Updates on Covid-19

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Missouri ACP Scientific Meeting
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Conflicts of Interest

None personally

Topics discussed are subject to change due to ongoing research and evolution of Covid-19

Objectives

- Updates in
  - Clinical COVID-19
  - Vaccination
  - Therapeutics
  - Variants
  - Testing
- Thoughts on the future

Case

Your 80 year old patient with hypertension, COPD, and DM comes in for a routine clinic visit. She is hesitant about new mRNA vaccinations and has yet to get any Covid vaccine due to this. She wants to discuss other options for Covid-19 prevention vs “just getting Covid because the new strain is mild.”

How would you advise her on the following?

- Non-mRNA Covid vaccines
- Evusheld?
- Potential short-term and long-term effects of Covid-19
- Protection after naturally-acquired immunity
- Her individual, specific risks with Covid-19 and/or vaccination

Clinical Updates

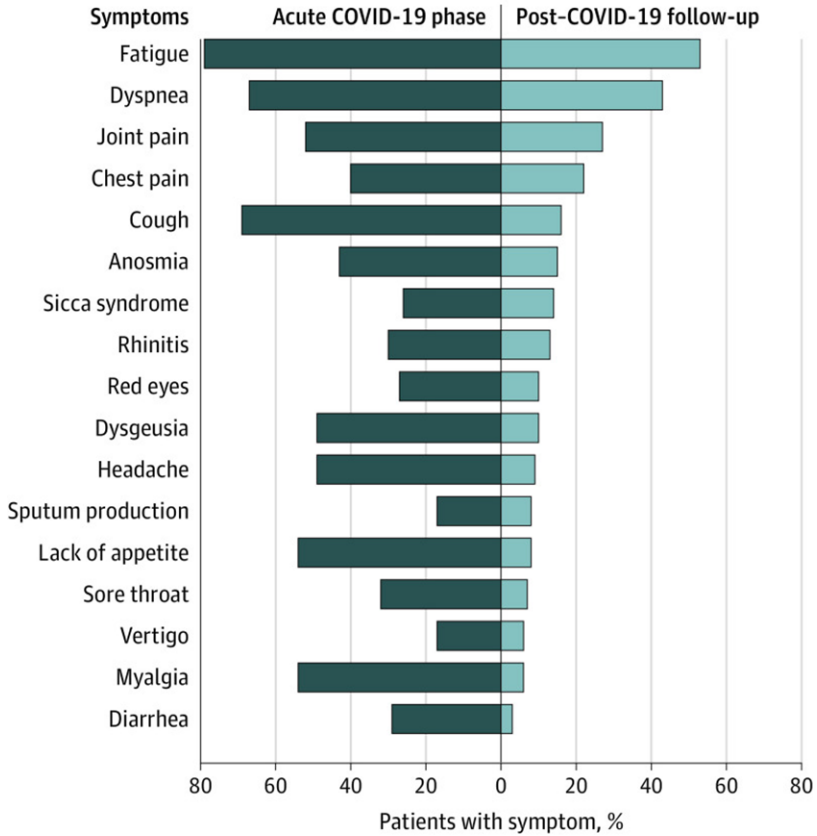
Long Covid

- How to define?
- Which terminology to use?
  - “Long Covid”
  - “Post-Covid condition(s)”
  - “Post-acute sequelae of SARS-CoV-2 infection (PASC)”
- Some aspects of prolonged recovery may be specific to COVID-19
- But, overlap with other conditions

Long Covid

- 2 stages of recovery (not infectivity)
- Acute Covid
  - Symptoms of Covid up to 4 weeks from onset
- Post-COVID condition (or whatever you choose to call it)
  - Broad range of physical, mental symptoms persisting > 2 months beyond acute phase
  - Symptoms impact a person's life
  - No alternative diagnoses

As of 10/2021 - ICD-10 code for "unspecified post-Covid conditions"



Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020 Aug 11;324(6):603-605. doi: 10.1001/jama.2020.12603. PMID: 32644129; PMCID: PMC7349096.

Long Covid

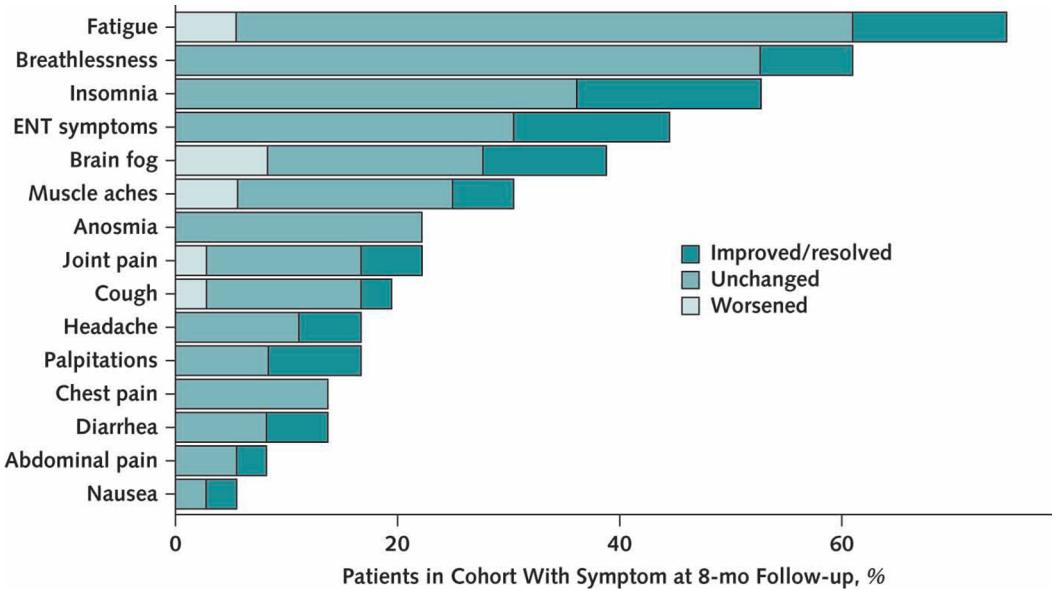
Guidance on "Long COVID" as a Disability Under the ADA, Section 504, and Section 1557

- If the condition or any of its symptoms is a "physical or mental" impairment that "substantially limits" one or more major life activities
- An individualized assessment is necessary to determine whether a person's long COVID symptoms substantially limits a major life activity

Guidance on "Long COVID" as a Disability Under the ADA, Section | HHS.gov

Long Covid - Vaccination

- Post-Covid vaccination may help long Covid symptoms



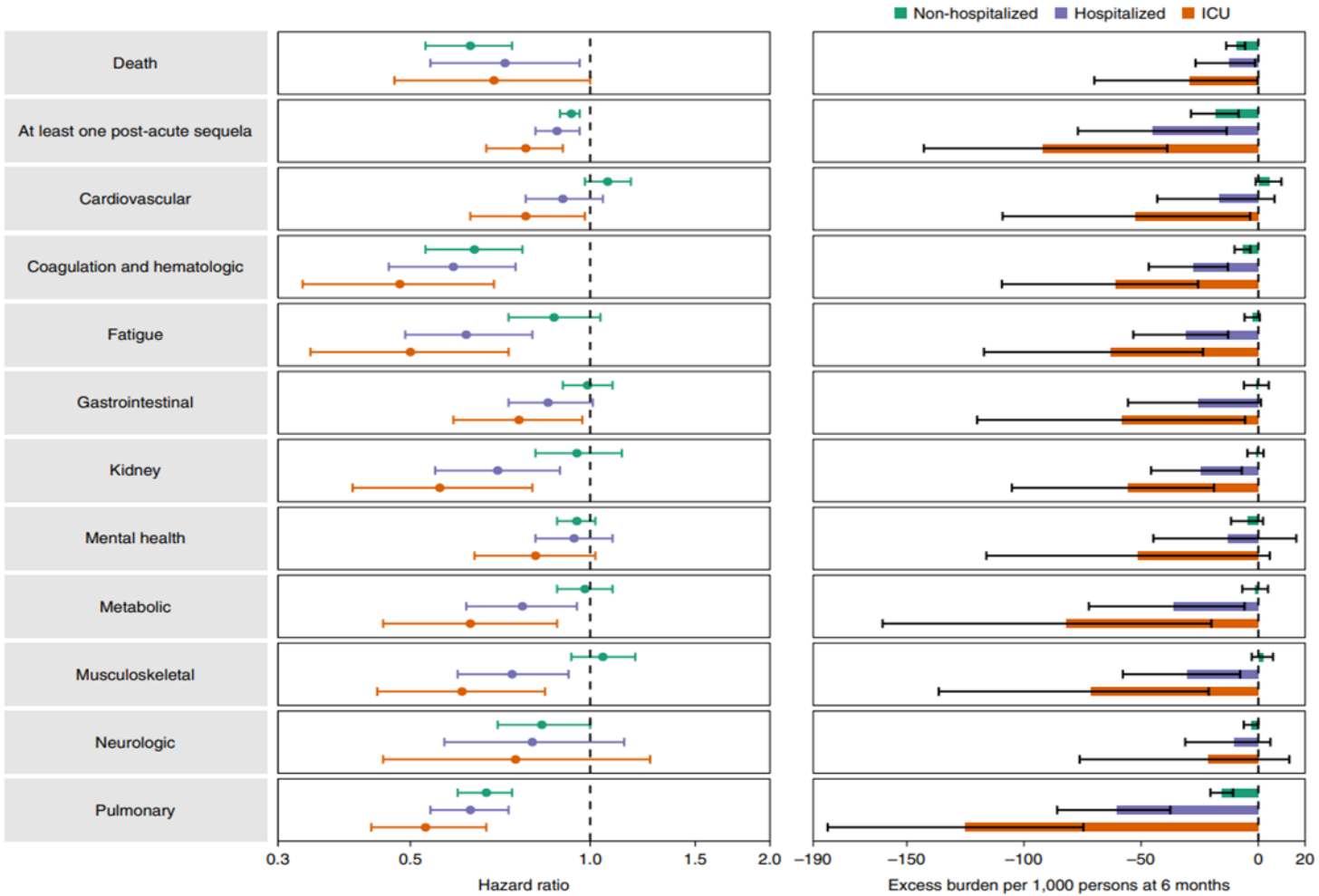
Arnold DT, Milne A, Samms E, Stadon L, Maskell NA, Hamilton FW. Symptoms After COVID-19 Vaccination in Patients With Persistent Symptoms After Acute Infection: A Case Series. Ann Intern Med. 2021 Sep;174(9):1334-1336. doi: 10.7326/M21-1976. Epub 2021 May 25. PMID: 34029484; PMCID: PMC8252827.

Long Covid - Vaccination

- Risk of post-Covid sequelae (including “long Covid”) was lower in vaccinated vs unvaccinated
  - mRNA vaccines more protective than J&J
  - Vaccination was progressively more protective w/ higher disease acuity
  - Most pronounced for pulmonary and coagulation disorders
- However, breakthrough Covid infection resulted in higher risk of death and post-acute sequelae compared to seasonal influenza
  - So, post-Covid symptoms are not trivial even in vaccinated individuals

Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. Nat Med. 2022 Jul;28(7):1461-1467. doi: 10.1038/s41591-022-01840-0. Epub 2022 May 25. PMID: 35614233; PMCID: PMC9307472.

Long Covid - Vaccination



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Long Covid - Vaccination in HCWs

- Observational study March 2020 - April 2022
- 9 Italian healthcare facilities, 2560 HCWs with routine Covid PCR testing
  - 739 + Covid during study period
- All HCWs got primary Pfizer primary series (Dec 2020) & booster (Nov 2021)
- “Long Covid” in this study = at least 1 Covid-related symptom persisting beyond 4 weeks
- 229 of 739 Covid+ HCWs had Long Covid symptoms

Azzolini E, Levi R, Sarti R, Pozzi C, Mollura M, Mantovani A, Rescigno M. Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. JAMA. 2022 Aug 16;328(7):676-678. doi: 10.1001/jama.2022.11691. PMID: 35796131; PMCID: PMC9250078.

Long Covid - Vaccination in HCWs

- Number of vaccine doses was associated with lower long Covid prevalence
- Compared Covid waves - long Covid more common in wild type

			Had long COVID		Did not have long COVID	
COVID-19 wave[d]						<.001[b]
1	**Wild type**	74	48.1 (39.9-56.2)	80	51.9 (43.8-60.1)	
2	**Alpha**	108	35.9 (30.5-41.6)	193	64.1 (58.4-69.5)	
3	**Delta + Omicron**	47	16.5 (12.4-21.4)	237	83.5 (78.6-87.6)	
Vaccine doses before SARS-CoV-2 infection[e]						<.001[b]
0		176	41.8 (37.0-46.7)	245	58.2 (53.3-63.0)	
1		3	30.0 (6.7-65.2)	7	70.0 (34.8-93.3)	
2		8	17.4 (7.8-31.4)	38	82.6 (68.6-92.2)	
3		42	16.0 (11.8-21.0)	220	84.0 (79.0-88.2)	

Azzolini E, Levi R, Sarti R, Pozzi C, Mollura M, Mantovani A, Rescigno M. Association Between BNT162b2 Vaccination and Long COVID After Infections Not Requiring Hospitalization in Health Care Workers. JAMA. 2022 Aug 16;328(7):676-678. doi: 10.1001/jama.2022.11691. PMID: 35796131; PMCID: PMC9250078.

