The Daily COVID-19 Literature Surveillance Summary

April 12, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".

Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Transmission & Prevention

- Where do we stand with the SARS-CoV-2 vaccines? In this extensive review, authors from Mangla Hospital & Research Center and Kumar Child Clinic in India detail the current state of promising COVID-19 vaccines. They present the current understanding of the immune response to SARS-CoV-2, including innate and humoral immunity, intensity and duration of response, and the applications this has for vaccines targets. They also point out practical limitations and possible conflicts regarding global vaccine distribution needed to achieve widescale herd immunity. The authors are hopeful as they outline current vaccines trials but acknowledge various issues that could prove problematic as the urge for an unprecedented turnaround time for a viable vaccine continues.

TABLE OF CONTENTS

SPATIAL INEQUITIES IN COVID-19 TESTING, POSITIVITY, CONFIRMED CASES, AND MORTALITY IN 3 U.S. CITIES : AN ECOLOGICAL STUDY

Bilal U, Tabb LP, Barber S, Diez Roux AV.. Ann Intern Med. 2021 Mar 30. doi: 10.7326/M20-3936. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Investigators from Drexel Dornsife School of Public Health, Philadelphia PA conducted an observational study analyzing inequities of COVID-19 spatially distributed using ZIP code tabulation area (ZCTA), encompassing 58 ZIP codes in Chicago, 177 in New York, and 46 in Philadelphia from the beginning of the pandemic through the end of September 2020. The results revealed higher rates of SARS-CoV-2 positivity, confirmed COVID-19 cases, and mortality along with lower rates of testing in all three cities: Chicago $p < 0.001$ (Figure 1), New York $p < 0.001$ (Figure 2), Philadelphia $p = 0.011$ (Figure 3). These findings were especially evident in neighborhoods with high Social Vulnerability Indexes (SVI) with mortality rates from COVID-19 increasing by 50% for each 1 standard deviation in SVI. The authors call to address social factors linked to income inequality, structural racism, and systematic disinvestment in these neighborhoods to minimize the effects of COVID-19 and promote health equality in the future.

ABSTRACT

BACKGROUND: Preliminary evidence has shown inequities in coronavirus disease 2019 (COVID-19)-related cases and deaths in the United States. OBJECTIVE: To explore the emergence of spatial inequities in COVID-19 testing, positivity, confirmed cases, and mortality in New York, Philadelphia, and Chicago during the first 6 months of the pandemic. DESIGN: Ecological, observational study at the ZIP code tabulation area (ZCTA) level from March to September 2020. SETTING: Chicago, New York, and Philadelphia. PARTICIPANTS: All populated ZCTAs in the 3 cities. MEASUREMENTS: Outcomes were ZCTA-level COVID-19 testing, positivity, confirmed cases, and mortality cumulatively through the end of September 2020. Predictors were the Centers for Disease Control and Prevention Social Vulnerability Index and its 4 domains, obtained from the 2014-2018 American Community Survey. The spatial autocorrelation of COVID-19 outcomes was examined by using global and local Moran I statistics, and estimated associations were examined by using spatial conditional autoregressive negative binomial models. RESULTS: Spatial clusters of high and low positivity, confirmed cases, and mortality were found, co-located with clusters of low and high social vulnerability in the 3 cities. Evidence was also found for spatial inequities in testing, positivity, confirmed cases, and mortality. Specifically, neighborhoods with higher social vulnerability had lower testing rates and higher positivity ratios, confirmed case rates, and mortality rates. LIMITATIONS: The ZCTAs are imperfect and heterogeneous geographic units of analysis. Surveillance data were used, which may be incomplete. CONCLUSION: Spatial inequities exist in COVID-19 testing, positivity, confirmed cases, and mortality in 3 large U.S. cities. PRIMARY FUNDING SOURCE: National Institutes of Health.

