Risk Factors for Severe COVID-19 Breakthrough Infections: A Retrospective, Nationwide Cohort Study

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Disclosures

- Site PI for PINETREE Study (Gilead Sciences, Funds to Institution)

Rationale

Identification of patient profiles with persistent risk of severe COVID-19 despite vaccination remains an important clinical question

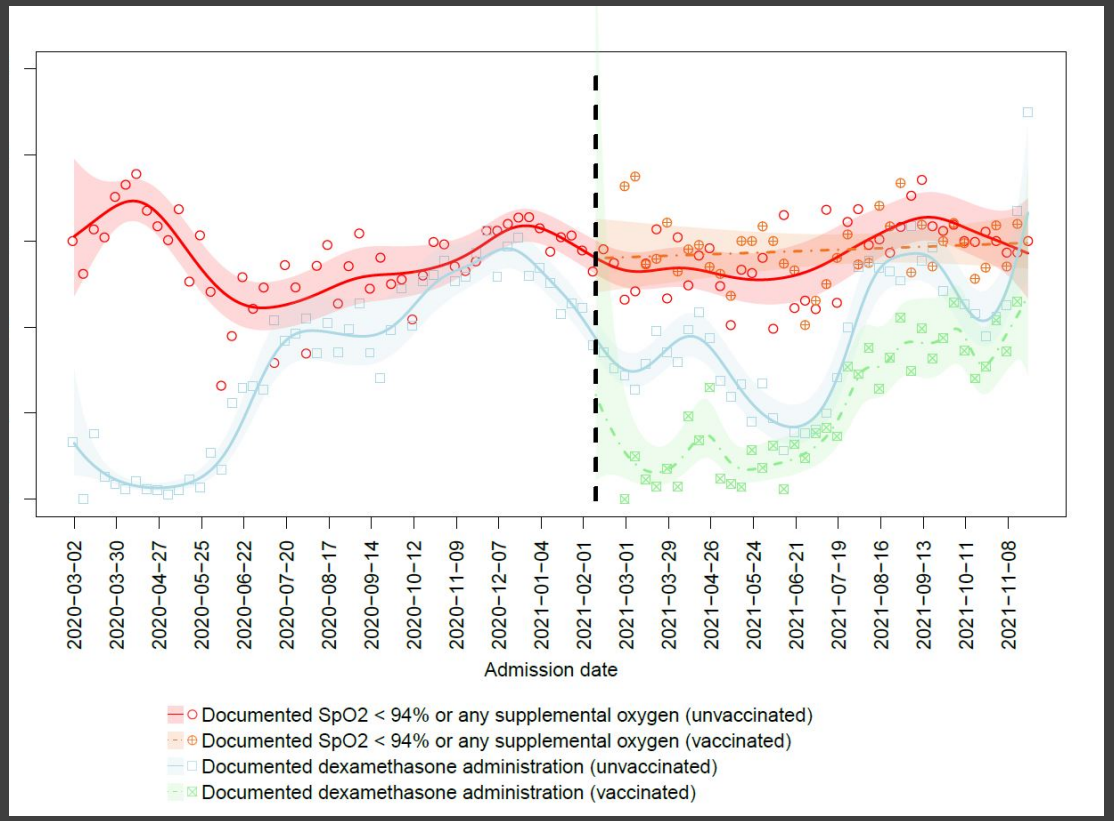
- Risk profiles can be used to target different mitigation strategies (e.g., repeated boosting campaigns, early treatment) to those who remain at high risk of severe disease
- Identification of risk factors the first step toward developing decision support tools to inform clinical practice

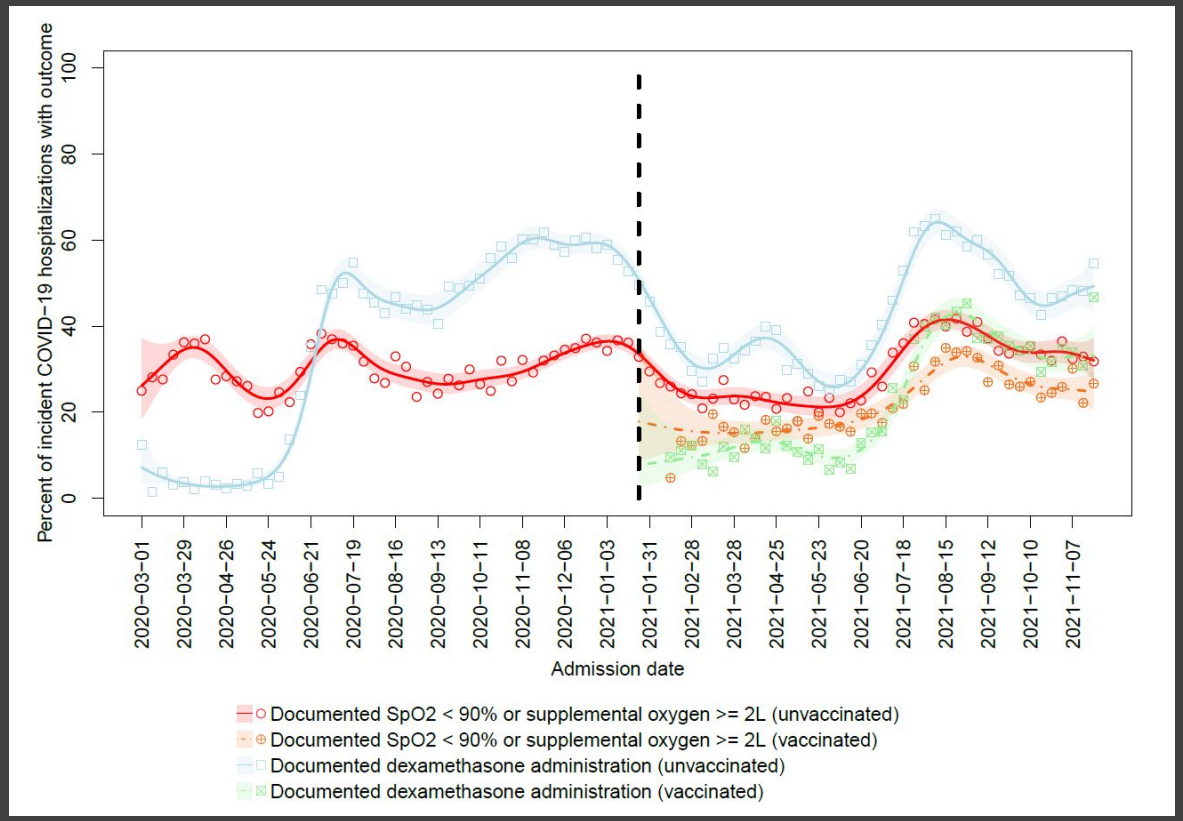
Methods:

Risk Factors for Severe Breakthrough Infections

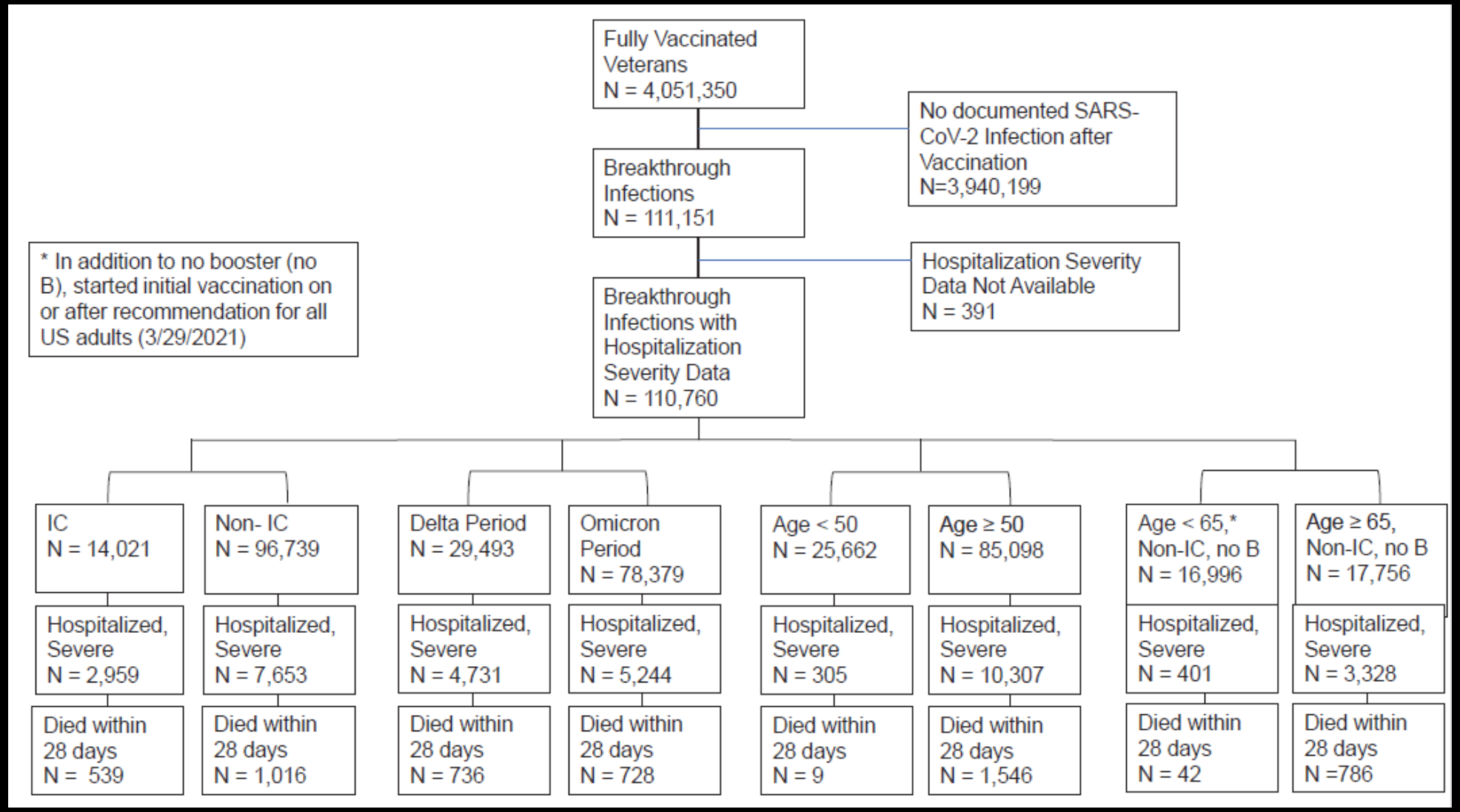
- **Cohort Inclusion:**
  - Nationwide, retrospective cohort of all Veterans who received the primary COVID-19 vaccination series and who subsequently developed microbiologically-confirmed SARS-COV-2
- **Outcomes:**
  - Non-severe: Outpatients or inpatients with mild disease
  - Severe: Inpatients with moderate to severe disease defined by SpO2 and/or receipt of supplemental oxygen and/or dexamethasone, ICU patients, patients who died within 30 days of COVID-19 diagnosis
- **Exposures:**
  - Demographics, comorbidities, administration of immunocompromising medications, vaccine-related variables
- **Study period:** 12/15/2020-2/28/2022
- **Analysis:** Logistic Regression

