Vaccinations including COVID-19

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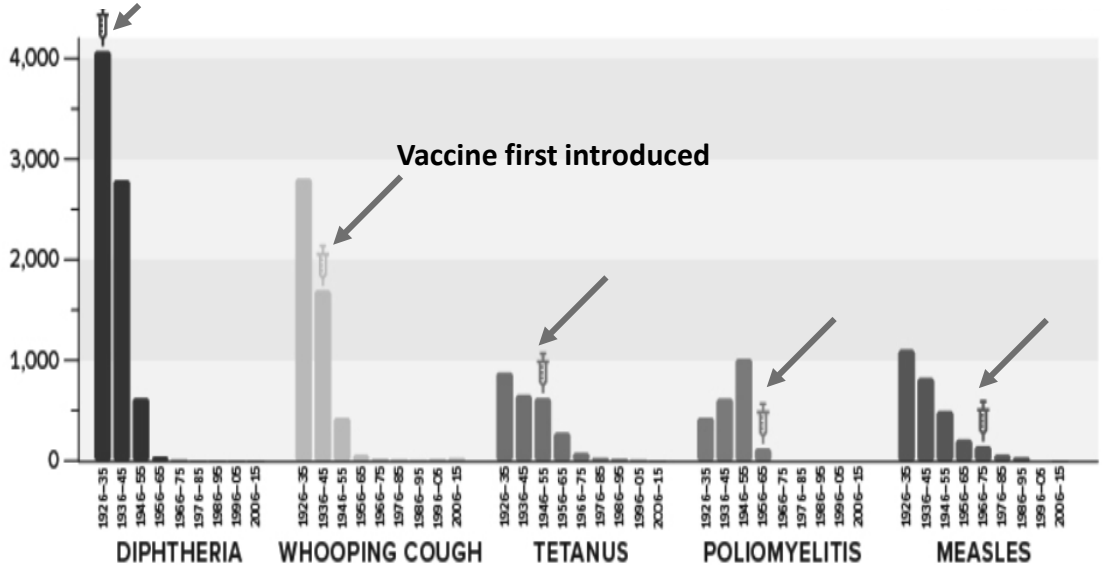
Vaccines represent one of the greatest public health achievements of modern medicine. Blumenthal KG JAMA 2021

Vaccination has safed more lives than any other medical intervention

Vaccination has eradicated

- **Smallpox**
- **Polio**
- **(Measles)**

Australia: Number of deaths from diseases now vaccinated against, by decade (1926-2015)



When a large proportion of a community is immunised, it can lead to a situation where there are very low disease levels in that population. This is referred to as control of the disease.

USA: Comparison of 20th century annual morbidity and current estimates of vaccine-preventable disease

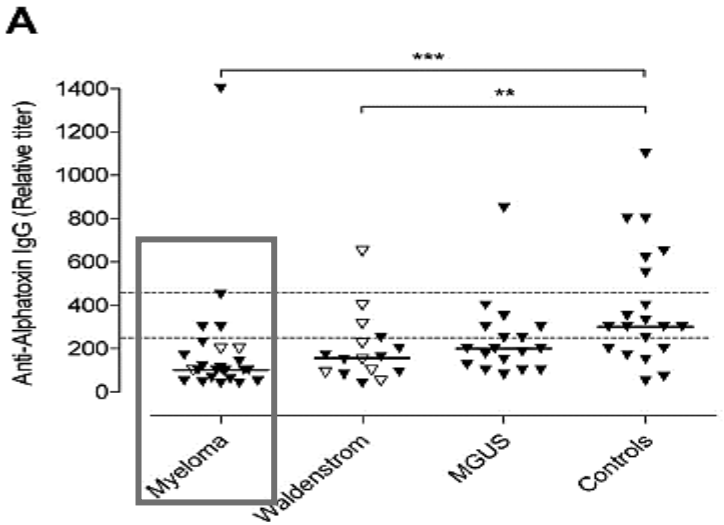
Disease	20th Century annual morbidity (2)	2016 Reported cases (3)	Percent decrease (%)
Smallpox	29,005	0	100
Diphtheria	21,053	0	100
Measles	530,217	69	>99
Mumps	162,344	5,311	97
Pertussis	200,752	15,737	92
Polio (paralytic)	16,316	0	100
Rubella	47,745	5	>99
Congenital rubella syndrome	152	1	99
Tetanus	580	33	94
Haemophilus influenzae	20,000	22*	>99

**Haemophilus influenzae* type b (Hib) < 5 y of age.

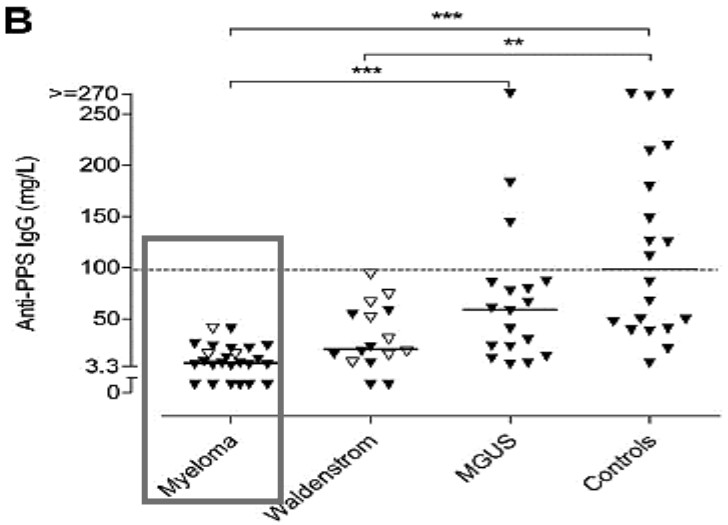
Orenstein WA et al., PNAS 2017

Myeloma patients frequently lack protective immunity

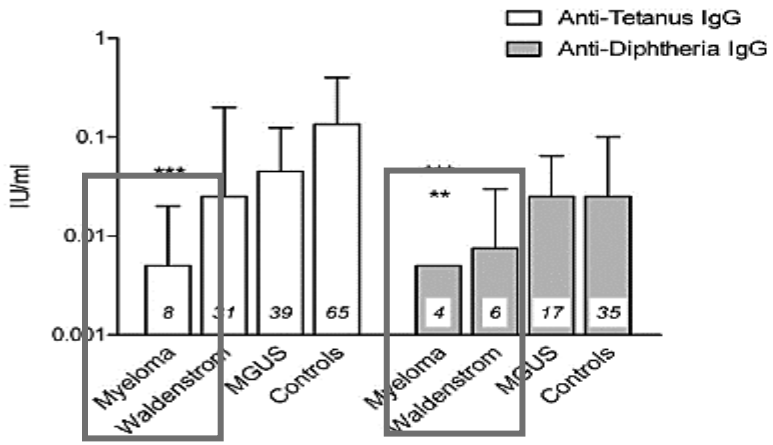
Anti-staphylococcal IgG



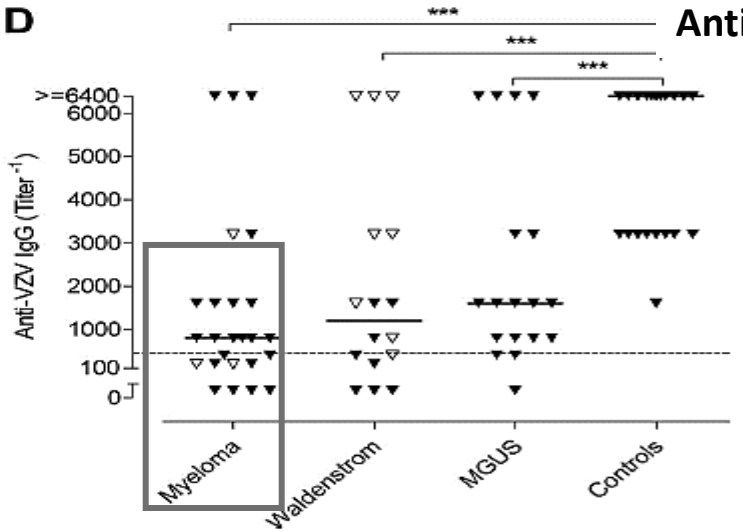
Anti-pneumococcal IgG



Anti-tetanus, anti-diphtheria IgG



Anti-VZV IgG



Karlsson J Clin and Vaccine Immunol 2011

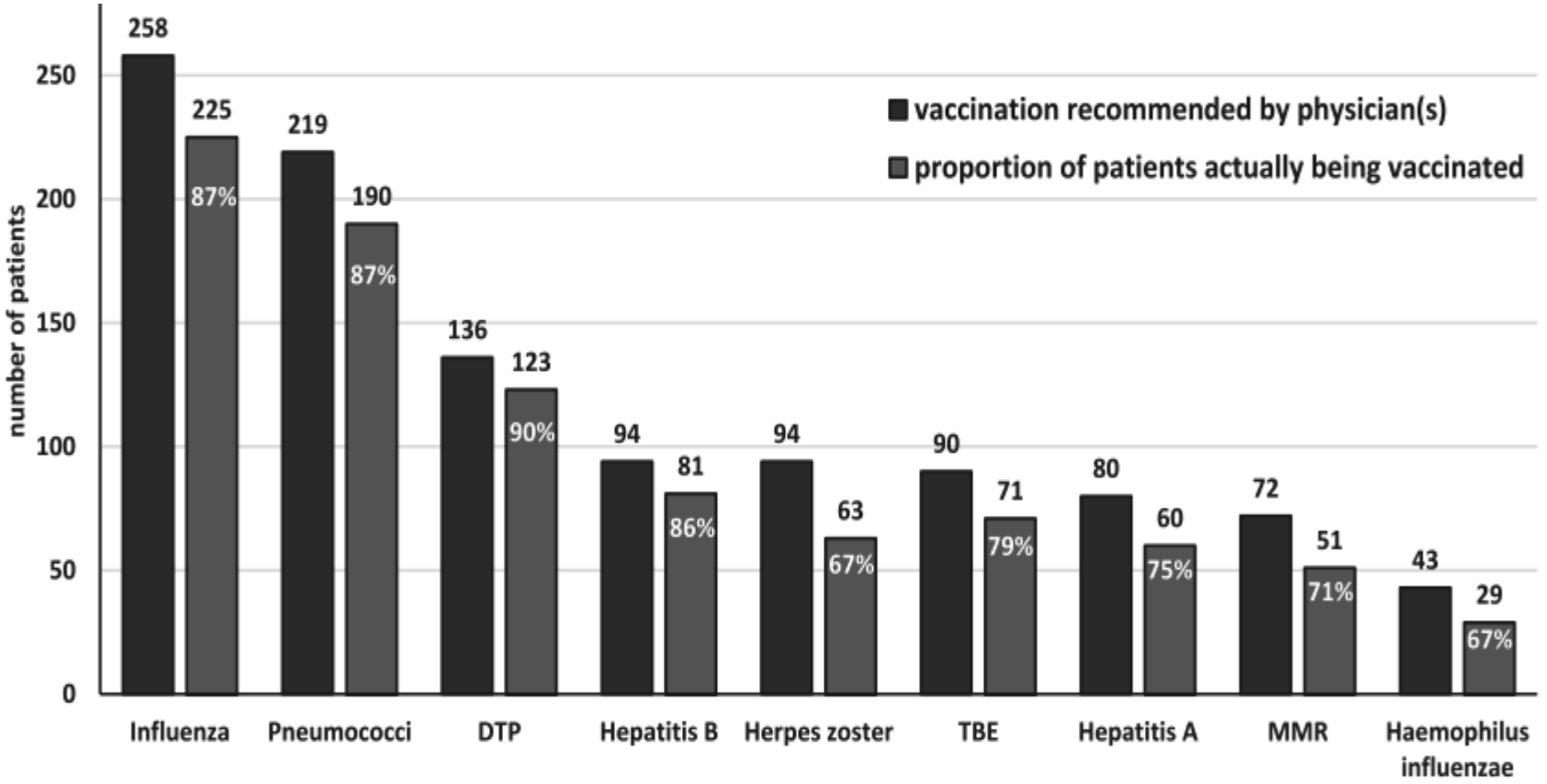
Recommendations for vaccination of patients with MM

Vaccine	Recommendation	No. of doses	Recommended by
Influenza	Tri- or quadri-valent vaccine	1 annually	CDC, NCCN
Pneumococci	PCV13 followed by PPSV 23	1	NCCN
Herpes zoster	Shingrix (recombinant glycoprotein)	2	NCCN
	or Zostavax (live-attenuated)	4	EMN
Haemophilus influenzae type b	Vaccination	3	CDC, NCCN
Hepatitis A	Nonimmune pts & close contacts travelling to endemic areas	2	NCCN
Hepatitis B	Nonimmune pts & close contacts travelling to endemic areas	3	NCCN
Meningococci	Pts with complement deficiency or splenectomy	1-2	CDC, NCCN
Tetanus, Diphtheria, Pertussis	Only if no primary vaccination, Tetanus based on epidemiology		CDC, NCCN, WHO, EMN

