COVID-19 Update February 15, 2021

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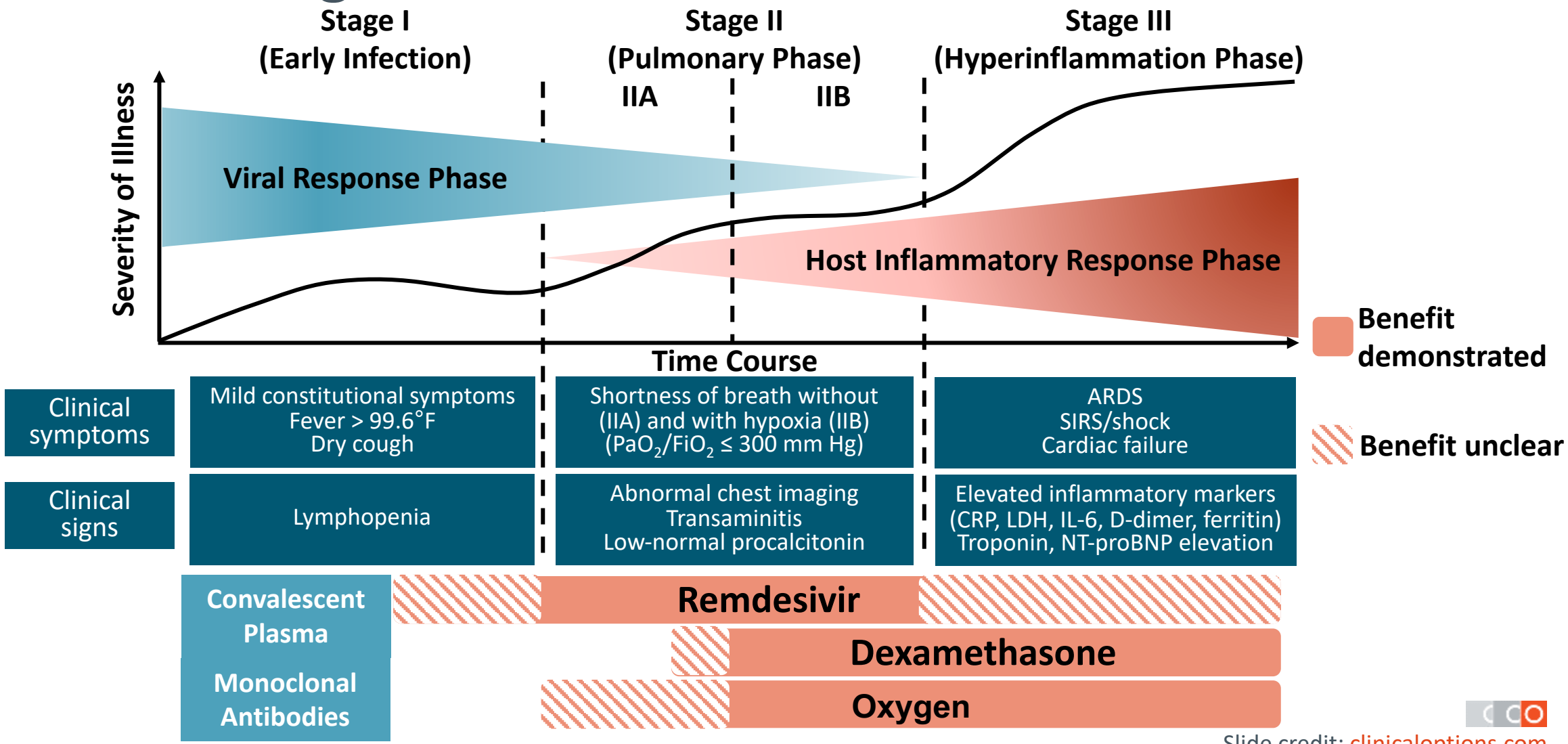
Outline

- Treatment Update
- Mask Update
- Mutant Variants Update
- Population testing of SARS-CoV-2
- Antigen vs PCR for evaluating the risk of SARS-CoV-2 transmission in symptomatic patients.

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



Slide credit: clinicaloptions.com

Siddiqi. J Heart Lung Transplant. 2020;39:405.

Monoclonal Antibodies for COVID-19

Original Investigation

ONLINE FIRST FREE

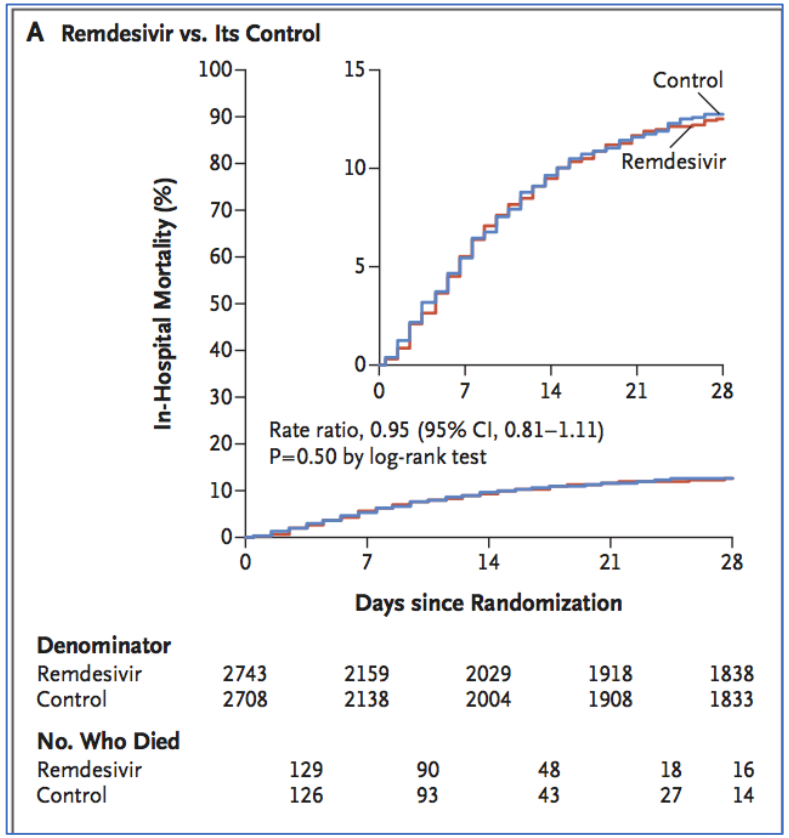
January 21, 2021

Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19

A Randomized Clinical Trial

- **Conclusions and Relevance**
  - Among nonhospitalized patients with mild to moderate COVID-19 illness, treatment with bamlanivimab and etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11;
  - No significant difference in viral load reduction was observed for bamlanivimab monotherapy.
  - Further ongoing clinical trials will focus on assessing the clinical benefit of antispike neutralizing antibodies in patients with COVID-19 as a primary end point.

Repurposed Antiviral Drugs for Covid-19



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 11, 2021 VOL. 384 NO. 6

Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results

WHO Solidarity Trial Consortium*

On 20 November 2020, the WHO published an update of its "Therapeutics and COVID-19: Living Guideline" . In this guideline, the WHO

"suggests against administering remdesivir in addition to standard care, in hospitalized patients with COVID-19, regardless of disease severity" (conditional recommendation).