FIGURES

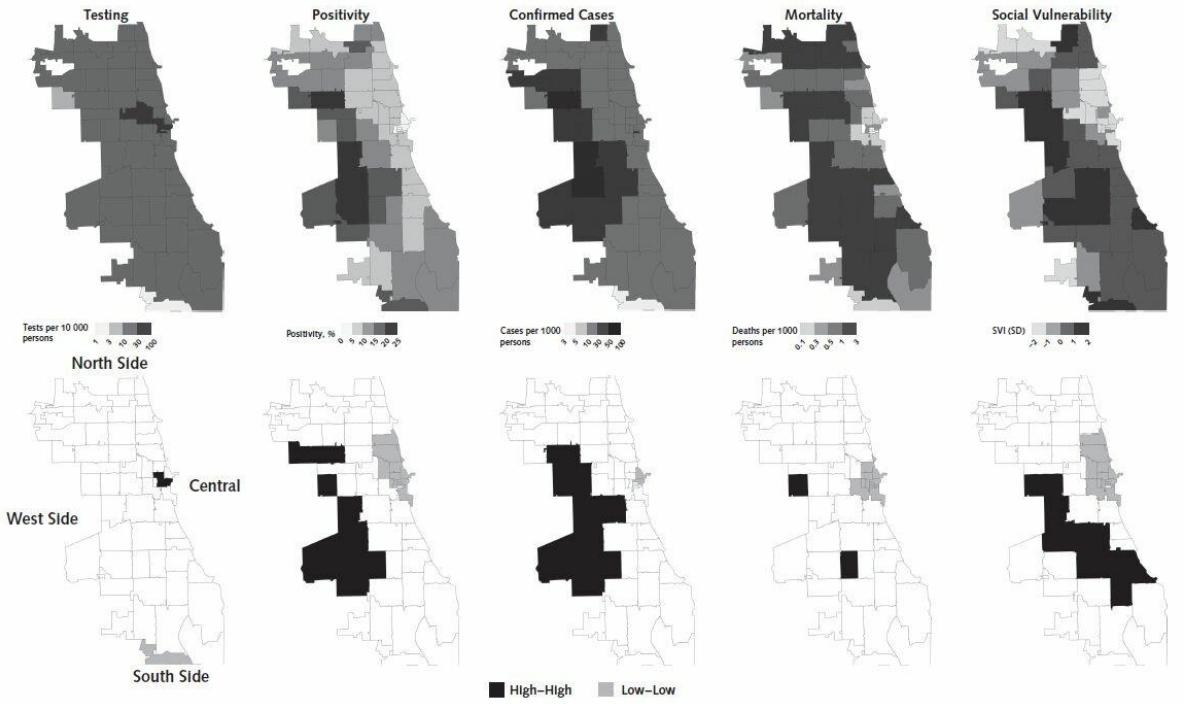

Figure 1. Spatial distribution and clusters of coronavirus disease 2019 testing, positivity, confirmed cases, and mortality and social vulnerability in ZIP code tabulation areas of Chicago.