Modified according to Ludwig H et al., Leukemia 2020

Myeloma patients show a high compliance rate with Recommendations for vaccination

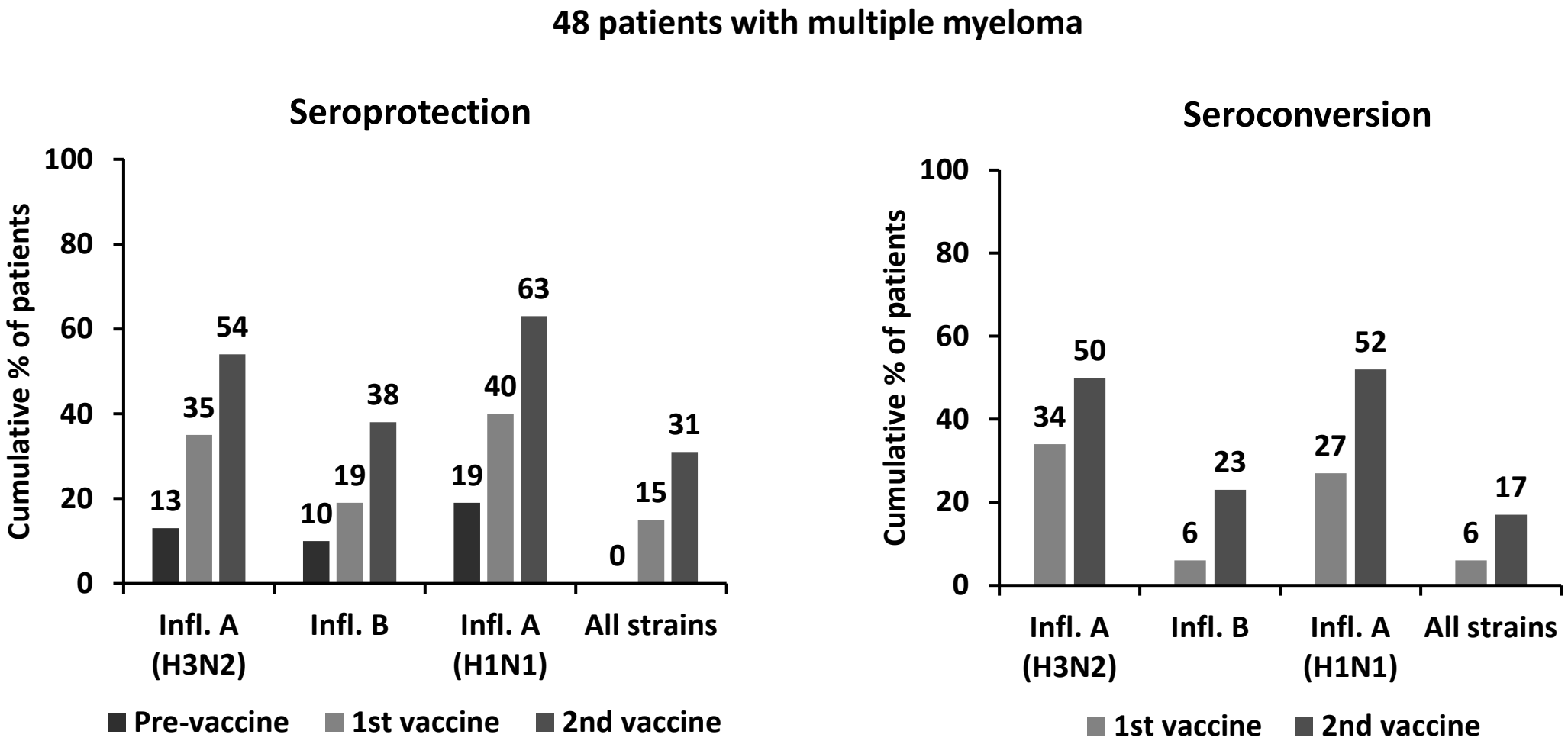
335 patients responded during the survey



DTP = diphtheria, tetanus, pertussis; MMR = measles, mumps, rubella; TBE = tick borne encephalitis

Ludwig H et al. Hemasphere 2021

Patients with MM show reduced antibody formation to influenza vaccination. A second dose improves immune response



Hahn M, et al. Haematologica 2015;100:e285.

Pneumococcal diseases

Pneumococci cause
Pneumonia, Bacteriemia, Meningitis, Otitis Media

PCV 13 → > 8 weeks apart → PPSV23 → > 5 years apart → PPSV23 → > 5 years apart → PPSV23

Response to Pneumovax II (23 valent) in 52 patients with multiple myeloma
Protective titer defined as ≥1/640, the geometric mean titre of the normal adult UK population

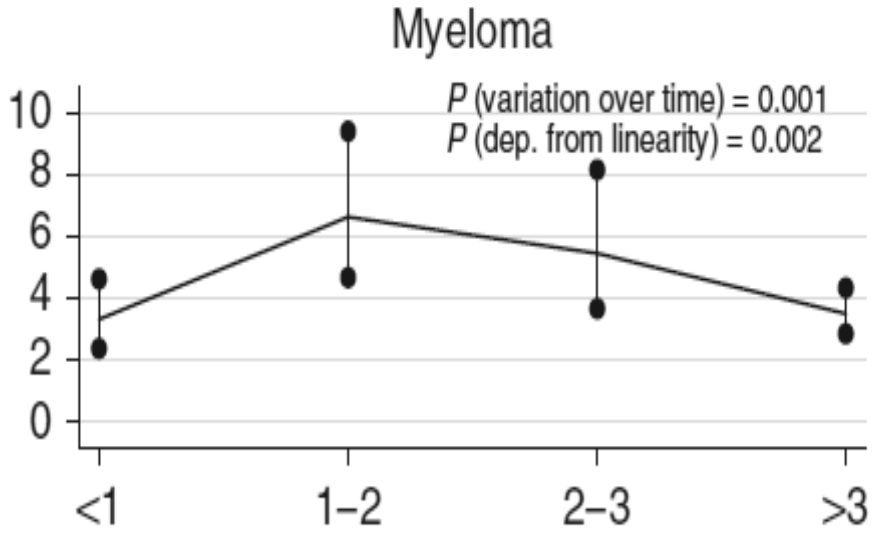
	Pre-vaccination (*n* = 48)		Post-vaccination (*n* = 43)	
Protective antibody titre	3	6%	17	39%
Suboptimal antibody titre	45	94%	26	61%
Titre below 10th percentile	31	70%	13	30%
Fourfold increase in titre			24	56%
Geometric mean titre	1/53		1/287	

Robertson JD et al. Br J Cancer 2000

Herpes Zoster

Herpes zoster subunit vaccine (HZ/su) containing recombinant varicella–zoster virus glycoprotein E and the AS01B adjuvant system (Shingrix©)

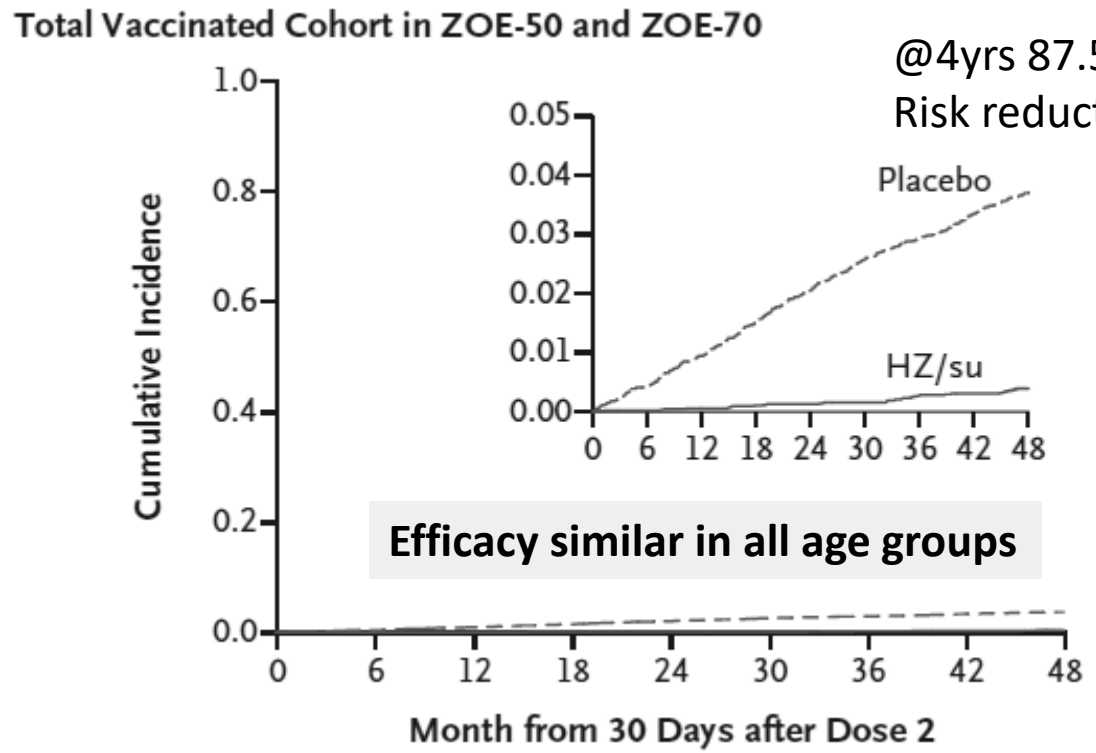
Zoster odds ratio by time since diagnosis of multiple myeloma



Risk of post herpetic neuralgia in myeloma similar to general population (Forbes at el., 2016)

