New Hampshire Coronavirus Disease 2019 Weekly Call for Healthcare Providers and Public Health Partners

January 21, 2021

Ben Chan
Elizabeth Talbot
Beth Daly
Lindsay Pierce

Thursday noon-time partner calls will focus on science, medical, and vaccine updates geared towards our healthcare partners
Agenda

• Epidemiology Update


• [MMWR Publication](https://www.cdc.gov/mmwr/index.html): Evaluation of Abbott BinaxNOW rapid antigen test

• Pfizer-BioNTech vaccine *vs.* VOC B.1.1.7 (“UK variant”)

• Therapeutic update: Ivermectin

• Questions & Answers (Q&A)
National Daily Incidence of COVID-19
Number of New COVID-19 Cases per Day in NH

https://www.nh.gov/covid19/dashboard/overview.htm#dash
% of Tests (Antigen and PCR) Positive for COVID-19 (7-Day Average)
Number of People Hospitalized with COVID-19 Each Day in NH (Hospital Census)
In the last 7 days:
• 65 people have died
• 34 (52%) associated with a LTCF
• 31 (48%) are community-associated
Abbott BinaxNOW Antigen Test
Evaluation of Abbott BinaxNOW Rapid Antigen Test for SARS-CoV-2 Infection at Two Community-Based Testing Sites — Pima County, Arizona, November 3–17, 2020

• Abbott BinaxNOW antigen test card was compared to PCR
• Specimen collection occurred at two community testing centers in Pima County Arizona, November 2020
• 3,419 paired specimens – bilateral anterior nares swab for antigen testing & bilateral nasopharyngeal swab for PCR:
  – 2,592 (76%) were asymptomatic (no symptoms of COVID-19)
  – 827 (24%) were symptomatic (one or more symptoms of COVID-19)
## Asymptomatic Testing (N=2,592)

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- **Sensitivity**: 35.8%
- **Specificity**: 99.8%
- **PPV**: 91.7%
- **NPV**: 96.9%

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<td>Negative</td>
<td>63</td>
<td>651</td>
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Quidel Sofia Antigen Test
(Reviewed on Partner Call 1/7/2021)
Performance of an Antigen-Based Test for Asymptomatic and Symptomatic SARS-CoV-2 Testing at Two University Campuses — Wisconsin, September–October 2020

• Quidel’s Sofia SARS Antigen FIA test was compared to PCR testing (the “gold standard”)
• Occurred on 2 university campuses in Wisconsin
• 1,098 paired nasal swabs including:
  – 871 asymptomatic persons (no symptoms of COVID-19 at time of testing)
  – 227 symptomatic persons (one or more symptoms of COVID-19)
Asymptomatic Testing (N=871)

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- **Sensitivity**: 41.2%
- **Specificity**: 98.4%
- **PPV**: 33.3%
- **NPV**: 98.8%

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<td>7</td>
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<td>Negative</td>
<td>10</td>
<td>840</td>
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<td>8</td>
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Summary

• Both Quidel Sofia and BinaxNOW antigen tests showed very low sensitivity in picking up asymptomatic infection (~35-40%)

• Sensitivity of detecting infection is symptomatic individuals was substantially better (64-80%)

• Abbott BinaxNOW appears to have a lower rate of false positive results – unclear if this is intrinsic to the test, or due to possible user error in more complicated tests (i.e., Quidel Sofia)

• We continue to recommend that antigen tests be used primarily for symptomatic individuals

• Consider PCR-confirmation of a negative antigen test (in someone who is symptomatic) if there is a high pre-test probability/suspicion for COVID-19
New Hampshire’s **Recommendations** for Antigen Testing in Ambulatory Settings (1)

- We continue to recommend that antigen tests be used primarily in ambulatory/outpatient settings to test people with symptoms of COVID-19 (diagnostic purposes):
  
  - A positive antigen test in a symptomatic person should be treated as a true-positive and does not require PCR confirmation
  