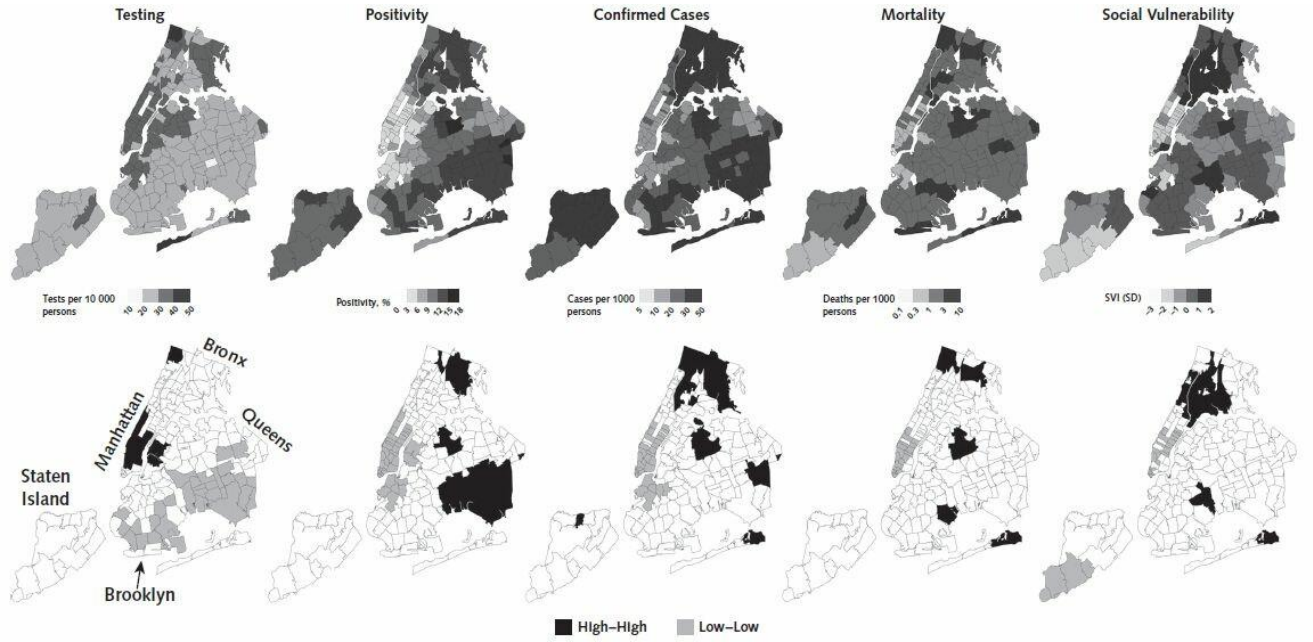

Figure 2. Spatial distribution and clusters of coronavirus disease 2019 testing, positivity, confirmed cases, and mortality and social vulnerability in ZIP code tabulation areas of New York.

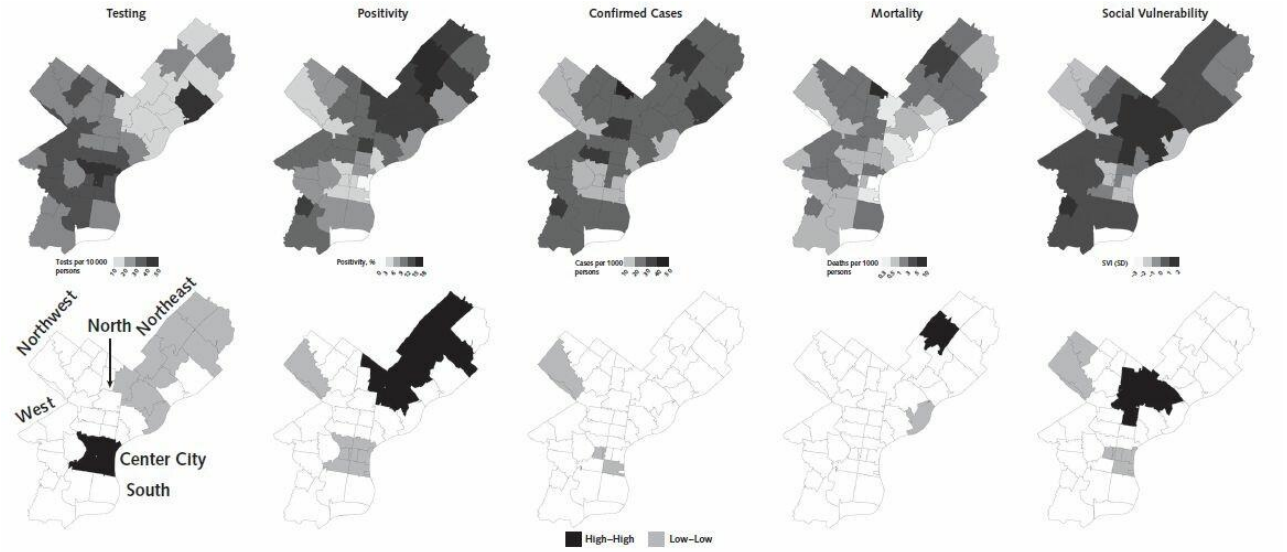

Figure 3. Spatial distribution and clusters of coronavirus disease 2019 testing, positivity, confirmed cases, and mortality and social vulnerability in ZIP code tabulation areas of Philadelphia.

DEVELOPMENT OF SARS-COV-2 VACCINES: CHALLENGES, RISKS, AND THE WAY FORWARD

Vashishtha VM, Kumar P.. Hum Vaccin Immunother. 2020 Dec 3:1-15. doi: 10.1080/21645515.2020.1845524. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

In this extensive review, authors from Mangla Hospital & Research Center and Kumar Child Clinic in India detail the current state of promising COVID-19 vaccines. They present the current understanding of the immune response to SARS-CoV-2, including innate and humoral immunity, intensity and duration of response, and the applications this has for vaccines targets. They also point out practical limitations and possible conflicts regarding global vaccine distribution needed to achieve widescale herd immunity. The authors are hopeful as they outline current vaccines trials (Table 1) but acknowledge various issues that could prove problematic as the urge for an unprecedented turnaround time for a viable vaccine continues.

