Infection Prevention Strategies for Waldenstrom's Macroglobulinemia

IWMF Webinar
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Agenda

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1. Overview of immunosuppression in Waldenstrom's macroglobulinemia (WM)
2. Review infections encountered in patients with WM
3. Review infection prophylaxis strategies in WM
4. Summarize recent research studies and evidence supporting a novel influenza vaccination strategy for WM
5. Highlight ongoing research efforts designed to study and improve immune responses to COVID-19 vaccination in WM

Immunosuppression in WM

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- Plasma cell dyscrasias including multiple myeloma (MM) and WM are associated with immunosuppression and diminished immune responses to infection or vaccination
  - B cell dysfunction / hypogammaglobulinemia (decreased normal antibodies)
  - T cells (inv of CD4:CD8 ratio, Tregs, abnormal Th1/Th2 $CD4^{+}$ratio, disruption of T cell diversity, & dysfunction of NK cells), functional abnormalities of dendritic cells
  - Age related immune senescence
  - Anti-cancer therapies such as cytotoxic chemotherapy, corticosteroids, monoclonal antibodies, alkylator / nucleoside analogue chemotherapy, and BTK inhibitors may further diminish immune responses

Abbreviations: BTK, Bruton's tyrosine kinase; NK, natural killer

Immunosuppression in WM

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- MGUS, MM, and WM are associated with depressed protective antibodies to several infections including the following: staphylococcal alpha-toxin, Moraxella, Pneumococci, tetanus, Varicella zoster, Candida, and Aspergillus
  - Antibody depression significantly worsens on disease progression in MM and WM
  - Having low total IgG antibodies increases the risk particularly for encapsulated bacteria such as Pneumococci and Haemophilus influenza

Abbreviations: IGG, immunoglobulin G; MGUS, monoclonal gammopathy of undetermined significance

Immunosuppression in WM

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- Therapy-related immunosuppression
  - Corticosteroids: (prednisone, dexamethasone) may suppress cell-mediated immunity and increase risk for zoster, CMV, PJP.
  - Proteosome inhibitors: (bortezomib, carfilzomib, ixazomib) may increase risk of zoster reactivation. Antiviral ppx is recommended.
  - Cytotoxic chemotherapy: (nucleoside analogs, e.g. fludarabine; purine analogs, e.g. cladribine; alkylators, e.g. bendamustine, cyclophosphamide) may be associated with neutropenia and disruption of mucosal barriers
  - BTK Inhibitors: (ibrutinib, zanubrutinib, acalabrutinib) are associated with neutrophil dysfunction and may increase risk of pneumonia
  - CD20 monoclonal antibodies (rituximab, obinutuzumab) may deplete normal B cells and worsen reduction in total IGGs

Abbreviations: CMV, cytomegalovirus; PJP, Pneumocystis jiroveci pneumonia; ppx, prophylaxis

Risk Stratification for Patients with WM

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FACTOR	LOW RISK	INTERMEDIATE RISK	HIGH RISK
Age (years)	<55	55-70	>70
Frailty	Absent	Absent	Present
ECOG Performance Status	0-1	2	≥ 2
Renal dysfunction	Absent	Moderate	Severe
Co-morbidity Index	Favorable	Intermediate	Unfavorable
Recent Infection	No	Yes	Yes, several/recurrent
Asplenia	No	Hyposplenism	Asplenia
DISEASE			
WM burden	Limited	Significant	Large
WM remission status	Remission	1st. Relapse	Relapsed/Refractory
TREATMENT			
Prior line(s) of therapy	One	Two-Three	More than three
Glucocorticosteroid dose	Low	Intermediate	High
Cytotoxic chemotherapy	<3 months	> 1 month earlier	< 1 month earlier
Neutropenia (ANC < 100 /µL)	None	Yes, < 7 days	Yes, >10 days
Autologous stem cell transplant	None	> 2 years earlier	<2 years earlier

Abbreviations: ANC, absolute neutrophil count; ECOG, Eastern Cooperative Oncology Group

Real World Data for Infections in WM

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- Infections more common in WM pts: Large population study in Sweden 2.6K pts compared to >10K controls (Lund, ASH 2014):
  - 3.2x risk for any infection
  - 6x risk for viral infections

    - Bacterial infections: septicemia, endocarditis, pneumonia, meningitis, cellulitis, osteomyelitis, and pyelonephritis
    - Viral infections: herpes zoster and influenza

Immunizations for Patients with WM

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VACCINE*	Individuals Who Should Receive the Vaccine	Dose – schedule and comments
Streptococcus pneumoniae: **Pneumococcal 13-valent conjugate (PCV13) (Prevnar)** **Pneumococcal 23-Valent polysaccharide (PPSV23) (Pneumovax)** **Pneumococcal conjugate vaccine (PCV 10)**	**All patients, particularly survivors of invasive pneumococcal disease (IPD) and patients with asplenia, which may be present with AL-amyloidosis.**	**Vaccination as early as possible, ideally before commencing anti-WM therapy.** PCV13 is more immunogenic than PPSV23, and the response to PPSV23 is reduced after immunosuppression. **If no prior vaccination, give one dose of PCV13 at diagnosis followed by one dose of PPSV23 ≥ eight weeks later.** If prior vaccination with ≥ one dose of PPSV23 (but not PCV 13) give one dose of PCV13 one year after the last PPSV23 treatment. **For severely immunocompromised patients, consider a dose of PPSV 23 every five years once they are ≥ 65 years.** In patients with recurrent pneumococcal infections and survivors of IPD: Consider antibiotic prophylaxis because the response to the pneumococcal vaccine may be suboptimal. PCV10 is used in some countries, including in Europe.
Influenza viruses: **High-dose inactivated (Fluzone High-Dose)**	**All patients (2 high-dose vaccines).** **Non-immune family, close contacts, and healthcare workers (HCWs) (standard vaccination).**	**Vaccinate annually before the onset of influenza activity in the community. Give two doses of the Fluzone High-Dose (separated by at least 30 days) to all patients, regardless of age.** During the Flu season, we give antiviral prophylaxis [oseltamivir (Tamiflu) or zanamivir (Relenza)] to patients at risk for severe complications (e.g., during ASCT). If close contacts and HCWs are vaccinated during an influenza outbreak, they should also receive around two weeks of chemoprophylaxis, based on toleration, and possibly strain susceptibility. However, if a nosocomial outbreak occurs with a strain that is not contained in the vaccine, close contacts, and HCWs, should be administered influenza chemoprophylaxis based on strain susceptibility until the end of the outbreak. Avoid the live attenuated influenza vaccine (nasal spray)
Recombinant Herpes Zoster (RZV) adjuvanted vaccine (Shingrix)	**Recipients of autologous stem cell transplant (ASCT). Consider for all patients.**	**Give two doses of RZV**: the first between 50 and 70 days after ASCT (if prior ASCT) and the second 1 to 2 months later.

***Avoid live vaccines; Inactivated vaccines only**

Risk-adapted Antimicrobial Prophylaxis in Patients with WM

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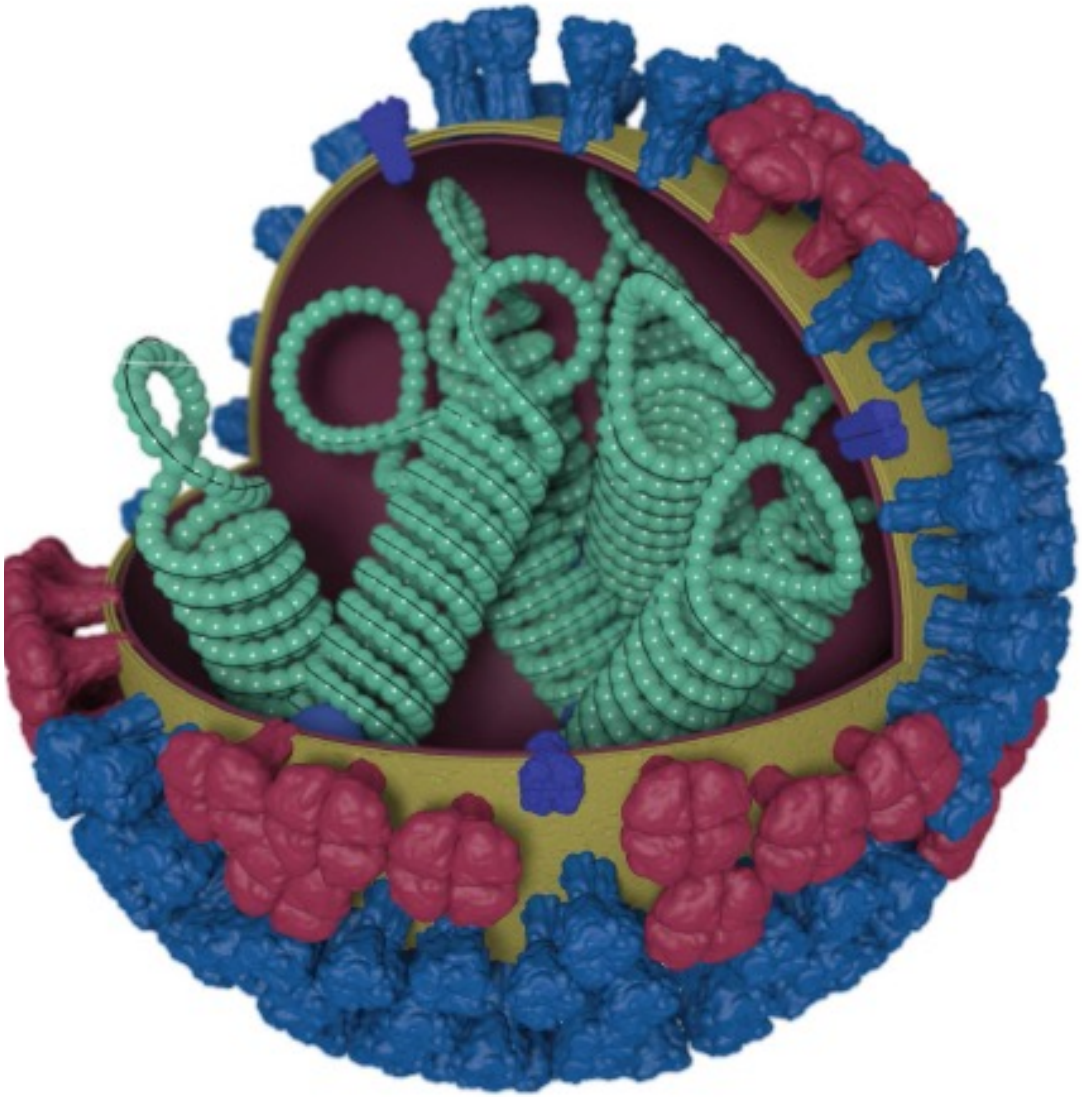
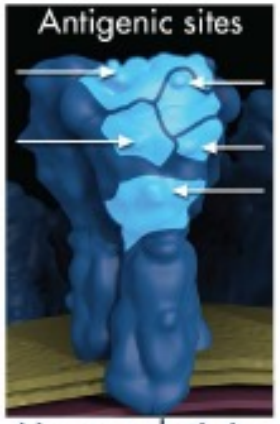
Risk for Infection	Antimicrobial Prophylaxis	
	Viral	**Fungal**
Low	None, unless prior HSV episode	None
Intermediate	**Acyclovir or valacyclovir for herpes simplex virus (HSV) and herpes zoster virus (VZV) seropositive patients.** **Acyclovir:** **For HSV: 400 or 800 mg orally twice daily** **For VZV: 800 mg orally twice daily Valacyclovir: 500 mg orally twice daily**	**Consider fluconazole or micafungin in the setting of prolonged neutropenia** (absolute neutrophil count (ANC) ≤ 100/μL for ≥ seven days) and severe mucositis
High	HSV and VZV seropositive patients: **Same as above.** Hepatitis B virus (HBV) seropositive patients: the risk for reactivation depends on HBV serostatus and type and duration of immunosuppressive therapies. **Consider prophylaxis for patients at intermediate to high-risk for HBV reactivation and early pre-emptive treatment for those at low risk.** Use tenofovir or entecavir rather than lamivudine and select tenofovir in patients with prior exposure to lamivudine. Maintain antiviral therapy for several months and monitor HBV viral load. Consider stopping antiviral agents upon normalization of the HBV viral load and stopping immunosuppressive agents.	**Same as above.** For patients with ANC ≤ 100/μL for > 7 days, consider voriconazole or Posaconazole prophylaxis. **Consider pneumocystis jirovecii pneumonia (PJP) prophylaxis with TMP-SMX or alternative agent(s) as clinically indicated.**

