COREB
mission nationale
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EPIDEMIOLOGY

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MALADIES INFECTIEUSES ÉMERGENTES

https://reacting.inserm.fr/

Scientific update on COVID-19

Updated on July 22nd July 2021

Redaction committee

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EPIDEMIOLOGY

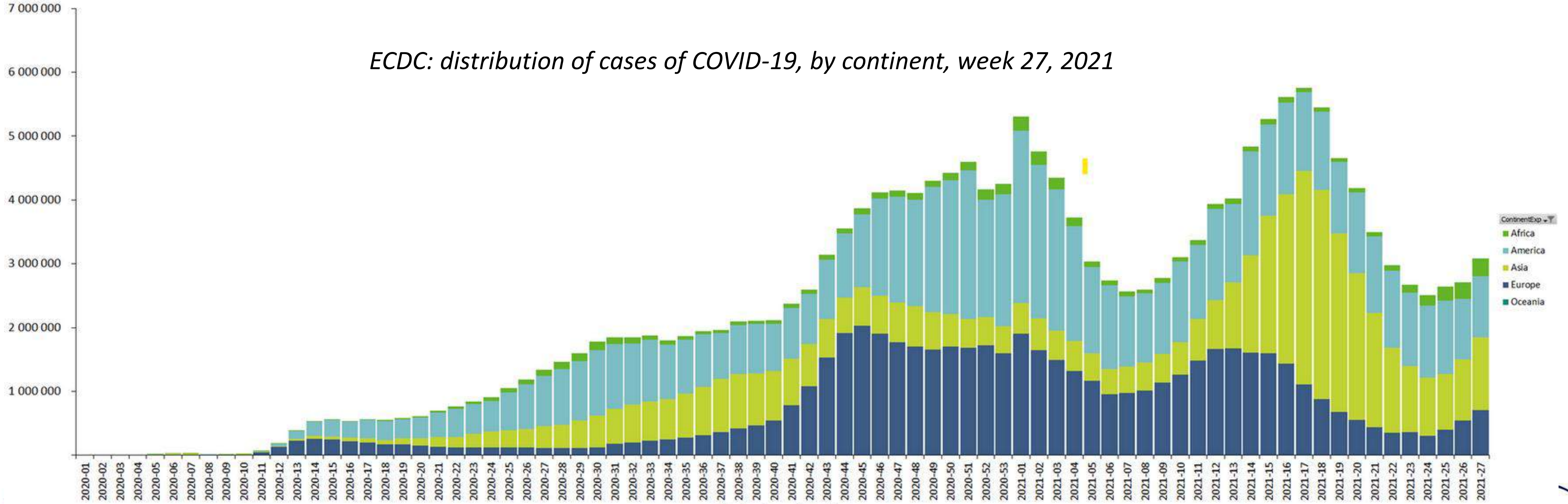
Questions:

- 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

- ***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

ECDC: distribution of cases of COVID-19, by continent, week 27, 2021

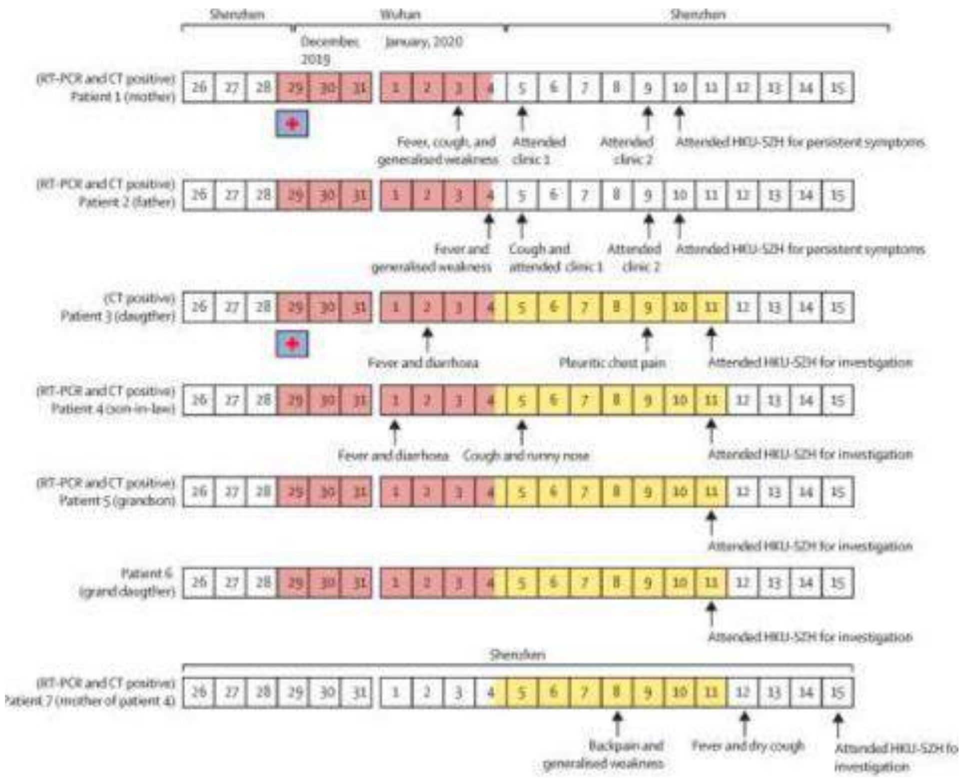


Week and year of reporting

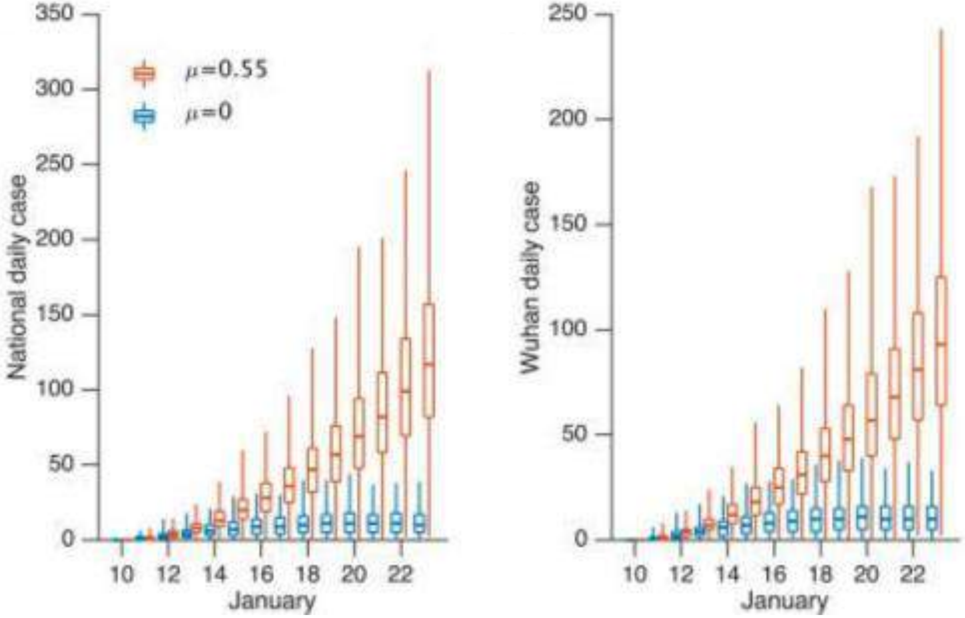
Epidemiology

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

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



Chronology of symptom onset of the family cluster



- Very high rate of undocumented infection
- **Dissemination by undocumented infection** (asymptomatic, presymptomatic…)

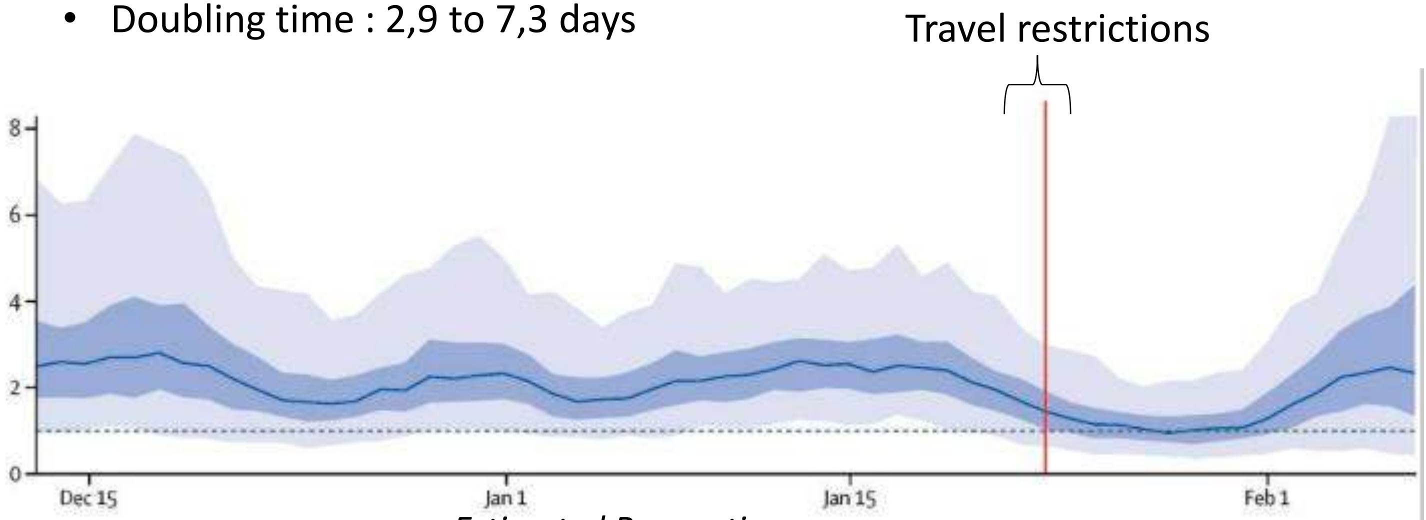
- <u>He and colleagues</u> estimation (slide 35): 44% ($CI_{95\%}$ [30 – 57%]) of secondary cases were infected during the index cases' presymptomatic stage

Infectiousness was estimated to decline quickly within 7 days

Epidemiology

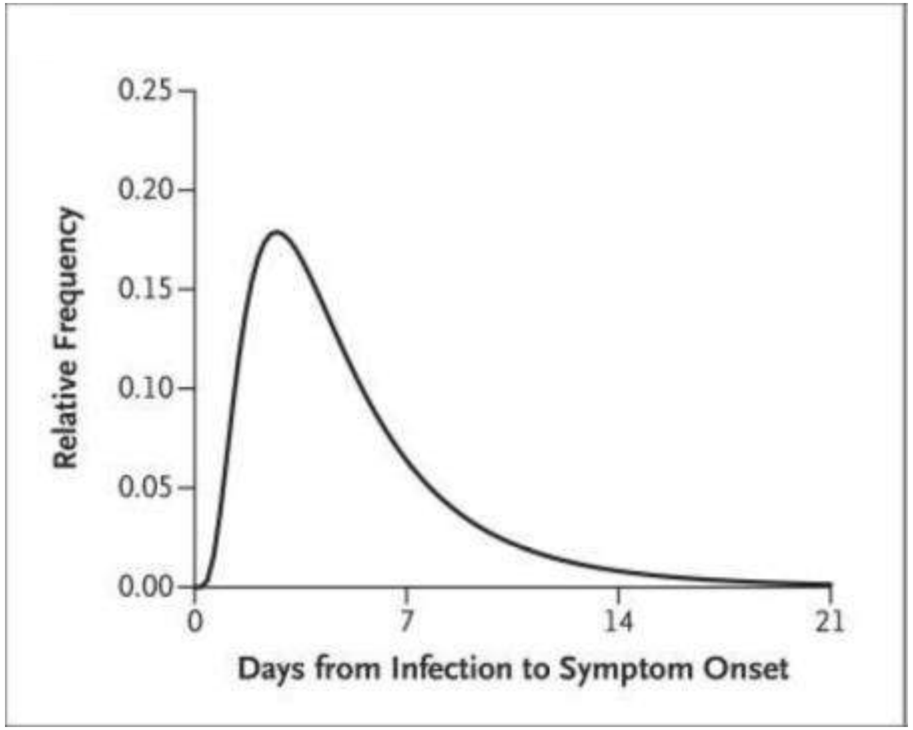
<u>At beginning & before controls measures:</u>

- 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



Estimated R_t over time

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



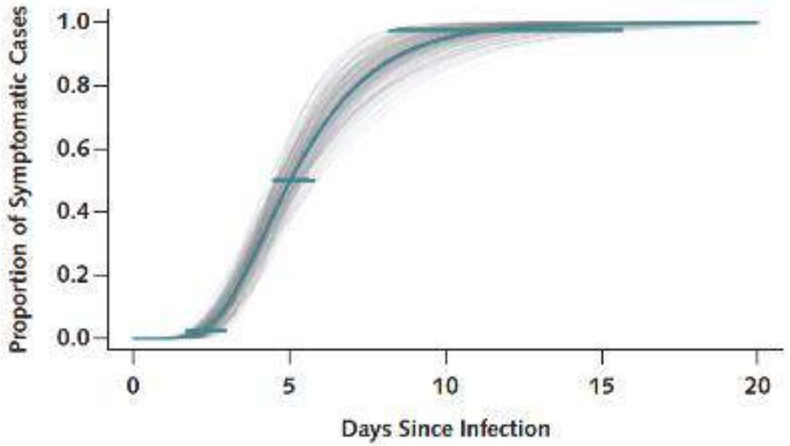
R_t: median daily reproduction number R_e: estimated daily reproduction number

Kucharski AJ, *et al. Lancet Infect Dis.* Mar 2020

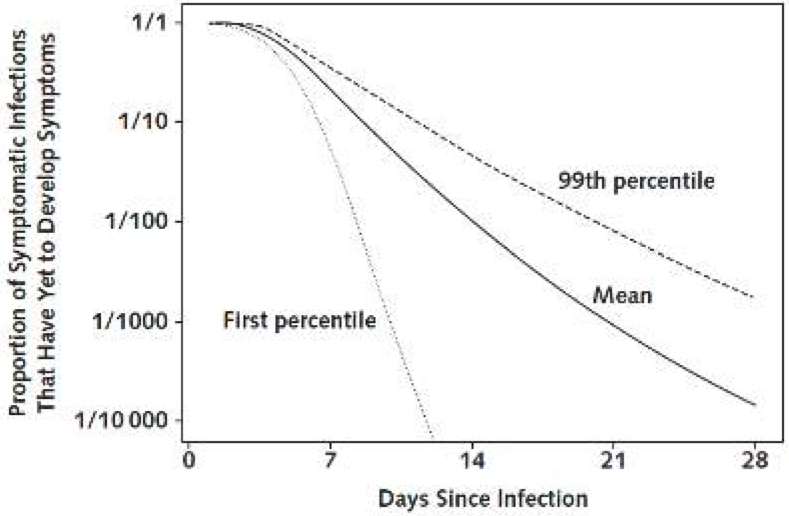
Li Q, *et al. NEJM.* Mar 2020

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]
    - < 2,5% of infected persons will shows symptoms within 2,2 days
    - 97.5% of symptomatic patients developing symptoms within 11.5 days
- <u>Analysis specific for cases detected outside of China</u>
    - 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)

