COVID-19 Updates: May 11, 2020

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- VIROLOGY
- EPIDEMIOLOGY
- INFECTION CONTROL
- DIAGNOSIS
- DISEASE
- TREATMENT

Steps to Reopening

Widespread Testing and Surveillance:

PCR and Antibody

Ability to Diagnose, Treat and Isolate:

Contact Tracing with an emphasis on populations vulnerable to health inequality and adverse health outcomes.

Scale Up of Health Care Capacity and Supplies:

With Rapid scale-up if needed

Maintain Appropriate Physical Distancing:

To prevent recurrent outbreaks (e.g., masks, face shields, limited gatherings, continued distancing for susceptible adults).

Effective Treatment and Prevention:

Fully lift physical distancing restrictions when treatments and vaccine are deployed

Preparedness:

Rebuild enhanced U.S. pandemic preparedness with investment into R&D, infrastructure, workforce, and clear governance structures.

Administrative, Policy, and Supply Interventions

COVID-19 diagnostic testing, including:

- Broad access to tests (e.g. nucleic acid amplification, point-of-care) that have high clinical sensitivity and specificity;
- Information on immunologic (antibody) response to COVID-19 coupled with large-scale deployment of validated serologic tests in order to understand patterns of exposure and levels of protective immunity in local populations, including “asymptomatic” infection prevalence and transmission, in order to target public health responses based on local risk; and
- An adequate supply of safe, short-term testing facilities that do not disrupt health care capacity (e.g. drive-through testing and pop-up sites) in areas considering lifting distancing restrictions.

Development of a testing pathway(s) that facilitates:

- Identification of patients most susceptible to infection and severe illness;
- Administration of tests;
- Rapid analysis of test results;
- Tracking of persons potentially exposed to individuals who test positive; and
- Communication of test results to patients, health care providers and public health authorities.

Massive investment;

- Expansion of the public health workforce to conduct testing, surveillance, contact tracing, coordination and support for the community and healthcare facilities.

Administrative, Policy, and Supply Interventions

Rapid expansion of the availability of rapid diagnostic tests in every community and adoption of new technologies dedicated to case identification and contact tracing in each state.

A national strategy to ensure supply chains that are responsive to surge needs for specialized swabs, pipettes, reagents, and other essential testing materials, as well as personal protective equipment for persons conducting the testing and health care system preparedness.

The creation of a national multi-agency public/private task force including members of the U.S. Department of Health and Human Services and the CDC as well as federal, academic and industry representatives and subject matter experts to inform the White House Coronavirus Task Force on an evidence-based process of easing social distancing measures over time.

Federal funding for the development of an effective COVID-19 surveillance program and requirements for testing to be covered by health insurers with resources to cover testing for the uninsured to ensure appropriate patient sampling.

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Associations of stay-at-home order and face-masking recommendation with trends in daily new cases and deaths of laboratory-confirmed COVID-19 in the United States

- OBJECTIVE:
  - To examine the associations of Stay at Home Orders (SAHO) and and face-masking recommendation with trends in **daily new cases and deaths** of COVID-19 in the United States
- PARTICIPANTS:
  - Residents in the U.S., who were affected by the SAHO and face-masking policies
- MAIN OUTCOME MEASURES:
  - Turning-points of the daily new cases and deaths of COVID-19, and COVID-19 time-varying reproduction numbers (Rt) in the U.S.