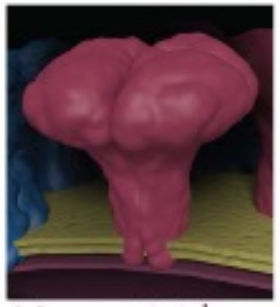
AN INFLUENZA VIRUS



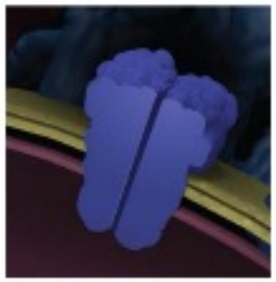
The above image shows the different features of an influenza virus, including the surface proteins hemagglutinin (HA) and neuraminidase (NA). Following influenza infection or receipt of the influenza vaccine, the body's immune system develops antibodies that recognize and bind to "antigenic sites", which are regions found on an influenza virus' surface proteins. By binding to these antigenic sites, antibodies neutralize flu viruses, which prevents them from causing further infection.



Hemagglutinin



Neuraminidase



M2 ion channel

Ribonucleoprotein

- Encapsulated NS, SS RNA virus of Orthomyxoviridae
- Core nucleoprotiens used to distinguish 3 types: A, B, C
- HA binds resp epithelial cells ➔ cellular infection
- 9HA/16NA variants identify subtypes: (H1N1, H3N2)
- Seasonal vaccines consist circulating Flu A subtypes and Flu B strains

(CDC image bank)

Background

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Worldwide: influenza source of morbidity / mortality

- Influenza responsible for 3-5 million severe infections and 250-500K deaths (WHO 2014)

Older adults, esp. w/ comorbidities such as cancer most susceptible

- 90% of flu-related deaths in adults ≥65 yo
- Estimated flu mortality rate 9% all cancer patients (ACS 2005)

US: High-Dose Flu Vaccine Recommended for adults >65

- 4x the HA antigen content elicited substantially higher Ab titers (Couch et al, Vaccine 2007)

Despite standard flu vaccination, serologic response poor in plasma cell dyscrasia patients (5-20% seroprotection rates)

Background

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Study of High-dose Influenza Vaccine Efficacy by Repeated dosing IN Gammopathy patients: (SHIVERING) Trial

- Clinicaltrials.gov (NCT02267733)
- Combination of high-dose vaccine with booster dosing
- This strategy well tolerated, seroprotection rates achieved in 65% patients

(Branagan, et al. Clinal Lymphoma Myeloma Leukemia, 2017)

SHIVERING 2 Schema

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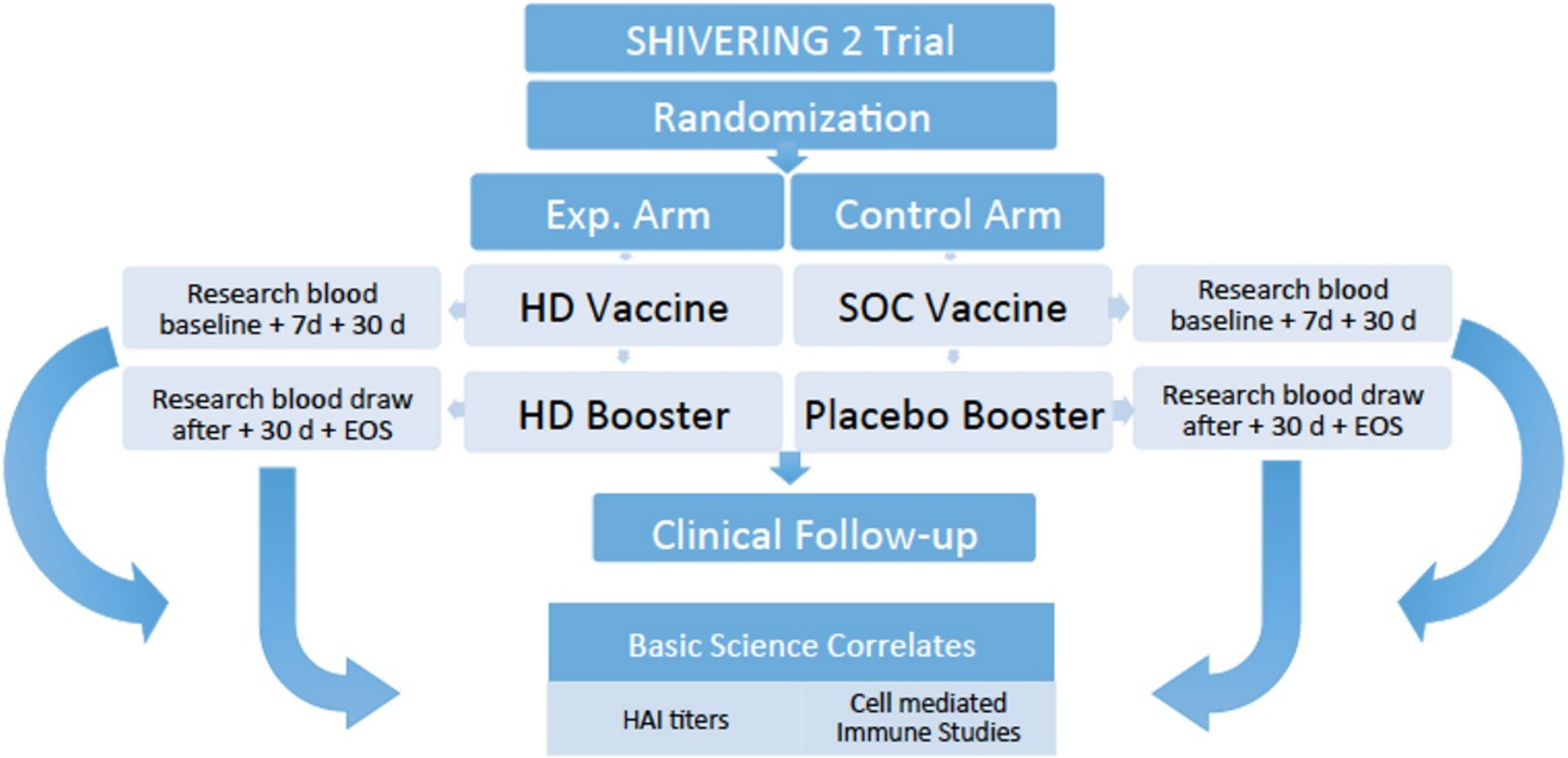

SHIVERING 2: Serologic Responses

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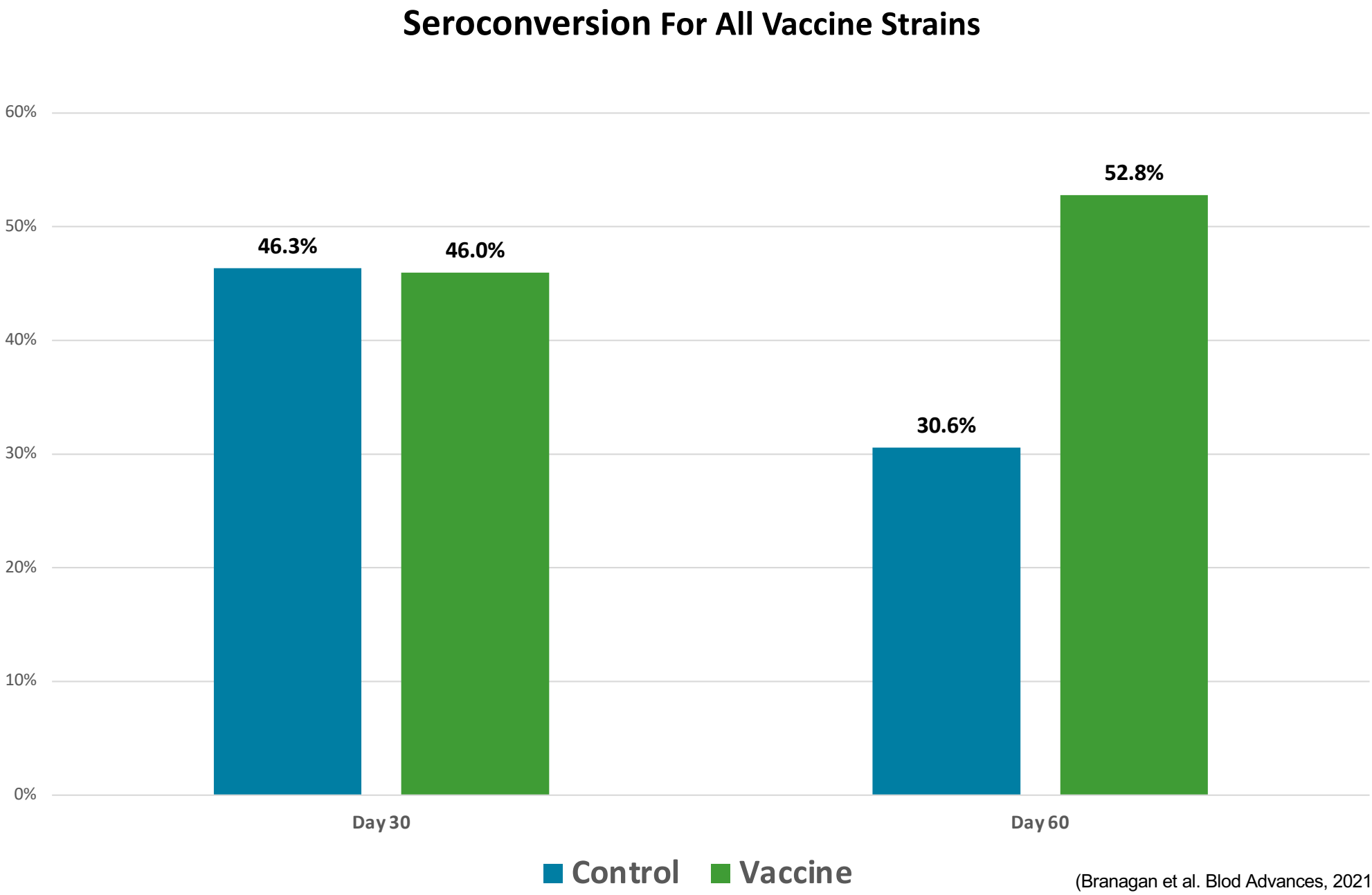

