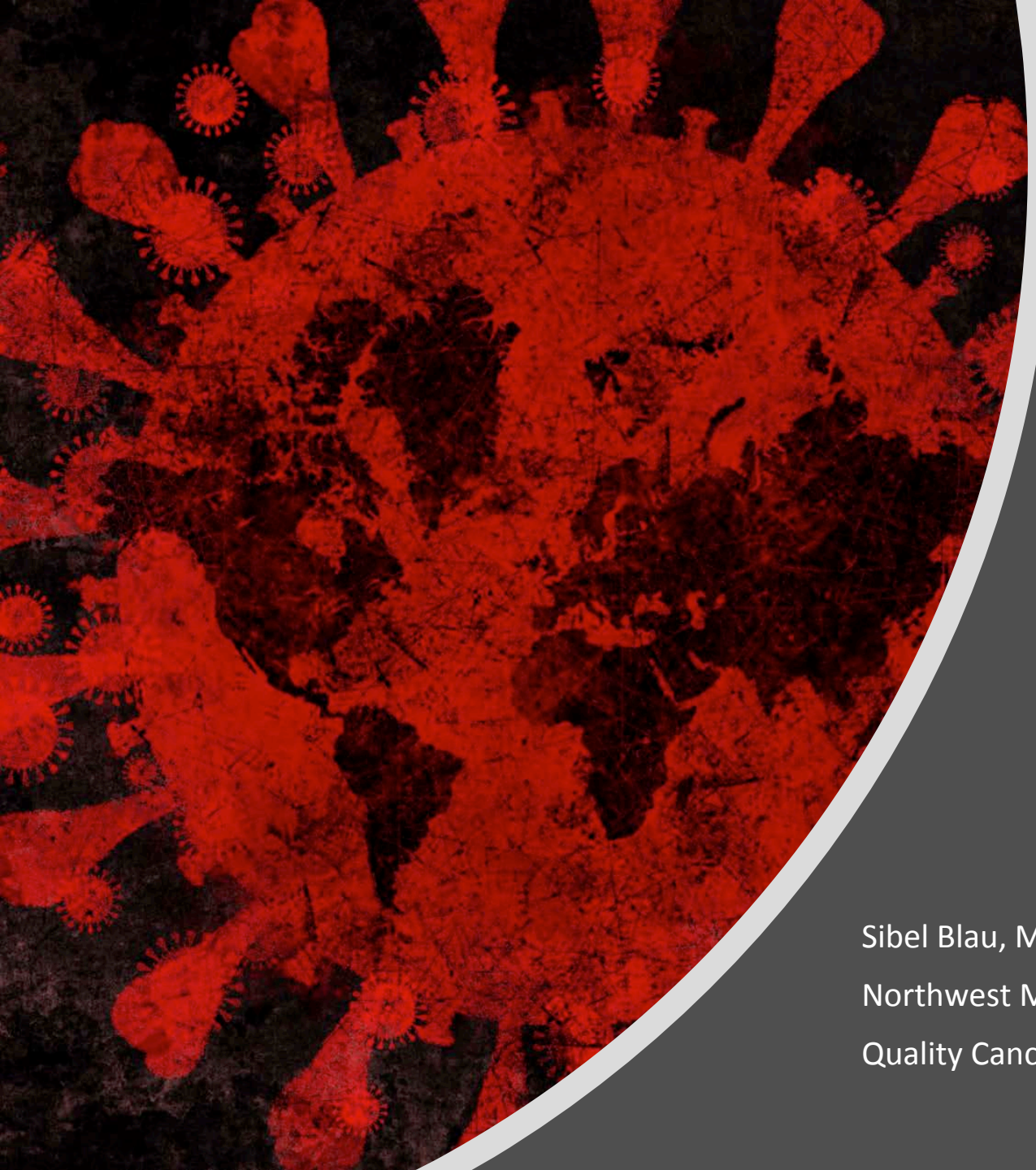


“What does the Progress in COVID-19 Pandemic Mean for Myeloma Patients”

MM Fighters
August 28, 2021

Sibel Blau, MD

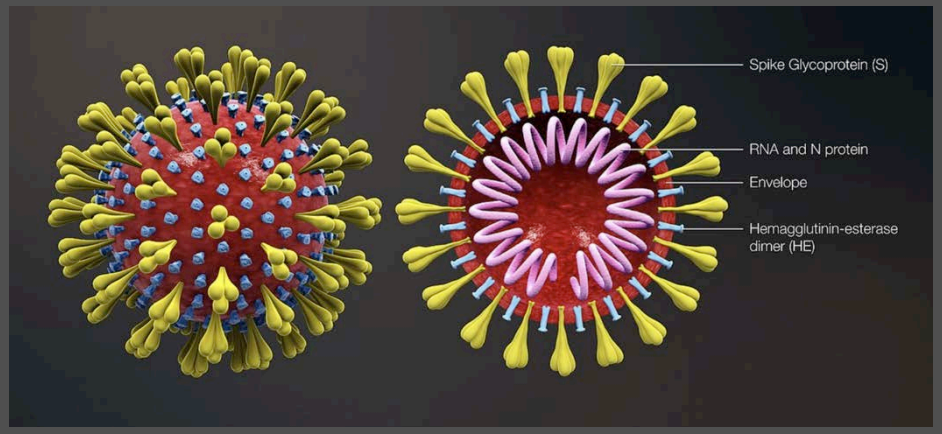
Northwest Medical Specialties, Medical Director

Quality Cancer Care Alliance Network, President/CEO

Objectives

- Introduction
- Epidemiology of SARS-2
- Variants
- Vaccines
- What about Immunocompromised?

SARS-CoV-2 (COVID-19)



- The virus that causes a respiratory disease called coronavirus disease 19 (COVID-19)
- SARS-CoV-2 is a member of a large family of viruses called coronaviruses
- These viruses can infect people and some animals. SARS-CoV-2 was first known to infect people in 2019

