Covid 19 Update

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1.26.21

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Annals of Internal Medicine

REVIEW

Transmission of SARS-CoV-2: A Review of Viral, Host, and Environmental Factors

Eric A. Meyerowitz, MD*; Aaron Richterman, MD, MPH*; Rajesh T. Gandhi, MD; and Paul E. Sax, MD

- Major literature search aimed at answering the following:
  - What is the evidence for the environmental viability of the virus in experimental and real-world settings?
  - What viral and host factors affect transmission?
  - What is the evidence for various modes of transmission?
  - What is the period of infectiousness for a person with SARS-CoV-2 infection?
  - What are the population transmission dynamics, and what is the role of superspreading events?

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- Environmental stability of the virus
  - In experimental settings
    - Virus isolated from aerosols for up to 3 hrs and other surfaces for up to 72 hrs
    - Longest reported viability was on plastics and stainless steel (half life 6 hours)
    - Highly stable at low temps, but sensitive to heat (inactivated after 5 min at 70ºC)
    - Unable to be cultured after exposure to various disinfectants
  - In real world settings
    - Virus has been isolated from various environmental surfaces
    - Viral loads are markedly lower on surfaces compared to human nasopharynx
    - Replication-competent virus has been cultured rarely from air particles of varying size

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- Viral and host factors affecting transmission
  - Early in disease course, viral load highest in upper respiratory tract; over time, viral load increases in the lower respiratory tract
  - Susceptibility to infection increases with age
    - Children <10 are about half as susceptible as adults [maybe partly due to decreased expression of ACE2 in children?]
  - Probability of transmission from children (as compared to adults) is not well understood, though replication-competent virus is easily isolated from infected children
  - Household contacts of immunocompromised patients have increased risk of infection, suggesting immunocompromised may be more likely to transmit virus (makes sense: higher risk for prolonged shedding)

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- Viral and host factors affecting transmission
  - D614G mutation has markedly increased over time, suggesting an evolutionary advantage; this mutant more easily infects human ACE2 cells than wild-type virus
  - Not mentioned in this review article which was written prior to its identification, but UK variant seems to increase transmissibility (more on variant strains in a bit)

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- Evidence for various modes of transmission…
- Respiratory – the dominant mode of transmission
  - Droplets are classically particles large than 5 μm that fall to the ground within 6 feet, and aerosols are smaller and can remain suspected in air longer/further – but this may be an oversimplified definition
    - Distinguishing droplets from aerosolized particles in a clinical setting may be difficult
  - Dominant route of transmission is respiratory, and proximity, ventilation, and masking are key determinants of transmission risk
  - There is a growing body of evidence suggesting aerosolized spread especially during aerosol-generating procedures, while singing, or in indoor settings with poor ventilation

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- Evidence for various modes of transmission…
- Direct contact or fomite spread
  - Currently no conclusive evidence for fomite or direct contact transmission in humans
    - Rhesus macaques can be infected via direct conjunctival inoculation but develop less severe disease than those inoculated via intratracheal route
  - Reports suggesting fomite spread are circumstantial and respiratory spread cannot be excluded in any of these investigations
  - Poor hand hygiene was associated with increased risk for infection among healthcare workers
    - Though, excellent hand hygiene may also be associated with better infection control practices in general
  - And keep in mind, viral loads are substantially lower on surfaces than nasopharynx

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- Evidence for various modes of transmission…
- Domestic pets and farm animals
  - SARS-CoV-2 can infect cats, dogs, and ferrets
  - Virus replicates well in cats and is transmissible between cats → ferrets
  - No confirmed cases of transmission from domestic pets to humans
  - Minks are farmed in some areas and there is some suspicion of transmission from mink → human
- Vertical transmission
  - Several reports of positive IgM in neonates (IgM does not cross placenta; IgM also prone to false positives)
  - Several reports of positive nasopharyngeal PCR after delivery in neonates, and virus also isolated from placental tissue
  - So, rarely, vertical transmission may occur

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- Evidence for various modes of transmission…
- Fecal-Oral (or Fecal Aerosol) Transmission
  - No evidence currently supports fecal-oral transmission in humans
  - Intragastric inoculation of SARS-CoV-2 in macaques did not result in infection
  - Live, replication-competent virus rarely isolated from stool
  - Aerosolization from toilet flushing is highly unlikely to cause infection except in unusual or extraordinary circumstances

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- Evidence of various modes of transmission…
- Sexual transmission
  - No current evidence supports sexual transmission of SARS-CoV-2
  - Respiratory transmission may occur during sexual encounters
- Bloodborne transmission
  - To date, no replication-competent virus has been isolated from blood samples and there are no documented cases of bloodborne transmission

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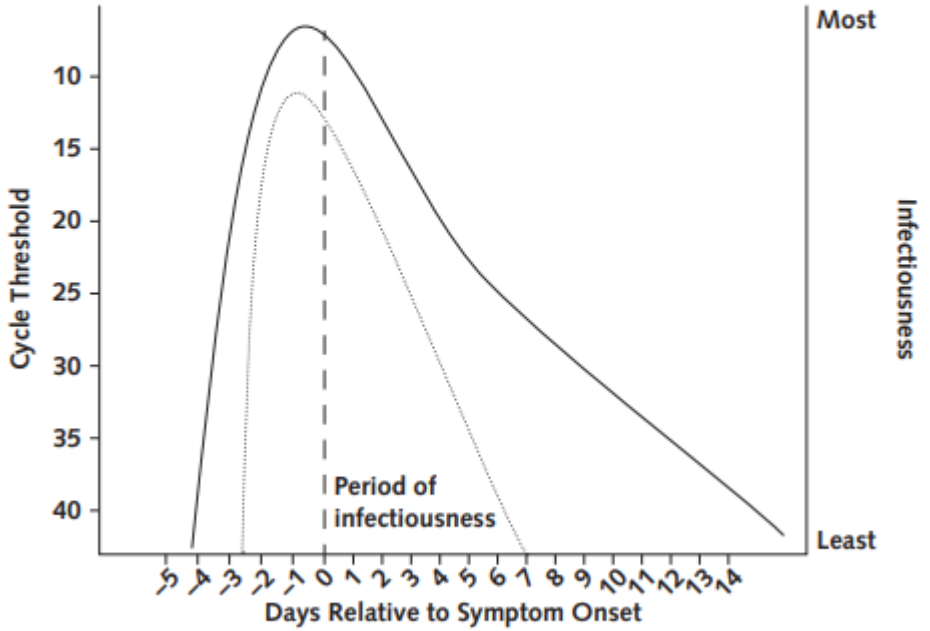
- Period of Infectiousness
  - Asymptomatic, pre-symptomatic, and symptomatic individuals with SARS-CoV-2 infection can transmit virus to others
    - Asymptomatic people seem less likely to transmit, and we don't really know when they are MOST infective
  - Duration of viral shedding is much longer than infectious period
    - Mild/moderate cases: virtually no infectious virus found after 10 days of symptoms even with +PCR
    - Critically ill or immunocompromised: latest isolation of infectious virus was day 20 after symptom onset (but, NO late transmissions have been documented)

Figure 1. The period of infectiousness for immunocompetent, symptomatic adults (*dotted line*) and respiratory tract viral load with time (*solid line*).



The vertical dashed line represents symptom onset.