(Branagan et al. Blod Advances, 2021)

SHIVERING 2: Serologic Responses

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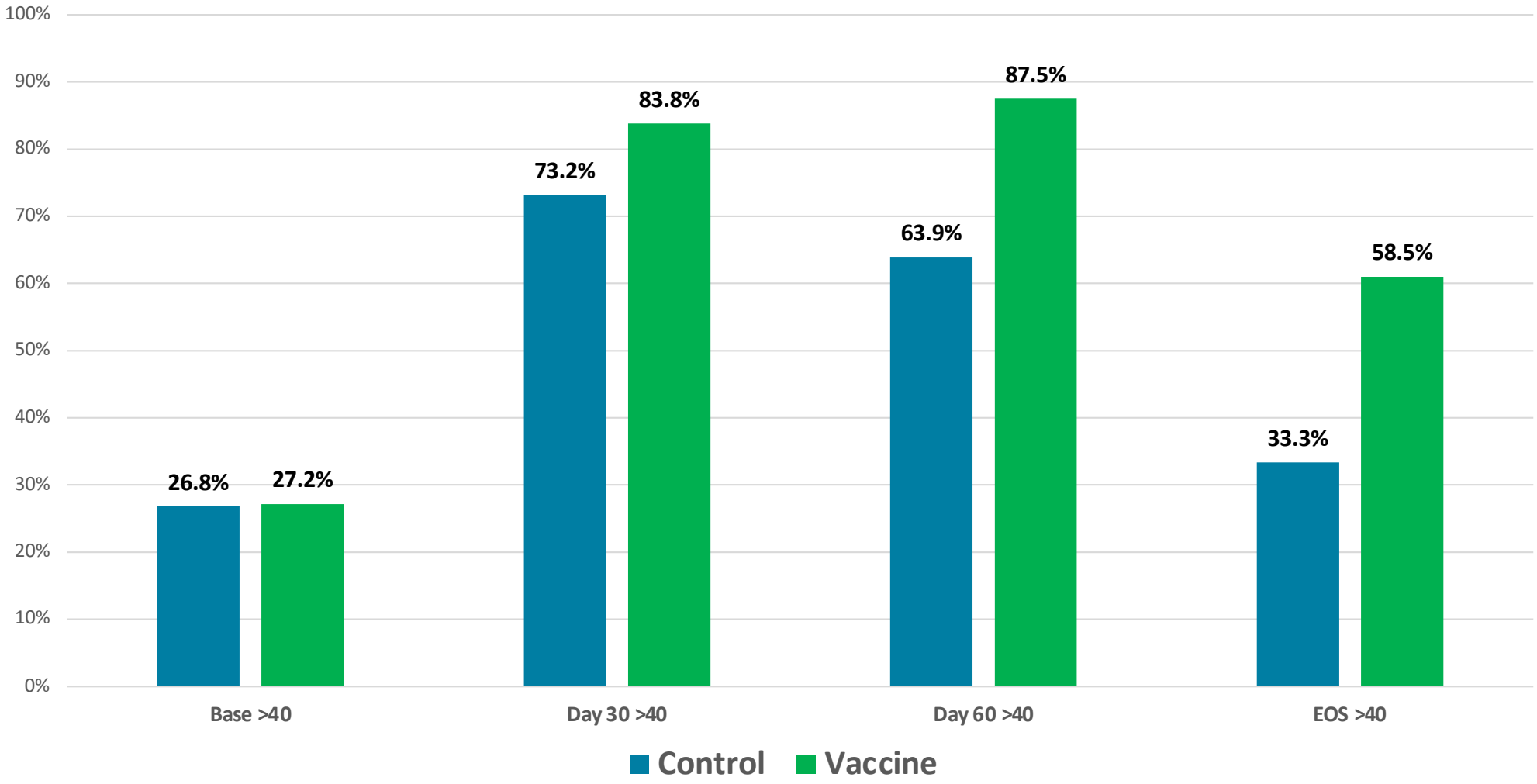
All Patients: Seroprotection Against All Vaccine Strains (HAI >40)



(Branagan et al. Blood Advances, 2021)

SHIVERING 2 Serologic Responses in WM

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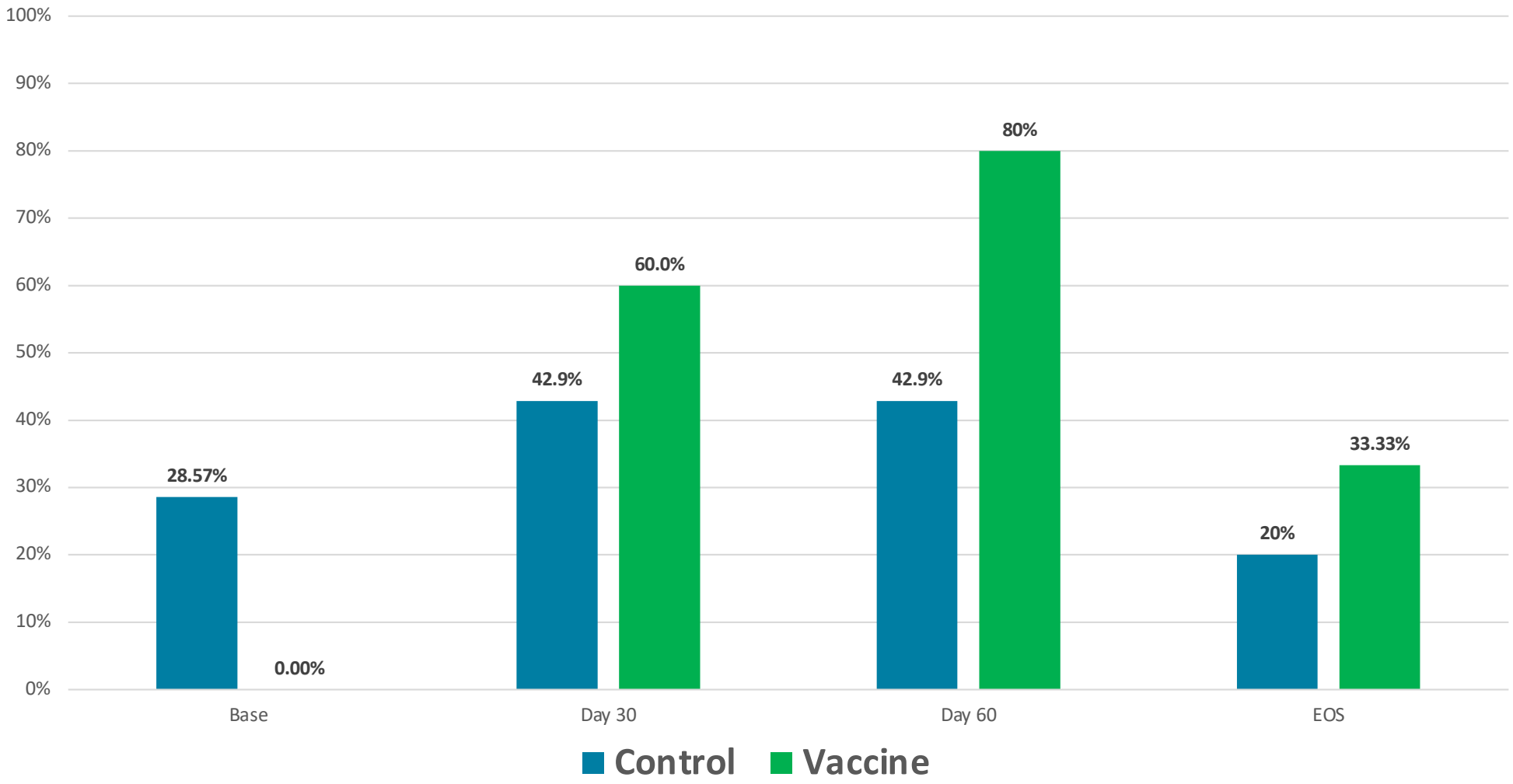
WM Patients: Seroprotection Against All Vaccine Strains (HAI >40)



(Branagan et al. IWWM10, 2018)