Should Remdesivir Be Used for the Treatment of Patients With COVID-19? Rapid, Living Practice Points From the American College of Physicians (Version 2)

Consider Remdesivir for 5 Days to Treat Hospitalized Patients With COVID-19 Who Do Not Require Mechanical Ventilation or ECMO

A 5-day course of remdesivir may be superior to a 10-day course for the following outcomes, with no evidence of increased harm with the shorter duration:

- **Mortality** (slight reduction)
- **Recovery** (modest increase)
- **Time to recovery** (slight reduction)
- **Clinical improvement** (modest increase)
- **Proportion of patients on invasive mechanical ventilation or ECMO at follow-up** (slight reduction).

Consider Extending the Use of Remdesivir to 10 Days to Treat Hospitalized Patients With COVID-19 Who Require Mechanical Ventilation or ECMO Within a 5-Day Course

With limited availability of other effective treatments to manage hospitalized patients with COVID-19, extending treatment to 10 days is a consideration, particularly for patients who have not demonstrated any adverse effect profile while receiving the 5-day course.

Ann Int Med, Feb 9, 2021

Should Remdesivir Be Used for the Treatment of Patients With COVID-19? Rapid, Living Practice Points From the American College of Physicians (Version 2)

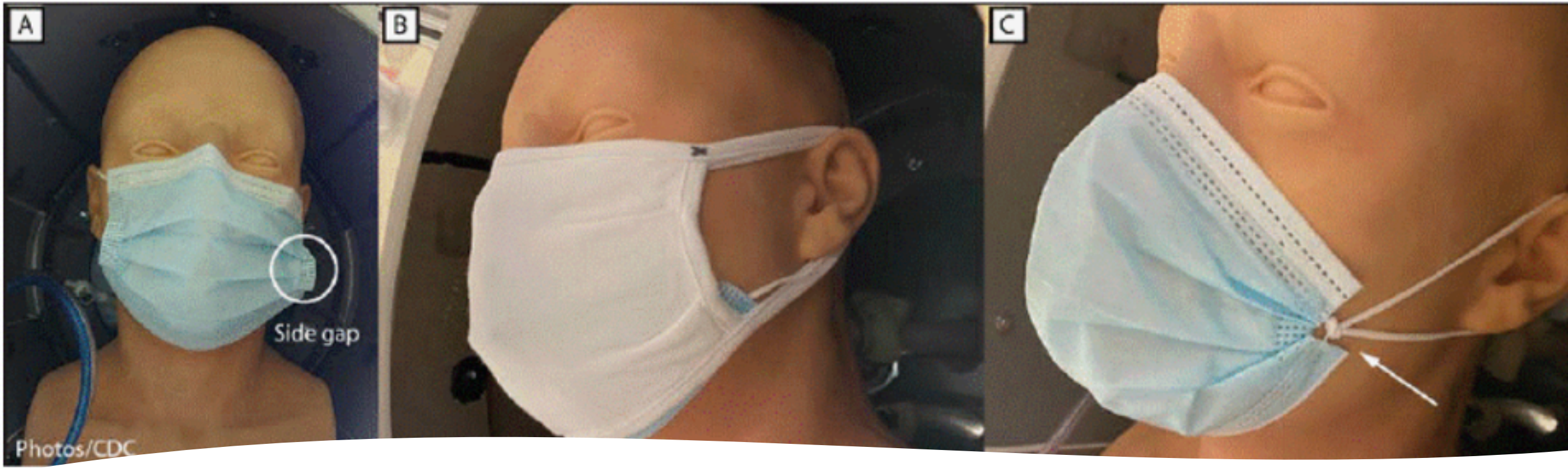
- **Avoid Initiating Remdesivir to Treat Hospitalized Patients With COVID-19 Who Are Already on Mechanical Ventilation or ECMO**
  - Although the evidence base is limited, the SMPC considers these findings a signal that the potential harms of remdesivir may outweigh the potential benefits in patients who are receiving invasive mechanical ventilation or ECMO at baseline and cautions against initiating remdesivir treatment in these patients.

Ann Int Med, Feb 9, 2021

Methodological Differences From the WHO Guideline

- The WHO guideline is based on a network meta-analysis comparing multiple drug treatments.
  - The ACP practice points were developed with the sole focus of evaluating the benefits and harms of remdesivir in hospitalized patients .
- The WHO guideline considered the effect of remdesivir regardless of its duration of use.
  - ACP practice points focused specifically on the effectiveness and comparative effectiveness of differing durations of remdesivir use—5 days and 10 days compared with placebo or standard care or the other duration.
- The WHO guideline did not make a recommendation based on disease severity because its network meta-analysis team judged the credibility to be insufficient when assessing the variation in effectiveness of remdesivir by disease severity
  - ACP provides clinical advice based on disease severity (baseline oxygen requirements). ACP considered subgroup analyses reported within the individual studies and those done de novo by the authors of the supporting rapid, living systematic review

Ann Int Med, Feb 9, 2021

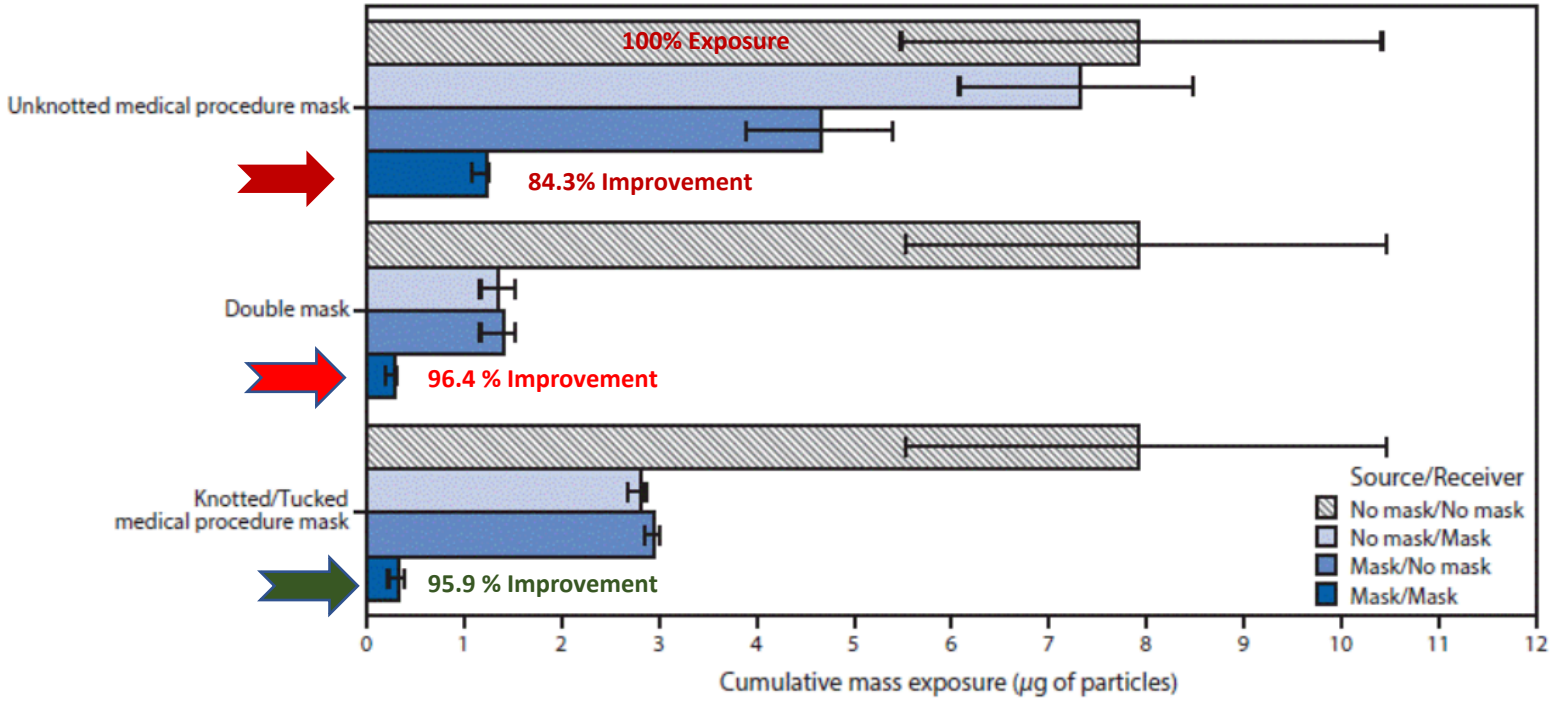


Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021

- **1. Masks tested, including *A,* unknotted medical procedure mask; *B,* double mask (cloth mask covering medical procedure mask); and *C,* knotted/tucked medical procedure mask**