  - Clinicians should use clinical judgement when deciding whether to confirm a negative antigen test in symptomatic persons – we recommend reflexing to PCR confirmation in high-risk or high-consequence settings, or if there is high suspicion of COVID-19 based on risk factors or symptoms (e.g., loss of taste or smell)
  
  - A negative test in a symptomatic person in a low-risk setting does **not** require PCR confirmation, and a person can return to school/work once fever-free off meds for 24 hours and other symptoms are improving
New Hampshire’s Recommendations for Antigen Testing in Ambulatory Settings (2)

• We do NOT recommend routine use of antigen testing for asymptomatic persons

• There are settings, however, where antigen testing in asymptomatic individuals may occur in consultation with public health, (e.g., LTCFs, State-sponsored screening/surveillance programs):
  o Any positive antigen result in an asymptomatic person should be confirmed with a PCR-based test as soon as possible after the positive result (ideally same day), but no longer than 48 hours after positive test (and person must isolate)
  o A negative test does not need PCR confirmation (especially if recurring testing is performed)
Clinical Decisions for Phase 1b

Technical Assistance
New Hampshire COVID-19 Vaccination Allocation Plan Summary
January 14, 2021

Phase 1
- Phase 1a (~110,000)
  - High-risk health workers
  - First responders
  - Residents and staff of long-term care and assisted living facilities
- Phase 1b (~325,000)
  - People ≥65 years old
  - Medically vulnerable at significantly higher risk 2 or more conditions (see list)
    - Family caregivers of those medically vulnerable persons, <16 years old, not eligible for vaccine
  - Residents and staff of residential facilities for persons with intellectual and developmental disabilities
  - Corrections officers and staff working in correctional facilities
  - First responders and health workers not already vaccinated

Phase 2
- Phase 2a (~75,000)
  - K-12 school and childcare staff
- Phase 2b (~200,000)
  - People 50 – 64 years old

Phase 3
- Phase 3a (~325,000)
  - Medically vulnerable <50 years old at moderately higher risk with 1 or more conditions (see list)
- Phase 3b (~325,000)
  - Everyone else not already vaccinated

Estimated Timeframe:
- DECEMBER - MARCH
- MARCH - MAY
- MAY AND BEYOND

***Estimated timeframe depends on vaccine doses allocated to New Hampshire from the federal government and vaccine uptake***

Equity is a crosscutting consideration: Vaccine access will be prioritized for geographic areas identified through the COVID-19 Community Vulnerability Index (CCVI).

Phase 1b

- **People ≥ 65 years old**
  - Medically vulnerable
    - Persons at significantly higher risk of morbidity or mortality, with 2 or more conditions (see list)
    - Family caregivers of those medically vulnerable persons, ≤16 years old (not eligible for vaccine)

- **Residents and staff of residential facilities for persons with intellectual and developmental disabilities**

- **Corrections officers and staff working in correctional facilities**

- **Health workers and first responders not already vaccinated**

NH will also allocate 10% of vaccine for disproportionately impacted populations identified through the COVID-19 Community Vulnerability Index (CCVI)
Practical suggestions (not requirements) regarding identifying patients who are at increased risk of severe COVID-19 and death based on the listed conditions intended for Phase 1b prioritization:

- **Cancer**: Patients who have current cancer or who were recently treated for cancer which continues to cause increased susceptibility to severe COVID-19. This category is not intended to include people with a history of cured cancer, even if at risk of recurrence, or people with a family history or genetic testing suggesting increased risk for cancer. Additionally, vaccination for persons with organ or blood cancers should be prioritized over those with superficial non-metastasized skin cancer pending local treatments.

- **Chronic kidney disease**: Patients who have chronic sustained elevated creatinine indicative of renal dysfunction, with associated health consequences such as fluid overload and blood electrolyte abnormalities (e.g., low calcium levels, high potassium levels, and high phosphorus levels), or have been diagnosed end-stage renal disease, those on hemo- or peritoneal-dialysis. We suggest delaying vaccination for patients who have had acute kidney disease due to a reversible condition (e.g., pre-renal azotemia).