Jie Xu, Sabiha Hussain, Guanzhu Lu, Shi Wei, Wei Bao, Lanjing Zhang medRxiv 2020.05.01.20088237;
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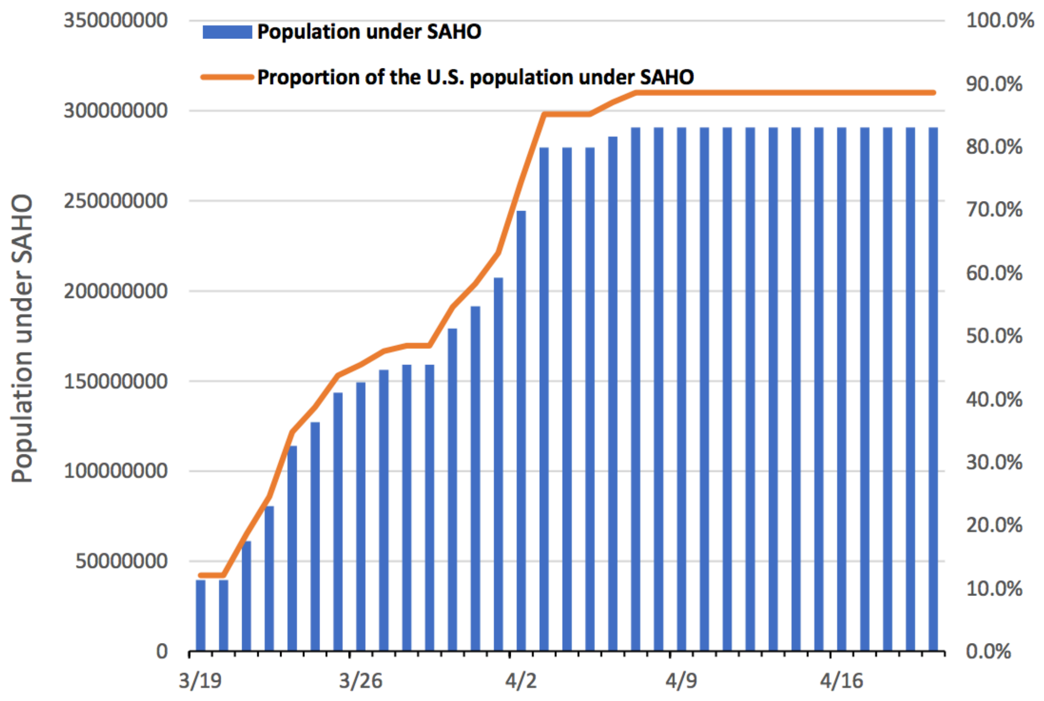
Associations of stay-at-home order and face-masking recommendation with trends in daily new cases and deaths of laboratory-confirmed COVID-19 in the United States



The population under a stay-at home (SAHO) order owing to the COVID-19 in the United States Since March 19, 2020 when the State of California started a SAHO, the number and proportion of the U.S. residents under SAHO have increased until April 7 and plateaued afterwards.

The number and the proportion of U.S. residents under SAHO increased between March 19 and April 7 and then plateaued

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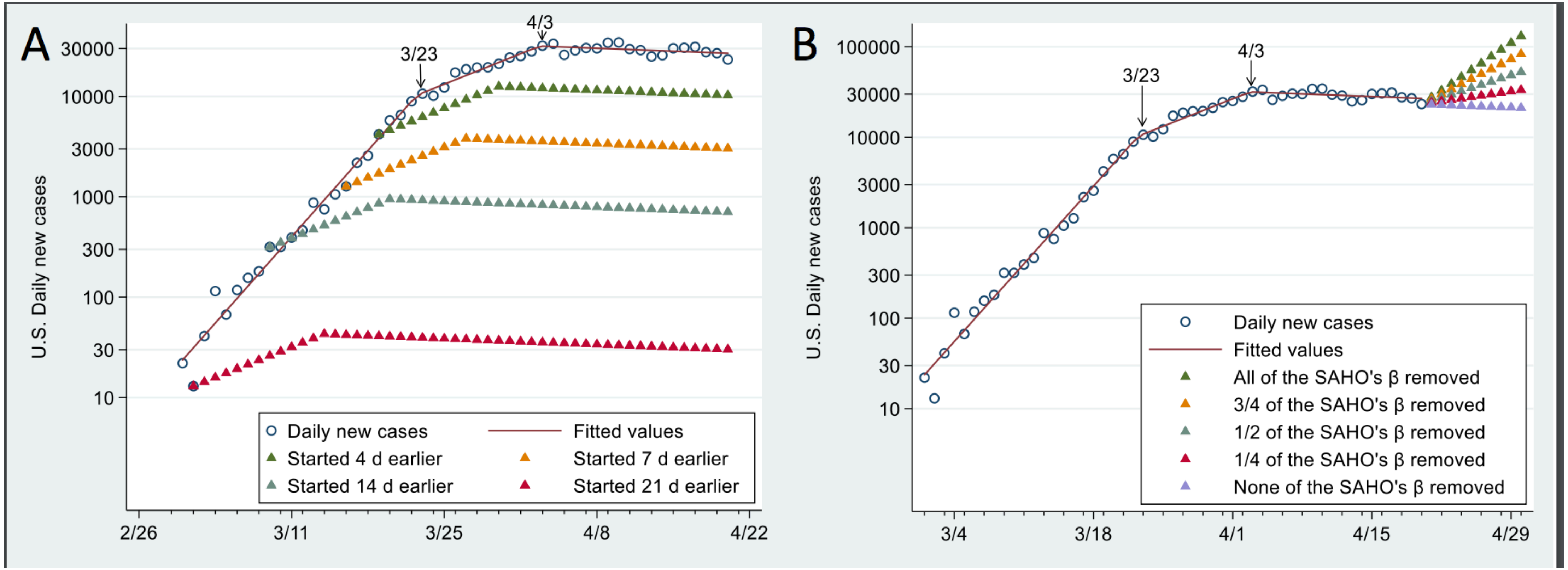