Number of Severe Hospitalizations Depends Upon Definition Selected





Cohort Creation and Outcomes

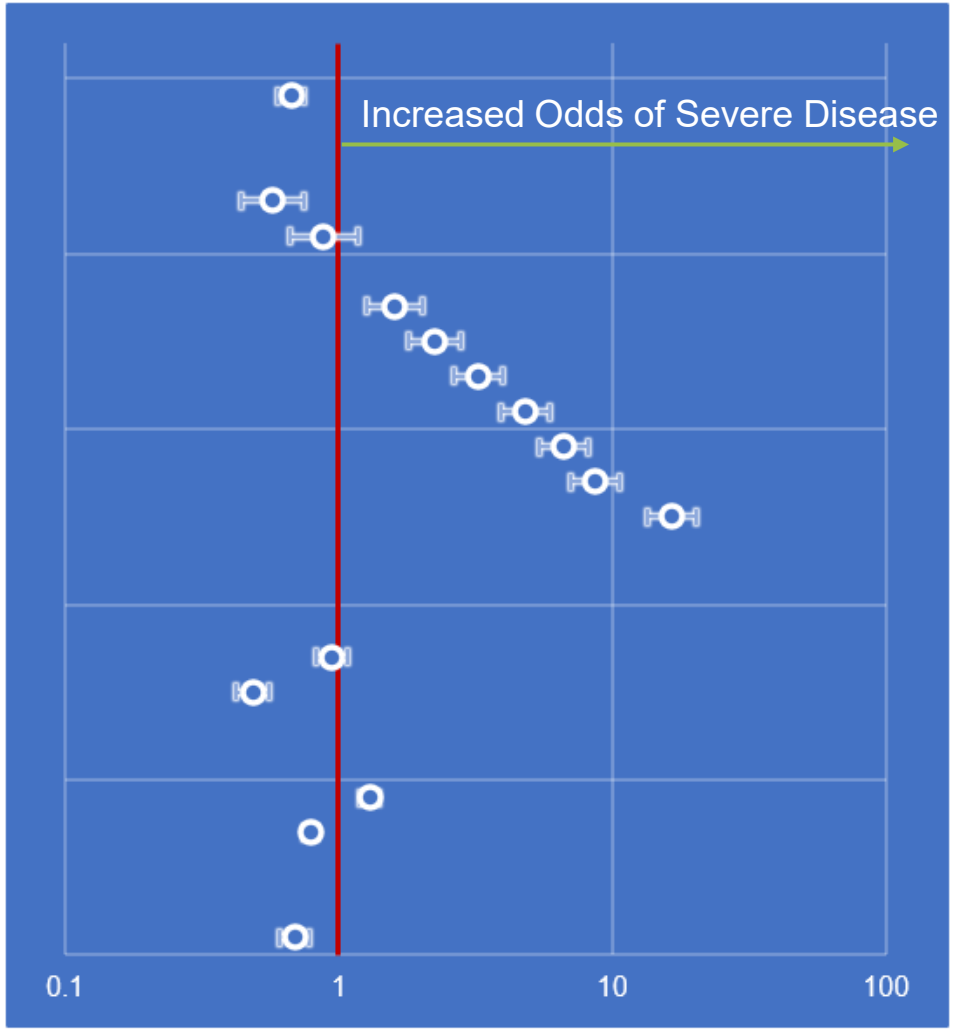


Risk Factors for Severe Breakthrough Infection

- **The strongest association with severe disease after vaccination was age**
  - Age ≥ 50 with an adjusted odds ratio (aOR) 1.42 (CI 1.40 - 1.44) per 5-year increase
  - Age ≥ 80 had aOR 16.1 (CI 13.1 – 19.9) relative to patients aged 45-50.
- **Immunocompromising conditions were also associated with increased risk of severe disease**
  - Immunosuppressive medications: aORs 1.66–2.80
  - Cytotoxic chemotherapy: aOR 2.71, CI 2.27–3.24 at the time of exposure
  - Leukemias/lymphomas: aOR 1.87, CI 1.61–2.17
- **Chronic conditions associated with end-organ disease**
  - Heart failure: aOR 1.74, CI 1.61-1.88
  - Dementia: aOR 2.01, CI 1.83-2.20
  - Chronic kidney disease: aOR 1.59, CI 1.49-1.69
- **Receipt of an additional (booster) dose of vaccine**
  - aOR 0.50