Brooks JT, Beezhold DH, Noti JD, et al. Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021. MMWR Morb Mortal Wkly Rep. ePub: 10 February 2021

Mean cumulative exposure* for various combinations of no mask, double masks, and unknotted and knotted/tucked medical procedure masks



Brooks JT, Beezhold DH, Noti JD, et al. Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021. MMWR Morb Mortal Wkly Rep. ePub: 10 February 2021

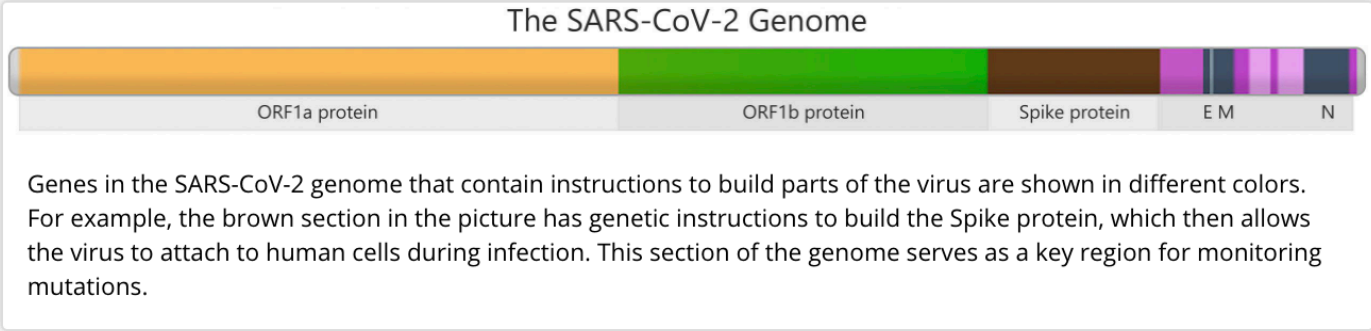
- * To an aerosol of 0.1–7 μm potassium chloride particles (with 95% confidence intervals indicated by error bars) measured at mouthpiece of receiver headform configured face to face 6 ft from a source headform, with no ventilation and replicated 3 times. Mean improvements in cumulative exposures compared with no mask/no mask (i.e., no mask wearing, or 100% exposure) were as follows: ***unknotted medical procedure mask*:** no mask/mask = 7.5%, mask/no mask = 41.3%, mask/mask = **84.3%**; ***double mask*:** no mask/mask = 83.0%, mask/no mask = 82.2%, **mask/mask = 96.4%; *knotted/tucked medical procedure mask*:** no mask/mask = 64.5%, mask/no mask = 62.9%, **mask/mask = 95.9%.**
- † Double mask refers to a three-ply medical procedure mask covered by a three-ply cloth cotton mask. A knotted and tucked medical procedure mask is created by bringing together the corners and ear loops on each side, knotting the ears loops together where they attach to the mask, and then tucking in and flattening the resulting extra mask material to minimize the side gaps.

In addition to consistently and correctly wearing masks, everyone should continue to take these important steps to reduce the spread of COVID-19

- Stay **at least 6 feet (at least 2 arm lengths) away** from others who do not live with you
- **Avoid crowds**
- Avoid **poorly ventilated** indoor spaces
- Stay home when you are sick with COVID-19
- **Wash hands** frequently with soap and water for at least 20 seconds (or use hand sanitizer containing at least 60% alcohol)
- **Get vaccinated** when the vaccine is available to you
- **Get tested** if you have signs or symptoms of COVID-19, or if you think you may have been exposed to someone

SARS-CoV-2 VARIANTS

- **SARS-CoV-2 mutates regula**rly, acquiring about one new mutation in its genome every two weeks.
- **Many mutations are silent** because they produce a three-letter codon that translates to the same amino acid (i.e., they are “synonymous”).
- **Other mutations may change the codon** in a way that leads to an amino acid change (i.e., they are “non-synonymous”), but this amino acid substitution does not impact the protein’s function.



Genes in the SARS-CoV-2 genome that contain instructions to build parts of the virus are shown in different colors. For example, the brown section in the picture has genetic instructions to build the Spike protein, which then allows the virus to attach to human cells during infection. This section of the genome serves as a key region for monitoring mutations.

https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

What are the potential consequences of these mutations?

- ***Ability to spread more quickly in humans***
- ***Ability to cause either milder or more severe disease in humans***
- ***Ability to evade detection by specific diagnostic tests***
- ***Decreased susceptibility to therapeutic agents such as monoclonal antibodies***
- ***Ability to evade vaccine-induced immunity***

Implications of the Emerging SARS-CoV-2 Variant VOC 202012/01
https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-emerging-variant.html

D614G identified in January 2020

- This variant of SARS-CoV-2 had a **D614G** substitution (Aspartic acid for Glycine) in the gene encoding the spike protein
- By June 2020, this variant became the dominant strain circulating globally
- Studies in human respiratory cells and in animal models demonstrated that the strain has **increased infectivity and transmission**
- **It does not cause more severe illness** or alter the effectiveness of existing laboratory diagnostics, therapeutics, vaccines, or public health preventive measures.

https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

SARS-CoV-2 Variants

Jan. 2020

SARS-CoV-2 **D614G** variant emerged

Aug. 2020

Denmark reports

SARS-CoV-2 **"Cluster 5"** variant

Dec. 2020

UK reports

SARS-CoV-2 **VOC 202012/01** variant

AKA B.1.1.7.

