Northwestern Medicine®

IRB Brown Bag Lunch

Michael G. Ison, MD MS FIDSA FAST

Professor, Divisions of Infectious Diseases and Organ Transplantation

Director, Transplant and Immunocompromised Host Infectious Diseases Service

Director, NUCATS Center for Clinical Research

Northwestern University Feinberg School of Medicine

Editor-in-Chief, ***Transplant Infectious Disease***

Northwestern IRB

19 January 2022

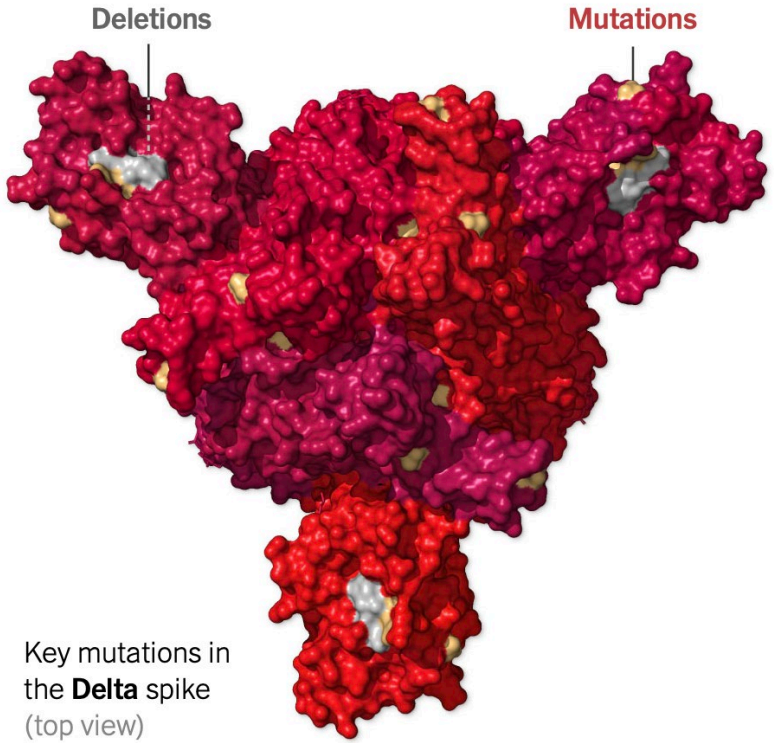
Disclosures

- Research Support°
  - GlaxoSmithKline, Pulmocide, Regeneron
- Paid Consultation
  - Adagio, ADMA Biologics, AlloVir, Cidara, Genentech/Roche, Janssen, Shionogi, Takeda, Viracor Eurofins
- Unpaid Consultation
  - Romark
- Data & Safety Monitoring Board Participation
  - Allovir, CSL Behring, Janssen, Merck, Sequiris, Takeda, Talaris

As of 12/13/21; ° Paid to Northwestern University.

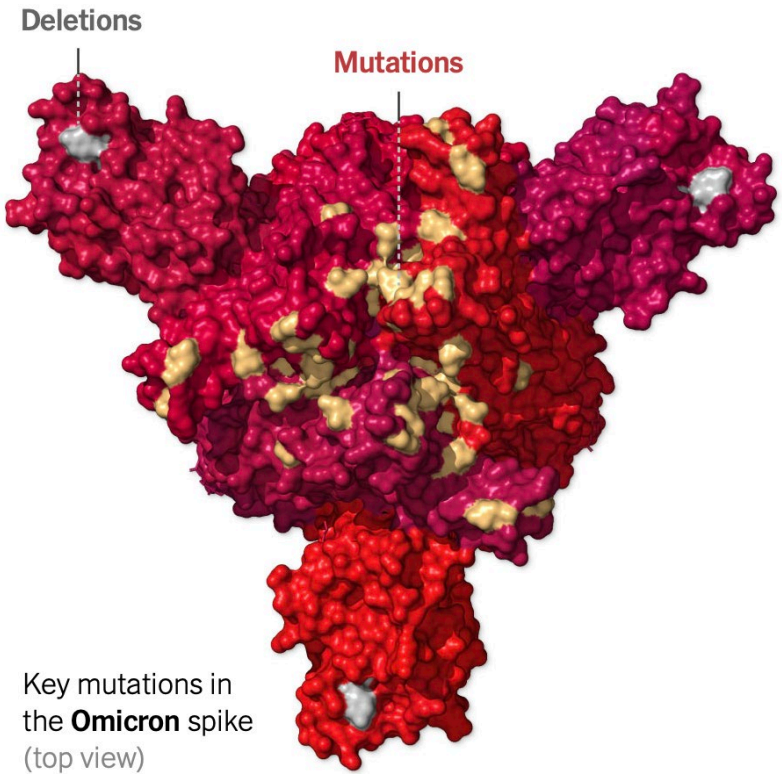
SARS-CoV-2 Key Variant

- Delta Variant:
  - Two key mutations: E484Q (antibody evasion) and L452R (increase spread)
  - Associated with increase rates of infection, hospitalization and spread



Key mutations in the **Delta** spike (top view)

- Omicron Variant:
  - 30 mutations and deletions in the spike protein
  - Associated with increase rates of infection, reduced protection from 2 doses of vaccine



Key mutations in the **Omicron** spike (top view)