Long Covid in Pediatrics

- Seropositive vs seronegative children
- Most frequently reported symptoms between 10/2020 - 4/2021
- 4 of 109 seropositive children with symptoms lasting > 12 weeks
  - Tiredness most common (in 4%)
- 10 of 109 seropositive children with symptoms lasting > 4 weeks

Table. Participant Characteristics, Most Frequently Reported Symptoms After Serologic Testing (October 2020 Through March-April 2021), and Self-rated Health Among Seropositive and Seronegative Children

	No. (%)	
	Seropositive (n = 109)	Seronegative (n = 1246)
Female sex	58 (53)	669 (54)
Age, y		
6-11	66 (61)	703 (56)
12-16	43 (39)	543 (44)
≥1 Symptom lasting >12 wk	4 (4)	28 (2)
Tiredness	3 (3)	10 (1)
Difficulty concentrating	2 (2)	8 (1)
Increased need for sleep	2 (2)	0
Congested or runny nose	1 (1)	3 (<1)
Stomachache	1 (1)	3 (<1)
Chest tightness	1 (1)	0
≥1 Symptom lasting >4 wk	10 (9)	121 (10)
Tiredness	7 (6)	51 (4)
Headache	5 (5)	39 (3)
Congested or runny nose	3 (3)	40 (3)
Stomachache	3 (3)	18 (1)
Sleep disturbances	3 (3)	14 (1)
Cough	2 (2)	15 (1)
Self-rated health[a]		
Excellent	43 (41)	497 (41)
Good	56 (53)	680 (55)
Fair	5 (5)	48 (4)
Poor	2 (2)	2 (<1)

[a] The item self-rated health was assessed with the Health Behavior in School-Aged Children–Survey Instrument (eMethods in the Supplement). Self-rated health was not reported for 3 seropositive and 19 seronegative children.

Radtke T, Ulyte A, Puhan MA, Kriemler S. Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents. *JAMA*. 2021;326(9):869–871. doi:10.1001/jama.2021.11880

Thrombotic Events in Covid-19

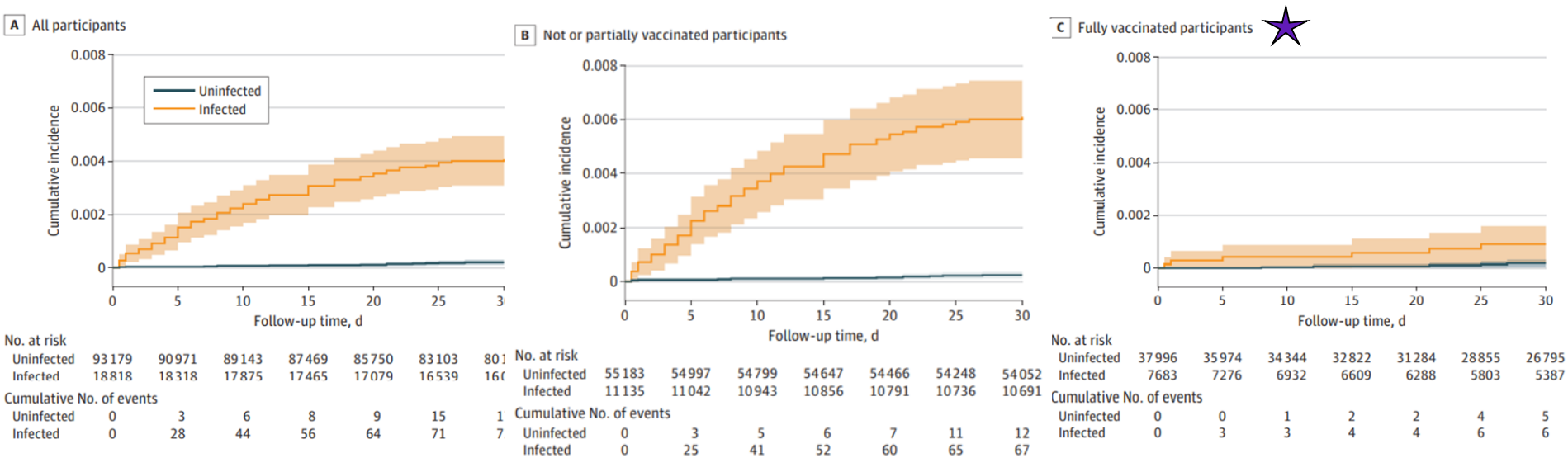
- VTE risk is high in Covid-19 patients (hospitalized 14.7%, ICU 23.2%)

- What about VTE risk in ambulatory Covid-19 patients?
- And, what are the clinical and genetic risk factors for VTE in Covid?

Xie J, Prats-Uribe A, Feng Q, Wang Y, Gill D, Paredes R, Prieto-Alhambra D. Clinical and Genetic Risk Factors for Acute Incident Venous Thromboembolism in Ambulatory Patients With COVID-19. JAMA Intern Med. 2022 Aug 18. doi: 10.1001/jamainternmed.2022.3858. Epub ahead of print. PMID: 35980616.

Thrombotic Events in Covid-19

Figure 1. Cumulative Incidence Curves of Venous Thromboembolism Within 30 Days Overall and in Subgroups by Vaccination Status



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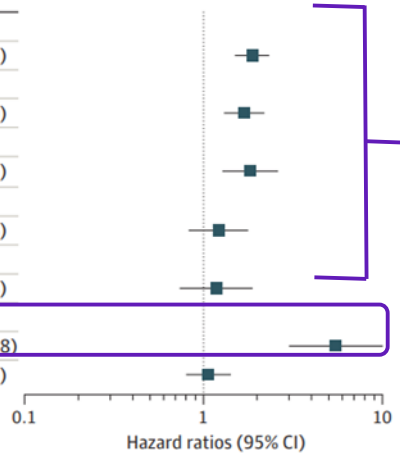
Thrombotic Events in Covid-19

Figure 2. Hazard Ratio of Clinical Risk Factors for Venous Thromboembolism (VTE) Among Patients With COVID-19

Variable	Hazard ratios (95% CI)
Age (per 10-y increase)	
Infection-related VTE	1.87 (1.50-2.33)
Sex (male vs female)	
Infection-related VTE	1.69 (1.30-2.19)
Obesity (BMI ≥30 vs <30)	
Infection-related VTE	1.83 (1.28-2.61)
Socioeconomic status (higher 50% IMD vs lower 50%)	
Infection-related VTE	1.21 (0.83-1.78)
Ethnicity (other ethnic vs White)	
Infection-related VTE	1.18 (0.74-1.88)
Vaccination status (not or partial vs full)	
Infection-related VTE	5.50 (3.00-10.08)
Other VTE	1.07 (0.80-1.42)



Known VTE risk factors

Table 3. Association of Inherited Thrombophilia With Venous and Arterial Thromboembolism Among Patients With COVID-19[a]

	Primary outcome, venous thromboembolism			Negative outcome, arterial thromboembolism		
	HR (95% CI)			HR (95% CI)		
Exposure	Unadjusted	Adjusted	*P* value	Unadjusted	Adjusted	*P* value
Inherited thrombophilia[b]	1.82 (1.02-3.23)	2.05 (1.15-3.66)	.01	0.94 (0.51-1.73)	0.98 (0.53-1.80)	.95
Factor V Leiden	1.97 (1.03-3.76)	2.17 (1.13-4.15)	.02	0.97 (0.48-1.98)	0.99 (0.49-2.01)	.97
Prothrombin G20210A[c]	1.31 (0.42-4.11)	1.52 (0.48-4.79)	.45	0.84 (0.27-2.62)	0.91 (0.29-2.84)	.86
Positive control						
Continuous PRS[d]	1.29 (1.08-1.54)	1.34 (1.11-1.60)	<.001	NC	NC	NC
Categorical PRS[e]	1.39 (0.73-2.66)	1.54 (0.80-2.95)	.20	NC	NC	NC

Xie J, Prats-Uribe A, Feng Q, Wang Y, Gill D, Paredes R, Prieto-Alhambra D. Clinical and Genetic Risk Factors for Acute Incident Venous Thromboembolism in Ambulatory Patients With COVID-19. JAMA Intern Med. 2022 Aug 18. doi: 10.1001/jamainternmed.2022.3858. Epub ahead of print. PMID: 35980616.

Covid and VTE risk

American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19

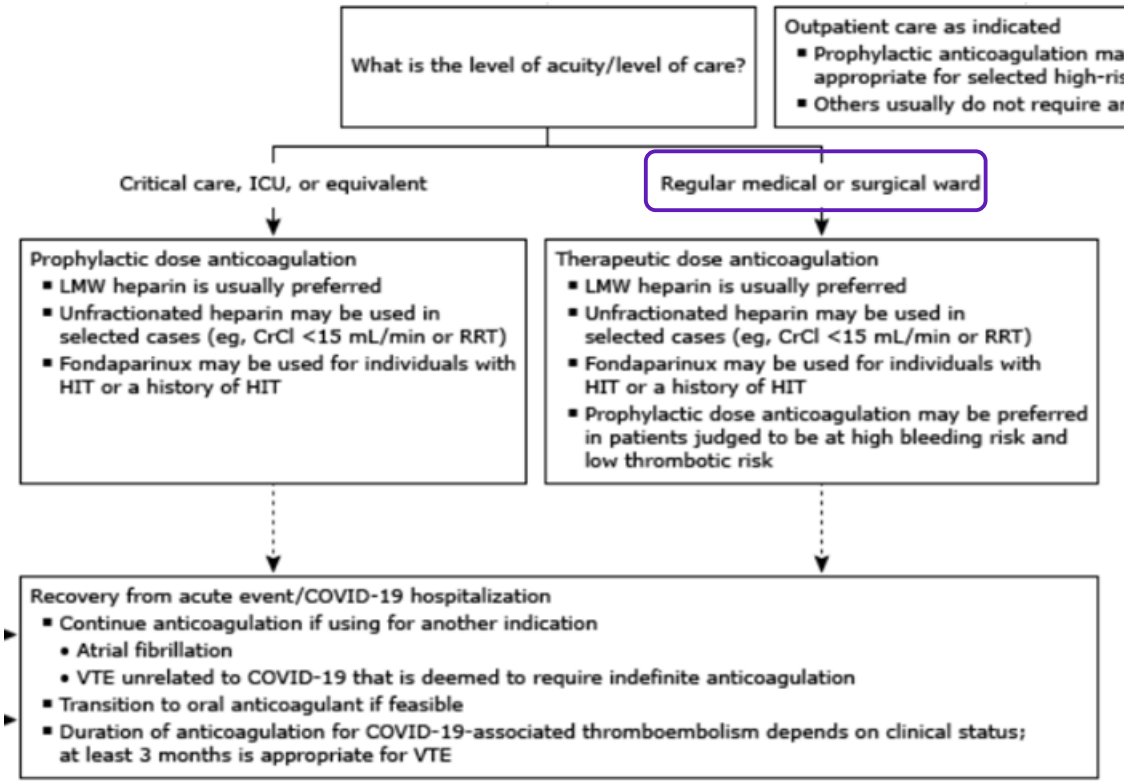
- May 2022 update
- The panel suggested therapeutic anticoagulation (rather than prophylactic dose) for all acutely ill Covid-19 patients without suspicion for or confirmed VTE
- Must individualize to patient's risk for thrombosis vs bleeding
- Based on low quality evidence, need more trials
- Heparin or LMWH may be preferred, majority of evidence

Cuker A, Tseng EK, Nieuwlaat R, Angchaisuksiri P, Blair C, Dane K, DeSancho MT, Diuguid DL, Griffin DO, Kahn SR, Klok FA, Lee AI, Neumann I, Pai A, Righini M, Sanfilippo K, Siegal DM, Skara M, Terrell DR, Touri K, Akl EA, Al Jabiri RN, Al Jabiri YN, Barbara AM, Bognanni A, Boulos M, Brignardello-Petersen R, Charide R, Colunga-Lozano LE, Dearness KL, Darzi AJ, Hussein H, Karam SG, Mansour R, Morgano GP, Morsi RZ, Muti-Schünemann G, Nadim MK, Philip BA, Qiu Y, Benitez YR, Stevens A, Solo K, Wiercioch W, Mustafa RA, Schünemann HJ. American Society of Hematology living guidelines on the use of anticoagulation for thromboprophylaxis in patients with COVID-19: January 2022 update on the use of therapeutic-intensity anticoagulation in acutely ill patients. Blood Adv. 2022 May 3:bloodadvances.2022007561. doi: 10.1182/bloodadvances.2022007561. Epub ahead of print. PMID: 35503027; PMCID: PMC9068240.

Covid and VTE Risk

- Hospitalized but non-critical - consider therapeutic anticoagulation
- Heparin → oral anticoagulant on recovery
- Duration? 3 months

- Outpatient? Rarely, only if very high risk



IDSA Update 8/30/22: Bacterial Coinfections

- Difference between coinfection (present at time of Covid-19 diagnosis) vs superinfection (occurring later during Covid course)
- Early in pandemic in Spanish study > 75% of Covid-19 cases received antibiotics at time of Covid diagnosis
- But coinfection rates are low
  - Early studies in China suggested coinfection rates around 8%, but newer studies:
  - 38 hospitals in Michigan: 1705 patients included, only 3.5% had a bacterial co-infection, though 59.5% received antibacterial drugs
  - 1016 patients in 5 Maryland hospitals: bacterial coinfection in 1.2%
  - Meta-analysis including 3338 patients in 24 studies reported bacterial co-infection in 3.5%

Bhimraj A, Morgan RL, Shumaker AH, Baden L, Cheng VC, Edwards KM, Gallagher JC, Gandhi RT, Muller WJ, Nakamura MM, O'Horo JC, Shafer RW, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2022; Version 10.0.0.

