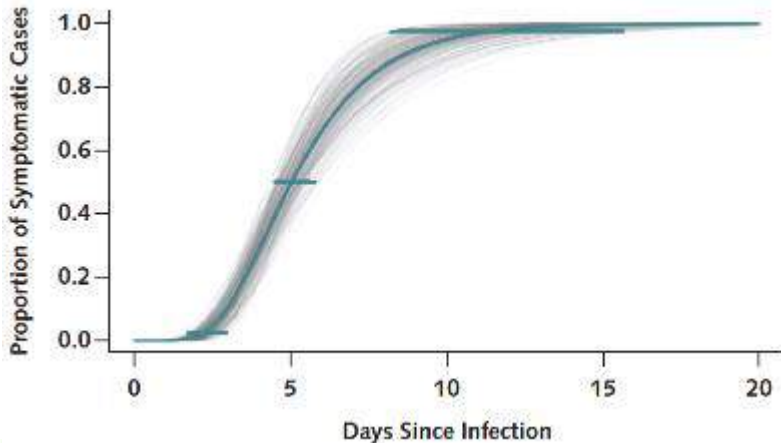
Epidemiology

- 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]
 - < 2,5% of infected persons will shows symptoms within 2,2 days
 - 97.5% of symptomatic patients developing symptoms within 11.5 days
- Analysis specific for cases detected outside of China
 - Median incubation (days): 5,5 [4,4 – 7,0]
 - 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



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

| Monitoring Duration | Mean Estimated Number of Undetected Symptomatic Infections per 10 000 Monitored Persons (99th Percentile) | | | |
|---------------------|---|-------------------------|----------------------|-------------------|
| | Low Risk (1 in 10 000) | Medium Risk (1 in 1000) | High Risk (1 in 100) | Infected (1 in 1) |
| 7 d | 0.2 (0.4) | 2.1 (3.6) | 21.2 (36.5) | 2120.6 (3648.5) |
| 14 d | 0.0 (0.0) | 0.1 (0.5) | 1.0 (4.8) | 100.9 (481.7) |
| 21 d | 0.0 (0.0) | 0.0 (0.1) | 0.1 (0.8) | 9.5 (82.5) |
| 28 d | 0.0 (0.0) | 0.0 (0.0) | 0.0 (0.2) | 1.4 (17.8) |

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_{day_i} as the R of the i th day of that phase (ie, since the NPI status changed) and defined R_{day_0} as the R of the last day of its previous phase
- R ratio between R_{day_i} and R_{day_0} 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

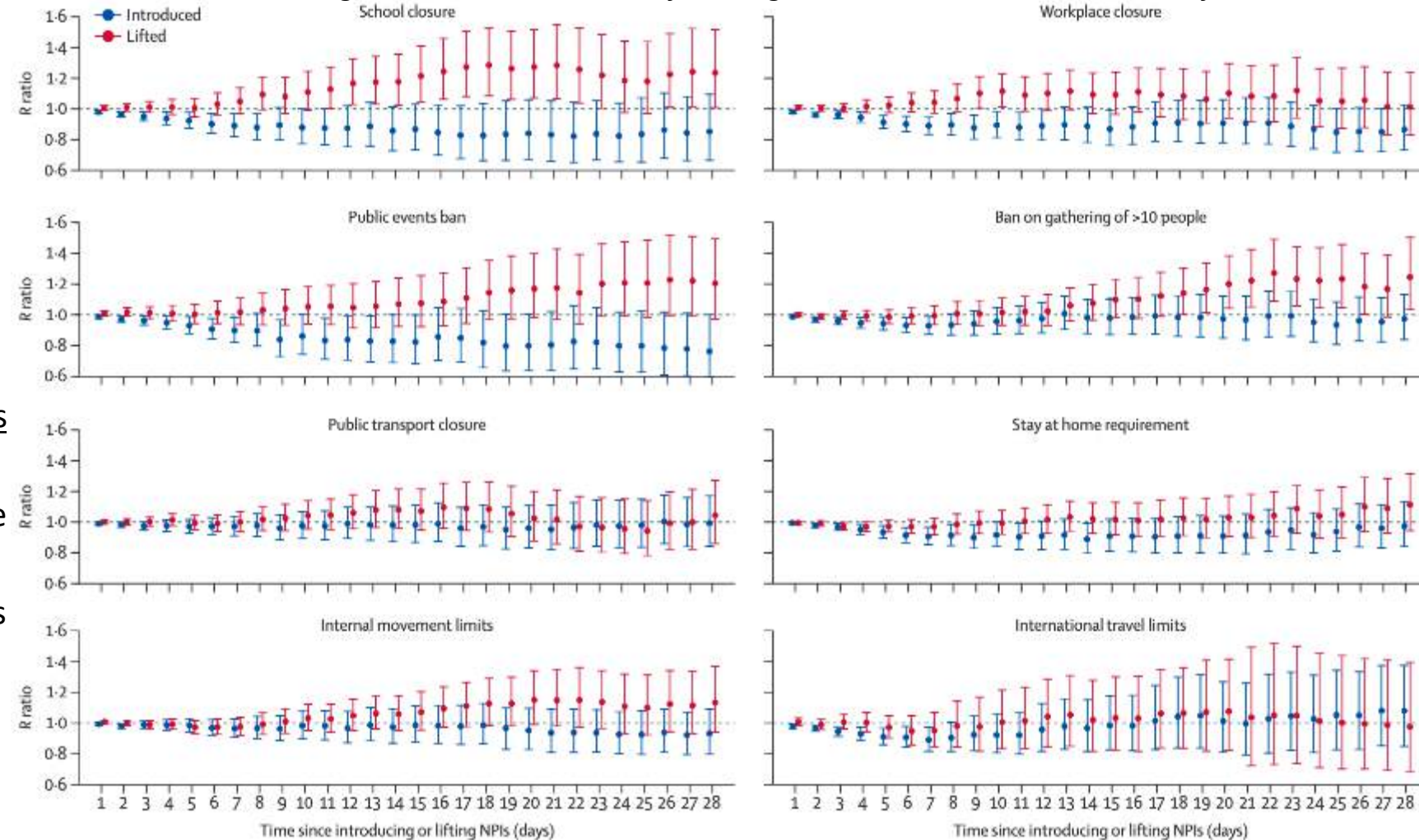
Greatest increase in R ratio:

- 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

Change over time in the R ratio following the introduction and relaxation of individual NPIs



Greatest reduction in R :

| | Day 7 | Day 14 | Day 28 |
|--|------------------|------------------|------------------|
| Candidate 4: 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 | 0.65 (0.54–0.78) | 0.58 (0.42–0.78) | 0.48 (0.32–0.71) |

Non pharmaceutical interventions and R

- 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 revue (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,

| | Studies and participants | Relative effect (95% CI) | Anticipated absolute effect (95% CI), eg, chance of viral infection or transmission | | Difference (95% CI) | Certainty* | What happens (standardised GRADE terminology) ²⁹ |
|---|---|---|---|-------------------------------------|-------------------------|------------|---|
| | | | Comparison group | Intervention group | | | |
| Physical distance ≥1 m vs <1 m | Nine adjusted studies (n=7782); 29 unadjusted studies (n=10736) | aOR 0.18 (0.09 to 0.38); unadjusted RR 0.30 (95% CI 0.20 to 0.44) | Shorter distance, 12.8% | Further distance, 2.6% (1.3 to 5.3) | -10.2% (-11.5 to -7.5) | Moderate† | 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 |
| Face mask vs no face mask | Ten adjusted studies (n=2647); 29 unadjusted studies (n=10170) | aOR 0.15 (0.07 to 0.34); unadjusted RR 0.34 (95% CI 0.26 to 0.45) | No face mask, 17.4% | Face mask, 3.1% (1.5 to 6.7) | -14.3% (-15.9 to -10.7) | Low‡ | 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§ |
| Eye protection (faceshield, goggles) vs no eye protection | 13 unadjusted studies (n=3713) | Unadjusted RR 0.34 (0.22 to 0.52)¶ | No eye protection, 16.0% | Eye protection, 5.5% (3.6 to 8.5) | -10.6% (-12.5 to -7.7) | Low | Eye protection might result in a large reduction in virus infection |

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

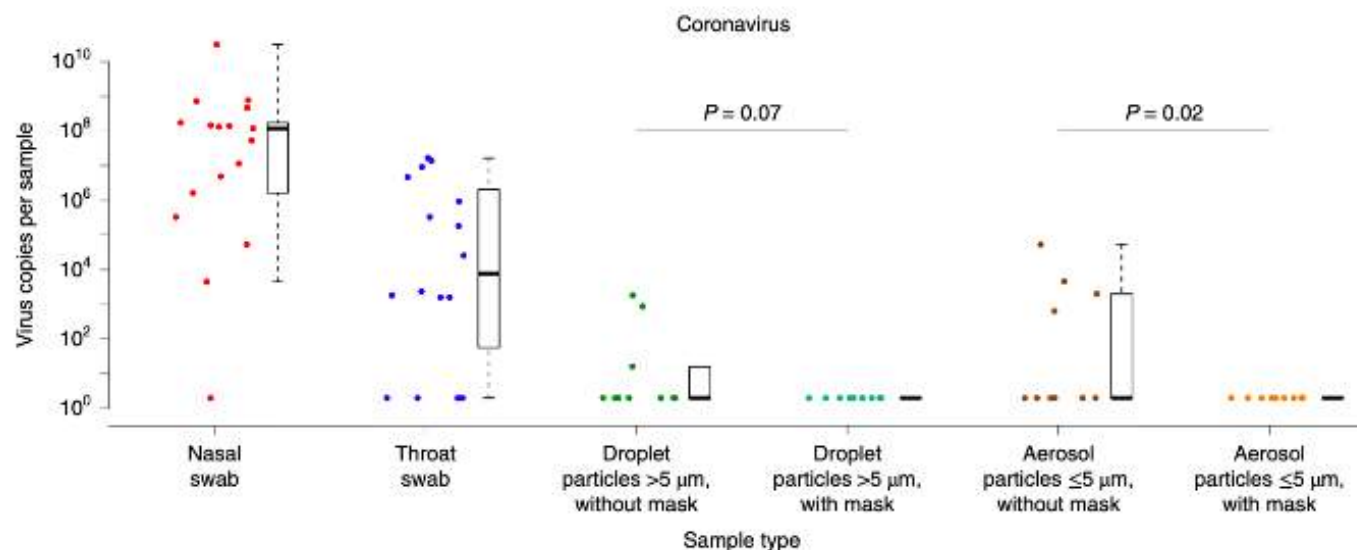
Face masks' effectiveness in respiratory viruses

- 246 participants
 - 122 without face masks and 124 with face mask
 - 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

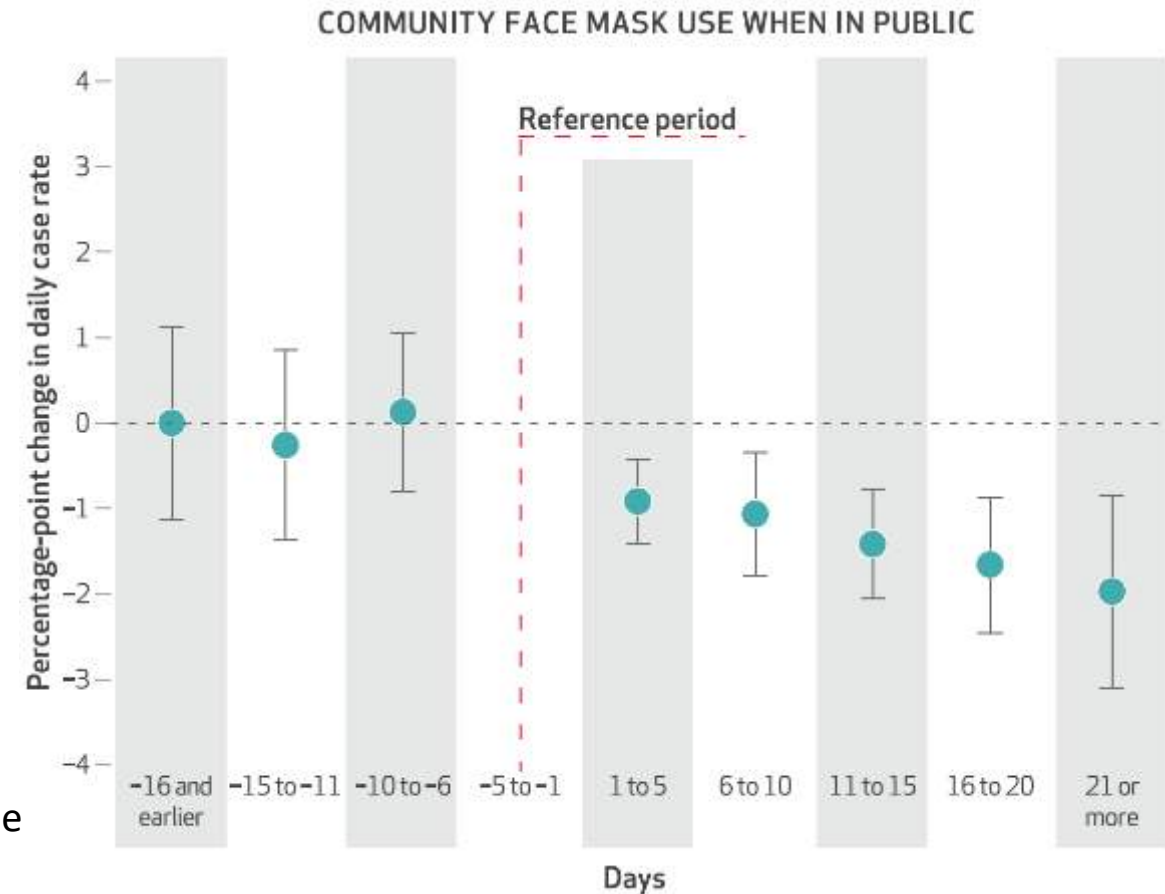
- Increasing over time after the orders were signed