Hanson E et al., Br J Cancer 2017

Vaccine efficacy in general population 89.9% during a 3 year FU

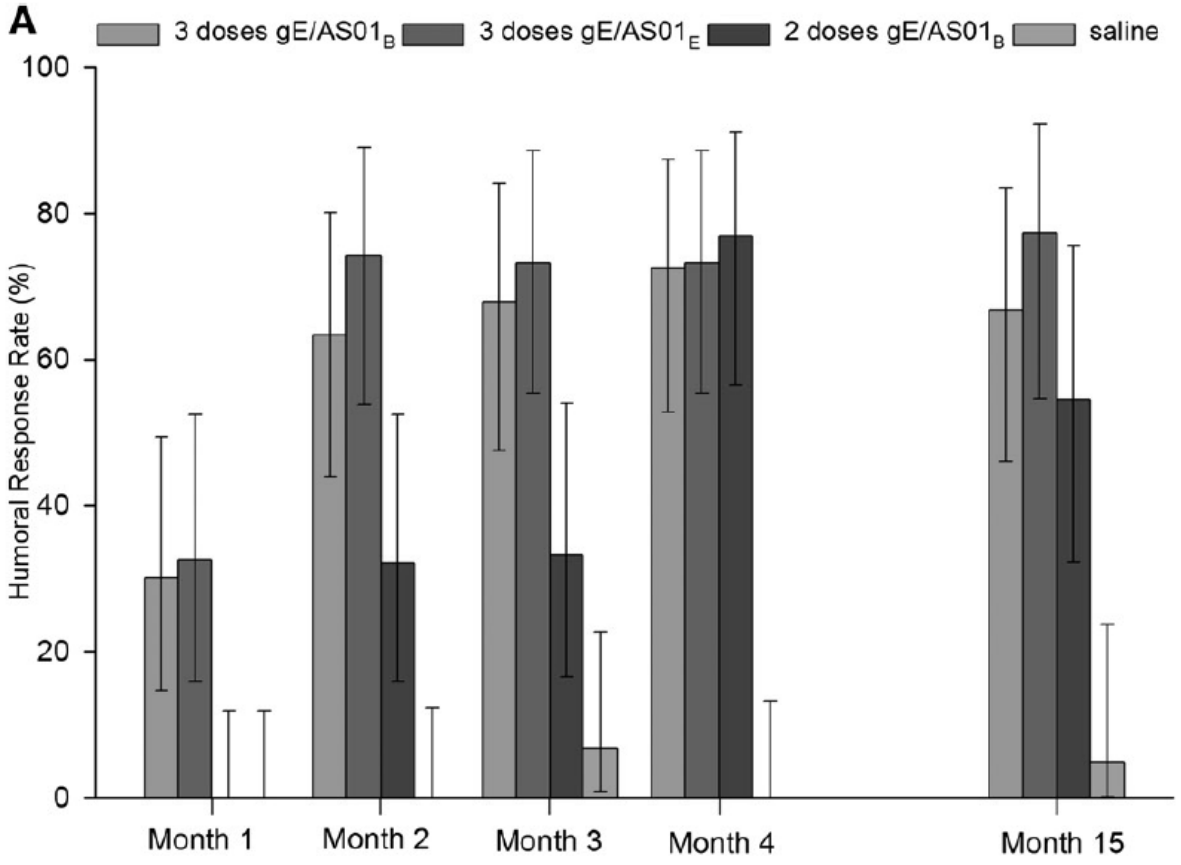


@4yrs 87.5% Risk reduction

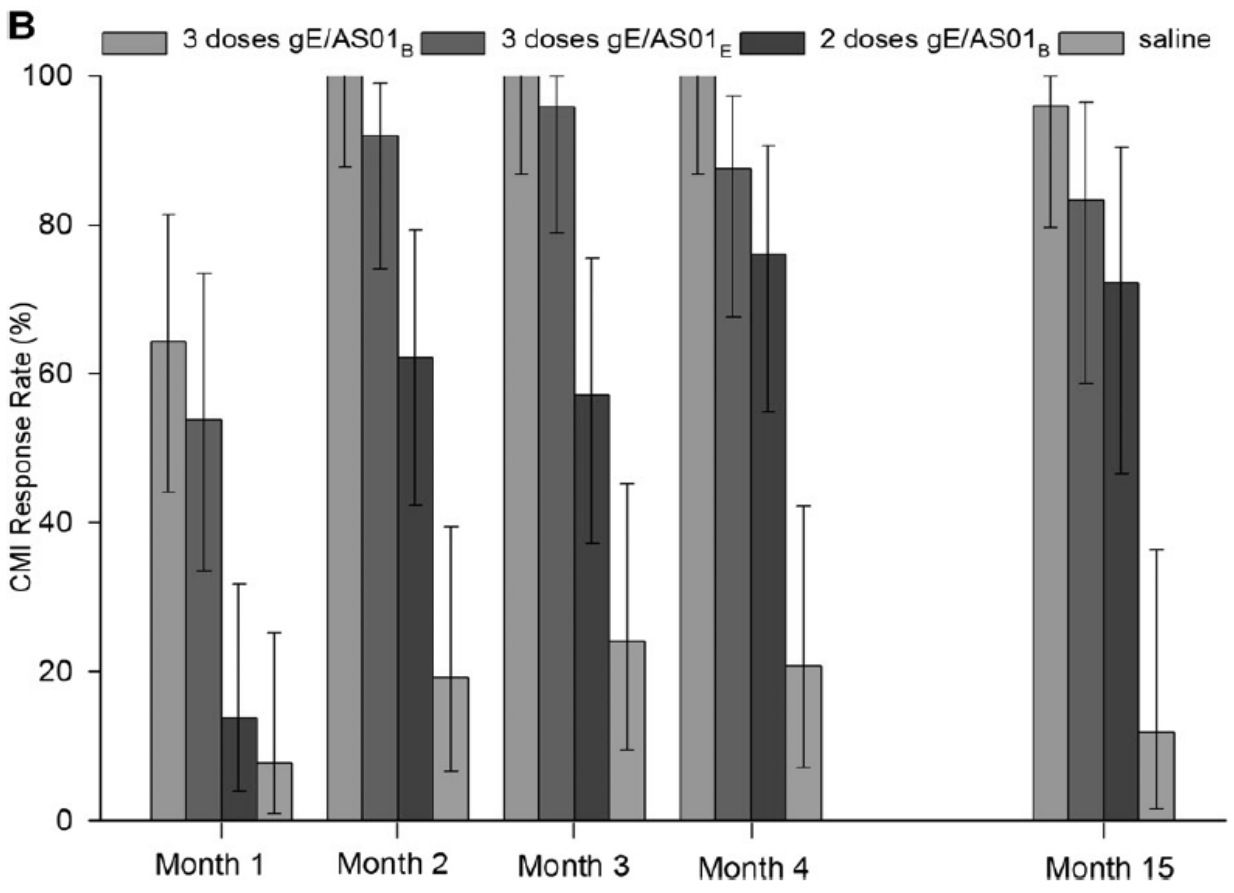
Efficacy similar in all age groups

Cunnigham AL et al., NEJM 2016

Varicella-zoster virus glycoprotein E (gE) adjuvanted either with AS01g or AS01E after ASCT in patients with MM, NHL, and Hodgkin‘s disease



Humoral immune response



Cellular immune response

Stadtmauer E et al., Blood 2014

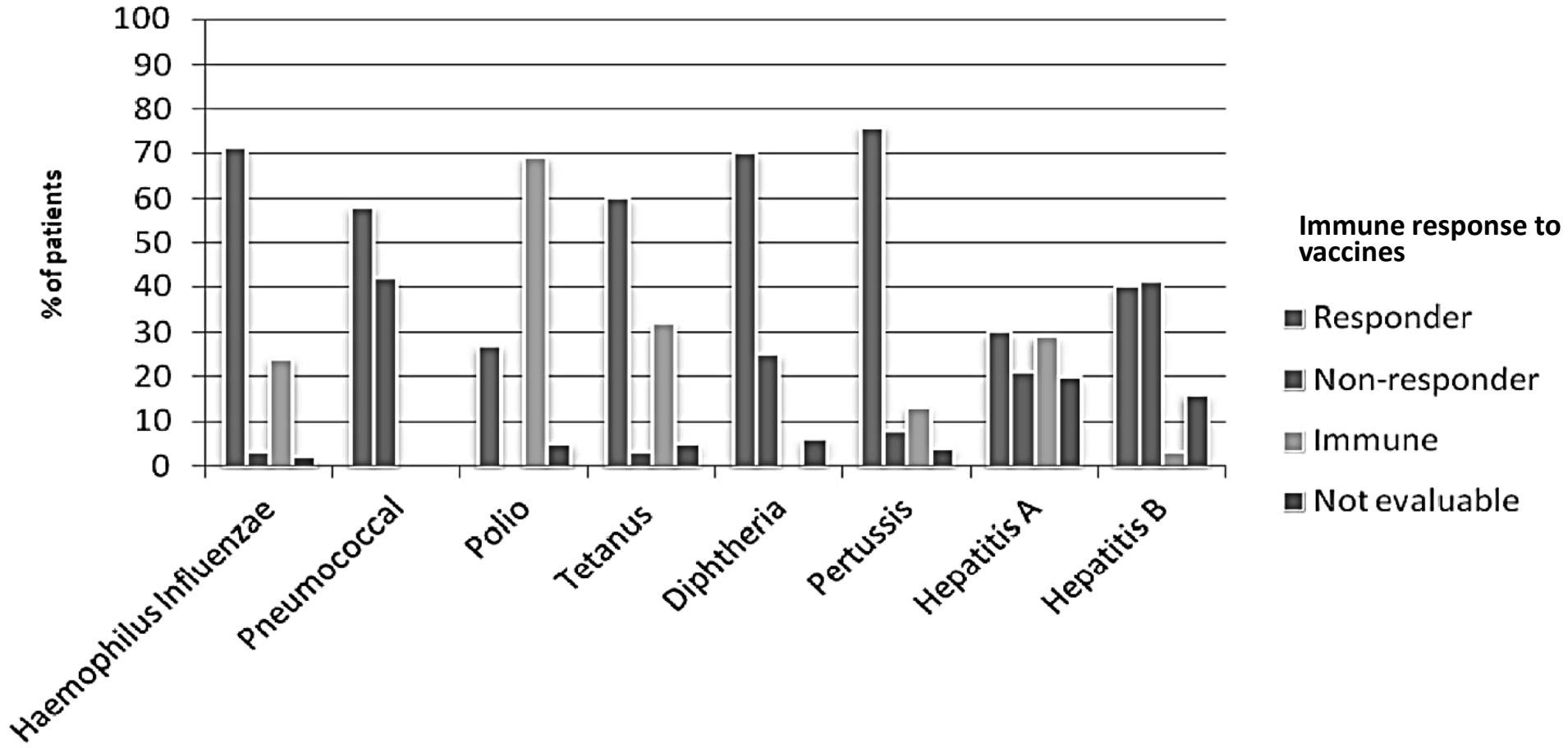
Vaccination recommendations after autologous or allogeneic stem cell transplantation (NCCN)

Inactivated Vaccines[1]	Recommended Timing after HCT	Number of Doses
DTaP (Diphtheria/Tetanus/Acellular Pertussis)	6-12 months	3
Pneumococcal vaccination		
• Conjugated 13-valent vaccine	6-12 months	3
• Upon completion of PCV13 series, then PPSV23	≥12 months	1
Hepatitis A[1] (Hep A)	6-12 months	2
Hepatitis B[1] (Hep B)	6-12 months	3
Meningococcal conjugate vaccine[2]	6-12 months	1-2
Influenza (injectable)[3]	4-6 months	1[3], annually
Inactivated Polio vaccine	6-12 months	3
Recombinant zoster vaccine	>2 months after autologous HCT, consider after allogeneic HCT[4]	2
Live Vaccines	**Recommended Timing after HCT**	**Number of Doses**
Measles/Mumps/Rubella (MMR)[5]	≥24 months (if no GvHD or ongoing immunosuppression and if patient is seronegative for measles, mumps, and/or rubella)	1-2
Varicella vaccine[5]	≥24 months (if no GVHD or ongoing immunosuppression and patient is seronegative for varicella)	1
Zoster vaccine[5,6] (category 3)	May be considered at ≥24 months (if no GVHD or ongoing immunosuppression)	1

1 Strongly consider if clinically indicated. May consider Hepatitis A and B combined vaccine if immunization for both is needed.
2 Meningococcal B vaccine should be considered for high-risk patients such as patients with asplenia or complement deficiency or patients receiving eculizumab.
3 As antibody response may be suboptimal, EMN recommends a second administration, or confirmation of antibody response by adequate testing
4 Efficacy in allogeneic HCT, in the presence of GVHD, or ongoing immunosuppression has not been established (Bastidas A et al. JAMA 2019;322:123-133)
5 MMR and varicella/zoster vaccines may be given together or 4 weeks apart
6 Because of insufficient data on safety and efficacy of live zoster vaccine among HCT recipients, physicians should assess the immune status of each recipient