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- Population-level transmission and the role of superspreading events
  - Estimates of R_0 for SARS-CoV-2 have ranged from 2-3, but this is highly heterogenous (termed: overdispersed)
    - In cases of overdispersion, most index cases do not lead to secondary transmissions, but a smaller minority lead to many secondary transmissions in clusters = **superspreading events**
  - Mounting evidence suggests that SARS-CoV-2 transmission is highly overdispersed such that superspreading events account for a majority of transmission
    - Globally, estimated that 10% of cases lead to 80% of secondary infections
  - The household is another very important site of transmission with household secondary attack rates averaging 18.8%
  - After superspreader events, household transmission frequently occurs

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- Conclusions:
  - We have made **remarkable** progress in our understanding of transmission of this virus and how to reduce its spread
    - On a personal note, thinking back to my first few webinars, the progress we have made in our understanding is incredible
  - Accumulated evidence suggests that most transmission is respiratory with droplets > aerosols
  - Transmission dynamics are heterogenous, with a major role for superspreading events in sustaining the pandemic
  - Superspreading events often include indoor events, close proximity, and poor ventilation

SARS-CoV-2 Variants

Emerging SARS-CoV-2 Variants

Updated Jan. 15, 2021 Languages Print

CDC Centers for Disease Control and Prevention
CDC 24/7: Saving Lives, Protecting People™

- **B.1.1.7 lineage (UK Variant)**
  - Primary mutation in receptor binding domain of spike protein (N501Y)
  - Other mutations are present (69/70 deletion, P681H, Q27stop)
  - First emerged in UK in 9/2020
  - Reported in other countries since 12/20/20, including the US
  - More efficient and rapid transmission than wild type virus
  - Data about severity and vaccine efficacy – see next slides

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SARS-CoV-2 Variants

- **B.1.351 lineage (South African Variant)**
  - Multiple mutations in spike protein
  - First identified in Nelson Mandela Bay, South Africa, in 10/2020
  - Identified in Zambia in 12/2020 and was the predominant strain
  - Currently no evidence to suggest impact on disease severity
  - One of the spike protein mutations (E484K) may affect neutralization by some polyclonal/monoclonal antibodies
  - Vaccine efficacy – more info in a bit

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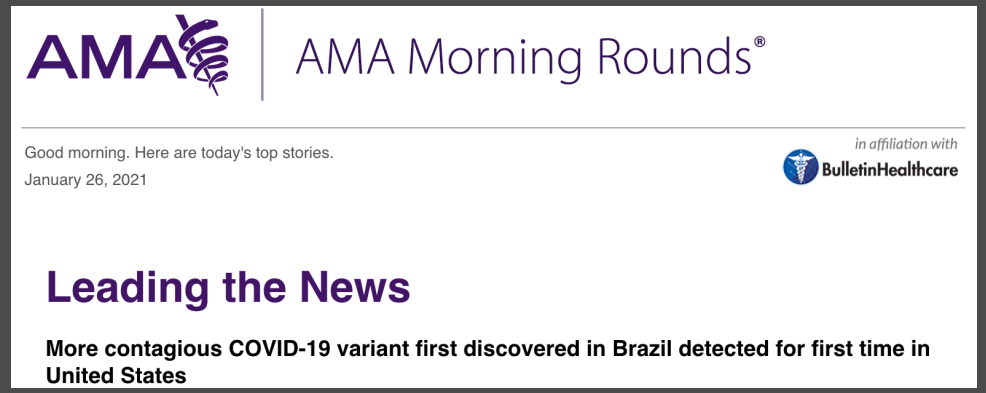
SARS-CoV-2 Variants

- **P.1 lineage (Brazilian Variant)**
  - A branch of the B.1.1.28 lineage first identified in Japan in four travelers from Brazil
  - ~~Not yet identified in the United States~~
  - Evidence to suggest that some mutations may affect transmissibility and antigenic profile, making it more difficult for antibodies to recognize and neutralize the virus



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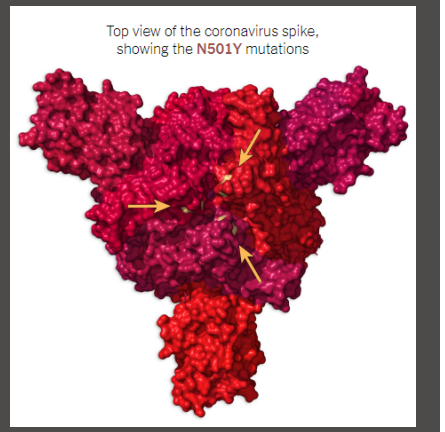
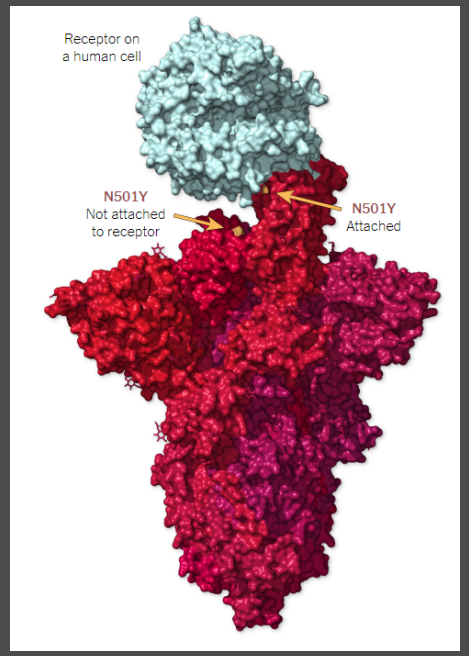
The New York Times