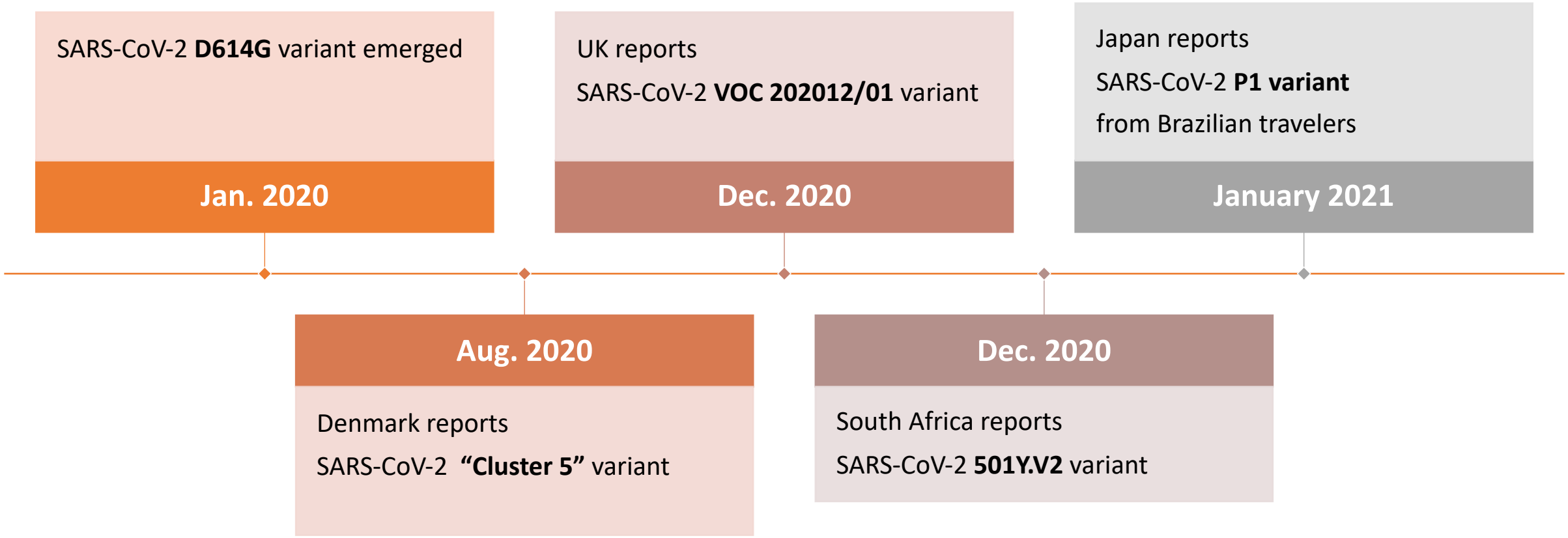
Dec. 2020

South Africa reports

SARS-CoV-2 **501Y.V2** variant

https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

SARS-CoV-2 Variants



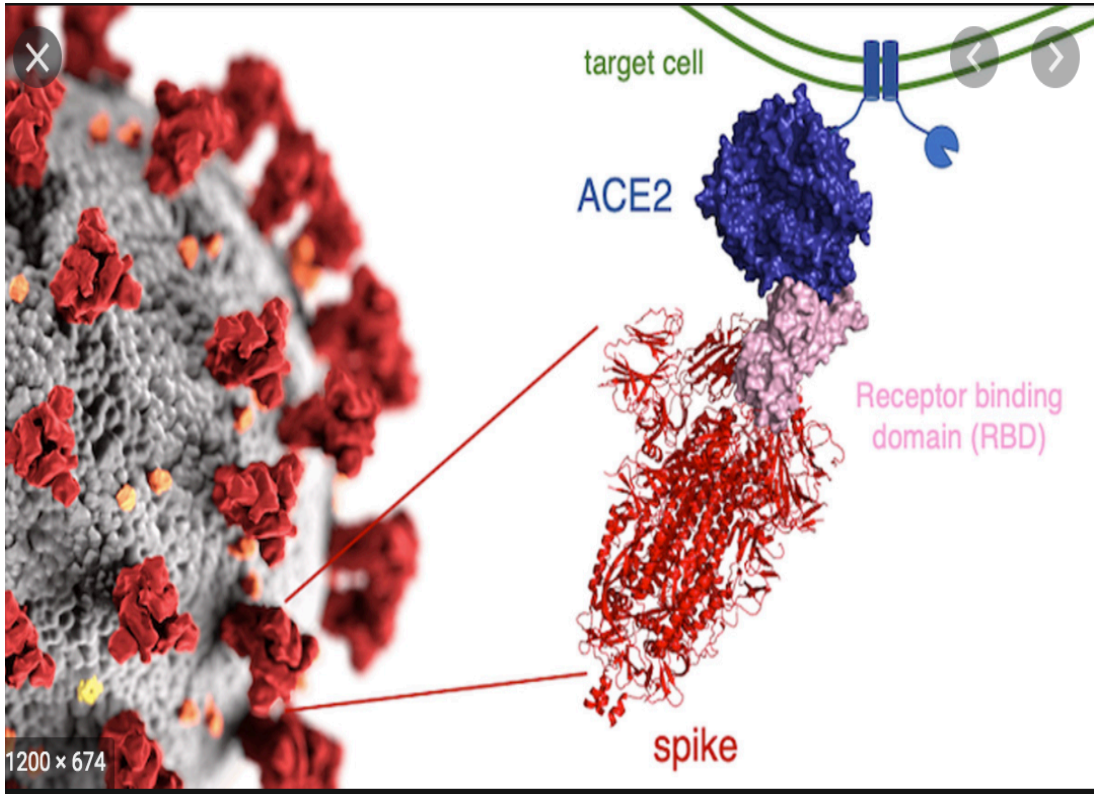
https://www.who.int/csr/don/31-december-2020-sars-cov2-variants/en/

SARS-CoV-2 Variants

Variant Mutations

- The **N501Y** mutation occurs in the receptor-binding domain of the spike protein S1 section at position 501, where asparagine (N) has been replaced with tyrosine (Y).
    - The resulting mutated protein may bind more tightly to the human host cell ACE2 receptor, but it is not known if that tighter binding is responsible for any significant clinical differences in virulence.
- The **E484K** mutation is also in the host ACE2 receptor-binding domain of the spike protein.
    - It has been investigated for possible contributions to increased transmission and has been associated with lesser vaccine efficacy.
- The **K417N** and **K417T** mutations occur at the same site on the RNA genome and affect the host ACE2 receptor-binding domain of the spike protein.
    - Concern for escape neutralization by antibodies directed to the ACE2-binding protein.

Receptor Binding Domain



SARS-CoV-2 Variants

Name (Pangolin)	Name (Nextstrain)	First Detected	Cases in the US	Countries Reporting Cases	Key Mutations	Transmissibility Rate
B.1.1.7	20I/501Y.V1	United Kingdom	Y	70	• 69/70 deletion • 144Y deletion • N501Y • A570D • D614G • P681H	~50% increase [14,15]
P.1	20J/501Y.V3	Japan/ Brazil	Y	>4	• E484K • K417N/T • N501Y • D614G	Not determined
B.1.351	20H/501.V2	South Africa	Y	>30	• K417N • E484K • N501Y • D614G	Not determined