Modified according to NCCN Guidelines V 1/2020

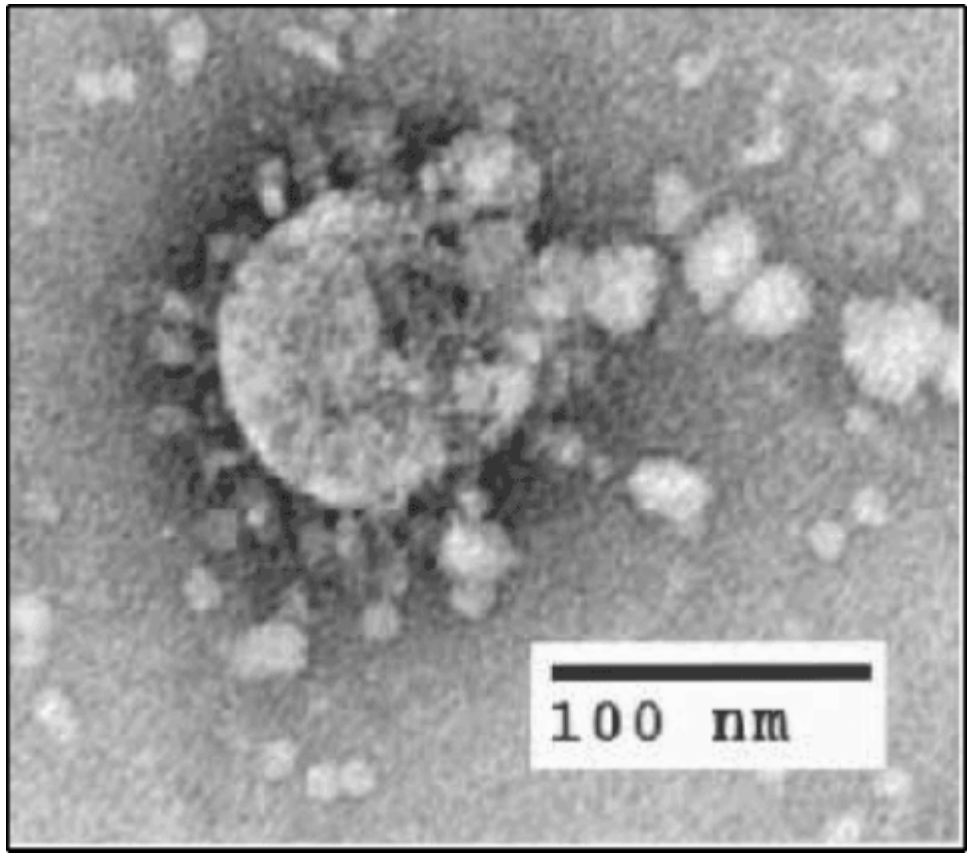
Re-vaccination following ASCT

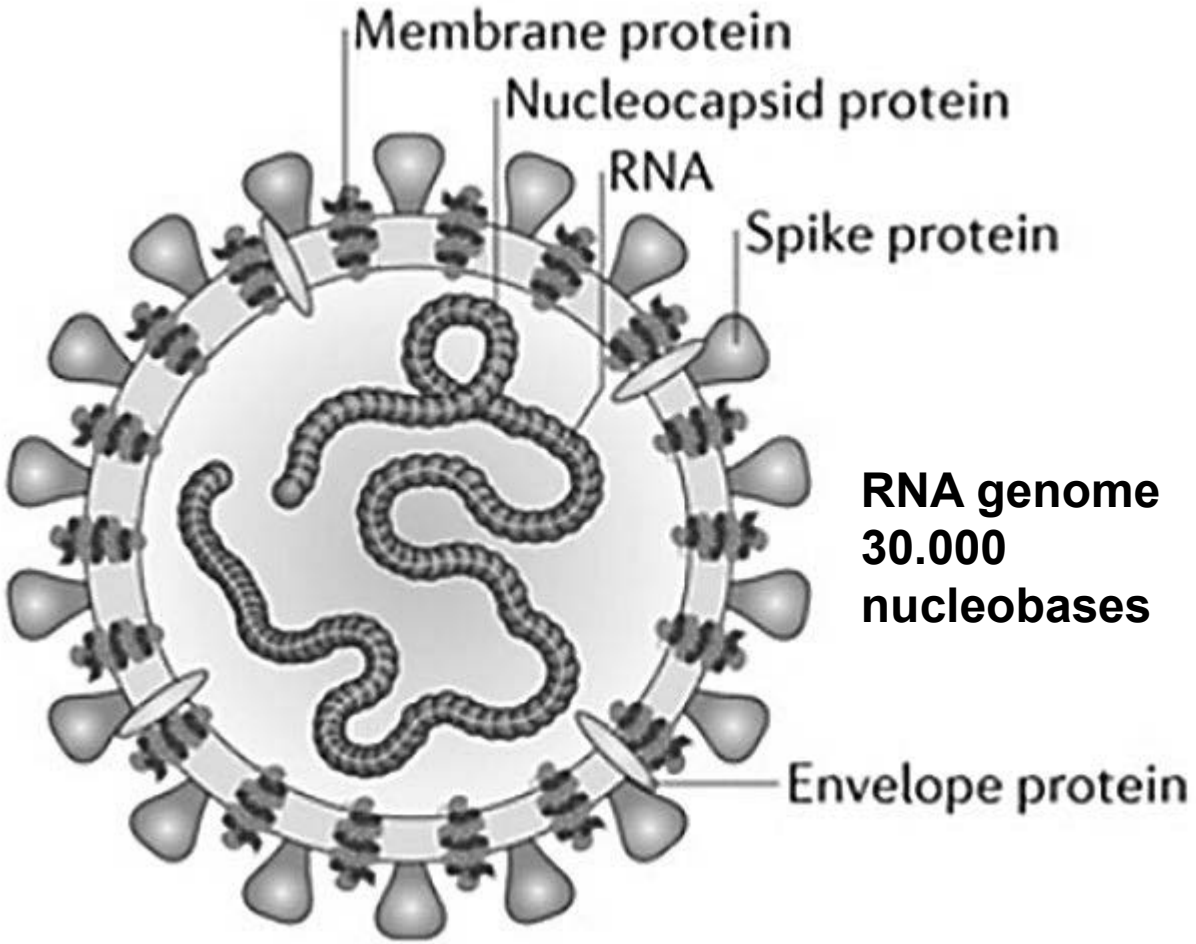


MMR and varicella was used in few patients only
No difference in response rates between patients on and off lenalidomide maintenance therapy

Palazzo M et al., Biol Bone Marrow Transpl 2019

COVID 19 (SARS-CoV-2 Virus)





RNA genome 30.000 nucleobases

- **Single strand RNA virus, genetic similarity to bat coronavirus**
- **Thought to be the successor** to SARS-CoV-1, the virus that caused the 2002–2004 SARS outbreak

Risk factors for mortality in selected studies on outcome of mainly hospitalized COVID-19 infected patients with multiple myeloma

	# of patients	Age Median	Time from diagnosis	Mortality rate	Risk Factors for Mortality					
					Age	ISS 3	HR cyto-genetics	Renal disease	Active Disease/PD	Co-morbidities
Chari A et al.	617	69y (34-92)		31.9%	1.04 (p=0.006)	1.05 (p=0.899)	2.35 (p=0.013)	2.71 (p=0.014)	1.91 (p=0.063)	0.88 (p=0.711)
Martinez-Lopez et al.	167	71y (62-78)		33.5%	3.0 (p=0.006)			5.6 (p<0.001)	2.7 (p=0.017)	1.7 (p=0.18)*
Wang B et al.	58	67y	30 mos	24%	1.32 (p=0.744)		1.44 (p=0.747)	0.82 (p=1.000)		2 (p=0.055)
Hultcrantz M et al.	100	68y (41-91)		22%	1.8 (p=0.26)					2.2 (0.12)*
Cook G et al.	75	73y (47-88)	28 mos	NDMM: 54.8%, RRMM: 50%						
Engelhardt M et al.	21	59y (46-83)	20 mos	0%						

Risk factors for mortality: Age, HR cytogenetics, poorly controlled MM, renal disease, comorbidities

Platforms used for manufactoring of SARS-CoV-2 vaccines

WCRI Wilhelminen Cancer Research Institute

Component Vaccines

Whole Virus

RNA-based

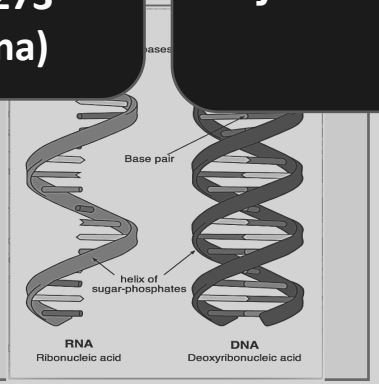
Genetic information for the

BNT162b2 (Biontech/Pfizer) mRNA1273 (Moderna)

DNA-based

Genetic information for the

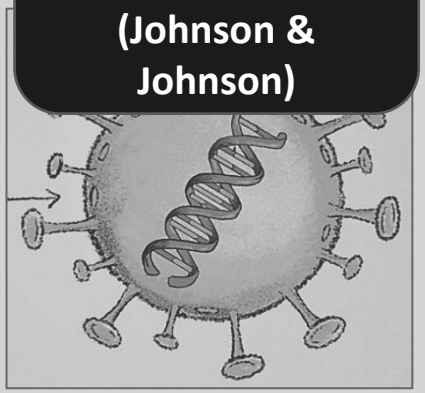
ZyVo-D Zydus Cadila



Viral vector

Another virus[1] carries the SARS-CoV-2

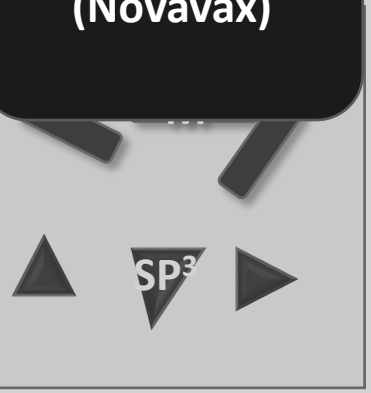
ChAdOx1 (Astra Zeneca) Ad26.COV2.S (Johnson & Johnson)



Protein subunit

A specific protein (Spike, RBD, others) of the

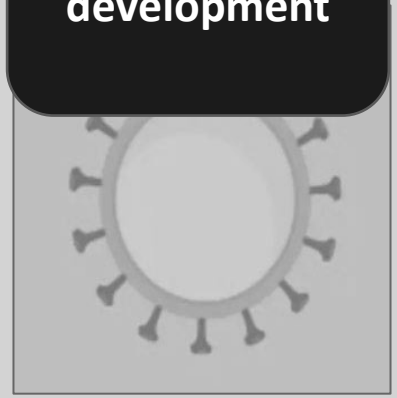
NVX-CoV2373 (Novavax)



Virus-like particles

Protein complex that mimics the SARS-CoV-2

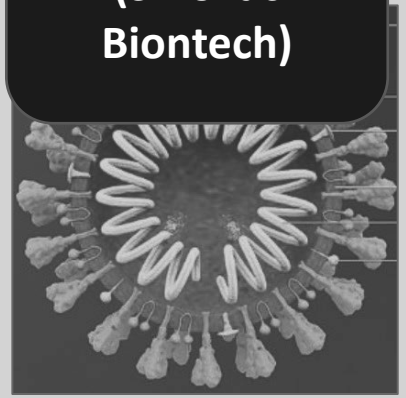
in development



Inactivated SARS-CoV-2

Killed SARS-CoV-2 that cannot

Coronavac (Sinovac Biontech)

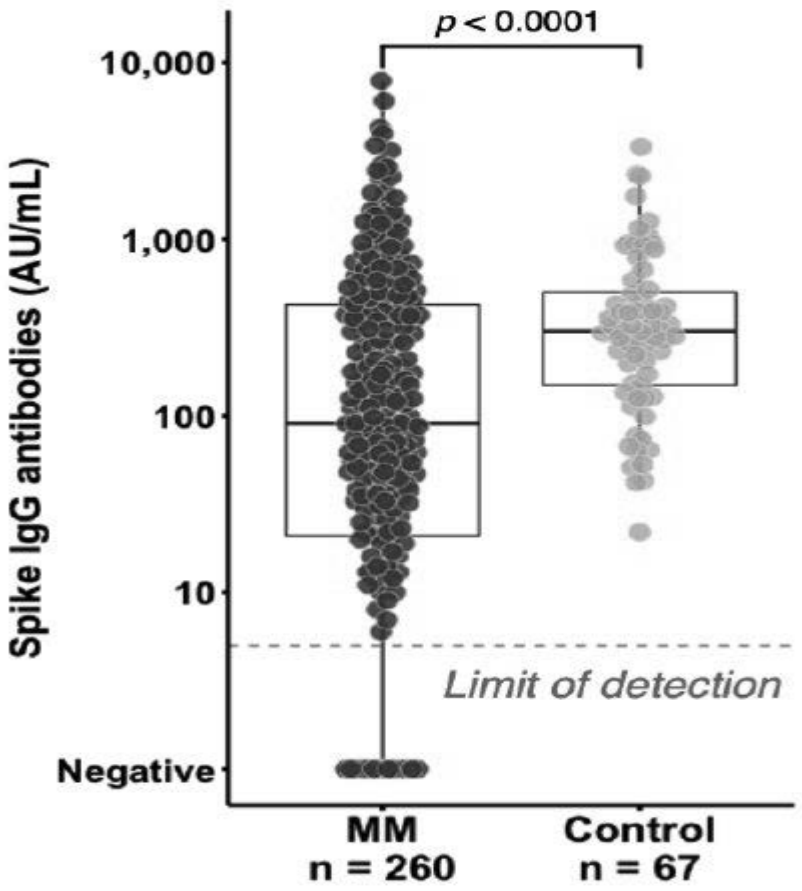


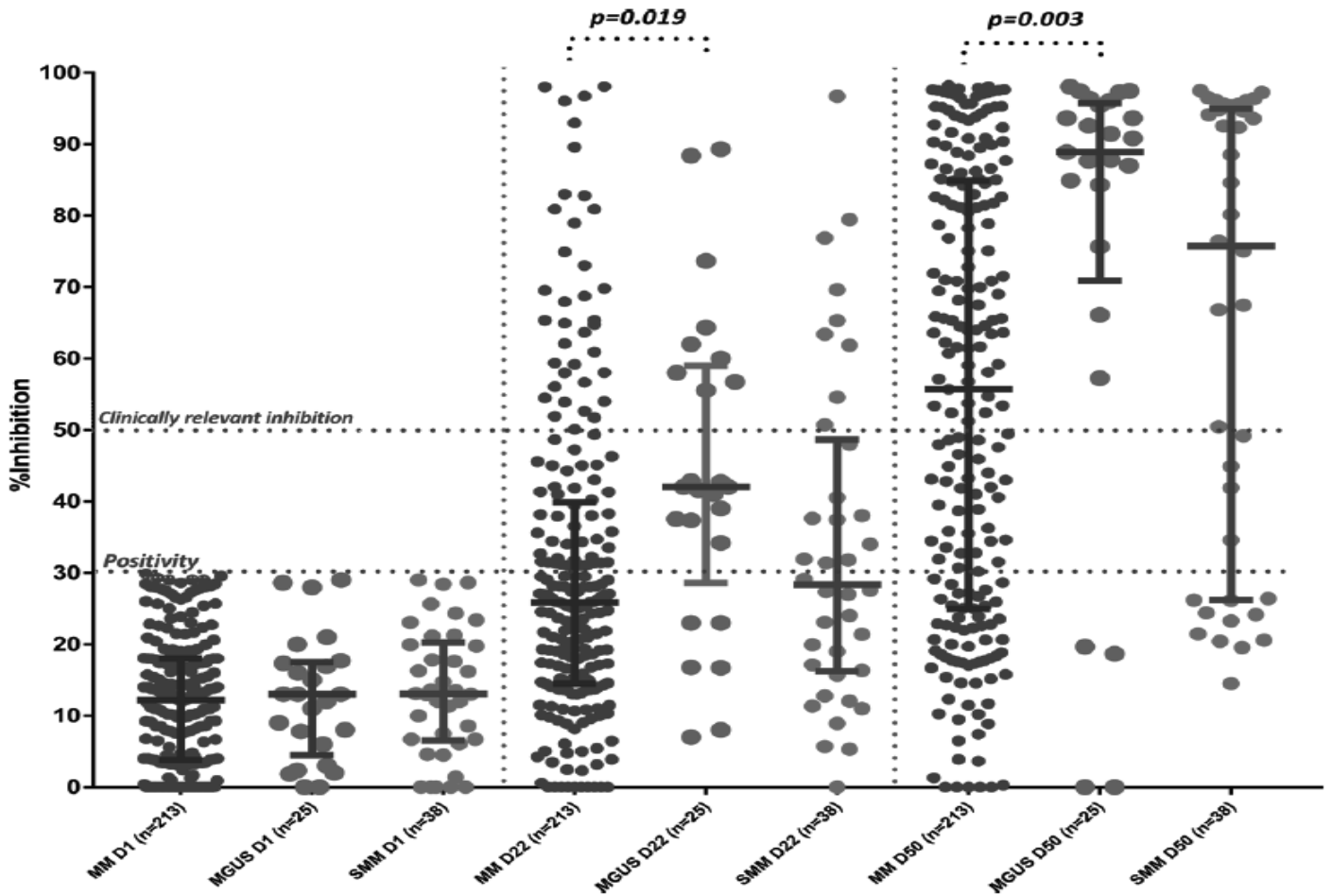
[1]Adenovirus, Newcastle disease virus, Lentivirus, Vesicular stomatitis virus, Measles virus, [2]Membrane proteins,[3] Spike proteins