IDSA Update 8/30/22: Bacterial Coinfections

- Superinfection rates are more heterogeneous
  - Entire hospitalized cohorts perhaps 4-21%
  - Critical care Covid-19 patients with ARDS / on mechanical ventilation perhaps 27-44%
  - Bacterial, fungal
- Antibiotic use during first 48 hours of admission is an independent risk factor for development of superinfections, including MDR, later in hospital course
- A real opportunity to improve antimicrobial stewardship

- So, how can we determine the need for antibiotics at time of diagnosis?
  - #1 is clinical judgment - easier said than done sometimes

Bhimraj A, Morgan RL, Shumaker AH, Baden L, Cheng VC, Edwards KM, Gallagher JC, Gandhi RT, Muller WJ, Nakamura MM, O'Horo JC, Shafer RW, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2022; Version 10.0.0.

Smith L, Karaba SM, Amoah J, et al. Hospital-acquired infections among adult patients admitted for coronavirus disease 2019 (COVID-19). Infect Control Hosp Epidemiol 2021: 1-4.

IDSA Update 8/30/22: Bacterial Coinfections

- *Procalcitonin - not very helpful*
- One study of 962 patients found
  - Procalcitonin is frequently initially elevated in Covid-19 patients withOUT bacterial CAP
    - In this study, 37% without coinfection had elevated procal (> 0.25 ng/mL)
    - Other studies have shown the same (ranging 10-35%)
  - Procalcitonin did NOT add anything to clinical reasoning among providers
  - LOW procalcitonin did not discourage early discontinuation of antibiotics
  - So, it doesn't change our diagnosis compared to clinical judgment alone, we don't use it to STOP antibiotics early, but it does lead to more unnecessary antibiotic use

Fabre V, Karaba S, Amoah J, Robinson M, Jones G, Dzintars K, Katz M, Landrum BM, Qasba S, Gupta P, Klein E, Cosgrove SE. The role of procalcitonin results in antibiotic decision-making in coronavirus disease 2019 (COVID-19). Infect Control Hosp Epidemiol. 2022 May;43(5):570-575.

IDSA Update 8/30/22: Bacterial Coinfections

- A group in the UK looked at other markers for distinguishing Covid-19 with bacterial coinfection from those without
  - Decline in CRP after 48-72 hours on antibiotics - trend may be helpful
  - Initially elevated WBC count is helpful - 6.78 COVID-19 vs. 12.48 CABP

Table 3. Discriminatory performance of WCC and ΔCRP cut-offs for diagnosis of CAP in RFH patients

Cut-off[a]	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio	Negative likelihood ratio
WCC > 8.2	79.2	58.8	24.6	94.4	1.92	0.35
WCC > 9.4	69.8	70.0	28.2	93.2	2.32	0.43
CRP > 65	84.9	33.2	17.7	92.9	1.27	0.45
CRP > 160	49.1	71.6	22.6	89.2	1.73	0.71
WCC > 8.2 AND CRP > 65	69.8	70.3	28.5	93.2	2.35	0.43
WCC > 8.2 OR CRP > 65	94.3	21.7	16.9	95.8	1.21	0.26
ΔCRP < −15	62.3	75.0	29.7	92.2	2.50	0.50
ΔCRP < 0	73.6	65.2	26.4	93.6	2.11	0.41
WCC > 8.2 AND ΔCRP < 0	62.3	80.8	35.4	92.6	3.25	0.47
WCC > 8.2 OR ΔCRP < 0	90.6	43.1	21.2	96.4	1.59	0.22

Populations included were all patients admitted >48 h for CAP ($n = 53$) and MR− COVID-19 ($n = 313$).
[a]WCC values represent cell numbers $\times 10^6$/mL. CRP values represent concentrations in mg/L.

Mason CY, Kanitkar T, Richardson CJ, Lanzman M, Stone Z, Mahungu T, Mack D, Wey EQ, Lamb L, Balakrishnan I, Pollara G. Exclusion of bacterial co-infection in COVID-19 using baseline inflammatory markers and their response to antibiotics. J Antimicrob Chemother. 2021 Apr 13;76(5):1323-1331.

IDSA Updates 8/30/22

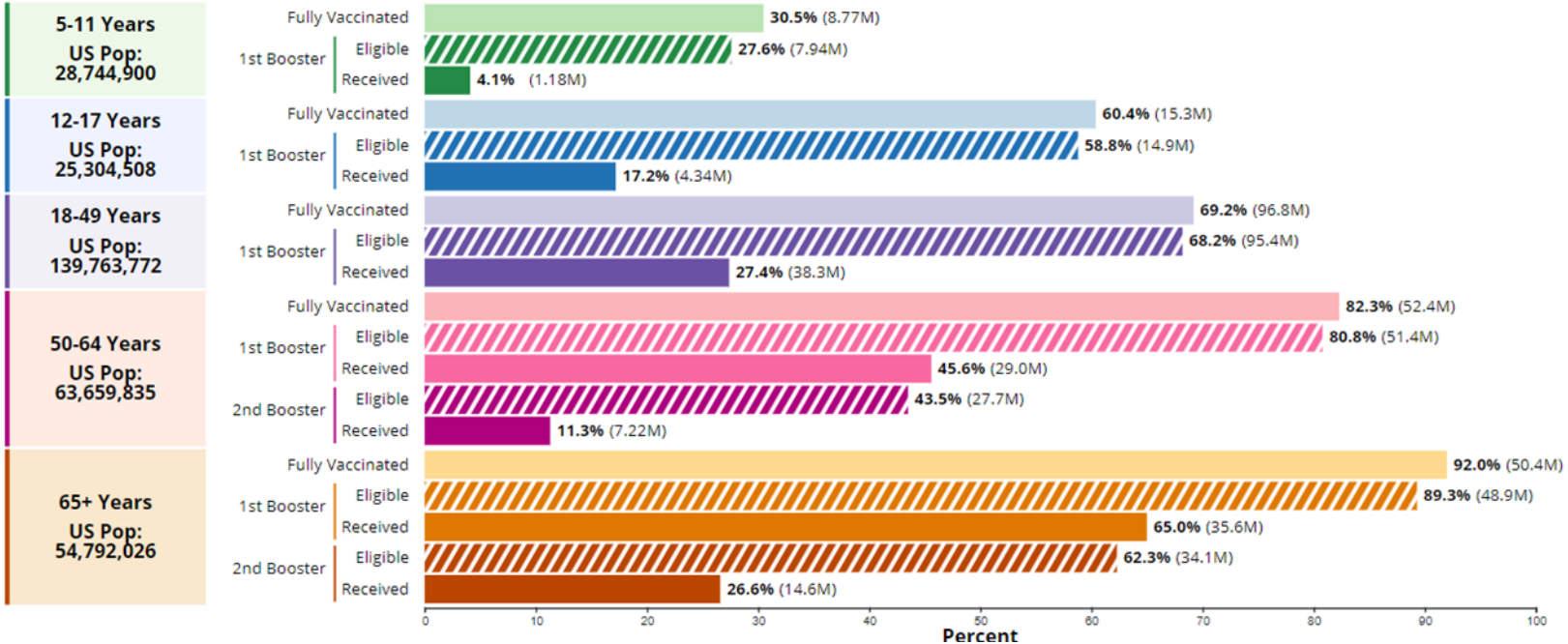
- Added two other new updated sections:
- How to Approach a Patient when Considering Pharmacologic Treatments for COVID-19
- Pediatric Considerations for Treatment of SARS-CoV-2 Infection and Multisystem Inflammatory Syndrome in Children

Bhimraj A, Morgan RL, Shumaker AH, Baden L, Cheng VC, Edwards KM, Gallagher JC, Gandhi RT, Muller WJ, Nakamura MM, O'Horo JC, Shafer RW, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America 2022; Version 10.0.0.

Vaccination Updates

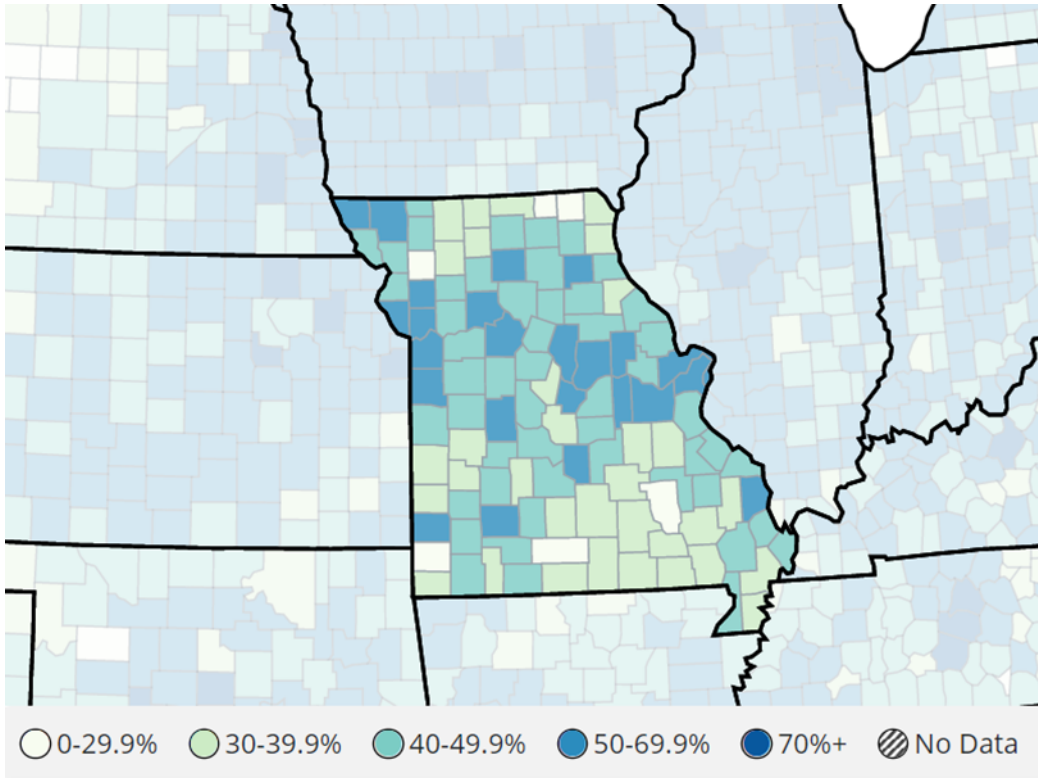
Where are we now? - US

Primary Series Completion, Booster Dose Eligibility, and Booster Dose Receipt by Age, United States



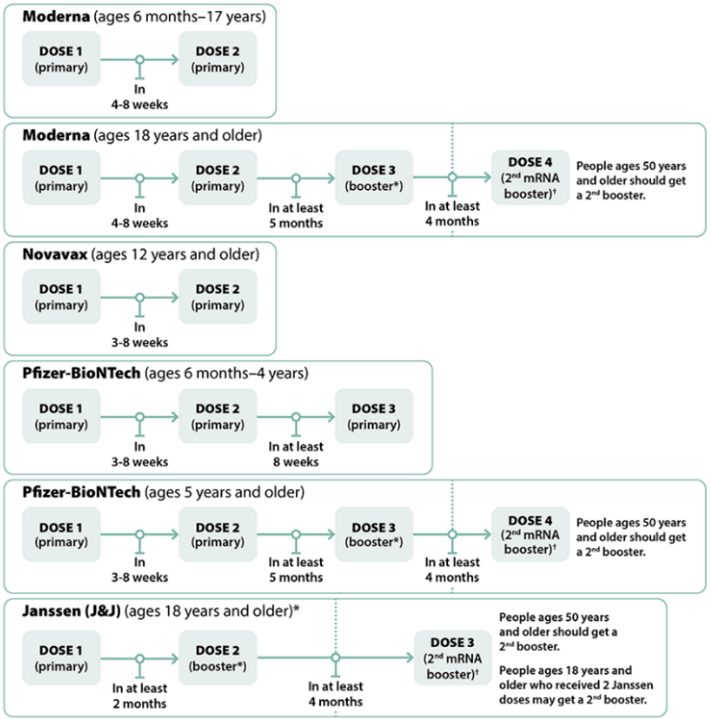
CDC

Where are we now? - MO

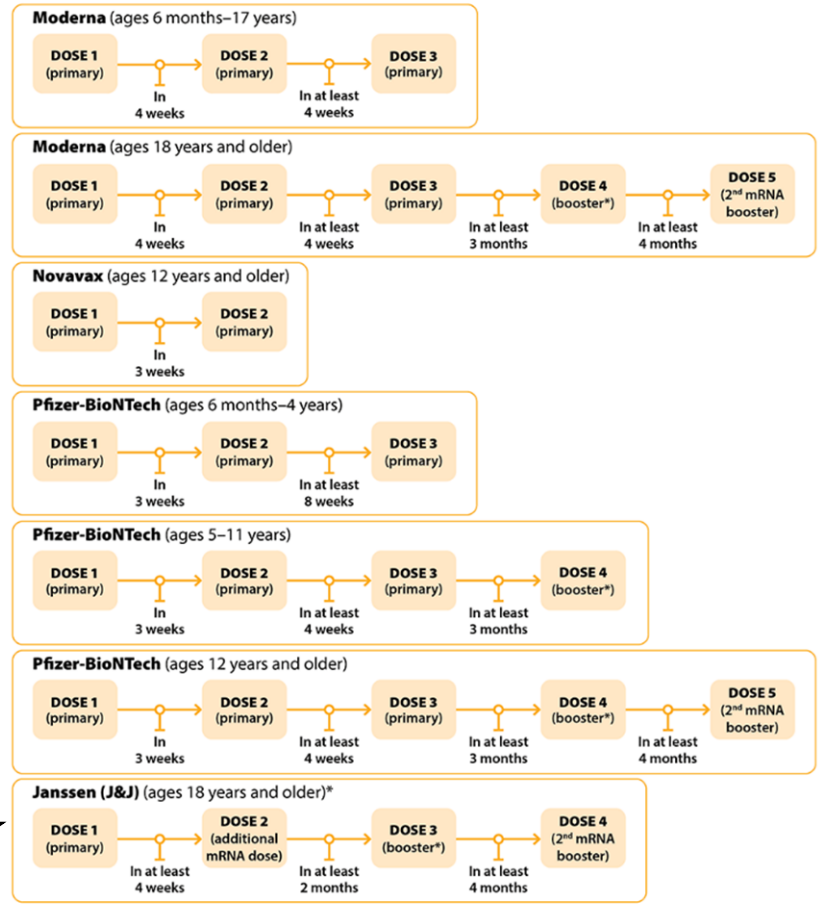


Vaccine schedules

COVID-19 Vaccination Schedule for People who are **NOT** Moderately or Severely Immunocompromised