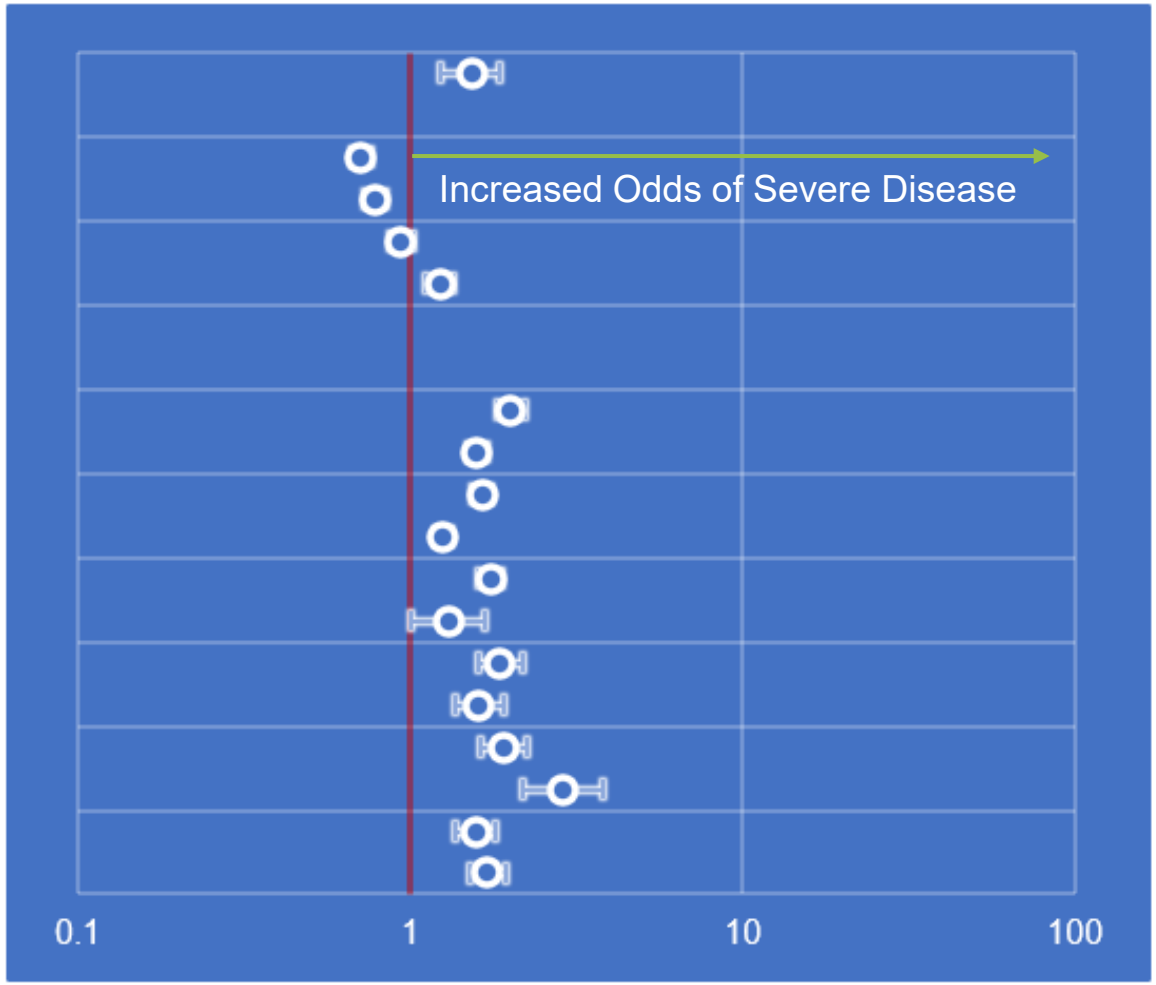
Demographic and Vaccine-Related Risk Factors

	Severe	Non	OR (95% CI)
Sex			
Male	10225	87389	1.0 (R)
Female	387	22759	0.67 (0.60 – 0.75)
Age			
< 40	110	13004	0.57 (0.44 – 0.75)
40 – 45	88	6153	0.88 (0.66 – 1.18)
45 – 50	107	6200	1.0 (R)
50 – 55	277	9444	1.60 (1.27 – 2.01)
55 – 60	476	10458	2.24 (1.80 – 2.78)
60 – 65	889	12082	3.24 (2.64 – 3.99)
65 – 70	1340	11013	4.82 (3.93 – 5.92)
70 – 75	2624	15703	6.63 (5.42 – 8.11)
75 – 80	2016	9546	8.72 (7.10 – 10.7)
≥ 80	2685	6545	16.6 (13.5 – 20.4)
Period of dominant variant			
Pre-delta	637	2251	1.0 (R)
Delta	4731	24762	0.95 (0.83 – 1.08)
Omicron	5244	73135	0.49 (0.42 – 0.56)
Vaccine type			
Janssen	1038	10028	1.30 (1.20 – 1.41)
Moderna	4241	41289	0.79 (0.75 – 0.83)
Pfizer	5333	48831	1.0 (R)
Previous infection	414	3959	0.69 (0.61 – 0.78)



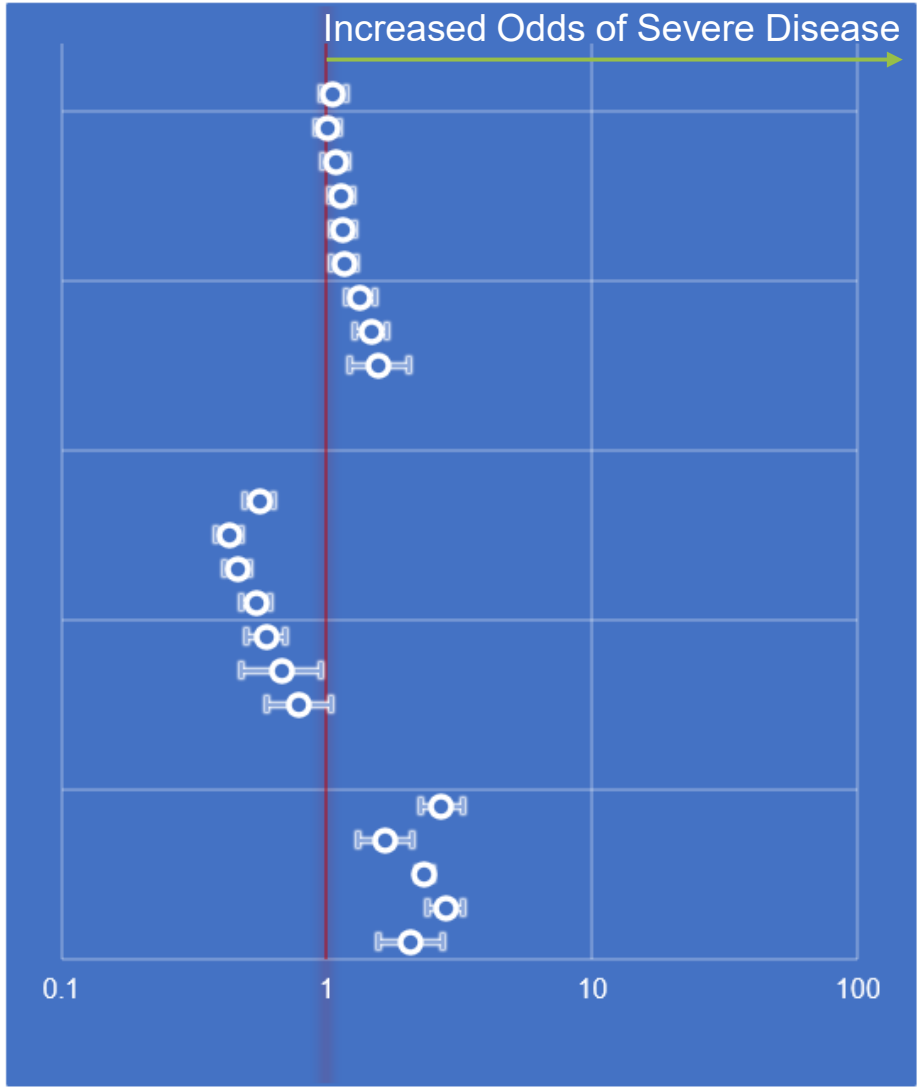
Comorbidities Associated with Increased Risk