The trend in COVID-19 daily cases reduced after March 23 (P<0.001) and further reduced on April 3 (P<0.001), which was associated with implementation of SAHO by 10 states and the CDC recommendation of face-masking, respectively.

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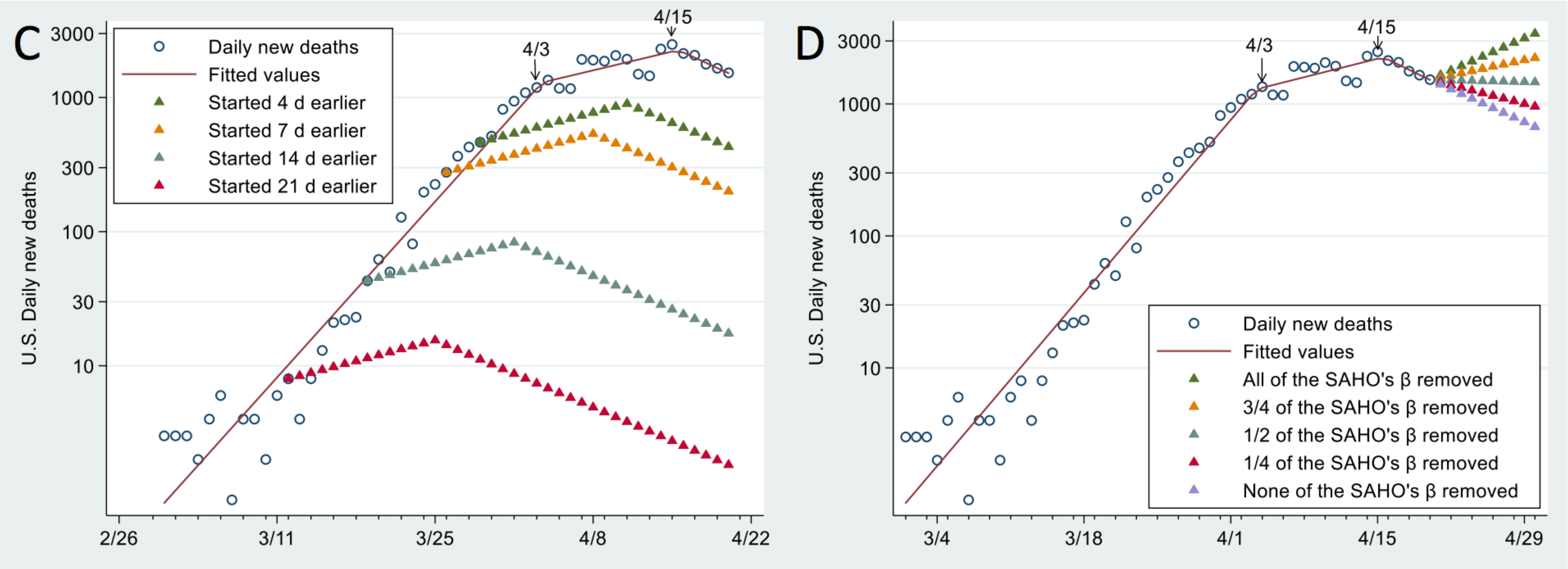

Observed and Simulated Trends in Daily New Cases and Deaths of Laboratory confirmed Coronavirus Disease 2019 (COVID-19) in the United States between March 1 and April 30, 2020. The Join point analyses with Poisson variance model show that the 2 turning points of March 23 and April 3 divided the trends in U.S. COVID-19 daily new cases into 3 segments, with the coefficients of 31.69 (95% CI, 26.82 to36.75, P<0.001), 9.75 (95% CI, 7.54 to 12.01, P<0.001), -0.90 (95% CI, -1.62 to -0.17, P=0.02), respectively. These turning points appeared to link to implementing a stay-at home order (SAHO) by 10 states on March 23, and the CDC's face-masking recommendation on April 3. Similarly, the 2 turning points of April 3 and April 15 divided the trends in U.S. COVID-19 daily new deaths into 3 segments, with the coefficients of 25.06 (95% CI, 21.44 to28.79, P<0.001), 5.22 (95% CI, 3.36 to 7.11, P<0.001), -7.90 (95% CI, -13.45 to -1.99, P=0.01), respectively. The simulated results on early-announcements of SAHO and face masking recommendation and early-removals of SAHO are shown in A and C, and B and D, respectively. The partial removals of SAHO's coefficients(ß) may reflex the situations when some of the U.S. states lift the SAHO.