Lauer SA, *et al. Ann Intern Med.* May 2020

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 ith day of that phase (ie, 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

Li Y, *et al. Lancet Infect Dis.* Oct 2020

Non pharmaceutical interventions and *R*

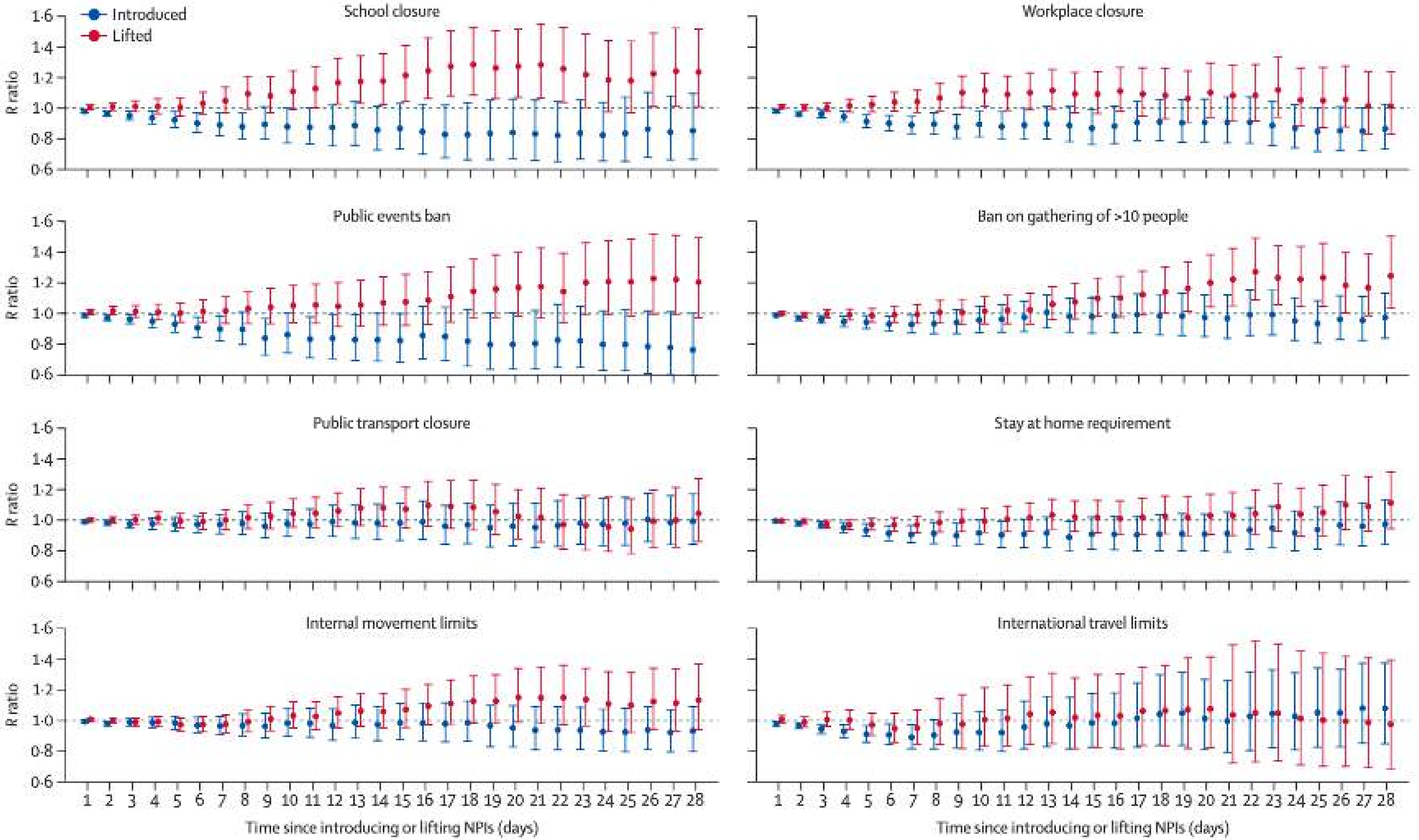
<u>Greatest increase in *R* ratio:</u>

- 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)

<u>Time in days needed to reach 60% of its maximum effect</u>:

- Median of 8 days following the indroduction
- 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)

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Li Y, *et al. Lancet Infect Dis.* Oct 2020

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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

→ Autors: "**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)[75]
			Comparison group	Intervention group			
Physical distance ≥1 m vs <1 m	Nine adjusted studies (n=7782); 29 unadjusted studies (n=10 736)	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=10 170)	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

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Chu DK, *et al. Lancet.* Jun 2020

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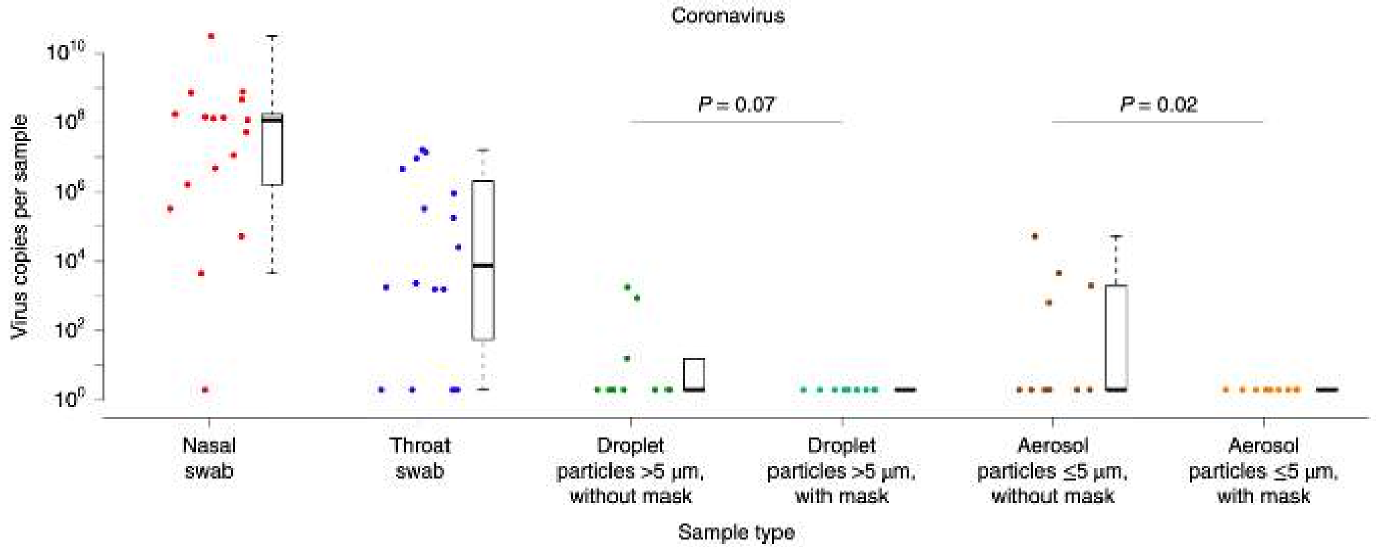
Face masks' effectiveness in respiratory viruses

- 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

Leung NHL, *et al. Nature Med.* May 2020

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

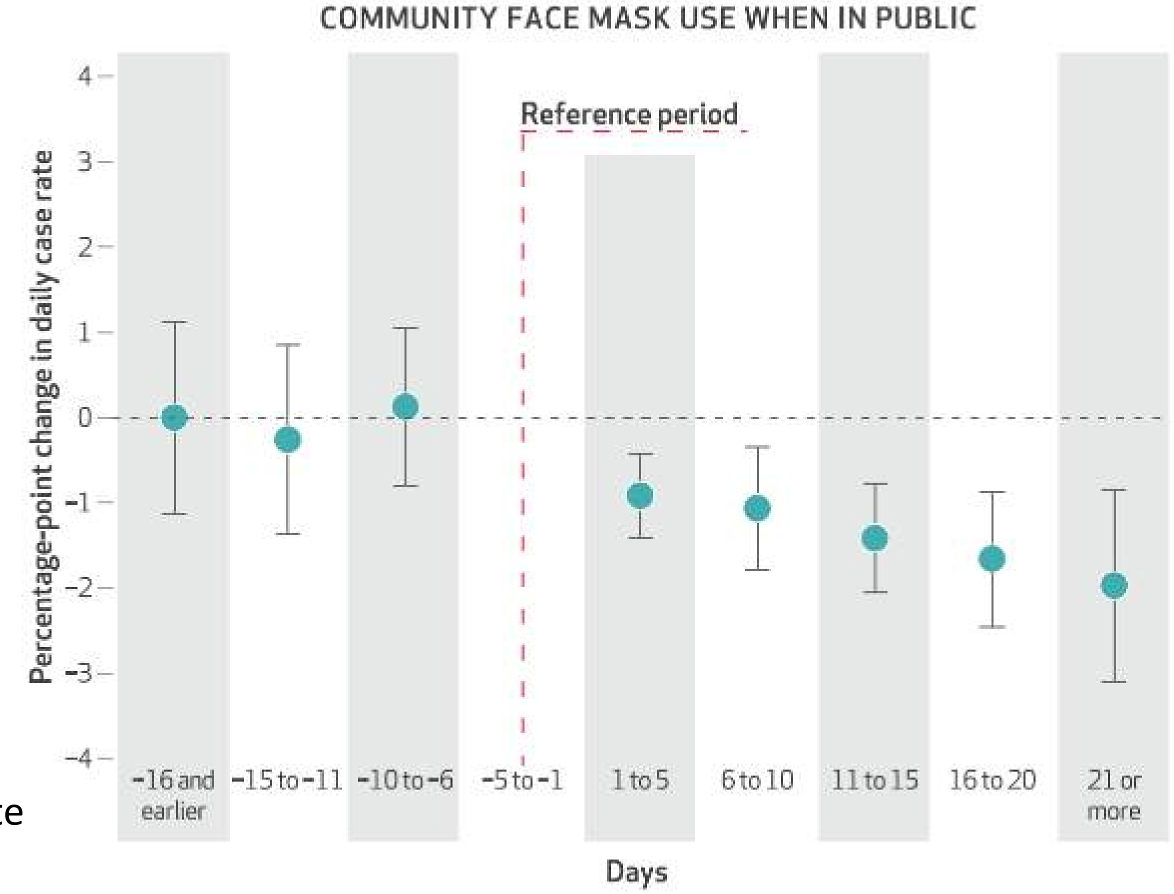
Estimated the effects of face cover mandates on the **daily county-level COVID-19 growth rate**,

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

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



<u>**Limits:**</u>

- 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

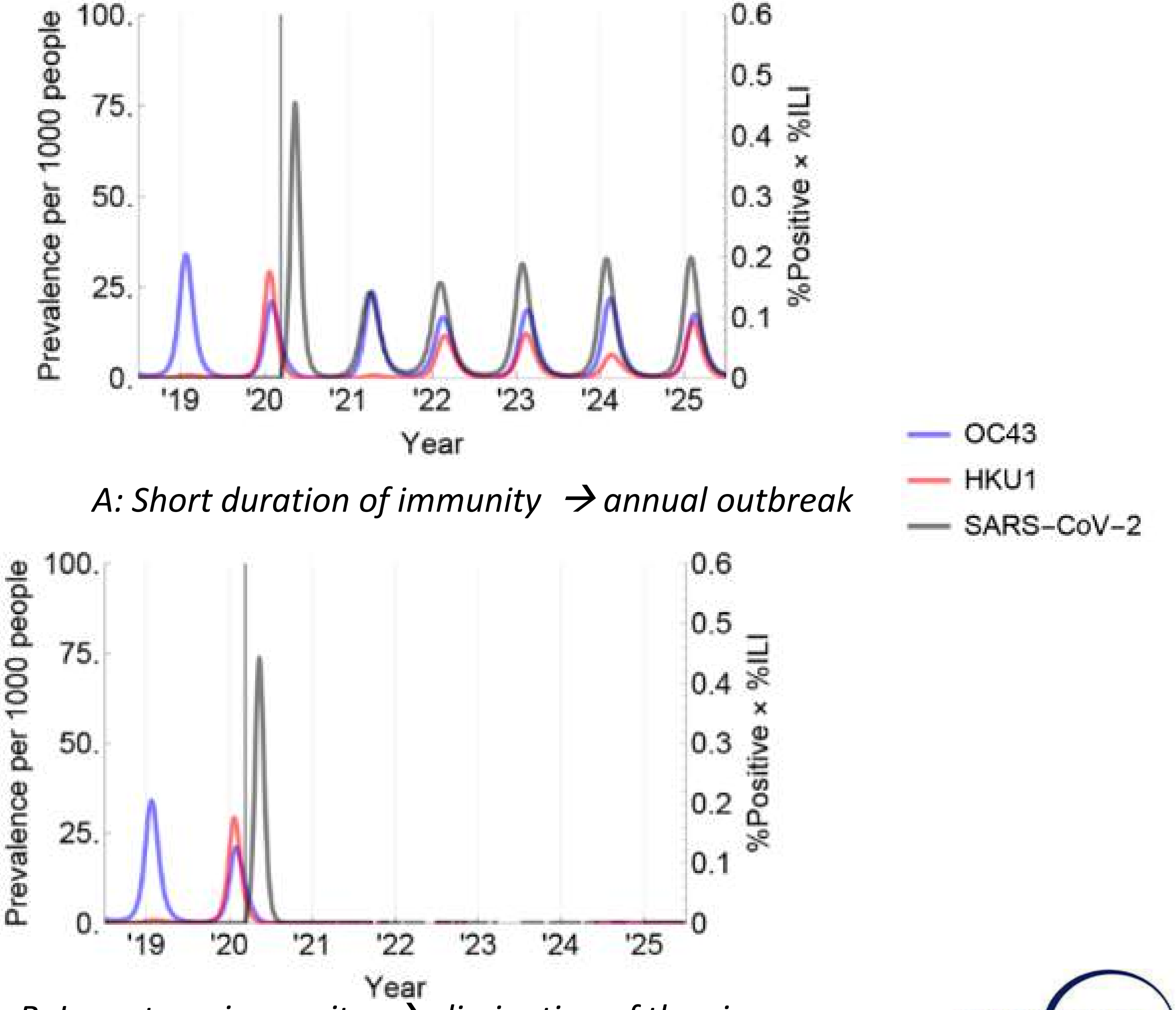
Used estimates of seasonality, immunity and cross-immunity for beta coronaviruses (OC43 & HKU1)