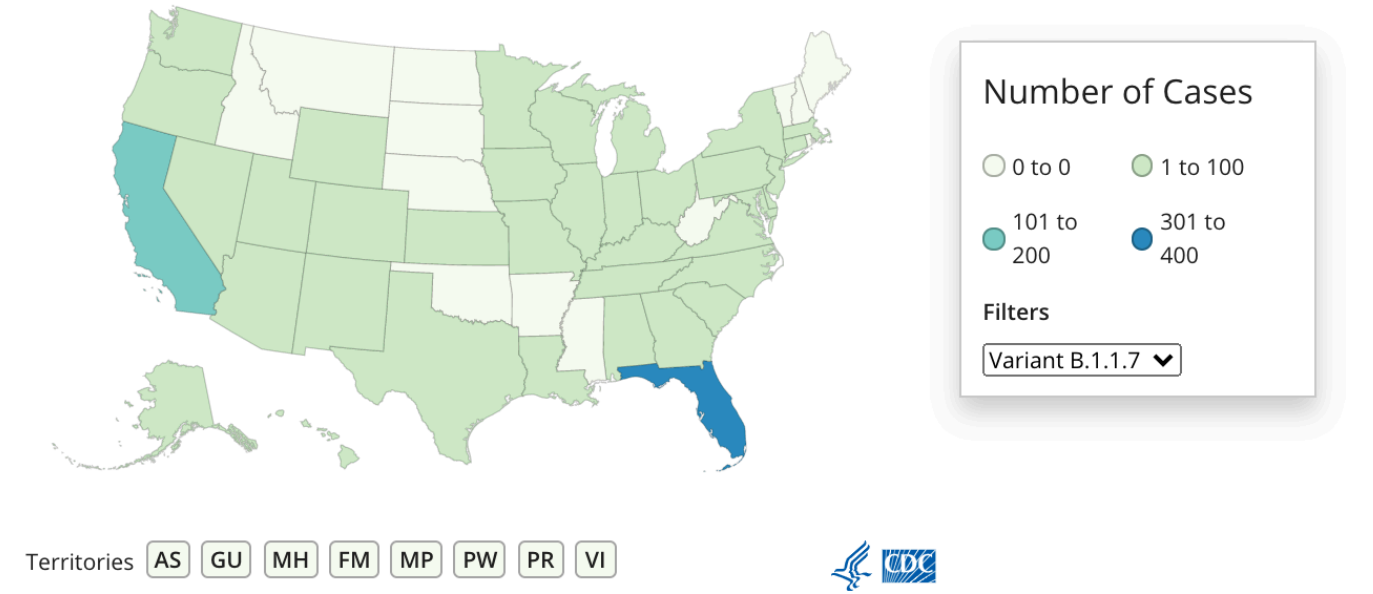
- https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

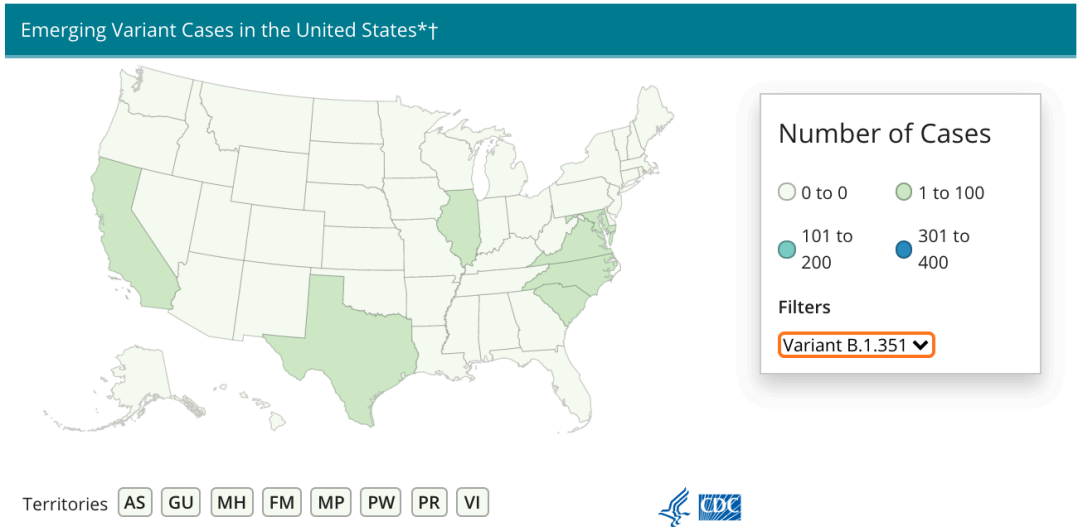
US COVID-19 Cases Caused by Variants

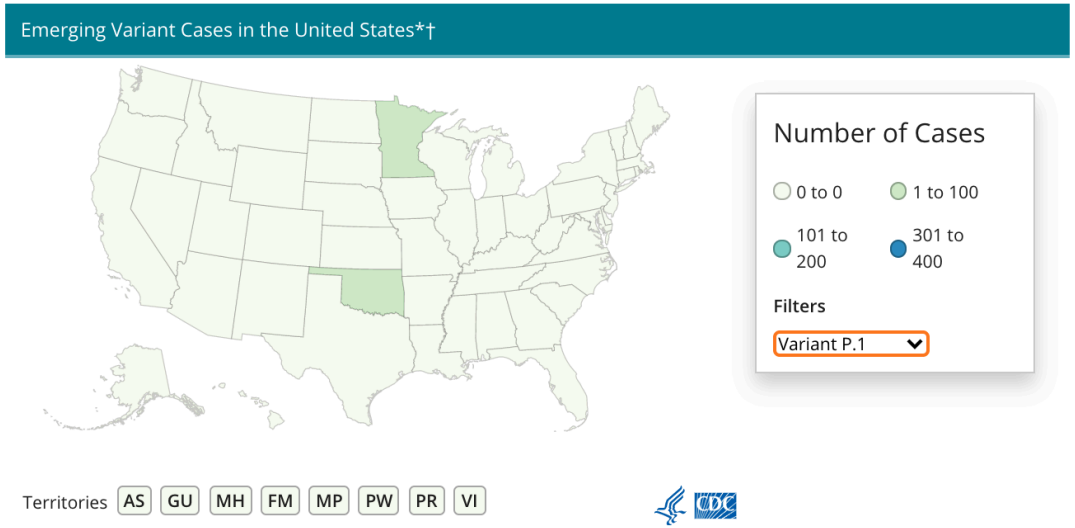
- https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

Variant	Reported Cases in US	Number of States Reporting
B.1.1.7	981	37
B.1.351	13	5
P.1	3	2

Emerging Variant Cases in the United States*†







US COVID-19 Cases Caused by Variants

- https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/variant-surveillance/variant-info.html

mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants

- **Background**
  - The Moderna mRNA-1273 vaccine has d ~94% efficacy in a Phase 3 study
  - The emergence of SARS-CoV-2 variants with mutations in the spike protein, from the United Kingdom (B.1.1.7) and Republic of South Africa (B.1.351), has led to lower neutralization from convalescent serum and resistance to certain monoclonal antibodies.
- **Methods**
  - Using two assays expressing spike variants of 20E (EU1), 20A.EU2, D614G-N439, mink cluster 5, B.1.1.7, and B.1.351 variants, we assessed the neutralizing capacity of sera from human subjects or non-human primates (NHPs) that received mRNA-1273.
- **Results:**
  - No significant impact on neutralization against the B.1.1.7 variant was detected in either case, however reduced neutralization was measured against the mutations present in B.1.351.
  - Despite the observed decreases, the antibody titers in human vaccinee sera against the B.1.351 variant remained at ~1/300. These data demonstrate reduced but still significant neutralization against the full B.1.351 variant following mRNA-1273 vaccination.

Kai Wu1*, et al. 1Moderna Inc., Cambridge, MA, USA National Institutes of Health, National Institute of Allergy and Infectious Diseases, VaccineResearch Center, Bethesda, MD, USA

bioRxiv preprint doi: https://doi.org/10.1101/2021.01.25.427948; this version posted January 25, 2021.

Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K, and N501Y variants by 2 BNT162b2 vaccine-elicited sera

- We engineered three SARS-CoV-2 viruses containing key spike mutations from the newly emerged United Kingdom (UK) and South African (SA) variants: N501Y from UK and SA; 69/70-deletion+N501Y+D614G from UK; and E484K+N501Y+D614G from SA.

- Neutralization geometric mean titers (GMTs) of twenty BTN162b2 vaccine-elicited human sera against the three mutant viruses were 0.81- to 1.46-fold of the GMTs against parental virus, indicating small effects of these mutations on neutralization by sera elicited by two BNT162b2 doses.

doi: https://doi.org/10.1101/2021.01.27.427998

What are the potential consequences of these mutations?