BMI class			
Underweight	181	496	1.53 (1.24 – 1.87)
Normal	2095	12299	1.0 (R)
Overweight	2915	29792	0.71 (0.67 – 0.76)
Obesity I	2599	28557	0.78 (0.73 – 0.84)
Obesity II	1527	15335	0.94 (0.87 – 1.02)
Severe obesity	1131	9510	1.23 (1.12 – 1.35)
Comorbidities			
Alzheimer's / dementia	1135	1915	2.01 (1.83 – 2.20)
Chronic kidney disease	2761	9071	1.59 (1.49 – 1.69)
COPD	2234	6103	1.65 (1.54 – 1.76)
Diabetes	4164	21919	1.25 (1.19 – 1.32)
Heart failure	1763	3681	1.74 (1.61 – 1.88)
HIV / AIDS	83	791	1.30 (1.01 – 1.68)
Leukemia / lymphoma	343	993	1.87 (1.61 – 2.17)
Lung cancer	251	573	1.61 (1.36 – 1.92)
Mobility impairments	302	728	1.92 (1.63 – 2.26)
Multiple sclerosis	92	362	2.86 (2.17 – 3.78)
Pressure ulcers	475	872	1.58 (1.37 – 1.81)
Schizophrenia	435	2320	1.71 (1.51 – 1.93)