COVID 19 Status

Total Cases

213,205,948

US: 37,988,577

Total Deaths

4,452,460

US: 623,900

Variants in US

B.1.1.7 (Alpha) – United Kingdom

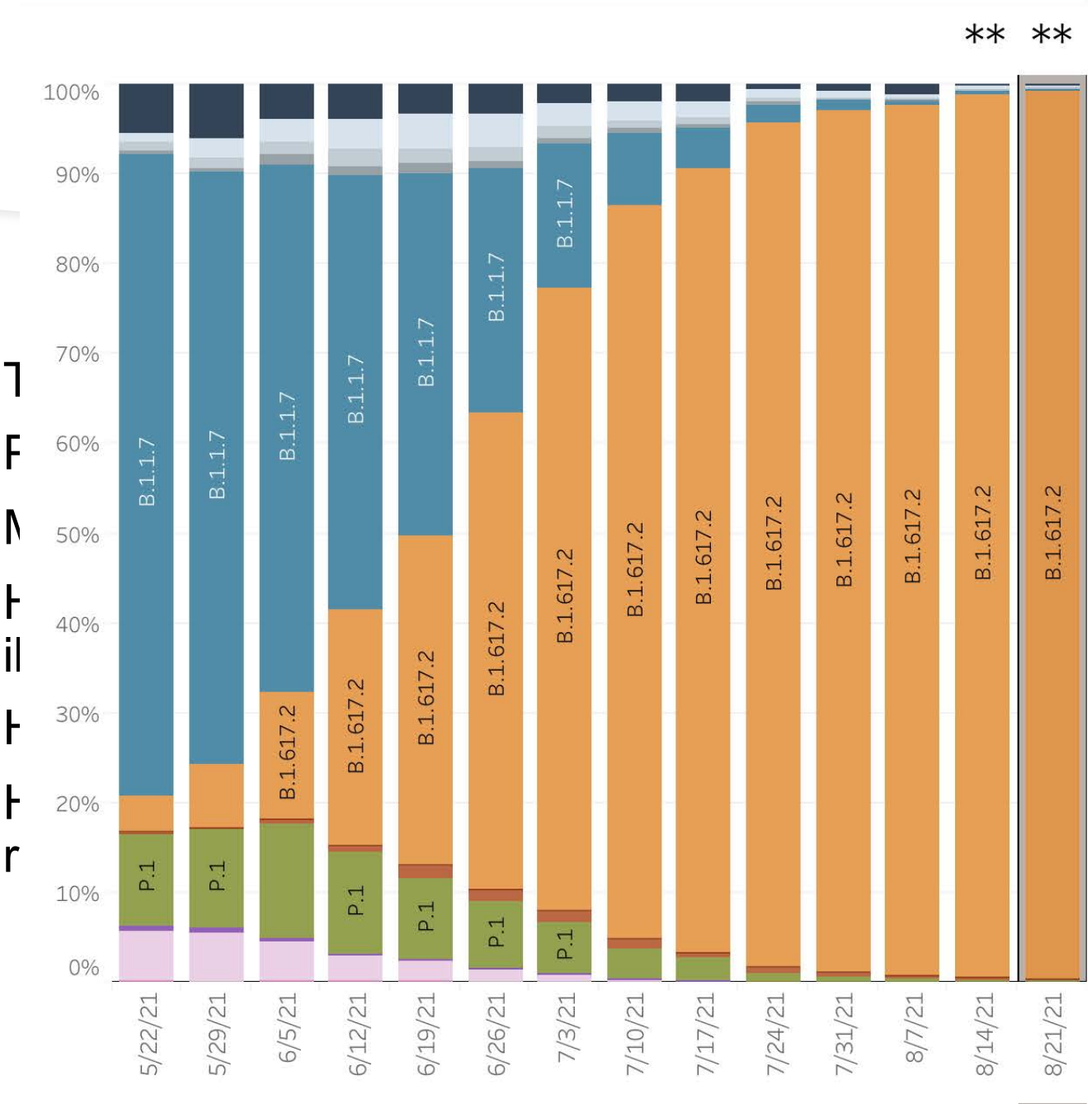
B.1.351 (Beta) – South Africa

P.1 (Gamma) - Brazil

B.1.617.2 (Delta) –India

United States: 5/16/2021 – 8/21/2021

United States: 8/15/2021 – 8/21/2021 NOWCAST



USA

WHO label	Lineage #	Type	%Total	95%PI
Alpha	B.1.1.7	VOC	0.2%	0.0-0.7%
Beta	B.1.351	VOC	0.0%	0.0-0.2%
Gamma	P.1	VOC	0.1%	0.0-0.5%
Delta	B.1.617.2	VOC	98.8%	97.6-99.8%
	AY.2	VOC	0.2%	0.0-0.7%
	AY.1	VOC	0.1%	0.0-0.5%
Eta	B.1.525	VOI	0.0%	0.0-0.2%
Iota	B.1.526	VOI	0.0%	0.0-0.2%
N/A	B.1.621		0.3%	0.0-0.7%
	B.1.621.1		0.1%	0.0-0.5%
	B.1.628		0.1%	0.0-0.5%
Other	Other*		0.1%	0.0-0.5%

* Enumerated lineages are VOI/VOC or are circulating >1% in at least one HHS region during at least one two week period; remaining lineages are aggregated as "Other".

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates

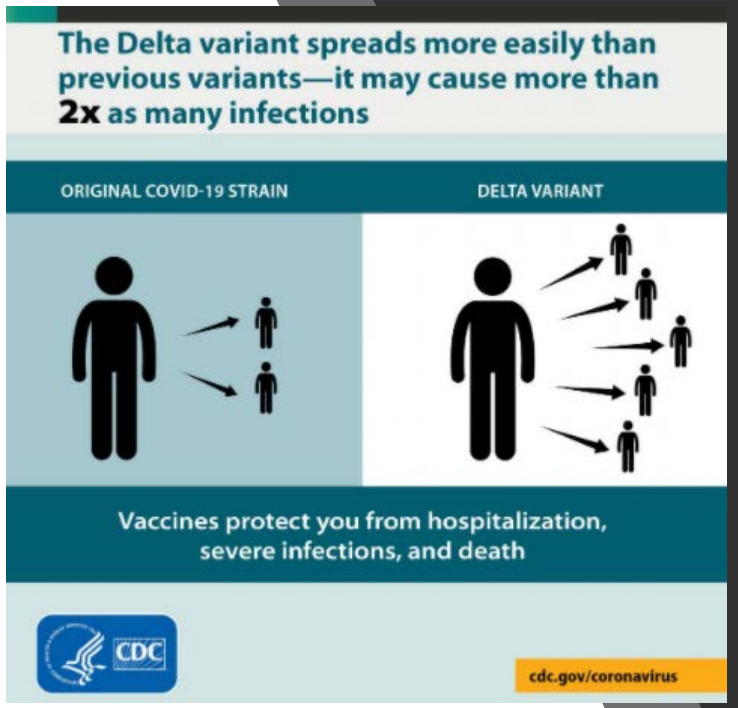
\# Sublineages of P.1 and B.1.351 are aggregated with the parent lineage and included in parent lineage's proportion. AY.3-AY.12 are aggregated with B.1.617.2

Delta Variant – B.1.617.2

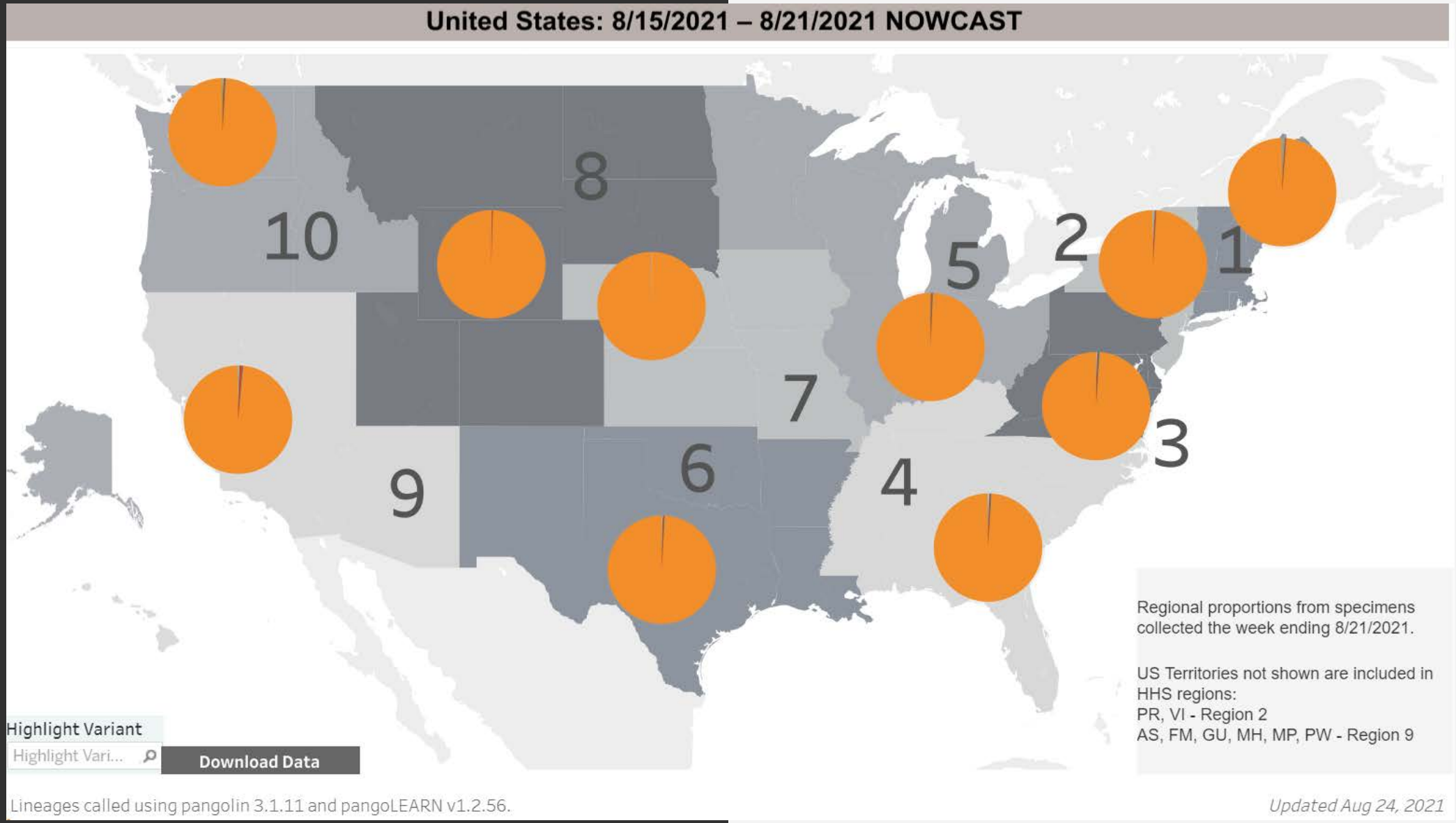
Spike protein mutations T19R, Δ157-158, L452R, T478K, D614G, P681R, and D950N