- ***Ability to spread more quickly in humans.***
  - D614G, has this property to spread more quickly as does B.1.1.7. (UK strain)
- ***Ability to cause either milder or more severe disease in humans.***
  - There is no evidence that B.1.1.7. produces more severe illness than other SARS-CoV-2
- ***Ability to evade detection by specific diagnostic tests.***
  - Most commercial polymerase chain reaction (PCR) tests have multiple targets to detect the virus, such that even if a mutation impacts one of the targets, the other PCR targets will still work.
- ***Decreased susceptibility to therapeutic agents such as monoclonal antibodies.***
- ***Ability to evade vaccine-induced immunity***
  - FDA-authorized vaccines are “polyclonal,” producing antibodies that target several parts of the spike protein.
  - Following mRNA-1273 vaccination no significant impact on neutralization against the B.1.1.7 variant was detected, reduced but still significant neutralization against the full B.1.351 variant
  - In a non peer reviewed publication serum from BTN162b2 vaccinees had neutralizing effect against engineered SARS-C0V-2 variants with the mutations of interest.

Implications of the Emerging SARS-CoV-2 Variant VOC 202012/01
https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-emerging-variant.html

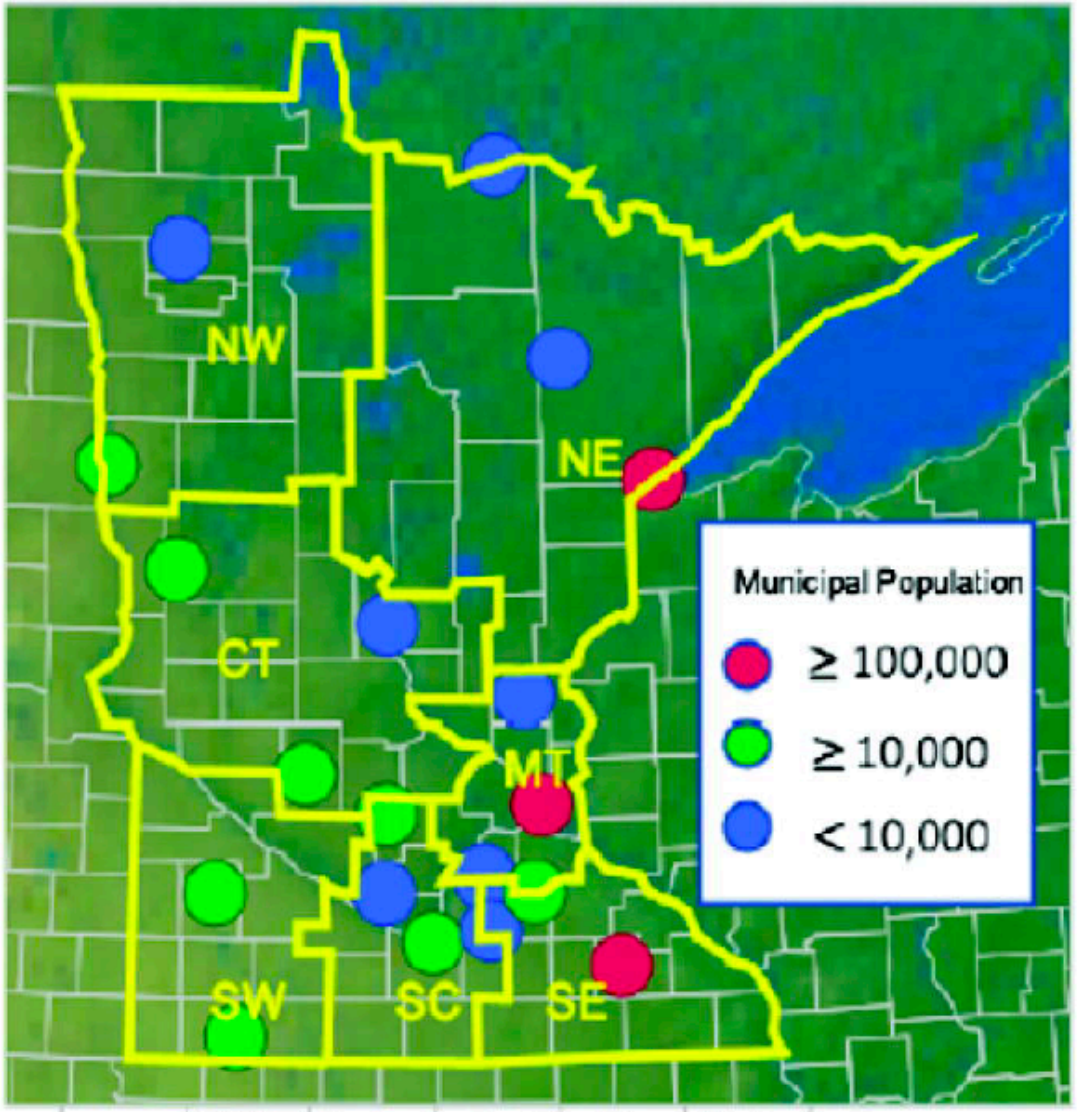
Predictive power of SARS-CoV-2 wastewater surveillance for diverse populations across a large geographical range

- What have other found using wastewater surveillance for SARS-CoV-2
  - Focus on major population centers (≥100,000 persons)
  - Lack of longitudinal breadth
  - Inconsistent use of reporting metrics and normalization across studies
- In this study, a normalized and standardized index for reporting wastewater SARS-CoV-2 levels was developed and It considers:
  - Differences in population size
  - Negates the contributions of variation in water flow
  - Treatment facility size

medRxiv preprint doi:https://doi.org/10.1101/2021.01.23.21250376; this version posted January 25, 2021

Predictive power of SARS-CoV-2 wastewater surveillance for diverse populations across a large geographical range:

- Our primary assumption was that increases in the number of COVID-19 infections in given city would increase the amount of SARS-CoV-2 RNA detected in that city's wastewater.
- There are several factors that could affect the concentration of SARS-CoV-2 in the wastewater systems
  - Flow rate
  - Population
  - Size of WWTP



WWTPs included in the pilot study

Predictive power of SARS-CoV-2 wastewater surveillance for diverse populations across a large geographical range

- **Background:**
  - The COVID-19 pandemic has exacerbated the disparities in healthcare delivery in the US.
  - Limited access to COVID-19 testing, makes it difficult to track the spread and impact of COVID-19 in early days of the outbreak.
- **Methods:**
  - Monitored SARS-CoV-2 RNA at the population-level using municipal wastewater influent from 19 cities across the state of Minnesota during the COVID-19 outbreak in Summer 2020.
  - Viral RNA was detected in wastewater continually for 20-weeks for cities ranging in populations from 500 to >1, 000, 000.
  - Using a novel indexing method, we were able to compare the relative levels of SARS-CoV-2 RNA for each city during this sampling period.
- **Results:**
  - Viral RNA trends appeared to precede clinically confirmed cases across the state by 15- 17 days.
  - At the regional level, new clinical cases lagged behind wastewater viral RNA anywhere from 4- 20 days.