Clinical Correlates Associated with Seroprotection

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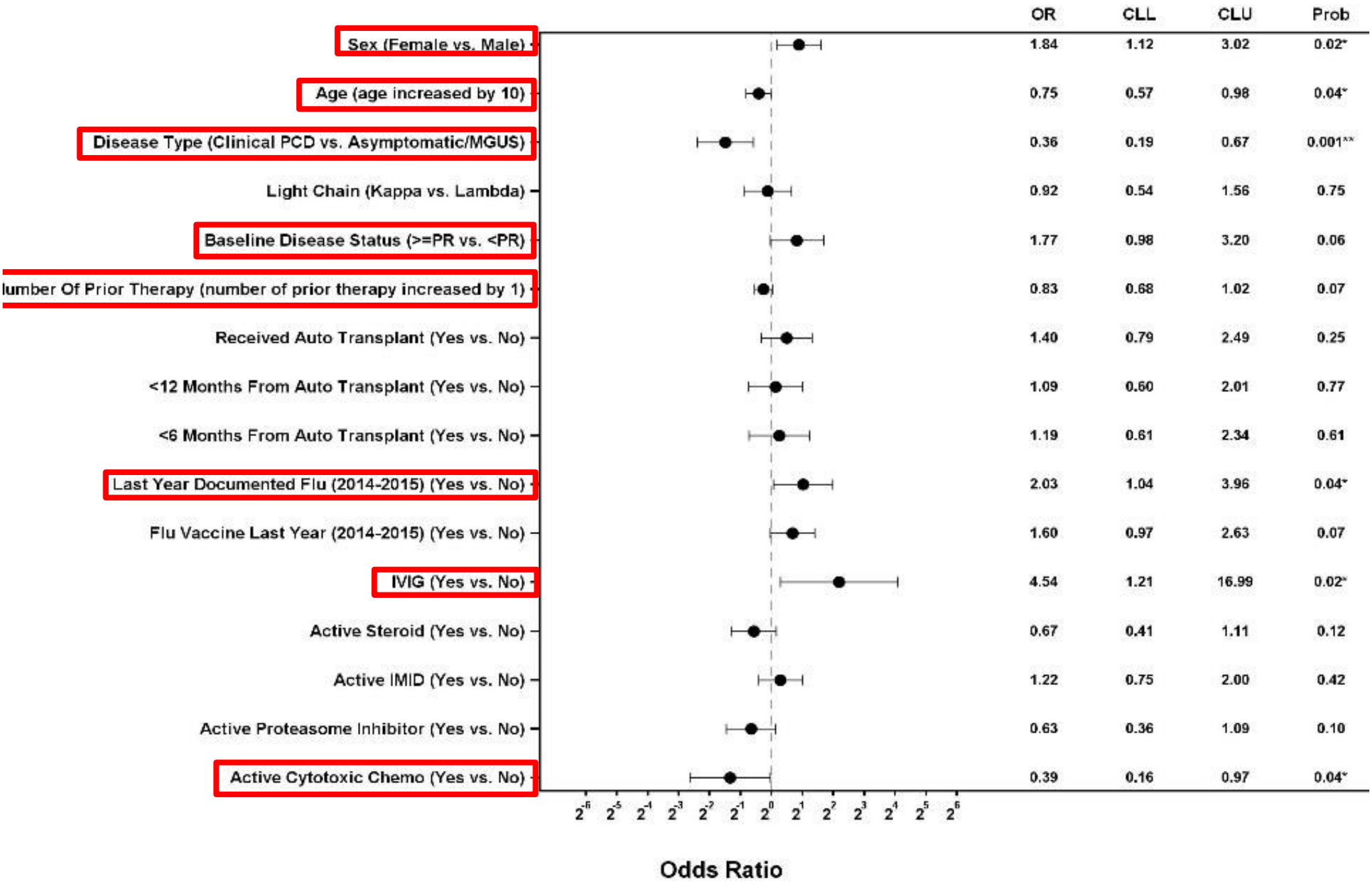

Tandem HD Flu Vaccine Summary

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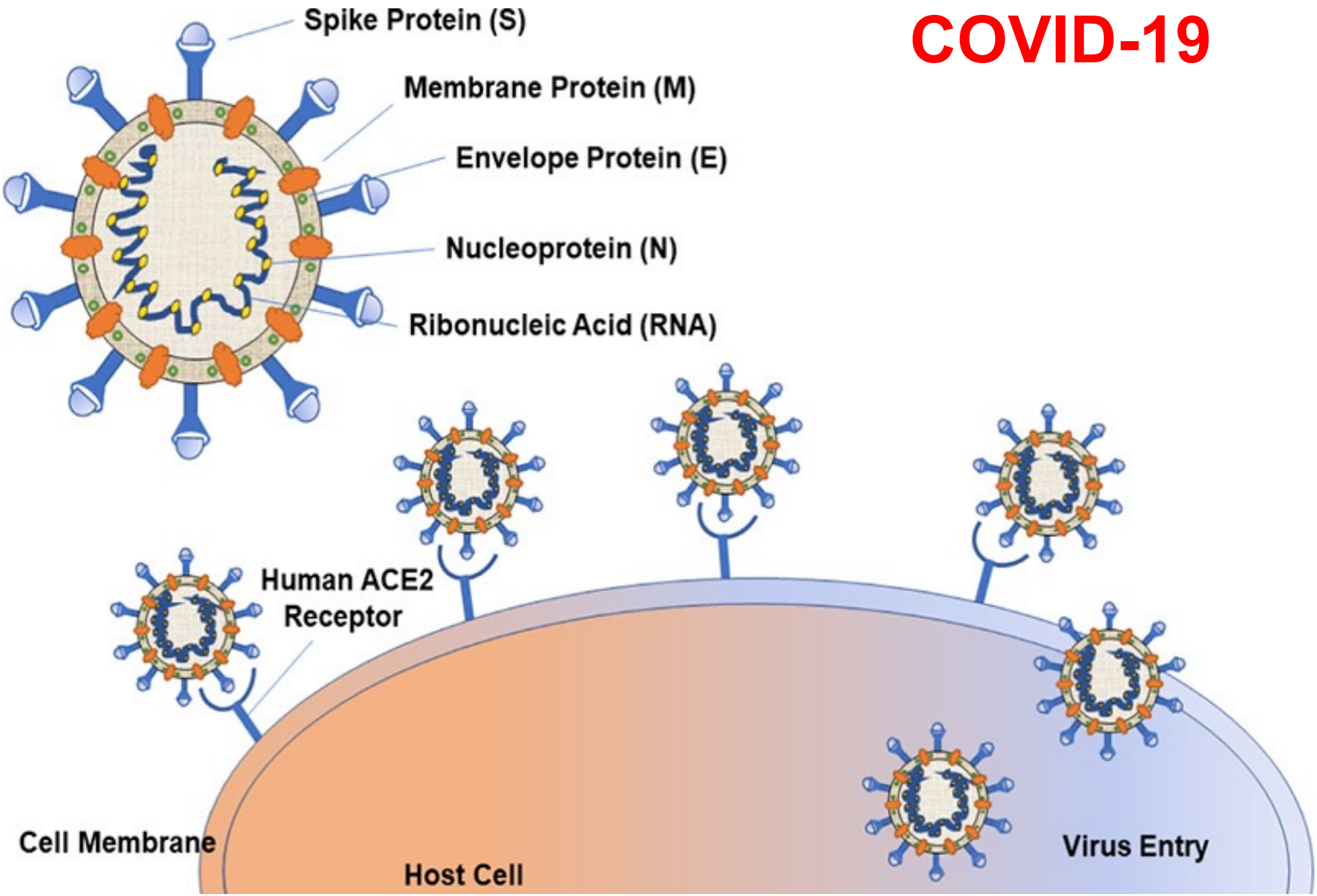
- A novel flu vax strategy: 2 doses of HD vaccine separated by 30 days is well tolerated and associated with high rates of seroprotection & seroconversion in plasma cell disorder patients, studied over two flu seasons (2014-2016)
- Serial measurement of antibody titers for the first time in plasma cell disorder patients reveal rapid and significant loss of protective titers during flu seasons
- This vax strategy vs. to S.O.C vax resulted in higher rates of seroprotection at the end of the flu season (mitigating the loss of protective titers)
- Subgroups of patients were identified based on likelihood of antibody responses following flu vax:
  - Lower likelihood: older age, male sex, progressive MM/WM, increased prior lines of cancer therapy, and active alkylator chemotherapy
  - Higher likelihood: Asymtomatic MM/WM, active IVIG therapy

COVID-19


Spike Protein (S)
Membrane Protein (M)
Envelope Protein (E)
Nucleoprotein (N)
Ribonucleic Acid (RNA)
Human ACE2
Receptor
Cell Membrane
Host Cell
Virus Entry

Background

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- Specific immune responses and degree of clinical protection following COVID-19 vaccines are largely unknown for cancer patients, plasma cell dyscrasia patients, and WM patients

COVID-19 Vaccine Response Trial

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Study of COVID-19 Vaccine Responsiveness in Patients with Multiple Myeloma and Waldenstrom's Macroglobulia

- Clinicaltrials.gov (NCT04830046)
- Open at Massachusetts General Hospital (MGH) and Dana-Farber Cancer Institute (DFCI)
- Overall Principal Investigator: Andrew Branagan, MD, PhD
- DFCI Co-Investigator: Shayna Sarosiek, MD

Protocol 21-108 Schema

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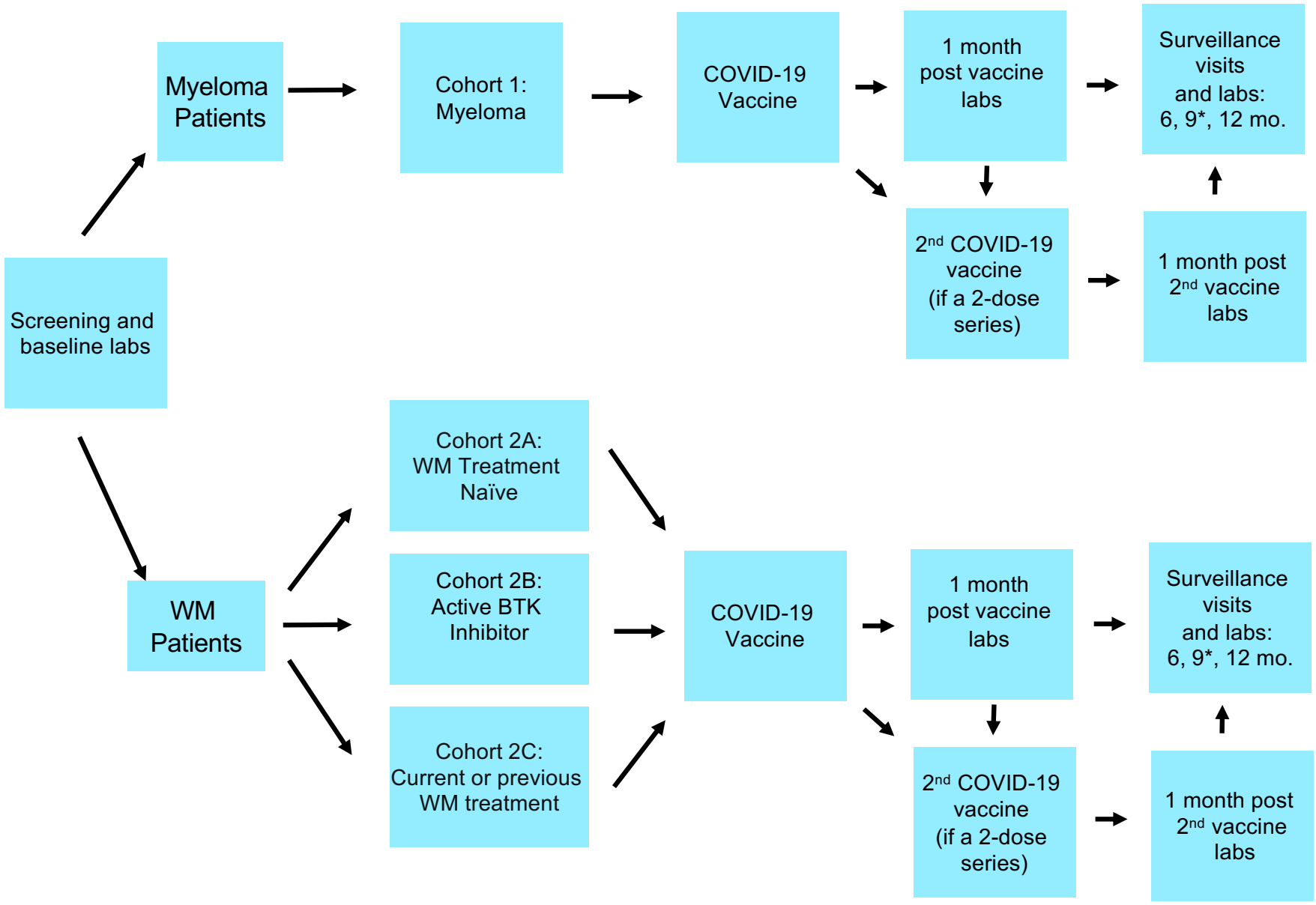