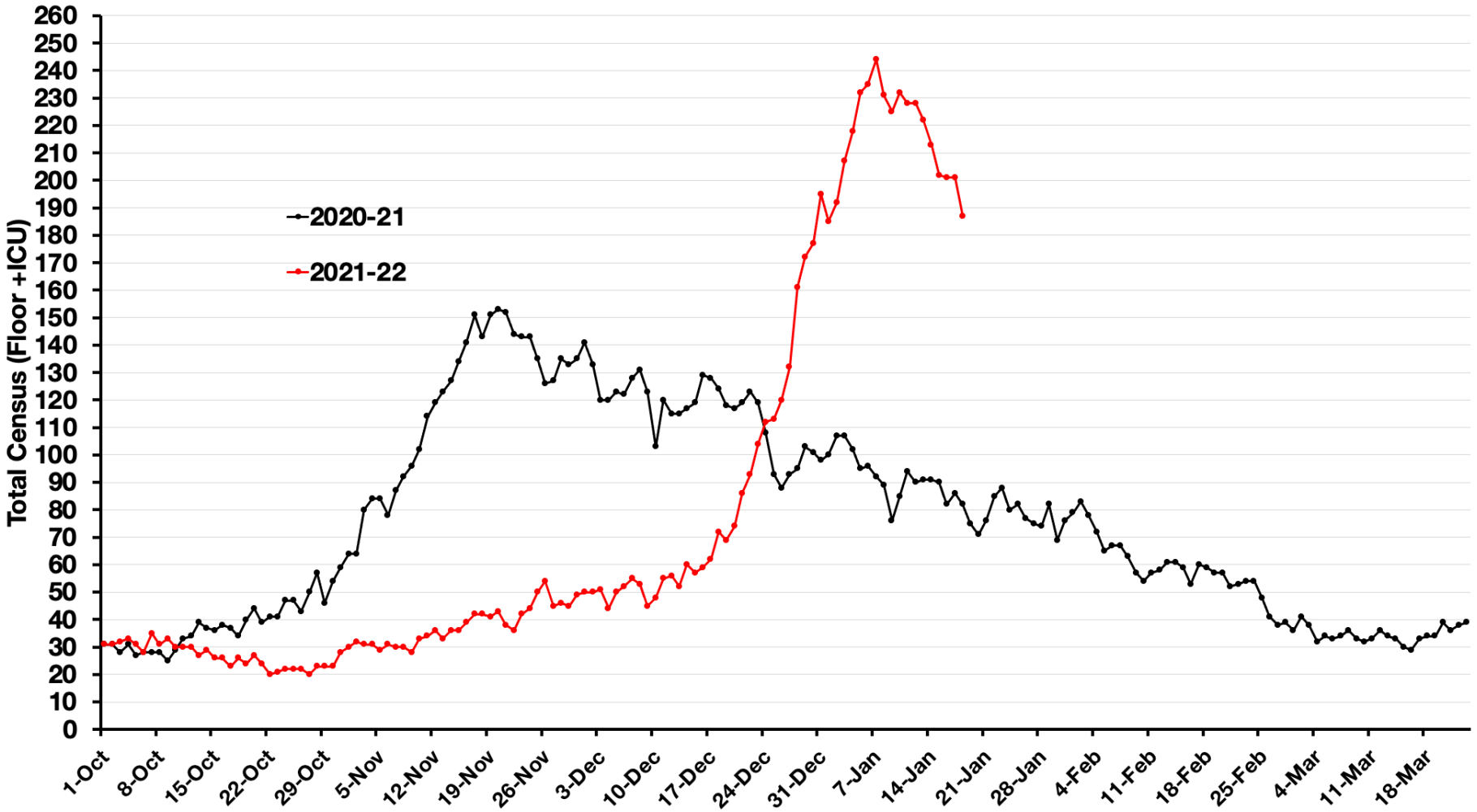
Northwestern Medicine®

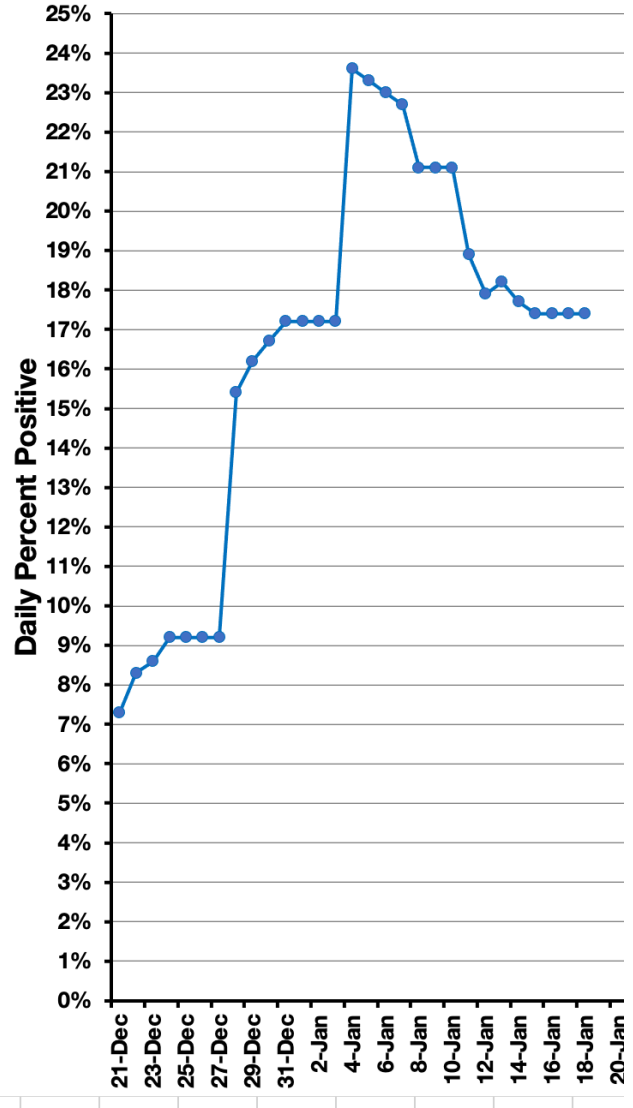
SARS-CoV-2 Omicron Variant

- What we know about the Omicron variant
  - Enhanced transmission in households compared to Delta
  - Need a third dose to optimize vaccine efficacy of virus
    - Protection against infection declines over 10 weeks from ~75% to 40%
    - Even with booster, you need multiple layers of mitigation
  - Shorter incubation period from exposure to infection (2-3 days)
  - Transmission to fully vaccinated and even boosted healthy individuals have been described
    - Generally associated with >15 min of indoor exposure with no mask
    - Mild symptoms in vaccinated patients but can still transmit infection
    - Reduced sensitivity of rapid antigen assays (PCR remains equally sensitive)

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1040076/Technical_Briefing_31.pdf

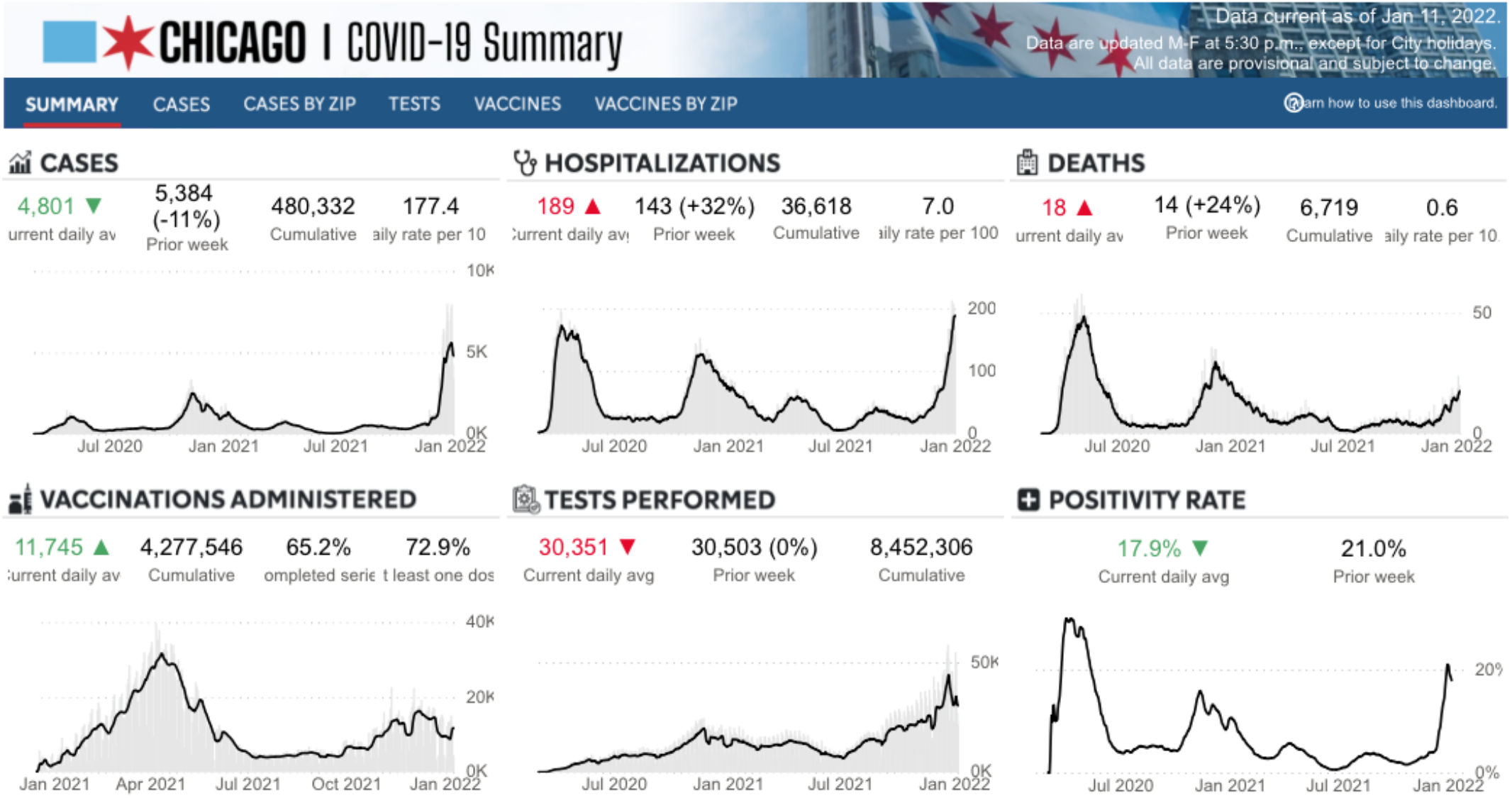
Current Situation: *Northwestern Memorial Hospital*