- First identified in December 2020 and became predominant strain in India and Great Britain
- By the end of August >90% of the cases in US
- Stared after July 4 weekend gathering in Provincetown, Mass. – cluster of 470 cases where ¾ of cases were vaccinated
- Vaccinated cases even without symptoms carried loads of virus in the nose and mouth

Delta Infection and Spread



- **The Delta variant is more contagious**
  - Alpha 50% more contagious than original strain, Delta 50% more contagious than Alpha
  - Unvaccinated and no masks, a person with Delta can infect 3.5-4 people
- **Some data suggest the Delta variant might cause more severe illness than previous variants in unvaccinated people**
- **Unvaccinated people remain the greatest concern**
- **Fully vaccinated people with Delta variant breakthrough infections can spread the virus to others**
- **However, vaccinated people appear to spread the virus for a shorter time**



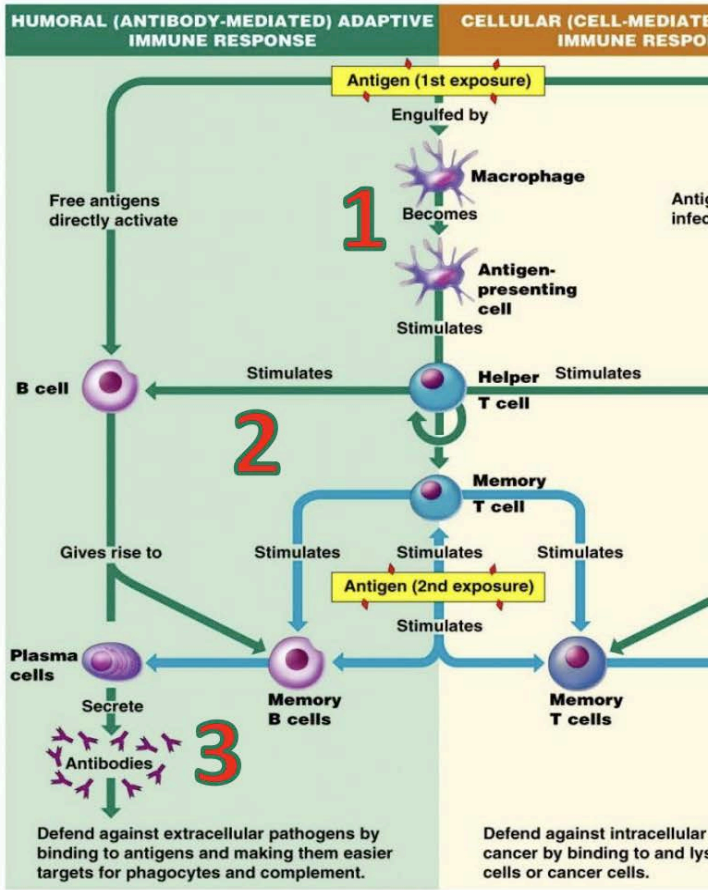
Delta Variant rate in US

Pacific NW: 98.7%

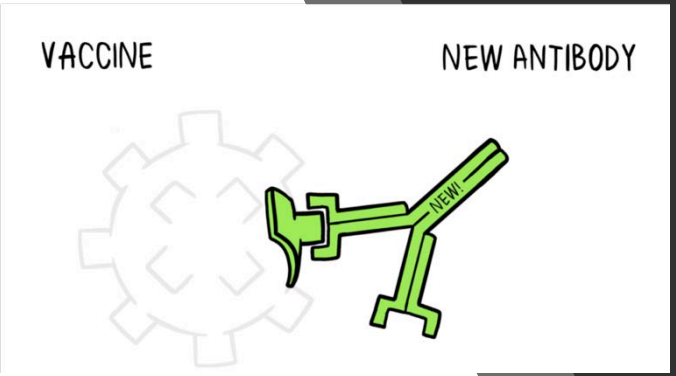
Complicated Immune System

Overview of the Adaptive Humoral Immune Response

1. Antigen ingestion and processing by antigen presenting cells; presentation to and stimulation of T helper cells
2. T helper cells stimulate B cells; direct activation of B cells also occurs
3. B cells mature into plasma cells; memory B cells are also generated
4. Antibodies are produced; IgM, then switch to IgG Binding antibodies, subset are neutralizing



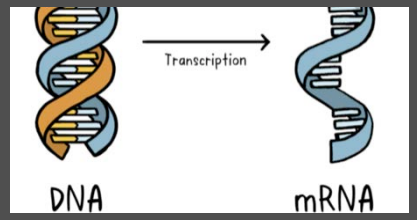
What is a vaccine?

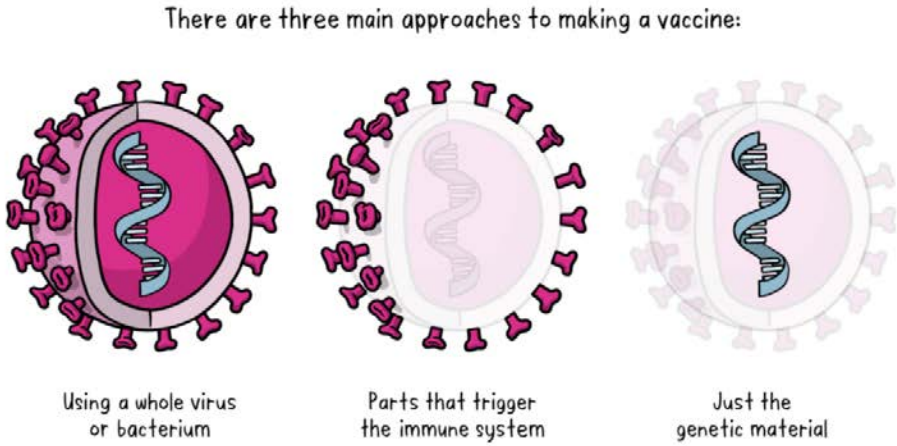


- Vaccines contain weakened or inactive parts of a particular organism (antigen) that triggers an immune response within the body
- Newer vaccines contain the blueprint for producing antigens rather than the antigen itself
- Regardless of whether the vaccine is made up of the antigen itself or the blueprint so that the body will produce the antigen, this weakened version will not cause the disease in the person receiving the vaccine, but it will prompt their immune system to respond much as it would have on its first reaction to the actual pathogen

Vaccine Types

- **The whole-microbe approach**
  - **Inactivated:**
    - **Polio**
    - **Flu**
  - **Attenuated live:**
    - **Chickenpox**
    - **Shingles**
    - **MMR**
- **The subunit approach -** subunit vaccine is one that only uses the very specific parts (the subunits) of a virus or bacterium that the immune system needs to recognize
    - **Most childhood vaccines**
- **The genetic approach (nucleic acid vaccine) -** a nucleic acid vaccine just uses a section of genetic material that provides the instructions for specific proteins, not the whole microbe. DNA and RNA are the instructions our cells use to make proteins. In our cells, DNA is first turned into messenger RNA, which is then used as the blueprint to make specific proteins.