<u>Post-pandemic transmission dynamics will depend on:</u>

- 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*

<u>Total incidence of COVID-19 illness over next years will depend on</u>

- 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:

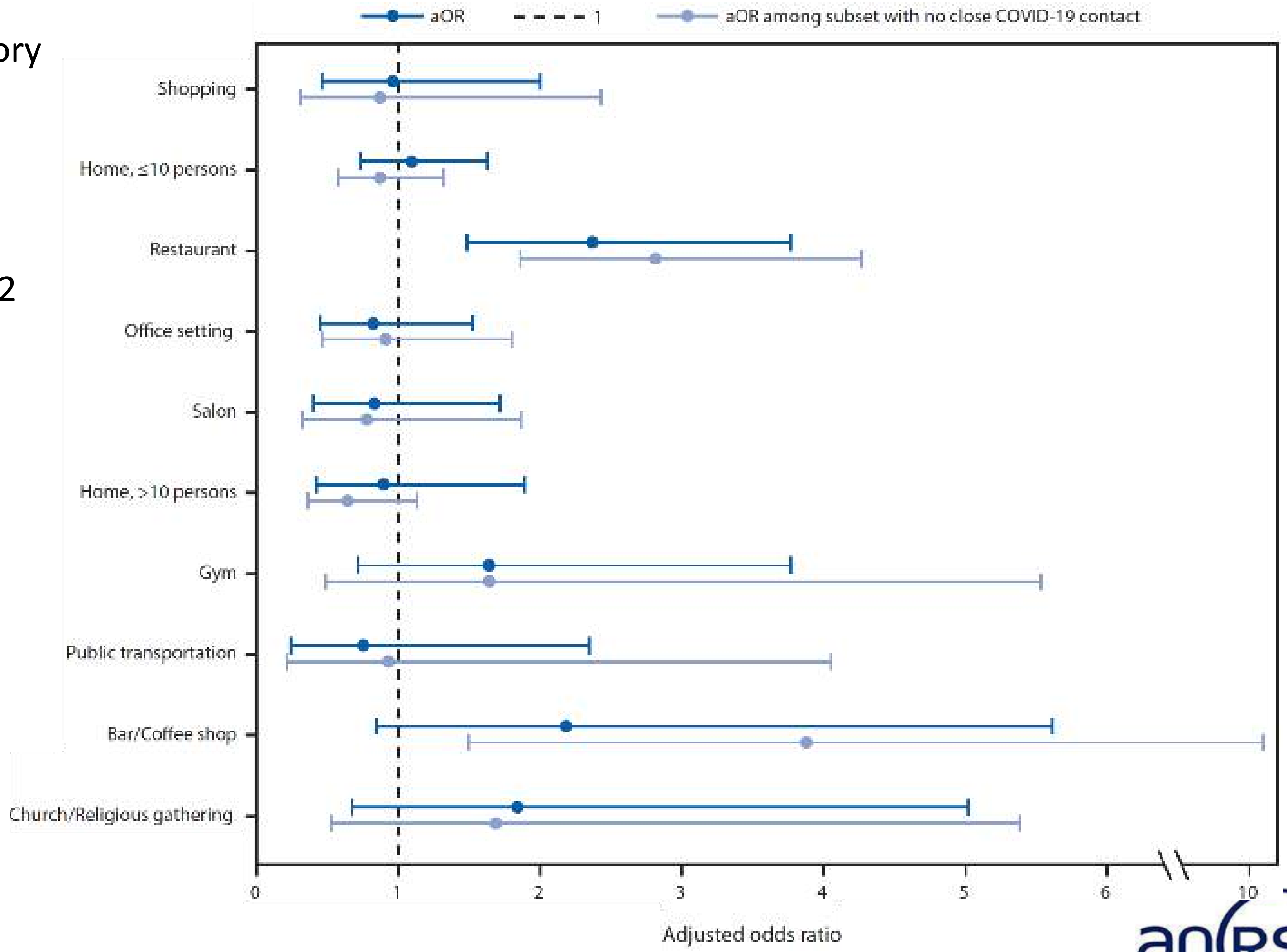
- Mask-wearing behavior, community activities <14 days before symptom onset (shopping, dining at restaurant, salon, gym, coffee/bar…) …

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



Fisher KA, *et al. MMWR.* Sep 2020

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?

Fisher KA, *et al. MMWR.* Sep 2020

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

Setting		Total				Active			
		Oubreaks		Cases		Oubreaks		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

Social setting = 35% of all active outbreaks

- Family gathering or private party
- Leisure facility

Occupational setting = 20% of all active outbreaks

- Agriculture seasonal worker

Two main settings to target efforts:

- Social gatherings
- Workers in vulnerable situations

New cases and cumulative incidence are currently increasing in all regions

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The National COVID-19 outbreak monitoring group. *Euro Surveill.* Aug 2020

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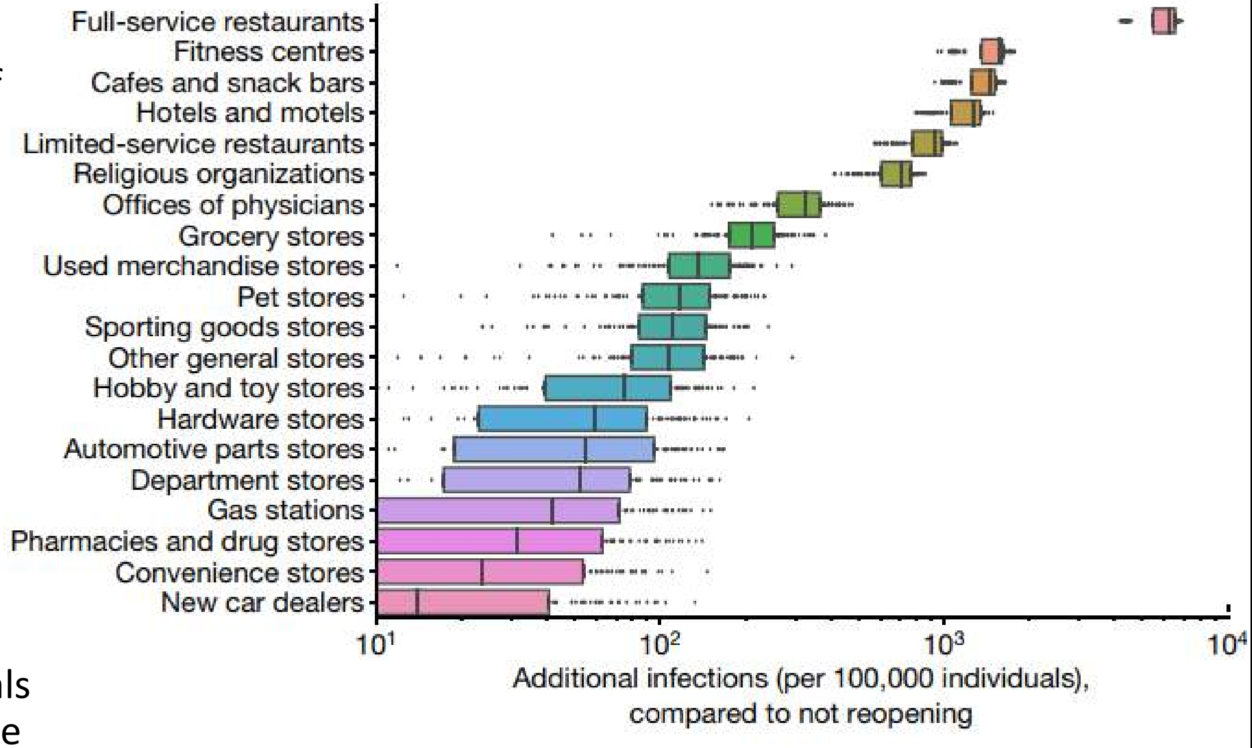
COVID-19 & community – Infection modelling

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

Chang S, *et al. Nature.* Nov 2020

Household transmission of SARS-CoV-2

Modelling study on 27 101 households – Wuhan
(Dec 2, 2019 – April 18, 2020)

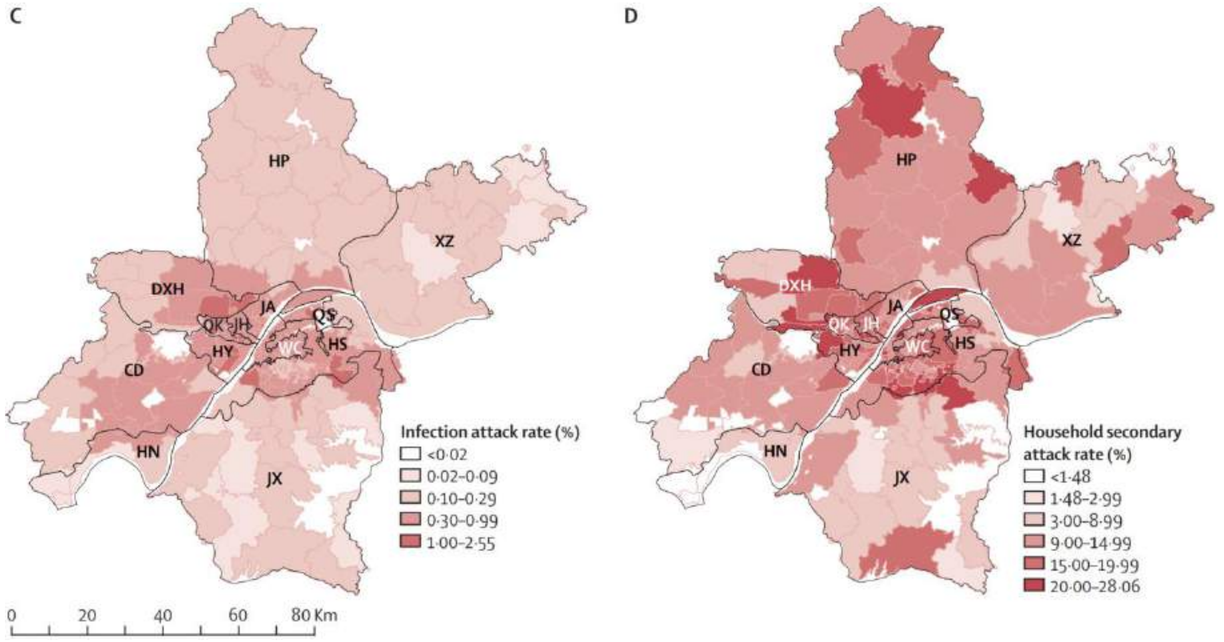
- 29 578 primary cases
- 57581 household contacts – 10 367 secondary cases, 29 658 test-negative contacts
- <u>Household</u>: group of family members or close relatives who did not necessarily live at the same address. Median size: 3 people.

➢ **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 ≥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

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.

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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 $\geq$1 contact.

Compared the difference in detected cases between household and nonhousehold contacts across the stratified age groups.

	Household	
Index patient age, y	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

<u>59 073 contacts of 5 706 COVID-19 index patients</u>:

- 10 592 household contacts → **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 → 1,9% ($CI_{95\%}$ [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)

<u>Limits</u>:

- 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**.

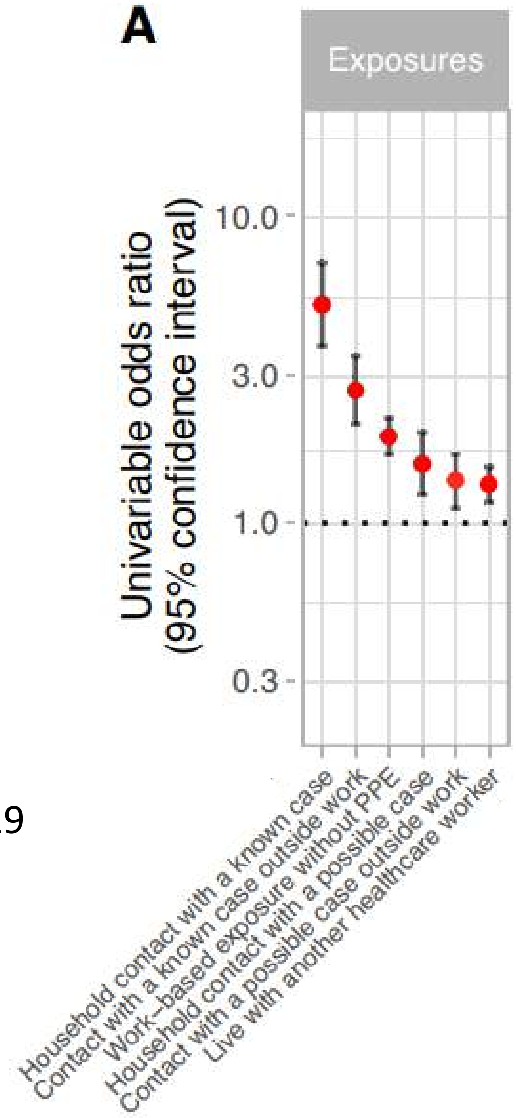
Risk of COVID-19: health-care workers

Prospective observational study on staff at Oxford University Hospitals, UK, mid-March – 8th June 202

- 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:

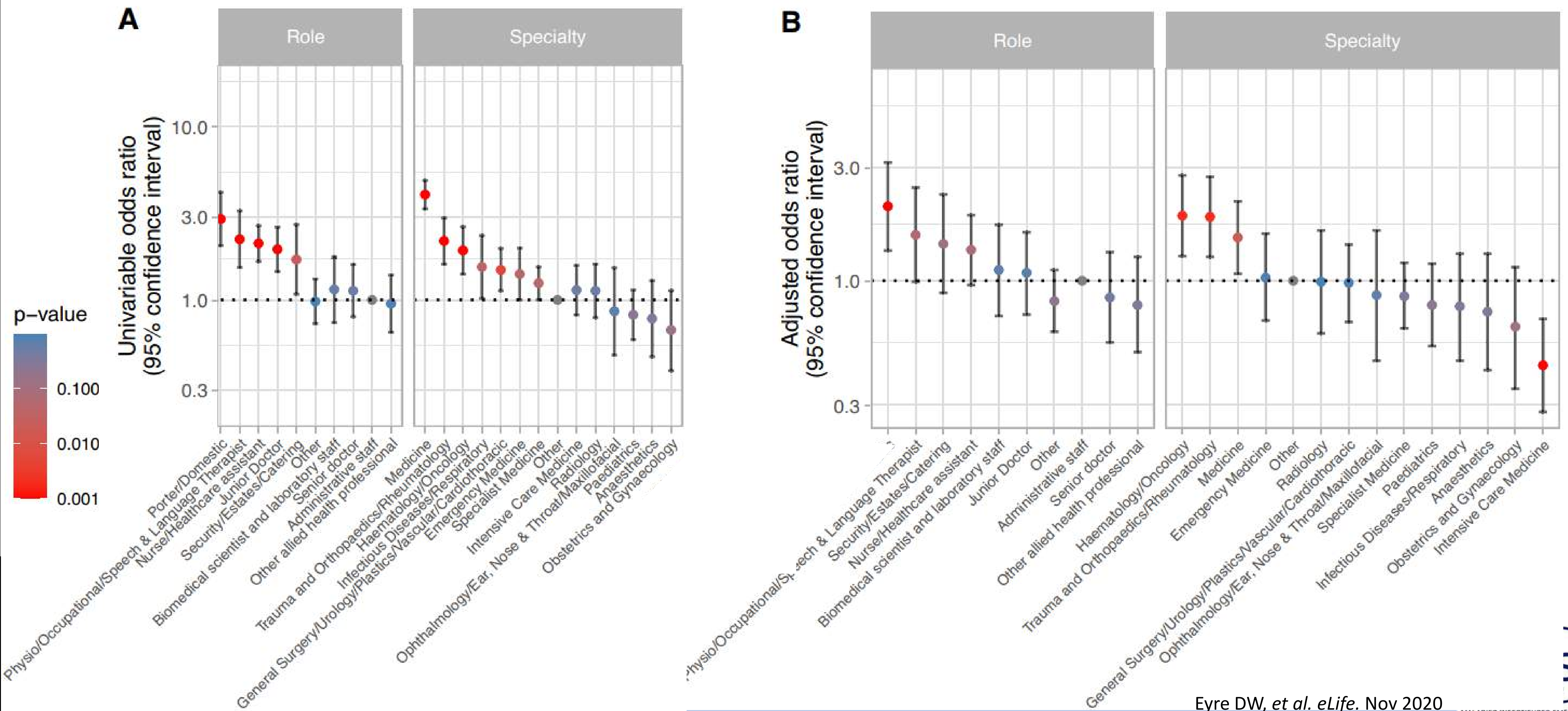
- 67/174 (38.5%) staff reporting household contact with a PCR-confirmed case tested positive, 1059/9858 (10.7%) without ($p<0.001$).
- 368/2165 (17.0%) staff reporting workplace contact without PPE with a known or suspected Covid-19 patient tested positive, 758/7867 (9.6%) not reporting similar exposure ($p<0.001$).
- 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.



Eyre DW, *et al. eLife.* Nov 2020

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%]

	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	1922/1 454 701	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)

Nguyen LH, *et al. Lancet Public Health.* Jul 2020

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)

PPE= Personal Protective Equipment

Nguyen LH, *et al. Lancet Public Health.* Jul 2020

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

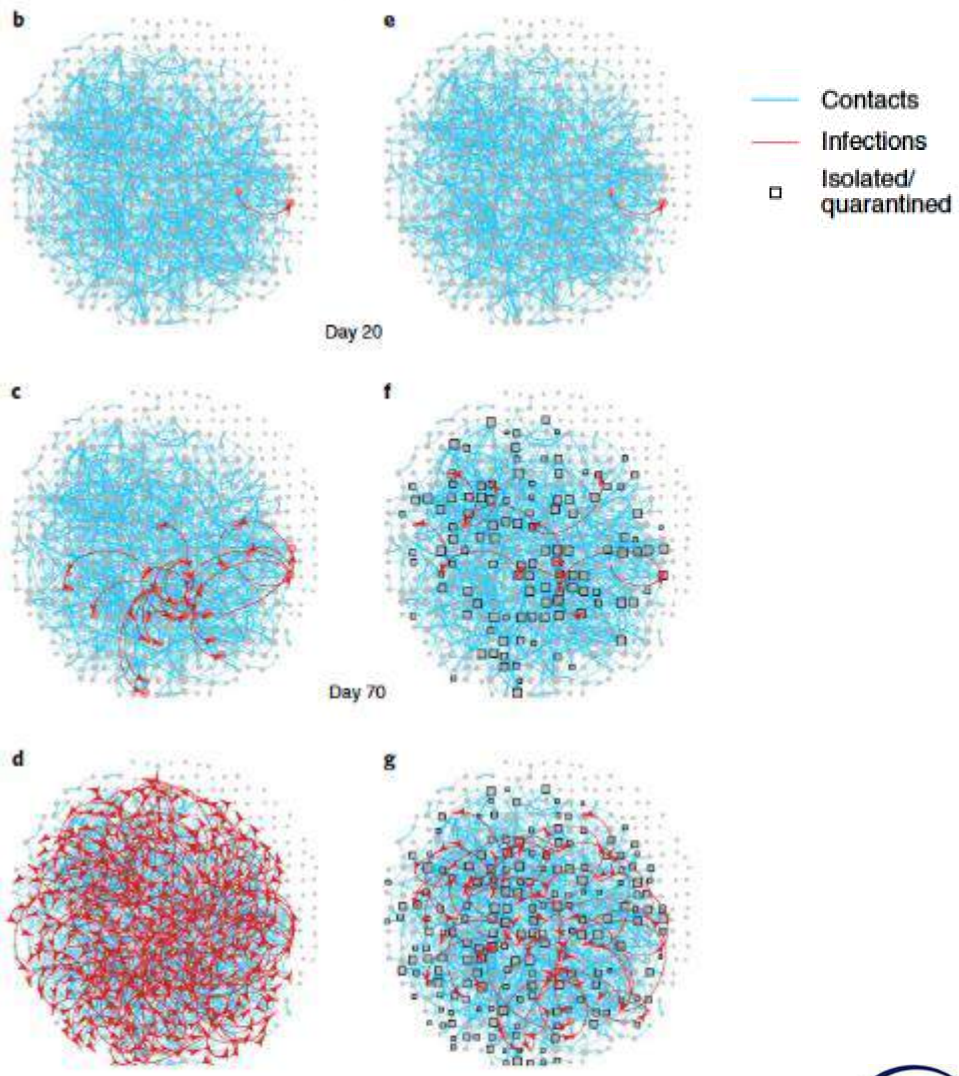


***Illustration of the Haslemere network with epidemic simulation predictions**.*
b–d: Progression of the COVID-19 epidemic under the no-intervention
e-g: under secondary contact tracing scenarios.

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Firth JA, *et al. Nature Med.* Aug 2020

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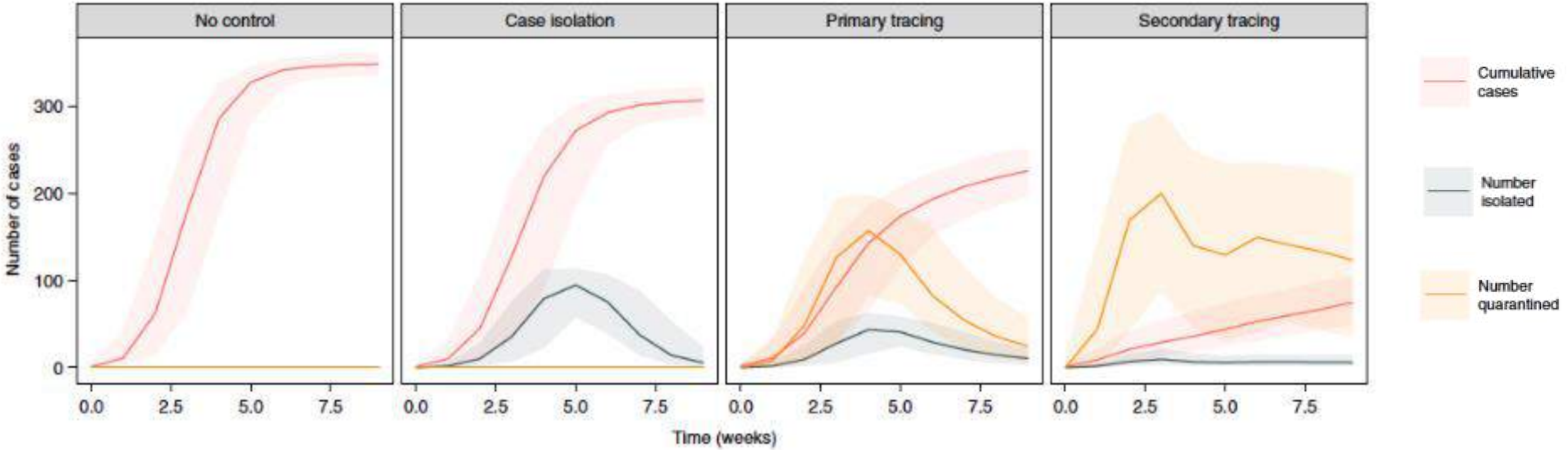
Real-world network – COVID-19 control strategies

- 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

Firth JA, *et al. Nature Med.* Aug 2020

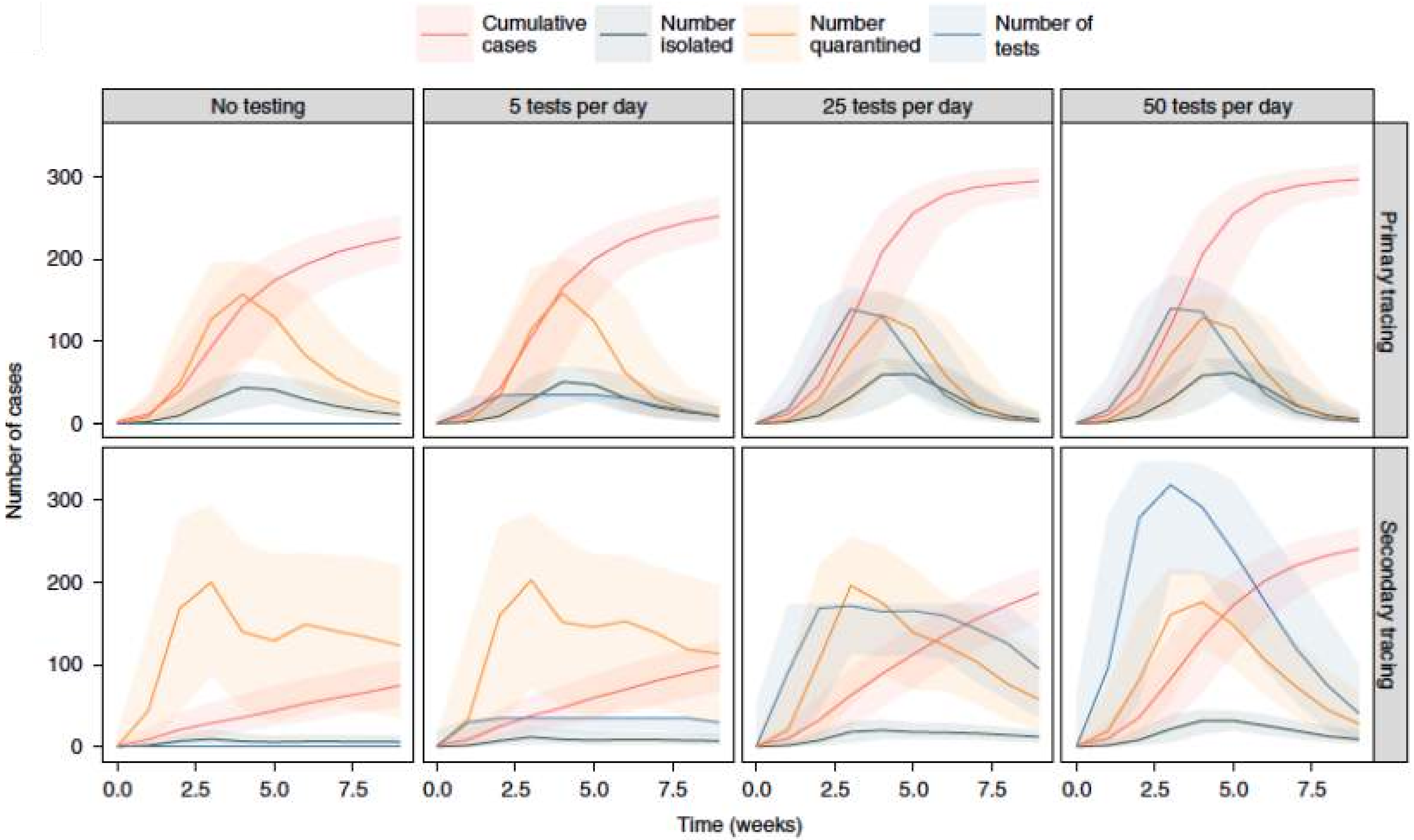
Real-world network – COVID-19 control strategies

- 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

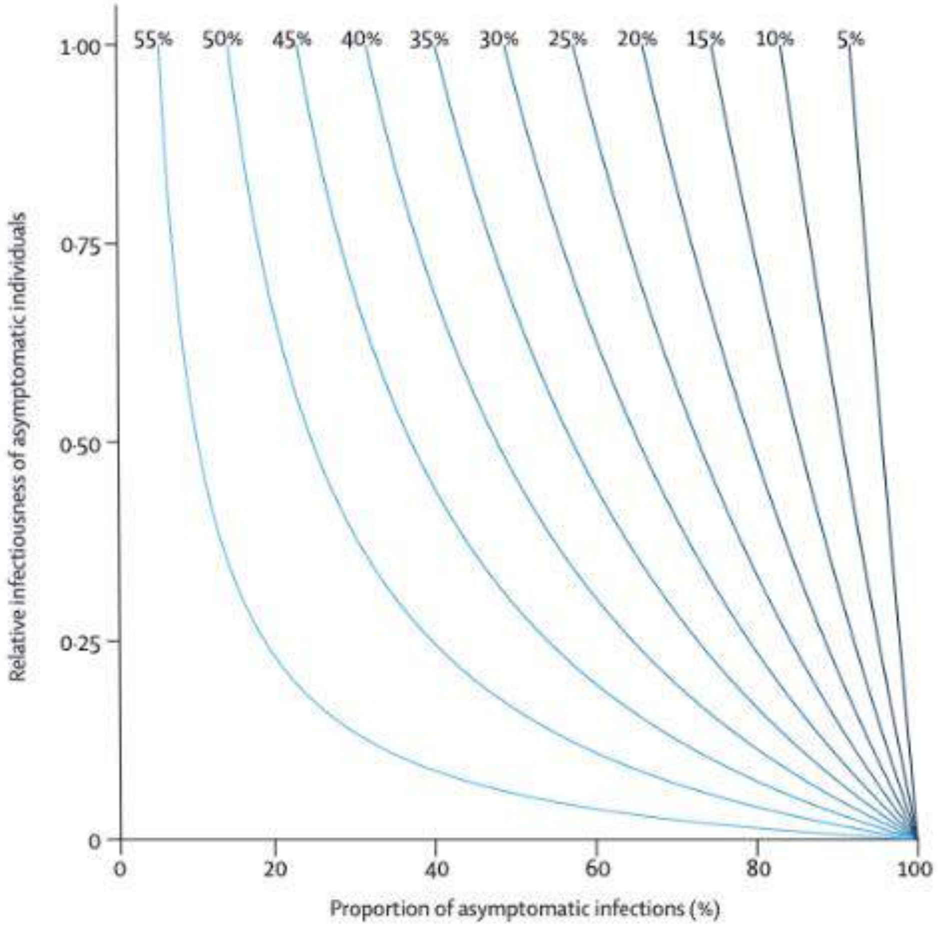


Epidemic model predictions of how testing affect outbreak and qurantine dynamics

Firth JA, *et al. Nature Med.* Aug 2020

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
- <u>Based on literature</u>: 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