*Month 9 visit and labs are recommended

Objectives/Endpoints

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Primary objectives:

- *To investigate the rate of achieving protective anti-spike* SARS-CoV-2 *antibodies 28 days following second or final dose of a COVID 19 vaccine*

Secondary objectives:

- *To investigate the durability of immune responses following COVID-19 vaccination following COVID-19 vaccine*
- *To investigate clinical correlates of immune response following COVID-19 vaccination in MM and WM patients;*
- *To investigate rates of COVID-19 infections following COVID-19 vaccination in MM and WM patients within the study period.*
- *To evaluate for biomarkers to predict response and to explore quantitative and qualitative humoral and cell-mediated immune responses to COVID-19 vaccination; including gene expression profiling, comprehensive systems serology, and SARS-CoV-2-specific T-cells.*

Baseline Characteristics

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	All (n=137)	MM (n=91)	WM (n=46)
Age, median (IQR)	66 (59.5-71)	65 (59.0-71)	66.5 (60.0-71.5)
Age greater than 75, n (%)	15 (10.9)	10 (10.9)	5 (10.9)
Male sex, n (%)	75 (55.1)	49 (53.8)	27 (58.7)
Race, n (%)			
White	124 (90.5)	81 (89.0)	43 (93.5)
Non-white	13 (9.5)	10 (11.0)	3 (6.5)
COVID-19 vaccine, n (%)			
BNT162b2	74 (54.0)	47 (51.6)	27 (58.7)
mRNA-1273	50 (36.5)	34 (37.4)	16 (34.8)
JNJ-78436735	13 (9.5)	10 (11.0)	3 (6.5)
Involved heavy chain and/or light chain			
IgG	-	42 (46.2)	-
IgA		16 (17.6)	
Kappa FLC		54 (59.3)	
Lambda FLC		22 (24.2)	
Non-secretory		1 (1.1)	
MYD88 mutational status, n (%)			
MYD88 mutant	-	-	35 (76.1)
MYD88 wild-type			7 (15.2)
Unknown			4 (8.7)
CXCR4 mutational status, n (%)			
CXCR4 mutant	-	-	12 (26.1)
CXCR4 wild-type			11 (23.9)
Unknown			23 (50.0)
Prior ASCT, n (%)	28 (20.4)	28 (30.8)	0 (0)
History IVIG use within 90 days, n (%)	18 (13.1)	14 (15.4)	4 (8.9)
Treatment status, n (%)			
Previously treated	118 (86.1)	85 (93.4)	33 (71.7)
Treatment naive	19 (13.9)	6 (6.6)	13 (28.3)
Current line of therapy, n (%)			
First line	61 (44.5)	44 (48.4)	17 (37.0)
Second line	33 (24.1)	26 (28.6)	7 (15.2)
Third line or greater	23 (16.8)	15 (16.5)	8 (17.4)
Hypogammaglobulinemia, n (%)*	87 (63.5)	58 (63.7)	29 (63.0)
IgG, median (IQR)	533.0 (405.3-779.5)	549.0 (411.5-828.5)	476.0 (368.0-739.0)

Median COVID-19 Spike Ab Titers After 2nd mRNA or Single J&J Vaccine

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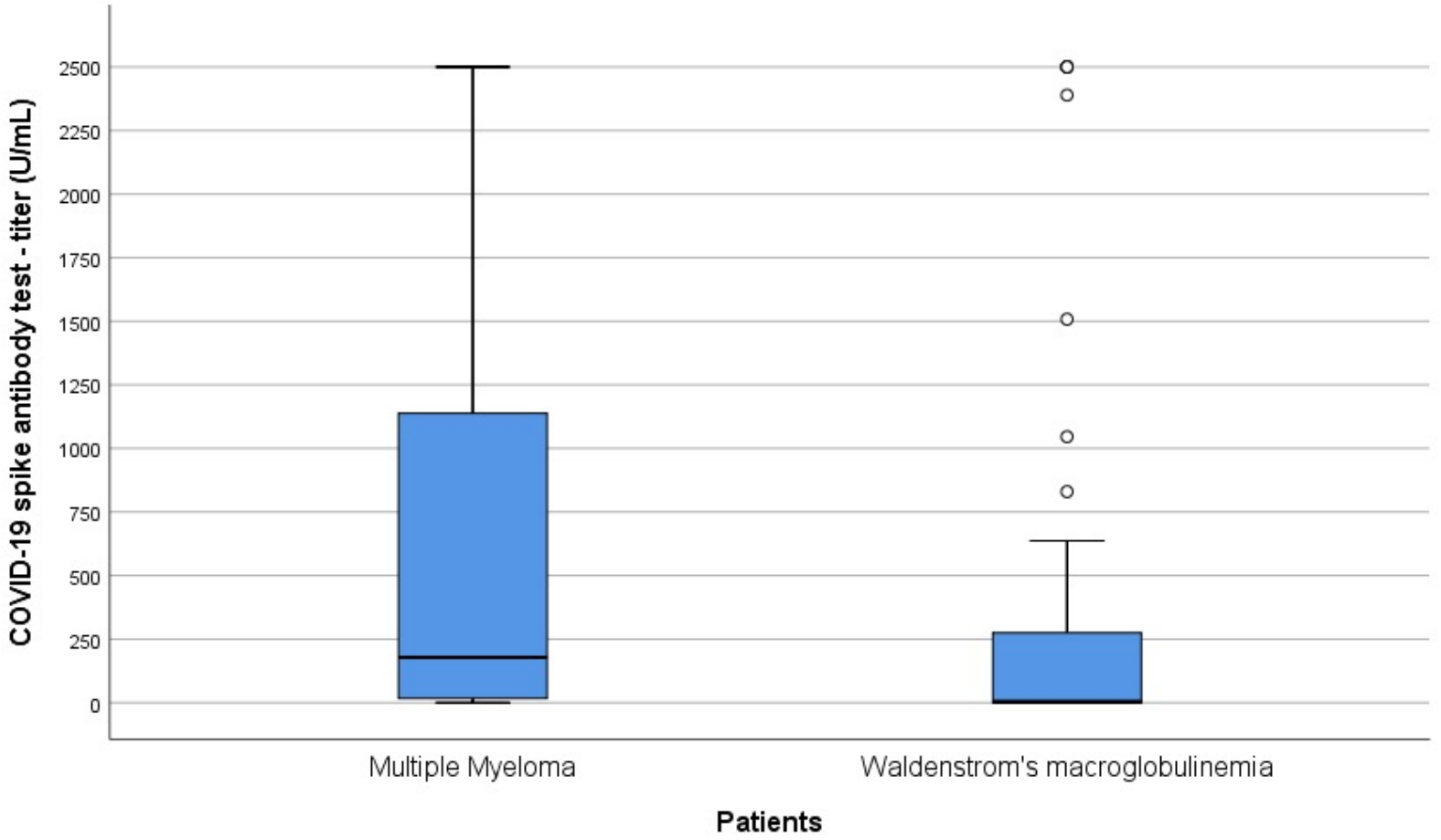

	COVID-19 spike antibody test – titer (U/mL)		
	25th Percentile	50th Percentile	75th Percentile
Multiple Myeloma	16.1	178	1166
Waldenstrom's macroglobulinemia	0	3.62	278

COVID-19 Spike Ab Responses Myeloma vs. Waldenstrom's macroglobulinema

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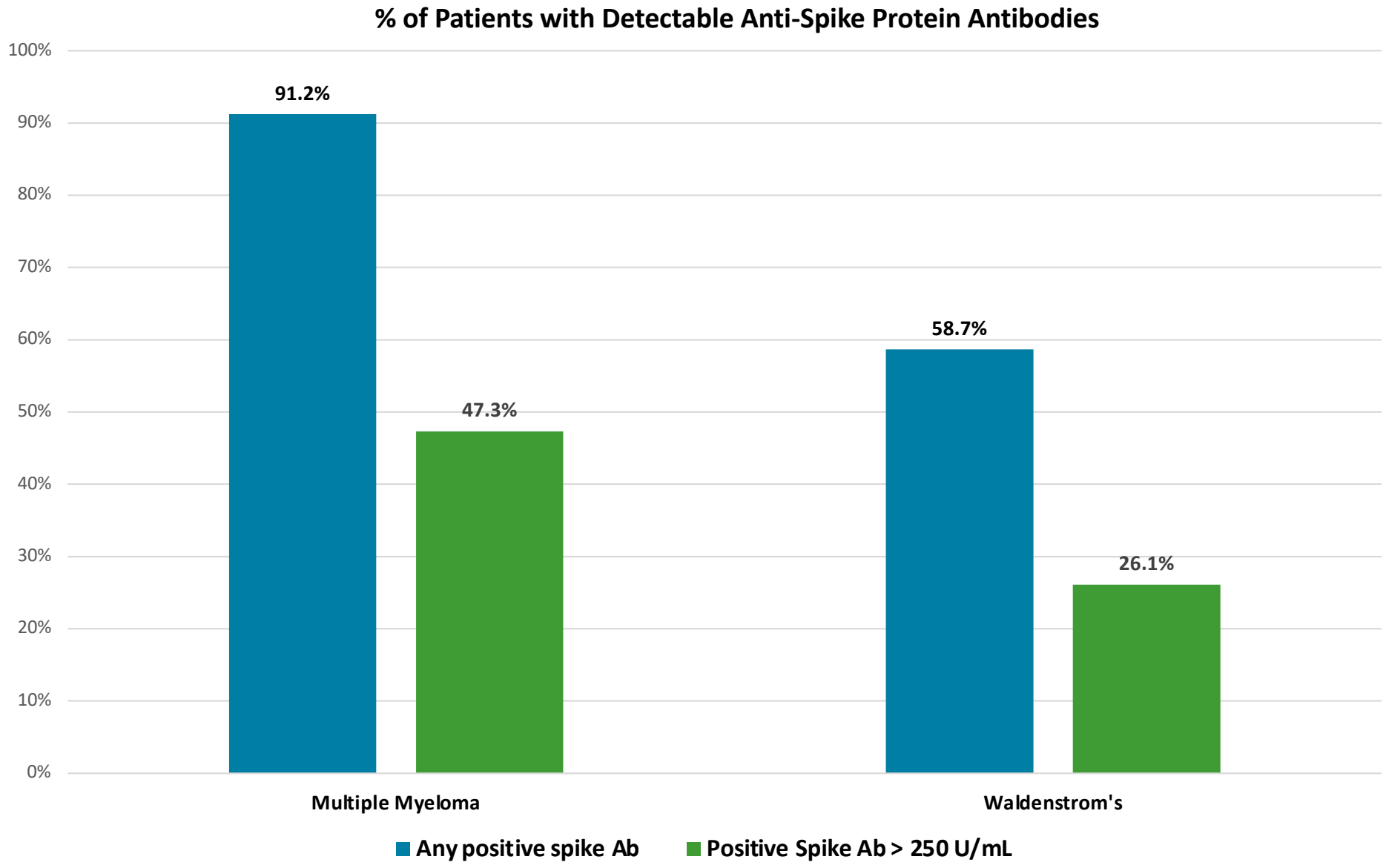

