

Airborne Transmission of SARS-CoV-2 Theoretical Considerations and Available Evidence

JAMA published online July 13, 2020 highlights

Experimental data support the possibility that SARS CoV-2 may be transmitted by aerosols (so-called airborne transmission) even in the absence of aerosol generating procedures. Investigators have demonstrated that speaking and coughing produce a mixture of both droplets and aerosols in a range of sizes, that these secretions can travel together for up to 27 feet, that it is feasible for SARS-CoV-2 to remain suspended in the air and viable for hours, that SARS-CoV-2 RNA can be recovered from air samples in hospitals, and that poor ventilation prolongs the amount of time that aerosols remain airborne. Demonstrating that speaking and coughing can generate aerosols or that it is possible to recover viral RNA from air does not prove aerosol-based transmission; infection depends as well on the route of exposure, the size of inoculum, the duration of exposure, and host defenses. SARS CoV-2 detected by PCR does not mean live viable viral capable of transmitting disease.

The authors go on to admit that data on infection and transmission during normal daily life is difficult to assess. They use a very compelling rationale to try and explain what the available evidence is for airborne transmission. First, the reproduction number for COVID-19 before measures were taken to mitigate its spread was estimated to be about 2.5. This reproduction number is similar to influenza [slightly higher for SARS-CoV-2] and quite different from that of viruses that are well known to spread via aerosols such as measles, which has production number closer to 18. They postulate that most people with COVID-19 are contagious for about 1 week. A reproductive number of 2-3 is quite small given the large numbers of interactions, especially in crowds and personal contact that most people have under normal circumstances with a typical week. They argue that either the amount of SARS-CoV-2 required to transmit infection is much larger than measles or aerosols are not the dominate mode of transmission. In addition, secondary attack rates for SARS-CoV-2 is also low. Published reports that evaluated close contacts of patients confirmed with COVID-19 report that only 5% on these contacts became infected. This low rate may depend on duration and intensity of exposure. [CDC defines close contact (< 6 feet for ≥15 minutes) with the person with COVID-19] The risk is highest among household contacts with published transmission rates between 10-40%. Close but less intense exposure such as sharing a meal is associated with a secondary rate ~7%, whereas passing interactions among people shopping is associated with a secondary attacked rate <1%. Secondary attack rate among HCWs who unknowingly cared for a COVID-19 patient while wearing a face mask alone or not using PPE is also low. They conclude the current evidence is inconsistent with aerosol transmission especially in well-ventilated spaces.

Comment: The exception to the analysis above may be prolonged contact in poorly ventilated spaces. This is why many guidelines advocate improving ventilation by bringing in fresh outdoor air, increasing the number of air exchanges, and improving the filtration. Given the current evidence, optimize indoor ventilation, wear masks, social distance (6-feet apart), in addition to frequent hand washing and environmental cleaning are important nonpharmaceutical interventions. Despite the evidence in this viewpoint, it is impossible to conclude aerosol-based transmission never occurs especially in a poorly ventilated room with singing, shouting, sneezing, or coughing.

Tocilizumab for treatment of mechanically ventilated patients with COVID-19

Clin Infect Dis published online July 12, 2020

In this observational study the investigators assessed the effective and safety of tocilizumab in patients infected with SARS-CoV-2 on ventilators. 154 patients were included, of whom 78 received tocilizumab

and 76 who did not. Among patients with COVID-19 who required mechanical ventilation, receipt of tocilizumab was associated with a 45% lower mortality risk relative to not receiving it. During a median follow-up of 47 days, tocilizumab was associated with a higher rate of superinfections (54% vs. 26%), mostly driven by ventilator-associated pneumonia; however, tocilizumab patients who had a superinfection didn't have higher mortality rates than those without a superinfection. Tocilizumab recipients had lower 28-day mortality rates than other patients (18% vs. 36%). *S. aureus* accounted for ~50% of bacterial pneumonia.

Comment: Although there were slight imbalances between the 2 groups with regards to age, D-dimer, CRP, etc. they used risk adjustment propensity factors as well as sensitivity analyses and tocilizumab remained associated with better outcomes. Although this article alone is not conclusive, there is a growing body of evidence of using that IL-6 inhibitors may have a place in select patients infected with SARS-CoV-2. The issue of superinfections appears to be real and should be addressed. We await results of RCTs. See below

Safety and Efficacy of Anti-IL6-Receptor Tocilizumab Use in Severe and Critical Patients Affected by Coronavirus Disease 2019: mA Comparative Analysis