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Grassly NC, *et al. Lancet Infect Dis.* Aug 2020

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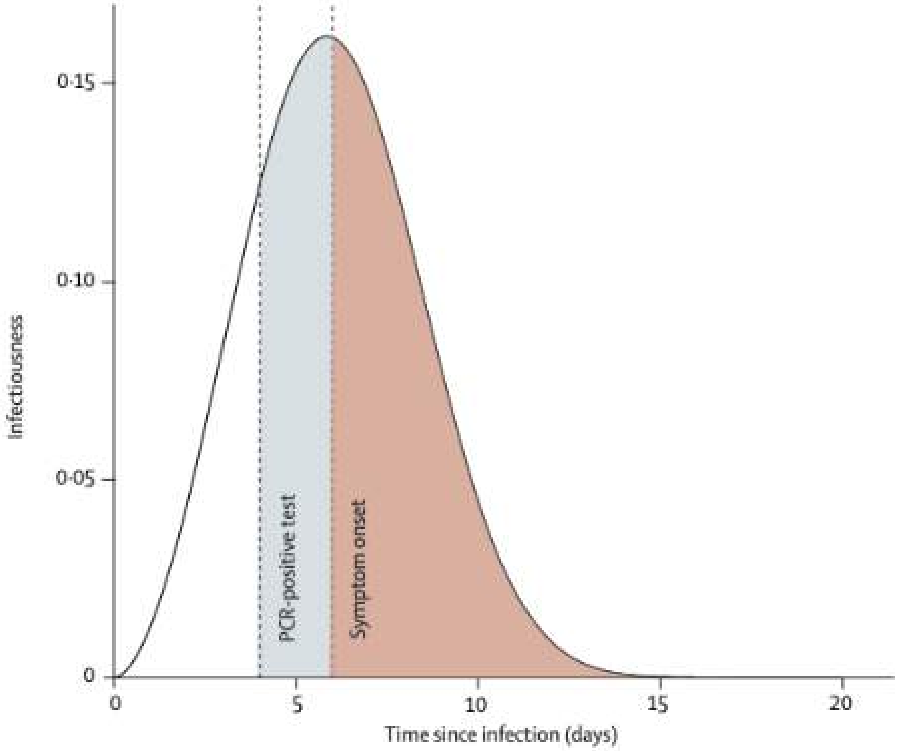
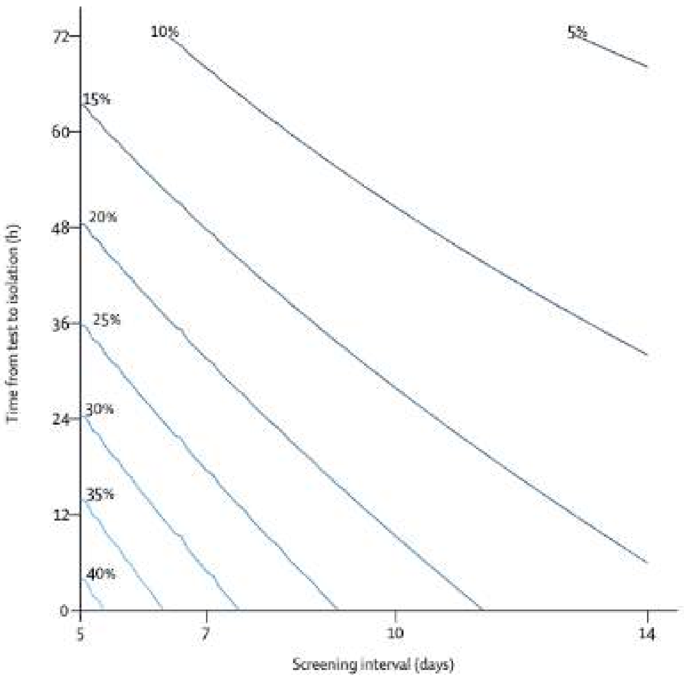
Testing strategies for COVID-19 control

- 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

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Grassly NC, *et al. Lancet Infect Dis.* Aug 2020

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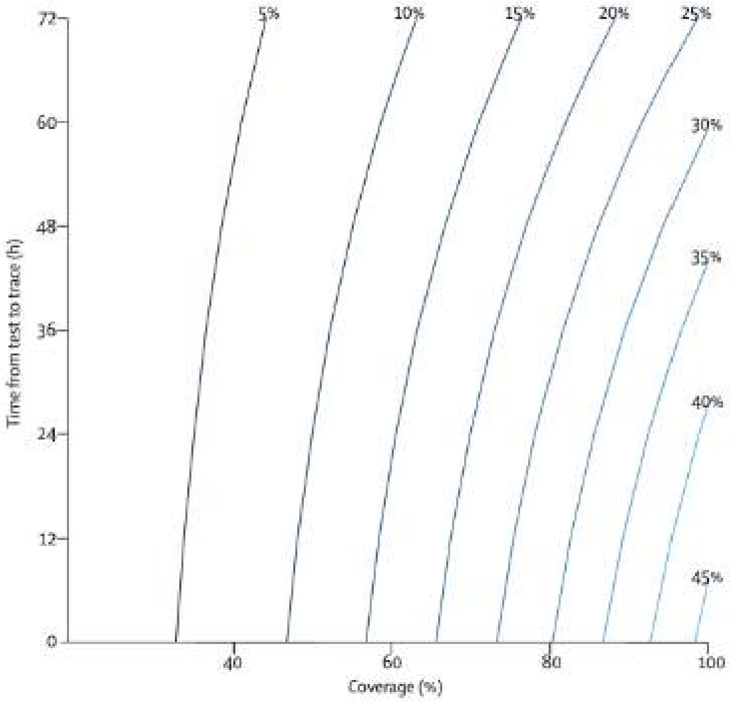
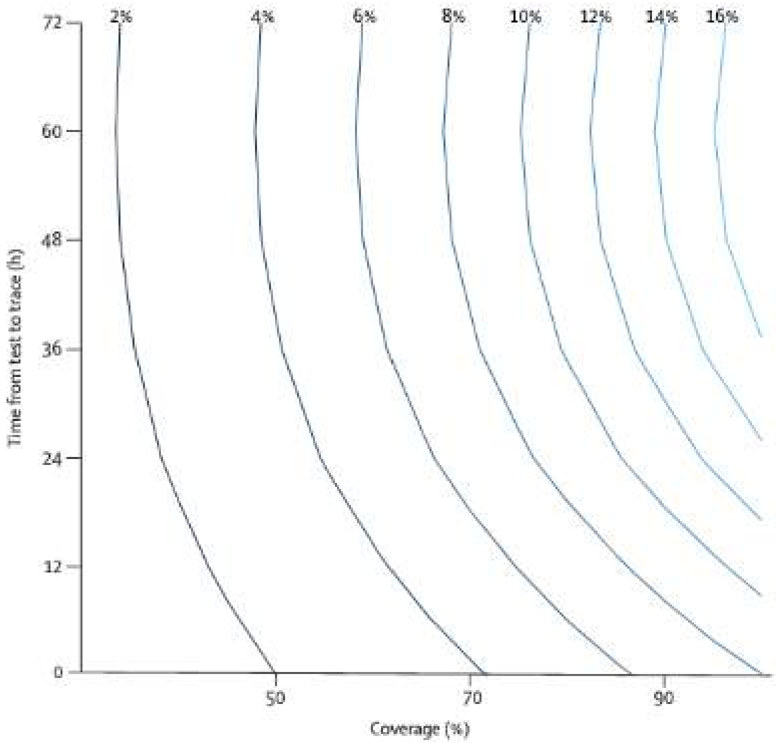
Testing strategies for COVID-19 control

- 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-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-and-trace strategies





Test-trace-test strategies

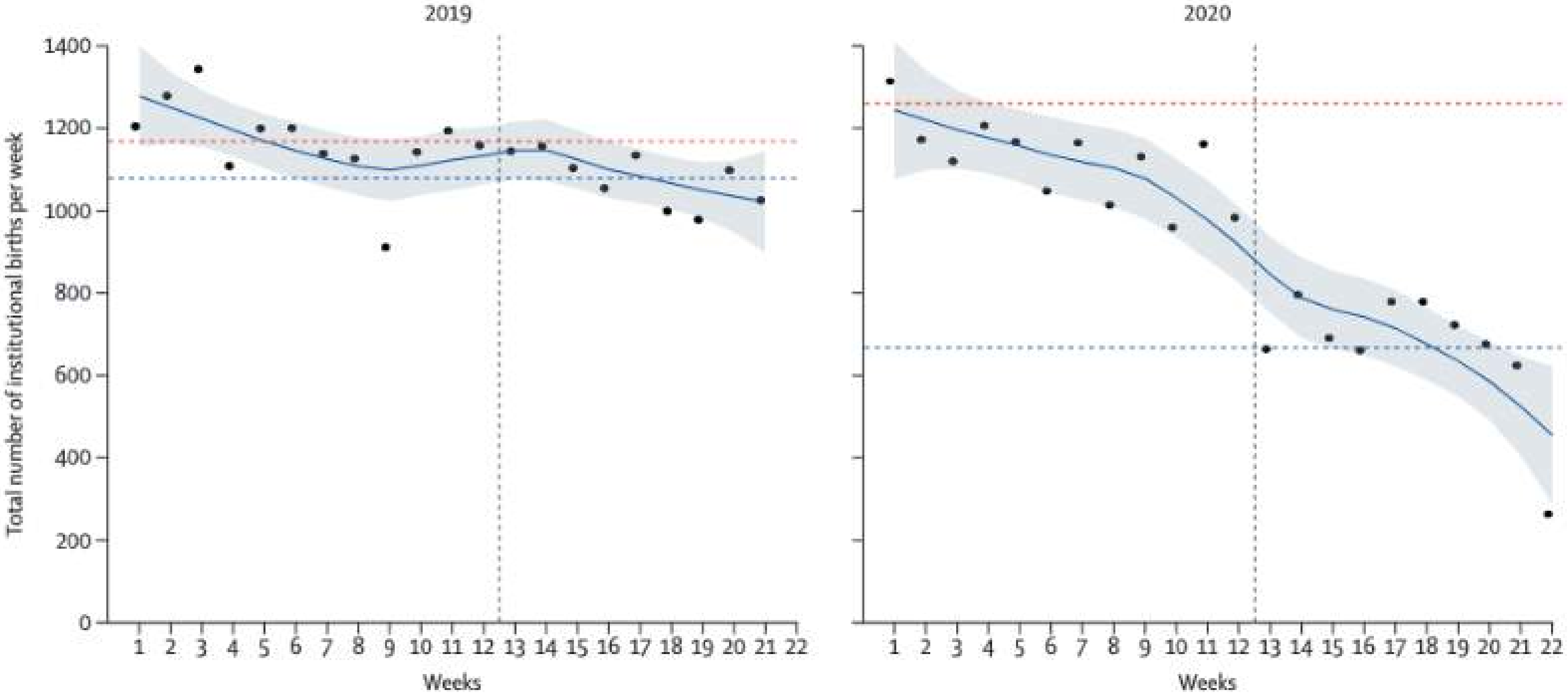
Grassly NC, *et al. Lancet Infect Dis.* Aug 2020

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**

KC A, *et al. Lancet Glob Health.* Aug 2020

Impact of COVID-19 pandemic response - Nepal

	Before lockdown	**During lockdown**	***P value***
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

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KC A, *et al. Lancet Glob Health.* Aug 2020

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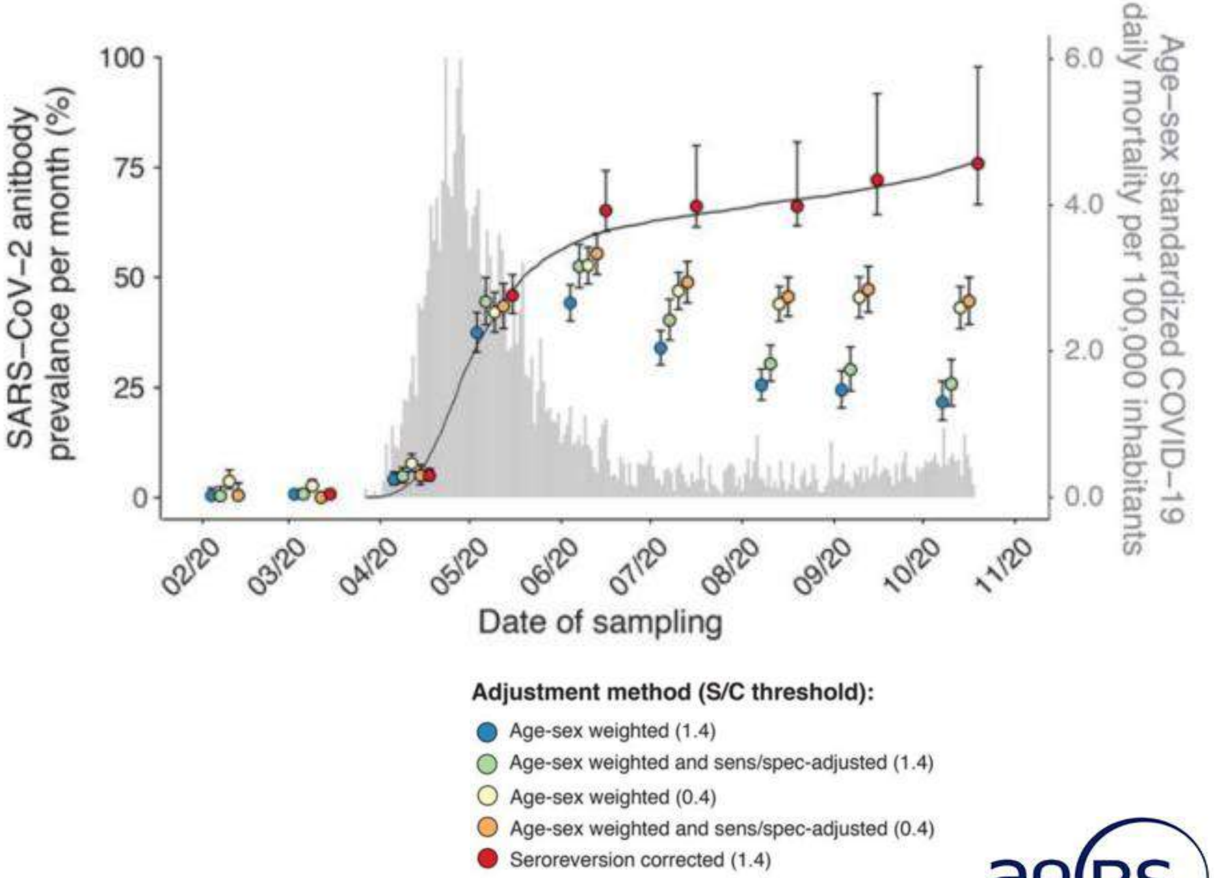
Impact of COVID-19 pandemic response – Manaus, Brazil

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

- Prevalence of SARS-CoV-2 IgG peaked at 52.5% in June, then seroconvertion 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 deffered.