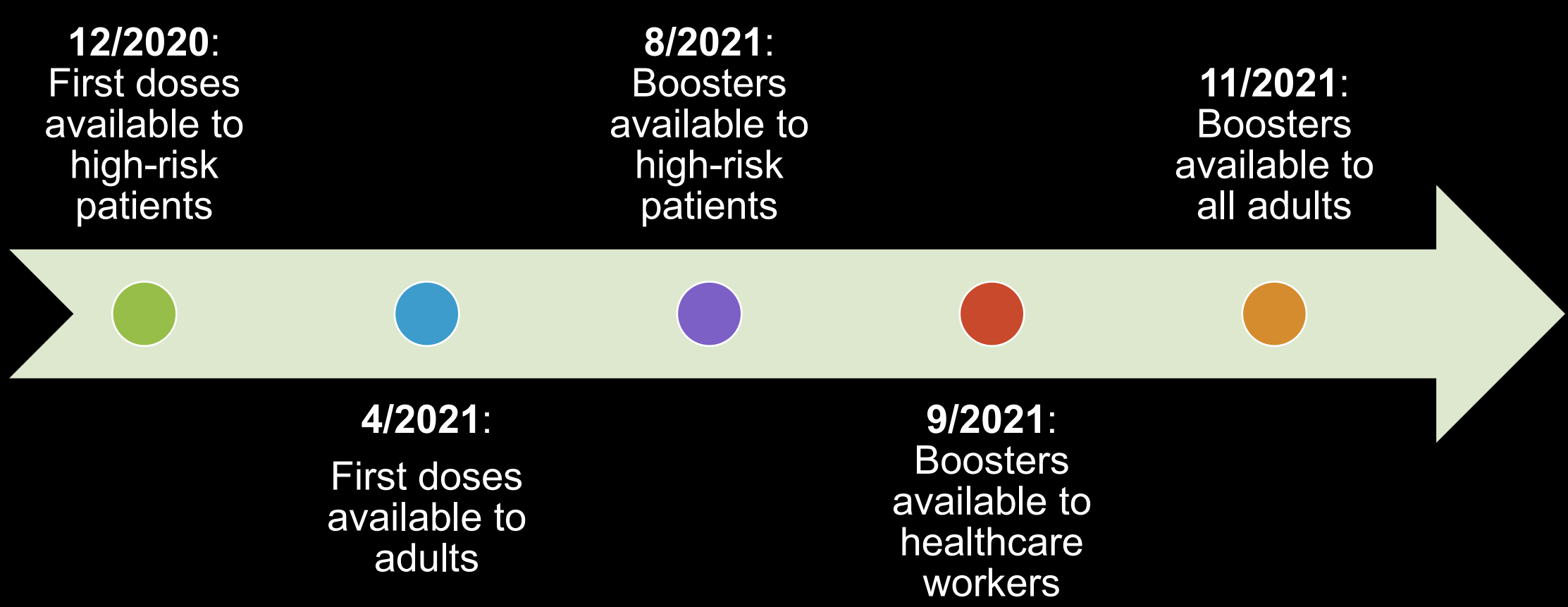


Impact of Time Since Last Dose and Immunosuppression

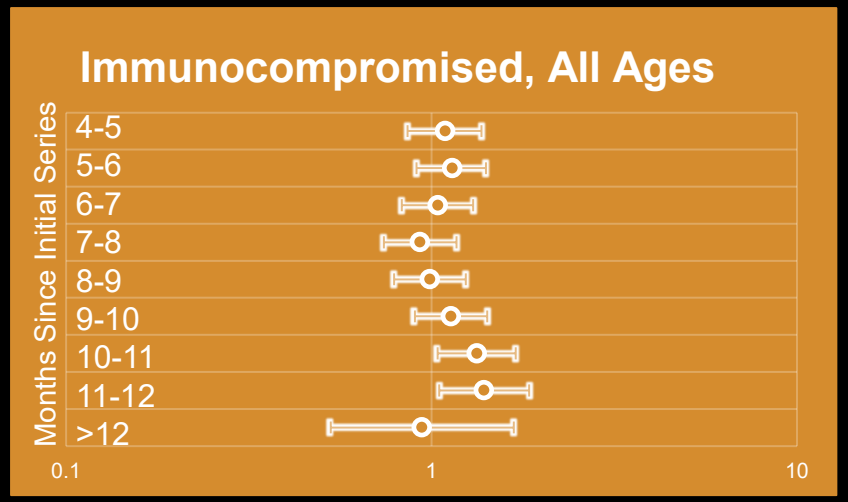
Months since vaccination at breakthrough			
< 4	1514	10983	1.0 (R)
4 – 5	861	6355	1.06 (0.95 – 1.18)
5 – 6	1109	7039	1.01 (0.91 – 1.12)
6 – 7	1139	7763	1.08 (0.97 – 1.20)
7 – 8	1074	10665	1.13 (1.02 – 1.26)
8 – 9	1245	17873	1.15 (1.03 – 1.28)
9 – 10	1427	18570	1.16 (1.03 – 1.30)
10 – 11	1479	14252	1.34 (1.19 – 1.51)
11 – 12	666	5853	1.47 (1.28 – 1.69)
≥ 12	98	795	1.57 (1.22 – 2.04)
Months since boosted			
Not boosted	8556	72483	1.0 (R)
< 1	354	5041	0.56 (0.49 – 0.63)
1 – 2	391	7341	0.43 (0.38 – 0.48)
2 – 3	554	7996	0.46 (0.41 – 0.51)
3 – 4	436	4197	0.54 (0.48 – 0.61)
4 – 5	206	1543	0.59 (0.50 – 0.70)
5 – 6	50	320	0.68 (0.48 – 0.95)
≥ 6	65	867	0.78 (0.59 – 1.03)
Immune-suppressive medications after vaccination			
Chemotherapy	310	696	2.71 (2.27 – 3.24)
Cytokine-blocking	200	1401	1.66 (1.32 – 2.09)
Glucocorticoids	1821	5783	2.34 (2.18 – 2.50)
Leukocyte-blocking	486	1438	2.80 (2.39 – 3.28)
Lymphocyte-depleting	179	406	2.07 (1.57 – 2.72)

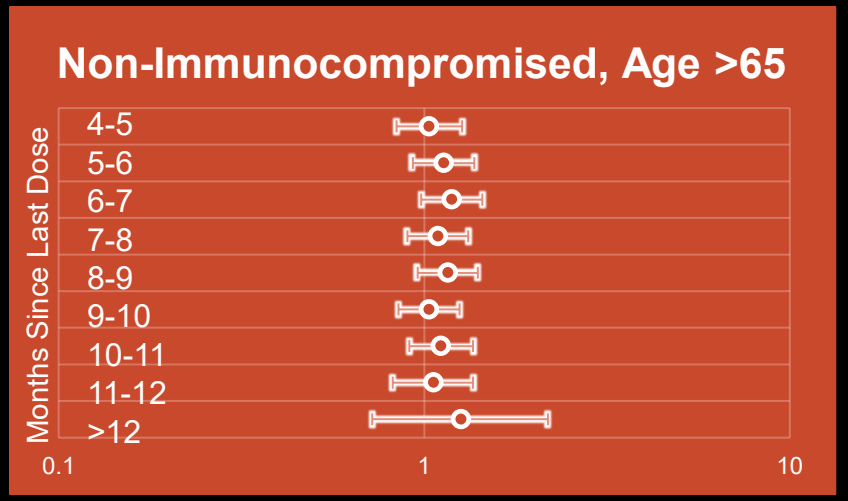


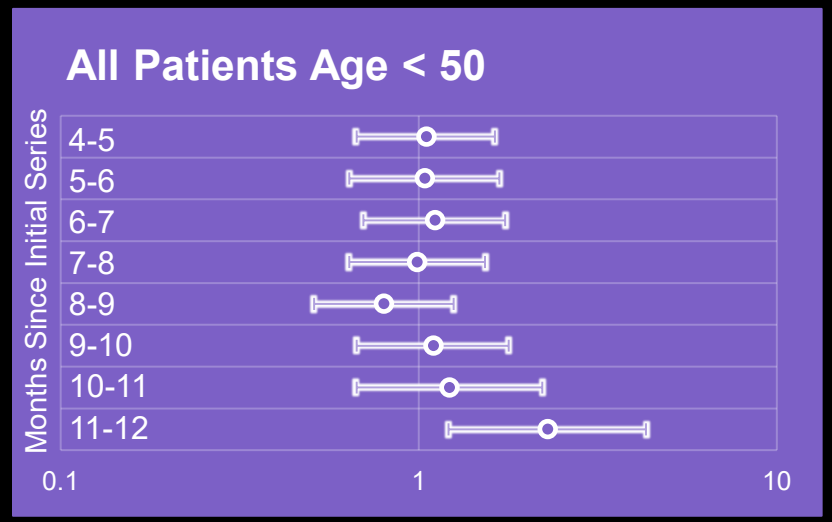
Vaccine and Booster Availability: Timeline