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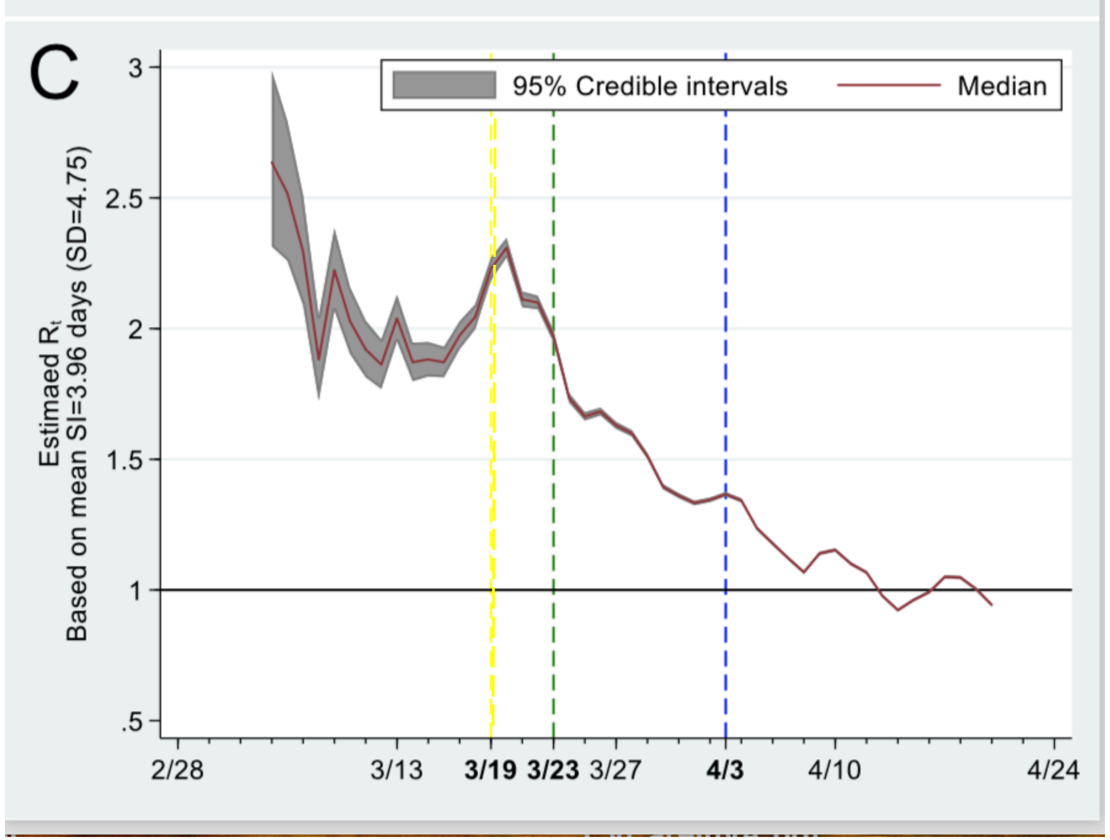

Estimated Effective Reproduction Number (Rt) Based on Laboratory- Confirmed COVID-19 Cases in the United States and the Reported Serial Intervals.

- The effective reproduction number (Rt) was estimated using the previously-reported COVID-19 mean serial intervals (SI) of 7.5, 4.7 and 3.96 days, as well as the corresponding standard deviations (SD).
- The state-wide stay- at-home-order was first implemented by the state of California on March 19, 2020 (yellow dash line). Ten states had implemented a stay- at-home order by March 23, 2020 (green dash line), affecting 114,047,753 residents (37.45% of the U.S. population).
- The CDC recommended face- masking on April 3, 2020 (blue dash line). These dates were linked to the declines of Rt's at the times of an increase or plateau of the Rt.

The estimates of Rt started to decline on March 19, when SAHO was first implemented and declined faster after March 23.
After a short plateau, Rt continued to decline after April 3 and fell below/around 1.0 on April 13.