SARS-CoV-2 antibody prevalence estimates in Manaus adjusted with different methods



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Buss LF, *et al. Science.* Jan 2021

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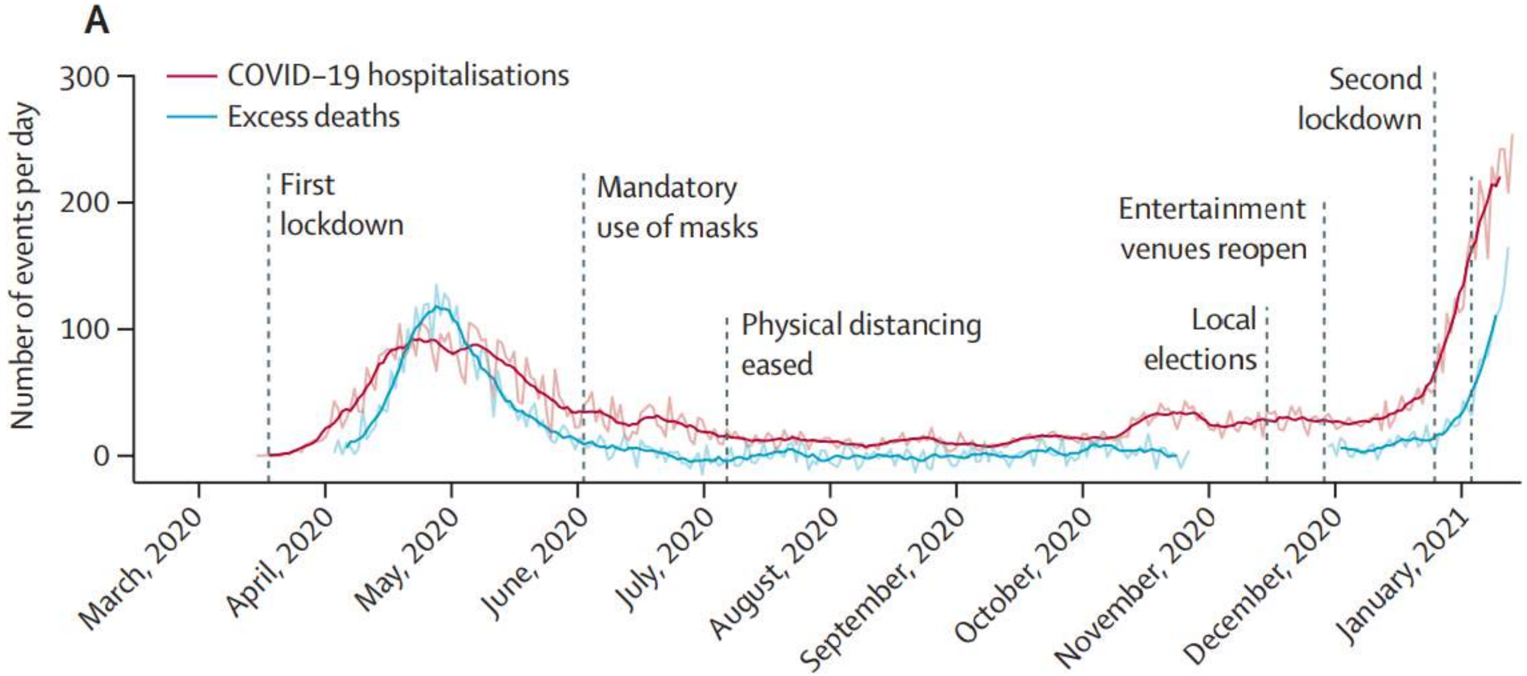
Impact of COVID-19 pandemic response – Manaus, Brazil

- 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 waine 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



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

Sabino EC, *et al*. *Lancet*. Jan 2021

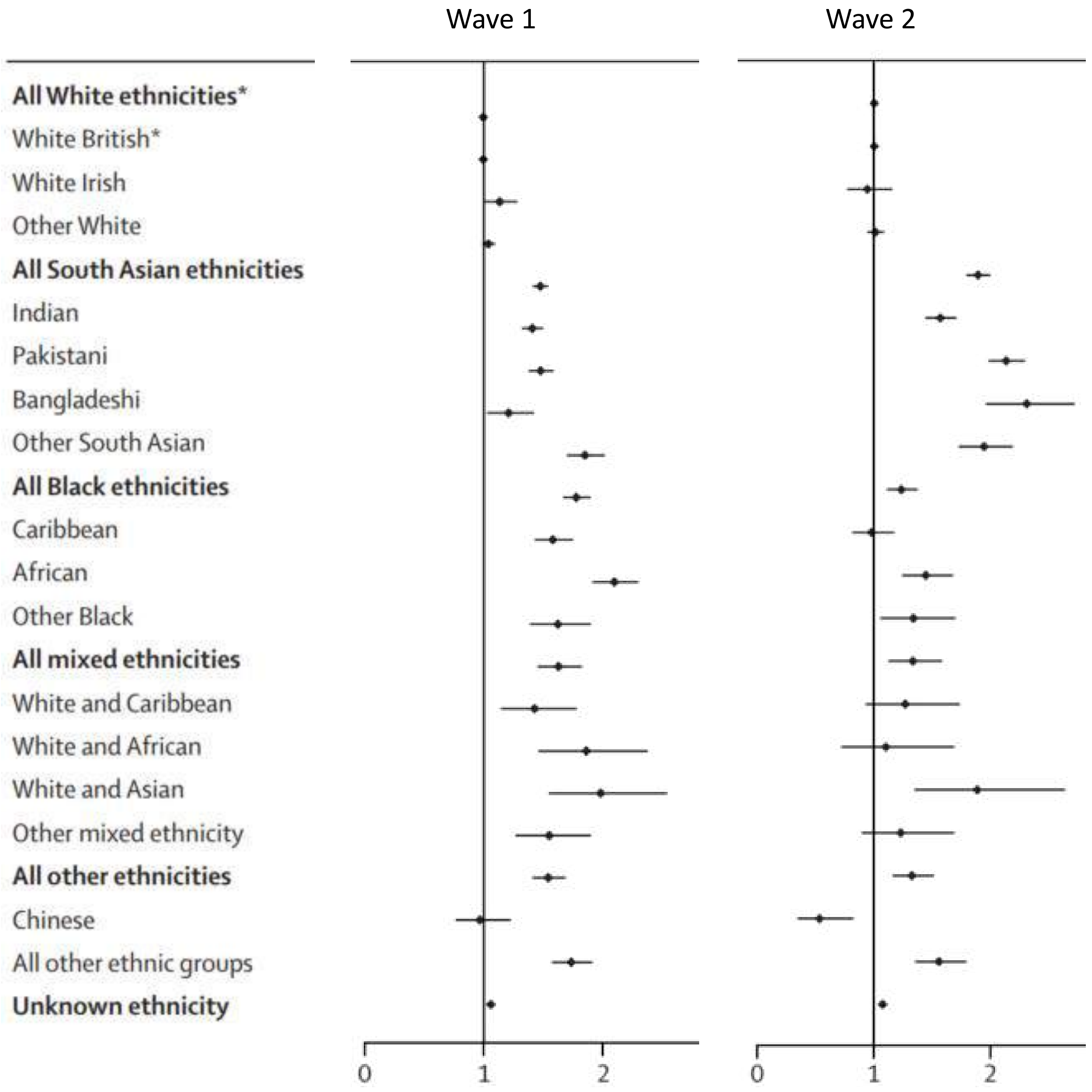
Ethnic differences in SARS-COV-2 infection and COVID-19

17 288 532 adults – South Asian, Black, Mixed ethnicity group, Other ethnicity group (OpenSafetly platform – UK)

WAVE 1

- 1 216 801 tested for SARS-CoV-2, 71 246 were positive. After accounting for variables (age, sex, household size…), compared to White ethnic group:
  - More likely to be tested: South Asian, (HR 1.08), Black (1.08) mixed ethnicity groups (1.04)
  - More likely to test positive: South Asian, (HR 1.99), Black (1.69) mixed ethnicity groups (1.49)

- 32 473 admitted to hospital for COVID-10, 3 096 admitted ICU for COVID-19, 11 649 COVID-19-related deaths. Compared to White ethnic group, in the 4 broad minority ethnic groups:
  - Risk of hospitalisation was increased
  - Risk of ICU admission was increased 2-3 folds
  - Risk of COVID-19-related death was increased by 22-51%



Ethnic differences in the risk of COVID-19-related hospital admission

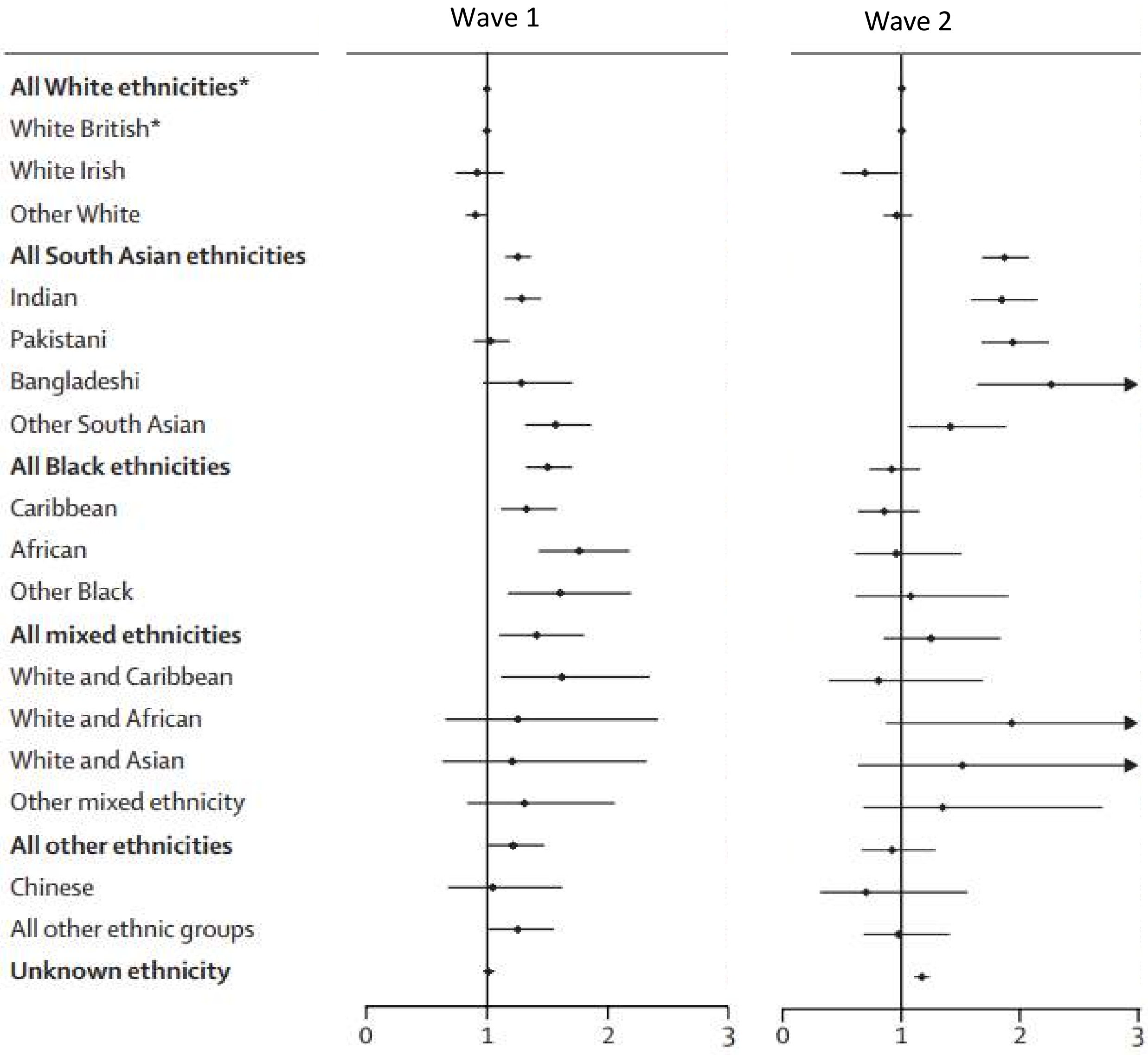
Mathur R. *et al*. *Lancet*. April 2021

Ethnic differences in SARS-COV-2 infection and COVID-19

WAVE 2

- 2 647 756 tested for SARS-CoV-2, 506 773 positive, 18 885 admitted to hospital for COVID-10, 3 351 admitted ICU for COVID-19, 7 366 COVID-19-related deaths

- Compared to Wave 1:
  - South Asian group remained at higher risk of testing positive (HR 1.32) than White ethnicity, and at high risk of hospital admission (1.89), ICU admission (2.68) and death (1.87)
  - Black group was less likely than White to test positive (0.85), but more likelt to be admitted to hospital (1.23) and ICU (1.67)