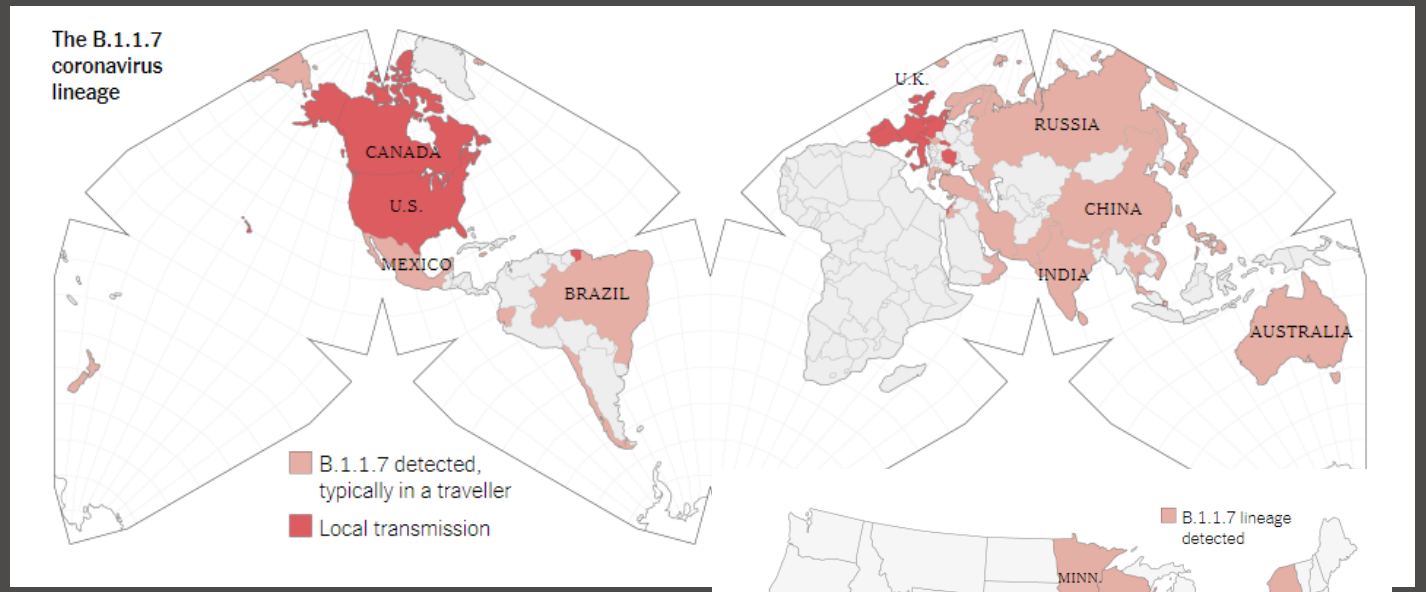
Inside the B.1.1.7 Coronavirus Variant

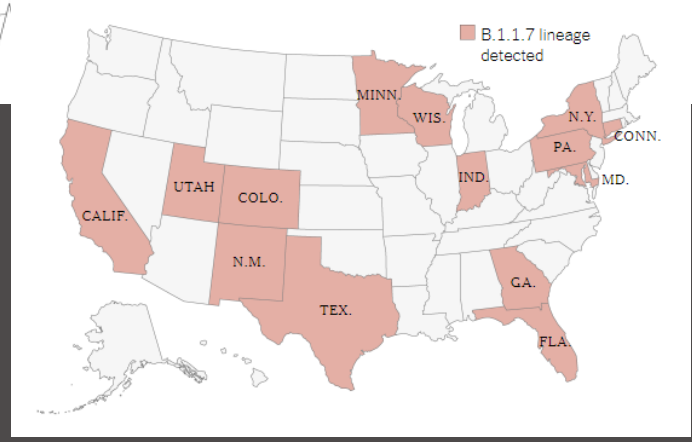
By Jonathan Corum and Carl Zimmer Jan. 18, 2021

- A really cool article that explains more about the UK strain and its various mutations









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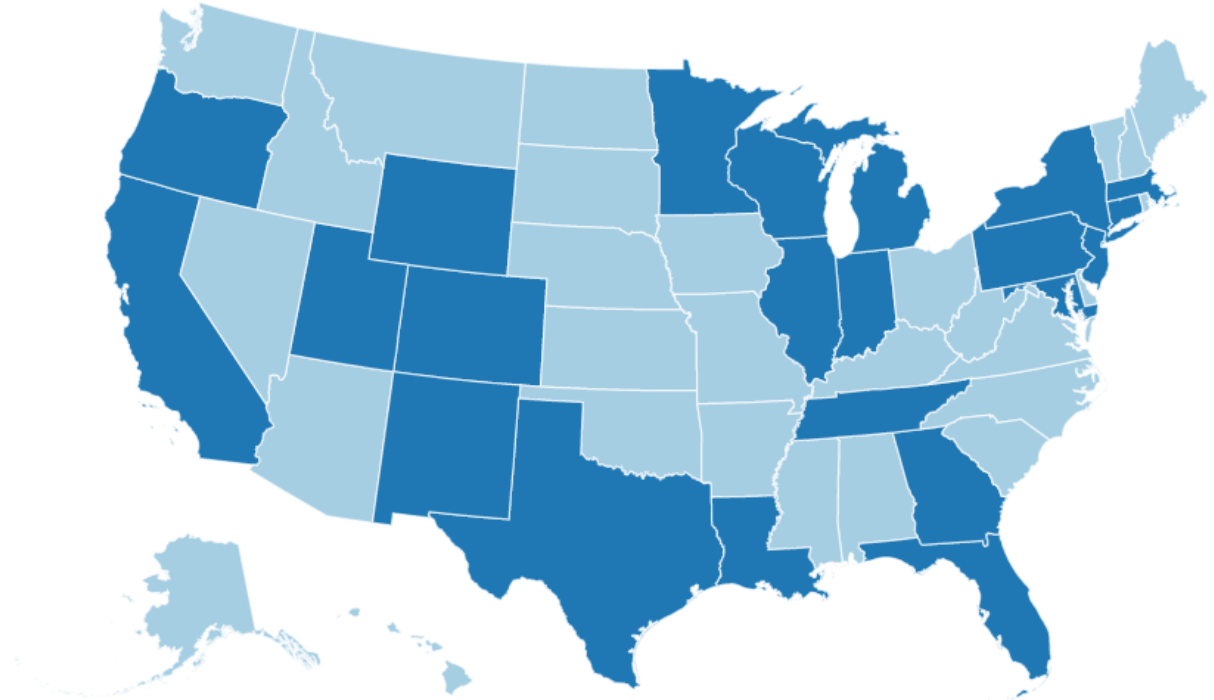
CDC: B.1.1.7 Updates

US COVID-19 Cases Caused by Variants

Updated Jan. 22, 2021 Languages Print

B.1.1.7 Lineage Cases in the United States* Total Cases: 195



Territories AS GU MH FM MP PW PR VI

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B.1.1.7 Updates

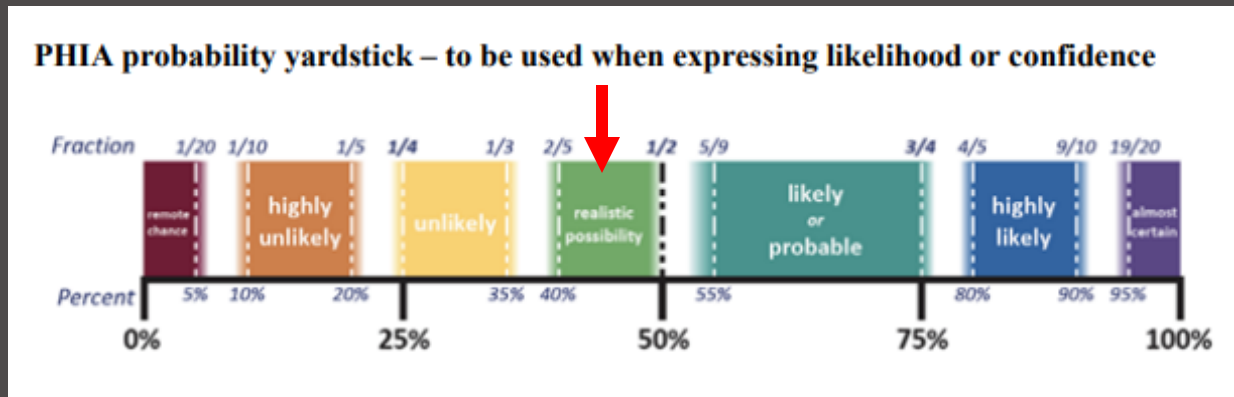
SAGE meeting date:	21/01/2021
Paper title:	NERVTAG note on B.1.1.7 severity

- B.1.1.7 seems to have significantly increased transmissibility and has quickly become the dominant strain in the UK
- Initial assessment of disease severity reported no significant different in hospitalization/death risk, but new analysis are consistent in reporting increased disease severity
  - Updated matched cohort analyses report a death risk ratio of 1.65 for B.1.1.7 infected individuals compared to non-B.1.1.7
  - There are several limitations including limited inclusion of deaths in the available study datasets (<10% of deaths included in some datasets)

B.1.1.7 Updates

SAGE meeting date:	21/01/2021
Paper title:	NERVTAG note on B.1.1.7 severity

- Based on available analyses, there is a realistic possibility that B.1.1.7 infection is associated w/ increased risk of death compared to non-B.1.1.7 strain
  - Realistic possibility = 40-50% probability on the yardstick below
- Of note: the absolute risk of death still remains low
- We need more information about this



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Variants and Vaccines

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

Kai Wu, Anne P. Werner, Juan I. Moliva, Matthew Koch, Angela Choi, Guillaume B.E. Stewart-Jones, Hamilton Bennett, Seyhan Boyoglu-Barnum, Wei Shi, Barney S Graham, Andrea Carfi, Kizzmekia S. Corbett, Robert A. Seder, Darin K. Edwards

doi: https://doi.org/10.1101/2021.01.25.427948

This article is a preprint and has not been certified by peer review [what does this mean?]. Posted January 25, 2021.