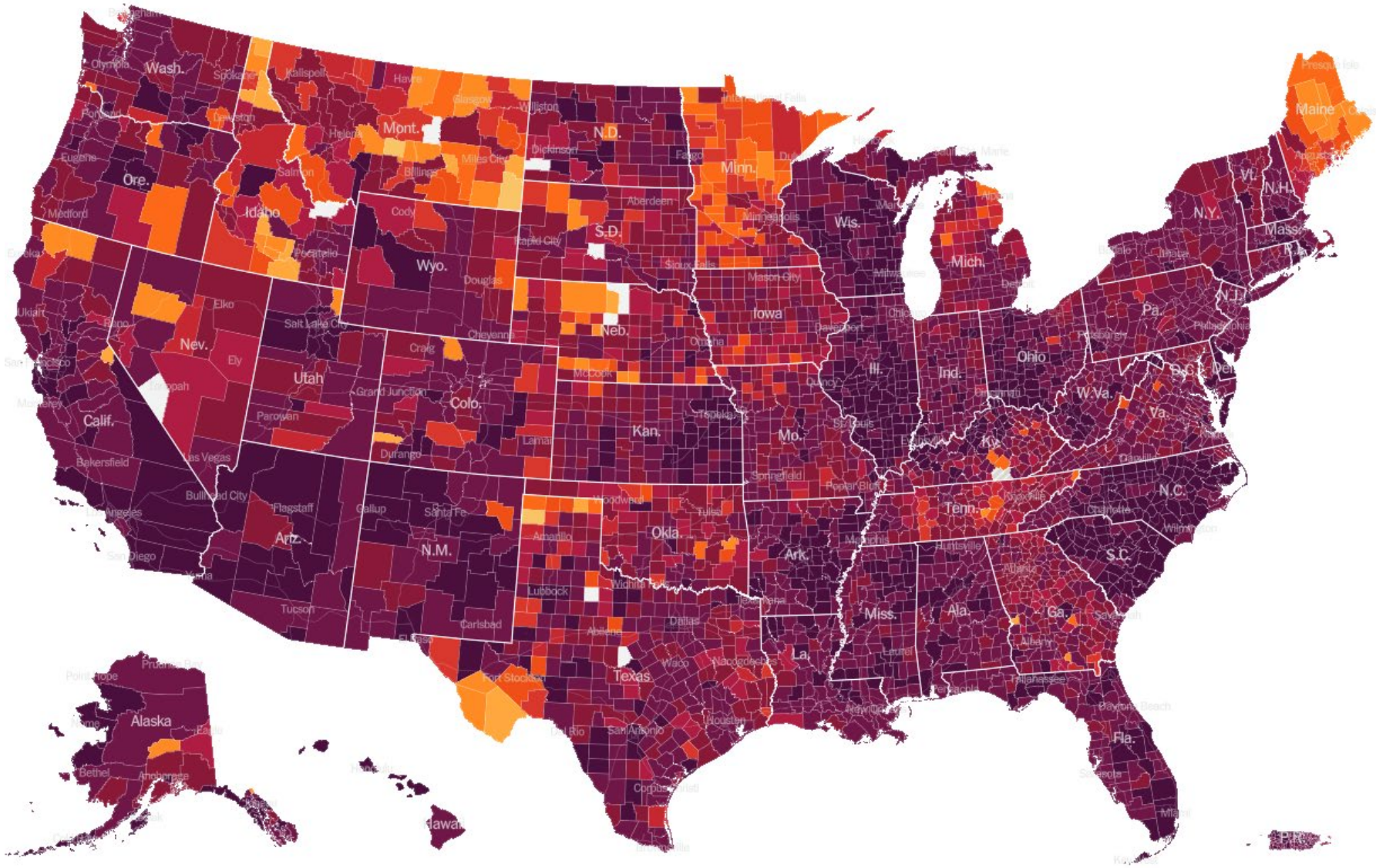
Northwestern Medicine®

Current Situation: *Chicago*



Northwestern Medicine®

Current Situation: *United States*



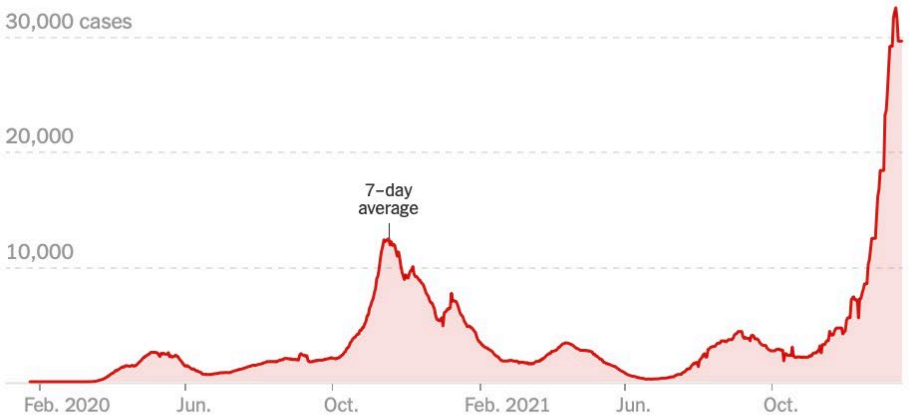
- Cases:
  - Total: 67,705,330
  - Daily: 756,752
- Hospitalizations
  - Daily: 156,894
- Deaths
  - Total: 853740
  - Daily: 1,889