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

Estimates of the effects of states mandating community face mask use in public on the daily county-level growth rate of COVID-19 cases, 2020



Projection - Transmission dynamics

Model of SARS-CoV-2 transmission

Projected that recurrent wintertime outbreaks will probably occur after the initial outbreak

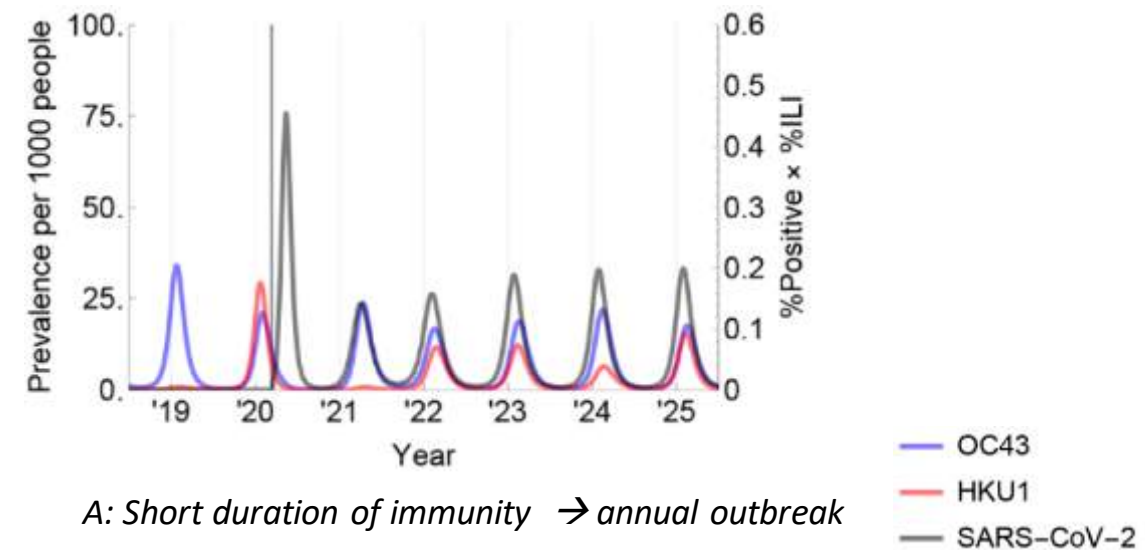
Used estimates of seasonality, immunity and cross-immunity for beta coronaviruses (OC43 & HKU1)

Post-pandemic transmission dynamics will depend on:

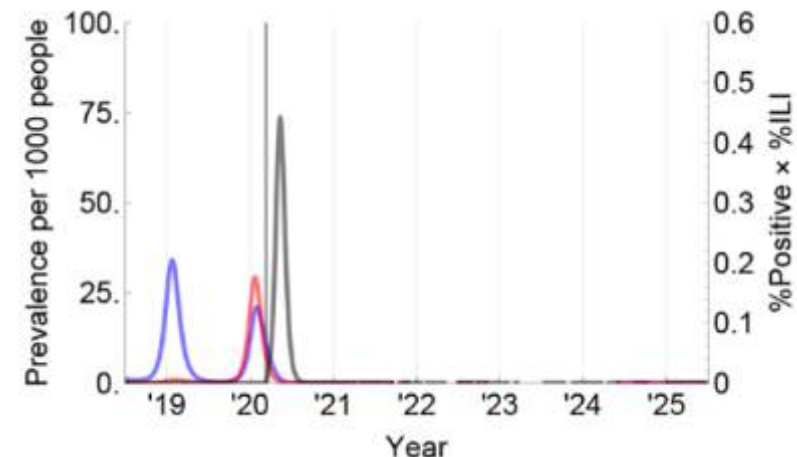
- Degree of season variation in transmission
- Duration of immunity
- Degree of cross-immunity between SARS-CoV-2 and other coronaviruses
- Intensity and timing of control measures

Presentation of different scenarios

Invasion scenario for SARS-CoV-2 in temperate regions



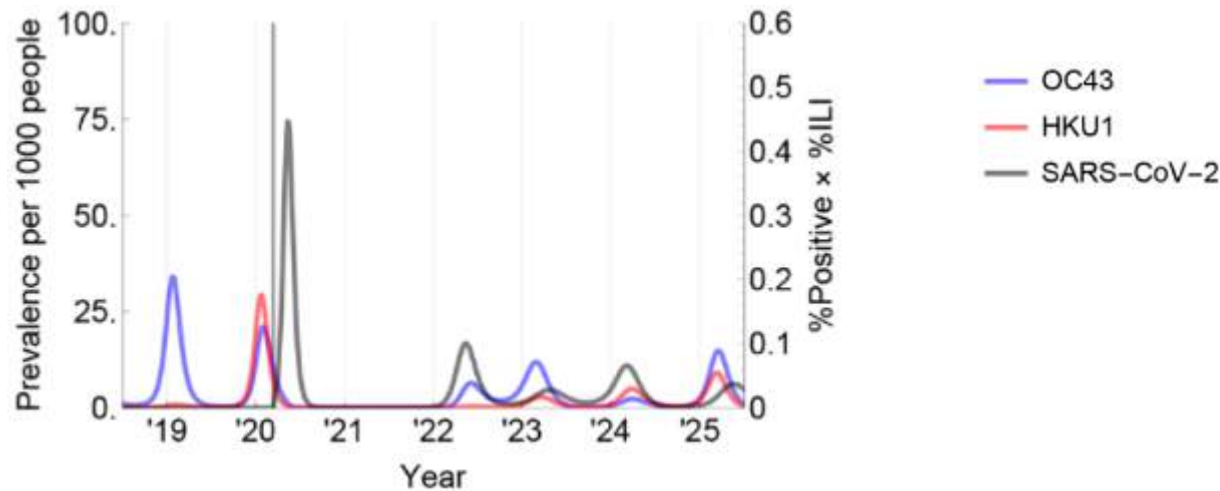
A: Short duration of immunity → annual outbreak



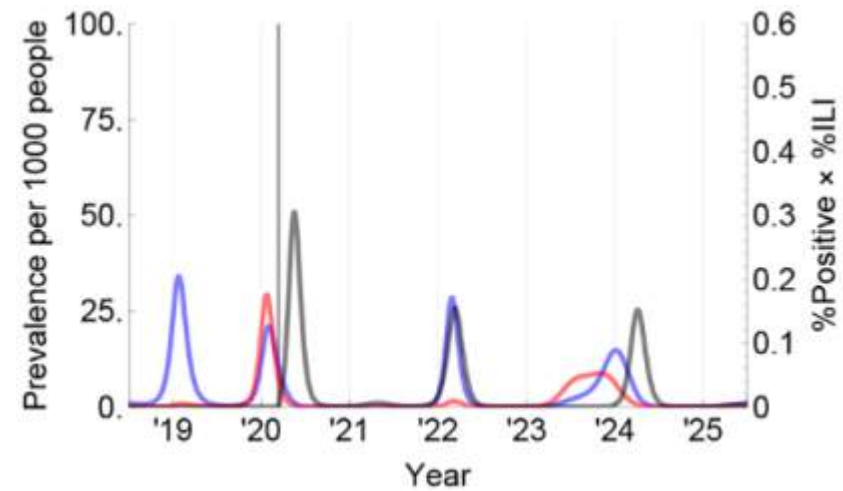
B: Long-term immunity → elimination of the virus

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

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:

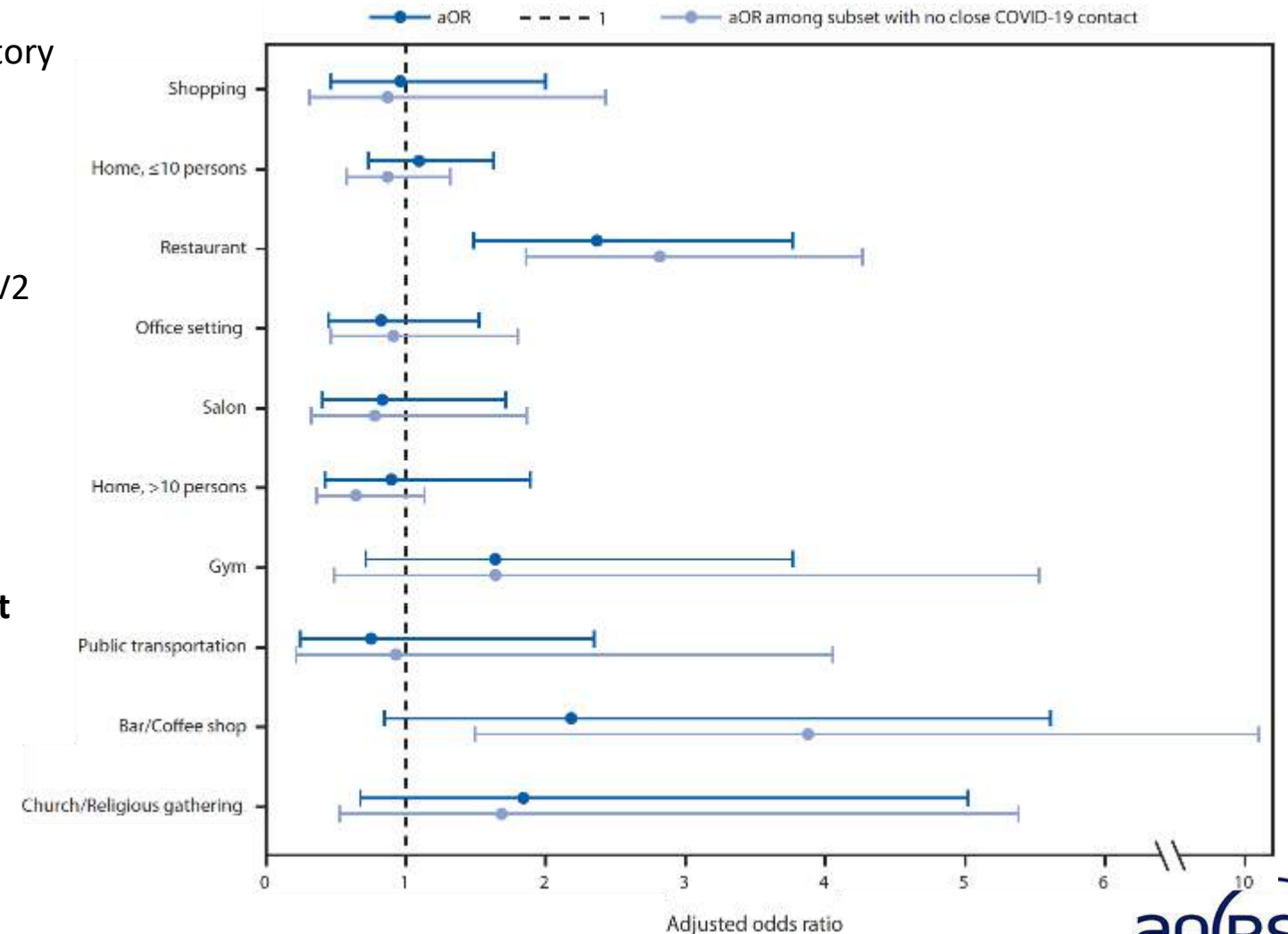
- Mask-wearing behavior, community activities <14 days before symptom onset (shopping, dining at restaurant, salon, gym, coffee/bar...) ...