- Moderna mRNA vaccine in vitro study evaluating several mutant strains
  - Big ones are B.1.1.7 and B.1.351 (South African strain)
- Assessed neutralizing capacity of sera from human subjects or non-human primates after receiving mRNA-1273

mRNA-1273 neutralization against mutant strains

Variant Name	Amino Acid Changes in Spike
20E (EU1)	A222V-D614G
20A.EU2	S477N-D614G
N439K-D614G	N439K-D614G
Mink Cluster 5 Variant	ΔH69ΔV70-Y453F-D614G-I692V-M1229I
B.1.1.7 (a.k.a., 20I/501Y.V1, VOC 202012/01)	ΔH69ΔV70-ΔY144-N501Y-A570D-D614G-P681H-T716I-S982A-D1118H
B.1.351 (a.k.a., 20H/501Y.V2)	L18F-D80A-D215G-ΔL242ΔA243ΔL244-R246I-K417N-E484K-N501Y-D614G-A701V

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doi: https://doi.org/10.1101/2021.01.25.427948

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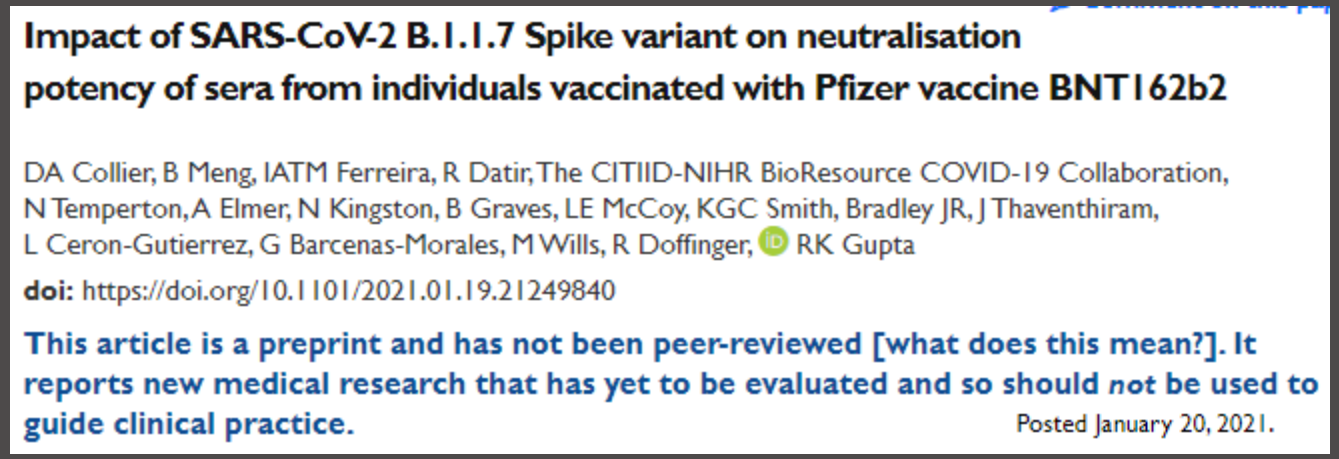
- No significant impact on neutralization against B.1.1.7 variant
- Reduced neutralization seen in B.1.351 variant
  - 2.7-fold reduction in partially mutated B.1.351 variant and 6.4-fold reduction in fully mutated B.1.351 variant
  - BUT – the *neutralization was still significant*, with neutralizing titers remaining around 1/300, above the level expected to be protective
    - Will need to test in a live virus neutralization assay

Variants and Vaccines



Impact of SARS-CoV-2 B.1.1.7 Spike variant on neutralisation potency of sera from individuals vaccinated with Pfizer vaccine BNT162b2

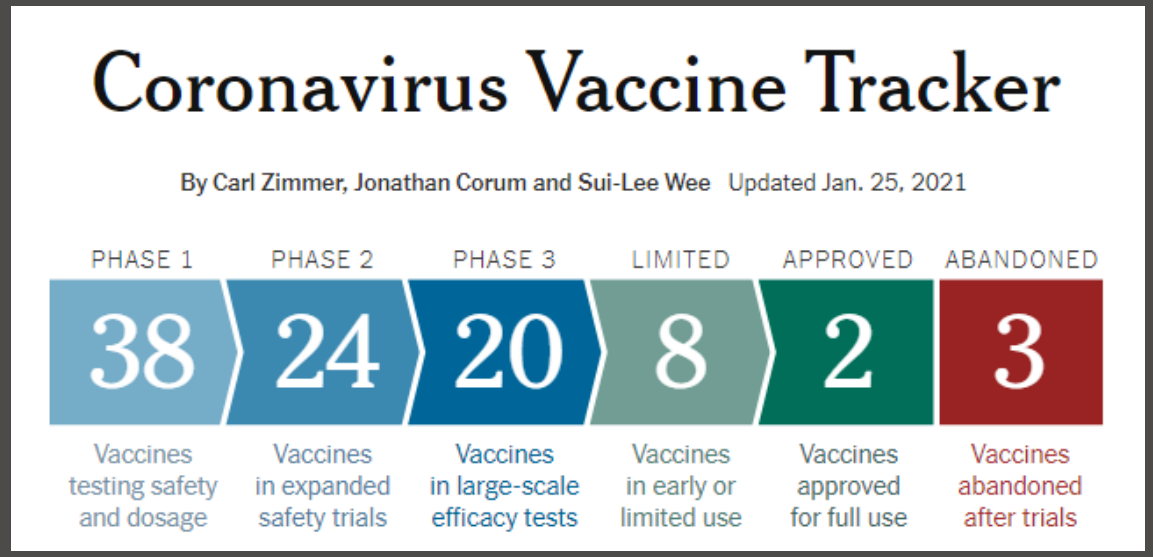
DA Collier, B Meng, IATM Ferreira, R Datir, The CITIID-NIHR BioResource COVID-19 Collaboration, N Temperton, A Elmer, N Kingston, B Graves, LE McCoy, KGC Smith, Bradley JR, J Thaventhiram, L Ceron-Gutierrez, G Barcenas-Morales, M Wills, R Doffinger, RK Gupta

doi: https://doi.org/10.1101/2021.01.19.21249840

- Tested pseudo-viruses expressing wild type spike protein VS expressing 3 key mutations present in B.1.1.7, in addition to a strain expressing ALL spike mutations in the B.1.1.7 variant
- Neutralization titers were not significantly impacted by the combination of the 3 key mutations
  - However they were reduced against the full set of spike mutations present in the B.1.1.7 variant
  - Highest reduction in neutralization was 6-fold, with mean reduction of 3.85-fold
- Million dollar Q – How does this translate to real world efficacy?