SUMMARY

Although continued research is being conducted around the clock, given the unprecedented occurrence of the COVID-19 pandemic, there is still much unknown about SARS-CoV-2 including the strength and length of immune response. Conclusions have been drawn from immune responses in general regarding viruses, including recognition of viral RNA and Toll-like receptors (TLR), triggering downstream cascade of immune cells response, however some coronaviruses have shown to evade and/or suppress this cascade. Patients with COVID-19 have shown some development of immune response including IgM, IgG, and IgA antibodies against N and S viral proteins. Some of these neutralizing antibodies (NAbs) recovered from COVID-19 patients have been providing promising vaccine targets, specifically against the S protein, with reports of administration of monoclonal NAbs decreasing risk of hospitalization of severe disease by 75%. The authors suggest the most effective protection will come from coordinated CD4+ T cells, CD8+ T cells, and NAbs response. Given the short time SARS-CoV-2 has been in circulation, the length of immune protection is still unknown. Hypotheses have been extrapolated from previous coronaviruses, with SARS-CoV-1 immunity lasting for 1-2 years and MERS immunity lasting for 34 months. Some studies have suggested a robust presence of antibodies still present at least 3-4 months after infection of COVID-19 patients, however, only time will tell the true length of protection. The quick achievement of heard immunity will be crucial to decrease continued transmission of SARS-CoV-2, therefore vaccination programs should aim to cover at least two-thirds of the population as quickly as possible once vaccines are available to the public.

ABSTRACT

The COVID-19 pandemic mandates the development of a safe and effective Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) vaccine. This review analyzes the complexities, challenges, and other vital issues associated with the development of the SARS-CoV-2 vaccine. A brief review of the immune responses (innate, antibody, and T-cell) to SARS-CoV-2, including immune targets, correlates of protection, and duration of immunity is presented. Approaches to vaccine development including different vaccine platforms, critical attributes of novel vaccine candidates, the status of the ongoing clinical trials, and the ways to speed up vaccine development are also reviewed. Despite a historical average success rate of only 6%, and a usual gestation period of 10-12 years for the development of a new vaccine, the world is on the verge of developing COVID-19 vaccines in an extraordinary short time span.

FIGURES

Vaccine platform	Vaccine candidates under clinical trials*	Safety	Speed of development	Global distribution and scalability	NAb production	T-cell immune responses	Advantage	Disadvantage	Existing example/Same platform for non-HCoV candidates
Inactivated	Seven	Some concerns	Medium	Feasible	Moderate	Probably lower	-Traditional & easy to develop -Preserve virus particle structure -Can be formulated with various adjuvants	-Possible hypersensitivity -Th-2 bias? -Possible ADE?	SARS
Live attenuated	None	Significant concerns	Slow	Feasible	Probably high	Probably good	-Highly immunogenic -Good cellular responses -Can be given intranasally that can induce mucosal immunity too	-Substantial safety concerns (Reversion to virulent strain) -Cold chain requirement, -Risk to immunocompromised	Several (OPV, MMR, Varicella, Influenza, etc)
Non-Replicating Viral Vector	Nine	High	Medium	Feasible	Moderate	Probably good	-Despite a live virus vaccine, safety not an issue, -should elicit better immune responses than killed/subunit vaccines -Good cellular responses	-Selection of safe vector-a must. -Immune response to vector may render vaccine less effective	Ebola, MERS, influenza, TB, Chikungunya, Zika, MenB, plague
Replicating Viral Vector	Three	Some concerns	Medium	Feasible	Probably good	Good	-Mimic natural infection "dose sparing effect" (less dose required as compared to non-replicating viral vector vaccine-Often induce innate immune response too -Some vectors may be given intranasally and induce mucosal immunity	Selection of safe vector-a must. -Immune response to vector may render vaccine less effective	HIV
RNA	Six	High	Fast	May be difficult	Moderate	Probably good	-Rapid development. -Easy to make	- No approved RNA vaccines -Unlikely to induce mucosal immunity -Required frozen storage: big challenge in developing and underdeveloped countries	multiple candidates in the pipeline
DNA	Four	High	Fast	Some concerns	Moderate	Probably good	Rapid development; Easy to make	-Low immunogenicity -Approved for veterinary cases; -No approved vaccines for use in humans	None (multiple candidates in the pipeline)
Protein Subunit	Thirteen	High	Slow	Feasible	High	Probably lower	-High safety profile -Consistent production -High NAbs production	-Need appropriate adjuvant, -Cost-effectiveness may vary	RSV, CCHF, HPV, VZV, Influenza, Ebola
VLP	Two	High	Slow	Feasible	High	Probably lower	-Multimeric antigen display -Preserve virus particle structure	-Require optimum assembly condition	Flu, Rotavirus, Norovirus, West Nile virus, Cancer, HPV

Table 1. Landscape of SARS-CoV-2 candidate vaccines: Vaccine platform, their attributes, and status of development.