Case-patients were more likely to have reported dining at restaurant (aOR: 2,4, IC_{95%}: 1,5 – 3,8).

Analysis restricted to 225 participants:

- Dining at restaurant (aOR: 2,8, CI_{95%}: 1,9 – 4,3)
- Going bar/coffee shop (aOR: 3,9, CI_{95%}: 1,5 – 10,1)

Adjusted odds ratio (aOR) and 95% confidence intervals for community exposures



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

| Setting | Total | | | | Active | | | | |
|------------------------------|---|------------|--------------|------------|------------|------------|--------------|------------|------|
| | Outbreaks | | Cases | | Outbreaks | | Cases | | |
| | N | % | N | % | N | % | N | % | |
| Healthcare facility | 20 | 3.0 | 274 | 3.3 | 17 | 3.1 | 219 | 3.5 | |
| Long-term care facility | 59 | 8.8 | 829 | 9.9 | 39 | 7.1 | 376 | 6.1 | |
| Vulnerable social group | 44 | 6.5 | 576 | 6.9 | 32 | 5.8 | 337 | 5.4 | |
| Family- different households | 65 | 9.7 | 406 | 4.8 | 52 | 9.4 | 315 | 5.1 | |
| Occupational | Total | 146 | 21.7 | 2,331 | 27.8 | 110 | 20.0 | 1,269 | 20.4 |
| | Slaughterhouse/meat plant | 19 | NA | 767 | NA | 12 | NA | 365 | NA |
| | Agriculture seasonal worker/fruit-vegetable company | 45 | NA | 1,022 | NA | 31 | NA | 500 | NA |
| | Other/not specified | 82 | NA | 542 | NA | 67 | NA | 404 | NA |
| Social | Total | 206 | 30.6 | 2,627 | 31.3 | 193 | 35.0 | 2,546 | 41.0 |
| | Organised event/public space | 31 | NA | 349 | NA | 29 | NA | 324 | NA |
| | Family/friends reunion or private party | 120 | NA | 900 | NA | 112 | NA | 854 | NA |
| | Leisure facility (restaurant, bar, club...) | 35 | NA | 1,234 | NA | 34 | NA | 1,231 | NA |
| | Other/not specified | 20 | NA | 144 | NA | 18 | NA | 137 | NA |
| Mixed | 111 | 16.5 | 1,218 | 14.5 | 92 | 16.7 | 1,050 | 16.9 | |
| Other | 22 | 3.3 | 129 | 1.5 | 16 | 2.9 | 96 | 1.5 | |
| Total | 673 | 100 | 8,390 | 100 | 551 | 100 | 6,208 | 100 | |

Two main settings to target efforts:

- Social gatherings
- Workers in vulnerable situations

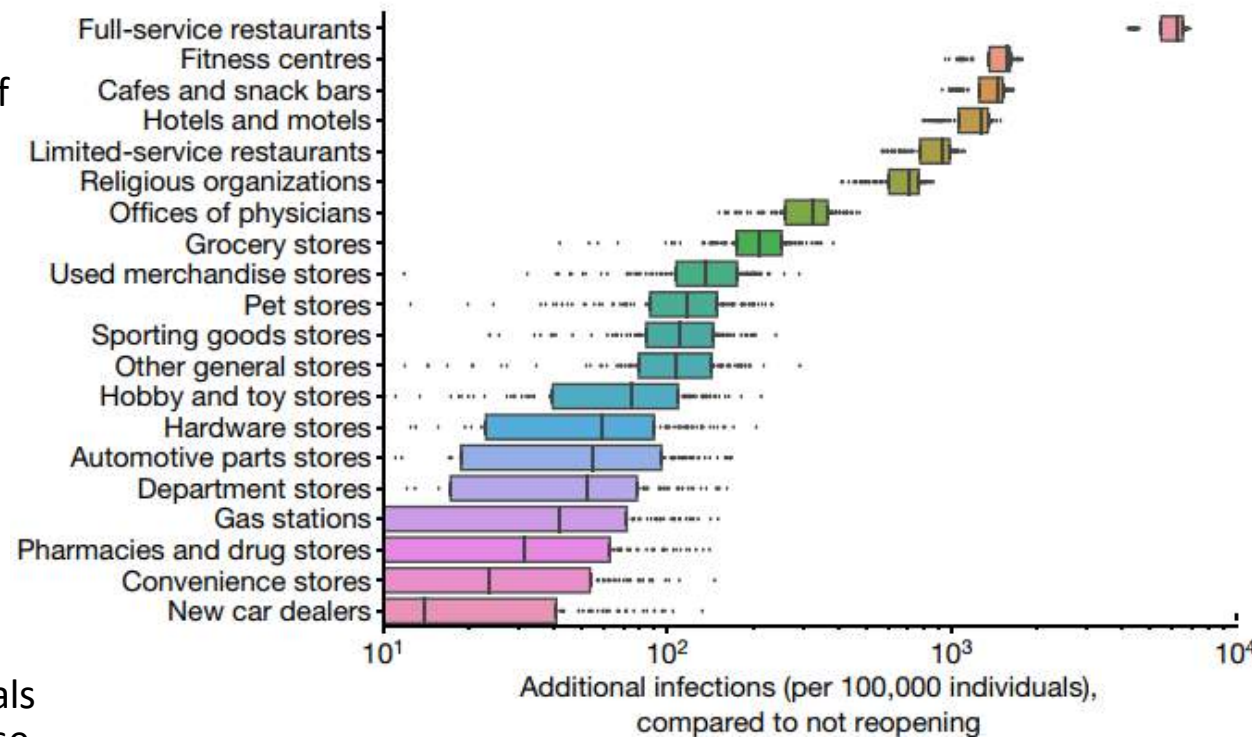
New cases and cumulative incidence are currently increasing in all regions

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

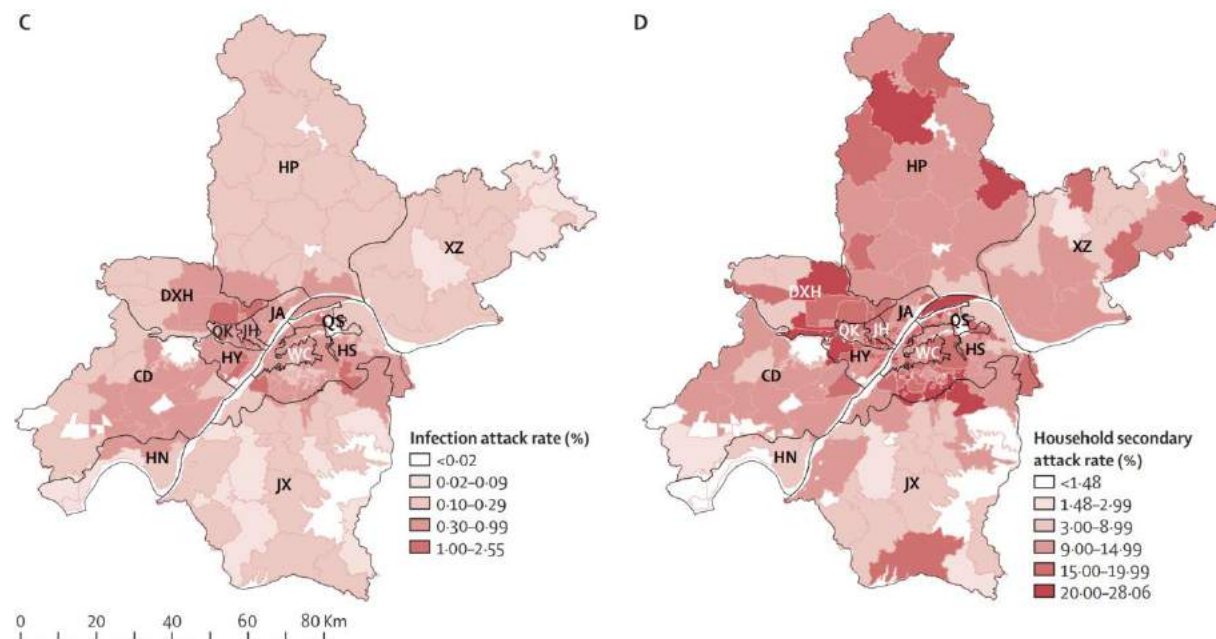
Household transmission of SARS-CoV-2

Modelling study on 27 101 households – Wuhan

(Dec 2, 2019 – April 18, 2020)

- 29 578 primary cases
 - 57581 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.è-86.1) of secondary cases developed symptoms after infection
- Young adults (20-39y) were more likely to develop symptoms than $\geq 60y$ (78.8% vs. 87.5%)
 - Pathogenicity of infection in children and adolescent resembled that of adults $\geq 40y$, although the latter were more likely to show severe or critical symptoms
 - Pathogenicity and severity did not differ between sexes

Distribution of confirmed Covid-19 cases and observed household secondary attack rate



- 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.

| Index patient age, y | Household | |
|----------------------|---|------------------------|
| | No. contacts positive/ no. contacts traced | % Positive (95% CI) |
| 0–9 | 3/57 | 5.3 (1.3–13.7) |
| 10–19 | 43/231 | 18.6 (14.0–24.0) |
| 20–29 | 240/3,417 | 7.0 (6.2–7.9) |
| 30–39 | 143/1,229 | 11.6 (9.9–13.5) |
| 40–49 | 206/1,749 | 11.8 (10.3–13.4) |
| 50–59 | 300/2,045 | 14.7 (13.2–16.3) |
| 60–69 | 177/1,039 | 17.0 (14.8–19.4) |
| 70–79 | 86/477 | 18.0 (14.8–21.7) |
| ≥ 80 | 50/348 | 14.4 (11.0–18.4) |
| Total | 1,248/10,592 | 11.8 (11.2–12.4) |

Rates of coronavirus disease among household

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

- 10 592 household contacts \rightarrow **11,8% (CI_{95%} [11,2% - 12,4%]) had COVID-19**
 - with an index patient 10–19 years, 18.6% (CI_{95%} [14.0%–24.0%]) of contacts had COVID-19
- 48 481 nonhousehold contacts \rightarrow 1,9% (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)

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 adolescents,**
 \rightarrow **Possibly more effective transmission in adolescents than in adults.**

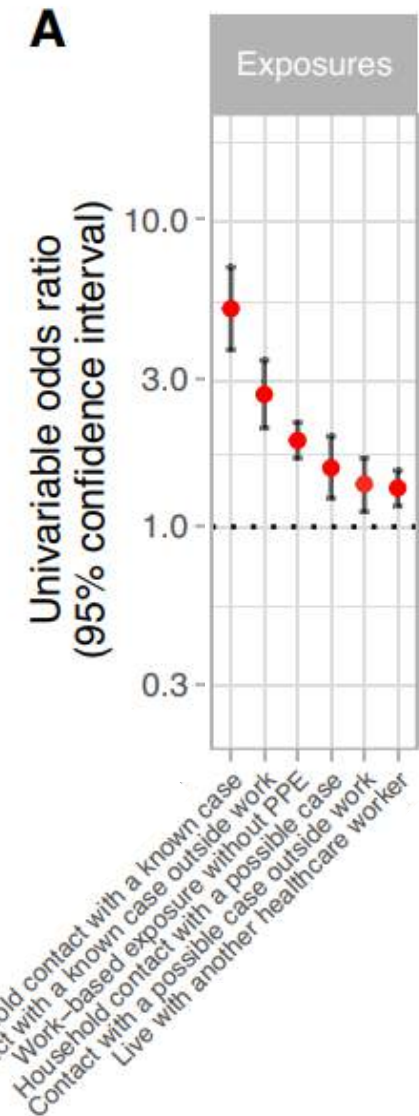
Risk of COVID-19: health-care workers

Prospective observational study on staff at Oxford University Hospitals, UK, mid-March – 8th June 2020