- **Chronic obstructive lung disease (COPD) and other high risk pulmonary disease**: Patients who have any of the group of diseases that comprise COPD, including emphysema and chronic bronchitis, or who have other chronic lung diseases that are actively compromising pulmonary function, such as chronic bronchiectasis, idiopathic pulmonary fibrosis, cystic fibrosis, lung transplantation, and moderate/severe asthma that requires daily medication for control. Assuming no other qualifying comorbidities, we suggest delaying vaccination for those with less severe pulmonary diseases such as a remote history of asthma, smoking with no known pulmonary complications, history of treated bacterial or viral pneumonia, and/or those who have a pulmonary disease but normal lung function tests.
• **Down syndrome:** Patients who have trisomy 21, regardless of degree of disability. There is limited data regarding other chromosomal abnormalities (e.g., Edward’s syndrome [trisomy 18], or Cri du chat syndrome [5p minus syndrome]), anoxic birth injury (e.g., cerebral palsy), birth defects (e.g., spina bifida) or severe autism spectrum disorder (ASD) so DPHS suggests including such patients with inability to independently perform activities of daily living or require mechanical support (e.g., mechanical ventilation, feeding tubes). Note those with ASD is a large and diverse group of patients, most of whom are not thought to be at increased risk from COVID-19.

• **Heart conditions and other cardiovascular and cerebrovascular disease:** Patients who have been diagnosed with heart failure (either reduced ejection fraction or heart failure with preserved ejection fraction), coronary artery disease (e.g., myocardial infection, stable or unstable angina, aortic aneurysm and dissection), cardiomyopathies, arrhythmias, pulmonary hypertension, repaired or symptomatic congenital heart defects, valvular disease, other atherosclerotic conditions (e.g., peripheral vascular/arterial disease), valve disease (e.g., rheumatic heart disease, significant stenoses and regurgitation). Also include those with cerebrovascular disease, including people with stokes who have impaired ability to carry out activities of daily living (ADLs). Delay those with family history of such diseases, recovered infective endocarditis, and uncomplicated mitral valve prolapse.

• **Immunocompromised states:** Patients who are immunocompromised due to solid organ or bone marrow transplant; primary immunodeficiency (e.g., severe combined immunodeficiency, idiopathic CD4 lymphopenia); HIV or AIDS, especially people with CD4 cell count less than 200 cells/mm3 or not on antiretroviral treatment; prolonged use of corticosteroids; or people who are undergoing a work-up for planned organ or bone marrow transplantation can be prioritized due to anticipated immunosuppression. To date, there is not evidence that patients with autoimmune disease are at increased risk of worse outcomes even if taking disease-modifying antirheumatic drugs (DMARDS, such as TNF-alpha inhibitors or
Biden Administration First 100 Days

• Renaming Operation Warp Speed and placing it under new leadership
• 2-dose vaccine series available to more priority groups, esp ≥ 65y
• 100 FEMA-operated, National Guard-supported, mass vaccination sites in hardest hit areas to supplement large vaccination centers in stadiums, arenas, and convention centers
• Mobile vaccination clinics to service hard-to-reach and underserved
• Independent and chain pharmacies enabled
• Defense Production Act to expand production of vaccine and supplies
• Timely and transparent shipping plans so jurisdictions can plan better
• Public vaccine education campaign to overcome VH, improve equitable access
Variant Viruses

Global and Local Relevance
Since 9/20, UK had rapid increase in cases in SE England, leading to enhanced virological investigations

Analysis of viral genome sequence data identified >50% belonged to new phylogenetic cluster

- Variant includes 23 mutations, 8 in spike protein
VUI/VOC B.1.1.7

• Preliminary analysis suggests is 1.4 to 1.7 times more transmissible
  o Increased reproductive number (R) 1.1 to 1.5
  o 70% more transmissible
  o 11 to 15% of contacts

• Binds more easily to receptor cells, or replicates more easily, so spreads more easily and may shed longer
Worldwide B.1.1.7

- Identified >50 countries
- Dec 29 CO reported first case
  - Now 76 cases in 12 states, often no travel history or travel contacts
  - Expect to be dominant strain by March
B.1.1.7 Lineage Cases in the United States**† Total Cases: 144
Impact of B.1.1.7