PREVENTION IN THE COMMUNITY

QUANTIFYING SARS-COV-2 TRANSMISSION SUGGESTS EPIDEMIC CONTROL WITH DIGITAL CONTACT TRACING

Ferretti L, Wymant C, Kendall M, Zhao L, Nurtay A, Abeler-Dörner L, Parker M, Bonsall D, Fraser C.. Science. 2020 May 8;368(6491):eabb6936. doi: 10.1126/science.abb6936. Epub 2020 Mar 31.
Level of Evidence: 5 - Modeling

BLUF

A modeling study conducted by a group of senior researchers and epidemiologists in March 2020 to determine the infectiousness of SARS-CoV-2 (Figure 2), quantify the contribution of different transmission routes, and to ascertain best epidemic control methods. The authors accomplish this through developing mathematical models for SARS-CoV-2 infectiousness and by analyzing 40 well-characterized source-recipient pairs (Figure 1) to estimate the distribution of generation times (time from infection to onward transmission). The authors suggest that if used by enough people, a contact-tracing app that builds a memory of proximity contacts and immediately notifies contacts of positive cases would be sufficient to stop the epidemic (Figure 4).

SUMMARY

- Between 1/3-1/2 of transmissions occur from pre-symptomatic individuals.

- Since SARS-CoV-2 is spreading too fast to be contained by manual contact tracing, it can only be controlled by a faster, more efficient method.

- Using apps to contact-trace would be particularly effective when combined with other measures such as physical distancing.

- The proposed app offers benefits for both society and individuals through enabling people to continue their lives uninterrupted while staying safe.

ABSTRACT

The newly emergent human virus SARS-CoV-2 (severe acute respiratory syndrome-coronavirus 2) is resulting in high fatality rates and incapacitated health systems. Preventing further transmission is a priority. We analyzed key parameters of epidemic

spread to estimate the contribution of different transmission routes and determine requirements for case isolation and contact tracing needed to stop the epidemic. Although SARS-CoV-2 is spreading too fast to be contained by manual contact tracing, it could be controlled if this process were faster, more efficient, and happened at scale. A contact-tracing app that builds a memory of proximity contacts and immediately notifies contacts of positive cases can achieve epidemic control if used by enough people. By targeting recommendations to only those at risk, epidemics could be contained without resorting to mass quarantines ("lockdowns") that are harmful to society. We discuss the ethical requirements for an intervention of this kind.

FIGURES

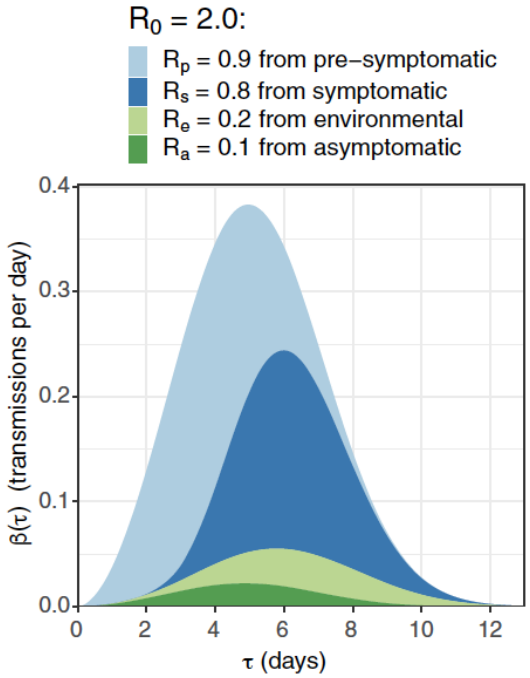

Figure 2. Our model of infectiousness. The average infectiousness (rate of infecting others), b, is shown as a function of the amount of time since infection, t. The total colored area found between two values of t is the number of transmissions expected in that time window. The total colored area over all values of t is the number of transmissions expected over the full course of one infection (i.e., the basic reproduction number R0). The different colors indicate the contributions of the four routes of transmission, so that the total area of one color over all values of t is the average number of transmissions via that route over the whole course of infection: RP, RS, RE, and RA for presymptomatic, symptomatic, environmentally mediated, and asymptomatic transmission, respectively. Note that the colors are stacked on top of one another (i.e., the lower colors are not in front, and the higher colors are not behind and partially obscured). Values are rounded to one decimal place. Stopping the spread of disease requires reduction of R to less than 1: blocking transmission, from whatever combination of colors and values of t we can achieve, such that the total area is halved.