- 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

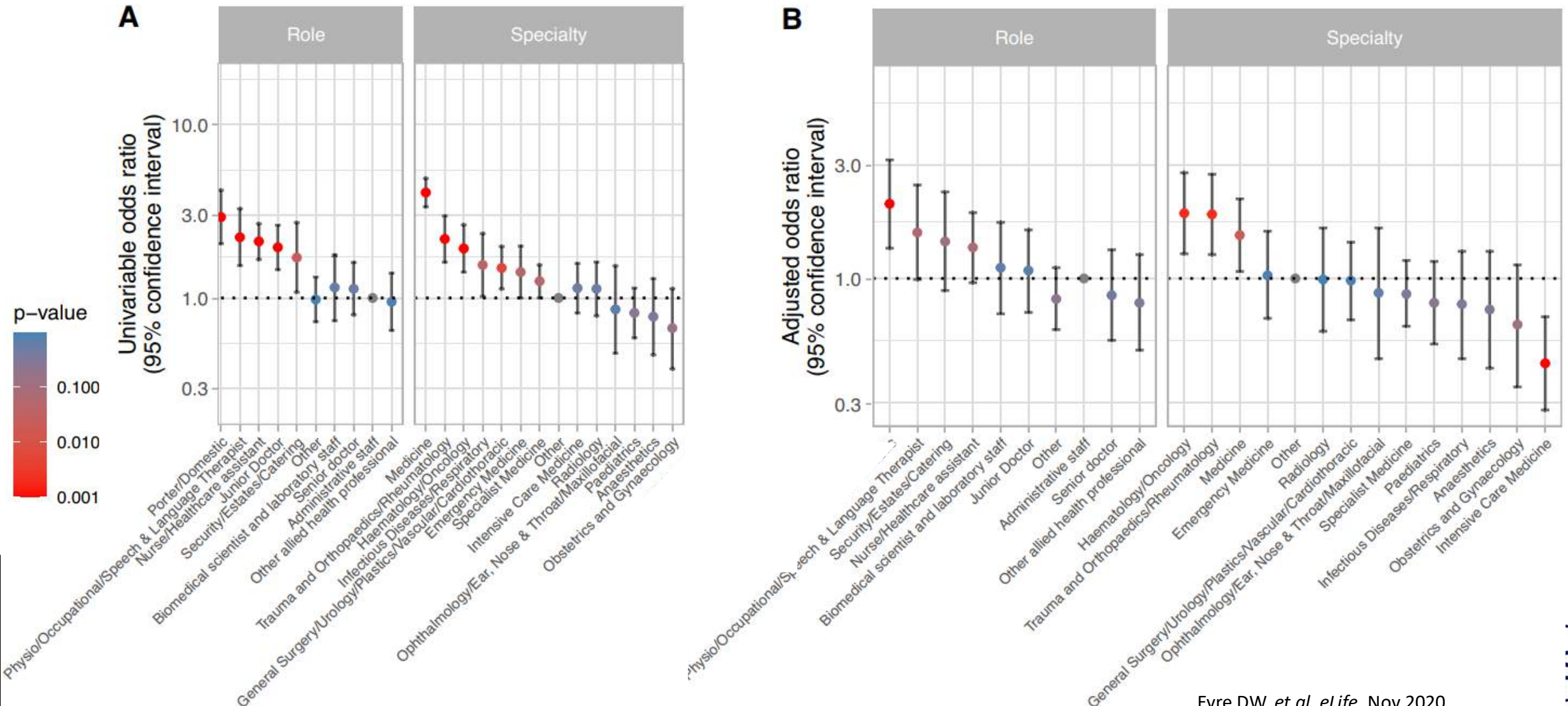
Risk factors for SARS-CoV-2 infection:

- 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.



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%]

| | Event/person-days | Incidence (30-day) | Multivariate-adjusted hazard ratio (95% CI) | Inverse probability-weighted hazard ratio (95% CI) |
|-----------------------------------|-------------------|--------------------|---|--|
| Overall (primary analysis) | | | | |
| General community | 3623/32 980 571 | 0.33% | 1 (ref) | 1 (ref) |
| Front-line health-care worker | 1922/1454701 | 3.96% | 11.61 (10.93-12.33) | 3.40 (3.37-3.43) |

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

| | Adequate PPE | Reused PPE | Inadequate PPE |
|--|------------------|------------------|------------------|
| Overall | | | |
| Event/person-days | 592/332 901 | 146/80 728 | 157/60 916 |
| Unadjusted hazard ratio (95% CI) | 1 (ref) | 1.46 (1.21-1.76) | 1.32 (1.10-1.57) |
| Multivariate-adjusted hazard ratio (95% CI) | 1 (ref) | 1.46 (1.21-1.76) | 1.31 (1.10-1.56) |
| No exposure to patients with COVID-19 | | | |
| Event/person-days | 186/227 654 | 19/37 599 | 48/35 159 |
| Unadjusted hazard ratio (95% CI) | 1 (ref) | 0.96 (0.60-1.55) | 1.53 (1.11-2.11) |
| Multivariate-adjusted hazard ratio (95% CI) | 1 (ref) | 0.95 (0.59-1.54) | 1.52 (1.10-2.09) |
| Exposure to patients with suspected COVID-19 | | | |
| Event/person-days | 126/54 676 | 36/19 378 | 26/14 083 |
| Unadjusted hazard ratio (95% CI) | 2.40 (1.91-3.02) | 3.23 (2.24-4.66) | 1.87 (1.24-2.83) |
| Multivariate-adjusted hazard ratio (95% CI) | 2.39 (1.90-3.00) | 3.20 (2.22-4.61) | 1.83 (1.21-2.78) |
| Exposure to patients with documented COVID-19 | | | |
| Event/person-days | 280/50 571 | 91/23 751 | 83/11 675 |
| Unadjusted hazard ratio (95% CI) | 4.93 (4.07-5.97) | 5.12 (3.94-6.64) | 5.95 (4.57-7.76) |
| Multivariate-adjusted hazard ratio (95% CI) | 4.83 (3.99-5.85) | 5.06 (3.90-6.57) | 5.91 (4.53-7.71) |

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

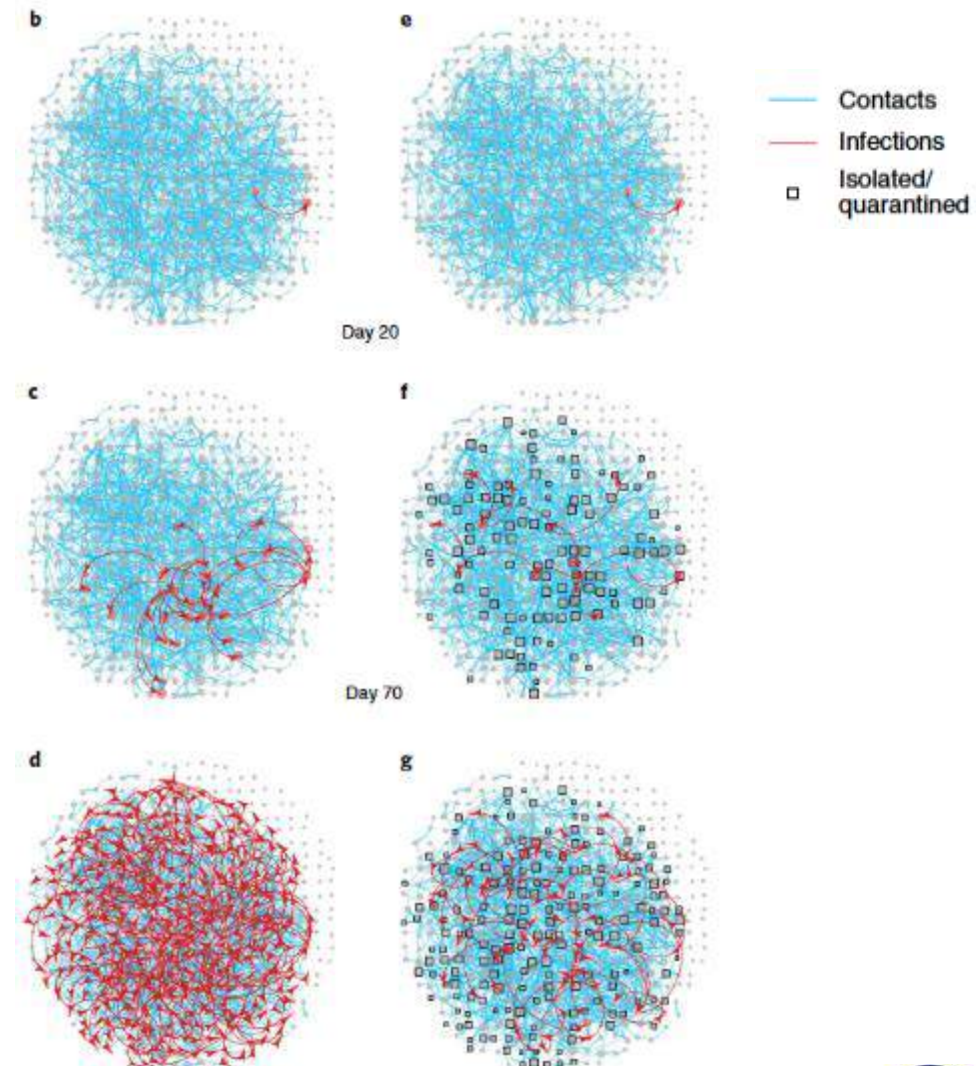


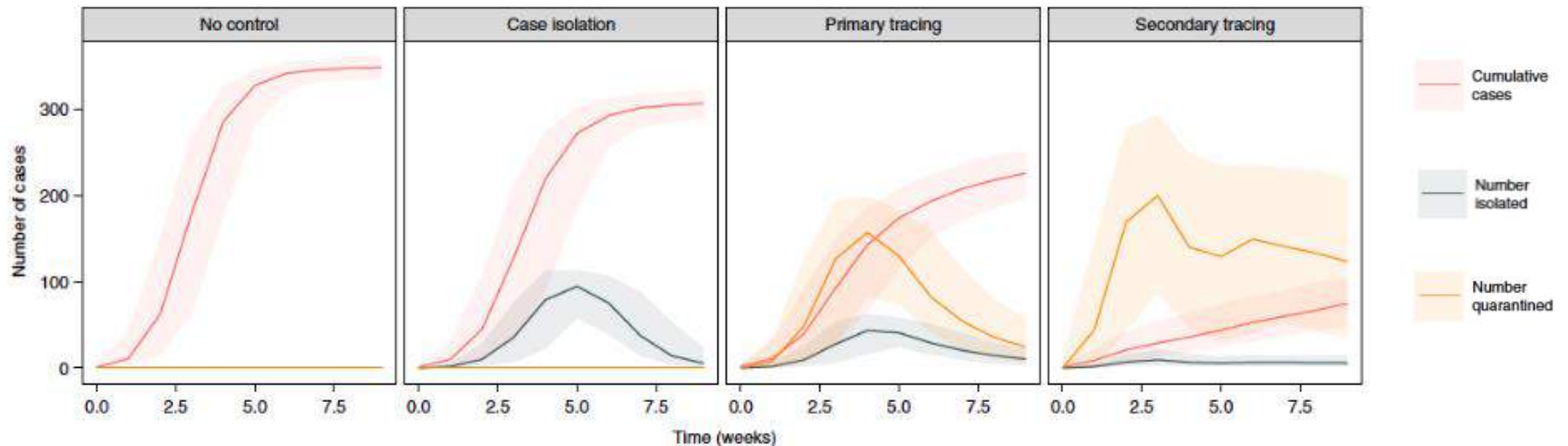
Illustration of the Haslemere network with epidemic simulation predictions.