General Vaccine Updates

- Abandoned Trials
  - Merck + IAVI oral dose viral vector vaccine – abandoned 1/25 due to failure to trigger adequate immune response
  - Merck + Themis viral vector vaccine abandoned 1/25 due to failure to trigger adequate immune response



- Australian University of Queensland vaccine abandoned 12/10 – caused false positive HIV screens in some volunteers due to structure of the protein clamp inducing HIV-like aby production

General Vaccine Updates

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine — United States, December 21, 2020–January 10, 2021

Early Release / January 22, 2021 / 70

- Between 12/21/20 – 1/10/21 the Vaccine Adverse Event Reporting System detected 10 cases of anaphylaxis out of 1,041,296 first doses of Moderna vaccine administered
  - That = 2.5 cases per million doses administered
- In 9 cases, anaphylaxis onset occurred within 15 min of administration
- All 10 cases occurred in women
- 5 patients had anaphylaxis in the past (though none to vaccines)
- No anaphylaxis-related deaths were reported

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General Vaccine Updates

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Moderna COVID-19 Vaccine — United States, December 21, 2020–January 10, 2021

Early Release / January 22, 2021 / 70

TABLE 2. Characteristics of patients with reported anaphylaxis and nonanaphylaxis allergic reactions after receipt of the first dose of Moderna COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 21, 2020–January 10, 2021

Return

Characteristic	Type of reported reaction, no. (%)	
	Anaphylaxis (n = 10)	Nonanaphylaxis allergic reactions (n = 43)*
Median age, yrs (range)	47 (31–63)	43 (22–96)
Female	10 (100)	39 (91)
Minutes to symptom onset, median (range)	7.5 (1–45)	15 (<1–1,440 [24 hrs])
Symptom onset ≤15 mins	9 (90)	21 (51)†
Symptom onset ≤30 mins	9 (90)	30 (73)†
Documented history of allergies or allergic reactions	9 (90)§	26 (60)

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General Vaccine Updates

- Between 12/14/20 – 12/23/20 the VAERS detected 21 cases of anaphylaxis out of 1,893,360 first doses of Pfizer vaccine
  - 11.1 cases per million doses
- 71% of anaphylactic reactions occurred within 15 minutes
- Two of the 21 cases had previous anaphylaxis to vaccines (rabies, influenza)

Allergic Reactions Including Anaphylaxis After Receipt of the First Dose of Pfizer-BioNTech COVID-19 Vaccine — United States, December 14–23, 2020

Weekly / January 15, 2021 / 70(2);46–51

TABLE 2. Characteristics of patients with report of anaphylaxis and nonanaphylaxis allergic reactions after receipt of Pfizer-BioNTech COVID-19 vaccine — Vaccine Adverse Events Reporting System (VAERS), United States, December 14–23, 2020

Return

Characteristic	Type of reported reaction, no. (%)	
	Anaphylaxis (n = 21)	Nonanaphylaxis allergic reactions (n = 83)*
Median age, yrs (range)	40 (27–60)	43 (18–65)
Female	19 (90)	75 (90)
Mins to symptom onset, median (range)	13 (2–150)	12 (<1–1,200 [20 hrs])
Symptom onset ≤15 mins	15 (71)	44 (61)†
Symptom onset ≤30 mins	18 (86)	61 (85)†
Documented history of allergies or allergic reactions	17 (81)§	56 (67)

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Vaccine Allergic Reactions

- Anaphylaxis was much more prevalent in females
- Allergic reactions were more common in people with prior history of allergic reactions
- Most severe allergic reactions occur relatively quickly after dose administration
- How will numbers change after 2nd dose data is analyzed?
- Limitations – self-reported data

Johnson & Johnson Vaccine

ORIGINAL ARTICLE

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

Jerald Sadoff, M.D., Mathieu Le Gars, Ph.D., Georgi Shukarev, M.D., Dirk Heerwegh, Ph.D., Carla Truyers, Ph.D., Anne M. de Groot, Ph.D., Jeroen Stoop, Ph.D., Sarah Tete, Ph.D., Wim Van Damme, M.D., Isabel Leroux-Roels, M.D., Pieter-Jan Berghmans, M.D., Murray Kimmel, D.O., et al.

Article | Figures/Media | The NEW ENGLAND JOURNAL of MEDICINE | Metrics | January 13, 2021 | DOI: 10.1056/NEJMoa2034201

- Adenovirus 26 vector vaccine
  - AstraZeneca vaccine is similarly an adenovirus vector vaccine
- Multicenter, placebo-controlled, phase 1–2a trial
- Evaluated high and low dose vaccines for efficacy and safety in age cohorts (18 – 55 compared to 65+) compared to placebo
- Longer term data comparing single vs two-dose regimens is pending
- Conclusion: safety and immunogenicity profiles of Ad26.COV2.S support further development of this vaccine candidate

The New York Post

Fauci suggests Johnson & Johnson COVID-19 vaccine could win emergency-use authorization in just two weeks

Last Updated: Jan. 24, 2021 at 12:15 p.m. ET

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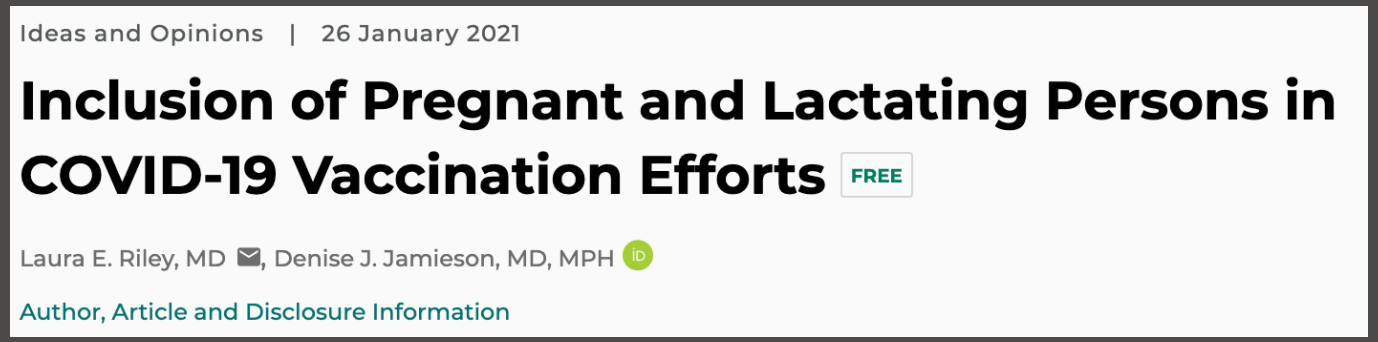


Ideas and Opinions | 26 January 2021

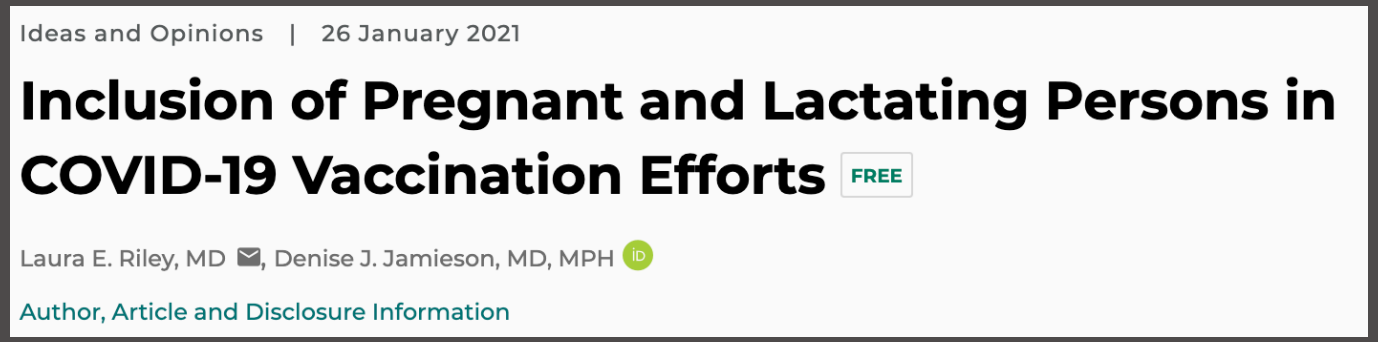
Inclusion of Pregnant and Lactating Persons in COVID-19 Vaccination Efforts