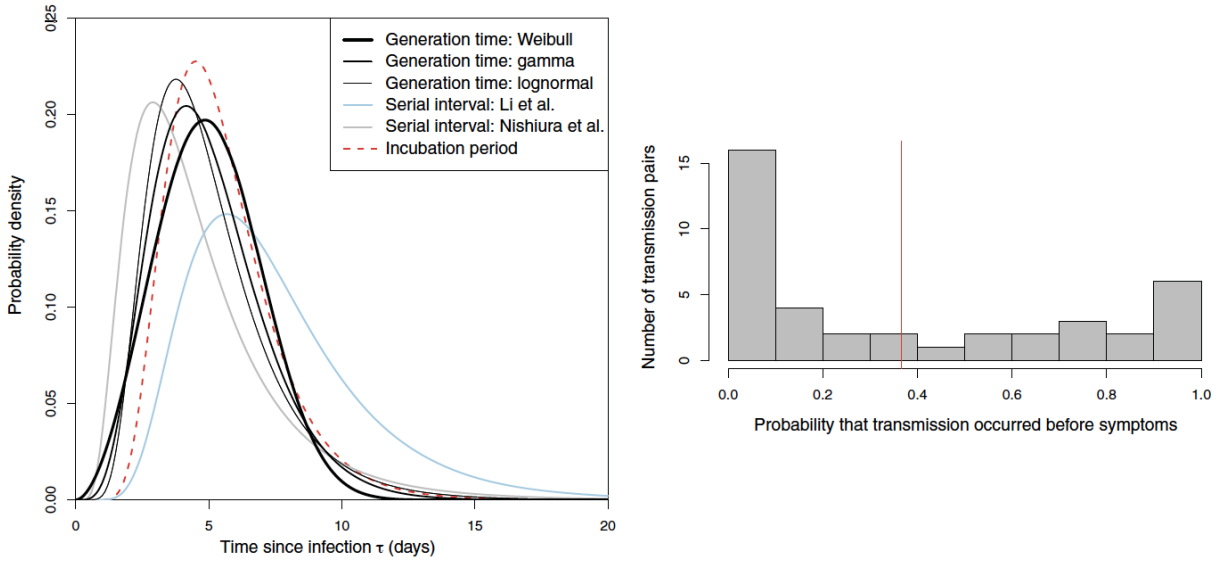

Figure 1. Quantifying transmission timing in 40 transmission pairs. Left: Our inferred generation time distributions, in black; thicker lines denote higher support for the corresponding functional form, with the Weibull distribution being the best fit. For comparison, we also include the serial interval distributions previously reported by Li et al. (12) (light blue) and Nishiura et al. (22) (gray) and the incubation period distribution we used here, from Lauer et al. (21) (dashed red line). Right: Distribution of the posterior probability of presymptomatic transmission for each of the 40 transmission pairs. The red vertical line shows the mean probability.