b–d: Progression of the COVID-19 epidemic under the no-intervention

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

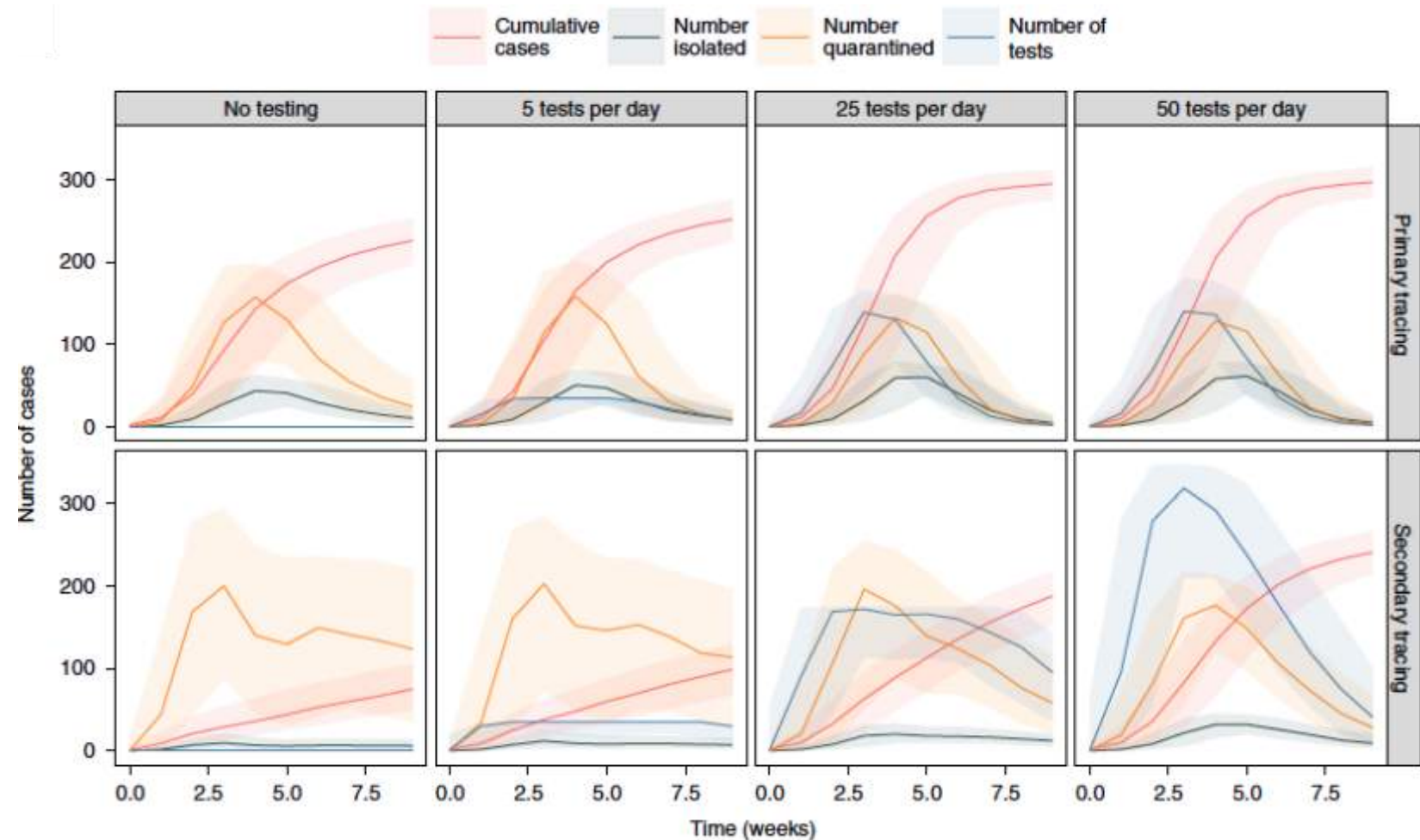
Real-world network – COVID-19 control strategies

- 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

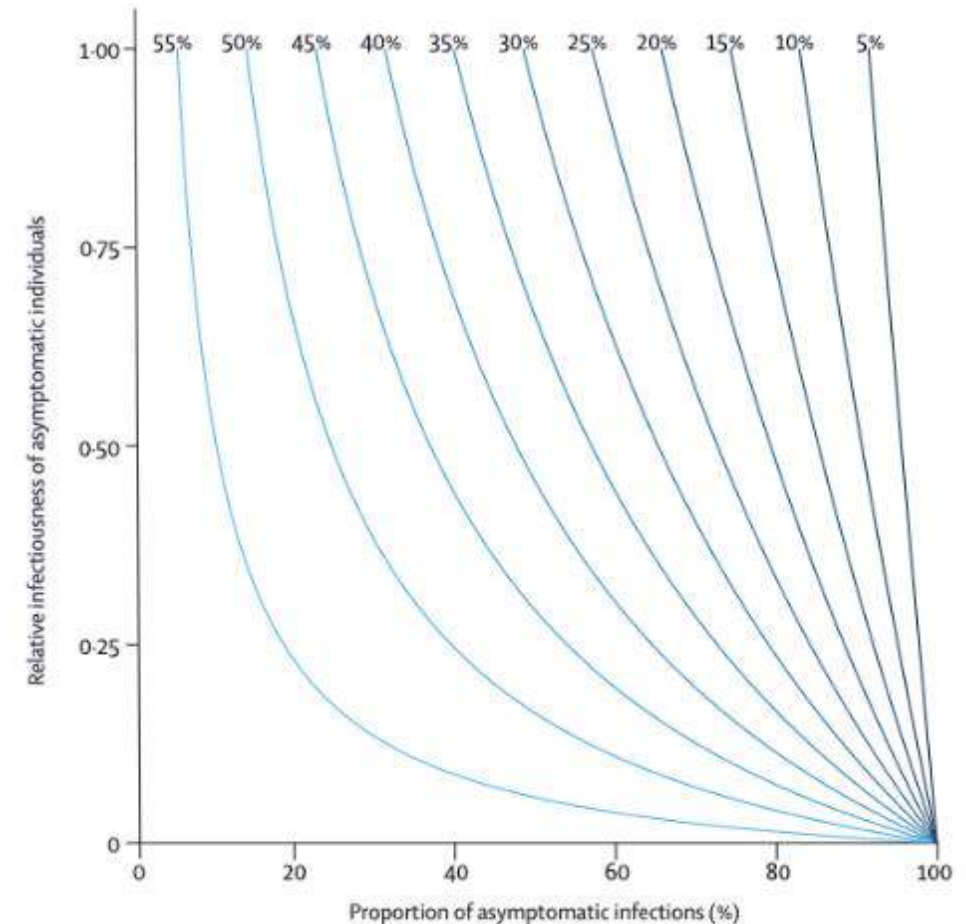
→ Would be most efficient when combined with other control measures such as physical distancing



Epidemic model predictions of how testing affect outbreak and quarantine dynamics

Testing strategies for COVID-19 control

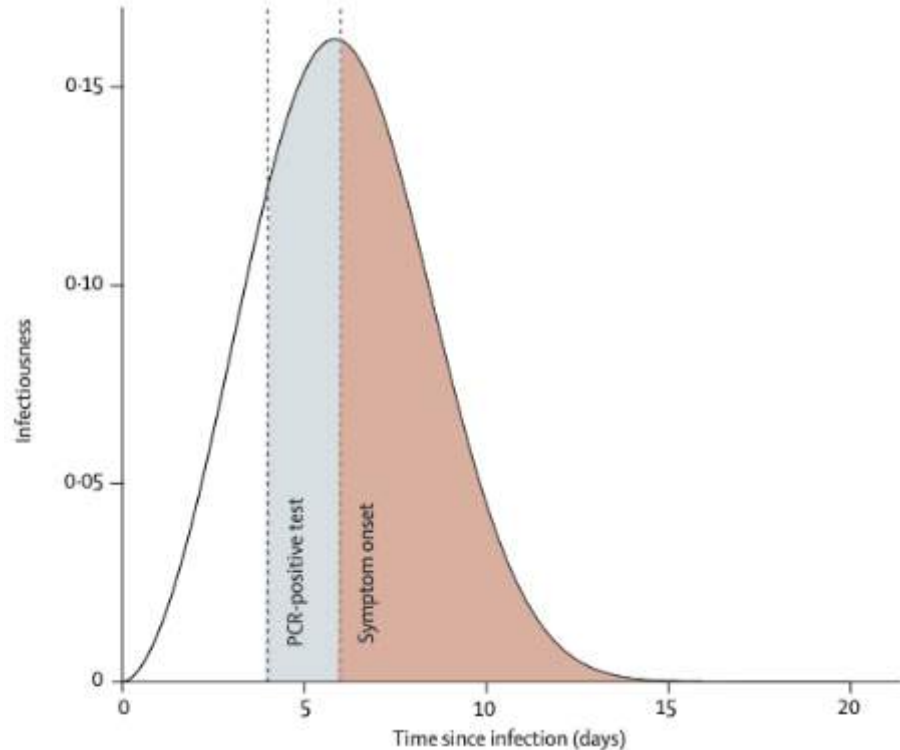
- Mathematical model of SARS-CoV-2 transmission based on:
 - Infectiousness: proportion of infection that are asymptomatic and their infectiousness
 - PCR test sensitivity over time since infection
- Evaluate
 - The impact of self-isolation following either a positive test result or symptom onset
 - The impact of quarantine of contacts of laboratory confirmed cases
- Percentage of reduction in R = 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 → 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

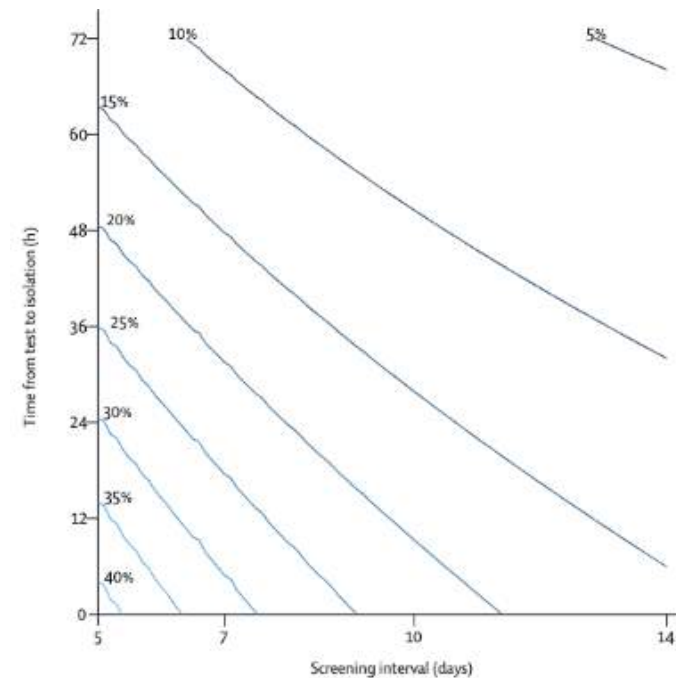
Testing strategies for COVID-19 control

- 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

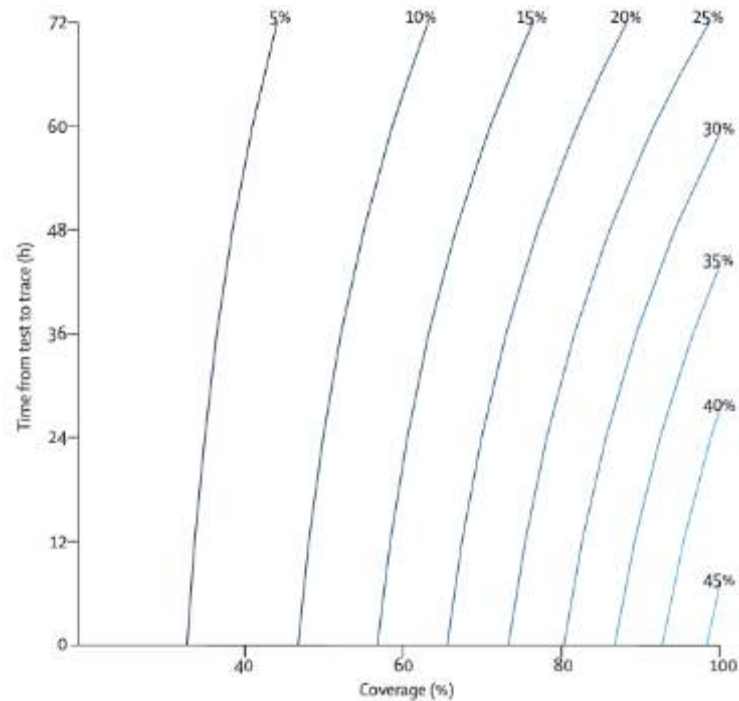
- PCR testing of symptomatic individuals → reduces the number of individuals needing self-isolate BUT would reduce the effectiveness of self-isolation (false negative)
- Regular PCR testing, irrespective of symptoms, could reduce transmission
 - Depends on the frequency of testing – timeliness of results – sensitivity of the test