Predictive power of SARS-CoV-2 wastewater surveillance for diverse populations across a large geographical range

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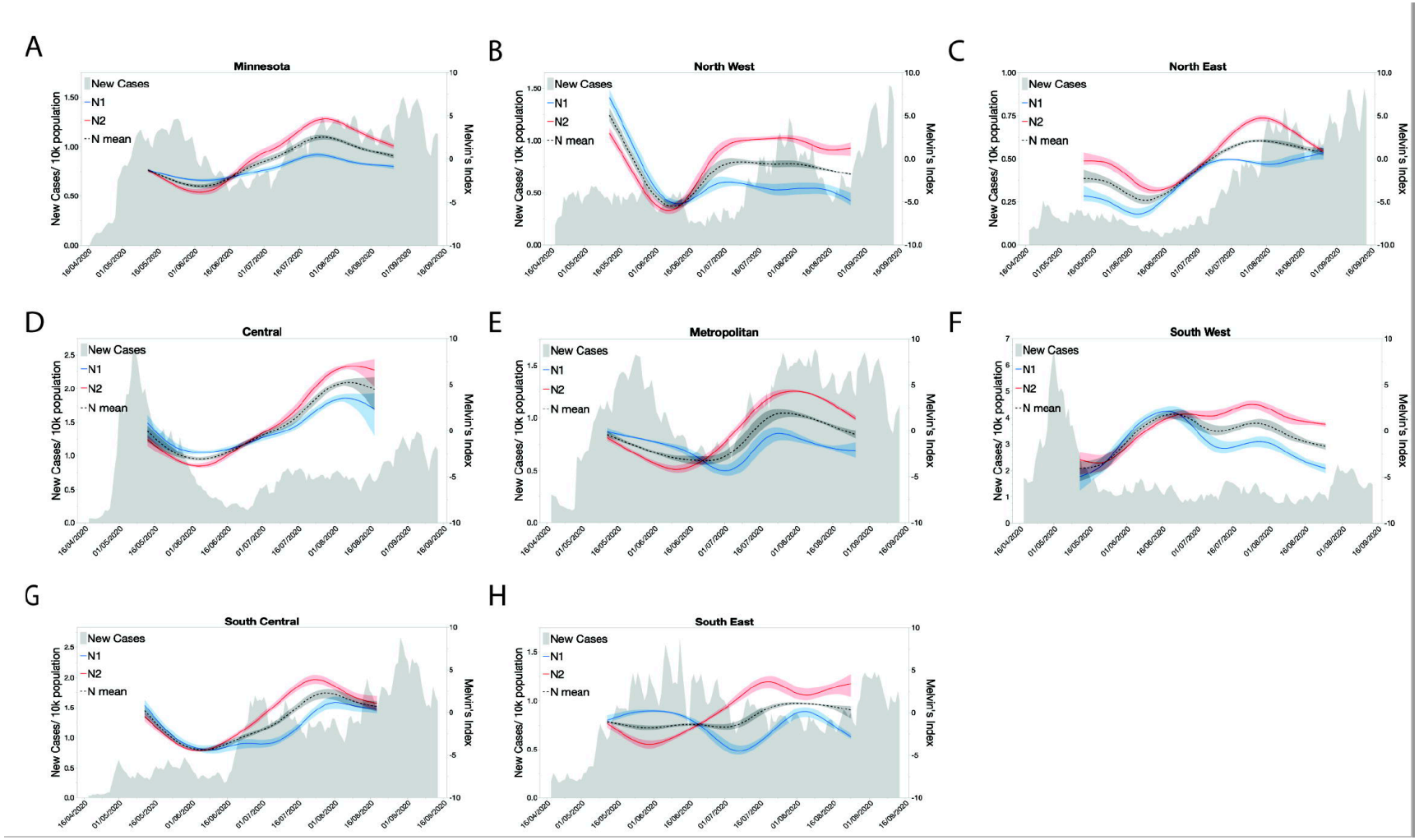
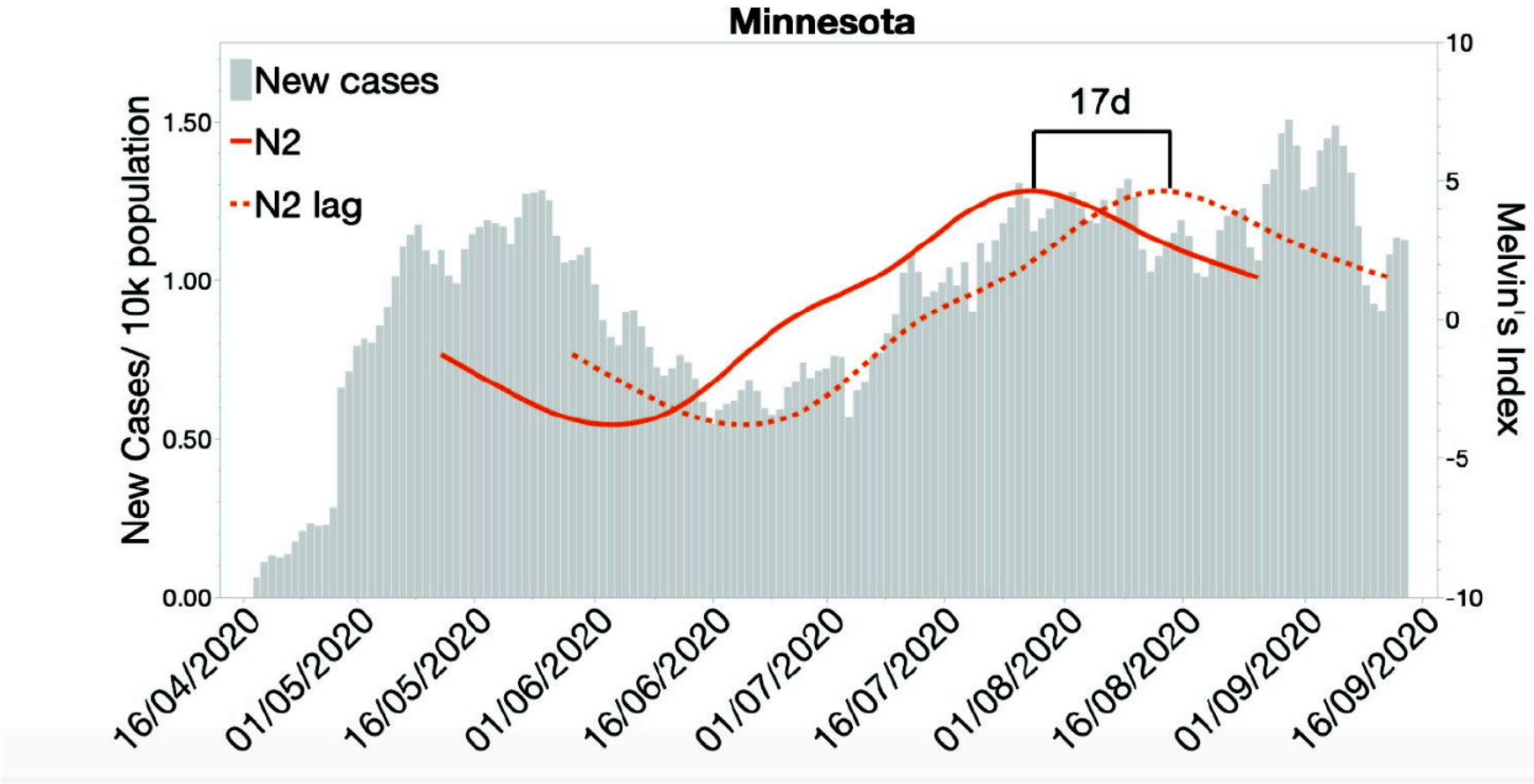
Predictive power of SARS-CoV-2 wastewater surveillance for diverse populations across a large geographical range



Predictive power of SARS-CoV-2 wastewater surveillance for diverse populations across a large geographical range



Predictive power of SARS-CoV-2 wastewater surveillance for diverse populations across a large geographical range: CONCLUSIONS