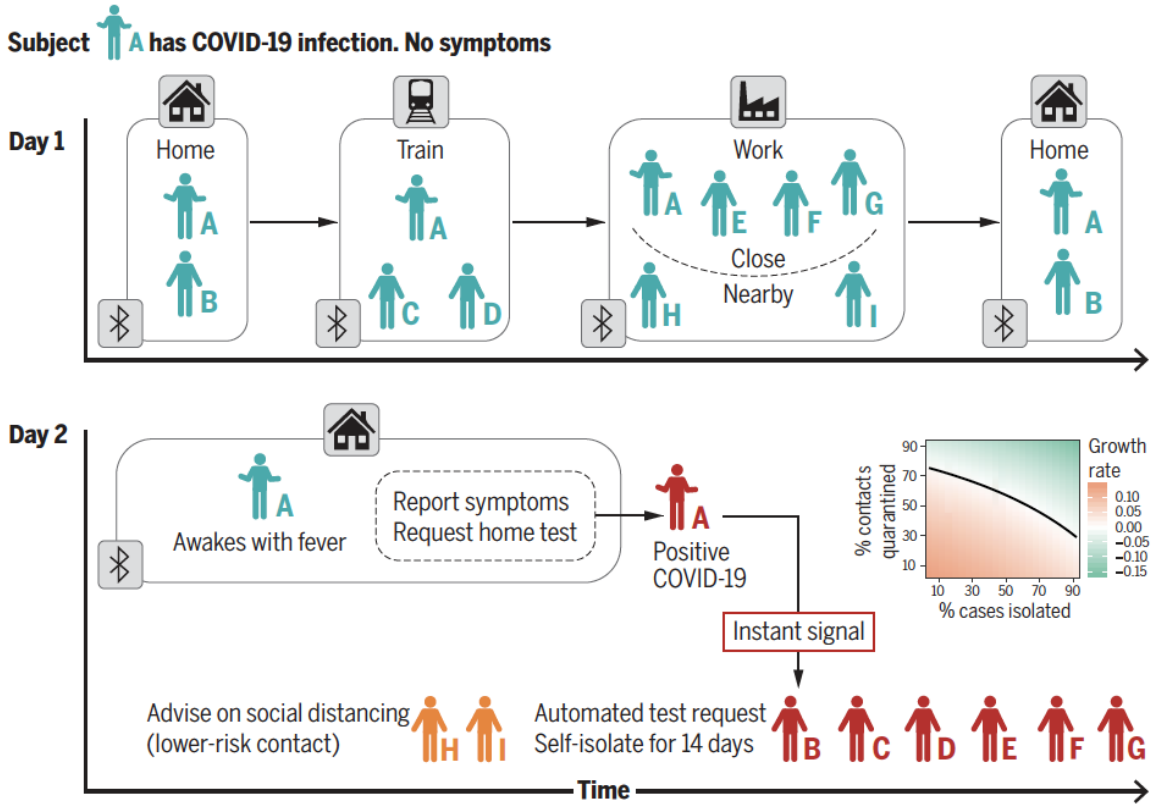

Figure 4. A schematic of app-based COVID-19 contact tracing. Contacts of individual A (and all individuals using the app) are traced using low-energy Bluetooth connections with other app users. Individual A requests a SARS-CoV-2 test (using the app) and that person’s positive test result triggers an instant notification to individuals who have been in close contact. The app advises isolation for the case (individual A) and quarantine of the individual’s contacts.

PROVIDING SAFE CARE FOR PATIENTS IN THE CORONAVIRUS DISEASE 2019 (COVID-19) ERA: A CASE SERIES EVALUATING RISK FOR HOSPITAL-ASSOCIATED COVID-19

Habermann EB, Tande AJ, Pollock BD, Neville MR, Ting HH, Sampathkumar P.. Infect Control Hosp Epidemiol. 2021 Apr 5:1-7. doi: 10.1017/ice.2021.38. Online ahead of print.
Level of Evidence: 4 - Case-series

BLUF

A case series conducted by doctorate researchers from Mayo Clinic in Rochester, MN which included 2,068 patients hospitalized for 2 or more nights at a tertiary-care hospital located in the midwest between May 15 to June 15, 2020 with 1,778 (86%) undergoing PCR and 1,339 (64.7%) serology upon admission (Figure 2) to determine incidence of healthcare-associated COVID-19 (Table 1). Out of 1,310 eligible PCR and seronegative adults, there were no positive PCR tests during hospital admission (95% CI, 0.0-0.3%) and out of 445 (34%) post-discharge serology testing 14-21 days after admission, there were no seroconversions (0.0%, 95% CI 0.0-0.9%). These findings suggest a low-likelihood of hospital-associated COVID-19 infection when adhering to screening upon admission with PCR testing, universal masking, hand hygiene, limited visitors, and physical distancing.

ABSTRACT

OBJECTIVE: We evaluated the risk of patients contracting coronavirus disease 2019 (COVID-19) during their hospital stay to inform the safety of hospitalization for a non-COVID-19 indication during this pandemic. METHODS: A case series of adult patients hospitalized for 2 or more nights from May 15 to June 15, 2020 at large tertiary-care hospital in the midwestern United States was reviewed. All patients were screened at admission with the severe acute respiratory coronavirus virus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test. Selected adult patients were also tested by IgG serology. After dismissal, patients with negative serology and PCR at admission were asked to undergo repeat serologic testing at 14-21 days after discharge. The primary outcome was healthcare-associated COVID-19 defined as a new positive SARS-CoV-2 PCR test on or after day 4 of hospital stay or within 7 days of hospital dismissal, or seroconversion in patients previously established as seronegative. RESULTS: Of the 2,068 eligible adult patients, 1,778 (86.0%) completed admission PCR testing, while 1,339 (64.7%) also completed admission serology testing. Of the 1,310 (97.8%) who were both PCR and seronegative, 445 (34.0%) repeated postdischarge serology testing. No healthcare-associated COVID-19 cases were detected during the study period. Of 1,310 eligible PCR and seronegative adults, no patients tested PCR positive during hospital admission (95% confidence interval [CI], 0.0%-0.3%). Of the 445 (34.0%) who completed postdischarge serology testing, no patients seroconverted (0.0%; 95% CI, 0.0%-0.9%). CONCLUSION: We found low likelihood of hospital-associated COVID-19 with strict adherence to universal masking, physical distancing, and hand hygiene along with limited visitors and screening of admissions with PCR.