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Associations of stay-at-home order and face-masking recommendation with trends in daily new cases and deaths of laboratory-confirmed COVID-19 in the United States

- There were 2 turning points of COVID-19 daily new cases or deaths in the U.S., which appeared to associate with implementation of SAHO and the CDC's face-masking recommendation.
- Simulation on early-implementation and removal of SAHO reveals considerable impact on COVID-19 daily new cases and deaths.
- These findings may inform decision-making of lifting SAHO and face

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Impact of policy interventions and social distancing on SARS-CoV-2btransmission in the United States

- **AIMS:**
  - Measure the impact of NPIs on the Rt and other COVID-19 outcomes in U.S. states.
- **Methods:**
  - Weeks immediately after each state reached 500 cases were measured
- **Outcomes:**
  - Average R_t in the week following 500 cases and doubling time from 500 to 1000 cases.
    - Adjusted for population density, GDP, and certain health metrics.
  - This analysis was repeated for deaths with doubling time from 50 to 100 deaths

States with SAHO have a 93% decrease in the odds of having a positive Rt
States that plan to scale back such measures should carefully monitor transmission metrics.

R_t: Effective Reproductive Number, NPI: Non Pharmaceutical Interventions, SAHO: Stay at Home Orders

Dreher N, Spiera, McAuley F, Kuohn L, et al. medRxiv 2020.05.01.20088179; doi: https://doi.org/10.1101/2020.05.01.20088179

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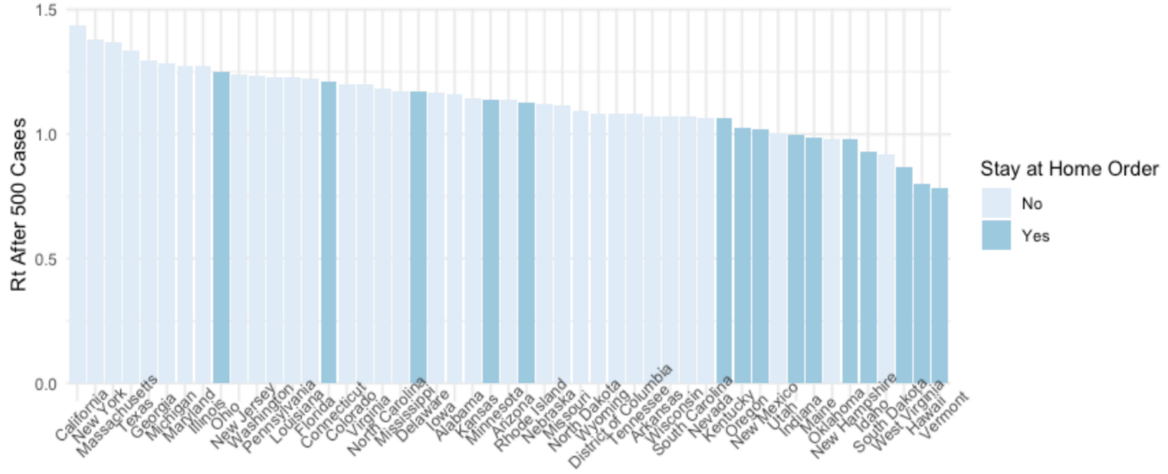
Figure 1: Average R_t during the week following the 500th case by each state.



In Kaplan Meier analyses, implementation of a stay-at-home order prior to the date of 500 cases was associated with a decreased probability of reaching 1000 cases within 5 days (log rank sum, p = 0.02). Similarly, in cox proportional hazards regression, stay-at-home orders correlated with an increase in time to reach 1000 cases (OR = 0.35, CI 0.17 to 0.92, p = 0.004, **Table 3, Figure 2**). States in the highest quartile of average percent time spent at home were also less likely to reach 1000 cases (log rank sum, p<0.001, HR 0.18, 95% CI 0.06 to 0.53, p=0.002). Other distancing measures did not affect the time from 500 to 1000 cases.

- States that had SAHO in place at the time of their 500th case are associated with lower average R_t the following week compared to states without SAHO
  - (p < 0.001) and are significantly less likely to have an R_t >1 (OR 0.07, 95% CI 0.01 to 0.37, p = 0.004).
- These states also experienced a significantly longer doubling time from 500 to 1000 cases
  - (HR 0.35, 95% CI 0.17 to 0.72, p = 0.004).
- States in the highest quartile of average time spent at home were also slower to reach 1000 cases than those in the lowest quartile
  - (HR 0.18, 95% CI 0.06 to 0.53, p = 0.002).