- No decreased utility of treatments
- Diagnostics retain sensitivity
  - ThermoFisher TaqPath assay gives characteristic pattern (“S-target dropout”)
- Previous infection still offers protection
- No increased severity
  - But higher rate of transmission leads to more cases, and more burden on health systems
South Africa

Variant 501Y.V2 or B.1.351

- Like the “UK variant,” preliminary data suggests that it may spread more easily and has become predominant in parts of South Africa
  - No evidence more severe
- 20 countries
Jan 9: Japan Identifies B.1.1.28

- Also called P.1
- 4 travelers from Brazil with 12 mutations in spike protein, including those common in 501Y.V2
- Impacts transmissibility but also impacts host immune response
  - Unpublished studies
Does Spike N501Y Substitution Affect Pfizer-BioNTech Vaccine Efficacy?

- S glycoproteins are key targets of virus neutralizing antibodies
- Mutation in viral receptor binding site for cell entry, increases binding to angiotensin converting enzyme 2 receptor
  - Enables virus to expand its host range to infect mice
- Researchers generated isogenic N501 and Y501 SARS-CoV-2 strains
- 20 participants’ sera drawn 2 or 4 weeks after 2 30-µg doses of BNT162b2 21d apart tested for neutralization of N501 and Y501 viruses by 50% plaque reduction neutralization assay (PRNT50)

Xie, X et al. Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. bioRxiv: https://doi.org/10.1101/2021.01.07.425740; posted Jan 7, 2021
Does Spike N501Y Substitution Affect Pfizer-BioNTech Vaccine Efficacy?

• Ratio of PRNT50 of blood samples against Y501 virus to against N501 virus 1.46
  - No reduction in neutralization activity against the SARS-CoV-2 that contains the Y501 spike

• Limitation is Y501 virus does not include full set of spike mutations found on variant strains
Treatment Update

Ivermectin
Plasma – neutralizing Ab’s

Camostat mesylate – inhibits TMPRSS2 (primes S protein)

CQ/HCQ – increase pH, compromise endosome and subsequent virus release

Anti-inflammatories
CQ/HCQ – TNF, IL-6
Steroids
Tocilizumab (anti-IL-6)

HIV PI (Kaletra) – protease inhibitor (weak)

Ribavirin - mRNA

remdesivir – nucleotide analog
favipiravir – nucleoside analog

CQ/HCQ – alters glycosylation of receptors

lungs, arteries, heart, kidney, and intestines

Nature Reviews | Microbiology

U.S. Department of Health and Human Services
CQ/HCQ – increase pH, compromise endosome and subsequent virus release
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• Ivermectin antiparasitic drug around 40 years
• Inhibits replication of multiple virus and SARS-CoV-2
  • In vitro at concentrations not readily achievable with currently approved doses
• Mechanism of action proposed binding at host tissue and replication
  • Ivermectin also has anti-inflammatory effects

CQ/HCQ – ?alters glycosylation of receptors
Clinical Course of COVID-19

Stage I (Early Infection)
- Viral response phase

Stage II (Pulmonary Phase)
- IIA
- IIB

Stage III (Hyperinflammation Phase)
- Host inflammatory response phase

Severity of Illness vs. Time course

Clinical Symptoms
- Mild constitutional symptoms
  - Fever >99.6°F
  - Dry Cough, diarrhea, headache

Clinical Signs
- Lymphopenia, increased prothrombin time, increased D-Dimer and LDH (mild)
- Shortness of Breath
- Hypoxia (PaO2/FiO2≤300mmHg)
- Abnormal chest imaging
  - Transaminitis
  - Low-normal procalcitonin

- ARDS
- SIRS/Shock
- Cardiac Failure

~81% mild/mod
14% Severe
5% Critical

Siddiqi et. al 2020
Yang, Lancet Resp Med 2020
NIH (National Institutes of Health) Revises Treatment Guidelines for Ivermectin for the Treatment of COVID-19

Ivermectin is Now a Treatment Option for Health Care Providers!