FREE

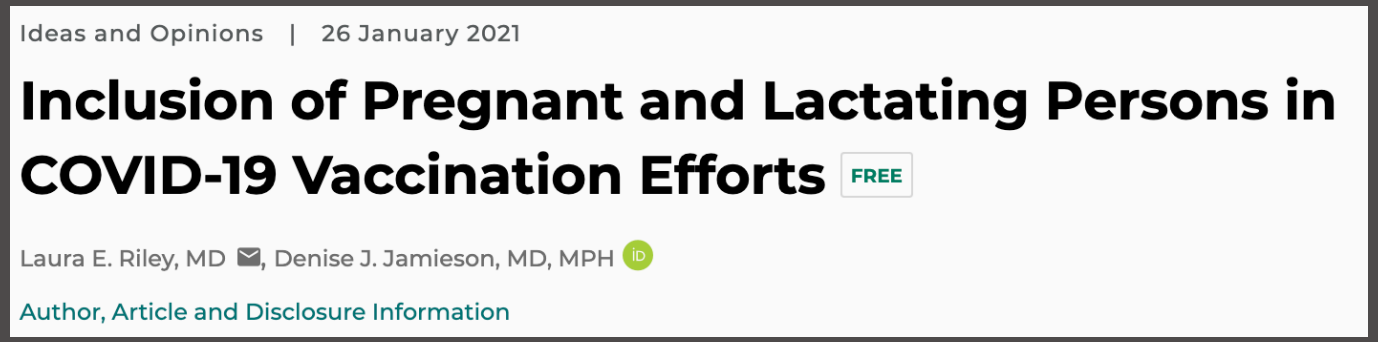
Laura E. Riley, MD, Denise J. Jamieson, MD, MPH

Author, Article and Disclosure Information

- Vaccines → important → we must determine who should and should not get them, and when
- Healthcare workers are highest priority for vaccination; as many as 300,000 may be pregnant
- Lack of data contributes to confusion about inclusion of pregnant and lactating people in this tiered system
- American College of Obstetrics and Gynecology has recommended:
  - Pregnant persons be offered the vaccine, and should discuss it with their healthcare provider(s) (though the discussion is not required)
  - Lactating persons should be encouraged to get the vaccine
  - And, persons planning to become pregnant should complete the vaccine series prior to conception to ensure protection before pregnancy



- The interplay between Covid-19 and pregnancy
  - Relative risks in pregnancy are increased, but absolute risks for severe disease remain low
  - About 1% of pregnant women in the United States require admission to an ICU and 1.5 deaths occur per 1000 pregnant women with Covid-19
  - Pregnant patients with other risk factors are at even higher risk (medical comorbidities, obesity, as well as racial/ethnic disparity)
  - Some (but not all) studies have observed an association between Covid-19 and preterm births and cesarean sections
  - So, pregnant women seem to be higher risk for poor outcomes, and risk may also be increased for the child
- Pregnant women have been excluded from initial phase 3 clinical trials so efficacy and safety data is lacking



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Laura E. Riley, MD, Denise J. Jamieson, MD, MPH

Author, Article and Disclosure Information

- According to the authors, we can infer a few things about Covid-19 vaccines in pregnancy
  - There is no biological reason to suspect mRNA vaccine immunogenicity is different in pregnancy – so efficacy should be similar
  - mRNA vaccines contain no live virus or adjuvants which could or would affect the fetus
  - In animal studies, the Moderna mRNA vaccine showed no developmental or reproductive toxicity in female rats
  - If pregnant women develop post-vaccine fever, they can be safely treated with acetaminophen

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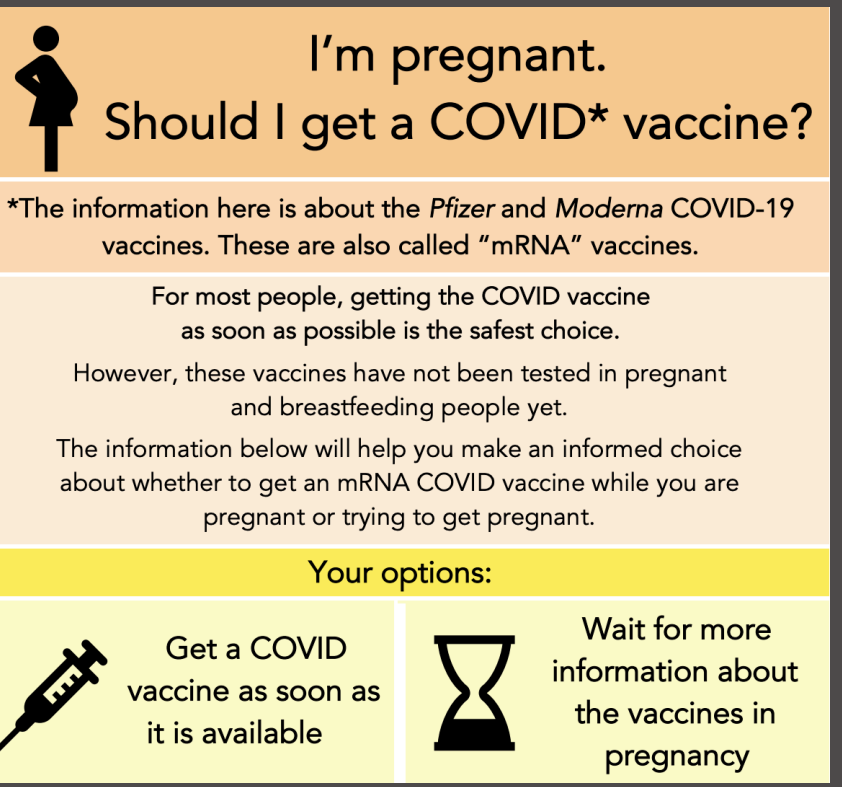
Ideas and Opinions | 26 January 2021

Inclusion of Pregnant and Lactating Persons in COVID-19 Vaccination Efforts FREE

Laura E. Riley, MD, Denise J. Jamieson, MD, MPH

Author, Article and Disclosure Information

- Questions will linger until human data re: vaccination in pregnancy is available
  - Pregnancy-specific trials are needed
- As providers, many of us will need to continue discussions and counseling with our pregnant patients
  - This article references a good resource for discussions with pregnant patients:
    - Baystate Health: "***I'm Pregnant. Should I get a Covid* vaccine?***"



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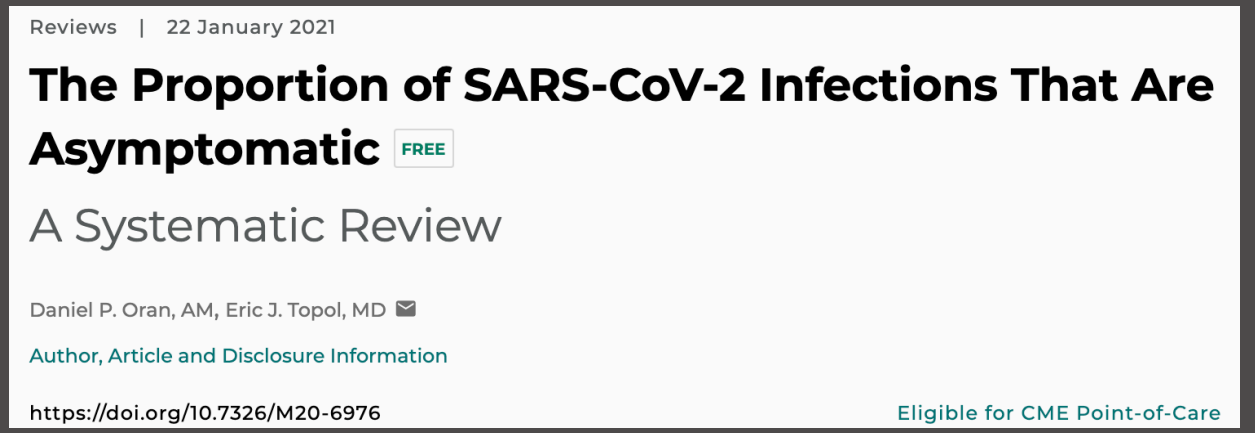
Asymptomatic Covid