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Figure 2: Hazards curve demonstrating the probability of reaching 1000 cases separated by (A) states with and without a stay-at-home order prior to the 500th case and (B) the highest vs. lowest quartile of % time spent at home based on Google mobility data.

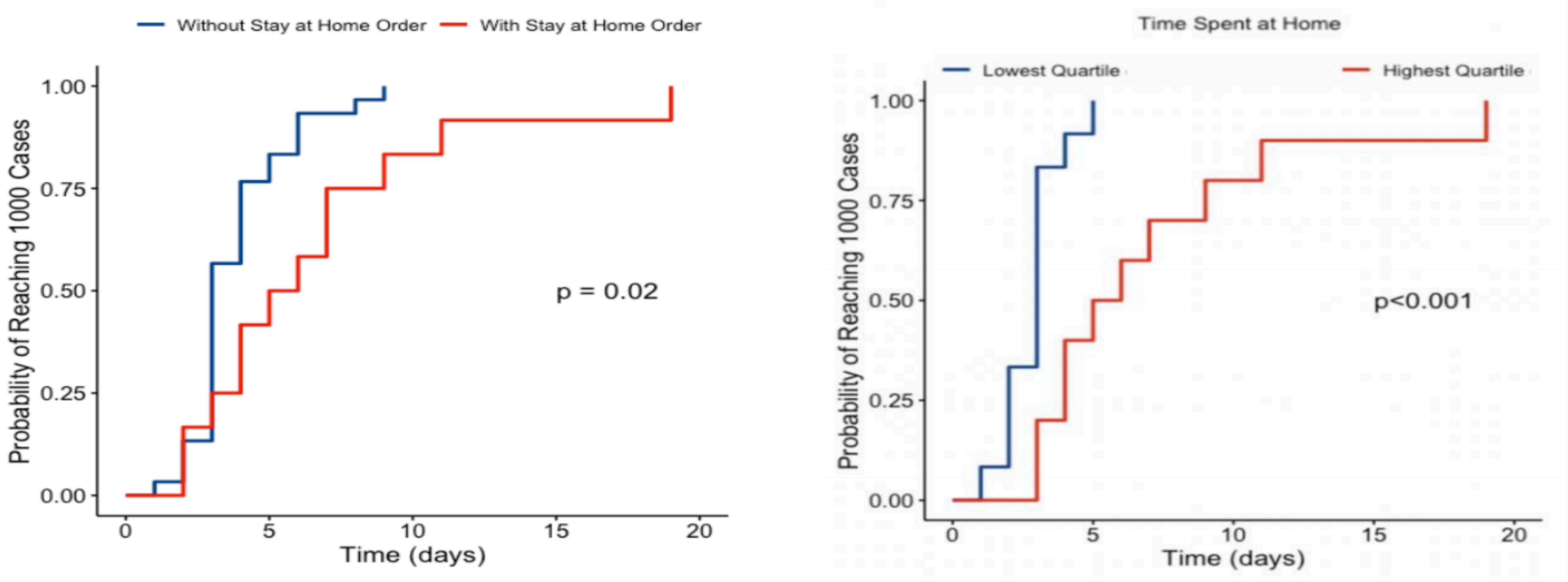

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Table 3: Cox proportional hazards regression for time to event analysis

	Time to 1000th Case	
Covariate	Hazard ratio (95% CI)	p
Stay-at-home order	**0.35 (0.17 to 0.72)**	**0.004***
Educational facilities closure	0.63 (0.25 to 1.63)	0.3
Non-essential business closure	0.55 (0.28 to 1.10)	0.08
Limitation on mass gatherings	0.75 (0.31 to 1.79)	0.5
Average % time spent at home (Q4 vs. Q1)	**0.18 (0.06 to 0.53)**	**0.002***

NPI effects on deaths

In linear regression, this study found that none of the included policies (stay-at-home orders, school closures, bans on mass gatherings, or closure of non-essential businesses) were associated with a decrease in case fatality rate (CFR). In Kaplan Meier event analysis, stay-at-home orders were non-significant in predicting time from 50 deaths to 100 deaths (**Figure 3**).