How vaccines work:

Typical vaccine timeline in years

Basic Science

Animal studies

Clinical Trials

Approval Process

Manufacturing

8-10 years

4-7 years

1 year

***varied**

Vaccine Development Advantages in 2020

AdV vector technology had been previously studied in HIV vaccines and had been approved for use with Ebola vaccine (Ad26.ZEBOV [Zabdeno – Jannsen], cAd3-EBO Z [GSK])

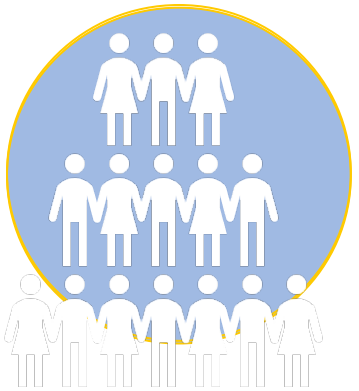
Clinical and pre-clinical research experience with mRNA vaccines for influenza, Zika, among others (none approved)

Experience with protein subunit vaccines (e.g. HepB, meningococcus)

Technologies ready to move forward quickly and adaptable to novel virus

Experience with SARS virus, rapid sequencing and isolation of virus allowed for early determination of vaccine target (spike protein)

“Expedited” vaccine timeline in months



Basic Science

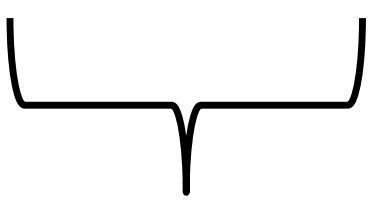
Animal studies

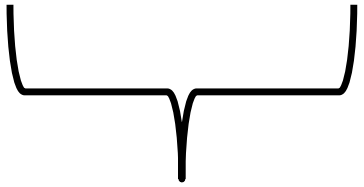
Clinical Trials

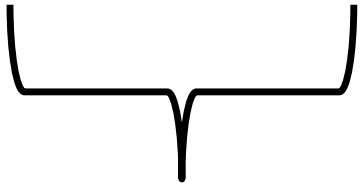
Approval Process

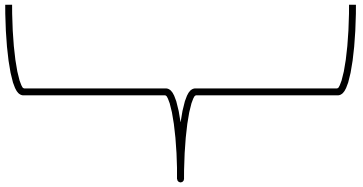
Manufacturing

Pre-existing









2-3 months

6 months

1 month

***prior to approval**

Novel SARS-CoV-2 Vaccines

- Vector vaccines
  - Astra-Zeneca (AZD1222)
  - **Janssen/J&J (Ad26.COV2.S)**
  - Sputnik (Ad26/Ad5)
- m-RNA vaccines
  - **Moderna (mRNA-1273)**
  - **Pfizer/BioNTech (BNT162b2)**
- Protein sub-unit vaccines
  - Novavax (NVX-CoV2373)
- Killed virus vaccines
  - Covaxin (adjuvant/killed SARS-CoV-2)
  - CoronVac (Sinovac)

Vaccination Trial Data

Janssen/J&J	**66.9/76.7% severe 14 days** **66.1/85.4% severe 28 days**	2 (both <28 days) in vaccine arm 28 in placebo	**7 fainting/100,000** **7 blood clots/1 million** **1 death**	Effective against all variants
Moderna	**94.1%**	0 severe disease in vaccine arm 30 in placebo	**0 in vaccine arm** **Allergic reactions within 7 days**	Effective against all variants
Pfizer	**94.6%**	1 severe disease in vaccine arm 9 in placebo	**0 in vaccine arm** **Allergic reactions within 7 days**	Effective against all variants

Novel SARS-CoV-2 Vaccines in US

The Pfizer-BioNTech vaccine (Comirnaty): authorized for people 12 years and over

- As of August 2021 the Pfizer vaccine is **fully approved by the FDA**.
- 91% effective at preventing COVID-19 and provides strong protection against serious illness.
- **0 death in vaccine arm**
- Allergic reactions within 7 days
- Transient myocarditis in young adults and adolescents

The Moderna vaccine: authorized for people 18 years and over

- 94% effective at preventing COVID-19 and provides strong protection against serious illness.
- **0 death in vaccine arm**
- Allergic reactions within 7 days

Johnson & Johnson's Janssen vaccine: authorized for people 18 years and over

- 66.3% effective at preventing COVID-19 and provides strong protection against serious illness.
- 7 fainting/100,000
- 7 blood clots with low plateles/ 1 million
- **1 death**

Vaccinations for Variants

Vaccines are effective, but not 100%, but virtually all hospitalized cases and deaths are unvaccinated people

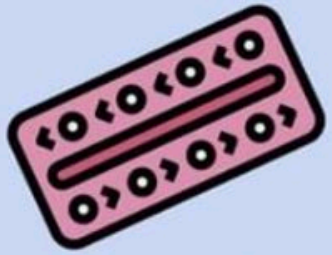
Low vaccination coverage in many communities is driving the current rapid surge in cases involving the Delta variant, which also increases the chances that even more concerning variants could emerge

High vaccination coverage will reduce spread of the virus and help prevent new variants from emerging. CDC recommends that everyone aged 12 years and older get vaccinated as soon as possible.

Thrombosis and AdV Vaccines

- Early data on AZ vaccine and clotting suggesting increased risk[1]
  - 28 pts in Austria/Germany developed different types of clots, or thromboses, five to 16 days after vaccination, and all had made antibodies against platelets
  - 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died
  - Additional data from Norway with similar findings[2]
  - Canada limits AZ use to those >50 yrs of age, Europe no restrictions; UK only >30 yrs
- On 4/13/2021, FDA and CDC have put a hold on use of Janssen/Johnson & Johnson vaccine
  - Reported 6 thrombosis events among over 6.8 million doses, all women (1 death)
  - Available again with guidance to discuss with patients prior to use (particularly women <40)
- No reported thrombotic issues with mRNA vaccines (over 200 million doses given)

Risk of Blood Clots

AstraZeneca Vaccine	Birth Control Pill	Smoking	COVID Infection
			
4 cases in 1,000,000 Vaccines	500 - 1200 cases in 1,000,000 women	1,763 cases in 1,000,000 Smokers	165,000 cases in 1,000,000 Cases
0.0004%	0.05% to 0.12%	0.18%	16.5%