COVID-19 Vaccination Schedule for People who **ARE** Moderately or Severely Immunocompromised

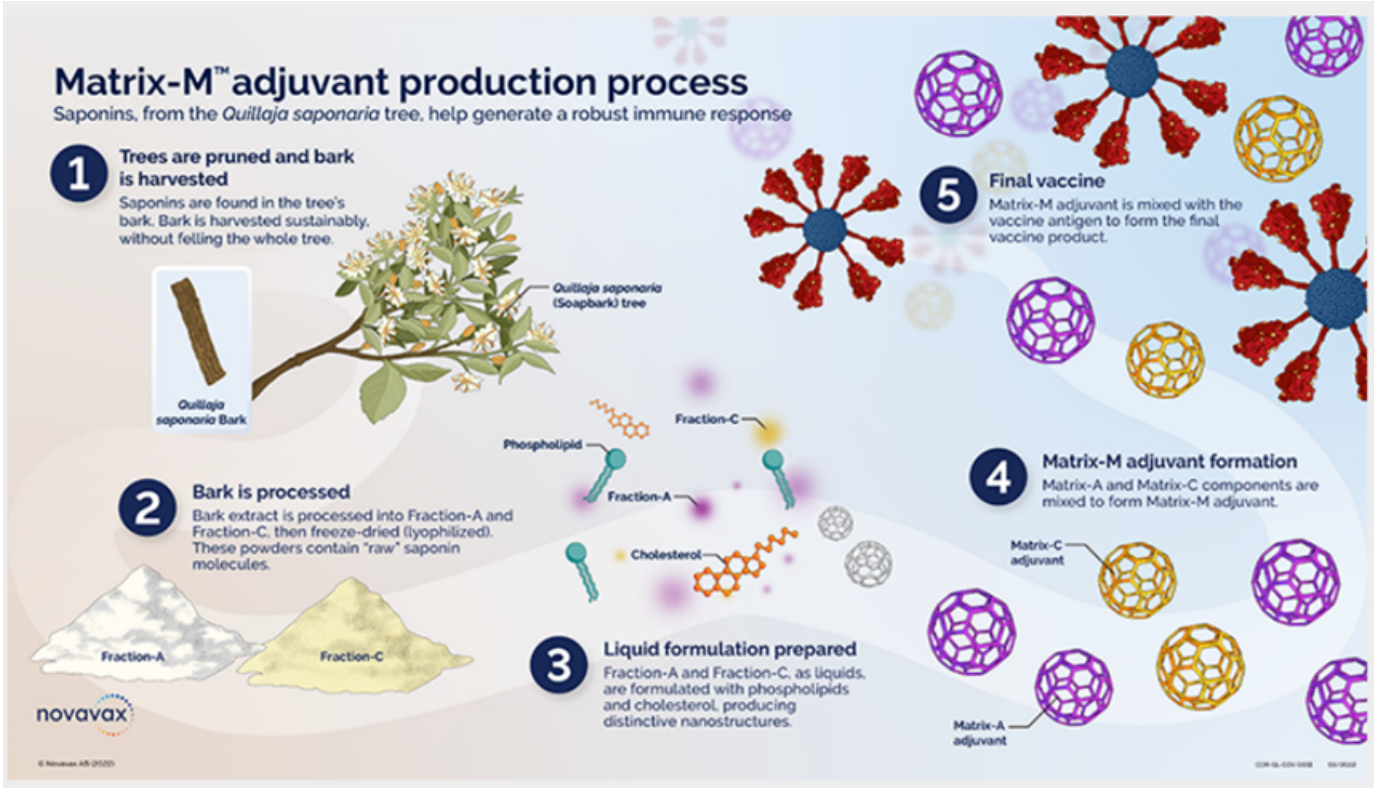


Novavax

- The new-ish kid on the block - received EUA for adults on July 13
- EUA for adolescents 12-17 on August 19
- Global clinical trial for ages 6-11 initiated August 4

- What is Novavax? Recombinant protein subunit vaccine with potent adjuvant
  - Other recombinant protein vaccines = Engerix-B (hep B), Shingrix, Gardasil (HPV)
- What does the data say?

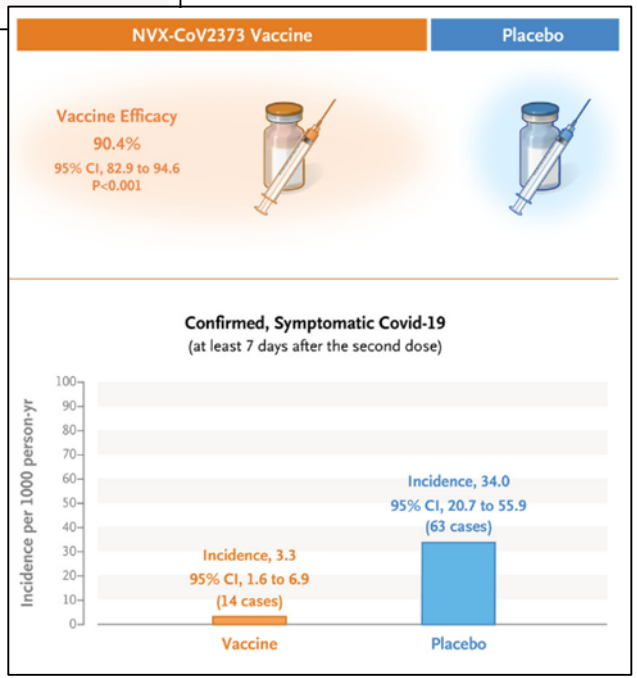
Novavax


Matrix-M™ adjuvant production process
Saponins, from the Quillaja saponaria tree, help generate a robust immune response
1
Trees are pruned and bark is harvested
Saponins are found in the tree's bark. Bark is harvested sustainably, without felling the whole tree.
Quillaja saponaria Bark
Quillaja saponaria (Soapbark) tree
2
Bark is processed
Bark extract is processed into Fraction-A and Fraction-C, then freeze-dried (lyophilized). These powders contain "raw" saponin molecules.
Fraction-A
Fraction-C
3
Liquid formulation prepared
Fraction-A and Fraction-C, as liquids, are formulated with phospholipids and cholesterol, producing distinctive nanostructures.
Phospholipid
Fraction-C
Fraction-A
Cholesterol
4
Matrix-M adjuvant formation
Matrix-A and Matrix-C components are mixed to form Matrix-M adjuvant.
Matrix-C adjuvant
Matrix-A adjuvant
5
Final vaccine
Matrix-M adjuvant is mixed with the vaccine antigen to form the final vaccine product.
novavax

Novavax efficacy

Vaccine Efficacy in Specific Subgroups

	Vaccine Efficacy (95% CI)	Placebo	NVX-CoV2373
Per-Protocol Population	89.7% (80.2 to 94.6)	96/7019	10/7020
Non-B.1.1.7 Variant	96.4% (73.8 to 99.5)	28/7020	1/7020
B.1.1.7 Variant	86.3% (71.3 to 93.5)	58/7020	8/7020



- US/Mexico trial: 90.4%
  - Took place before Delta emergence, primarily alpha variant
- UK trial:
  - Overall efficacy 89.7%
  - With B.1.1.7 (alpha): slightly lower at 86.3%
- Adverse effects?
  - Similar to placebo
  - 5 cases myocarditis vs 1 in placebo group

Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, Chadwick DR, Clark R, Cosgrove C, Galloway J, Goodman AL, Heer A, Higham A, Iyengar S, Jamal A, Jeanes C, Kalra PA, Kyriakidou C, McAuley DF, Meyrick A, Minassian AM, Minton J, Moore P, Munsoor I, Nicholls H, Osanlou O, Packham J, Pretswell CH, San Francisco Ramos A, Saralaya D, Sheridan RP, Smith R, Soiza RL, Swift PA, Thomson EC, Turner J, Viljoen ME, Albert G, Cho I, Dubovsky F, Glenn G, Rivers J, Robertson A, Smith K, Toback S; 2019nCoV-302 Study Group. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med. 2021 Sep 23;385(13):1172-1183.

Dunkle LM, Kotloff KL, Gay CL, Áñez G, Adelglass JM, Barrat Hernández AQ, Harper WL, Duncanson DM, McArthur MA, Florescu DF, McClelland RS, Garcia-Fragoso V, Riesenberg RA, Musante DB, Fried DL, Safirstein BE, McKenzie M, Jeanfreau RJ, Kingsley JK, Henderson JA, Lane DC, Ruíz-Palacios GM, Corey L, Neuzil KM, Coombs RW, Greninger AL, Hutter J, Ake JA, Smith K, Woo W, Cho I, Glenn GM, Dubovsky F; 2019nCoV-301 Study Group. Efficacy and Safety of NVX-CoV2373 in Adults in the United States and Mexico. N Engl J Med. 2022 Feb 10;386(6):531-543. doi: 10.1056/NEJMoa2116185.

The “niche” role of Novavax

- Great efficacy
- Great safety
- Hopefully a *good option for those who remain hesitant about the “new” mRNA technology*
- Perhaps a good option for *heterogeneous boosters*, once approved

- Phase I/II data looking at Novavax CIC (Covid-Influenza Combined) vaccine showed good tolerability and immunogenicity
- Phase II dose confirmation study should begin by end of 2022
- Phase III trial planned for 2023 influenza season at the earliest

Changes in vaccine efficacy with viral evolution

- Lancet *Preprint* study from Portugal evaluated vaccine efficacy during time of transition from Omicron BA.2 to BA.5…
- Vaccine efficacy appeared to be similar between the strains
- Reinfection risk in those NOT vaccinated was higher for BA.5 vs BA.2
  - If infected with pre-Omicron strain: natural immunity only 14% protective against BA.5
  - If infected with BA.1 strain: natural immunity 46% effective against BA.5
  - If infected with BA.2 strain: natural immunity 76% effective against BA.5
- Booster vaccinations were less effective at preventing hospitalization in BA.5
  - But, booster prevented about 77%, compared to primary series only 22%
- Protection against death was still robust in both BA.5 and BA.2 infection w/ vaccination + booster

Kislaya, Irina and Casaca, Pedro and Borges, Vítor and Sousa, Carlos and Ferreira, Bibiana I. and Fonte, Ana and Fernandes, Eugenia and Matias Dias, Carlos and Duarte, Silvia and Almeida, José Pedro and Grenho, Inês and Coelho, Luís and Ferreira, Rita and Pita Ferreira, Patrícia and Borges, Cláudia Medeiros and Isidro, Joana and Pinto, Miguel and Menezes, Luís and Sobral, Daniel and Nunes, Alexandra and Santos, Daniela and Maia Gonçalves, António and Vieira, Luís and Gomes, João Paulo and Leite, Pedro Pinto and Nunes, Baltazar and Machado, Ausenda and Peralta-Santos, André, Comparative COVID-19 Vaccines Effectiveness in Preventing Infections, Hospitalizations, and Deaths with SARS-CoV-2 BA.5 and Ba.2 Omicron Lineages: A Case-Case and Cohort Study Using Electronic Health Records in Portugal.

Variant-specific vaccines

For Immediate Release: August 31, 2022 FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Moderna, Pfizer-BioNTech Bivalent COVID-19 Vaccines for Use as a Booster Dose

- Bivalent vaccine formulations are now EUA-approved as an "updated booster"
  - Can be given at least 2 months after primary series or previous booster
- Bivalent vaccines = original mRNA component to provide broad protection, along with a second mRNA component targeting BA.4 and BA.5 Omicron variants
  - BA.4 and BA.5 make up > 99% of variants in the US
- How did they make this decision?
  - Extensive safety and efficacy data of original mRNA vaccines
  - Clinical data from BA.1 lineage mRNA vaccine
  - In vitro data from BA.4 and BA.5 lineage mRNA vaccine
- These will REPLACE monovalent Covid vaccine boosters for 12+ y/o

Therapeutics

Outpatient

- One of the few things which has remained relatively unchanged for a while

Patient Disposition	Panel's Recommendations
Does Not Require Hospitalization or Supplemental Oxygen 	**For All Patients:** • All patients should be offered symptomatic management **(AIII)**. • The Panel **recommends against** the use of **dexamethasone**[a] or **other systemic corticosteroids** in the absence of another indication **(AIIb)**. **For Patients Who Are at High Risk of Progressing to Severe COVID-19**[b] *Preferred therapies. Listed in order of preference:* • **Ritonavir-boosted nirmatrelvir (Paxlovid)**[c,d] **(AIIa)** • **Remdesivir**[d,e] **(BIIa)** *Alternative therapies. For use ONLY when neither of the preferred therapies are available, feasible to use, or clinically appropriate. Listed in alphabetical order:* • **Bebtelovimab**[f] **(CIII)** • **Molnupiravir**[d,g] **(CIIa)**
Discharged from Hospital Inpatient Setting in Stable Condition and Does Not Require Supplemental Oxygen	The Panel **recommends against** continuing the use of **remdesivir (AIIa)**, **dexamethasonea (AIIa)**, or **baricitinib (AIIa)** after hospital discharge.
Discharged from Hospital Inpatient Setting and Requires Supplemental Oxygen *For those who are stable enough for discharge but still require oxygen*[h]	There is insufficient evidence to recommend either for or against the continued use of remdesivir or dexamethasone.
Discharged from ED Despite New or Increasing Need for Supplemental Oxygen *When hospital resources are limited, inpatient admission is not possible, and close follow-up is ensured*[i]	The Panel recommends using **dexamethasone** 6 mg PO once daily for the duration of supplemental oxygen (dexamethasone use **should not exceed** 10 days) with careful monitoring for AEs **(BIII)**. Because remdesivir is recommended for patients with similar oxygen needs who are hospitalized,[i] clinicians may consider using it in this setting. As remdesivir requires IV infusions for up to 5 consecutive days, there may be logistical constraints to administering remdesivir in the outpatient setting.