Ethnic differences in the risk of COVID-19-related death

Mathur R. *et al*. *Lancet.* April 2021

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**

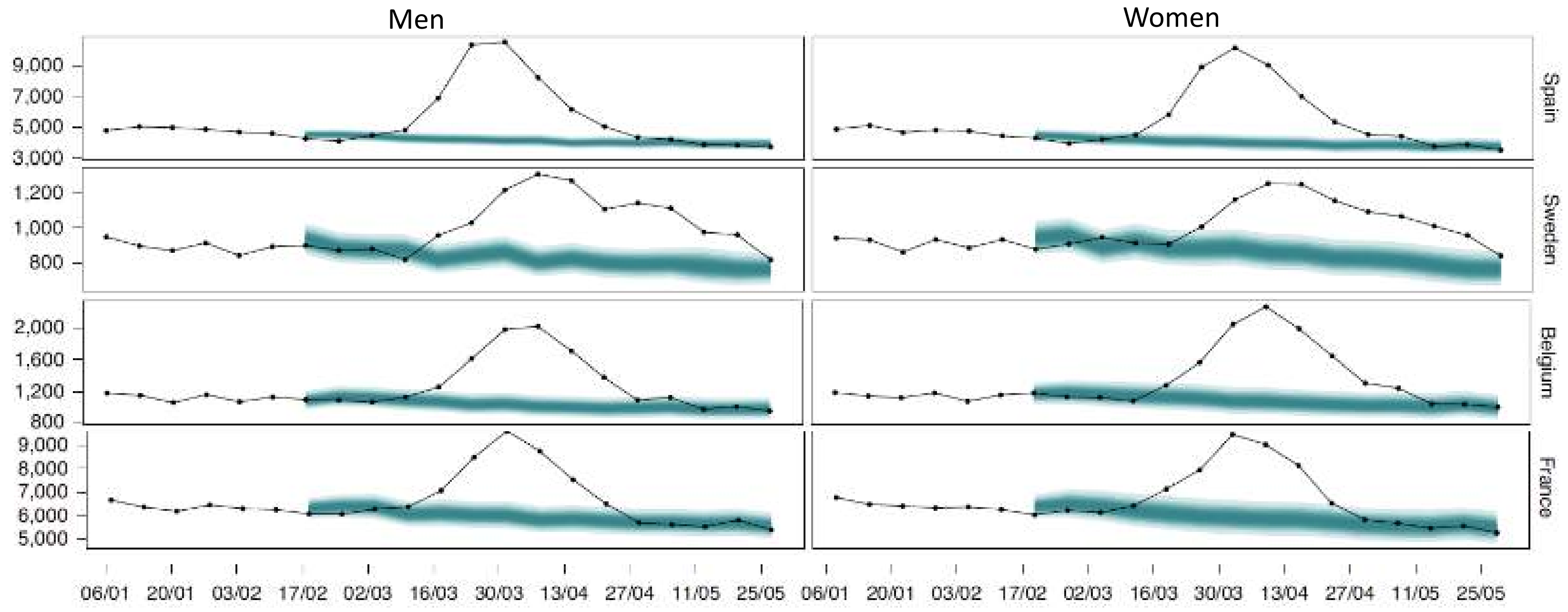
Countries: From Europe and the Pacific

- 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

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

From mild-February through en 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

Kontis V, *et al. Nature Med.* Oct 2020

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Effect of the first wave on all-cause mortality

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

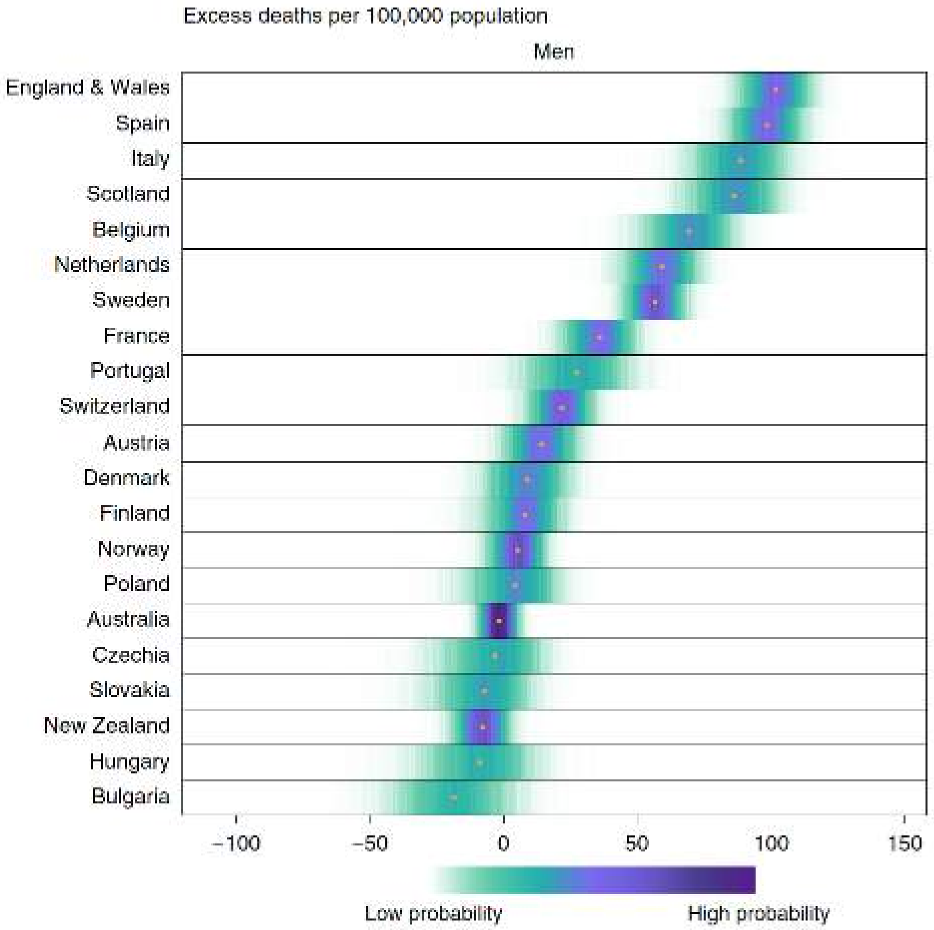
The largest rise in mortality was most likely to be in England & Wales followed by Spain and Italy.

<u>For the 21 countries</u>:

- 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.

<u>4 groups:</u>

- (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)



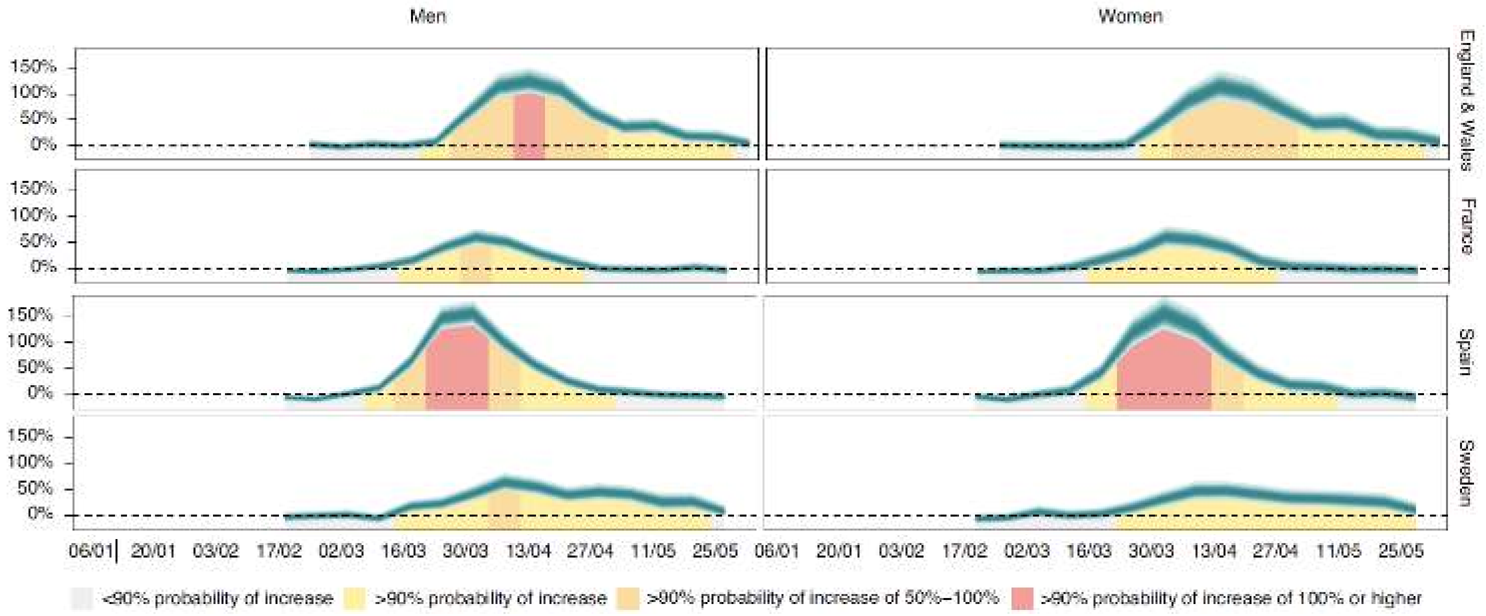
Posterior distribution of excess deaths from any cause per 100,000 people from mid-February to the end of May 2020. Gold dots in the top panels show the posterior medians.

Kontis V, *et al. Nature Med.* Oct 2020

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)



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.

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

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 %

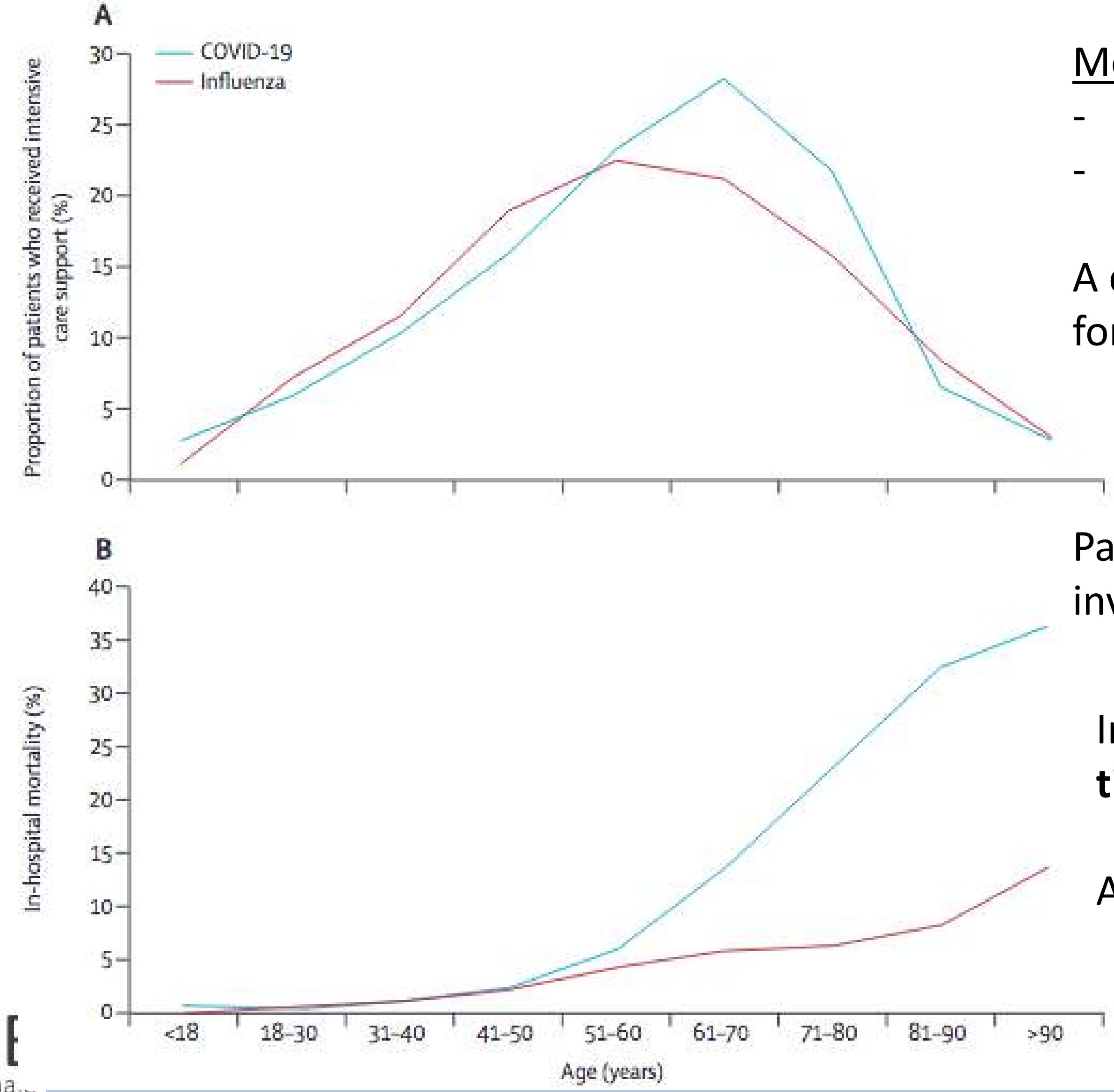
2. Outcomes

	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 %

Piroth L et *al. Lancet Resp Med.* Dec 2020

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)

VoC Alpha – Mortality

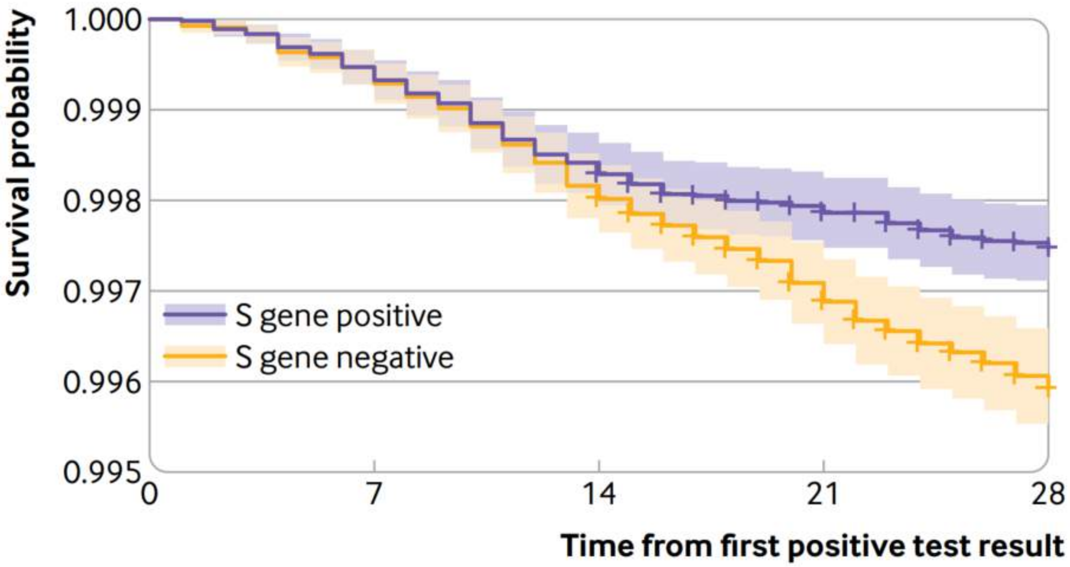
Sample

- >30 year-old SARS-CoV-2 positive community individuals (UK, 1 Oct 2020 – 28 Jan 2021), identified as S positive (previous variants) or S negative (B.1.1.7)
- 54 906 pairs of participants (S-pos and S-neg), matched on age, sex, ethnicity, index of multiple deprivation, lower tier local authority region, sample date o positive specimen → minimum bias

Main outcome: death within 28 days of first positive test

- 227 deaths in S-neg arm, 114 in S-pos arm → **Hazard ratio (HR) 1.64** (95% CI, 1.32-2.04; P<0.001)
- Rate of death in S-pos and S-neg diverged after day 14
  - Day 0-14 – HR was not increased
  - Day 15-28 – HR 2.40 (1.66-3.47)
- No evidence of asymmetrical delays in time from hospital admission
- Higher viral load at timing of sampling in S-neg arm
  - Either due to intrisic property of the variant → higher mortality associated with high viral load
  - Or to timing in testing: S-neg patients presenting at peak of infectiousness

Kaplan-Maier survival curve for S-pos (previously circulating variants) and S-neg (B.1.1.7)



Infection with B.1.1.7 is associated to higher mortality
Most probable HR 1.64, or 64% increased risk of death

Challen R, *et al. BMJ*. March 2021

COREB mission nationale Coordination Opérationnelle Risque Epidémique et Biologique

anRS MALADIES INFECTIEUSES ÉMERGENTES

VoC Alpha – Prevalence and mortality

2,245,263 individuals who had a positive community test (1 Nov 2020 – 14 Feb 2021).