Ludwig H et al., Am J Hematol 2021

IgG antibody response to COVID-19 in MM and neutralizing antibody response in MGUS, SMM and MM

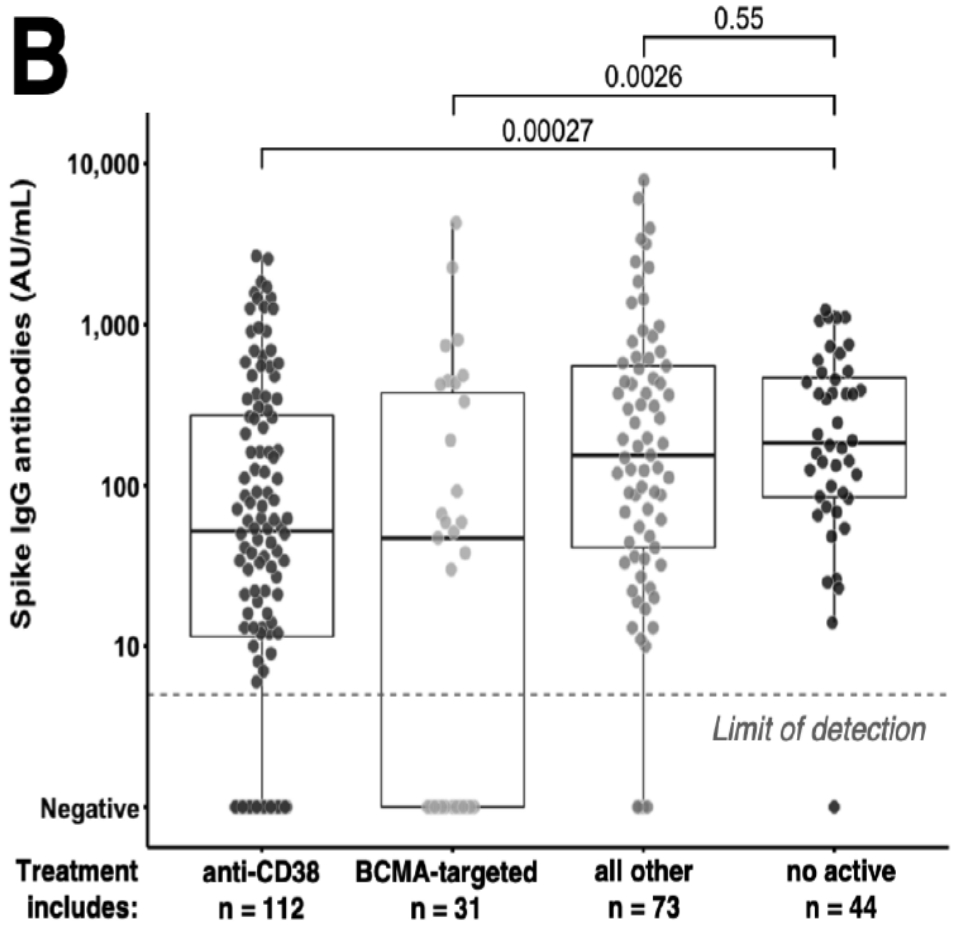
median 51 days after second dose





Van Oekelen O et al., Cancer Cell 2021, Terpos E et al., Blood Cancer Journal 2021

Antibody response and therapy and risk factors for poor response

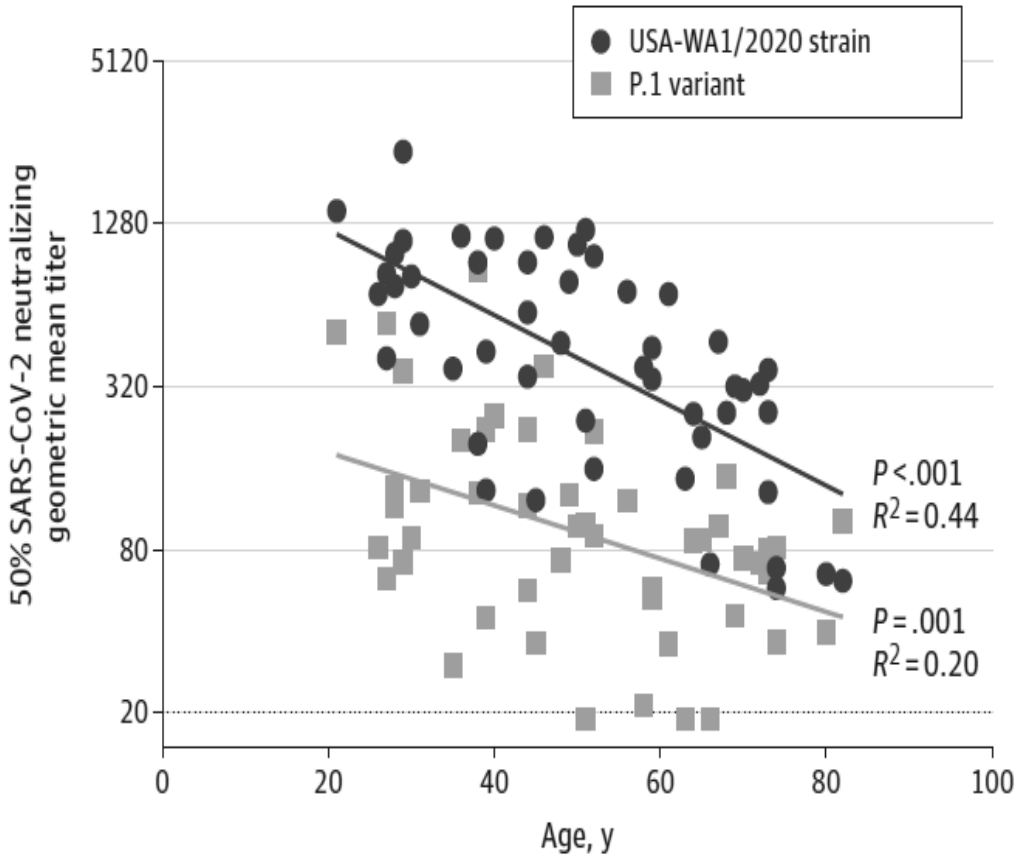


Clinical data	OR	P value
Univariate analysis		
> 3 previous lines of treatment	2,16	0,035
> 5 previous lines of treatment	2,93	0,009
Lymphopenia ≥ G3 (< 500/µL)	2,89	0,018
Anti-CD38 mAb	2,02	0,042
BCMA-targeted therapy	5,14	<0.001
BCMA-targeted bispecific	29,80	<0.001
No active treatment	0,10	0,005
Multivariate analysis		
Response status (s)CR (0/1)	0,389	0.037
Lymphopenia ≥ Grade 3 (0/1)	2,463	0.076
BCMA-targeted treatment (0/1)	10,269	<0.001
anti-CD38 monoclonal antibody (0/1)	4,258	0.005

Van Oekelen O et al., Cancer Cell 2021

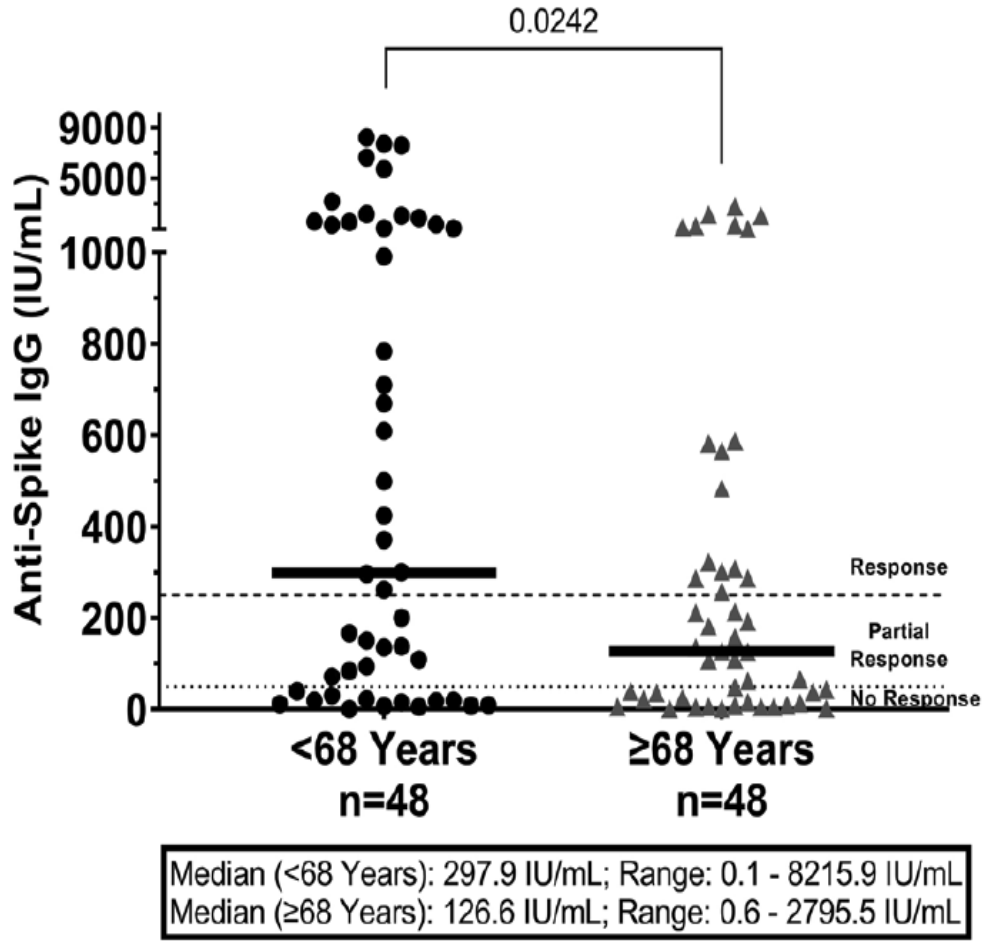
Neutralizing antibody titers correlate with age