Jan 14, 2021 – One week after Dr. Paul Marik and Dr. Pierre Kory – founding members of the Front Line Covid-19 Critical Care Alliance (FLCCC) – along with Dr. Andrew Hill, researcher and consultant to the World Health Organization (WHO), presented their data before the NIH Treatment Guidelines Panel, the NIH has upgraded their recommendation and now considers Ivermectin an option for use in COVID-19.

Their recommendation has now been upgraded to the same level as those for widely used monoclonal antibodies & convalescent plasma.

- [https://covid19criticalcare.com/](https://covid19criticalcare.com/)
- Media-blitz arguing ivermectin is being ignored by mainstream science and media
- 2 protocols for prophylaxis (iMASK+) and treatment (MATH+)
- Most data appear positive but small studies or biased
- Limited safety at high doses
FLCCC Review of Available Data

5 observational, 4 RCTs
• Half RCTs peer-reviewed publications
• Half pre-prints

Figure 1. Meta-analysis of ivermectin prophylaxis trials in COVID-19

Figure 1 legend – OBS: Observational study, RCT: Randomized Controlled Trial
The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial

Carlos Chaccour\textsuperscript{a,b,c,*}, Aina Casellas\textsuperscript{a,d}, Andrés Blanco-Di Matteo\textsuperscript{b}, Iñigo Pineda\textsuperscript{b}, Alejandro Fernandez-Montero\textsuperscript{b}, Paula Ruiz-Castillo\textsuperscript{a}, Mary-Ann Richardson\textsuperscript{a}, Mariano Rodríguez-Mateos\textsuperscript{b}, Carlota Jordán-Iborra\textsuperscript{b}, Joe Brew\textsuperscript{e} Francisco Carmona-Torre\textsuperscript{b,f}, Ibarzain\textsuperscript{b}, Esteban Jaso\textsuperscript{b}, Javier\textsuperscript{a}, Ezequiel\textsuperscript{a}, Carmen Gálvez\textsuperscript{a}, Ezequiel\textsuperscript{a}, Carmen Gálvez\textsuperscript{a}, Festrato\textsuperscript{b}, Javier\textsuperscript{a}.

- Consecutive patients with non-severe COVID-19 and no risk factors for complicated disease at ED at Universidad de Navarra July 31, 2020 and Sept 11, 2020
  - 72 h of onset of fever or cough
  - Randomized 1:1 to receive ivermectin, 400 mcg/kg, single dose ($n = 12$) or placebo ($n = 12$)
  - Measured SARS-CoV-2 RNA by PCR from NP swab at day 7 post-treatment

- Median age 26 years; 12 [50\%] women

- At day 7, no difference in proportion of PCR positive patients (RR 0·92, 95\% CI: 0·77–1·09, $p = 1·0$) but ivermectin group
  - Trend lower viral loads at day 4 ($p = 0·24$ for gene E; $p = 0·18$ for gene N) and day 7 ($p = 0·16$ for gene E; $p = 0·18$ for gene N)
  - Lower IgG titers at day 21 post treatment ($p = 0·24$)
  - Recovered earlier from hyposmia/anosmia (76 vs 158 patient-days; $p < 0.001$)
The COVID-19 Treatment Guidelines Panel’s Statement on the Use of Ivermectin for the Treatment of COVID-19

Last Updated: January 14, 2021

Recommendation

- The COVID-19 Treatment Guidelines Panel (the Panel) has determined that currently there are insufficient data to recommend either for or against the use of ivermectin for the treatment of COVID-19. Results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance on the role of ivermectin for the treatment of COVID-19.

Rationale

- NIH Treatment Guidelines Panel upgraded recommendation from “against” to “neither for nor against”
  - Same as monoclonal Abs and convalescent plasma
- No IDSA recommendation
New Hampshire Coronavirus Disease 2019
Weekly Call for Healthcare Providers and Public Health Partners
January 21, 2021

Ben Chan
Elizabeth Talbot
Beth Daly
Lindsay Pierce

Thursday noon-time partner calls will focus on science, medical, and vaccine updates geared towards our healthcare partners.