Northwestern Medicine®

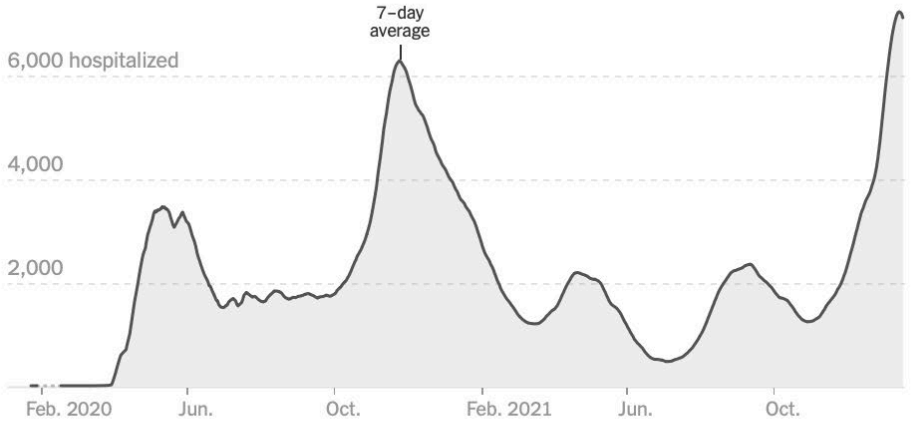
https://www.nytimes.com/interactive/2021/us/covid-cases.html. Accessed 1/19/22