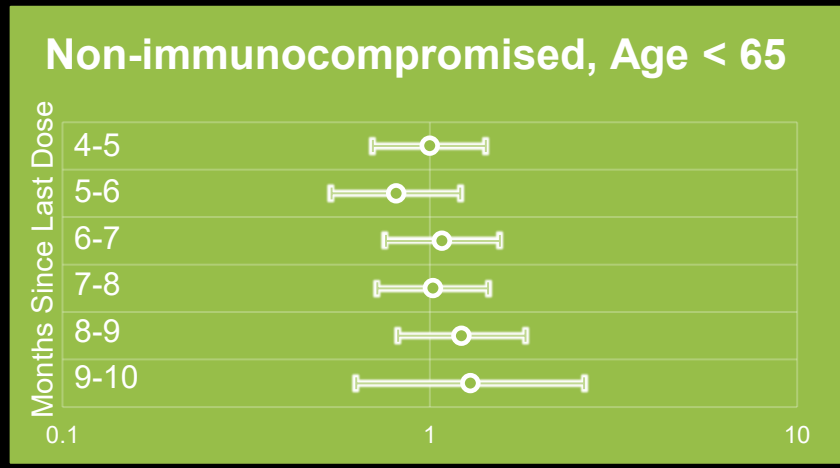


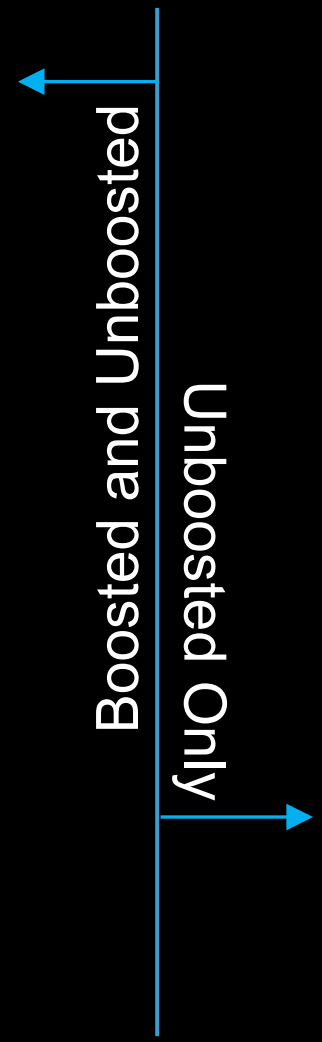
Time Since Last Vaccine Dose, Stratified by Time-Since Eligibility and Boosting