Rating of Recommendations: A = Strong; B = Moderate; C = Weak
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

NIH

Paxlovid - Rebound

- What is it?
- Positive antigen, symptoms, Paxlovid → symptom improvement, negative antigen → 2-8 days later symptoms return briefly and antigen positive again
  - Does not represent reinfection or Paxlovid resistant in available case reports
- No reports of SEVERE disease - so symptoms are mild
- Symptoms improve or resolve in about 3 days
- But, individual should restart the isolation period from day 0
- Not recommended to repeat Paxlovid treatment after completion, or give any other antiviral treatment for Covid

Inpatient

NIH

Disease Severity	Recommendations for Antiviral or Immunomodulator Therapy		Recommendations for Anticoagulant Therapy
	Clinical Scenario	Recommendation	
Hospitalized for Reasons Other Than COVID-19	Patients with mild to moderate COVID-19 who are at high risk of progressing to severe COVID-19[a]	See Therapeutic Management of Nonhospitalized Adults With COVID-19.	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients
Hospitalized but Does Not Require Oxygen Supplementation	All patients	The Panel **recommends against** the use of **dexamethasone** (AIIa) or **other systemic corticosteroids** (AIII) for the treatment of COVID-19.[b]	
	Patients who are at high risk of progressing to severe COVID-19[a]	**Remdesivir**[c] (BIII)	
Hospitalized and Requires Conventional Oxygen[d]	Patients who require minimal conventional oxygen	**Remdesivir**[e] (BIIa)	For nonpregnant patients with D-dimer levels above the ULN who do not have an increased bleeding risk: • **Therapeutic dose of heparin**[g] (CIIa) For other patients: • **Prophylactic dose of heparin**, unless contraindicated (AI); (BIII) for pregnant patients
	Most patients	Use **dexamethasone plus remdesivir**[e] (BIIa). If remdesivir cannot be obtained, use **dexamethasone** (BI).	
	Patients who are receiving dexamethasone and who have rapidly increasing oxygen needs and systemic inflammation	Add **PO baricitinib**[f] or **IV tocilizumab**[f] to 1 of the options above (BIIa).	

NIH

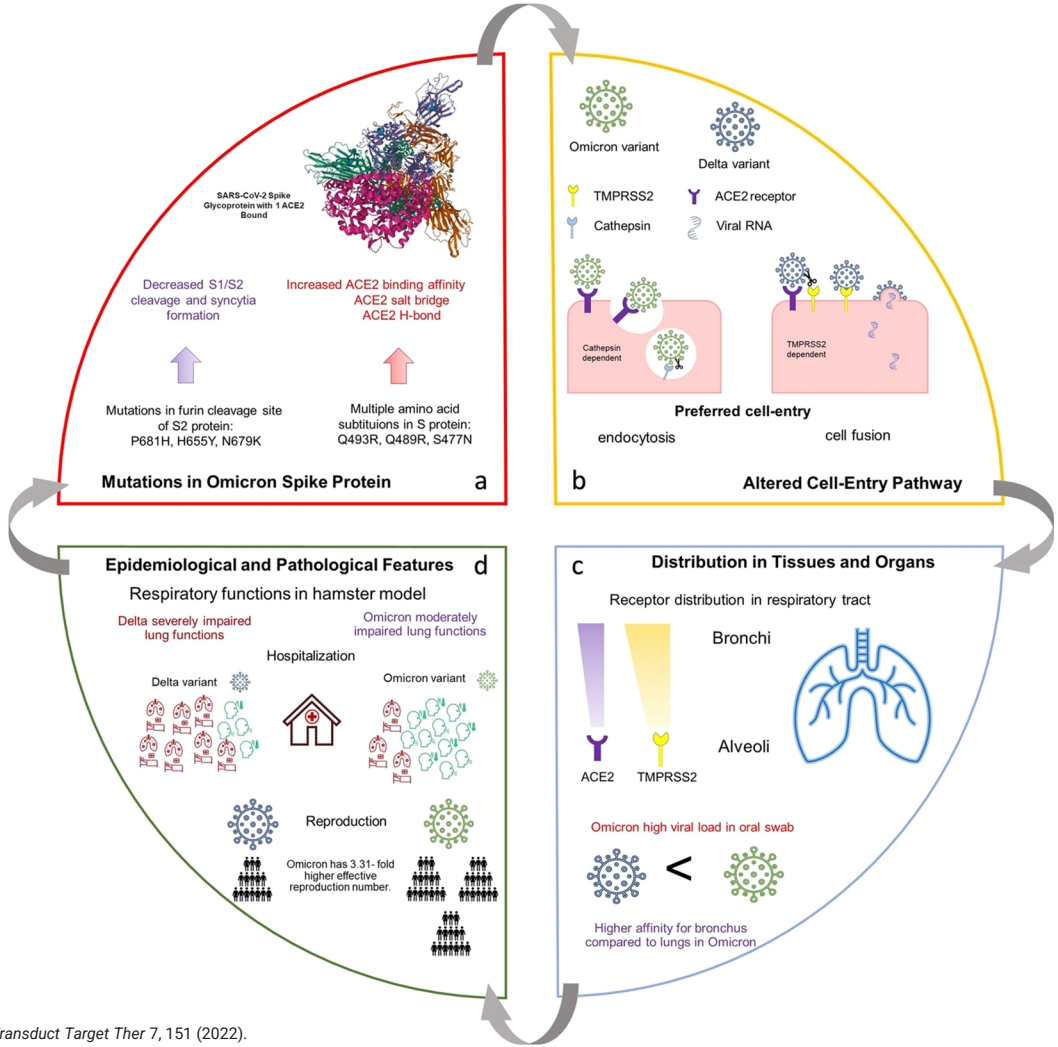
Inpatient

Hospitalized and Requires HFNC Oxygen or NIV	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib[f] (AI)** • **Dexamethasone plus IV tocilizumab[f] (BIIa)** If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: • **Dexamethasone[h] (AI)** Add **remdesivir** to 1 of the options above in certain patients **(CIIa)**.[i]	For patients without an indication for therapeutic anticoagulation: • **Prophylactic dose of heparin**, unless contraindicated **(AI)**; **(BIII)** for pregnant patients For patients who are started on a therapeutic dose of heparin in a non-ICU setting and then transferred to the ICU, the Panel recommends switching to a **prophylactic dose of heparin**, unless there is another indication for therapeutic anticoagulation **(BIII)**.
Hospitalized and Requires MV or ECMO	Most patients	Promptly start 1 of the following, if not already initiated: • **Dexamethasone plus PO baricitinib[f] (BIIa)** • **Dexamethasone plus IV tocilizumab[f] (BIIa)** If **baricitinib, tofacitinib, tocilizumab,** or **sarilumab** cannot be obtained: • **Dexamethasone[h] (AI)**	

Variant Updates - Omicron

Omicron variant

- A: Omicron spike protein mutations
- B: Higher binding affinity toward ACE2 receptors
- C: Omicron distribution in respiratory tract
- D: Epidemiological and pathological properties of Delta and Omicron variants



Bálint, G., Vörös-Horváth, B. & Széchenyi, A. Omicron: increased transmissibility and decreased pathogenicity. *Sig Transduct Target Ther* 7, 151 (2022).

Omicron transmissibility

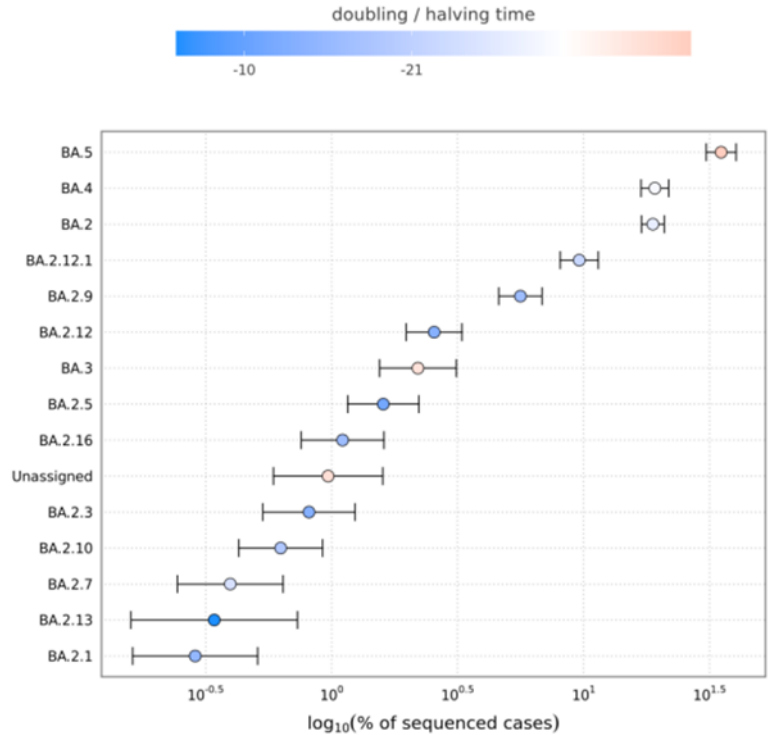
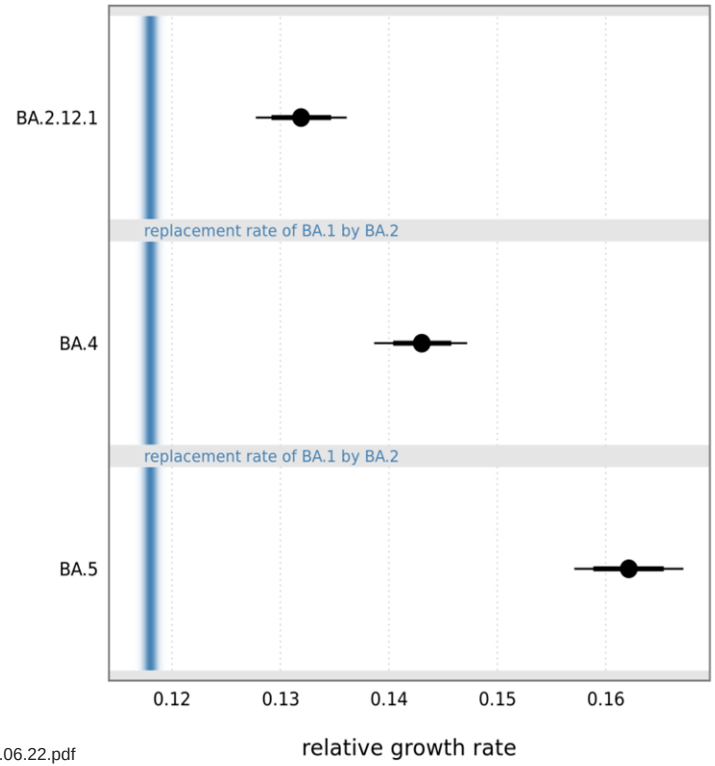


Figure 7. Estimated relative growth rates for BA.4, BA.5 and BA.2.12.1 from a multinomial model of sequenced cases in England



UK Health Security Agency. SARS-CoV-2 variants of concern and variants under investigation in England.Technical briefing 43
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1086494/Technical-Briefing-43-28.06.22.pdf

Omicron transmissibility

FIGURE 1. Interval[*,†] between index patient onset date and household contact onset date — four U.S. jurisdictions, November 2021–February 2022

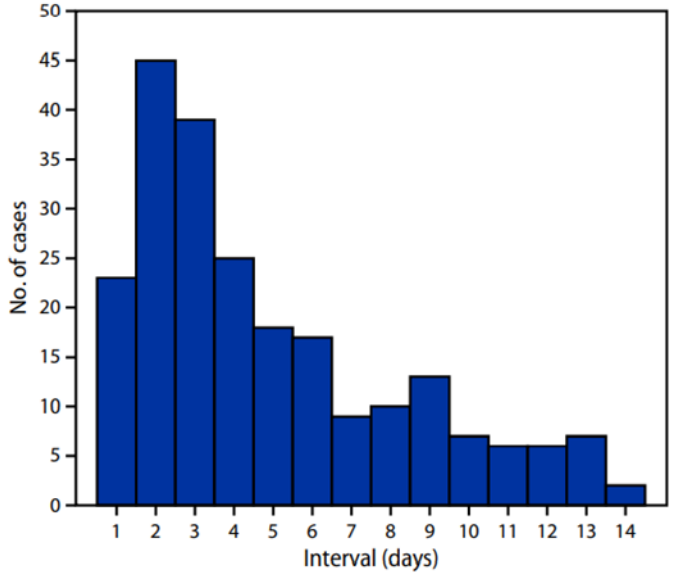


Table. Polymerase Chain Reaction–Confirmed Secondary COVID-19 Cases in Nonindex Household Members Within 7 Days After Index Case Patient Sampling Date[a]