Additional percentage reduction in the R by a policy of repeated PCR testing

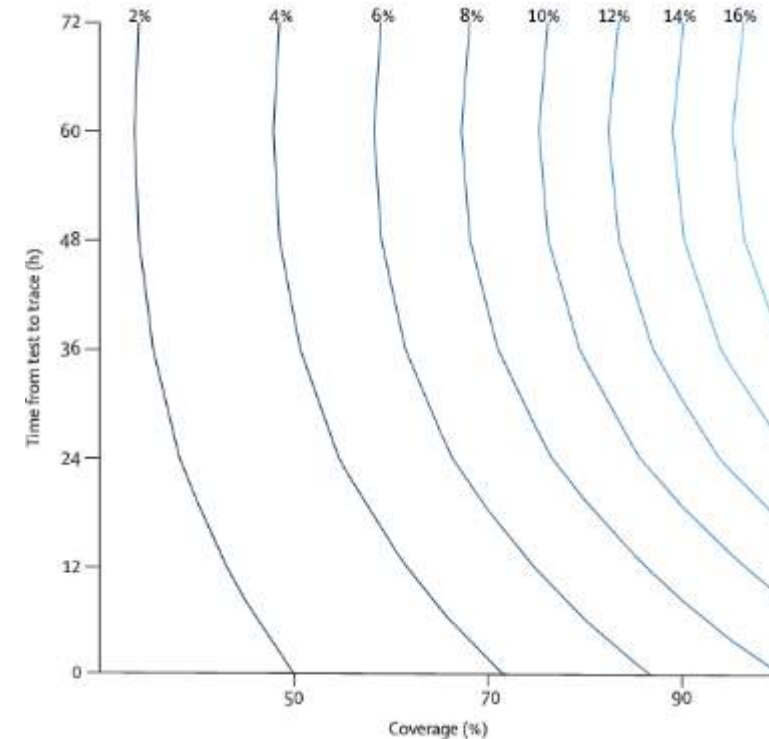
Testing strategies for COVID-19 control

- 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
 - Timeless of obtaining test results & identifying & quarantine them



Test-and-trace strategies

- 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



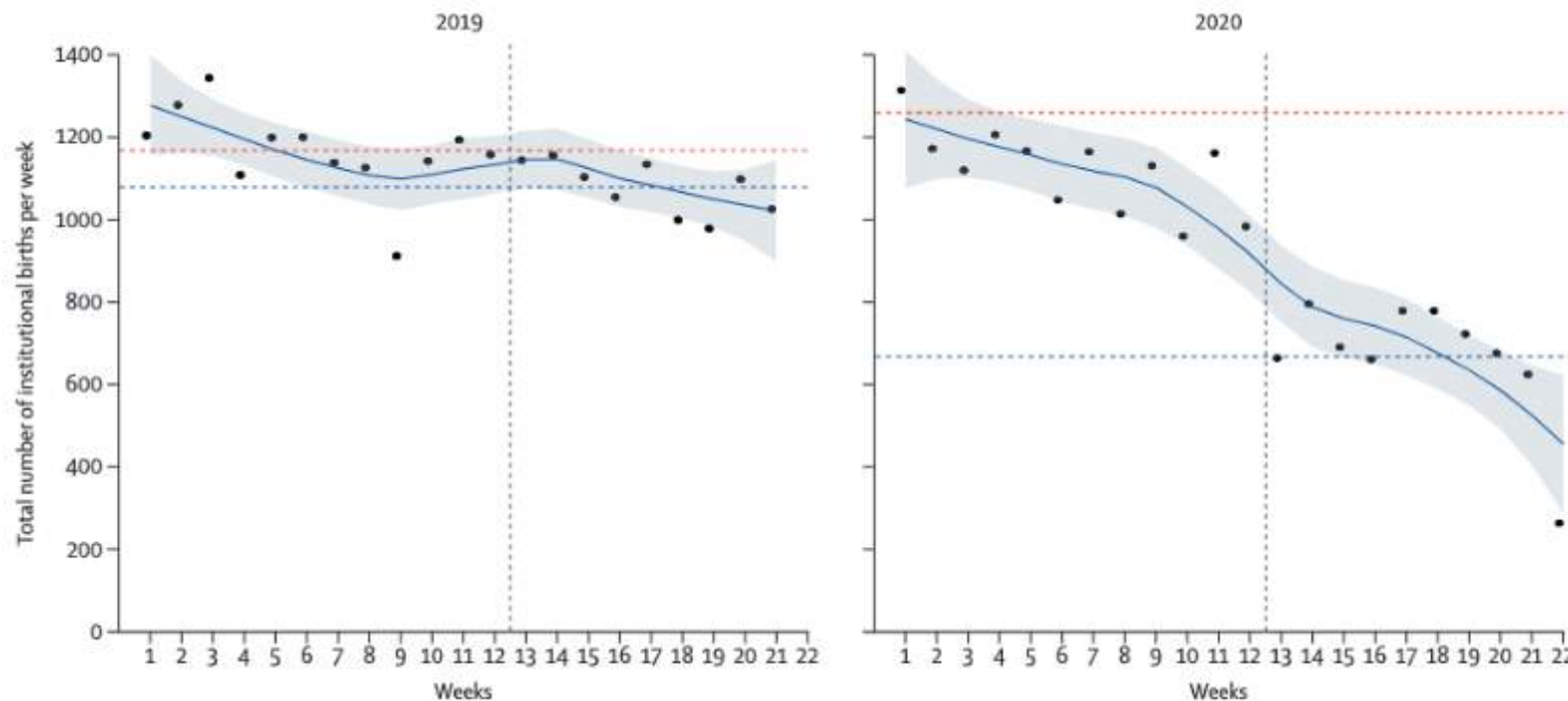
Test-trace-test strategies

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



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**

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

Impact of COVID-19 pandemic response - Nepal

| | Before lockdown | During lockdown | <i>P value</i> |
|--|-----------------|-----------------|----------------|
| Institutional stillbirth (per 1000 total births) | 14 | 21 | 0,0002 |
| Intitutional neonatal mortality (per 1000 livebirths) | 13 | 40 | 0,0022 |
| Intrapartum fetal heart rate monitoring (%) | 56,8 | 43,4 | <0,0001 |
| Skin to skin contact with the mother's chest (%) | 13,0 | 26,2 | <0,0001 |
| Health workers wash hand during childbirth (%) | 28,6 | 41,1 | <0,0001 |

| | Preterm birth rate | | Institutional stillbirth, rate per 1000 total births | | Institutional neonatal mortality rate, per 1000 livebirths | |
|---|--------------------|---------|--|---------|--|---------|
| | Estimate (95% CI) | p value | Estimate (95% CI) | p value | Estimate (95% CI) | p value |
| Adjusted effect, β | | | | | | |
| Baseline risk (risk before lockdown) | 0.14 (0.11-0.17) | <0.0001 | 3 (2-7) | <0.0001 | 0.9 (0.1-8) | <0.0001 |
| Risk ratio during lockdown vs before lockdown | 1.30 (1.20-1.40) | <0.0001 | 1.46 (1.13-1.89) | 0.0042 | 3.15 (1.47-6.74) | 0.0037 |

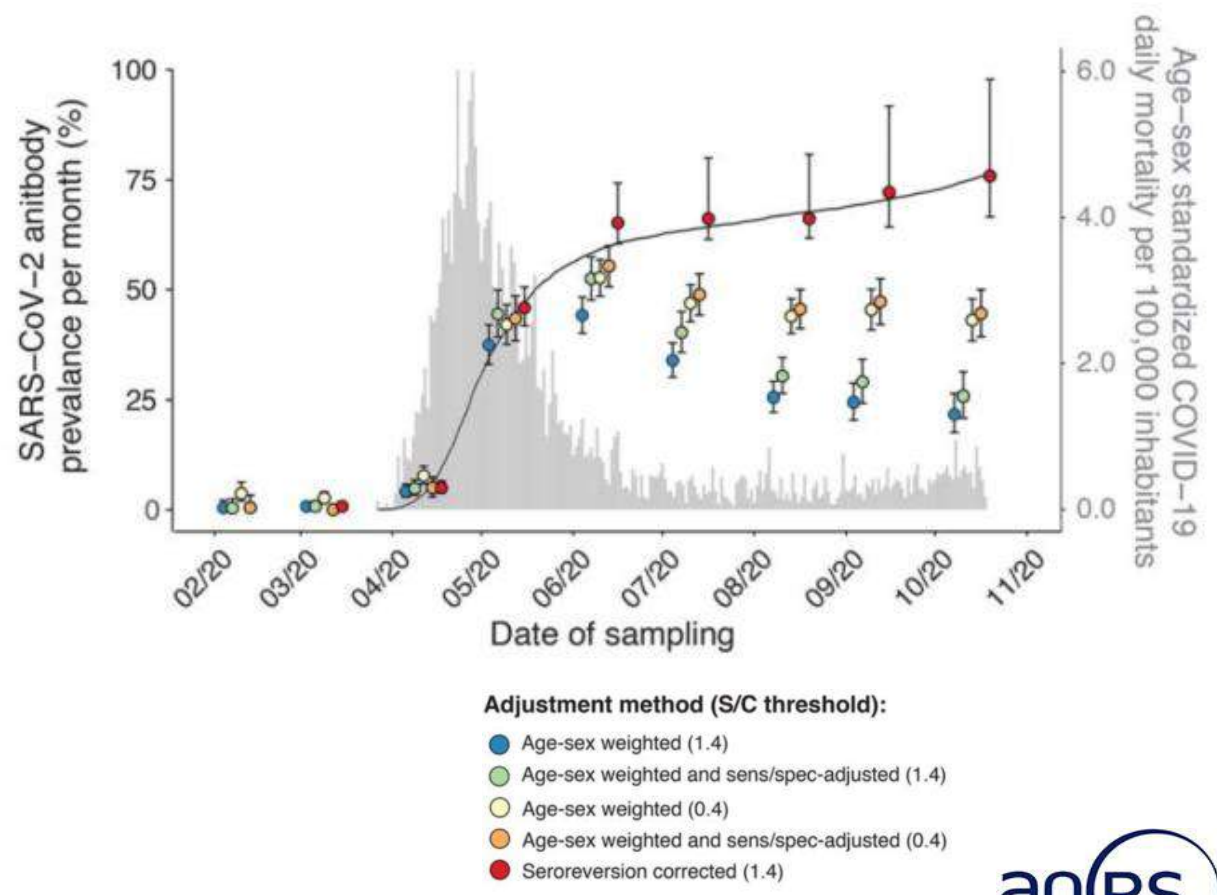
- These results raise questions on policies regarding strict lockdown in LMIC
- Pandemic lockdown jeopardize the progress that has been made in the past in Nepal
- Urgent need to protect access to high quality intrapartum care and prevent excess death