Spike Ab Response Based on Specific COVID-19 Vaccine

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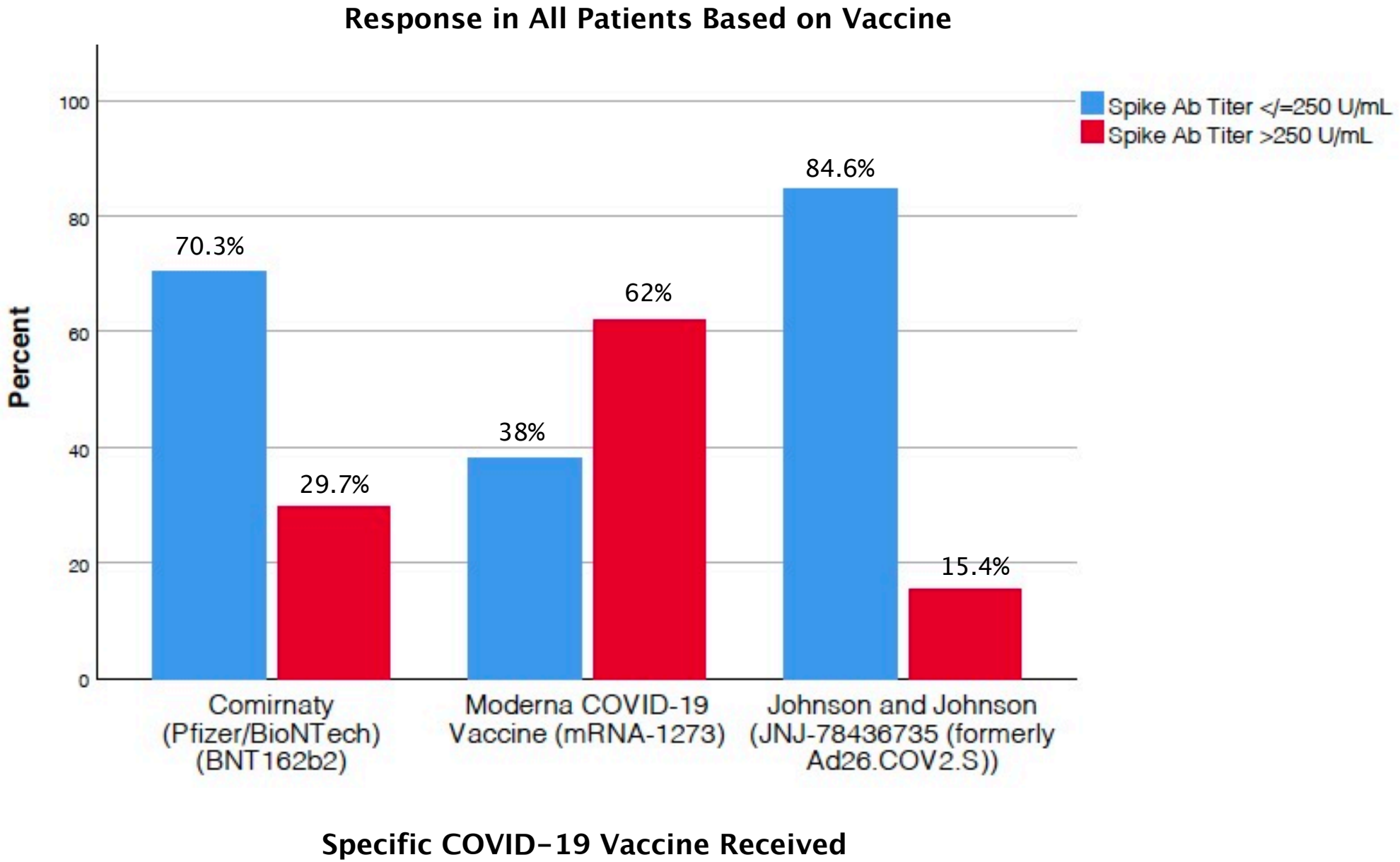

Spike Ab Response Based on Specific COVID-19 Vaccine

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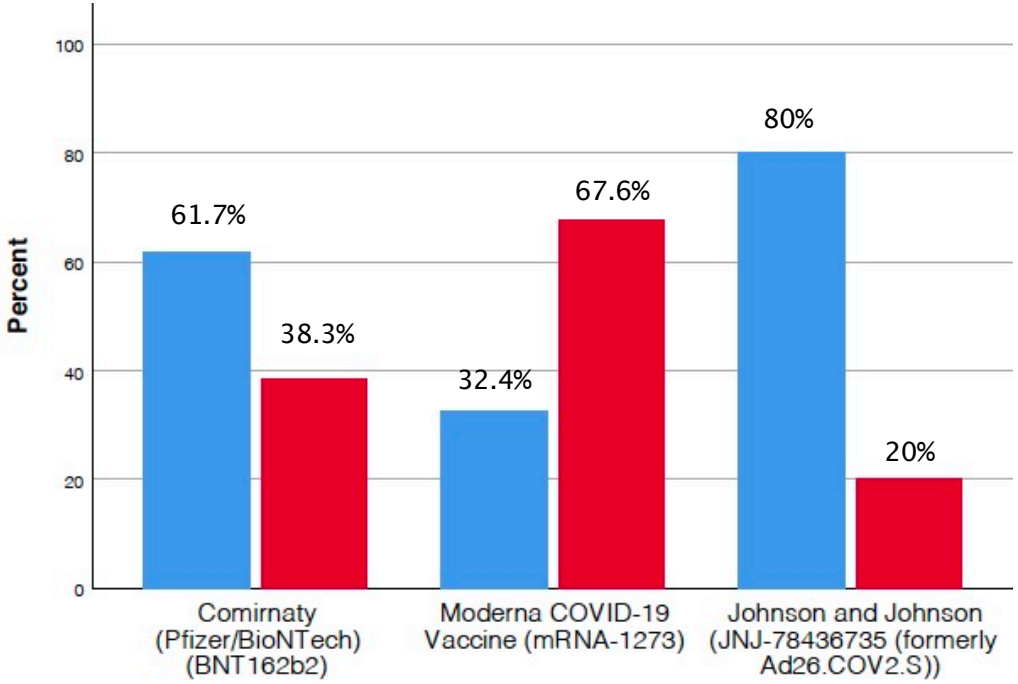
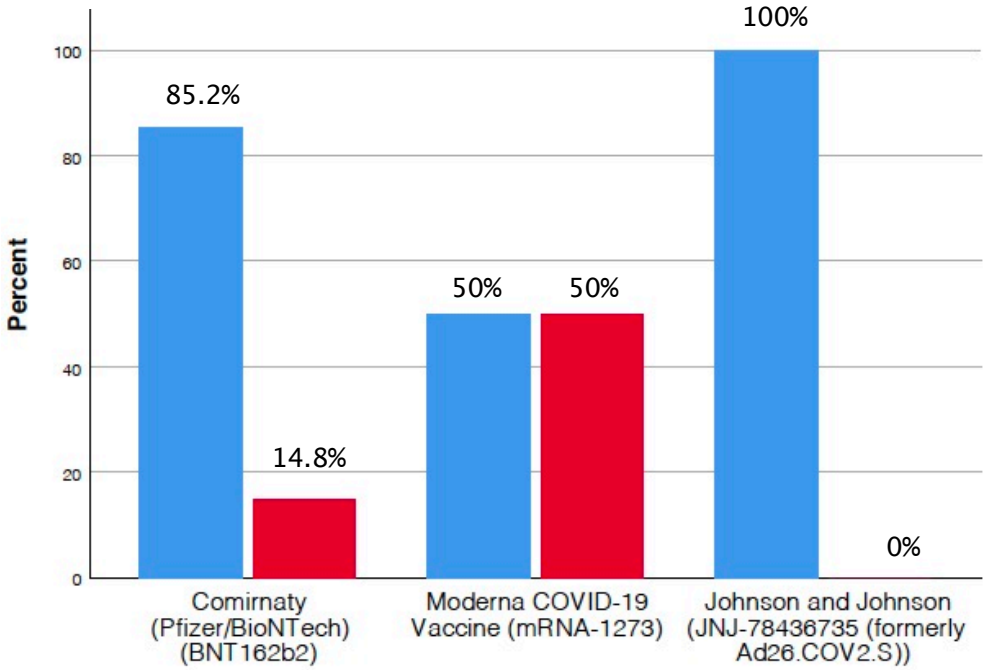
Spike Ab Titer </=250 U/mL
Spike Ab Titer >250 U/mL