Maria Leonor Ramos | Médica Interna de Medicina Geral e Familiar

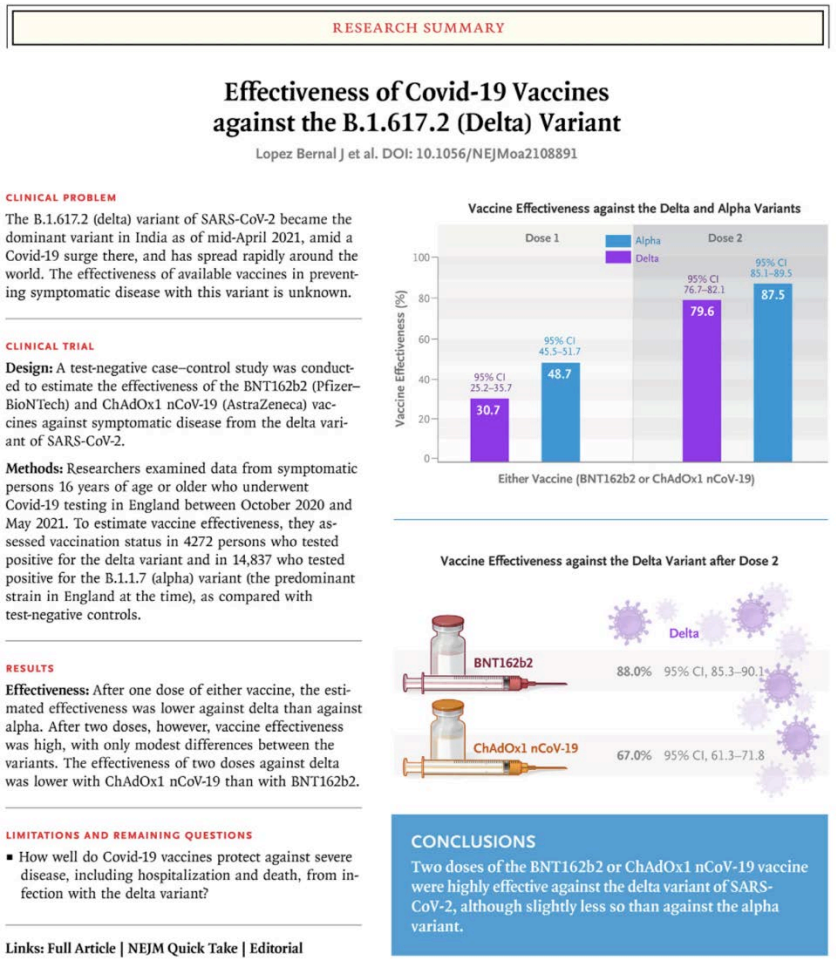
Fontes: Agência Europeia do Medicamento; Suh YJ, Hong H, Ohana M et al. Pulmonary Embolism and Deep Vein Thrombosis in COVID-19: A Systematic Review and Meta-Analysis. Radiology 2021.; Cheng, Yun-Jiu & Liu, Zhi-Hao & Yao, et al. (2013). Current and Former Smoking and Risk for Venous Thromboembolism: A Systematic Review and Meta-Analysis.

Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant

July 22, 2021
N Engl J Med 2021; 385:320-329
DOI: 10.1056/NEJMoa2107058

Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines

- Participants who were partially or fully vaccinated at the time of infection had a 40% lower viral RNA load and a 66% lower risk of viral RNA detection for more than 1 week.
- Partially or fully vaccinated participants also had a 58% lower risk of febrile symptoms and a shorter duration of illness, with approximately 6 fewer days of symptoms and 2 fewer days spent sick in bed, than unvaccinated participants.
- Effect is probably due to recall of immunologic memory responses that reduce viral replication and accelerate the elimination of virally infected cells.



RESEARCH SUMMARY

Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant

Lopez Bernal J et al. DOI: 10.1056/NEJMoa2108891

CLINICAL PROBLEM

The B.1.617.2 (delta) variant of SARS-CoV-2 became the dominant variant in India as of mid-April 2021, amid a Covid-19 surge there, and has spread rapidly around the world. The effectiveness of available vaccines in preventing symptomatic disease with this variant is unknown.

CLINICAL TRIAL

Design: A test-negative case–control study was conducted to estimate the effectiveness of the BNT162b2 (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (AstraZeneca) vaccines against symptomatic disease from the delta variant of SARS-CoV-2.

Methods: Researchers examined data from symptomatic persons 16 years of age or older who underwent Covid-19 testing in England between October 2020 and May 2021. To estimate vaccine effectiveness, they assessed vaccination status in 4272 persons who tested positive for the delta variant and in 14,837 who tested positive for the B.1.1.7 (alpha) variant (the predominant strain in England at the time), as compared with test-negative controls.

RESULTS

Effectiveness: After one dose of either vaccine, the estimated effectiveness was lower against delta than against alpha. After two doses, however, vaccine effectiveness was high, with only modest differences between the variants. The effectiveness of two doses against delta was lower with ChAdOx1 nCoV-19 than with BNT162b2.

LIMITATIONS AND REMAINING QUESTIONS

- How well do Covid-19 vaccines protect against severe disease, including hospitalization and death, from infection with the delta variant?

Links: Full Article | NEJM Quick Take | Editorial

Vaccine Effectiveness against the Delta and Alpha Variants

Vaccine Effectiveness against the Delta Variant after Dose 2

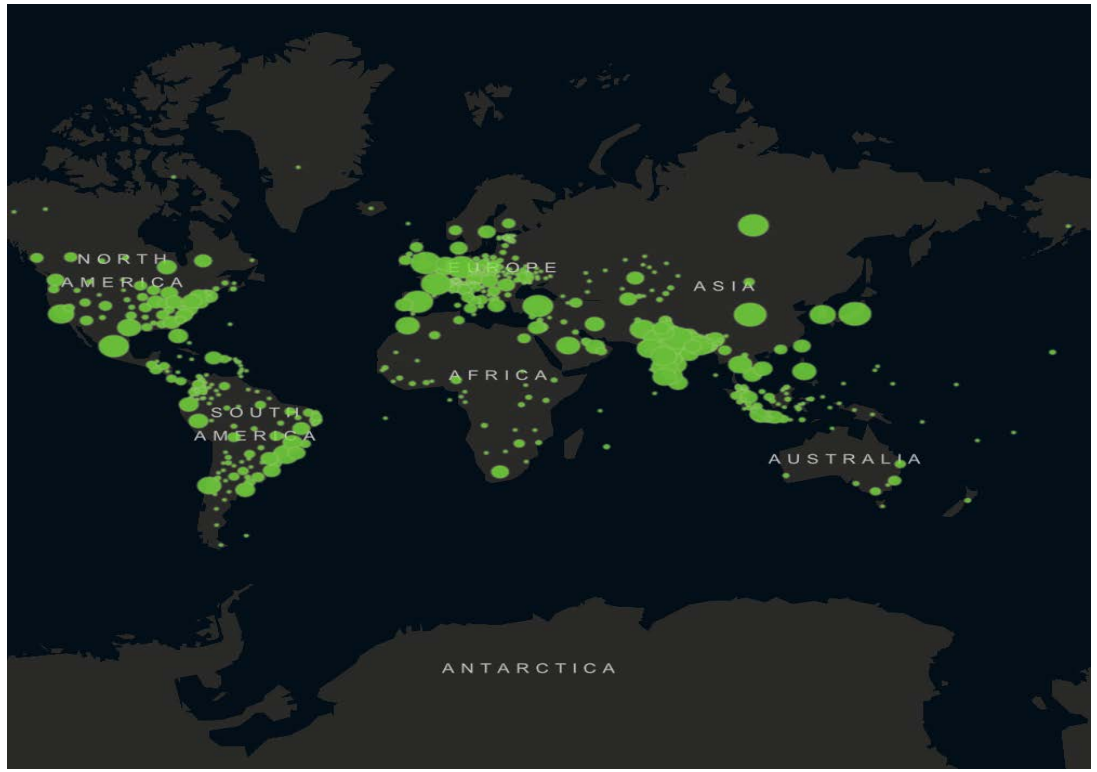
CONCLUSIONS

Two doses of the BNT162b2 or ChAdOx1 nCoV-19 vaccine were highly effective against the delta variant of SARS-CoV-2, although slightly less so than against the alpha variant.