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

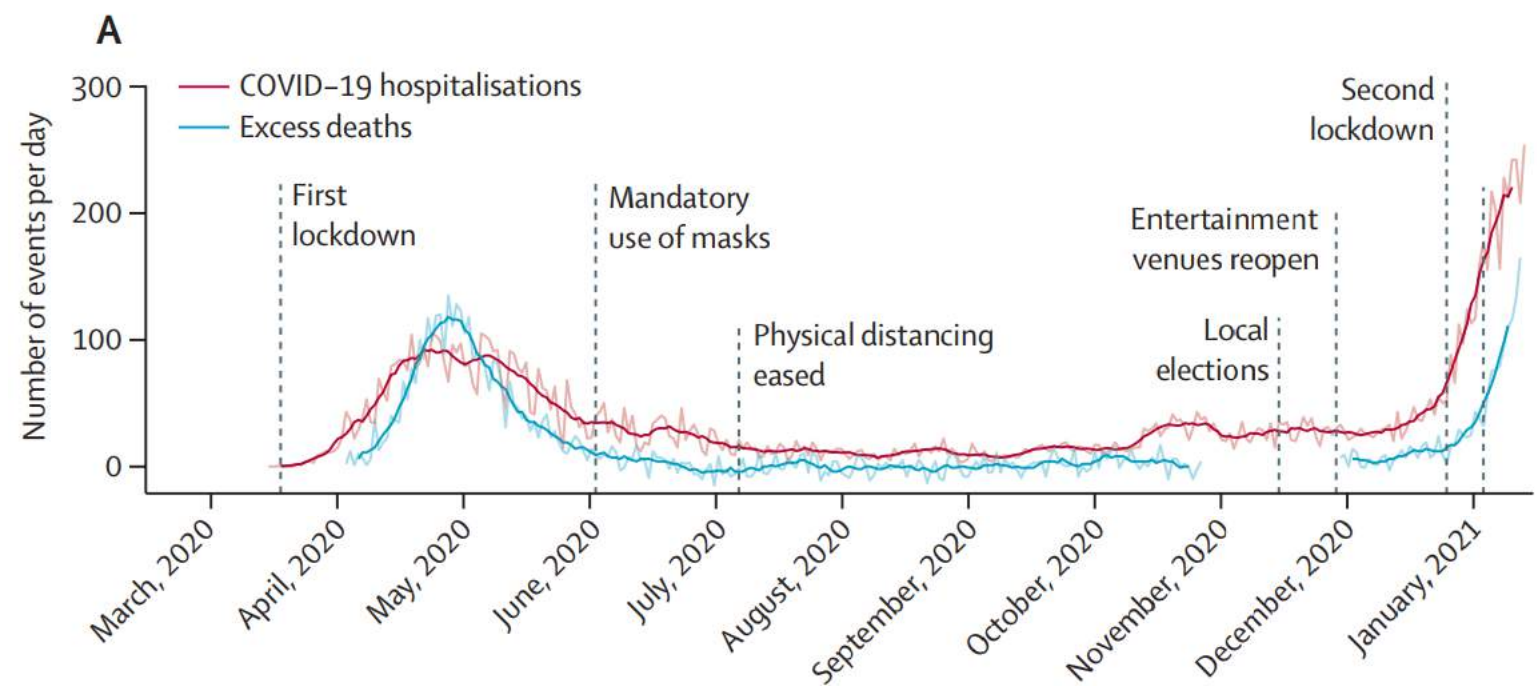


Impact of COVID-19 pandemic response – Manaus, Brazil

- 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 lineages 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



COVID-19 hospitalisations and excess deaths. Dark lines: 7-day rolling averages; Lighter lines: daily time series.

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

Countries: From Europe and the Pacific

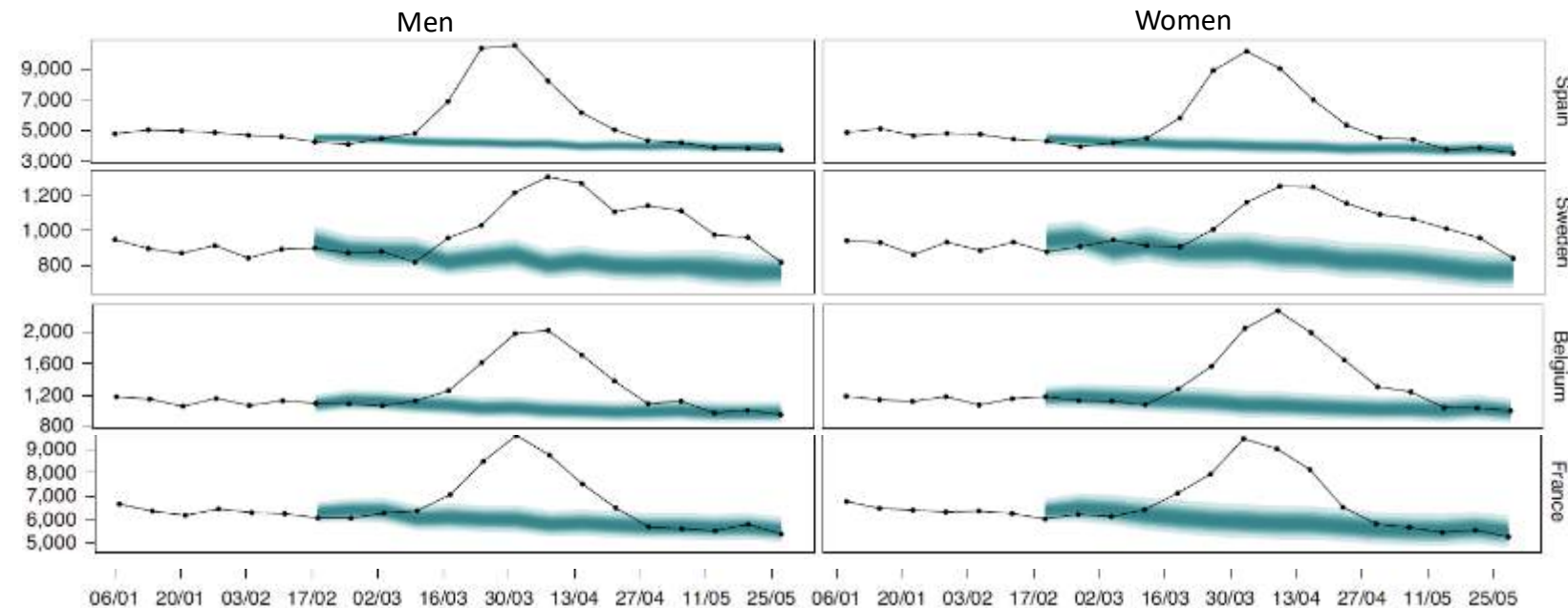
- Total population in 2020 > 4 million
- Up-to-date weekly data on all-cause mortality through May 2020
- Time series of data went back at least to 2015

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

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

From mid-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

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



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

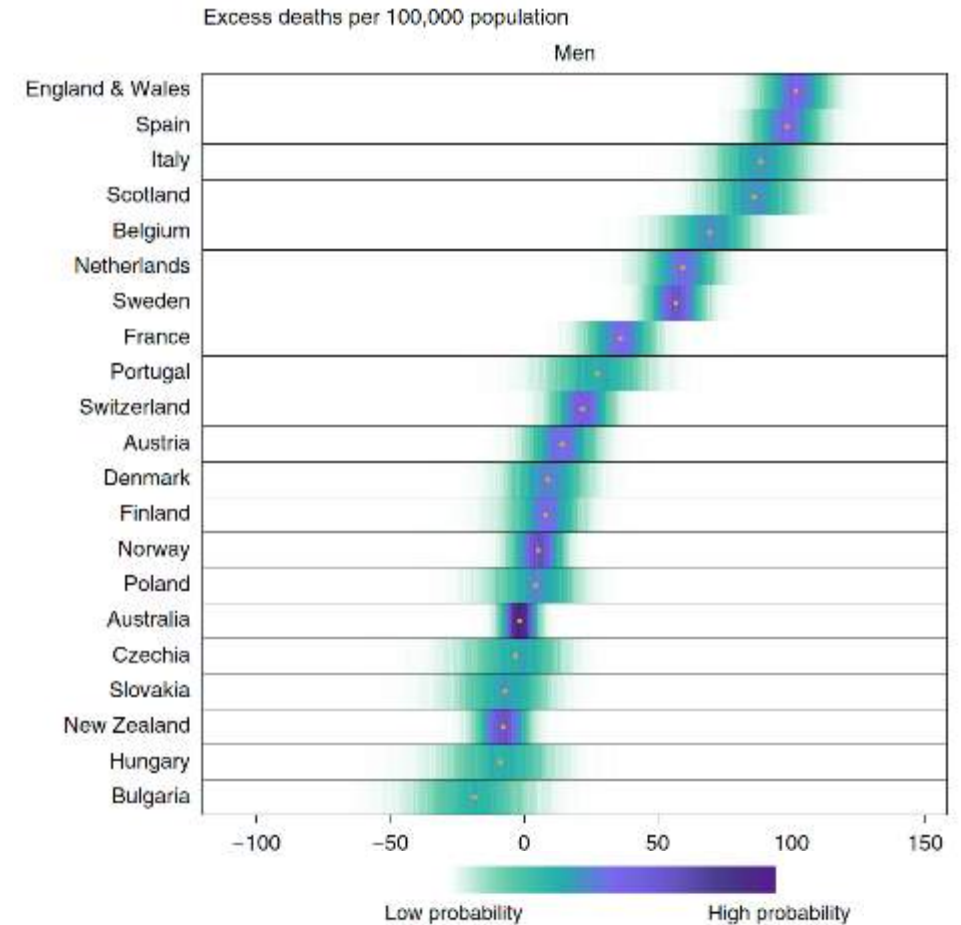
The largest rise in mortality was most likely to be in England & Wales followed by Spain and Italy.

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)



Posterior distribution of excess deaths from any cause per 100,000 people from mid-February to the end of May 2020. Gold dots in the top panels show the posterior medians.

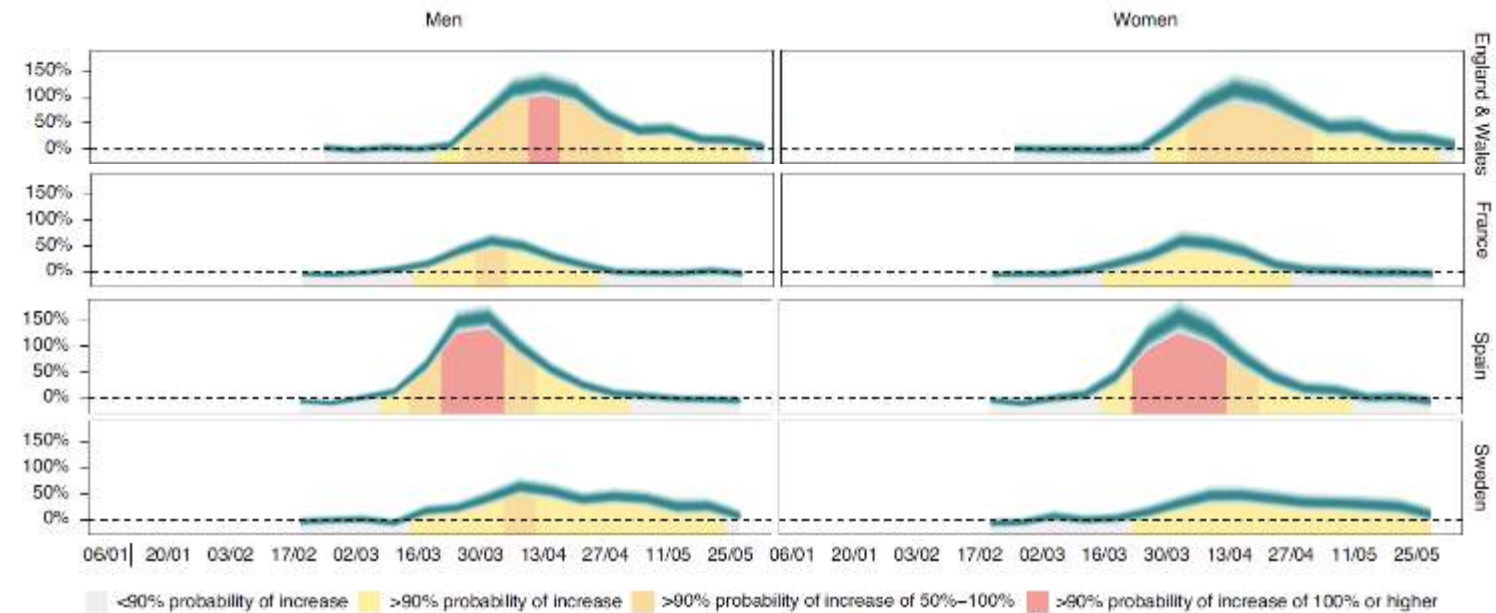
Effect of the first wave on all-cause mortality

Death returned to levels that would be 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 → comparison ?



Weekly percent increase in mortality from any cause as a result of the COVID-19 pandemic by country. The turquoise shading shows the credible intervals around the median prediction.