Reviews | 22 January 2021

The Proportion of SARS-CoV-2 Infections That Are Asymptomatic FREE

A Systematic Review

Daniel P. Oran, AM, Eric J. Topol, MD

Author, Article and Disclosure Information

https://doi.org/10.7326/M20-6976

Eligible for CME Point-of-Care

- A systematic review using Google News, Google Scholar, medRxiv, and PubMed
- 61 eligible studies were identified
  - 43 used PCR testing, 18 used antibody testing
- The highest quality data comes from nationwide serosurveys England (N = 365K) and Spain (N = 61K)
  - These suggest at least 1/3 of infections are asymptomatic
- Longitudinal studies suggest that nearly 75% of patients who are asymptomatic at the time of a positive PCR test, will remain asymptomatic

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Implementation and Evolution of Mitigation Measures, Testing, and Contact Tracing in the National Football League, August 9–November 21, 2020

Early Release / January 25, 2021 / 70

Christina D. Mack, PhD[1]; Erin B. Wasserman, PhD[1]; Cria G. Perrine, PhD[2]; Adam MacNeil, PhD[2]; Deverick J. Anderson, MD[3]; Emily Myers[4]; Sabrina Smith[1]; L. Clifford McDonald, MD[2]; Michael Osterholm, PhD[5]; Gary S. Solomon, PhD[4]; Thom Mayer, MD[6]; Allen Sills, MD[4]; NFL COVID-19 Advisory and Operational Team (View author affiliations)

- July – season began
  - NFL implemented extensive mitigation and surveillance measures in facilities and during gameplay and travel
- Midseason
  - Transmission was observed in cumulative interactions of < 15 min, so definition of high risk contact was revised to account for this
- Midseason
  - An intensive protocol was developed that imposed stricter infection prevention practices when a Covid + case was identified at a given NFL club
  - The intensive protocol effectively prevented transmission the occurrence of high risk interactions
    - No high risk contacts were identified for 71% of traced cases

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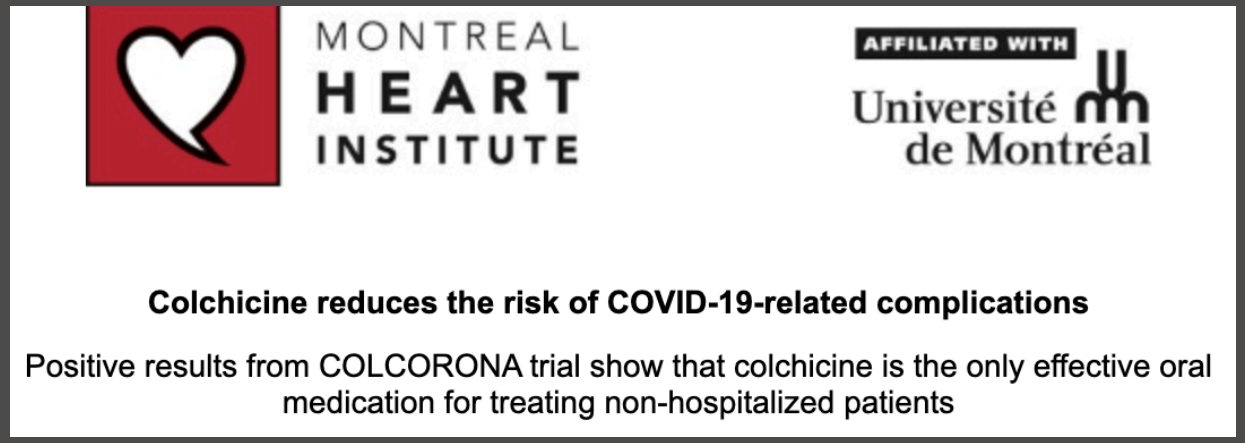
- What did we learn from the NFL?
  - Cumulative interaction of > 15 min not required for high risk contact
  - Transmission was reduced through implementation of an intensive protocol focused on
    - Environmental changes
    - Increased personal protection
    - Avoidance of high-risk interactions such as vehicle sharing, eating in the same room or common areas
    - And expansion of the components of contact tracing to incorporate high-risk contact designations
  - When thinking about exposure risk, must take into account mask use, setting of exposure, duration, and proximity of the exposure
  - COVID-19 mitigation measures must be continually optimized based on available data