Normal Population



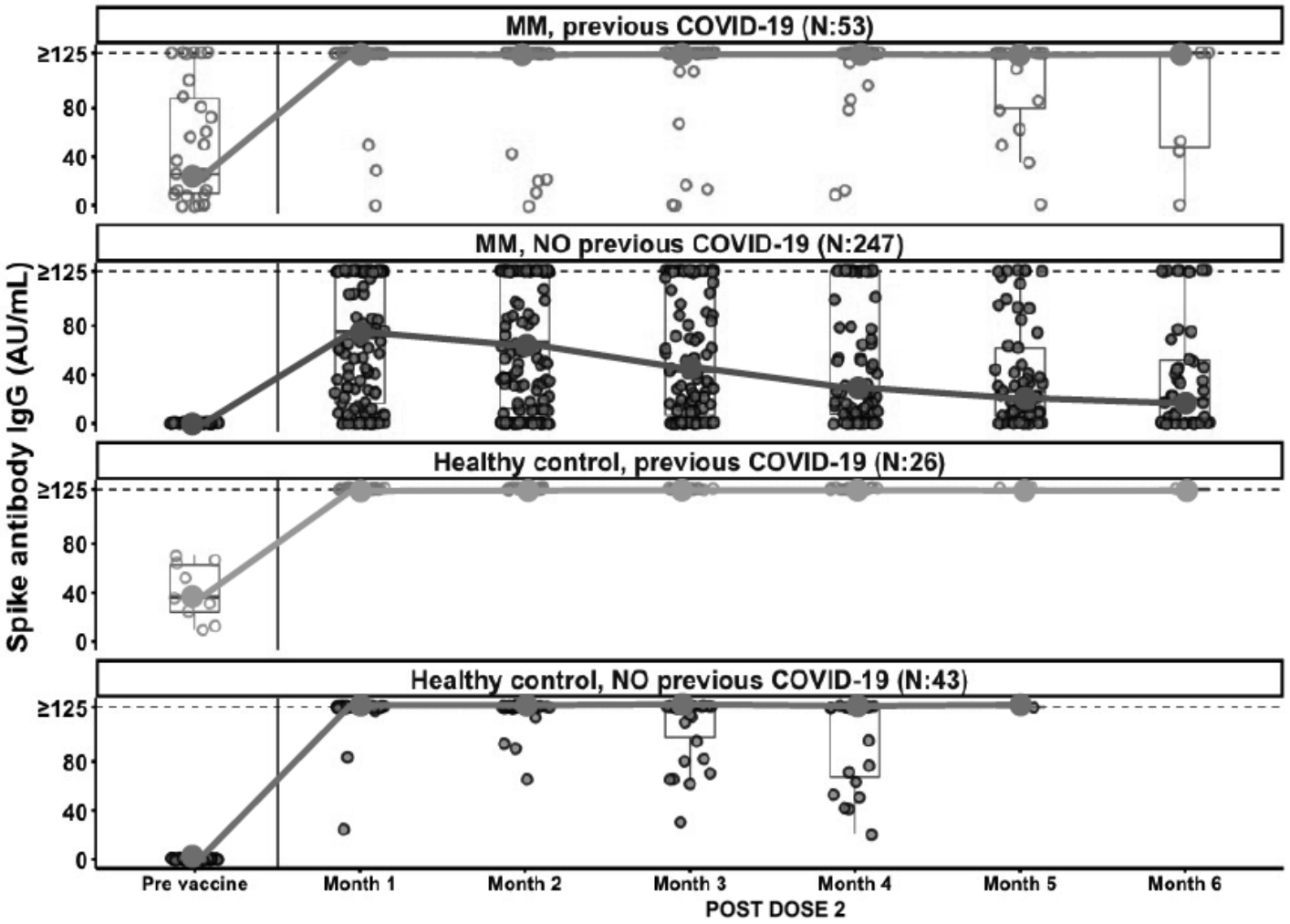
Bates T et al., JAMA 2021

Multiple Myeloma

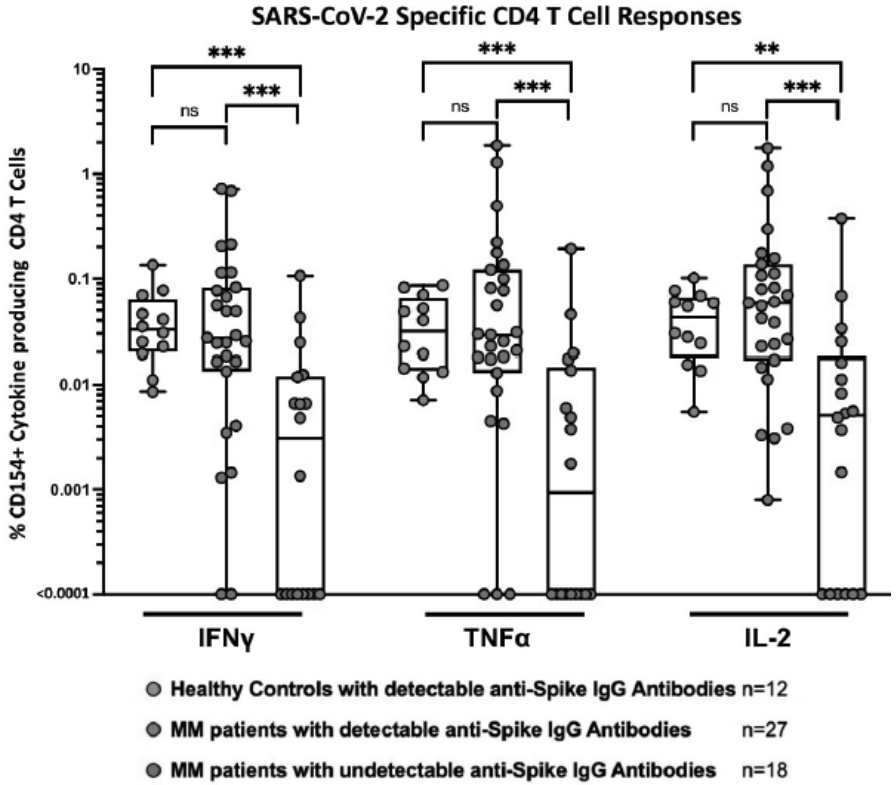


Stampfer SD et al., Leukemia 2021

Antibody response declines more rapidly in vaccinated patients

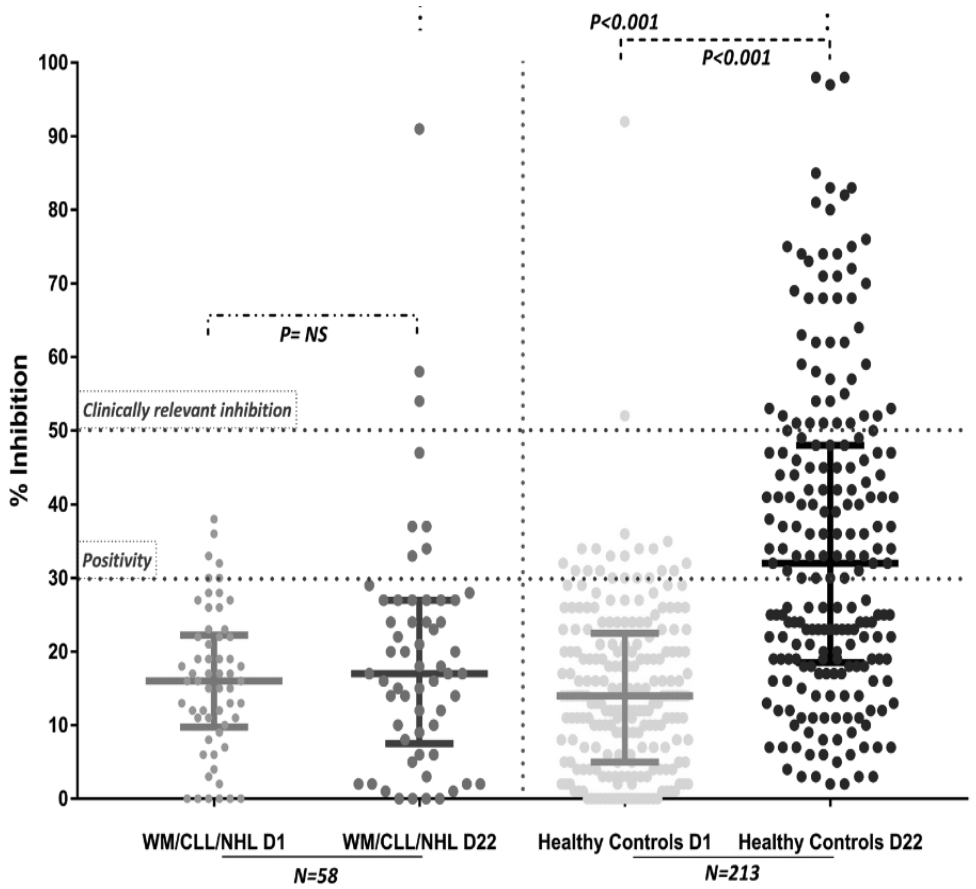


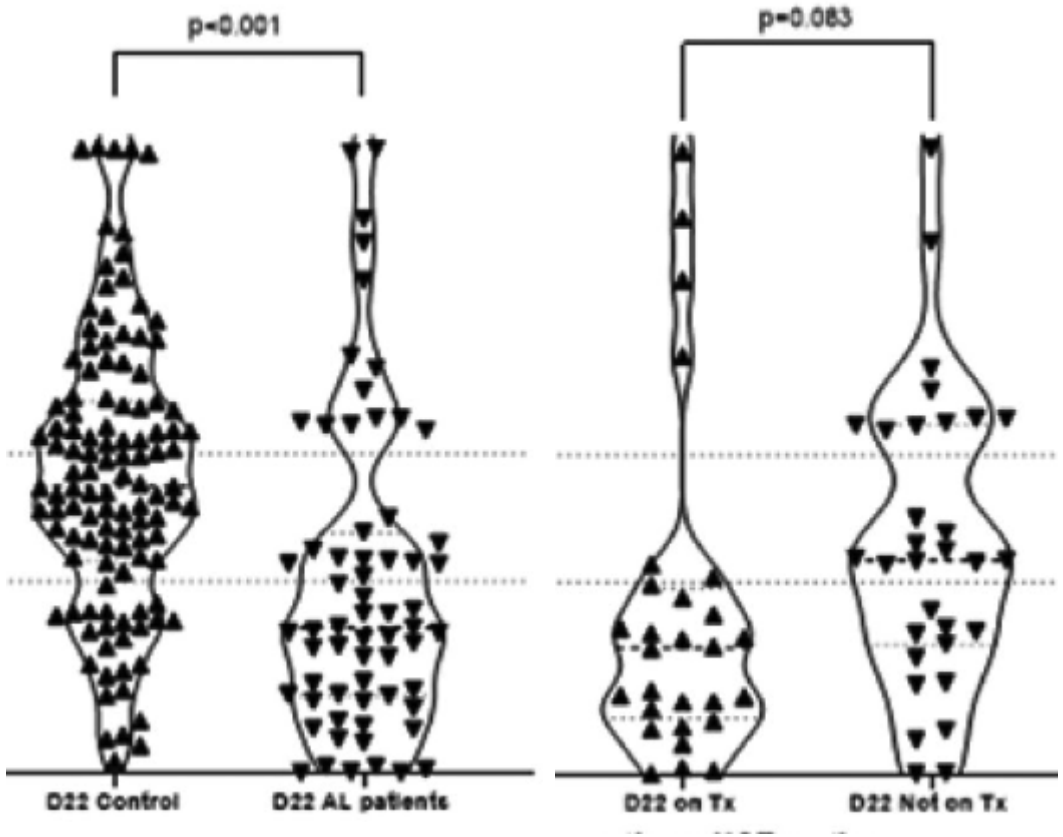
T cell responses are diminished in IgG non-responders



Courtsey van Oekelen (IMW2021)

Titers of neutralizing antibodies are low in MW, CLL, and Amyloidosis



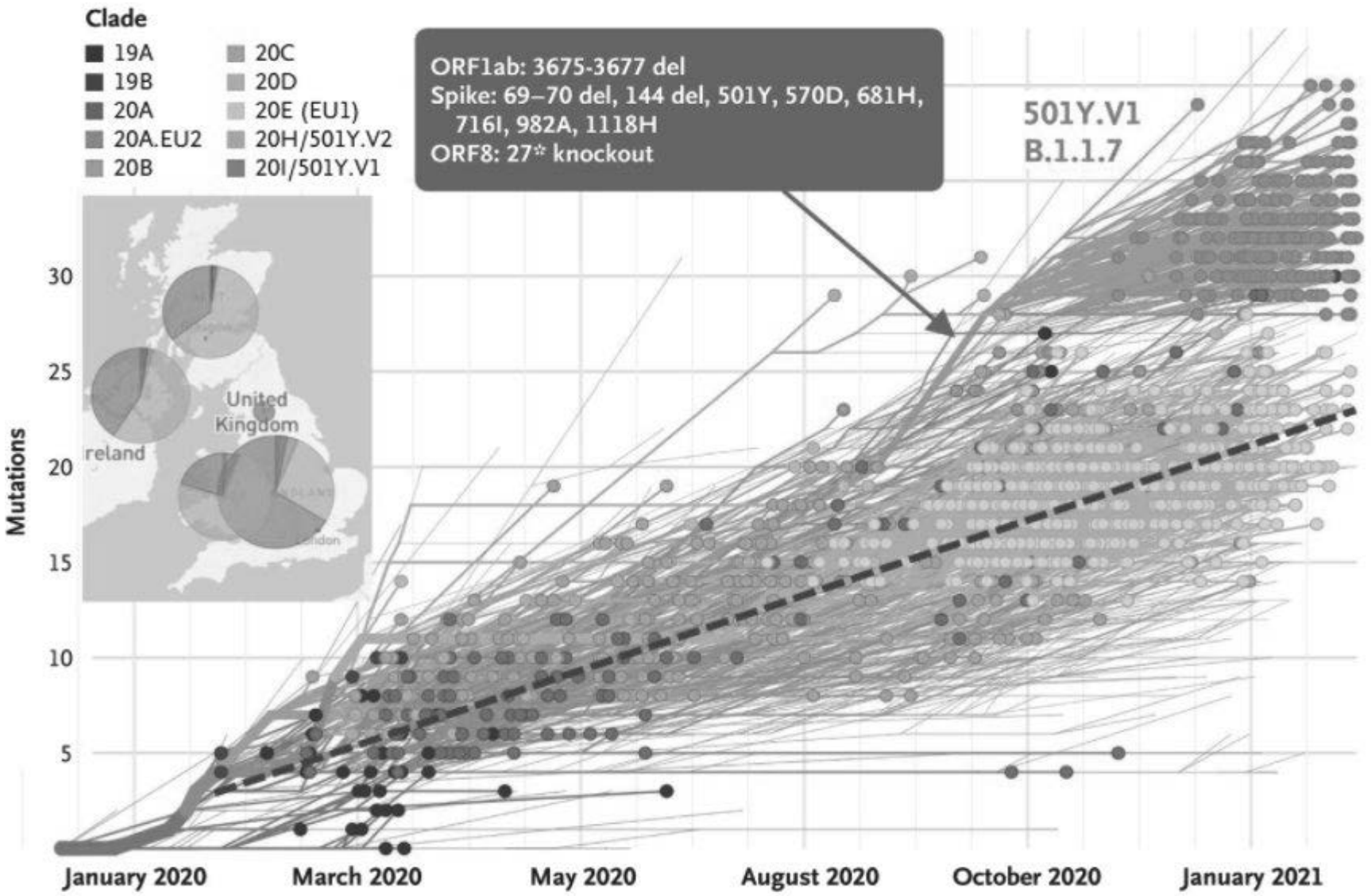


Gavriatopoulou M et al., Clin Exp Med 2021, Kastritis E et al., Hemasphere 2021

Occurrence of mutations of SARS-CoV- 2 over time in 1510 SARS-CoV-2 viruses

Mutations occur preferentially in a milieu of partial immune control

2 single letter mutations/month; half of as fast as influenza and 25% of the rate Of HIV