Current Situation: *Illinois*

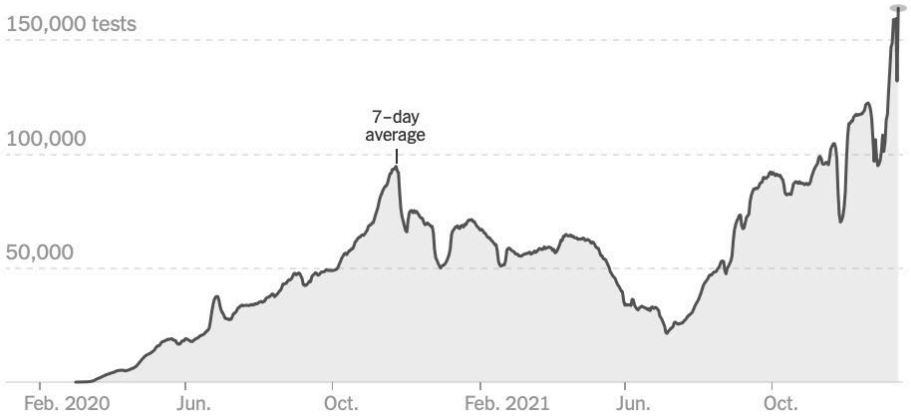
New reported cases by day



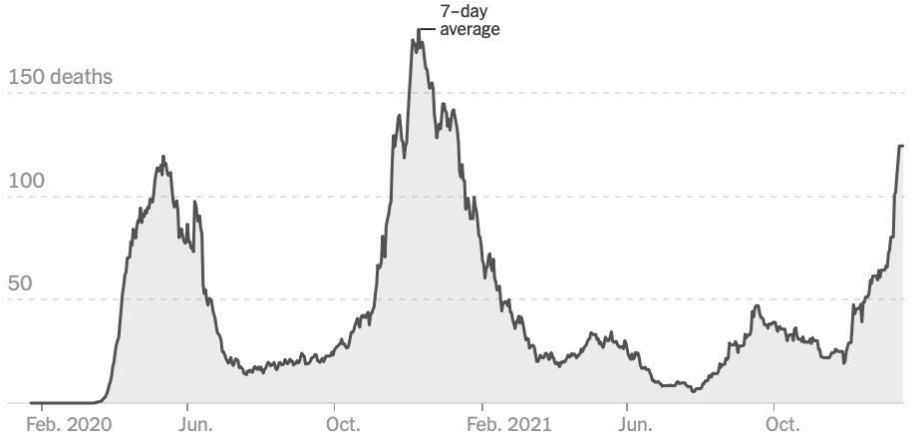
Hospitalizations



Tests by day



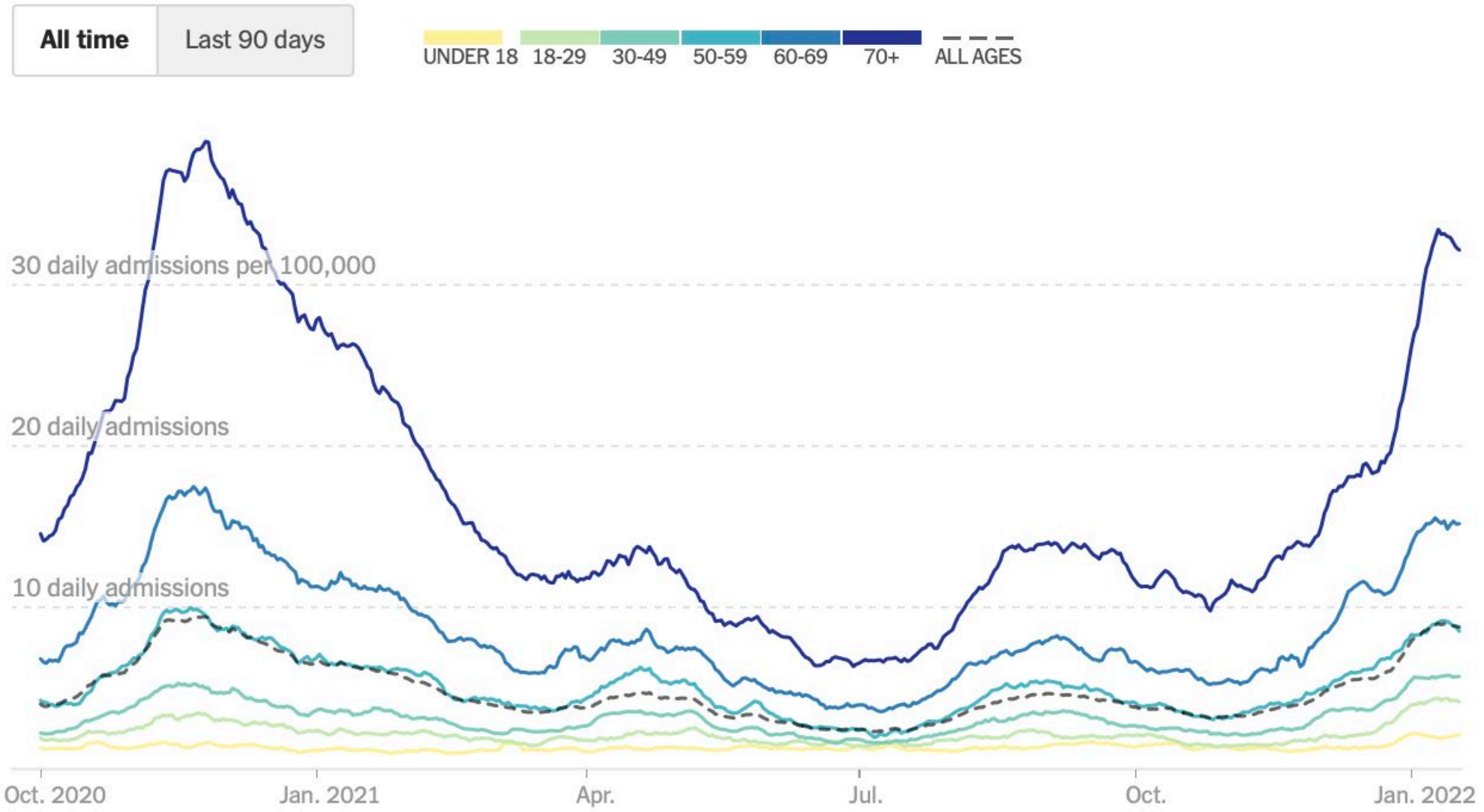
New reported deaths by day



Northwestern Medicine®

https://www.nytimes.com/interactive/2021/us/covid-cases.html. Accessed 1/18/22

Current Situation: *Illinois*



Northwestern Medicine®

https://www.nytimes.com/interactive/2021/us/covid-cases.html. Accessed 1/18/22

Current Guidance for COVID-19 Vaccine

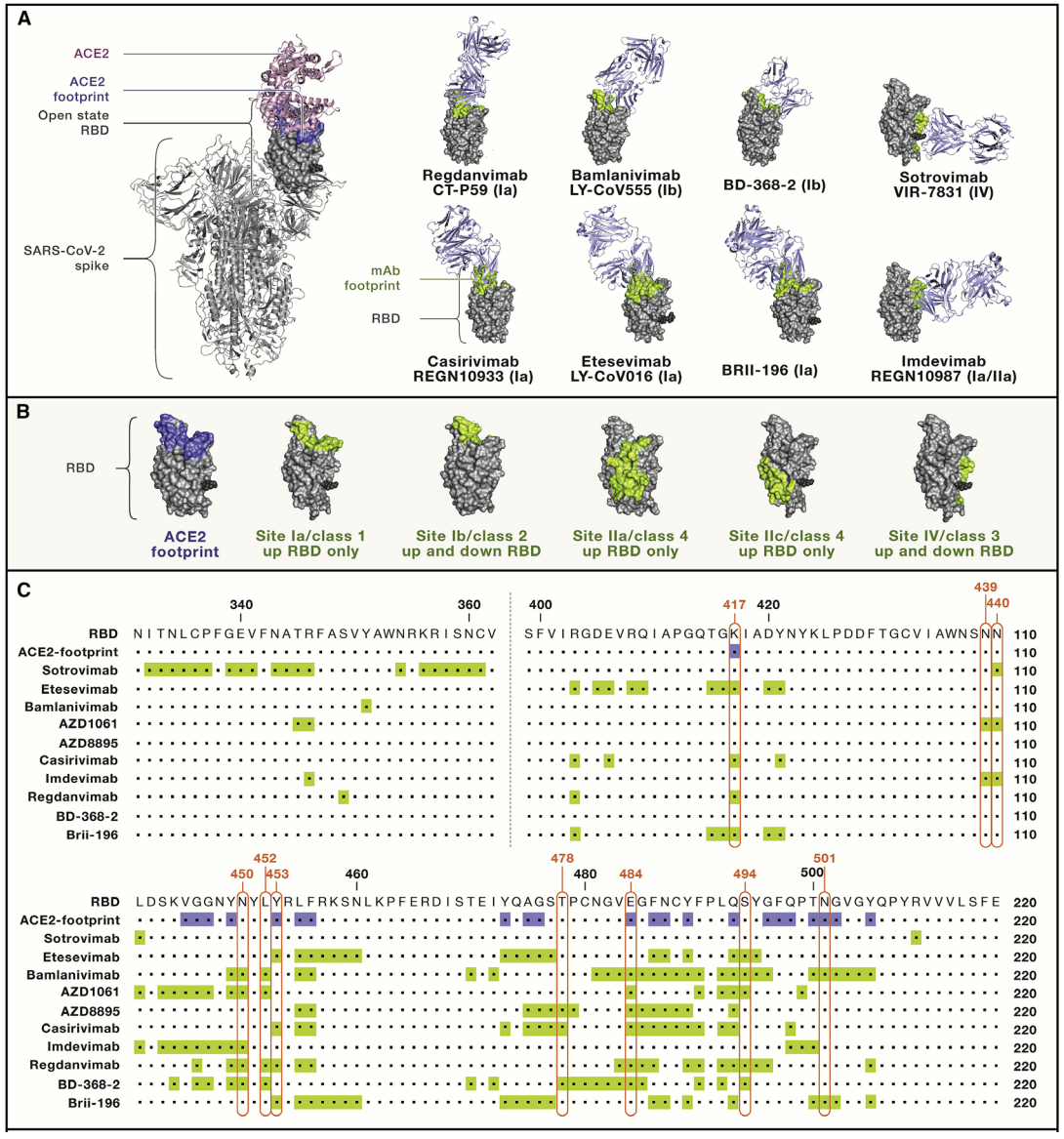
Pfizer-BioNTech [1]	Moderna [1]	Johnson & Johnson's Janssen [1,2]
Ages Recommended 5+ years old	**Ages Recommended** 18+ years old	**Ages Recommended** 18+ years
Primary Series 2 doses Given 3 weeks (21 days) apart [3]	**Primary Series** 2 doses Given 4 weeks (28 days) apart [3]	**Primary Series** 1 dose
Booster Dose Everyone ages 18 years and older should get a booster dose of either Pfizer-BioNTech or Moderna (COVID-19 vaccines) 5 months after the last dose in their primary series. Teens 12-17 years old should get a Pfizer-BioNTech COVID-19 Vaccine booster 5 months after the last dose in their primary series.	**Booster Dose** Everyone ages 18 years and older should get a booster dose of either Pfizer-BioNTech or Moderna (COVID-19 vaccines) 5 months after the last dose in their primary series.	**Booster Dose** Everyone ages 18 years and older should get a booster dose of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) at least 2 months after the first dose of J&J/Janssen COVID-19 vaccine. You may get J&J/Janssen in some situations.
When Fully Vaccinated 2 weeks after 2nd dose	**When Fully Vaccinated** 2 weeks after 2nd dose	**When Fully Vaccinated** 2 weeks after 1st dose

Eligible For	IF YOU RECEIVED Pfizer-BioNTech	IF YOU RECEIVED Moderna	Johnson & Johnson's Janssen
Additional Primary Shot	People **age 5+** who are moderately or severely immunocompromised **should** get an additional primary shot of Pfizer-BioNTech COVID-19 vaccine Given 28 days after 2nd shot	People age 18+ who are moderately or severely immunocompromised **should** get an additional primary shot of Moderna COVID-19 vaccine Given 28 days after 2nd shot	No additional primary shot is recommended at this time
Booster Shot	• Teens **ages 12–17** should only get a Pfizer-BioNTech COVID-19 vaccine booster shot • People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 5 months after additional primary shot	People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 5 months after additional primary shot	People **age 18+** should get a booster shot of either Pfizer-BioNTech or Moderna (mRNA COVID-19 vaccines) in most situations Given 2 months after 1st shot

Northwestern Medicine®

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html

COVID-19: *Monoclonal Antibodies*



Northwestern Medicine®

Corti *et al*. ***Cell***. 2021; 184: 3086-3108.

Northwestern University NUCATS Clinical and Translational Sciences Institute

COVID-19: *Sotrovimab for Treatment*

Table 3. Efficacy Results in Adults with Mild-to-Moderate COVID-19 at Day 29

	Sotrovimab n = 528	Placebo n = 529
Progression of COVID-19 (defined as hospitalization for >24 hours for acute management of any illness or death from any cause) (Day 29)[a]		
Proportion (n, %)	6 (1%)	30 (6%)
Adjusted Relative Risk Reduction (95% CI)	79% (50%, 91%)	
All-cause mortality (up to Day 29)		
Proportion (n, %)	0	2 (<1%)

EUA Fact Sheet for Healthcare Providers. Accessed 10/2/21.