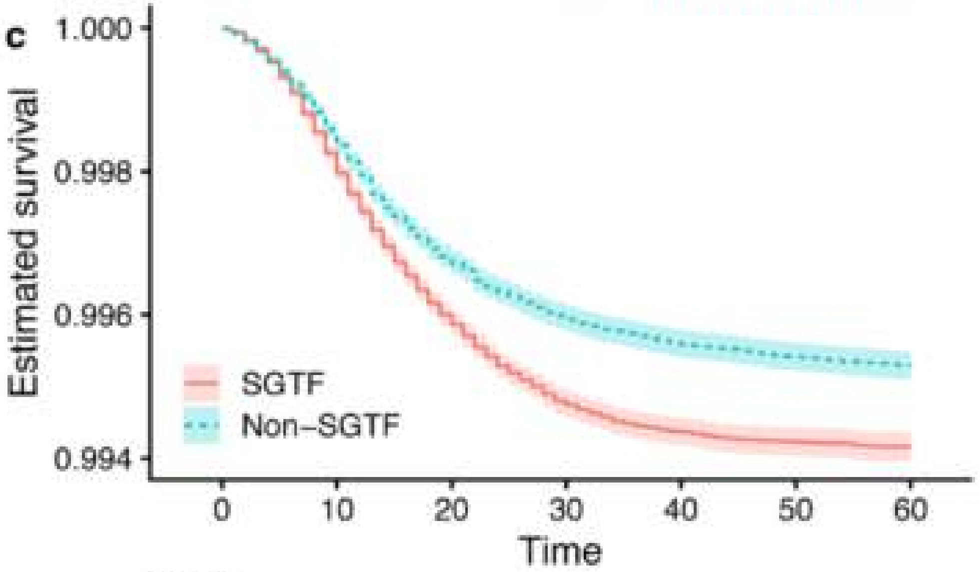
Prevalence

- 1,146,534 (51.1%) had a conclusive SGTF (S-Gene Target Failure) reading, of these, 58.8% had SGTF (→ **B.1.1.7 variant**)
- SGTF prevalence was lower in older age groups: 59.0% in 1-34 yo, 55.4% in ≥85 yo
- SGTF status was strongly associated with age and place of residence
- SGTF prevalence **increased over time**: from 5.8% (Nov 2020) to 94.3% (Feb 2021)

Mortality

- 19,615 people died in the study group (0.87%). 17,452 of observed deaths (89.0%) met criteria to be defined as Covid-19 death
- Crude Covid-19 death rate was **1.84 deaths per 10,000 person-days in the non-SGTF group vs. 1.42 deaths per 10,000 person-days in the non-SGTF group**
- **Absolute mortality risk** within 28 days of a positive SARS-CoV-2 test:
  - Females aged 70-84: 2.9% without SGTF, 4.4% with SGTF (95% CI 4.0–4.9%)
  - Females aged ≥85: 13% without SGTF, 19% with SGTF (17-21%)
  - Males aged 70-84: 4.7% without SGTF, 7.2% with SGTF (6.4-7.9%)
  - Males aged ≥85: 17% without SGTF, 25% with SGTF (23-27%)

Survival among individuals tested in the community in England with and without SGTF (Kaplan-Meier plot, 95% Cis)



SGTF

	0	10	20	30	40	50	60
At risk	674539	625587	549622	448192	303131	155715	0
Censored	0	47638	122338	223187	368094	515475	671181
Events	0	1314	2579	3160	3314	3349	3358

Non–SGTF

	0	10	20	30	40	50	60
At risk	471995	469441	463358	450813	420343	374946	0
Censored	0	1783	7095	19279	49595	94921	469822
Events	0	771	1542	1903	2057	2128	2173

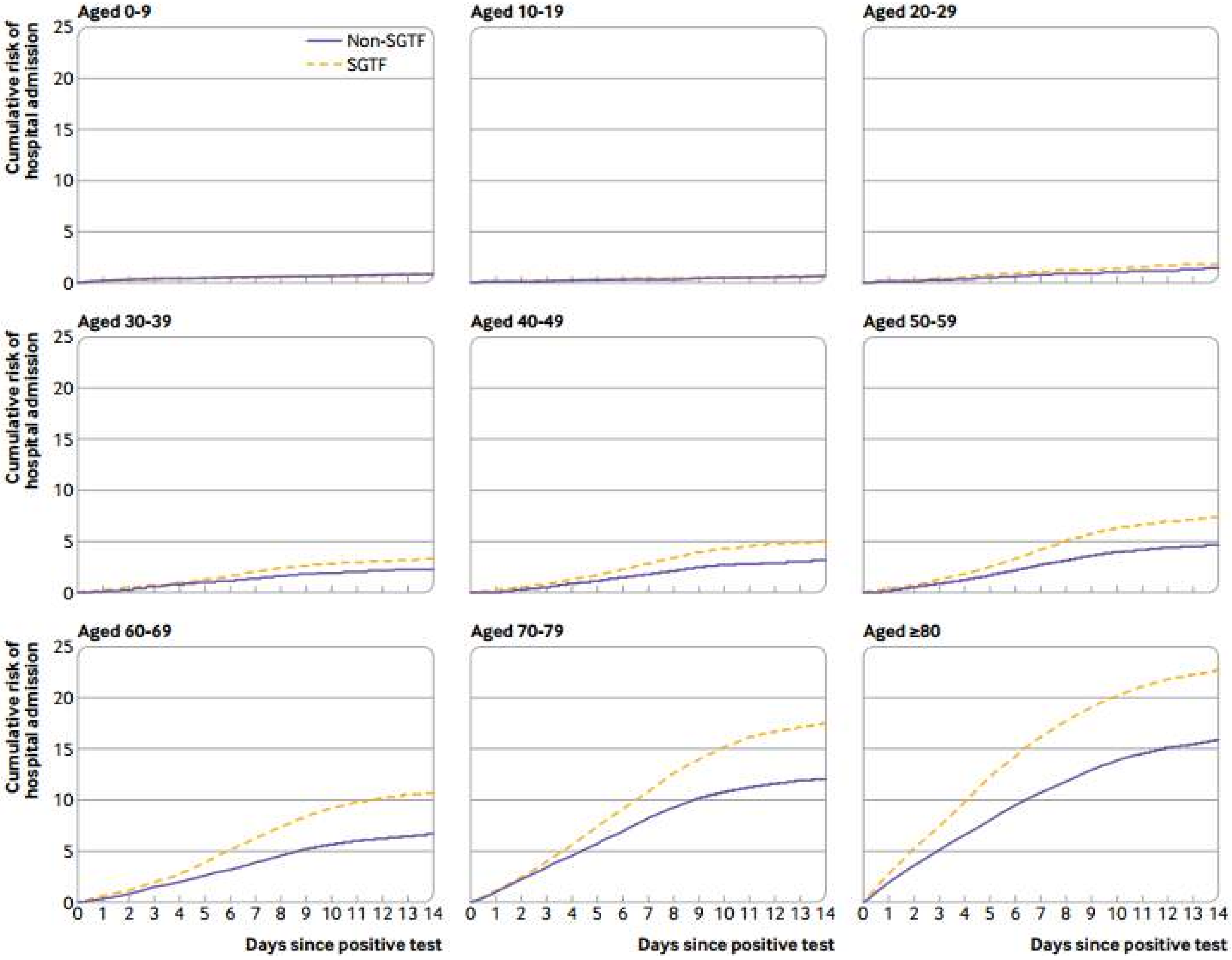
B.1.1.7 shows a substantial increase in absolute risk amongst older age groups, but the risk of COVID-19 death following a positive test in the community remains below 1% ≤70 years old

Davis NG, *et al. Nature*. March 2021

VoC Alpha – Risk of Hospital admission

Anslysis of 839 278 SARS-CoV-2 patients: 592 409 infected with alpha variant (SGTF), 246 869 with other strains (non-SGTF)

- Hospital admission
  - Within 14 days: 4.7% in SGTF vs 3.5% in non-SGTF. Adjusted HR (CI): 1.52 (1.47-1.58)
  - Within 60 days: 7.8% in SGTF vs 6.7% in non-SGTF. Adjusted HR (CI): 1.25 (1.22-1.28)
- 28-day mortality 0.44% in SGTF vs 0.36 in non-SGTF. Adjusted HR (CI): 1.59 (1.44-1.74)

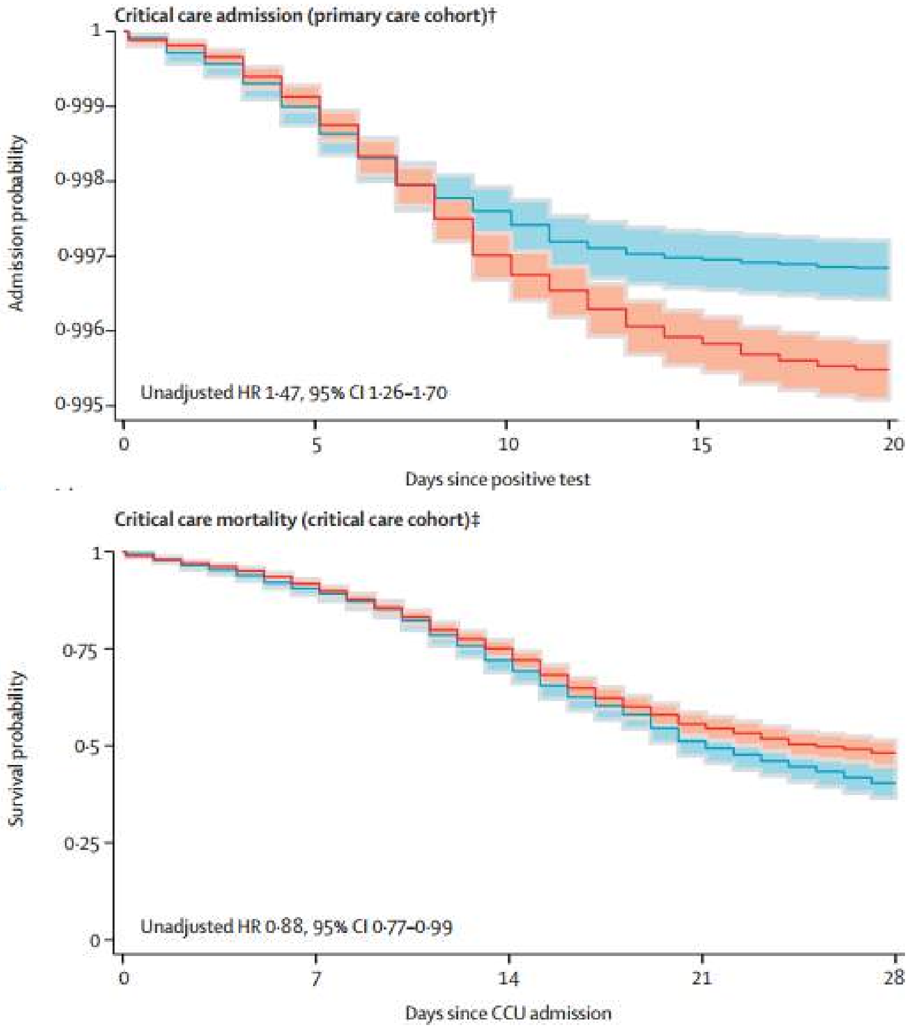


Cumulative risk of hospital admission within 1-14 days after SARS-CoV-2 test, by age group

VoC Alpha – Risk of Hospital admission

***Primary care cohort**: 198 420 SARS-CoV-2 patients – 117 926 infected with alpha variant (SGTF), 80 494 with other strains (non-SGTF)*

- 0.5% of patients died in the SGTF group, and 0.4% in the non-SGTF
    - 28-Day mortality adjusted HR (CI): 1.65 (1.36-2.01)
- 836 patients admitted to critical care unit (CCU)
    - 565/836 were SGTF
    - Adjusted HR (CI) for admission to CCU in SGTF compared to non-SGTF: 2.15 (1.75-2.65) → time varying HR 0·72 (0·40–1·26) 1 day after a positive test, 1·89 (1·41–2·53) 5 days after, 3·24 (2·41–4·36) 15 days after, 2·41 (1·59–3·63) 20 days after.



***Critical care cohort**: 4 272 SARS-CoV-2 patients who tested positive and then were admitted to CCU*

- 2685 (62.8%) were SGTF(+)
- Acute severity of illness tended to be lower in SGTF group, but the proportion receiving invasive mechanical ventilation within the first 24h of CCU was higher
- Mortality asjusted HR (CI) in SGTF vs non-SGTF: 0.91 (0.76-1.09) – no significant difference

Patone M. *et al. Lancet Infect Dis*. June 2021

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 1er surge
  - 72 (0,65 %) positive during 2^{e} surge
- 514 271 negative during 1er surge
  - 16 819 (3,27 %) positive during 2^{e} surge

Protection against repeat infection after previous SARS-CoV-2 infection was 80·5% (95% CI 75·4–84·5)

Hansen CH, *et al. Lancet. March* 2021

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

<u>Limits</u>:
- No correlation between symptoms with protection against repeat infection
- Misclassifications of reinfection might have occured
- Variant were not yet established in Denmark during the period

Hansen CH, *et al. Lancet. March* 2021

EPIDEMIOLOGY (July 2021)

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

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