Correy L et a., NEJM 2021

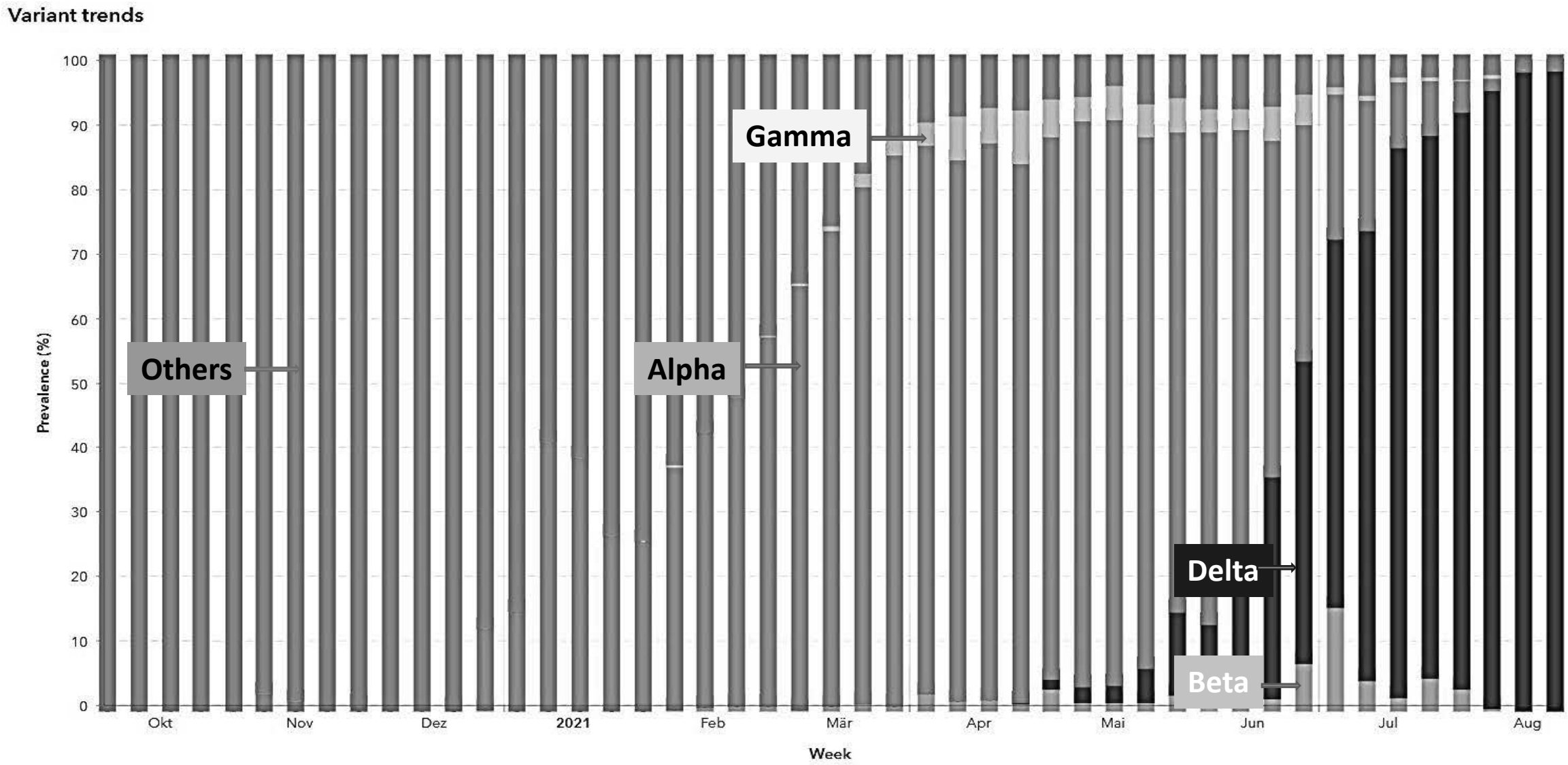
Variants of concern

WHO Label	Lineage + additional mutations	Country first detected (community)	Spike mutations of interest	Year and month first detected	Evidence for impact on transmissiblity	For impact on immunity	For impact on severity	Transmission in EU/EEA
Alpha	B.1.1.7	United Kingdom	N501Y, D614G, P681H	September 2020	Yes	No	Yes	Community
n/a	B.1.1.7+ E484K	United Kingdom	E484K, N501Y, D614G, P681H	December 2020	Yes	Yes	Yes	Outbreaks
Beta	B.1.351	South Africa	K417N, E484K, N501Y, D614G, A701V	September 2020	Yes	Yes	Yes	Community
Gamma	P.1	Brazil	K417T, E484K, N501Y, D614G, H655Y	December 2020	Yes	Yes	Yes	Community
Delta	B.1.617.2	India	L452R, T478K, D614G, P681R	December 2020	Yes	Yes	Yes	Dominant

Mutations in spike protein residues 319-541 (receptor binding domain) and 613-705 (the S1 part of the S1/S2 junction and a small stretch on the S2 side), and any additional unusual changes specific to the variant.

European Centre for Disease Prevention and Control, August 2021

Variant trends in Spain (October 2020 – August 2021)



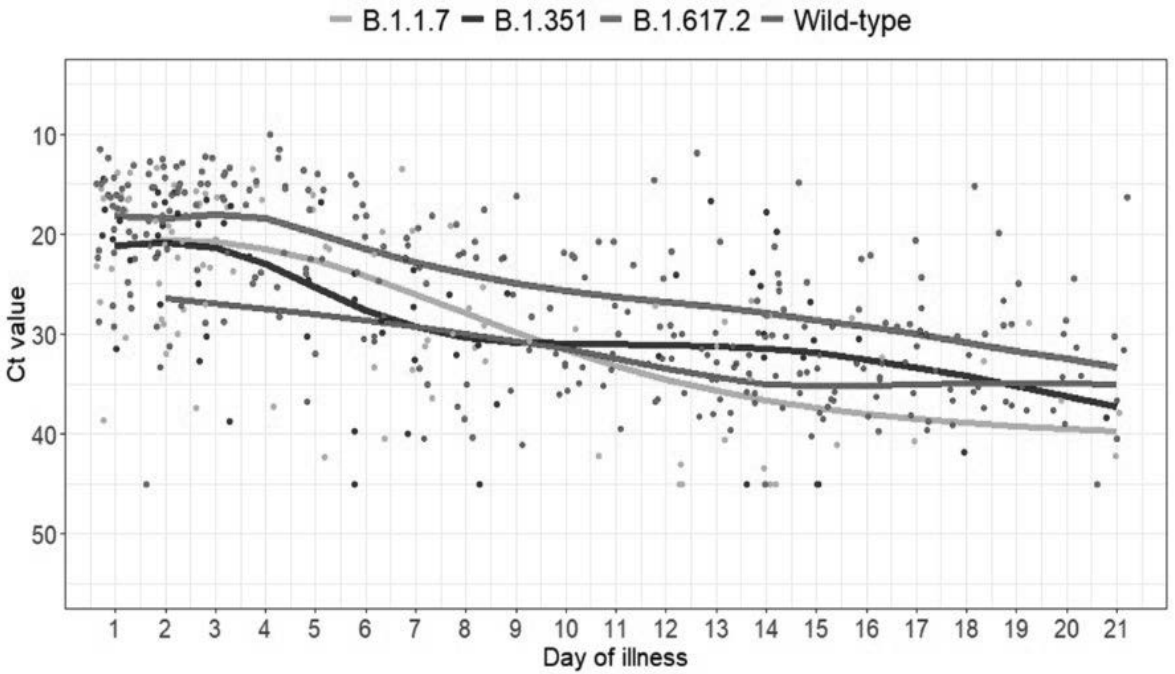
European Center of Disease Control and Prevention, assessed Sept 2021

Clinical and virologic features of variants of concern in Singapore
(January 1- May 22, 2021)

Predictors for composite outcome of oxygen requirement, ICU admission or death (Singapore, January 1 –May 22, 2021)

	Univariable model		Multivariable model^	
	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Variant				
Others	Ref	-	Ref	-
B.1.1.7 (Alpha)	1.10 (0.18 – 8.41)	0.920	1.88 (0.30 – 14.76)	0.500
B.1.351 (Beta)	0.78 (0.09 – 6.58)	0.807	1.69 (0.19 – 14.69)	0.610
B.1.617.2 (Delta)	5.55 (1.66 – 34.44)	0.020	4.90 (1.43 – 30.78)	0.033
Age group (years)				
<45	Ref	-	Ref	-
45-64	7.91 (3.64 – 18.52)	<0.001	6.62 (2.99 – 15.79)	<0.001
≥65	19.73 (8.13 – 49.99)	<0.001	13.84 (5.48 – 36.62)	<0.001
Female sex	1.91 (1.03 – 3.58)	0.041	1.42 (0.74 – 2.75)	0.291

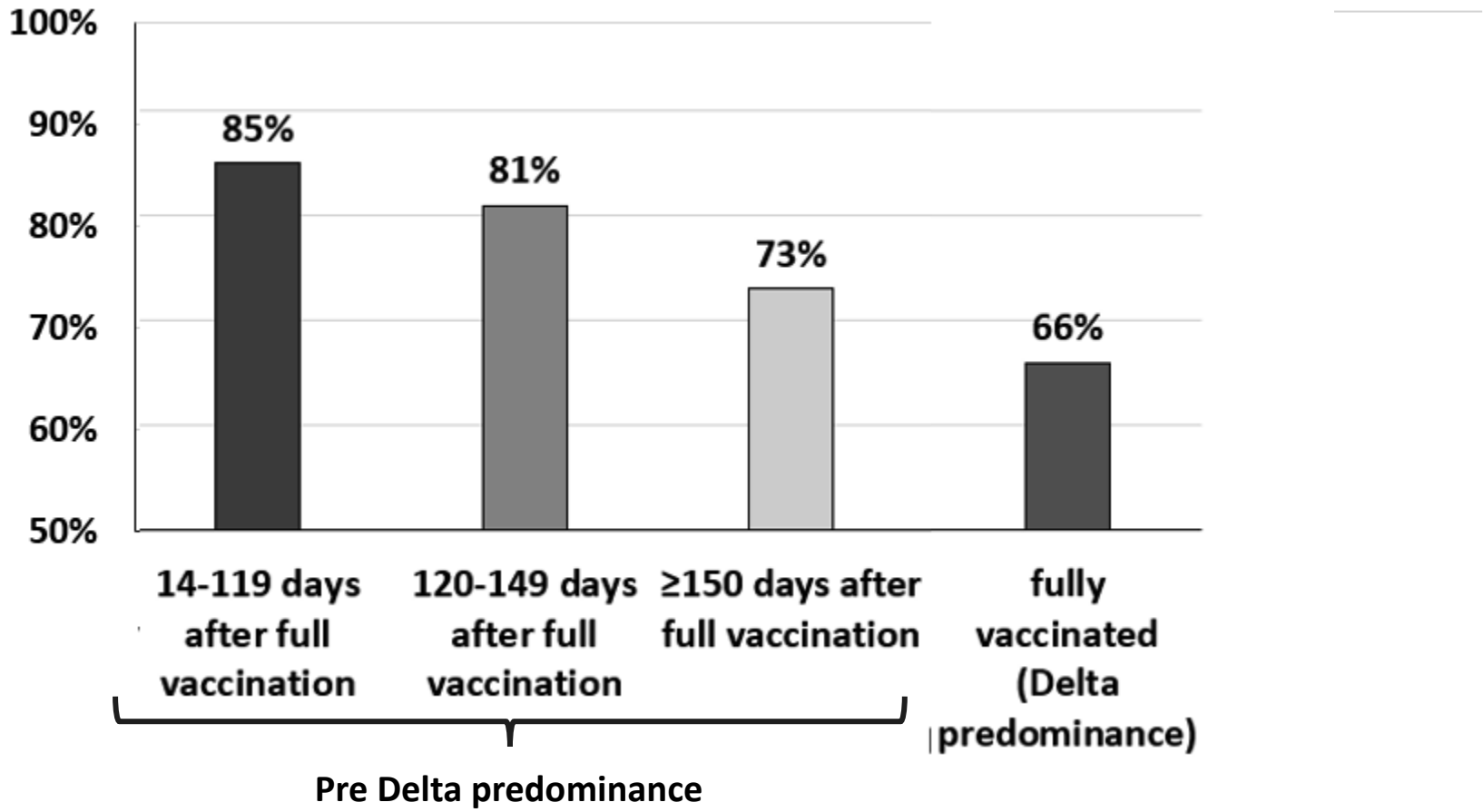
Ct values and days of illness with different variants (Singapore, January 1 –May 22, 2021)