Sotrovimab

- Only Tier 1 Current
  - Immunocompromised
  - Unvaccinated with 3+ Risk Factors
  - Pregnant with 1+ Risk Factors
- In near future
  - Only patients within 5 days of symptom onset or first test

COVID-19: *Evusheld (Tixagevimab & Cilgavimab)*

AstraZeneca: Tixagevimab and Cilgavimab

- PROVENT Phase 3, Pre-Exposure Trial: 2:1 randomization for pre-exposure prophylaxis at increased risk of infection or poor response to vaccine
  - Outcomes among 3460 MAb vs 1737 placebo (5197 total)
  - Reduced risk of symptomatic COVID-19: 8 (0.2%) vs. 17 (1%)
  - Reduced risk of severe disease: 0 vs. 1
  - Reduced risk of death: 0 vs. 2

	AZD7442 (N=3441)	Placebo (N=1731)
n (%)	8 (0.2)	17 (1.0)
RRR (95% CI)	77% (46.0, 90.0)	
P-value	< 0.001	

- STORM CHASER Post-Exposure Trial: 2:1 randomization for post-exposure prophylaxis after confirmed to case of SARS-CoV2
- TACKLE Study pending
  - Early Treatment

Table 1: STORM CHASER analyses

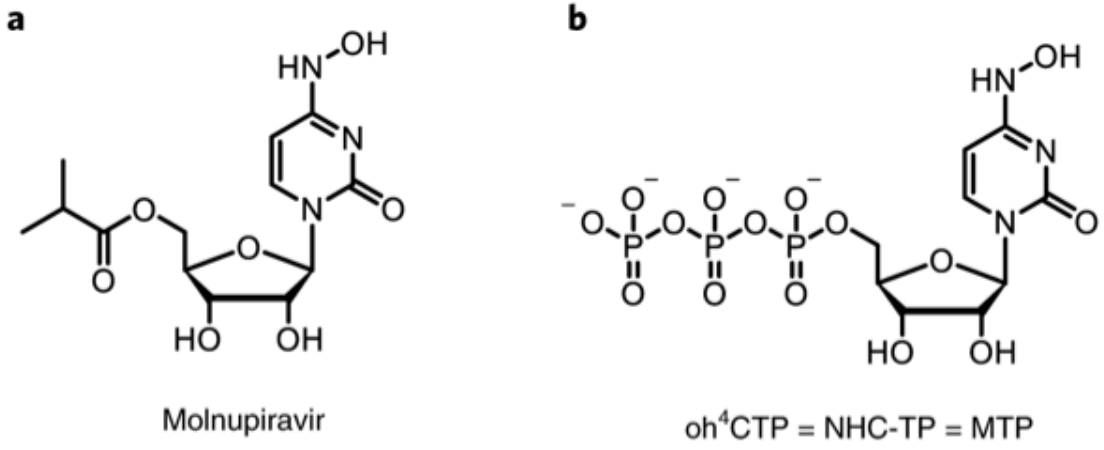
Baseline subgroup	Onset of case post dose	Number of cases / number of participants		Relative risk reduction (95% confidence interval)
		AZD7442 (300mg IM)	Placebo	
All participants (Primary analysis)	All cases	23 / 749 3%	17 / 372 4.6%	33% reduction[a] (-26 to 65)
PCR-negative[b] (Pre-planned subgroup analysis)	All cases	6 / 715 0.8%	11 / 358 3.1%	73% reduction (27 to 90)
PCR-negative[b] (Post hoc subgroup analysis)	≤7 days	5 / 715	5 / 358	51% reduction (-71 to 86)
	>7 days	1 / 710	6 / 353	92% reduction (32 to 99)

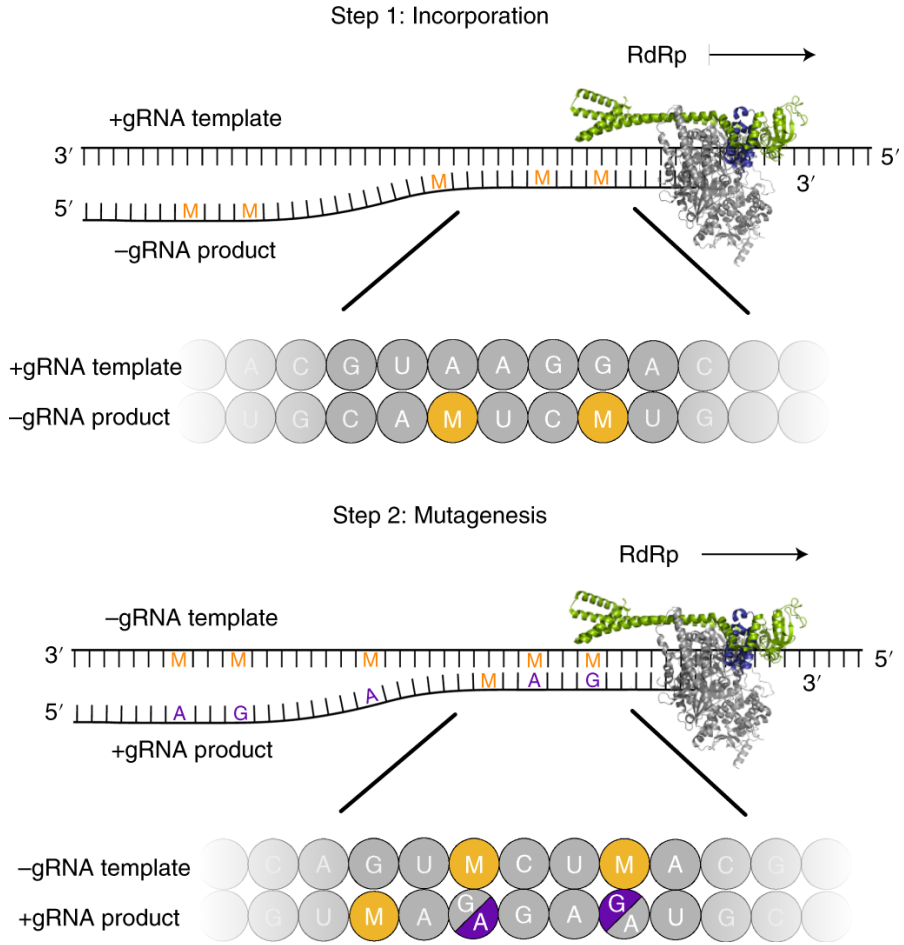
a: Not statistically significant.
b: Includes 974 participants (15 cases) confirmed PCR negative at baseline and 99 participants (2 cases) with PCR status missing at baseline.
48 participants were confirmed PCR positive at baseline with 23 cases (AZD7442: 17/34; placebo: 6/14).

Levin et al. IDWeek 2021 LB5 Abstract. https://www.astrazeneca.com/media-centre/press-releases/2021/update-on-azd7442-storm-chaser-trial.html. Accessed 10/2/21.