Response in Myeloma Patients



Response in Waldenstrom's Patients



Specific COVID-19 Vaccine Received

COVID-19 Spike Ab Responses in WM Pts Stratified by Study Cohort

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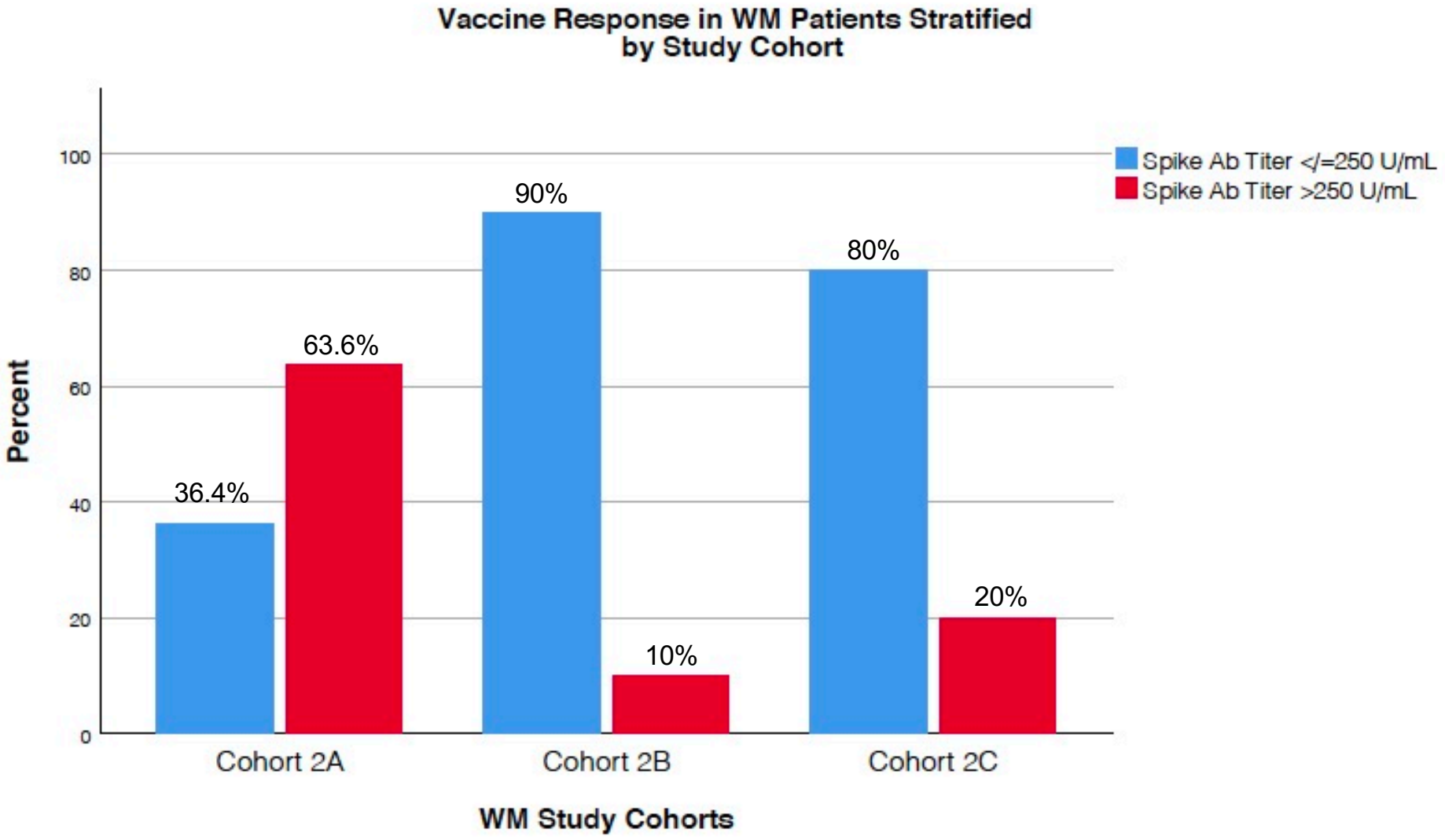

Cohort 2A	Cohort 2B	Cohort 2C
Treatment naïve WM patients	WM patients receiving BTK inhibitor	Currently or previously treated WM patients

COVID-19 Spike Ab Responses in WM Pts Stratified by BTK and Rituximab Treatment Status

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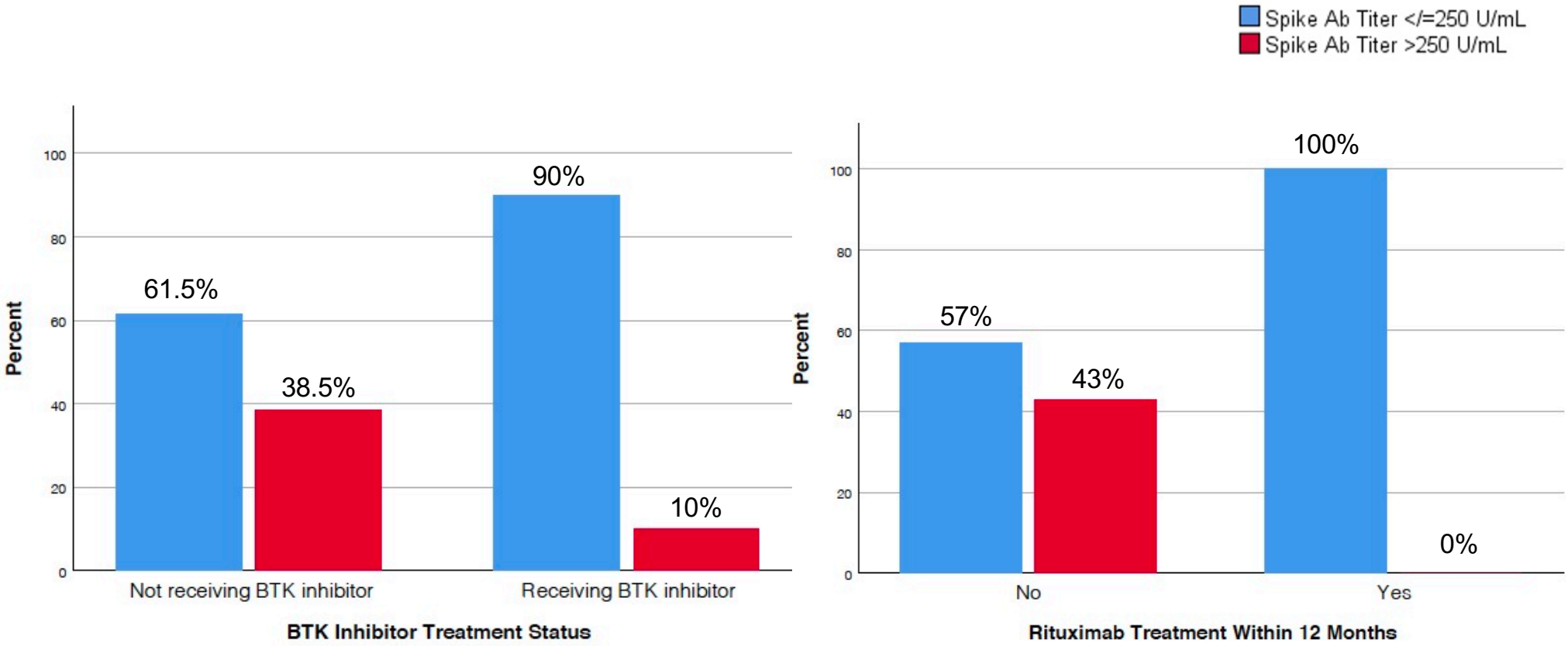

COVID-19 Spike Ab Responses in MM Patients Stratified by Disease Response Status

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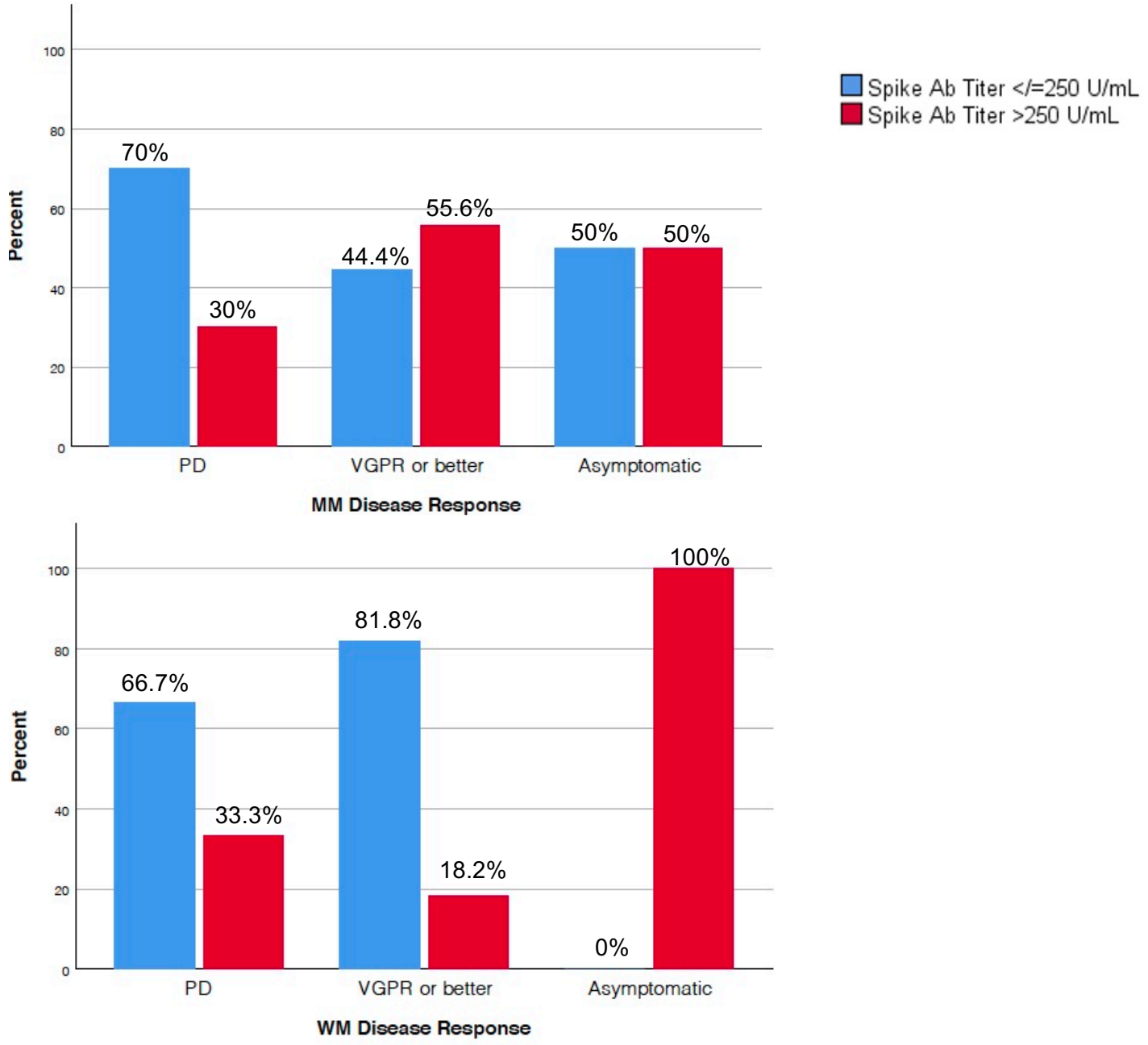