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COVID Virus a Genetic Cousin of Scaly Mammal Coronavirus

- SARS-CoV-2, shares high sequence identity to SARS-CoV and a bat coronavirus RaTG132.
  - While bats may be the reservoir host for various coronaviruses, whether SARS-CoV-2 has other hosts remains ambiguous.
- One coronavirus isolated from a Malayan pangolin showed high level identity with SARS-COV-2
  - 100%, 98.6%, 97.8% and 90.7% amino acid identity with SARS-CoV-2 in the E, M, N and S genes, respectively.
  - The the receptor-binding domain within the S protein of the Pangolin-CoV is virtually identical to that of SARS-CoV-2,
- SARS-CoV-2 might have originated from the recombination of a Pangolin-CoV-like virus with a Bat-CoV-RaTG13-like virus.
  - The Pangolin-CoV was detected in 17 of 25 Malayan pangolins analyzed, in which all were symptomatic.
  - Circulating antibodies against Pangolin-CoV reacted with the S protein of SARS-CoV-2.
- The isolation of a coronavirus highly related to SARS-CoV-2 in pangolins suggests that they have the potential to act as the intermediate host of SARS-CoV-2.
- The newly identified coronavirus in the most-trafficked mammal could represent a future threat to public health if wildlife trade is not effectively controlled.

Xiao K, Zhai J,Feng Y et al. Isolation of SARS-CoV-2-related coronavirus from Malayan pangolins Nature May 7, 2020

Interpreting Diagnostic Tests for SARS-CoV-2

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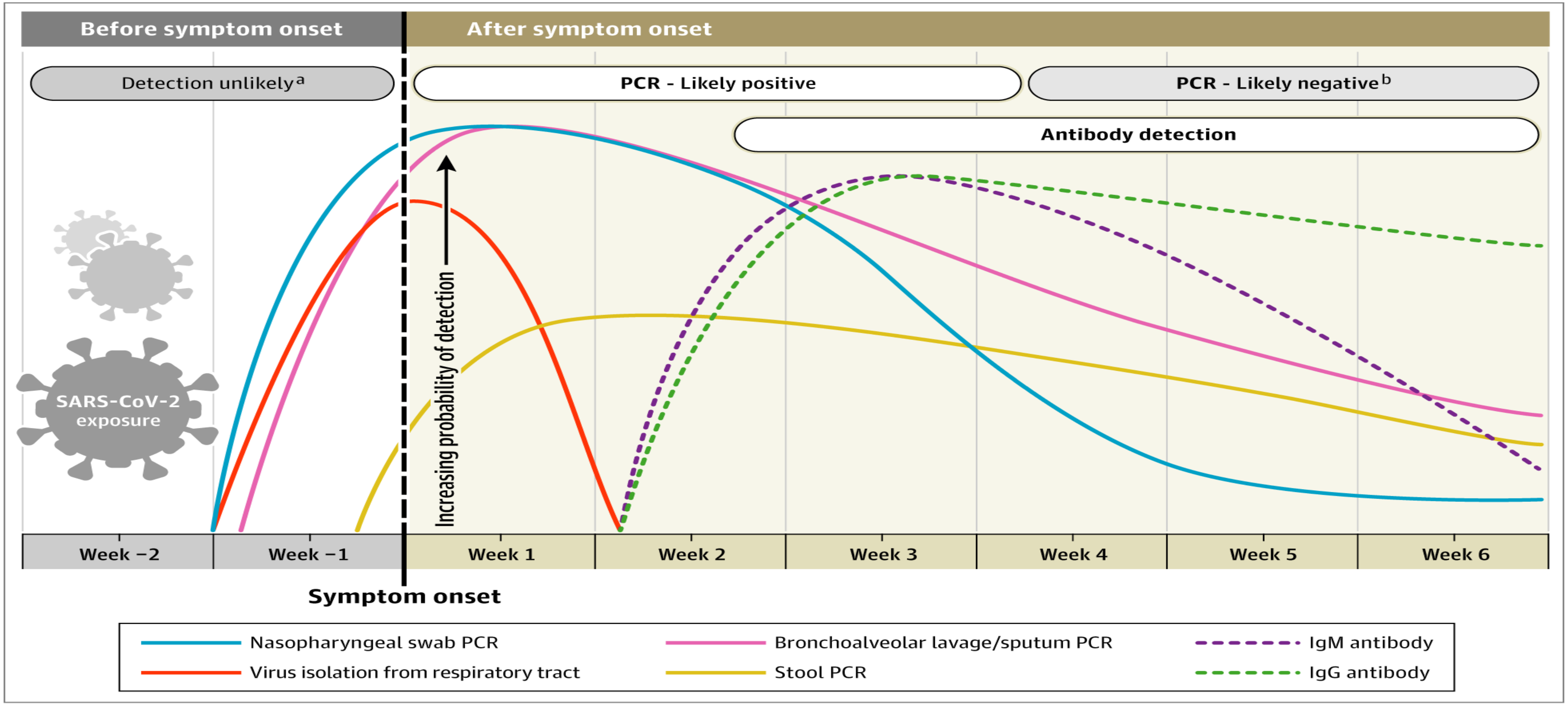

Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction. [a]Detection only occurs if patients are followed up proactively from the time of exposure. [b]More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Interpreting Diagnostic Tests for SARS-CoV-2

- **In most individuals with symptomatic COVID-19 infection, NP viral RNA becomes detectable as early as day 1 of symptoms and peaks within the first week of symptom onset.**
  - This positivity starts to decline by week 3 and subsequently becomes undetectable.
  - Patients with severe infection my have higher and prolonged viral load shedding but does not necessarily indicate presence of viable virus
- **In a study of 9 patients, attempts to isolate the virus in culture were not successful beyond day 8 of illness onset, which correlates with the decline of infectivity beyond the first week**.
  - That is in part why the "symptom-based strategy" of the CDC indicates that health care workers can return to work
- **The timeline of PCR positivity is different in specimens other than nasopharyngeal swab.**
  - PCR positivity declines more slowly in sputum and may still be positive after nasopharyngeal swabs are negative.
  - PCR positivity in stool was observed in 55 of 96 (57%) infected patients and remained positive in stool beyond nasopharyngeal swab by a median of 4 to 11 days
- **RT-PCR positivity is highest in bronchoalveolar lavage specimens (93%), followed by sputum (72%), nasal swab (63%), and pharyngeal swab (32%)**
  - False-negative results mainly occurred due to inappropriate timing of sample collection in relation to illness onset and deficiency in sampling technique, especially of nasopharyngeal swabs
- **Specificity of most of the RT-PCR tests is 100%**
  - Occasional false-positive results may occur due to technical errors and reagent contamination.

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Interpreting Diagnostic Tests for SARS-CoV-2

- Serology is important for 1) patients who may present late, beyond the first 2 weeks of illness onset, 2) to understand the extent of COVID-19 in the community and 3) to identify individuals who are immune and potentially "protected" from reinfection
- **The most sensitive and earliest serological marker (second week after symptom onset) is total antibodies (Ab)**
  - IgM and IgG can be positive as early as the 4th day after symptom onset but higher levels can be detected in most patients by the 4th week
- **Paired serum samples testing** with the initial PCR and the second 2 weeks later can increase diagnostic accuracy
- The majority of Ab are against Nucleo Capcid (NC) (the most abundant). **NC Ab would be the most sensitive**
- **Ab against the receptor-binding domain of S protein** would be **more specific** and are expected to be neutralizing.
- Many manufacturers of **PCT** do not reveal the nature of antigens used these **are purely qualitative in nature**
- The presence of **neutralizing Ab can only be confirmed** by a plaque reduction neutralization test
  - However**, high titers** of IgG Ab detected by ELISA have been shown to positively correlate with neutralizing Ab.
- The long-term persistence and duration of protection conferred by the neutralizing Ab remains unknown.

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Ab: Antibodies. PCT: Point of Care Testing

Pediatric Multi-System Inflammatory Syndrome ***Potentially Associated with COVID-19***

Fifteen cases compatible with multi-system inflammatory syndrome have been identified in children in New York City hospitals.

- Ages 2-15 years, hospitalized from April 17- May 1, 2020 with illnesses compatible with this syndrome (i.e., typical Kawasaki disease, incomplete Kawasaki disease, and/or shock)
- All patients had subjective or measured fever and more than half reported rash, abdominal pain, vomiting, or diarrhea
- Respiratory symptoms were reported in less than half of these patients. Polymerase chain reaction (PCR) testing for SARS-CoV-2 has been positive (4), negative (10), and initially indeterminate and then negative (1). Six patients with negative testing by PCR were positive by serology.
- More than half required blood pressure support and five required mechanical ventilation
- No fatalities have been reported

Early recognition and specialist referral are essential, including to critical care if warranted

Resources

- https://www1.nyc.gov/assets/doh/downloads/pdf/han/alert/2020/covid-19-pediatric-multi-system-inflammatory-syndrome.pdf
- https://www.idsociety.org/contentassets/9ba35522e0964d51a47ae3b22e59fb47/idsa-recommendations-for-reducing-covid-19-distancing_16apr2020_final-.pdf