J Infect published online July 8, 2020

This is a retrospective, single-center analysis including all the patients consecutively admitted to a hospital with severe or critical COVID-19 who started tocilizumab (TCZ) treatment from March 13-April 03, 2020. A 1:2 matching to patients not treated with TCZ was performed according to age, sex, severity of disease, P/F, Charlson Comorbidity Index and length of time between symptoms onset and hospital admittance. A severe case was defined as the presence of respiratory distress (respiratory rate ≥ 30 per min), oxygen saturation on room air at rest $\leq 93\%$ or P/F (or Horowitz Index, partial pressure of oxygen in arterial blood / fraction of inspired oxygen) ≤ 300 mmHg; a —critical case was defined as the presence of respiratory failure with need of ventilation (either invasive or not), septic shock or any other organ dysfunction requiring ICU monitoring and treatment Severe also included bilateral interstitial pneumonia; presence of an active inflammatory status alternatively defined by abnormal C reactive protein (CRP) levels (>1 mg/dL), IL-6 >40 pg/mL, D-dimer >1.5 mcg/mL, or ferritin >500 ng/mL. Seventy-four patients treated with TCZ were matched with 148 matched controls. They were mainly males (81.5%), Caucasian (82.0%) and with a median age of 59 years. The majority (69.8%) showed critical stage COVID-19 disease. TCZ use was associated with a better overall survival (HR 0.499 [95% CI 0.262-0.952], $p=0.035$) compared to controls but with a longer hospital stay (HR 1.658 [95% CI 1.088-2.524], $p=0.019$) mainly due to biochemical, respiratory and infectious adverse events. D-dimer showed a significant increase despite the improvement in other inflammatory markers, an observation which may suggest a persistent alteration of the coagulation. Their data indicate that the risk of thrombotic complications after treatment might not be completely reduced. Additionally, liver enzyme elevation in this population was common. A sudden rise in IL-6 level over the first hours after drug infusion was expected. The overall rate of infective complications was common (around 70%), but the proportion of severe events is relatively low (3%).

Comment: TCZ use resulted potentially effective on COVID-19 in terms of overall survival. As with the previous study (see above) caution is warranted given the potential occurrence of adverse events and secondary infections.

Factors Associated with Cloth Face Covering Use Among Adults During the COVID-19 Pandemic — United States, April and May 2020

MMWR early release July 14, 2020

Absence of Apparent Transmission of SARS-CoV-2 from Two Stylists After Exposure at a Hair Salon with a Universal Face Covering Policy — Springfield, Missouri, May 2020

MMWR early release July 14, 2020

Researchers surveyed 400 U.S. adults in April and another 400 in May about whether they used cloth face coverings when they left the house in the past week. The prevalence of face mask-wearing increased from 62% to 76% overall, with increases reported in all socioeconomic groups. Lower rates of mask-wearing in May were seen in the following groups: people in their 40s (68%), people with lower incomes, and people living with others at no cost (57%).

A separate study in *MMWR* describes the lack of SARS-CoV-2 transmission at a Missouri hair salon where face masks were required by city ordinance. Two stylists tested positive for SARS-CoV-2. Before their results came back, they saw 139 customers while symptomatic. Of the 100 clients who were interviewed, 98% were also wearing face coverings. No clients developed symptoms. Four household contacts of one stylist tested positive.



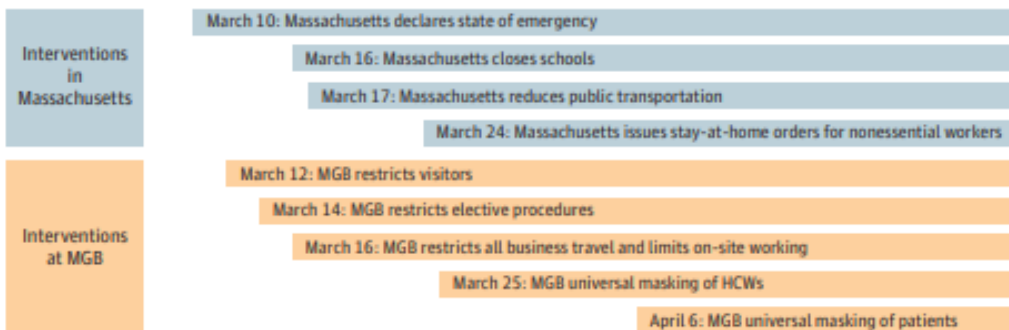
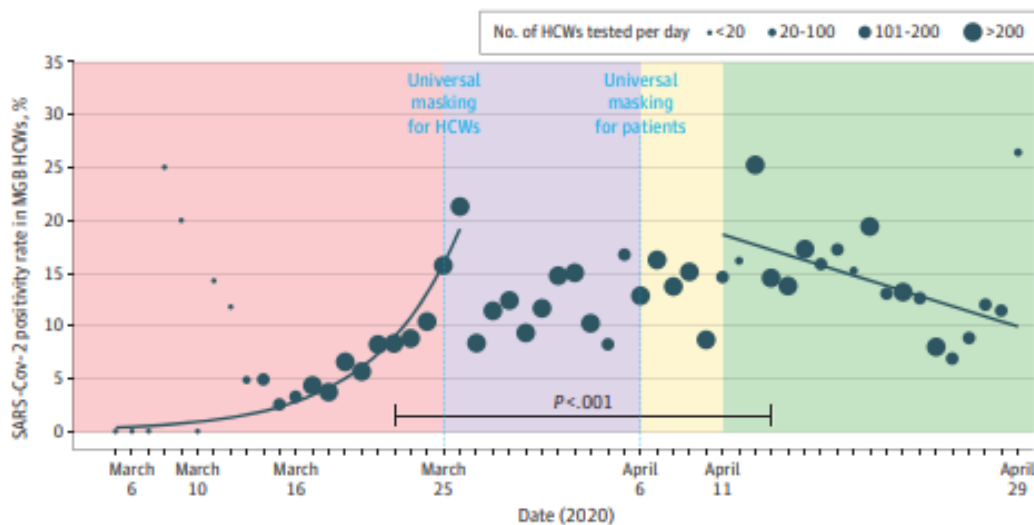
Comment: Previous studies show that both surgical masks and homemade cloth face coverings can reduce the aerosolization of virus into the air and onto surfaces. Although SARS-CoV-2 is spread largely through respiratory droplets when an ill person coughs or sneezes, data suggest that viral shedding starts during the 2-to-3-day period before symptom onset, when viral loads may be at their highest. Although the rate of transmission of SARS-CoV-2 from presymptomatic patients and asymptomatic persons is not entirely