Ong SWX et al., Journal of Infection, in press

Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection among frontline workers by (pre-) Delta variant dominance and time since full vaccination

8 US locations, December 2020-August 2021



Morbidity and Mortality Weekly Report, CDC 2021

What can be offered to those with insufficient antibody response

Heterologous prime boost vaccination

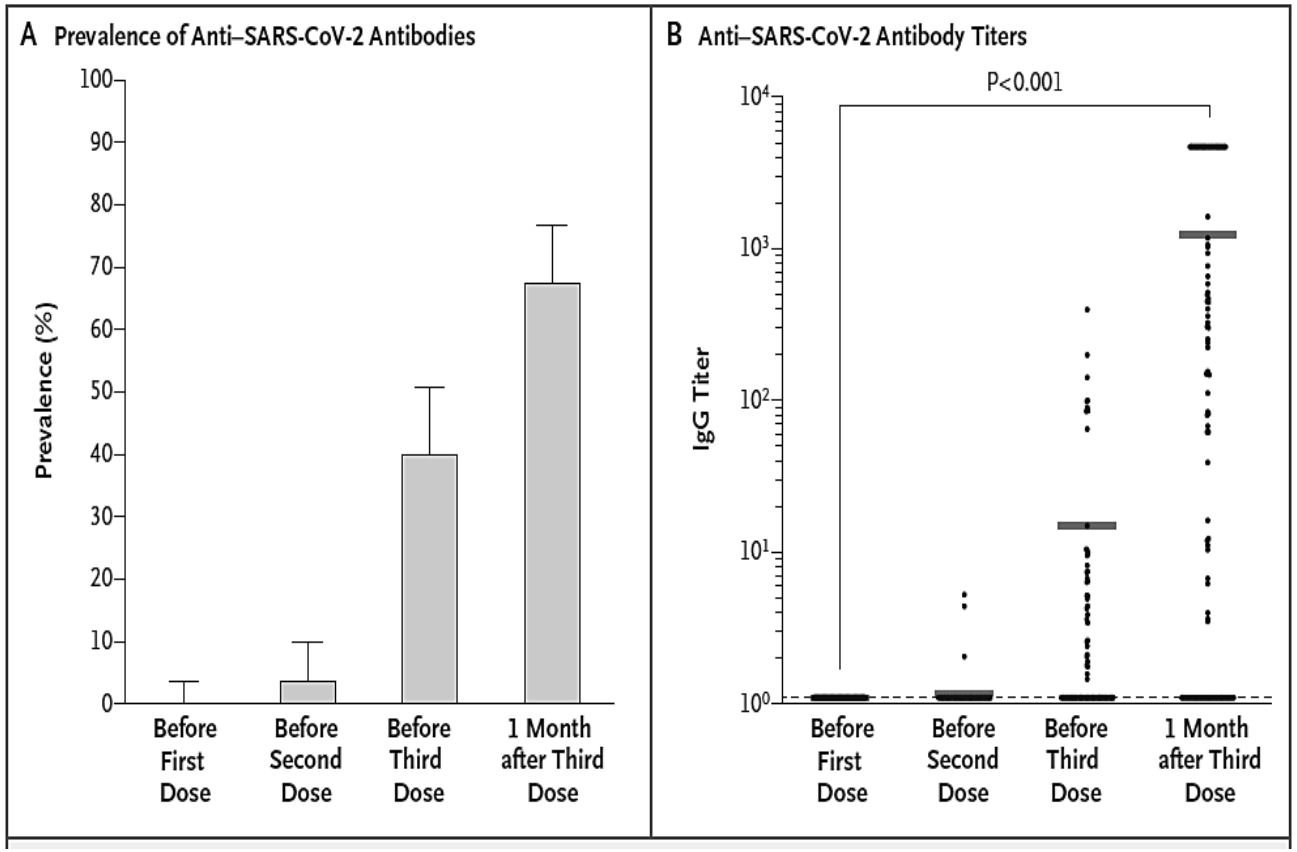
A third vaccine dose

Monoclonal antibody combination (REGEN-COV2®)

For those with insufficient immunity social distancing and mask wearing recommended until the end of the pandemic

Administer a third dose in patients with immunossupression*

Three doses of BNT162b2



NCCN

Recommends that all patients with hematologic malignancies receive a third dose, regardless whether they are receiving cancer therapy

101 solid-organ transplant recipients (mean [±SD] age, 58±2 years
Organ transplants: kidney 78, Liver 12, Lung or heart 8, pancreas 3 patients

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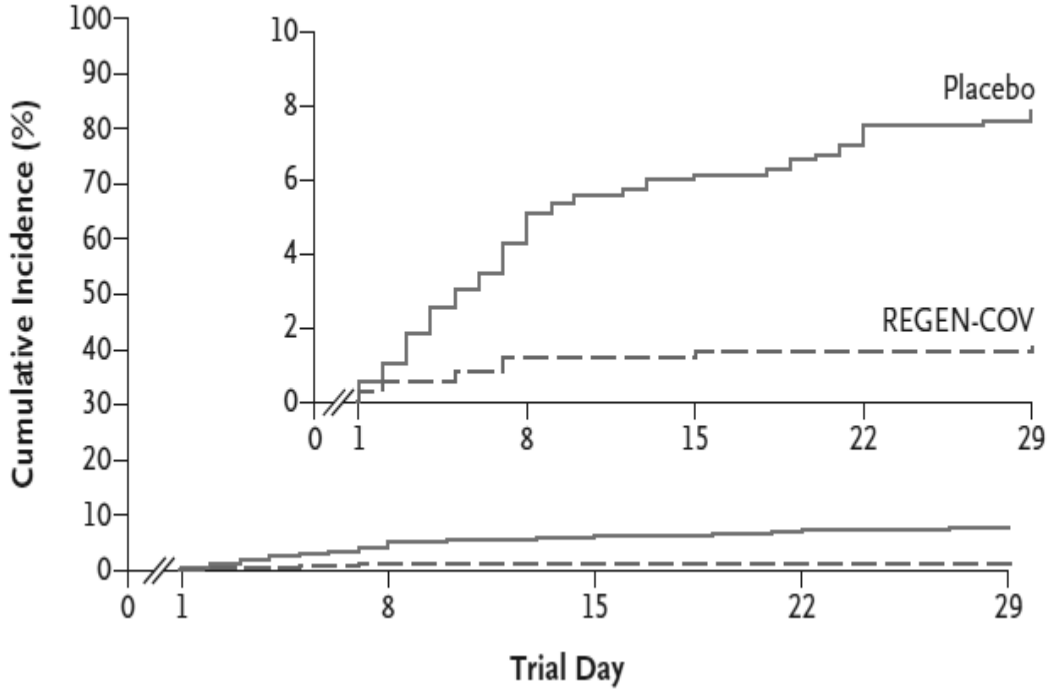
* FDA, News Release, August 12, 2021, Kramar N et al., NEJM 2021, NCCN Cancer and COVID-19 vaccination, 08/30/2021

Subcutaneous REGEN-COV2® antibody combination to prevent COVID-19

735 patients enrolled within 96 hrs after a household contact received diagnosis of SARS-CoV-2 infection

1200 mg single sc dose

A Incidence of Symptomatic Infection

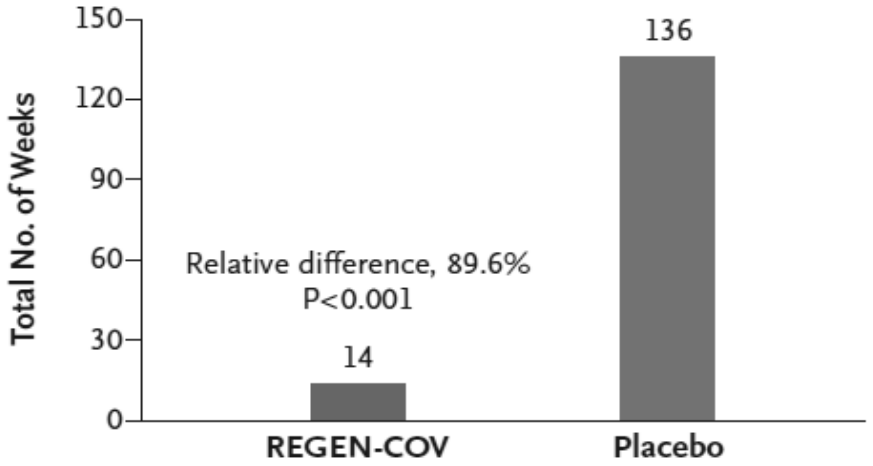


Participants with Symptomatic Infection	*no. (%)*
Placebo	59 (7.8)
REGEN-COV	11 (1.5)

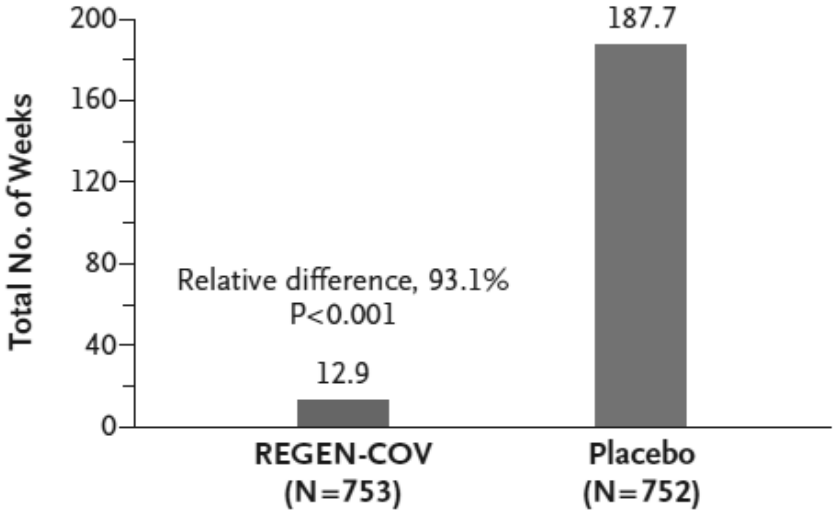
Relative risk reduction, 81.4%

Odds ratio, 0.17 (95% CI, 0.09–0.33)
P<0.001

F Duration of High Viral Load in Each Group



B Duration of Symptomatic Infection in Each Group



O'Brien NO et al., NEJM 2021

Summary

- **All patients with MGUS, SMM, MM, and monoclonal gammopathies of clinical significance should follow the recommendations for vaccination**

- **Patients should be vaccinated preferably**
  - **Before onset of active MM**
  - **During well controlled disease at times of MRD^{neg}, CR, or VGPR**
  - **Before start of therapy, before stem cell collection, >3 months after ASCT**
  - **During periods without therapy (exception: lenalidomide maintenance therapy)**

- **COVID-19: Consider risk factors for poor response**
  - **Uncontrolled disease**
  - **Immunoparesis, lymphopenia**
  - **Number of prior lines of therapy**
  - **Age, certain treatments such as CD38 antibodies, and BCMA targeted therapy including BiTEs and CAR-T cells**

Modified according to Ludwig et al., Lancet Haematology, in press

Summary

- **Routine evaluation of the immune response to vaccination is not supported by the CDC* and other organizations but enables identification of patients with poor anti-COVID response**

- **In case of insufficient anti-COVID-19 response**
  - **Consider a third vaccine dose**
  - **In patients who have been exposed to COVID-19 and in those unprotected and in need of immunosuppressive therapy use of monoclonal anti-spike antibodies may be considered**

- **Health care personnel caring for myeloma patients and household members should be vaccinated**

- **Patients without anti-COVID immunity will depend on 'herd immunity' and 'ring vaccination' of partners and close social contacts and will need to maintain protective measures**

- **Many questions remain unresolved**

Modified according to Ludwig et al., Lancet Haematology, in press

Have a safe journey home and keep the great science and our social gatherings in good memory