Index case characteristics	No./total	SAR, % (95% CI)[b]	Logistic regression, OR (95% CI)[c]	
			Unadjusted	Adjusted
Overall	15 961/80 957[d]	19.7 (19.4-20.0)		
Variant				
Delta	7960/41 015	19.4 (19.0-19.8)	1 [Reference]	1 [Reference]
Omicron	2926/11 643	25.1 (24.4-25.9)	1.39 (1.31-1.49)	1.52 (1.41-1.64)
Not classified	5075/28 299	17.9 (17.5-18.4)	0.91 (0.86-0.96)	0.93 (0.88-0.98)

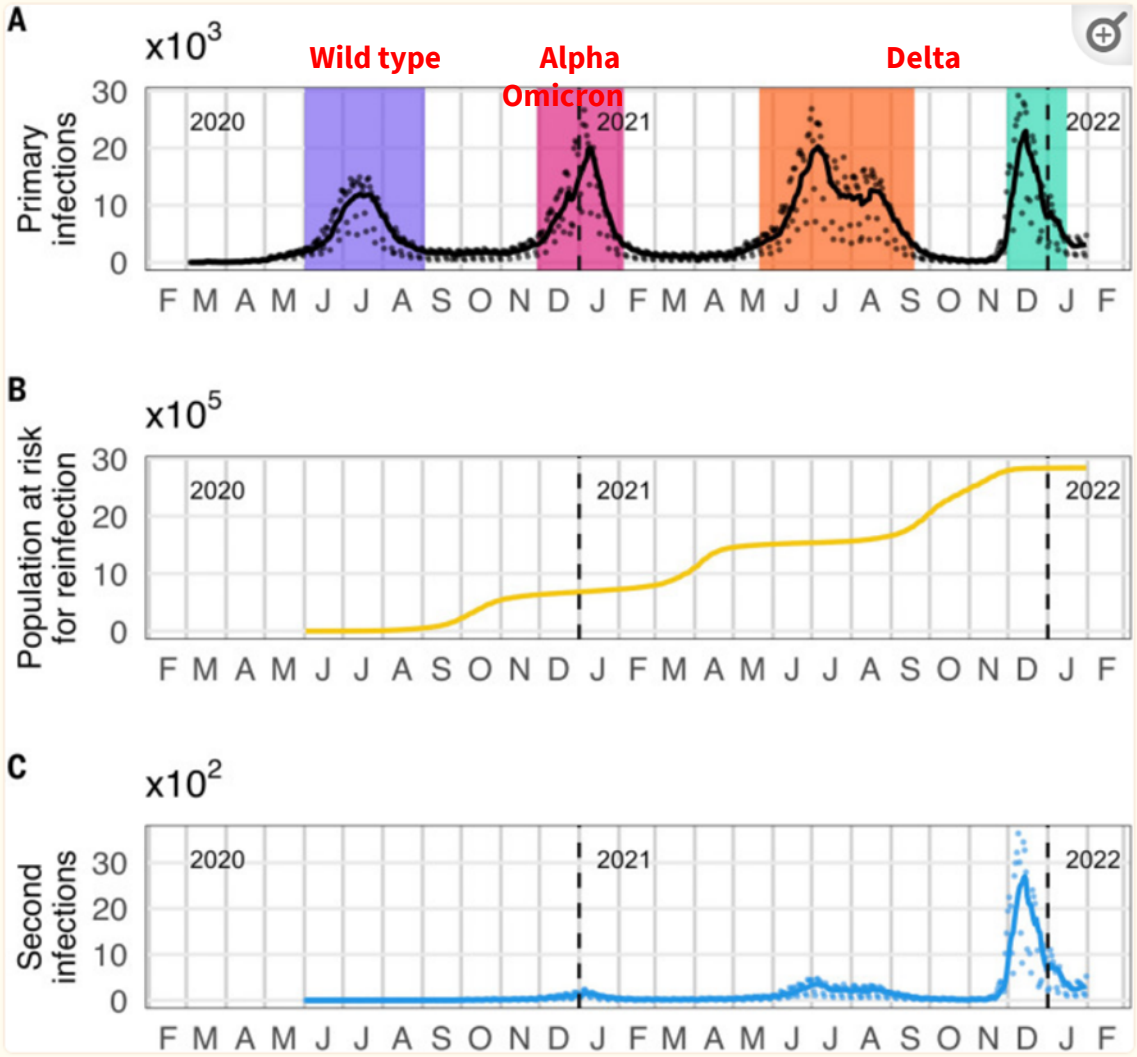
Omicron incubation period

- Recent meta-analysis published 8/24/22
- Data from 12/2019 - 2/2022 looking at incubation periods
  - 142 studies with total 8112 patients included
- Incubation periods ranged 1.8 - 18.8 days from infection to symptom onset
- Average incubation periods:
  - Wild type 5.20 days, Alpha 5.00 days, Beta 4.50 days, Delta 4.41 days
  - *Omicron 3.42 days*
- Incubation period may be longer in older adults and shorter in children
- No significant difference in incubation period based on severity of illness

Wu Y, Kang L, Guo Z, Liu J, Liu M, Liang W. Incubation Period of COVID-19 Caused by Unique SARS-CoV-2 Strains: A Systematic Review and Meta-analysis. *JAMA Netw Open.* 2022;5(8):e2228008.

Immune evasion

- Increasing population at risk for reinfection (B) - at least 90 days out from primary infection
- No real spikes in reinfection until Omicron (C)



Pulliam JRC, van Schalkwyk C, Govender N, von Gottberg A, Cohen C, Groome MJ, Dushoff J, Mlisana K, Moultrie H. Increased risk of SARS-CoV-2 reinfection associated with emergence of Omicron in South Africa. Science. 2022 May 6;376(6593):eabn4947.

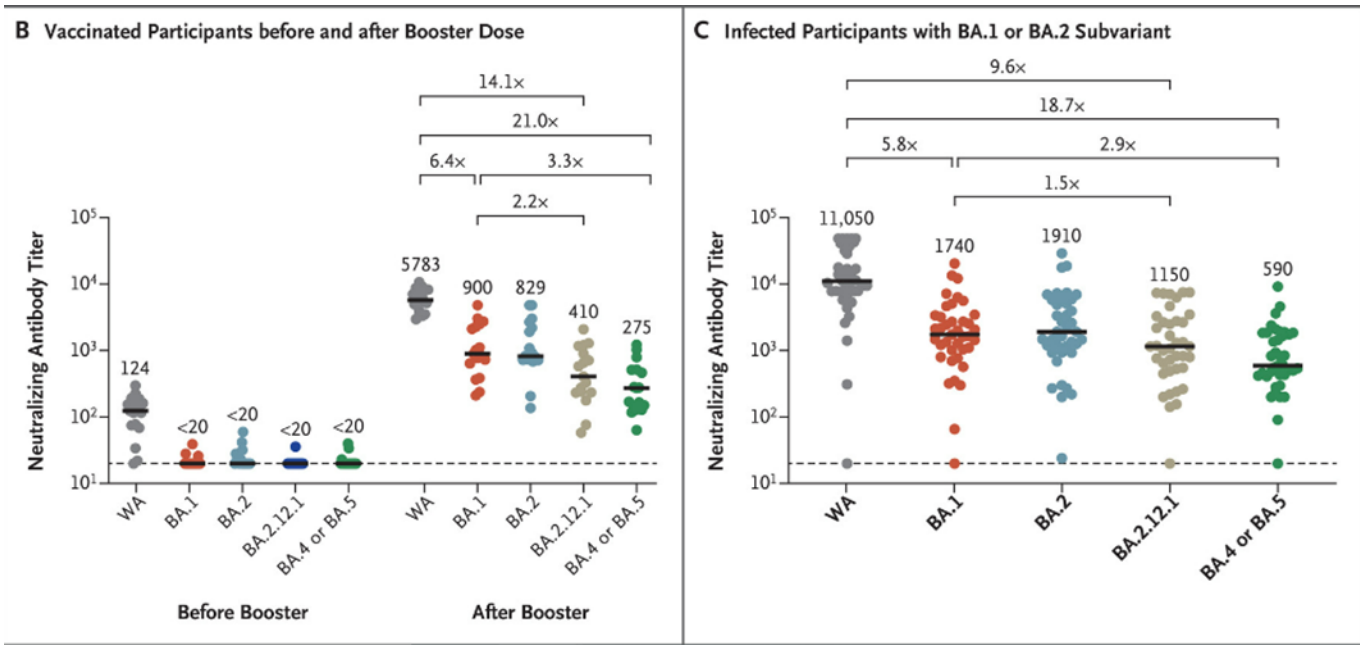
Immune evasion

- Another study looked at efficacy of previous SARS-CoV-2 infection to prevent reinfection (at least 90 days later)
- Case patients and controls were matched
- Excluded vaccinated individuals from analysis
- Effectiveness of previous infection in preventing reinfection was estimated to be
  - 90.2% against the alpha variant
  - 85.7% against the beta variant
  - 92.0% against the delta variant
  - *56.0% against the omicron variant*
- Effectiveness against severe, critical, or fatal Covid-19 reinfection was estimated to be
  - 69.4% against alpha, 88% against beta, 100% against delta, 88% against omicron

Altarawneh HN, Chemaitelly H, Hasan MR, Ayoub HH, Qassim S, AlMukdad S, Coyle P, Yassine HM, Al-Khatib HA, Benslimane FM, Al-Kanaani Z, Al-Kuwari E, Jeremijenko A, Kaleeckal AH, Latif AN, Shaik RM, Abdul-Rahim HF, Nasrallah GK, Al-Kuwari MG, Butt AA, Al-Romaihi HE, Al-Thani MH, Al-Khal A, Bertollini R, Tang P, Abu-Raddad LJ. Protection against the Omicron Variant from Previous SARS-CoV-2 Infection. N Engl J Med. 2022 Mar 31;386(13):1288-1290. doi: 10.1056/NEJMc2200133. Epub 2022 Feb 9

Immune evasion

- Omicron newer subtypes may evade the humoral immunity elicited by BA.1 infection
- BA.1-derived vaccine boosters may not achieve broad protection against newer Omicron variants



Cao Y, Yisimayi A, Jian F, Song W, Xiao T, Wang L, Du S, Wang J, Li Q, Chen X, Yu Y, Wang P, Zhang Z, Liu P, An R, Hao X, Wang Y, Wang J, Feng R, Sun H, Zhao L, Zhang W, Zhao D, Zheng J, Yu L, Li C, Zhang N, Wang R, Niu X, Yang S, Song X, Chai Y, Hu Y, Shi Y, Zheng L, Li Z, Gu Q, Shao F, Huang W, Jin R, Shen Z, Wang Y, Wang X, Xiao J, Xie XS. BA.2.12.1, BA.4 and BA.5 escape antibodies elicited by Omicron infection. Nature. 2022 Aug;608(7923):593-602.

Omicron severity

- Comparing disease severity in South Africa
- Only 24% were vaccinated during wave 4 (omicron)
- No vaccination in waves 1 & 2
- Unknown vaccination rate in wave 3
- Significantly *less severe in omicron wave compared to others in all categories*

Outcomes of Patients Admitted With a Positive COVID-19 Result in the 4 Waves[a]

	No. (%) of patients				*P* value
	Wave 1 (n = 2628)	**Wave 2 (n = 3198)**	**Wave 3 (n = 4400)**	**Wave 4[b] (n = 971)**	
Receiving oxygen therapy	2119 (80.3)	2624 (82.0)	3260 (74.0)	171 (17.6)	<.001
Receiving mechanical ventilation	431 (16.4)	259 (8.0)	548 (12.4)	16 (1.6)	<.001
Admission to intensive care	1104 (42)	1172 (36.6)	1318 (29.9)	180 (18.5)	<.001
Length of stay, median (IQR), d	8.0 (9)	7.8 (8)	7 (9)	3 (3)	<.001
Deaths	520 (19.7)	790 (25.5)	1284 (29.1)	27 (2.7)	<.001

Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves. JAMA. 2022 Feb 8;327(6):583-584. doi: 10.1001/jama.2021.24868.

Back to the case…

Case

Your 80 year old patient with hypertension, COPD, and DM comes in for a routine clinic visit. She is hesitant about new mRNA vaccinations and has yet to get any Covid vaccine due to this. She wants to discuss other options for Covid-19 prevention vs “just getting Covid because the new strain is mild.”

How would you advise her on the following?