Vaccination Status

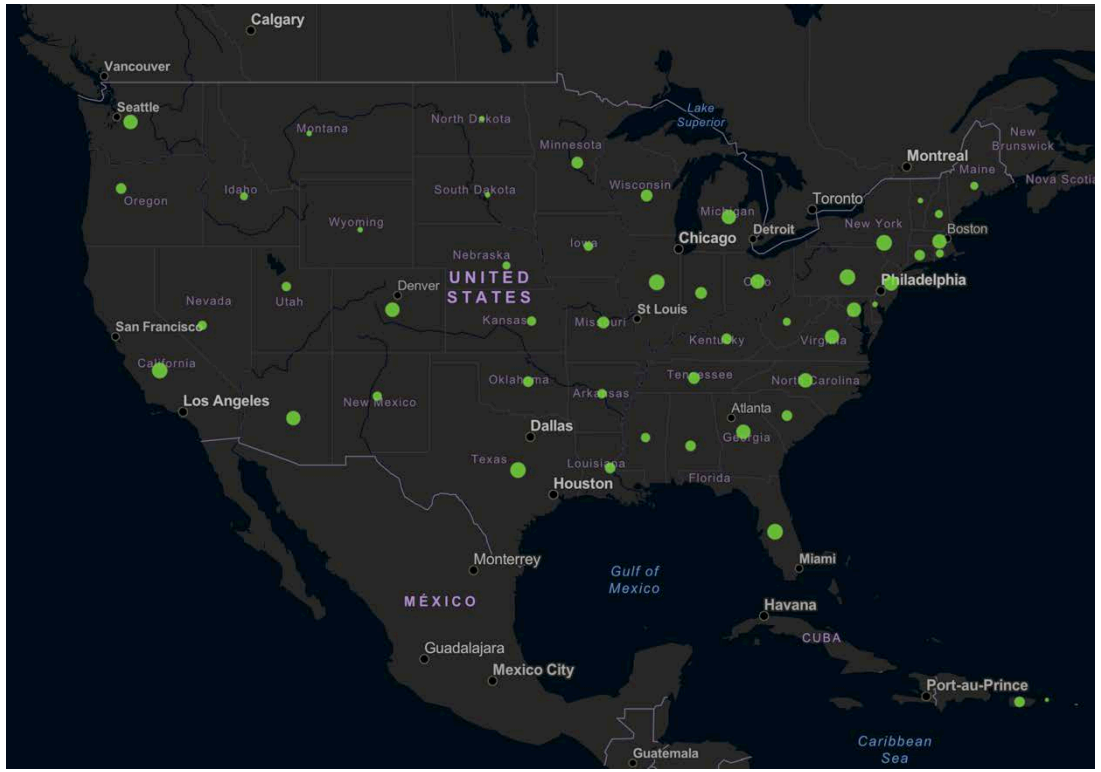
Total Vaccine Doses Administered

5,002,735,109

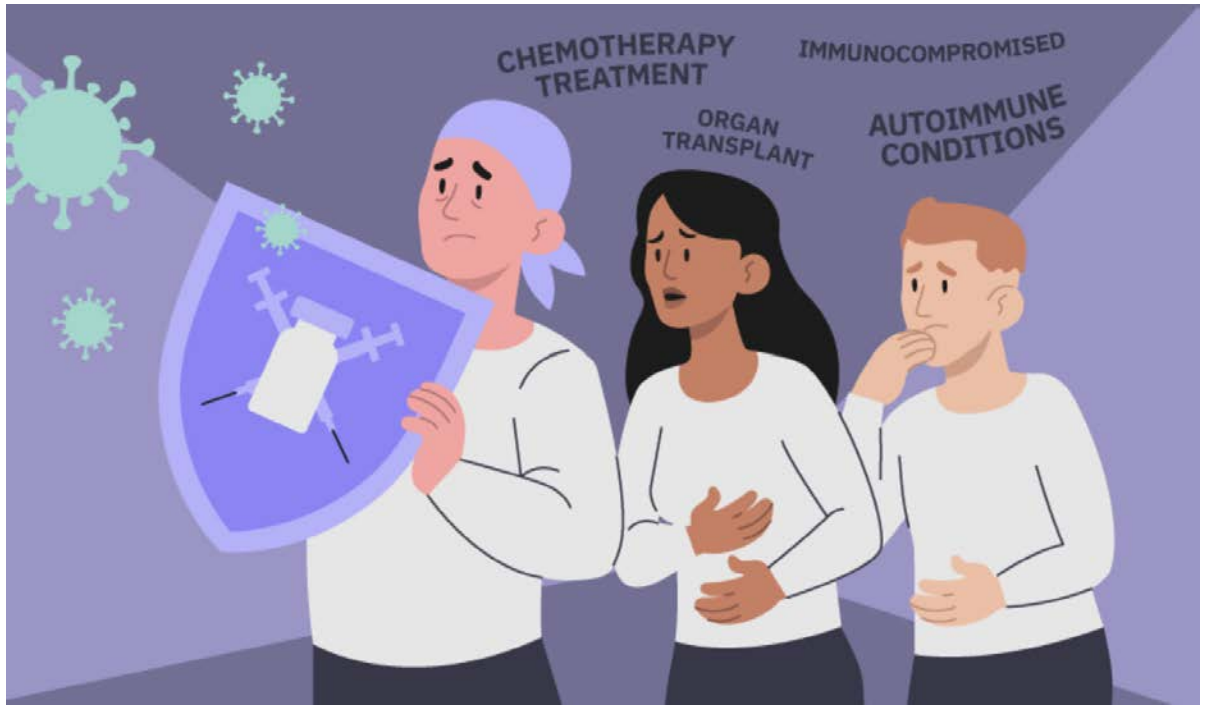


Vaccine Doses Administered in US

362,779,423



Immunocompromised and Vaccines



- Influenza vaccine responses are less robust among cancer and transplant patients, though high-dose vaccines or boosting may improve responses
- Data that responses can be seen as early as 3 months post-HCT

Data on Cancer and Transplant patients

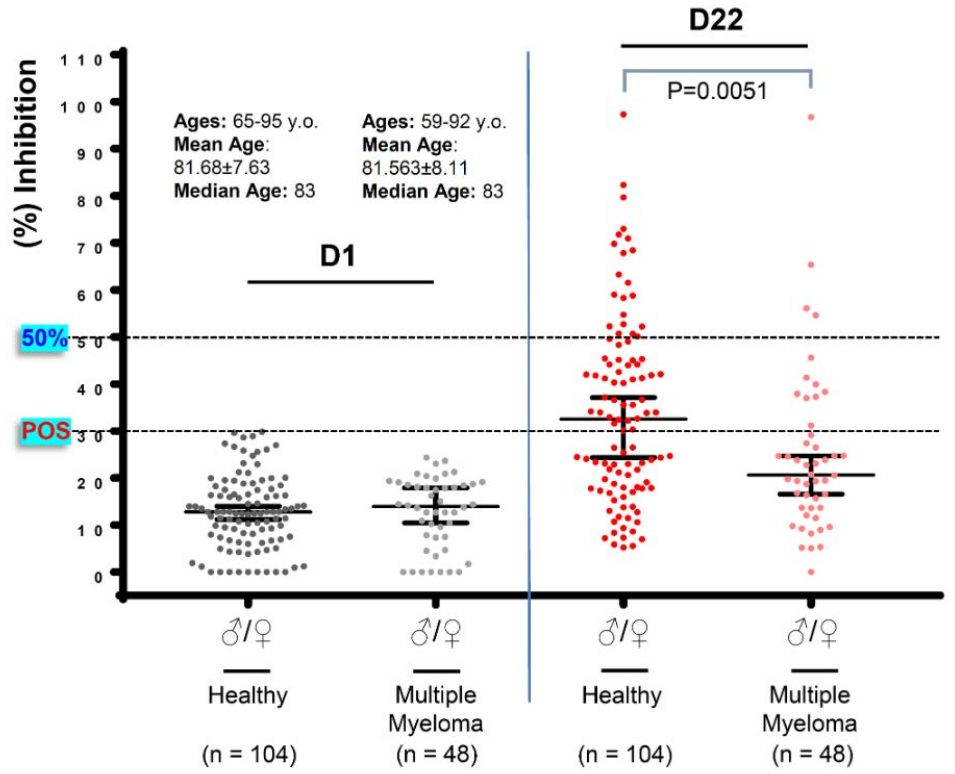
Pfizer trial enrolled 1395 (3.7%) cancer patients in trial, however no patients on active chemotherapy or immunosuppression allowed in trial[1]