FIGURES

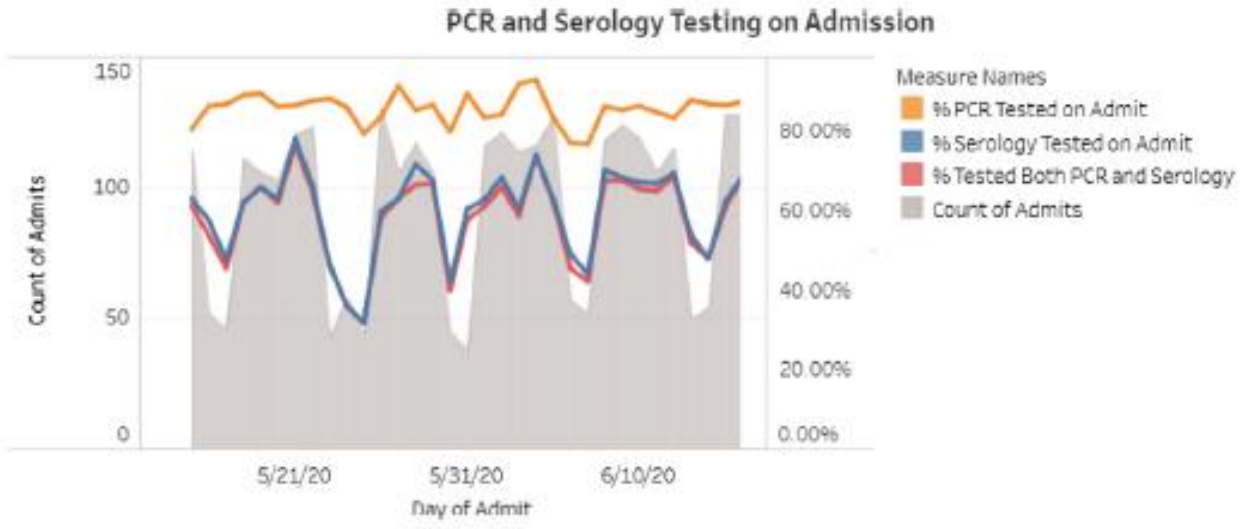

Fig. 2. Admission PCR and serology testing rates as displayed on nosocomial surveillance dashboard.

Classification	Test Results
Community-acquired COVID-19	Positive PCR or serology at admission (day −3 to day 3 of hospital stay)
Definite healthcare-associated COVID-19	Negative PCR and serology testing at admission AND 1 of the following: • Positive PCR test on ≥ day 7 of hospital stay OR • Positive PCR test within 7 days after discharge from a hospitalization of at least 7 days duration OR • Positive serology test on days 14–21 after hospital discharge
Possible healthcare-associated COVID-19	1. Negative PCR and serology testing at admission AND 1 of the following: • Positive PCR test on days 4–6 of hospital stay OR • Positive PCR test within 7 days after hospital discharge if the hospital stay was 3–6 days in duration 2. Missing PCR and serology at admission AND 1 of the following: • Positive PCR test on of after day 7 of hospital stay OR • Positive PCR test within 7 days after discharge from a hospital stay of at least 7 days duration 3. Missing or negative PCR and negative serology on admission AND • Positive serology at days 14–21 after hospital discharge OR • Positive PCR test on or after day 7 of hospital stay OR • Positive PCR test within 7 days after discharge from a hospital stay of at least 7 days duration

Table 1: Classification of COVID-19.

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CONTRIBUTORS

Renate Meckl
Veronica Graham
Zainab Awan

EDITORS

John Michael Sherman
Julia Ghering
Justin Doroshenko

SENIOR EDITORS

Allison Hansen

SENIOR EXECUTIVE EDITOR

Thamanna Nishath

CHIEF EDITOR

Jasmine Rah

ADVISOR

Will Smith