- Non-mRNA Covid vaccines
- Evusheld?
- Potential short-term and long-term effects of Covid-19
- Protection after naturally-acquired immunity
- Her individual, specific risks with Covid-19 and/or vaccination

My thoughts on counseling this patient…

- Non-mRNA vaccines
  - Novavax may be a good option for this patient, can reassure that the technology has already been used in other widely prescribed vaccinations
  - J&J no longer recommended unless as last resort
- Evusheld
  - Does not meet the criteria → high risk for vaccine non-response or can't get vaccine
- Long-term effects of Covid-19 → Long Covid
- Specific risk factors for this patient → high risk for hospitalization and/or death due to advanced age, comorbidities (COPD, HTN, DM), unvaccinated
- Naturally acquired immunity
  - Requires putting her at risk of the adverse effects of Covid itself (short and long term)
  - Is not very protective against the new variants

Testing

Performance of antigen testing

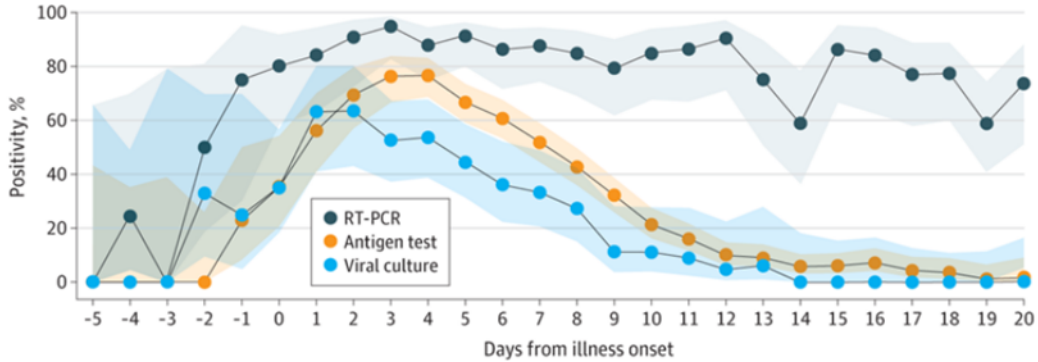
- As more home testing has become available, many individuals with symptoms rely on these for diagnosis and to determine isolation if needed
- *How has antigen performance changed with viral evolution?*
- Jan - May 2021 study period
  - Alpha (56%) variant
  - Epsilon (16%) variant
  - Gamma (4%) variant
  - Unknown (8%) variant
- Primary outcome = daily sensitivity of home antigen tests to detect PCR–confirmed cases

Chu VT, Schwartz NG, Donnelly MAP, et al. Comparison of Home Antigen Testing With RT-PCR and Viral Culture During the Course of SARS-CoV-2 Infection. *JAMA Intern Med.* 2022;182(7):701–709. doi:10.1001/jamainternmed.2022.1827

Performance of antigen testing

- Daily positivity
  - PCR = 95% (peak at day 3)
  - Antigen = 77% (peak at day 4)
  - Viral culture = 64% (peak at day 2)

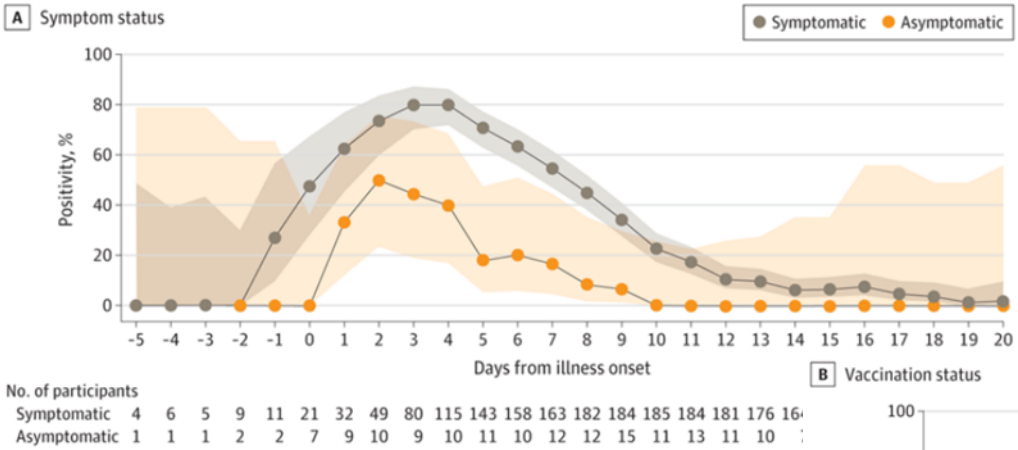
Figure 1. Daily Percentage of Positive SARS-CoV-2 Tests in Participants With Reverse Transcription–Polymerase Chain Reaction (RT-PCR)–Confirmed Infection

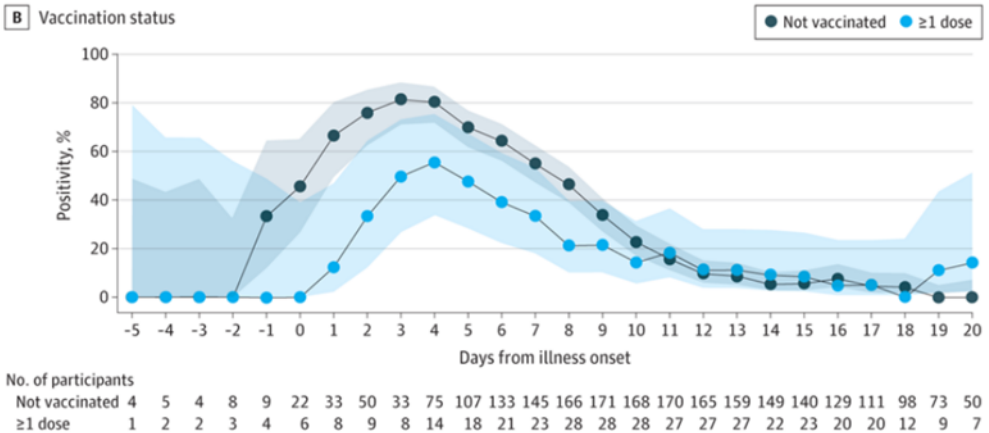


No. of participants																									
RT-PCR	2	4	1	6	4	20	19	22	38	41	47	36	40	33	29	27	22	21	16	17	22	19	26	31	29	19
Antigen test	5	7	6	11	13	28	41	59	89	125	154	168	175	194	199	196	197	192	186	171	163	149	131	110	82	57
Viral culture	2	4	1	6	4	20	19	22	38	41	47	36	39	33	27	27	22	21	16	17	21	19	26	31	29	19

Chu VT, Schwartz NG, Donnelly MAP, et al. Comparison of Home Antigen Testing With RT-PCR and Viral Culture During the Course of SARS-CoV-2 Infection. *JAMA Intern Med.* 2022;182(7):701–709. doi:10.1001/jamainternmed.2022.1827

Performance of antigen testing





Chu VT, Schwartz NG, Donnelly MAP, et al. Comparison of Home Antigen Testing With RT-PCR and Viral Culture During the Course of SARS-CoV-2 Infection. *JAMA Intern Med.* 2022;182(7):701–709. doi:10.1001/jamainternmed.2022.1827

Performance of antigen testing

- Antigen test sensitivity was 50% during the infectious period
  - Moderate sensitivity compared with same day PCR
  - High sensitivity compared with same day viral culture
- Antigen test sensitivity peaked 4 days after illness onset at 77%
- Antigen test sensitivity improved with a second antigen test 1 to 2 days later, particularly early in the infection
- Six days after illness onset, antigen test result positivity was 61%
- Conclusion? Antigen testing not too bad if done at the right time

Chu VT, Schwartz NG, Donnelly MAP, et al. Comparison of Home Antigen Testing With RT-PCR and Viral Culture During the Course of SARS-CoV-2 Infection. *JAMA Intern Med.* 2022;182(7):701–709. doi:10.1001/jamainternmed.2022.1827

Performance of antigen testing

- With more viral evolution, questions have been raised about antigen performance
- Early in Omicron (Jan 2022), one study looked a real-time antigen results

Table 1
Overall sensitivity of the Panbio™ COVID-19 Ag rapid test device according to the SARS-CoV-2 RNA load in nasopharyngeal specimens.

RT-PCR cycle threshold value	SARS-CoV-2 RNA load (log_{10} copies/ml)	Sensitivity (95% CI)
≤ 20	≥ 7.5	95.6 (89.2–98.3)
≤ 25	≥ 5.8	92.6 (86.6–96.1)
≤ 30	≥ 4.3	87.2 (80.7–91.8)
≤ 35	≥ 2.7	81.8 (75–87.1)

de Michelena P, Torres I, Ramos-García Á, Gozalbes V, Ruiz N, Sanmartín A, Botija P, Poujois S, Huntley D, Albert E, Navarro D. Real-life performance of a COVID-19 rapid antigen detection test targeting the SARS-CoV-2 nucleoprotein for diagnosis of COVID-19 due to the Omicron variant. J Infect. 2022 May;84(5):e64-e66. doi: 10.1016/j.jinf.2022.02.022. Epub 2022 Feb 22. PMID: 35217106; PMCID: PMC8863328.

Performance of antigen testing

Table 2. Analytical and Clinical Accuracy of SCoV-2 Ag *Detect* Rapid Self-Test Across SARS-CoV-2 Variants[a]

	Pre-Delta[b]	Delta	Omicron	Total[c]
Participants positive for COVID-19/participants with valid RT-PCR results, No. (%)[d]	64/296 (21.6)	43/289 (14.9)	73/212 (34.4)	180/797 (22.6)
Time since symptom onset, mean (SD), d	2.2 (0.2)	2.3 (1.2)	2.5 (1.3)	2.3 (1.2)
Cycle threshold values among specimens positive for SARS-CoV-2 by RT-PCR, mean (SD)	23.9 (5.2)	27.6 (4.6)	28.0 (4.8)	26.5 (5.3)
Agreement for rapid antigen test, % (95% CI)[e]				
Positive	81.2 (69.5-89.9)	90.7 (77.9-97.4)	83.6 (73.0-91.2)	84.4 (78.3-89.4)
Negative	100 (98.4-100)	99.6 (97.8-100)	100 (97.4-100)	99.8 (99.1-100)
Analytical limit of detection for rapid antigen test, $TCID_{50}$ per swab	62.5	62.5	62.5	62.5

Abbreviations: RT-PCR, reverse transcriptase–polymerase chain reaction; $TCID_{50}$, 50% tissue culture infectious dose.

[c] Five participants (3 from Delta phase, 2 from Omicron phase) were missing RT-PCR results and were excluded from analyses.

Drain PK, Bemer M, Morton JF, et al. Accuracy of 2 Rapid Antigen Tests During 3 Phases of SARS-CoV-2 Variants. *JAMA Netw Open.* 2022;5(8):e2228143. doi:10.1001/jamanetworkopen.2022.28143

Performance of antigen testing

- Participants > 2 years (154 PCR+ Covid of 5609 total)
  - 97 asymptomatic on day 0
- Day 0: nasal swab #1 (for rapid antigen), 15 min later swab #2 (PCR)
  - Repeated every 48h for 14 days (7 samples)
  - Plus one additional antigen 48 hours after last PCR
- 3 different FDA EUA tests were evaluated
- Symptomatic: serial testing twice over 48 hours had sensitivity of 93.4%
- Asymptomatic: serial testing twice over 48 hours showed sensitivity of 62%, increased to 79% with serial testing 3 times over 96 hours

doi: https://doi.org/10.1101/2022.08.05.22278466 - PrePrint

Antigen testing performance - key points

- Concerns remain re: performance with continued viral evolution
- We need more data for BA.2, BA.4, BA.5 subvariants
- More sensitive with higher viral loads / lower cycle thresholds
- Antigen testing is probably still useful, especially with serial testing
- If exposed but asymptomatic, test at least 3 times (48 hour intervals)
- Antigen performance may peak several days into illness onset
- If symptomatic but negative antigen, get a PCR

Preoperative testing

American Society of Anesthesiologists (ASA) along with Anesthesia Patient Safety Foundation (APSF) statement July 13, 2022 on preop testing:

- All patients should be screened for symptoms and/or exposure
  - If symptoms, test
- Population risk assessment: what is the local/regional transmission level
  - Low/moderate community transmission - if patient is asymptomatic, up to date on vaccination, and having a lower-risk procedure - may be more permissive about preop testing
  - High community transmission - continue preop testing

	Low	Moderate	Substantial	High
New cases per 100,000 persons in the past 7 days*	<10	10-49.99	50-99.99	≥100
Percentage of positive NAATs tests during the past 7 days**	<5%	5-7.99%	8-9.99%	≥10.0%

ASA and APSF Statement on Perioperative Testing for the COVID-19 Virus - Anesthesia Patient Safety Foundation

Preoperative testing - when to operate

Positive Covid testing preop

- If asymptomatic or mild symptoms - can operate based on time or symptom-based isolation guidelines (e.g. 10 days)
- For immunocompromised or severely ill - test-based strategy may be used +/- consultation with ID to determine appropriate timing of surgery
    - Differs from previous blanket time-based (20 days) or symptom-based strategy