Janssen/J&J enrolled 226 (0.5%) cancer patients and 79 (0.2%) patients “immunocompromised after blood transplant”[2]

Data on these sub-groups not clear, but thought to be likely limited immunosuppression (long-term survivors)

Multiple Myeloma

- Of 93 patients, 52 (56% [95% CI 46–66]), had positive Ab after first dose (on therapy lower response)[1]
- Of 48 patients, lower Ab levels compared to control, and only 12 (25%) with response after first dose of the vaccine (compared to >50% in normal hosts



Bird Lanct Hematol 2021

Terpos Blood 2021

Antibody levels

- Post-vaccine antibody levels vary by vaccine (mRNA highest)
- Following vaccination natural decay in antibody titers
- Modeled that 90% efficacious vaccines will drop to 70% efficacy in 131 days, 50% in 221
- For 70% efficacious vaccines 50% efficacy at ~90 days

Immune responses to COVID-19 vaccinations in immunocompromised people

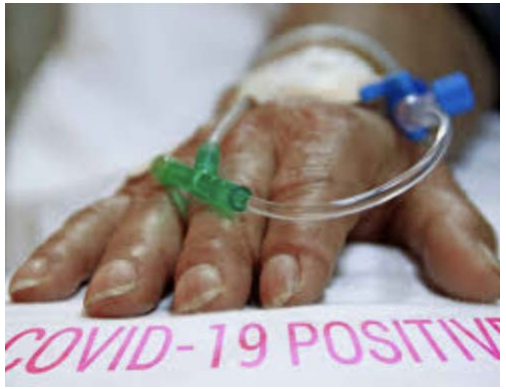
- **Underlying immune compromise or therapies** disrupt the adaptive immune response
- **Post-vaccine serological testing** has been performed as part of clinical trials or research studies
  - The clinical utility of post-vaccination serological testing has not been established
- **Evidence of decreased production of binding and neutralizing antibodies to COVID-19 vaccination** (small N in individual studies)
  - Dialysis patients
  - Chronic liver disease
  - Hematology-Oncology patients
  - Immunosuppressive therapies
  - Transplant patients
    - Solid organ
    - Hematopoietic stem cell transplant patients
  - **Variability noted based on severity of underlying immunocompromise and therapy**
- **Cellular immune responses are also impaired**

https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#laboratory-testing
Reviewed in https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-07/07-COVID-Oliver-508.pdf
J Hepatol. Apr 2021;74(4):944-951. doi:10.1016/j.jhep.2021.01.032

Cancer patients and COVID-19

- Antibody levels may be less in cancer patients
- Variants already have reductions in post-vaccine efficacy
- Significant risk with variants among those with less robust responses to vaccines
- IVIG levels not sufficient to provide protection

- Study: 218 cancer patients who tested positive for COVID-19 from March 18 to April 8, 2021 at Montefiore Medical Center, New York.
- 61 died from COVID-19, a fatality rate of 28%, as compared to the overall mortality rate of 5.8% for COVID-19 in the US (as per the World Health Organization)
- Highest mortality rate: 37% (20 of 54 patients) for blood cancers (leukemia, lymphoma, myeloma).
- For patients with solid malignancies, the mortality rate was 25% (41 of 164). The mortality rate for patients with lung cancer was 55% and colorectal cancer was 38%, compared with mortality rates of 14% for breast cancer and 20% for prostate cancer.



Immunosuppressed patients as source of variants?

- Emerging data suggests that IC hosts can be source of viral variants
- Present with higher viral loads
- Have viable virus detected for long periods of time
- Limited immunity may allow more ease of viral escape, and breakthrough of remaining aspects of immunity

Ongoing questions

- Boosters: 3rd dose of mRNA received FDA EUA for immunocompromised
- New vaccines are in the pipeline
- Antibody levels and other T-Cell studies for IC patients are ongoing

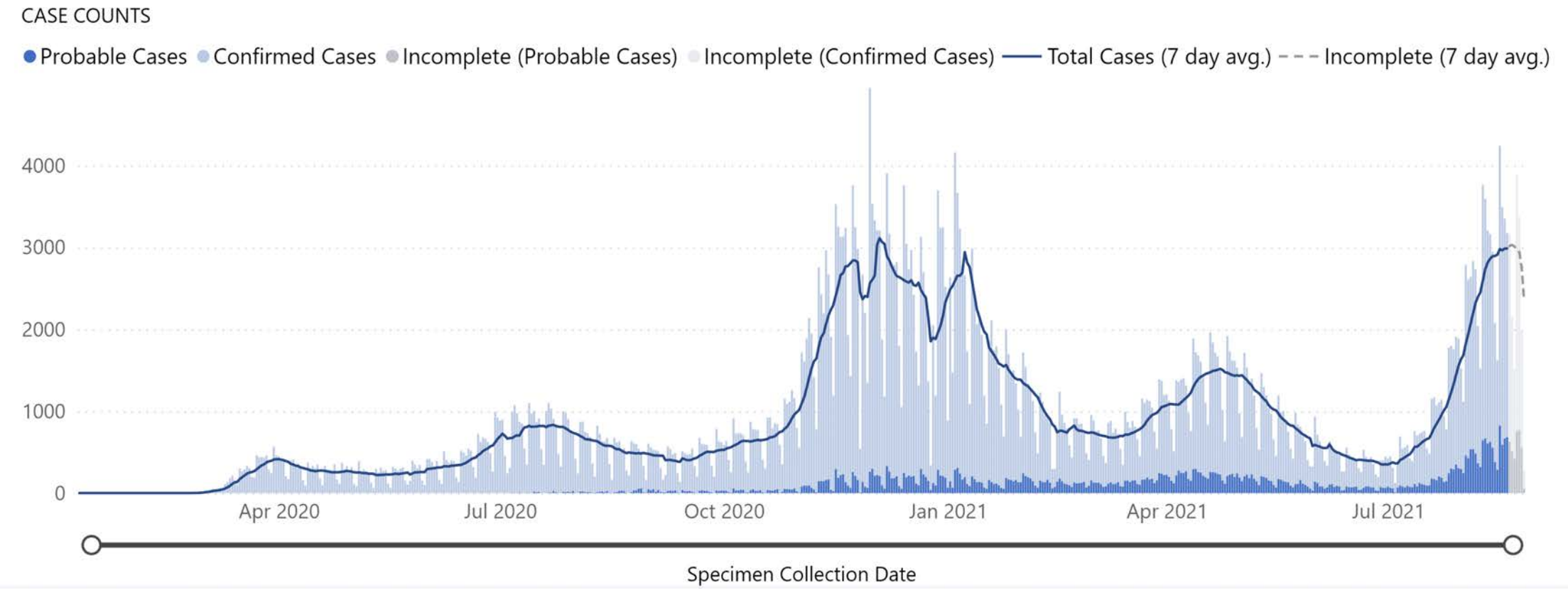
Caregivers/Family

- Household transmission is high
- Caregivers and family more likely to leave home and have at risk exposures