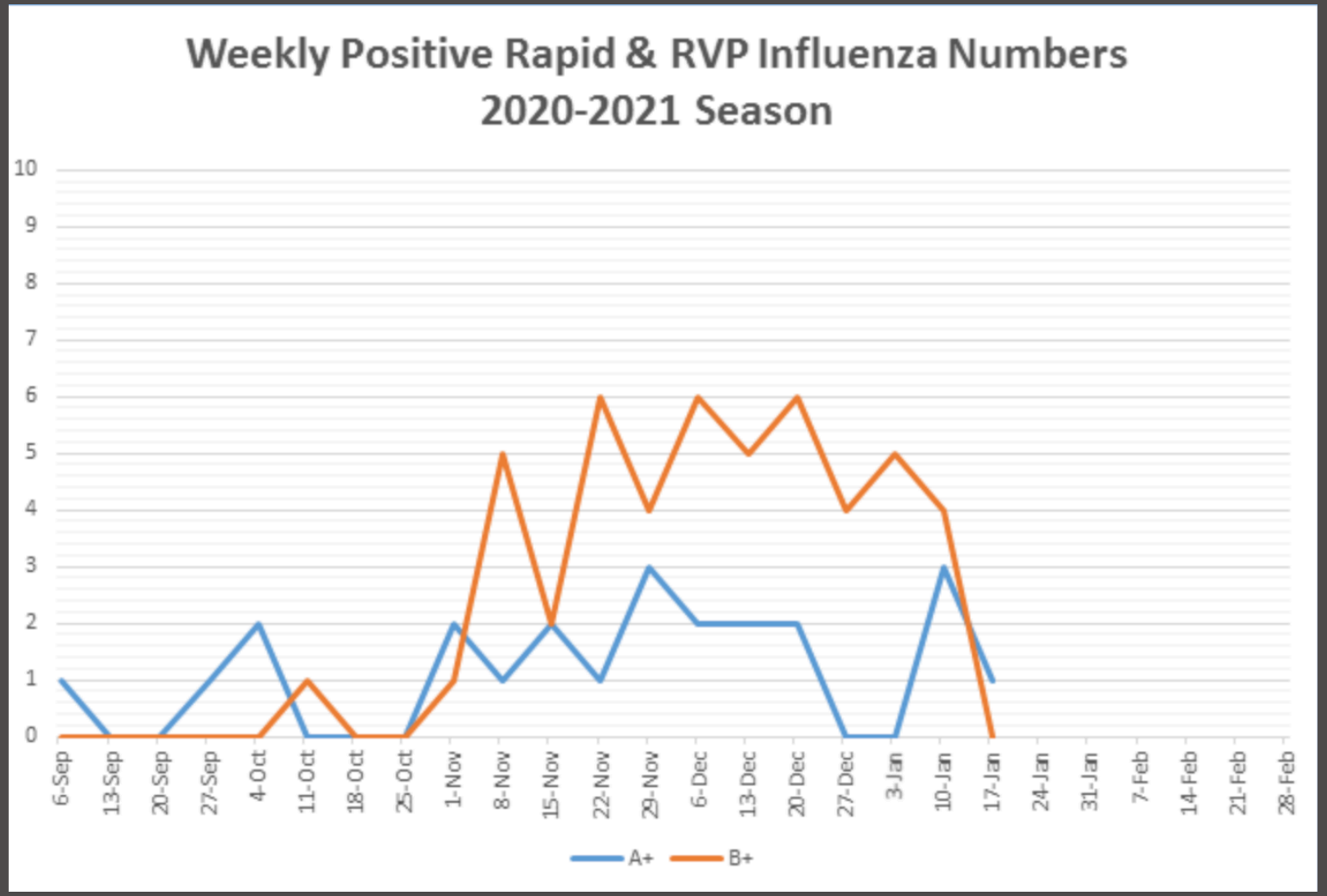
Other Topics
Colchicine



- Press release 1/22/21 claims that colchicine reduces risk of death or hospitalization by 21%
  - Data not available for review yet
- Contactless, randomized, double blinded, placebo controlled
  - 4488 patients with confirmed or suspected Covid – analysis “approached statistical significance”
  - 4159 patients with nasopharyngeal PCR+ confirmed Covid – analysis was statistically significant
    - Apparently reduced hospitalization risk by 25%, mechanical ventilation by 50%, and deaths by 44%

Other Topics
Influenza

- MU HealthCare Flu Report



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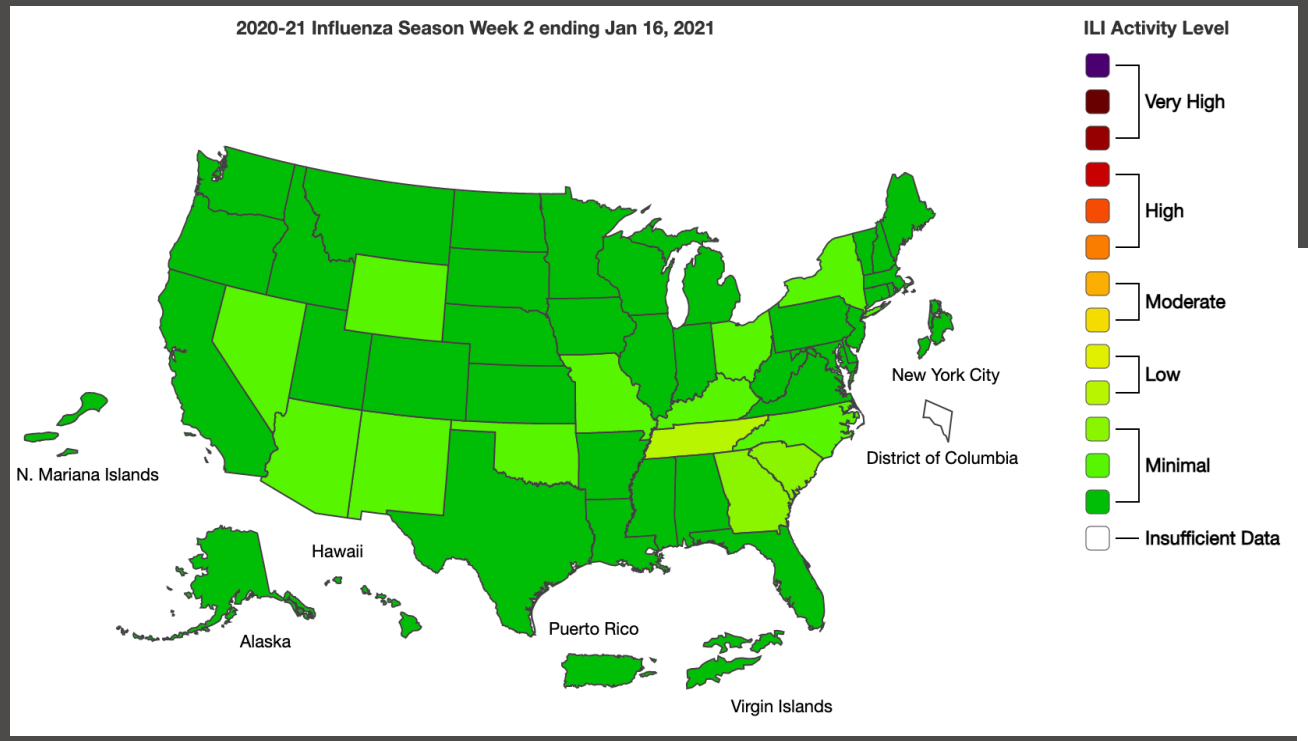
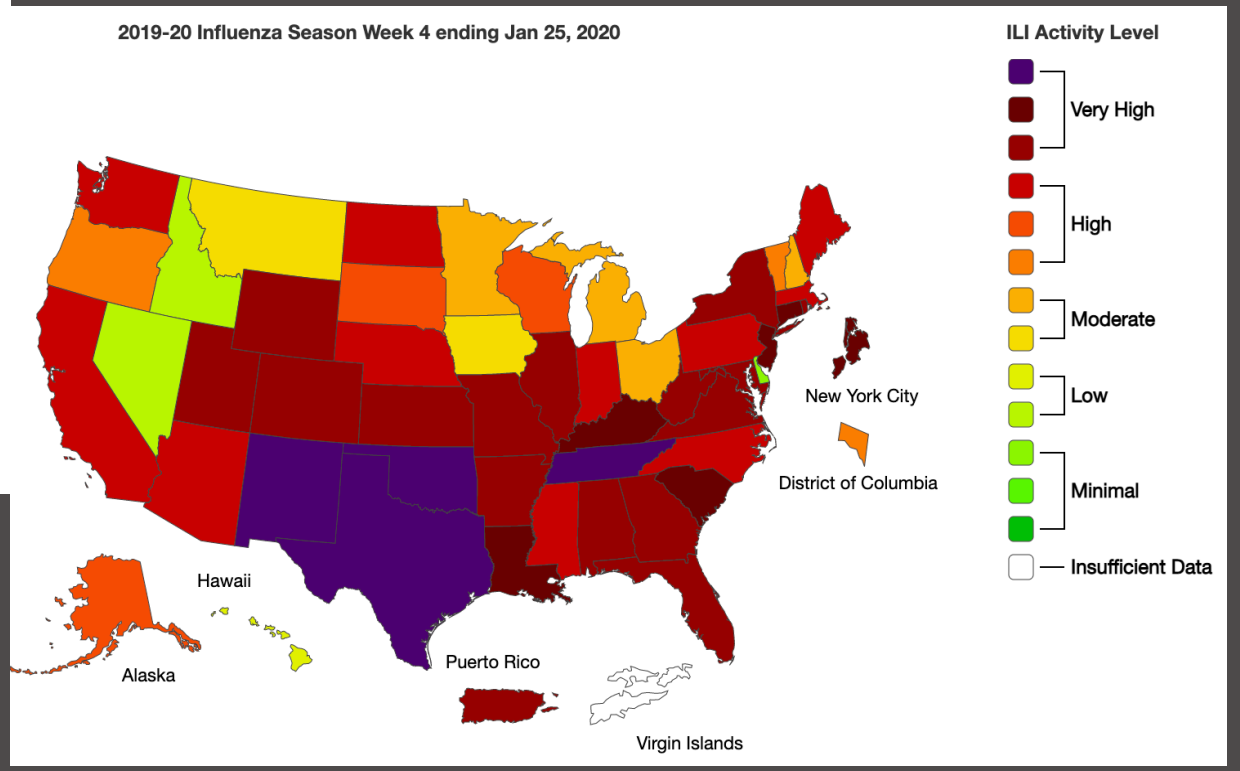
Other Topics
Influenza [CDC report]



Mid-January 2021

Mid-January 2020



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Thanks!

Questions? *nelsontb@health.missouri.edu*

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