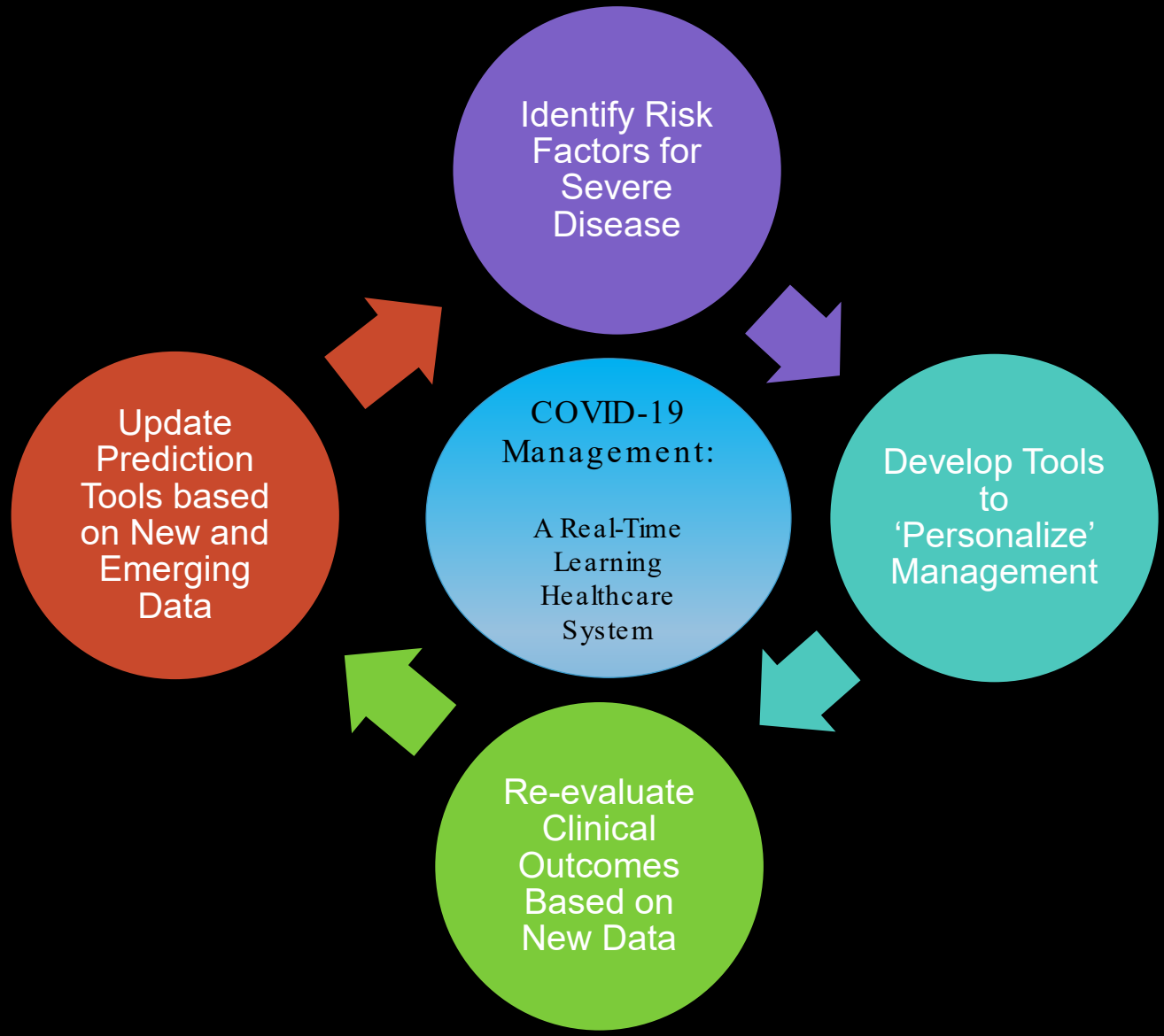






Future Directions

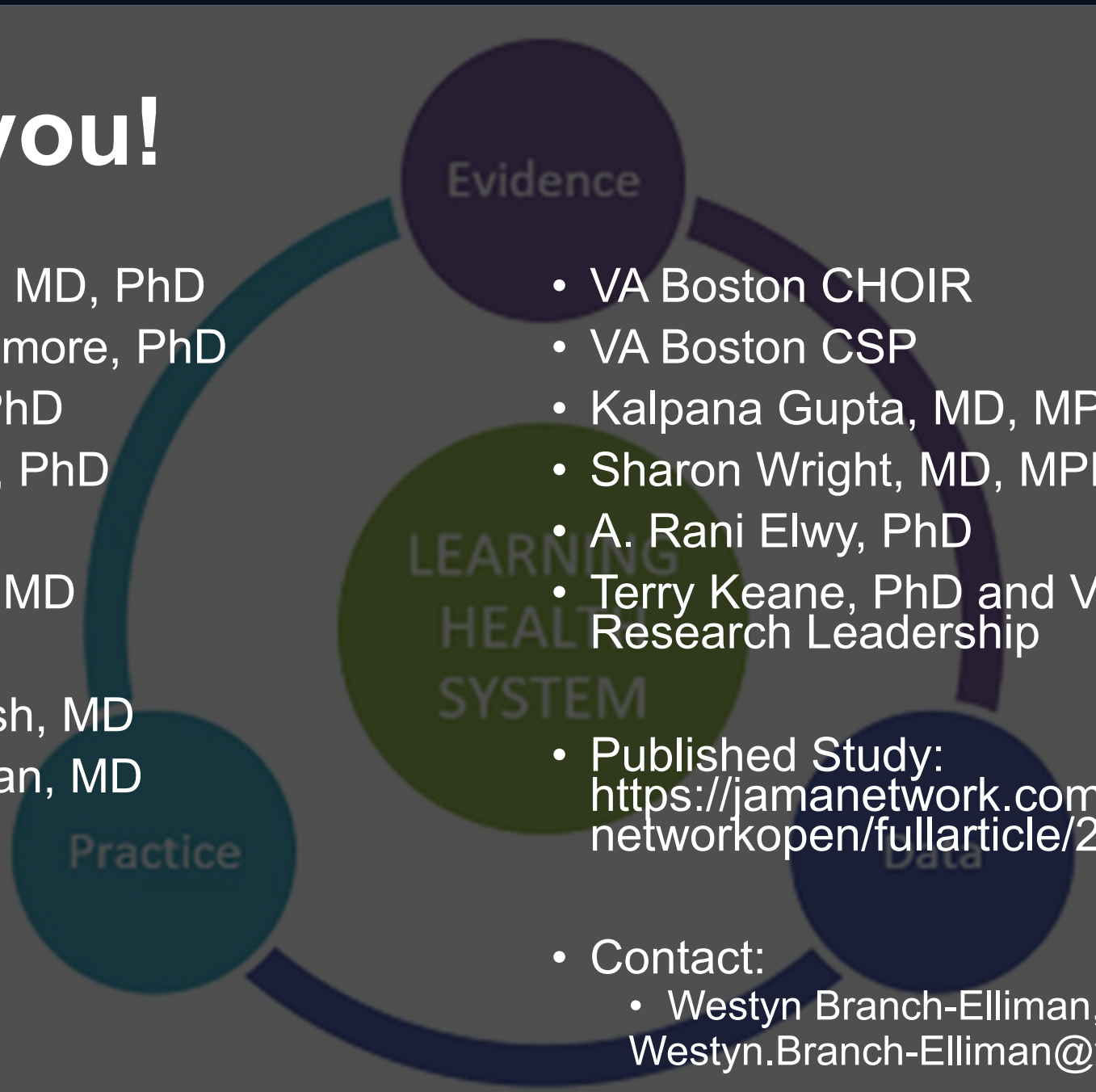
- Use machine learning model to develop patient and provider-focused web-based application that can provide individualized risk assessment
  - Will also include impacts of interventions (E.g., medication) on likely outcomes
- Automation of pipeline to collect new data and continuously train prediction model
- Continue to develop and refine prediction models as new COVID-19 variants and data emerge



Conclusions

- Identification of those who remain at high risk of severe COVID-19 despite vaccination remains an important question for informing outreach efforts and policy responses.
  - Age remains the primary risk factor for severe disease, even in the era of wide-spread availability of vaccination.
  - Receipt of immunocompromising medications are also associated with an increased risk, of a magnitude similar to a 5-10 year increase in age.
- Appropriate adjustment for indication for early vaccination is important when evaluating waning immunity against severe disease.
- Findings will be used to create a clinical decision support tool.

Thank you!



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