→ 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

Nationwide- 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

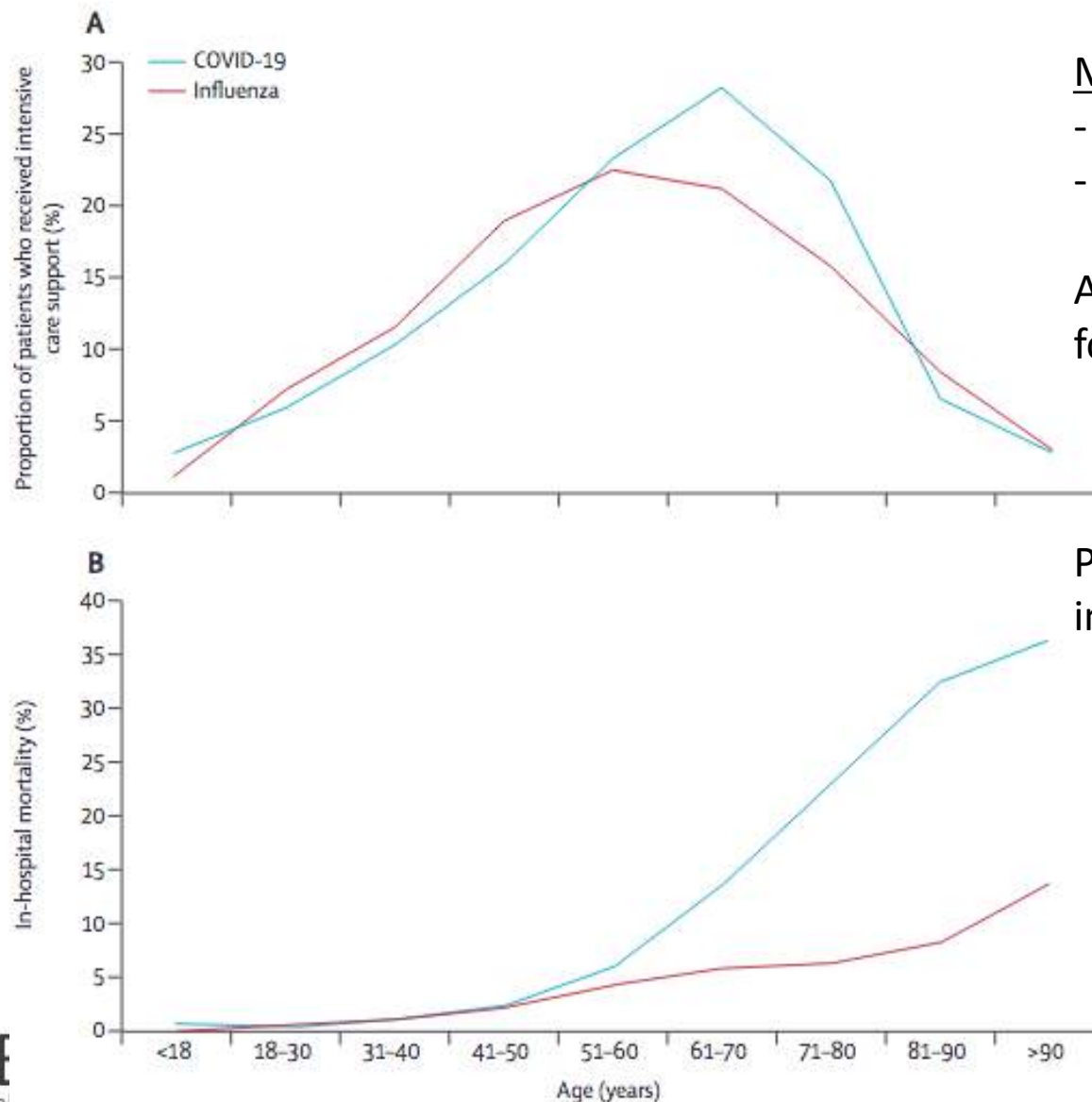
| | COVID-19 | Seasonal Influenza |
|-----------------------------|----------|--------------------|
| Male | 53 % | 48,3 % |
| Age, mean, years | 65 | 59 |
| Obese or overweight | 20,9 % | 11,5 % |
| Hypertension | 33,1 % | 28,2 % |
| Diabetes | 19 % | 16 % |
| Heart failure | 8 % | 13,7 % |
| Chronic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

2. Outcomes

| | COVID-19 | Seasonal Influenza |
|--|----------|--------------------|
| Acute respiratory failure | 27,2 % | 17,4 % |
| Pulmonary embolism | 3,4 % | 0,9 % |
| Septic shock | 2,8 % | 2 % |
| Myocardial infarction | 0,6 % | 1,1 % |
| Admission ICU | 16,3 % | 10,8 % |
| Invasive mechanical ventilation (ICU patients) | 71,5 % | 61 % |
| In-hospital death | 16,9 % | 5,8 % |
| Chronic respiratory disease | 1,6 % | 4 % |

COVID-19 versus seasonal influenza

Intensive care support and mortality of patients hospitalised in France for COVID-19 or seasonal influenza, by age at admission



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,**

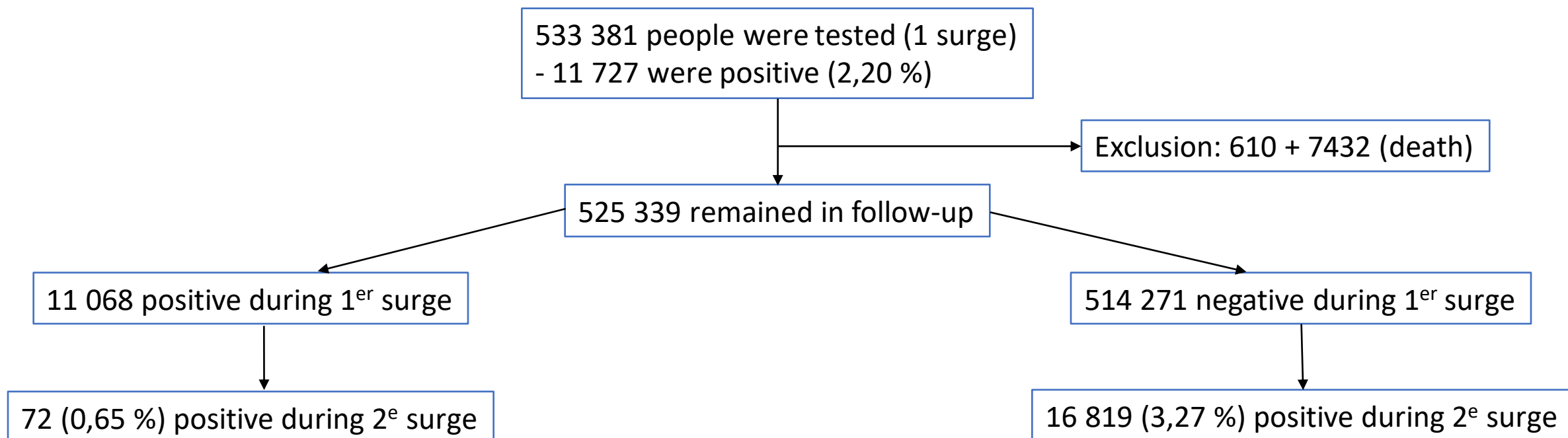
Age-standardised mortality ratio of 2.82 (COVID-19)

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



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 & 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.

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

1. Chan JF, *et al.* A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet*. 2020 Feb 15;395(10223):514-523. doi: 10.1016/S0140-6736(20)30154-9.
2. HE X, *et al.* Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020 May;26(5):672-675. doi: 10.1038/s41591-020-0869-5.
3. Li R, *et al.* Substantial undocumented infection facilitates the rapid dissemination of novel coronavirus (SARS-CoV-2). *Science*. 2020 May 1;368(6490):489-493. doi: 10.1126/science.abb3221.
4. Kucharski A, *et al.* Early dynamics of transmission and control of COVID-19: a mathematical modelling study. *Lancet Infect Dis*. 2020 May;20(5):553-558. doi: 10.1016/S1473-3099(20)30144-4.
5. Li A, *et al.* Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*. 2020 Mar 26;382(13):1199-1207. doi: 10.1056/NEJMoa2001316.
6. Lauer SA, *et al.* The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application. *Ann Intern Med*. 2020 May 5;172(9):577-582. doi: 10.7326/M20-0504.
7. Li Y, *et al.* The temporal association of introducing and lifting non-pharmaceutical interventions with the time-varying reproduction number (R) of SARS-CoV-2: a modelling study across 131 countries. *Lancet Infect Dis*. 2021 Feb;21(2):193-202. doi: 10.1016/S1473-3099(20)30785-4.
8. Chu DK, *et al.* Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet*. 2020 Jun 27;395(10242):1973-1987. doi: 10.1016/S0140-6736(20)31142-9.
9. Leung NH, *et al.* Respiratory virus shedding in exhaled breath and efficacy of face masks. *Nat Med*. 2020 May;26(5):676-680. doi: 10.1038/s41591-020-0843-2.
10. Lyu W, *et al.* Community Use Of Face Masks And COVID-19: Evidence From A Natural Experiment Of State Mandates In The US. *Health Aff (Millwood)*. 2020 Aug;39(8):1419-1425. doi: 10.1377/hlthaff.2020.00818.
11. Kissler SM, *et al.* Projecting the transmission dynamics of SARS-CoV-2 through the postpandemic period. *Science*. 2020 May 22;368(6493):860-868. doi: 10.1126/science.abb5793.

12. Fisher KA, *et al.* Community and Close Contact Exposures Associated with COVID-19 Among Symptomatic Adults ≥ 18 Years in 11 Outpatient Health Care Facilities - United States, July 2020. *MMWR Morb Mortal Wkly Rep.* 2020 Sep 11;69(36):1258-1264. doi: 10.15585/mmwr.mm6936a5.
13. National COVID-19 outbreak monitoring group. COVID-19 outbreaks in a transmission control scenario: challenges posed by social and leisure activities, and for workers in vulnerable conditions, Spain, early summer 2020. *Euro Surveill.* 2020 Sep;25(35):2001545. doi: 10.2807/1560-7917.ES.2020.25.35.2001545.
14. Chang S., *et al.* Mobility network models of COVID-19 explain inequities and inform reopening. *Nature.* 2021 Jan;589(7840):82-87. doi: 10.1038/s41586-020-2923-3.
15. Li F, *et al.* Household transmission of SARS-CoV-2 and risk factors for susceptibility and infectivity in Wuhan: a retrospective observational study. *Lancet Infect Dis.* 2021 Jan 18;S1473-3099(20)30981-6. doi: 10.1016/S1473-3099(20)30981-6. Online ahead of print.
16. Park YJ, *et al.* Contact Tracing during Coronavirus Disease Outbreak, South Korea, 2020. *Emerg Infect Dis.* 2020 Oct;26(10):2465-2468. doi: 10.3201/eid2610.201315.
17. Eyre DW, *et al.* Differential occupational risks to healthcare workers from SARS-CoV-2 observed during a prospective observational study. *Elife.* 2020 Aug 21;9:e60675. doi: 10.7554/eLife.60675.
18. Nguyen LH, *et al.* Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study. *Lancet Public Health.* 2020 Sep;5(9):e475-e483. doi: 10.1016/S2468-2667(20)30164-X.
19. Firth JA, *et al.* Using a real-world network to model localized COVID-19 control strategies. *Nat Med.* 2020 Oct;26(10):1616-1622. doi: 10.1038/s41591-020-1036-8.
20. Grassly NC, *et al.* Comparison of molecular testing strategies for COVID-19 control: a mathematical modelling study. *Lancet Infect Dis.* 2020 Dec;20(12):1381-1389. doi: 10.1016/S1473-3099(20)30630-7.
21. Kc A, *et al.* Effect of the COVID-19 pandemic response on intrapartum care, stillbirth, and neonatal mortality outcomes in Nepal: a prospective observational study. *Lancet Glob Health.* 2020 Oct;8(10):e1273-e1281. doi: 10.1016/S2214-109X(20)30345-4.

22. Buss LF, *et al.* Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic. *Science*. 2021 Jan 15;371(6526):288-292. doi: 10.1126/science.abe9728.
23. Sabino EC, *et al.* Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence. *Lancet*. 2021 Feb 6;397(10273):452-455. doi: 10.1016/S0140-6736(21)00183-5.
24. Kontis V, *et al.* Magnitude, demographics and dynamics of the effect of the first wave of the COVID-19 pandemic on all-cause mortality in 21 industrialized countries. *Nat Med*. 2020 Dec;26(12):1919-1928. doi: 10.1038/s41591-020-1112-0.
25. Pirot L, *et al.* Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med*. 2021 Mar;9(3):251-259. doi: 10.1016/S2213-2600(20)30527-0.
26. Hansen CH, *et al.* Assessment of protection against reinfection with SARS-CoV-2 among 4 million PCR-tested individuals in Denmark in 2020: a population-level observational study. *Lancet*. 2021 Mar 27;397(10280):1204-1212. doi: 10.1016/S0140-6736(21)00575-4.



Contacts

Dr. Guillaume Mellon
guillaume.mellon@aphp.fr

Dr Eric D'Ortenzio
eric.dortenzio@inserm.fr