unclear, these persons likely contribute to the spread of SARS-CoV-2. With the potential for presymptomatic and asymptomatic transmission, widespread adoption of policies requiring face coverings in public settings should be the new norm to reduce the impact and magnitude of additional waves of COVID-19.

Association Between Universal Masking in a Health Care System and SARS-CoV-2 Positivity Among Health Care Workers

JAMA online July 14, 2020

Mass General Brigham (MGB) is the largest health care system in Massachusetts, with 12 hospitals and more than 75 000 employees. In March 2020, MGB implemented a multipronged infection reduction strategy involving systematic testing of symptomatic HCWs and universal masking of all HCWs and patients with surgical masks. This study assessed the association of hospital masking policies with the SARS-CoV-2 infection rate among HCWs. In this brief report researchers report a reduction in SARS-CoV-2 positivity rates among healthcare workers at Mass General Brigham after universal masking was put into place, from 14.7% to 11.5%.



Comment: The decrease in HCW infections may have been confounded by other interventions inside and outside of the health care system (see above), such as restrictions on elective procedures, social distancing measures, and increased masking in public spaces, which are limitations of this study. Despite these local and statewide measures, the case number continued to increase in Massachusetts throughout the study period, suggesting that the decrease in the SARS-CoV-2 positivity rate in MGB HCWs took place before the decrease in the general public. Randomized trials of universal masking of HCWs during a pandemic are likely not feasible or ethical. Nonetheless, these results support universal masking as part of a multipronged infection reduction strategy in health care settings. Most hospitals have implemented universal masking. CDC Director Robert Redfield and other agency officials conclude in a *JAMA* editorial: "At this critical juncture when COVID-19 is resurging, broad adoption of cloth face coverings is a civic duty, a small sacrifice reliant on a highly effective low-tech solution that can help turn the tide favorably in national and global efforts against COVID-19."

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

N Engl J Med published online July 14, 2020 article provided by Malar Narayanan
The candidate vaccine mRNA-1273 encodes the stabilized prefusion SARS-CoV-2 spike protein. Forty-five healthy adults were given two injections of the vaccine (at 25-, 100-, or 250- μ g), spaced 28 days apart. All participants experienced seroconversion for binding antibodies by day 15. In the two higher doses, the median magnitude of antibody responses after the first vaccination was similar to what was observed in samples of convalescent serum. After the second vaccination, all dose groups had antibody values that were in the top quartile for convalescent serum. T-cell response was also observed. Neutralizing antibodies were present.

None of the patients experienced serious adverse events, although one patient developed hives after the first dose. Systemic adverse events were more common after the second dose and occurred in all patients who received the highest dose. One patient in the 250- μ g group developed a fever of 39.6° C (103° F).

Comment: The mRNA-1273 vaccine induced anti-SARS-CoV-2 immune responses in all participants, and no trial-limiting safety concerns were identified to date. These findings support further testing of this vaccine. The T-cell response may be an especially important component. Studies of mRNA-1273 in mice show that the structurally defined spike antigen induces robust not just neutralizing activity but the gene-based delivery promotes Th1-biased responses, including CD8 T cells that protect against virus replication in lung and nose without evidence of immunopathology.

(<https://www.biorxiv.org/content/10.1101/2020.06.11.145920v1>). It is important to note that mRNA-1273 also induces Th1-biased CD4 T-cell responses in humans.