Molnupiravir: *Drug and Mechanisms*

- Activity against a broad range of RNA viruses
- Triphosphate of molnupiravir incorporated and induces mutation
- Dosed 800mg BID



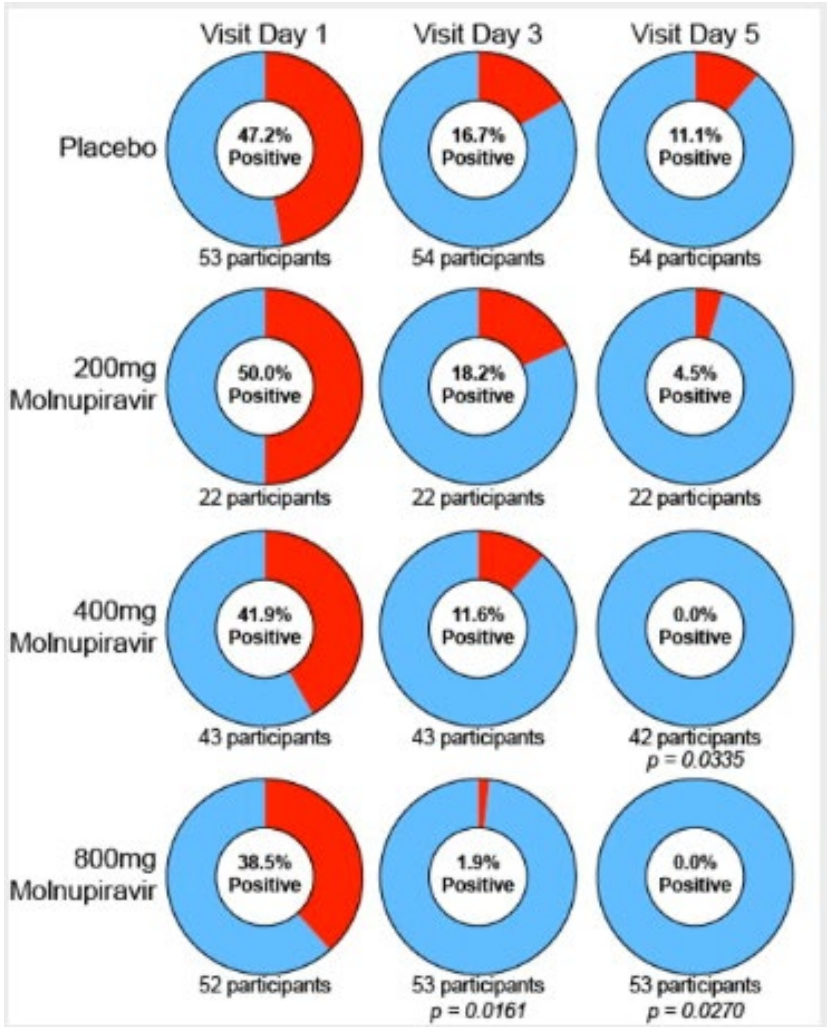


Kabinger *et al*. ***Nat Struc Mol Bio***. 2021; 28: 740-746.

Molnupiravir (EIDD-2801 - Merck/Ridgeback)

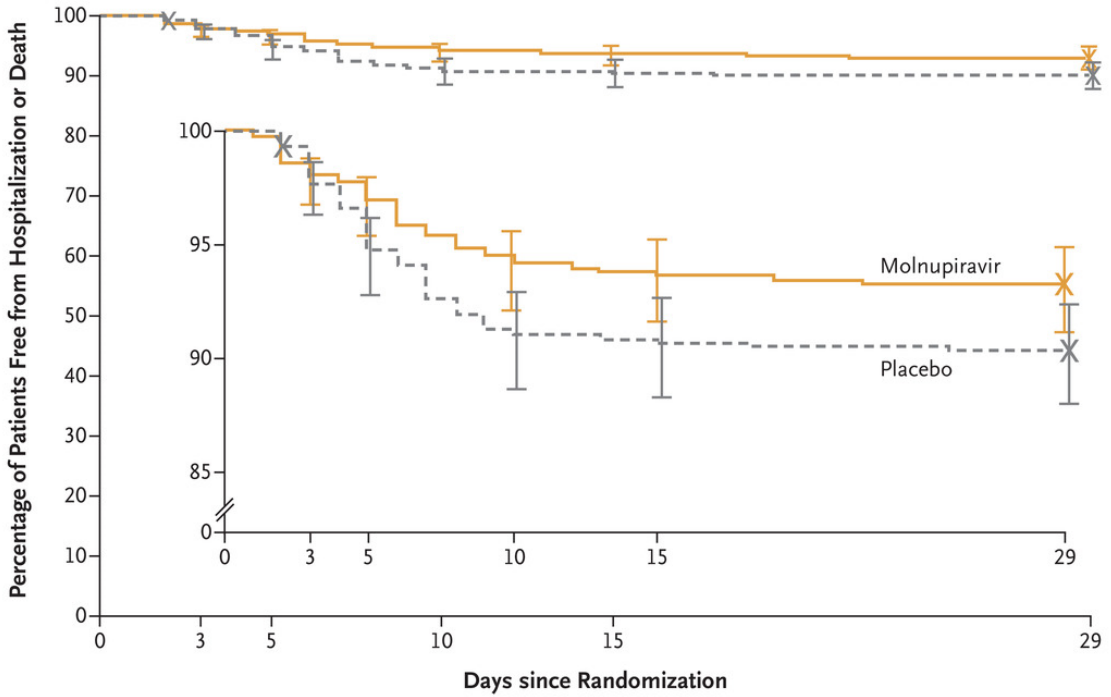
- Phase 2a Dose-Ranging Outpatient MOVe-OUT study (n = 202)
  - Reduced SARS-CoV-2 Culture at day 10: 24% in placebo vs. 0% in molnupiravir
  - Reduced risk of hospitalization
    - 4/107 (3.7%) molnupiravir vs. 4/34 (11.8%) placebo for all patients
    - 2/55 (3.6%) molnupiravir vs. 3/14 (21.4%) placebo for patients >60 yo
  - Greatest benefit when started ≤ 5 days after symptom onset

Number (%) of participants experiencing an event	Molnupiravir 200 mg N = 23	Molnupiravir 400 mg N = 62	Molnupiravir 800 mg N = 55	Placebo N = 62
Any adverse event	11 (47.8)	20 (32.3)	11 (20.0)	18 (29.0)
Adverse events reported by >5% subjects in any group				
Dizziness	2 (8.7)	1 (1.6)	0	0
Insomnia	2 (8.7)	1 (1.6)	1 (1.8)	4 (6.5)
Any adverse event grade 3 or higher	1 (4.3)	2 (3.2)	4 (7.3)	5 (8.1)
Any adverse event leading to discontinuation from study drug	0	1 (1.6)	1 (1.8)	1 (1.6)
Any serious adverse event	0	2 (3.2)	1 (1.8)	1 (1.6)
Any adverse event leading to death	0	0	0	1 (1.6)*



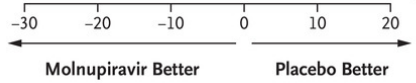
Fischer *et al*. ***medRxiv***. 2021:2021; DOI.org/10.1101/2021.06.17.21258639.