COVID-19 Vaccine Response Study Summary

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- Preliminary data suggest inadequate COVID-19 spike protein antibody responses in patients with MM and WM
- MRNA-1273 (Moderna) elicited significantly higher spike antibody response rates compared to other vaccines
- Age 75+ years was associated with lower rates of spike antibody response
- WM patients showed more severe impairment of spike antibody production
- Most previously untreated WM patients achieved spike antibody responses however the most significant reduction in antibody responses were seen in patients treated with active BTK inhibitors or rituximab within 12 months
- Longitudinal responses, functional antibody responses, and COVID-19 specific T cell responses are ongoing

Research Studies

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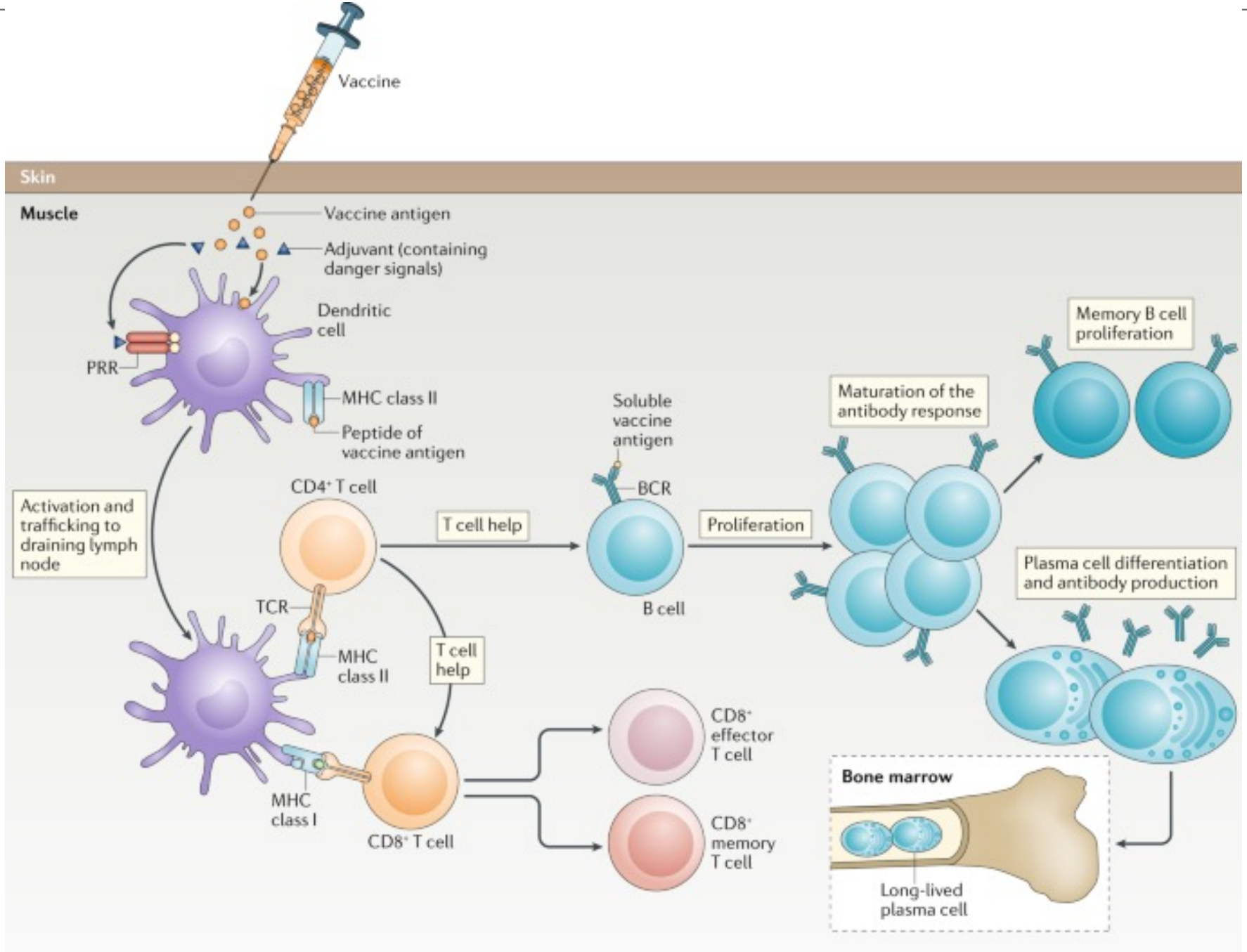
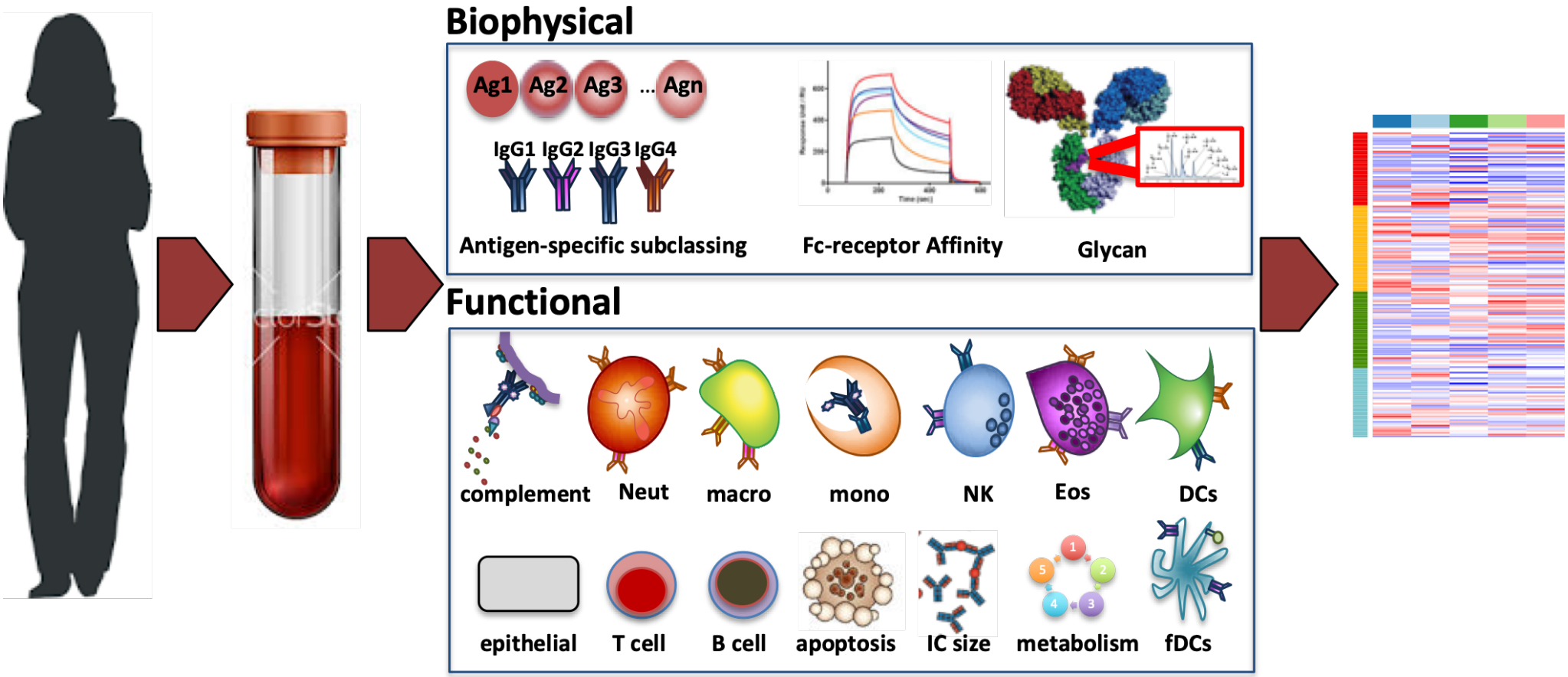


Systems Serology

A high-throughput pipeline that deeply interrogates disease-specific antibody profiles at unprecedented depths.



Research Studies

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Systems Serology

Antigens: We will profile the CoV2-specific humoral immune response against the Spike (S) antigen, the Spike receptor binding domain (RBD), the nucleocapsid (N), N-terminal domain of S (NTD), the membrane (M), and envelope (E) antigen. In addition, the humoral immune response will also be mapped against SARS, MERS, OC43, HKU1, NL63, 229E, CoV-2 variants: deletion 69-70, deletion 144, N501Y, A570D, D614G, P681H, T716I, S982A, D1118H, UK, SA. Control pathogens will pro HA (Cal09, Phuket13, Bis08, Tx12, Sing16, Co17, Switz13, Vic11), NA (N1, N2).

Functional profiling: The suite of functional assays covering a range of effector mechanisms (ADCC, phagocytosis, complement, antigen uptake) carried out by a diverse set of innate effector cells (NK, dendritic cells, neutrophils, monocytes, macrophages, etc.) will be utilized to assess antibody functionality.

- **Antibody-dependent phagocytosis.**
- **Activation/maturation of innate immune effector cells.**
- **Antibody-dependent cellular degranulation.**
- **Antibody-dependent complement deposition.**
- **Antibody-dependent cellular cytotoxicity**.
- **Neutralization.**

Conclusions

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- WM is associated with relative immunodeficiency evidenced by increased risk of infections and impaired response to vaccinations
- All WM patients should be aware of infection risks and discuss individual recommendations with their providers
  - Typically the following vaccines are recommended: pneumococcal vaccination, Shingrix zoster vaccination, two high-dose flu vaccines each season, and COVID-19 vaccination
  - Antimicrobial ppx may be recommended based on individual history and recent WM therapy
  - Immunoglobulin replacement therapy may be beneficial in certain individuals with WM
- Currently WM patients are eligible for a third dose of mRNA vaccines Pfizer or Moderna under the CDC's recommendation for moderately to severly immunocompromised people
- Our COVID-19 study and others are ongoing which hope to inform the optimal vaccination strategy, such as timing, booster dosing or specific vaccines
- Additional research is needed to better understand the specific immune deficits associated with WM and WM-directed therapies in order to minimize the risk of infections in patients with WM

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Thank you!!

All Our Patients

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