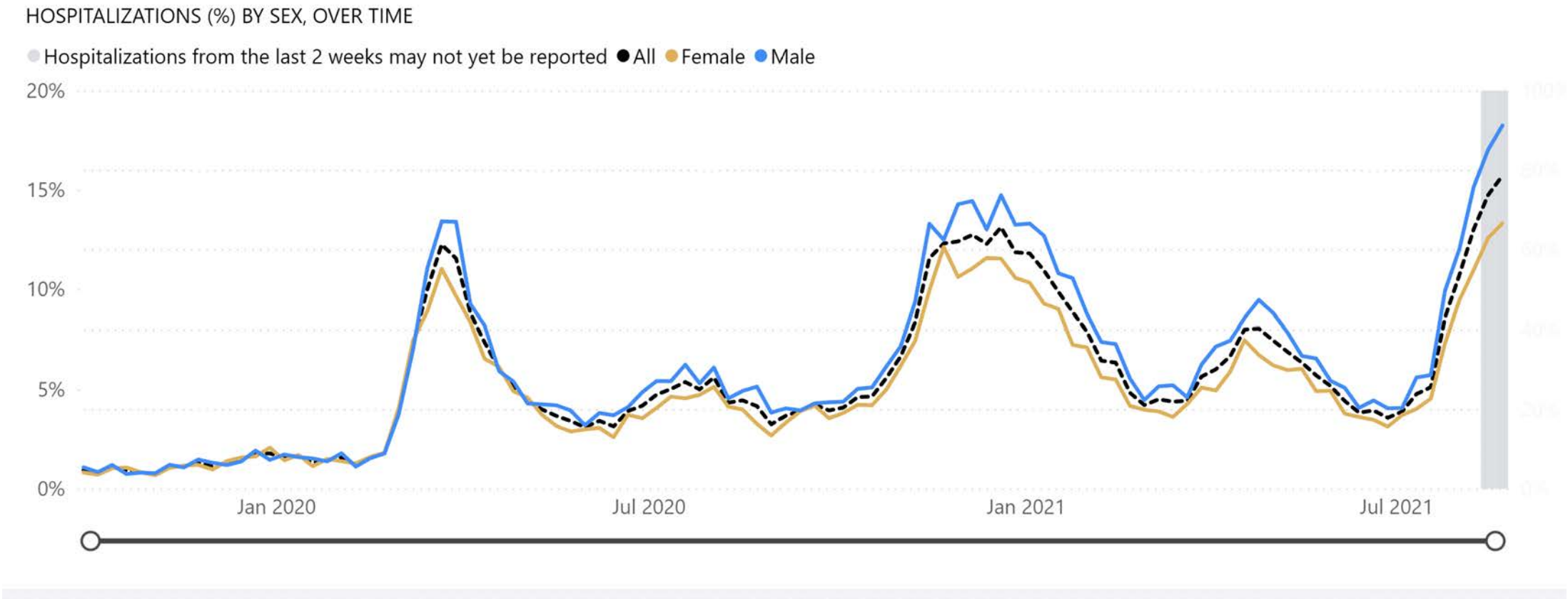
- Cannot prevent exposures
- **"Cocoon" strategy** to vaccinate all those close contacts of high-risk patients (known vaccine efficacy vs. unknown efficacy)[1]
- Renewed effort from cancer centers to target household contacts/caregivers for vaccine education
  - Few cancer center websites target any vaccine information/education to close contacts[2]

1. Woodfield Cancer 2021
2. Marellapudi Vaccine 2020

As of 8/26/2021- Washington State

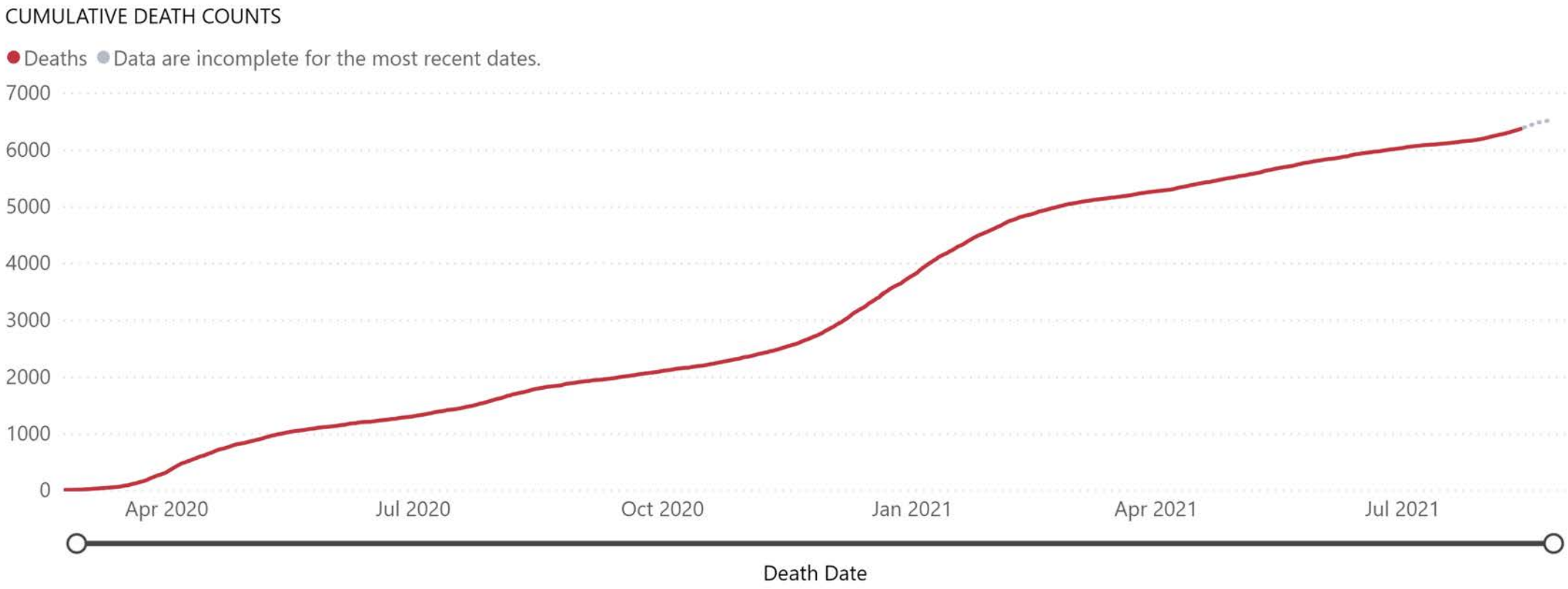


As of 8/26/2021, Washington State



6,766 total emergency inpatient admissions reported for the last full week.

As of 8/26/2021, Washington State



Expectation

- Vaccinated cancer patients will continue to develop COVID-19, become hospitalized and may die from SARS-CoV-2 despite vaccination
- Decreased community levels will decrease risk, but regression to poor vaccine coverage will assure SARS-CoV-2 remains in our communities
- Similar to H1N1, COVD-19 will become a continuing issue
- Expect a yearly vaccine for all of us and for our patients

Recommendations

Since the vaccine may not be as effective in IC patients:

- Please wear a mask in public spaces (even outside when there is crowd)
- Avoid crowds, stay away from symptomatic people
- Get the third dose of the vaccine if Moderna or Pfizer for the first one
- Wear a mask in enclosed spaces
- Avoid inside visits with family, friends if they do not have close contact with you already
- Can meet up outdoors, but please mask up!
- Continue to be cautious
- All caregivers and close contacts should be vaccinated!

Treatment/Prevention options

- Monoclonal antibodies (treatment)
- Casirivimab and imdevimab (REGEN-Cov) are recombinant human IgG1 monoclonal antibodies that target the receptor binding domain of the spike protein of SARS-CoV-2
  - Approved for the treatment of mild to moderate coronavirus disease 2019 (COVID-19) in adult and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death
  - In adult and pediatric individuals (12 years of age and older weighing at least 40 kg) for post-exposure prophylaxis of COVID-19 in individuals who are at high risk for progression to severe COVID-19, including hospitalization or death after exposure to COVID 19 positive individual (Includes IC patients)
  - Pre-prophylaxis studies are ongoing and being considered for high risk individuals

Conclusion

- We are at the worst time for COVID since the pandemic started
- But effective vaccines are available
- Despite effective vaccines, infection rate is high
- While vaccines prevent poor outcomes, immunocompromised patients may be more vulnerable and still at risk of dying
- Take extreme precautions always including adhering to mask use in public
- Contacts and caregivers should all be vaccinated
- If there is a known exposure to COVID, please call your doctor immediately for REGEN-Cov, a monoclonal antibody combination

Thank You!

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