CID, 2020; DOI: 10.1093/cid/ciaa1706

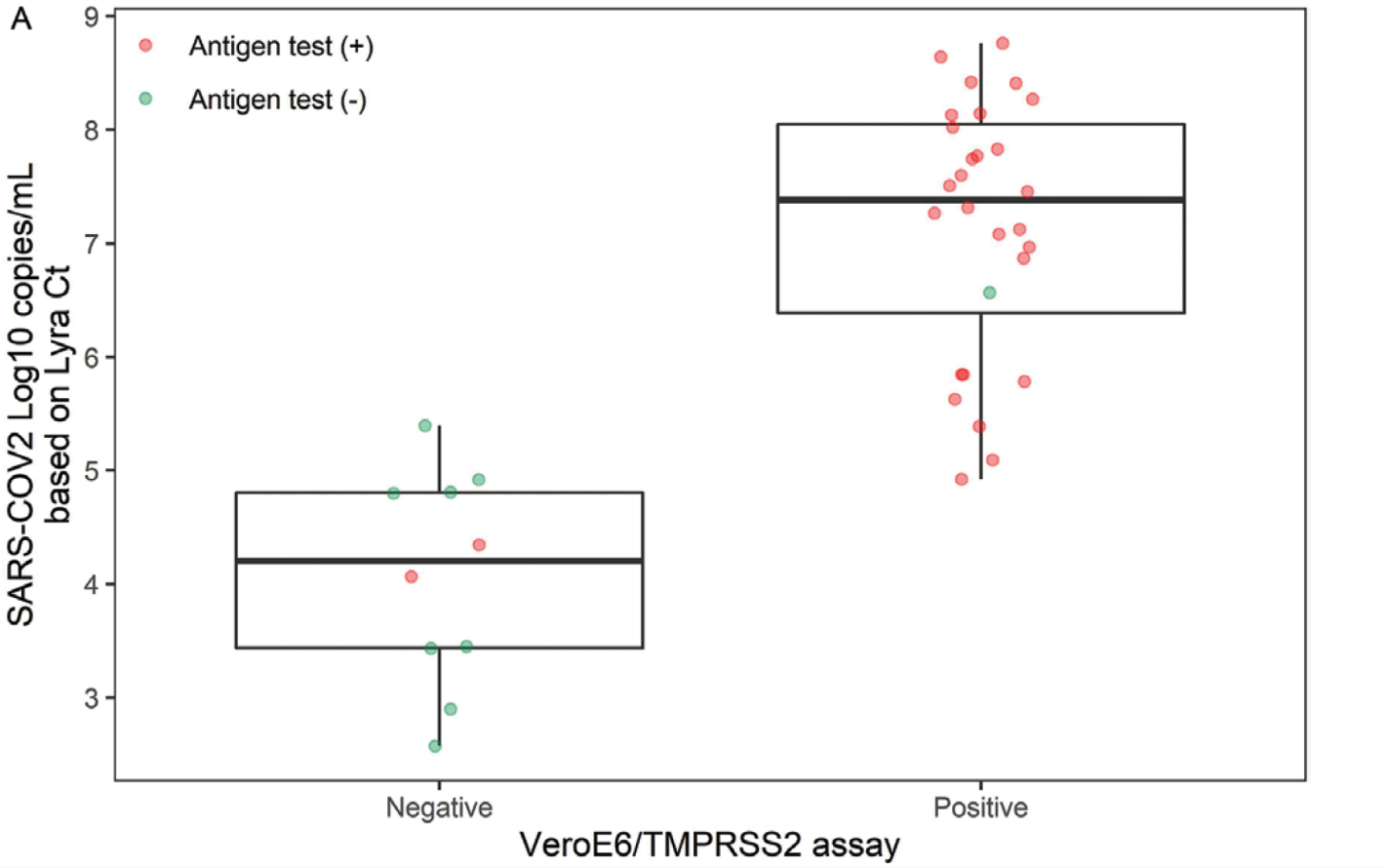
- “Our data illustrates the advantages of monitoring at the population-level to detect outbreaks. Additionally, by tracking infections with this unbiased approach, resources can be directed to the most impacted communities before the need outpaces the capacity of local healthcare systems”.

Antigen-Based Testing but Not Real-Time Polymerase Chain Reaction Correlates With Severe Acute Respiratory Syndrome Coronavirus 2 Viral Culture

CID, 2020; DOI: 10.1093/cid/ciaa1706

- **Background.**
  - Individuals can test positive forSARS-CoV-2 by molecular assays following the resolution of their clinical disease.
  - Recent studies indicate that SARS-CoV-2 antigen–based tests are likely to be positive early in the disease course, when there is an increased likelihood of high levels of infectious virus.
- **Methods.**
  - URT specimens from 251 participants with COVID-19 symptoms (≤7 days from symptom onset) were prospectively collected and tested with a lateral flow antigen test and a rt-PCR assay for detection of SARS-CoV-2. Specimens from a subset of the study specimens were utilized to determine the presence of infectious virus in the VeroE6TMPRSS2 cell culture model.

Antigen-Based Testing but Not Real-Time Polymerase Chain Reaction Correlates With Severe Acute Respiratory Syndrome Coronavirus 2 Viral Culture



CID, 2020; DOI: 10.1093/cid/ciaa1706

Antigen-Based Testing but Not Real-Time Polymerase Chain Reaction Correlates With Severe Acute Respiratory Syndrome Coronavirus 2 Viral Culture

Table 1. Performance of the BD Veritor Antigen Test and the Quidel Lyra Real-Time Polymerase Chain Reaction Assay Compared to Severe Acute Respiratory Syndrome Coronavirus 2 Viral Culture Using Specimens Collected Within 7 Days of Symptom Onset

Performance Values	Antigen Test Performance	rt-PCR Performance
PPA	96.4 (82.3–99.4)	100 (87.7–100)
NPA	98.7 (96.1–99.7)	95.5 (91.1–97.8)
PPV	90.0 (76.3–97.6)	73.7 (60.8–85.3)
NPV	99.5 (97.7–100)	100 (98.4–100)
OPA	98.4 (96.0–99.4)	96.0 (92.8–97.8)
Culture (+)/test (+)	27	28
Culture (–)/test (+)	3	10
Culture (+)/test (–)	1	0
Culture (–)/test (–)[a]	220	213

Prevalence was 11.2%.

Prevalence was 11.2%. Abbreviations: NPA, negative percentage agreement; NPV, negative predictive value; OPA, Overall percentage agreement; PPA, positive percentage agreement; PPV, positive predictive Value; rt-PCR, real-time polymerase chain reaction. Includes 176 specimen sets that were rt-PCR and antigen negative, with unavailable culture results

CID, 2020; DOI: 10.1093/cid/ciaa1706

Antigen-Based Testing but Not Real-Time Polymerase Chain Reaction Correlates With Severe Acute Respiratory Syndrome Coronavirus 2 Viral Culture

CID, 2020; DOI: 10.1093/cid/ciaa1706

- **Results.**
  - ***The antigen test demonstrated a higher positive predictive value (90%) than rt-PCR (70%)*** when compared to culture positive results.

- **Conclusions**
  - The correlation between SARS-CoV-2 antigen and SARS-CoV-2 culture positivity represents a significant advancement in determining the risk for potential transmissibility beyond that which can be achieved by detection of SARS-CoV-2 genomic RNA.
  - SARS-CoV-2 antigen testing can facilitate low-cost, scalable, and rapid time-to-result, while providing good risk determination of those who are likely harboring infectious virus, compared to rt-PCR.