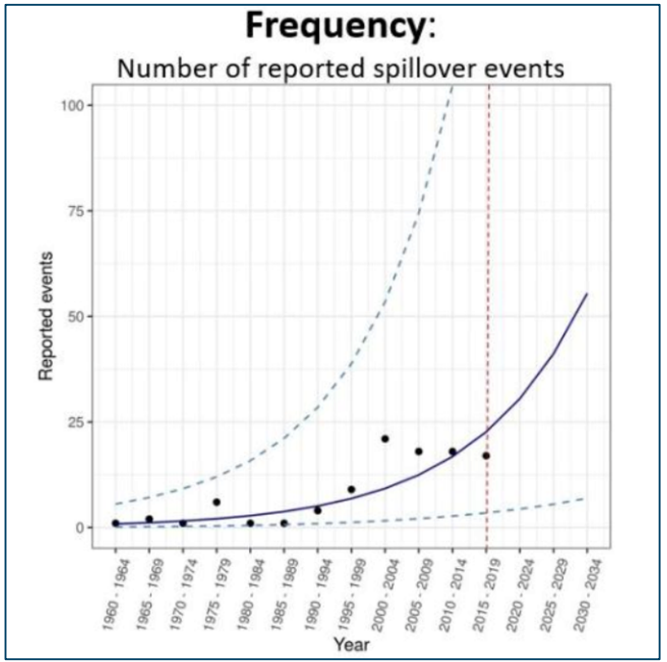
Elective procedures**

CDC

Looking Ahead

Preparing for the future

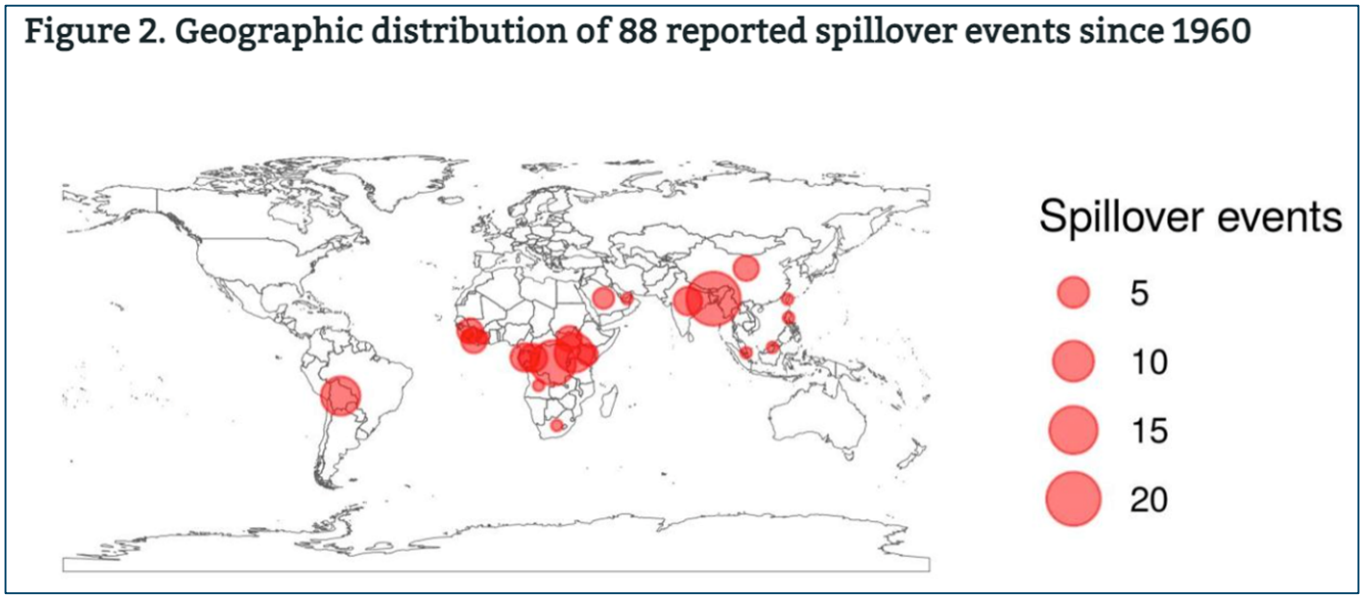
- The next pandemic could be sooner and more severe than we think
  - We often think of Covid-19 as a “once in a lifetime” rare event
  - Modeling based on historical data shows this is not necessarily true
  - Spillover from wildlife hosts to humans is steadily increasing →
  - One model (Metabiota) estimated impact of future outbreaks and assessed long-term pandemic risks
    - Annual probability of a pandemic on the scale of Covid-19 is 2.5 - 3.3%
    - This means 47-57% chance of Covid-scale pandemic in the next 25 years



1. https://www.cgdev.org/blog/the-next-pandemic-could-come-soon-and-be-deadlier
2. https://www.cgdev.org/event/whats-next-predicting-frequency-and-scale-future-pandemics

Predicting Future Pandemics

- The most vulnerable countries are more likely to have spillover events from animal to human, and less capable to response adequately



Predicting Future Pandemics

- Obviously, prevention is key
- How can we reduce spillover events?
  - Money
  - Planning
  - Priorities
  - Changing human behavior
  - In the highest risk places

Table 1. Impact of spillover reduction – estimates based on simulated event catalogs

Pathogen group	Expected deaths over next decade	Deaths averted over 10 years from 1% reduction in spillover events
Pandemic Flu (excluding seasonal flu)	2,200,000	22,000
Coronaviruses	1,500,000	15,000
Viral Hemorrhagic Fevers (e.g. ebola virus, nipah, etc.)	300,000	3,000
Total	4,000,000	40,000

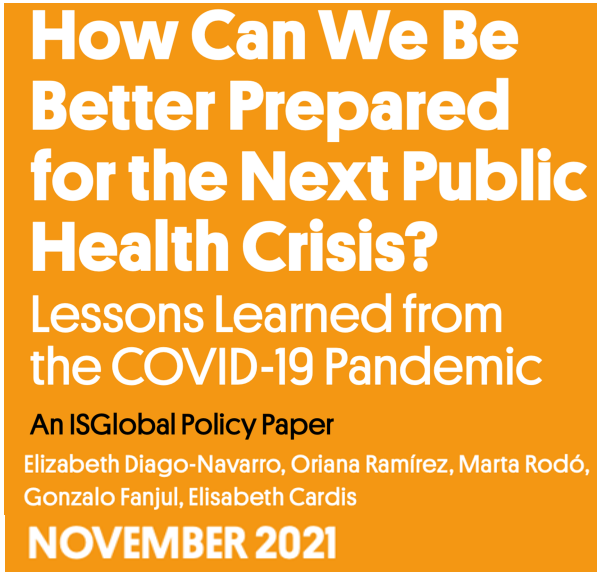
1. https://www.cgdev.org/blog/the-next-pandemic-could-come-soon-and-be-deadlier
2. https://www.cgdev.org/event/whats-next-predicting-frequency-and-scale-future-pandemics
3. https://www.usaid.gov/news-information/fact-sheets/emerging-pandemic-threats-program

Pandemics - always on the horizone

- In recent decades - increasing outbreaks/epidemics of various diseases, emerging or re-emerging
- Some have had the potential to turn into pandemics
  - Ebola, MERS, Zika, Avian flu, etc etc etc
  - SARS (2003-04) infected 8000 people in 29 countries, should have been a real warning
- Unfortunately, these emerging pathogens did not really prepare us for another true global pandemic
- In 2005, WHO developed the “international health regulations (IHR)” to provide an overarching legal framework for pandemic response
  - Requires states to maintain certain core capabilities for surveillance and response, tailored to specific country and available resources

Pandemic preparedness

- The IHR turned out to be pretty ineffective when Covid actually happened
- Some countries with baseline “low” preparedness performance indicators actually performed better than some countries with “high” performance indicators
    - E.g. Senegal, Ethiopia responded better than expected; U.S., South Korea, others were deficient compared to expected response
- Barcelona Institute of Global Health (ISGlobal) put together a global policy paper about lessons learned from Covid-19



Lesson 1: Wastewater surveillance

- Wastewater surveillance has been used in past (poliovirus, MDR bacteria, etc)
  - So, it's not new, but is an innovative approach
- With SARS-CoV-2, wastewater surveillance has allowed public health officials to anticipate possible outbreaks and monitor community variants
- The National Wastewater Surveillance System (NWSS) was created in 9/2020
- We can use this system more robustly going forward to monitor certain pathogens, but also other public health hazards like chemical levels, antimicrobial resistance

Lesson 2: Rapid expansion of medical countermeasures

- 12 days after ID, genomic sequence of SARS-CoV-2 was shared globally
- Immediate targeted testing, treatment, and prevention was not available
- Intensive scientific research ensued, with large randomized controlled trials with adaptive designs (add or remove drugs, etc)
- Regulatory agencies (like the FDA) developed emergency frameworks to prioritize efficacy and safety of rapidly developed drugs/vaccines (EUA)
- Shared data and best practices within the global medical community
- These measures will obviously remain important in future pandemics

Lesson 3: Integration of data in real time

- Epidemiologic intelligence: numerous research institutions worldwide have participated to develop monitoring and prediction systems
- Many governments requested help from modelling and forecasting agencies
- WHO developed a Hub for Pandemic and Epidemic Intelligence in Berlin to forecast and predict disease outbreaks
- This is a work in process, many countries lack the current capability to use real-time epidemic data to inform response strategies

Lesson 4: “If you don’t have the right tools, you can’t find the problem”

- Early policies and mitigation measures were based on incomplete or inadequate data
- A “One Health” approach is needed
  - A holistic, all-hazards preparedness system
  - Real-time access to all available population/environmental databases
    - Primary health data, disease registries, social/economic indicators, and linkage between all of these
    - Including animal data when tracking infectious diseases, and recognizing the link between animals and humans in environmental health

Lesson 5: This pandemic occurred during an era of infodemics

- What's an infodemic? WHO:
  - Too much information
  - Universally available during a disease outbreak
  - Including false or misleading information
  - In digital and physical environments
- Especially social media contributes to this
- Makes it difficult to identify information of good quality, fosters mistrust in authorities, healthcare providers
- Campaigns against vaccines, treatments, etc.
- The pandemic has really identified this as a major issue

Lesson 6: When too much unvetted information becomes a risk…

- Rapid open access publication during the pandemic has greatly improved our scientific knowledge and ability to advance treatment/vaccines/etc
- But, rapid preprint availability of articles which have not undergone peer review has definitely lead to publication of conflicting results, withdrawn results, etc
  - E.g. studies on hydroxychloroquine
- Treatment of patients before validation of results could lead to harm
- Contributes to mistrust in the public

Lesson 7: Lack of coordination is not optimal

- There has been a lot of independent and uncoordinated research, leading to duplication of research and competition
- Sometimes research results aren't translated into policy or innovation
- Less efficient than it could have been
- In the future, coordinated research efforts will be much more beneficial and effective/efficient

Lesson 8: We have to address mental health and socioeconomic impacts

- The pandemic itself, the measures taken to mitigate it, and uncertainties and mistrust have all negatively impacted the mental and socioeconomic well being of the general population
  - Increased prevalence of, or worsening of existing, anxiety/depression
  - Unemployment
  - Psychosocial effects of isolation/quarantine
- These effects are especially pronounced in populations already at risk, including the poorest and already isolated (migrant/refugee populations)
- Continued efforts both before and during the next pandemic are required to combat these issues

Lesson 9: Inequity amplified the impacts of the Covid-19 pandemic

- Covid-19 response has varied greatly depending upon the economic power of the country
- Low and middle-income countries struggled to access Covid vaccines
  - While others are in the process of 3rd and 4th dose boosting
- Marginalized communities continue to have poor access to healthcare
- Job losses, income insecurities, lapses in childhood education, supply chain shortages all amplified in lower income populations

ISGlobal Recommendations

1. Strengthen global governance during health emergencies
    a. Coordination and collaboration, including legal frameworks
2. Promote investment in preparedness during “peace” times
    a. Innovation in new surveillance methods and early alert systems, adaptable protocols and frameworks for response to health crises
3. Address mental health in preparedness and response plans
    a. Improve psychosocial impact, improved communication, and increased/universal access to mental health care; citizens should be involved in development of these plans
4. Address social and economic inequities
5. Incorporate risk communication and behavioral science expertise into communication with the public
    a. Clear, transparent, and timely communication to foster trust

Using Covid for good...

mRNA vaccines

- Phase 1 trial launched 3/2022, 3 vaccines
  - 1) BG505 MD39.3 mRNA, 2) BG505 MD39.3 gp151 mRNA, and 3) BG505 MD39.3 gp151 CD4KO mRNA
- Target 3 different regions of HIV-specific spike protein
- Enrolling 108 adults
- Phase 1 trials = safety and dosing assessment
- Immune response will also be assessed with blood/lymph node aspiration
- Expected completion 7/2023

mRNA advancements

- With recent success of mRNA vaccines, science/medicine is excited
- Can we bring this technology to other areas?
- Vaccines: SARS-CoV-2, HIV, influenza, Zika, Herpes, malaria
  - Moderna is in phase 1 of Zika and Chikungunya vaccine trials
- Autoimmune diseases: reduce inflammation by targeting auto-antibodies
- Cancer immunotherapy or cancer prevention
  - Specialized therapy based on your exact tumor sequencing
- Difficult pathogens: targeted therapy towards antigens (e.g. C diff), or multidrug resistant bacteria
- Even genetic issues: e.g. targeting specific gene that increases risk of hyperlipidemia

Telemedicine advancements

- Telemedicine was really utilized early in the pandemic
- What happens post-Covid?
- To some extent, telemedicine was here before, and is here to stay and hopefully expand
- Lots of factors to consider
  - Licensing for providers - restrictions have tightened again
  - Insurance coverage for patients and billing for providers
  - Expanding access to rural areas (poor internet connection, etc)
  - Aging population / technology gap

https://www.aamc.org/news-insights/what-happens-telemedicine-after-covid-19

Telemedicine advancements

- How can we make telemedicine more sustainable?

  The Disruption Theory:

- Sustaining innovation = incremental improvements on what we already do
  - This is what telemedicine does for most people, and it works well
- Disruptive innovation = simpler solutions for patients with simpler needs, or patients we are not already serving
  - Underserved patients need simplification of telemedicine methods

Telemedicine advancements

- How can we simplify things for patients?
- Less complex, more accessible, and more convenient solutions than a “traditional patient visit forced into a videoconference”
  - Convenient care via phone, text messages, electronic messaging by teams of trained nonphysician professionals, (e.g. pharmacists, navigators, etc) — rather than waiting for months for a compressed follow-up appointment with a physician
  - E.g. remote monitoring for chronic diseases (HTN monitor BP at home, DM at home A1c) with titration of medication by clinicians based on these

Questions?