Molnupiravir (EIDD-2801)



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

Subgroup	Molnupiravir	Placebo	Absolute Risk Reduction (95% CI)
	no. of events/no. of participants		*percentage points*
Sex			
Female	16/379	27/344	−3.6 (−7.4 to −0.2)
Male	32/330	41/355	−1.9 (−6.5 to 2.8)
Days since onset of symptoms			
≤3	25/339	28/335	−1.0 (−5.2 to 3.2)
>3	23/370	40/364	−4.8 (−9.0 to −0.7)
Baseline Covid-19 severity			
Mild	19/395	27/376	−2.4 (−5.9 to 1.0)
Moderate	29/311	40/321	−3.1 (−8.1 to 1.8)
Baseline SARS-CoV-2 nucleocapsid antibody status			
Positive	5/136	2/146	2.3 (−1.7 to 7.1)
Negative	39/541	64/520	−5.1 (−8.8 to −1.6)
Risk factors for severe Covid-19			
>60 yr of age	12/118	16/127	−2.4 (−10.6 to 5.8)
Obese	29/535	46/507	−3.7 (−6.9 to −0.5)
Diabetes mellitus	17/107	17/117	1.4 (−8.2 to 11.1)
Serious heart condition	8/86	9/78	−2.2 (−12.4 to 7.5)
Race			
American Indian or Native American	18/207	21/199	−1.9 (−7.8 to 4.0)
Asian	7/25	7/23	−2.4 (not calculated)
Black	10/157	15/142	−4.2 (−11.1 to 2.2)
White	29/556	54/573	−4.2 (−7.3 to −1.2)
Baseline SARS-CoV-2 qualitative assay			
Detectable	45/614	61/613	−2.6 (−5.8 to 0.5)
Undetectable	0/54	0/51	0.0 (−7.1 to 6.7)
Unknown	3/41	7/35	−12.7 (−29.9 to 2.9)



Northwestern Medicine®

Jayk Bernal *et al*. ***N Engl J Med***. 2021. DOI: 10.1056/NEJMoa2116044

Northwestern University NUCATS Clinical and Translational Sciences Institute

Molnupiravir (EIDD-2801)

Table 2. Incidence of Adverse Events in the Safety Population.

Adverse Events and Discontinuation	Molnupiravir (N=710)	Placebo (N=701)	Estimated Difference (95% CI)*
	number (percent)		*percentage points*
Participants with adverse events			
≥1 Adverse event	216 (30.4)	231 (33.0)	−2.5 (−7.4 to 2.3)
≥1 Adverse event related to the assigned regimen†	57 (8.0)	59 (8.4)	−0.4 (−3.3 to 2.5)
≥1 Serious adverse event	49 (6.9)	67 (9.6)	−2.7 (−5.6 to 0.2)
≥1 Serious adverse event related to the assigned regimen†	0	1 (0.1)	−0.1 (−0.8 to 0.4)
Death	2 (0.3)	12 (1.7)	−1.4 (−2.7 to −0.5)
Participants who discontinued the assigned regimen because of an adverse event			
Adverse event	10 (1.4)	20 (2.9)	−1.4 (−3.1 to 0.1)
Adverse event related to the assigned regimen†	4 (0.6)	3 (0.4)	0.1 (−0.8 to 1.1)
Serious adverse event	5 (0.7)	13 (1.9)	−1.2 (−2.5 to 0.0)
Serious adverse event related to the assigned regimen†	0	0	0.0 (−0.5 to 0.5)

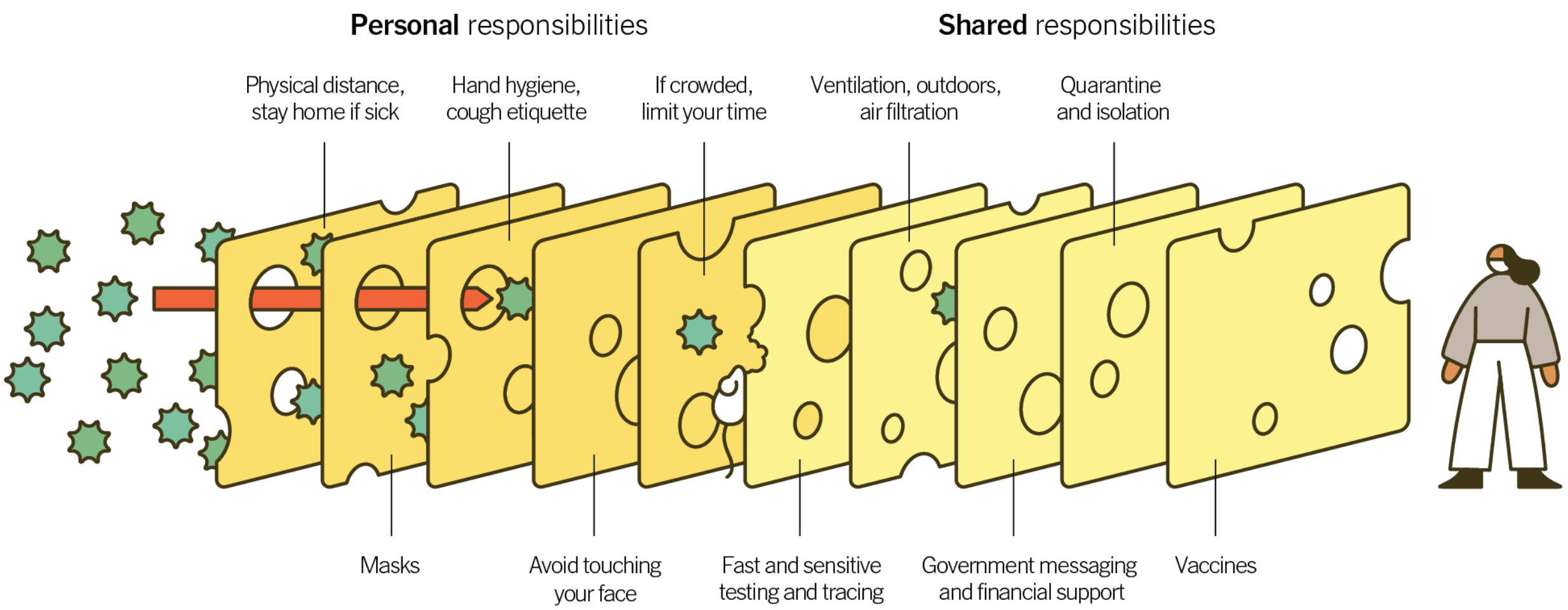
Jayk Bernal *et al*. ***N Engl J Med***. 2021. DOI: 10.1056/NEJMoa2116044

PF-07321332: *Drug, Mechanisms and Planned Studies*

- Coronavirus 3C Protease inhibitor
  - $3CL^{pro}$ digests the virus P1a and P1ab polyprotein
  - Prevents production of RdRp, the helicase, and the $3CL^{pro}$ itself among others
- Co-administered with ritonavir
- Major CyP450 Interactions
- Active vs. most CoVs

- Planned Studies
  - Post-Exposure Prophylaxis: 2,660 household contacts of cases
  - Outpatient management of symptomatic COVID-19
  - Inpatient treatment study IV without ritonivir (ACTIV3)
    - 24 hour infusion due to half-life issues

To Be Successful: *High Vaccine Rates and Layered Mitigation*



Source: Adapted from Ian M. Mackay (virologydownunder.com) and James T. Reason. Illustration by Rose Wong

Northwestern Medicine®

Don’t Forget your Mask: *Required Indoors!*

Northwestern Medicine®