



Executive Summary

Project Salus provides answers to these questions

Basic questions which require data-driven answers

- Is vaccine effectiveness (VE) waning over time?
- Is VE reduced for the Delta variant?
- Does the need vary by sub-population?

- VE of both mRNA vaccines appears to wane over time in this large 5.6M US-based 65 & over vaccinated cohort
- Risk of breakthrough hospitalization increases with time elapsed since mRNA vaccination with odds ratio increasing to 2.5 at 6 months post vaccination
- VE against Delta breakthrough hospitalization (62%) exceeds VE against Delta infection (41%)
- Prior COVID-19 infection has a major protective effect against breakthrough hospitalization
- Older age groups (75-84 & 85 and older) experienced further reduction in vaccine protection against hospitalization
- Hospitalization rate (21% vs 32%) and death rate (2% vs 12%) of breakthrough infections lower than rates observed in Covid-19 cases in pre-vaccination pandemic phase in 2020

Graphic adapted from CDC Presentation ACIP Meeting August 30, 2021
Oliver, S. Framework for Booster Doses of COVID-19 Vaccines



JAIC is the US Department of Defense Joint Artificial Intelligence Center

Effectiveness of mRNA COVID-19 Vaccines Against the Delta Variant Among 5.6M Medicare Beneficiaries 65 Years and Older

Weekly update of September 28, 2021



Project Salus





Salus Platform for COVID-19 Analyses

VE Study Attributes

Cohort

20M Medicare beneficiaries nationwide with 16M individuals 65 years and older

Exposure

5.6M fully vaccinated with 2.7M Pfizer and 2.9M Moderna

Period of study

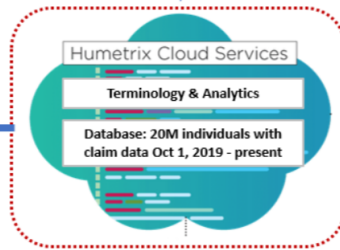
January - August 21 2021

Breakthrough Key Metrics

161K Breakthrough cases

33K Breakthrough hospitalizations

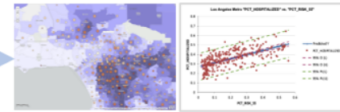
10.4K requiring ICU admissions



Other Platform Applications



Nationwide Mapping of COVID-19 Outcomes Hospitalizations, ICU, Ventilator Rx, Deaths



Disease Risk Models with Population Risk Profiling: Severe COVID-19 risk with Validation with Hospitalization Rates



Vaccination Mapping overlaid on severe COVID-19 risk



Salus Platform for COVID-19 Analyses

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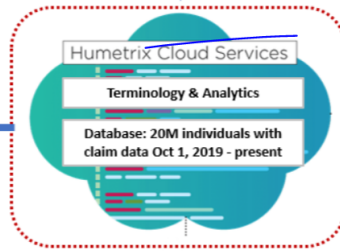
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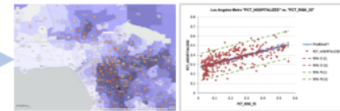
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Salus Breakthrough Analysis Methodology and Limitations

- **Breakthrough case definition:** new COVID-19 diagnosis (by COVID-19 ICD-10 code) occurring no earlier than 2-weeks post the second vaccine dose (see appendix for more details on case definition)
- **Breakthrough analysis methodology:** to estimate weekly breakthrough cases and hospitalizations we multiplied our Medicare claim-based weekly breakthrough case counts and hospitalization counts by the corresponding weekly ratio of the claims-based vaccination rate to the CDC vaccination rate to compensate for missing COVID-19 vaccination data from Medicare claim data (Medicare claims only provide ~45% of the published CDC vaccination rate in the 65 and over age group)
- **Breakthrough data limitations:**
 - Possible overestimation of breakthrough rates due to breakthroughs clinically defined with a COVID-19 diagnosis but not confirmed by PCR or antigen test (unavailable in claim data)
 - Possible overestimation of breakthrough rates due to assuming identical breakthrough rates between individuals with claim-based vaccination data and those lacking vaccination data in their claims
 - Overestimation of breakthrough rates would lead to underestimating vaccine VE against breakthrough infections and breakthrough hospitalizations



COVID-19 Case Definitions

- **COVID-19 case definition:** COVID-19 ICD-10-CM code U071 found in any claim type. Date of diagnosis based on first claim with U071. Note: 29% have either a COVID-19 PCR or antigen test in a claim.
- **COVID-19 breakthrough infection definition:** COVID-19 diagnosis more than 2 weeks after second dose of mRNA vaccine or single dose of J&J vaccine with no COVID-19 ICD-10 code U071 between first and second dose of mRNA vaccine. Note: 36% of breakthrough cases have either a COVID-19 PCR or antigen test in a claim.
- **COVID-19 hospitalization definitions:** (1) Inpatient claim with primary admitting diagnosis ICD-10-C code U071 with data of admission within 14 days after COVID-19 diagnosis or date of discharge within 10 days of post hospitalization COVID-19 diagnosis OR (2) Carrier claim with ICD10 code U071 and place of service code = 21 and date of service either 14 days after COVID-19 diagnosis or 10 days before COVID-19 diagnosis.
- **COVID-19 associated death definitions:** (1) Inpatient claim patient discharge status code = 41 (expired in facility) OR (2) MBSF file Date of Death are within 60 days of COVID-19 diagnosis. 85% of COVID-19 deaths using this definition occurred within 30 days and 72% within 20 days of COVID-19 diagnosis



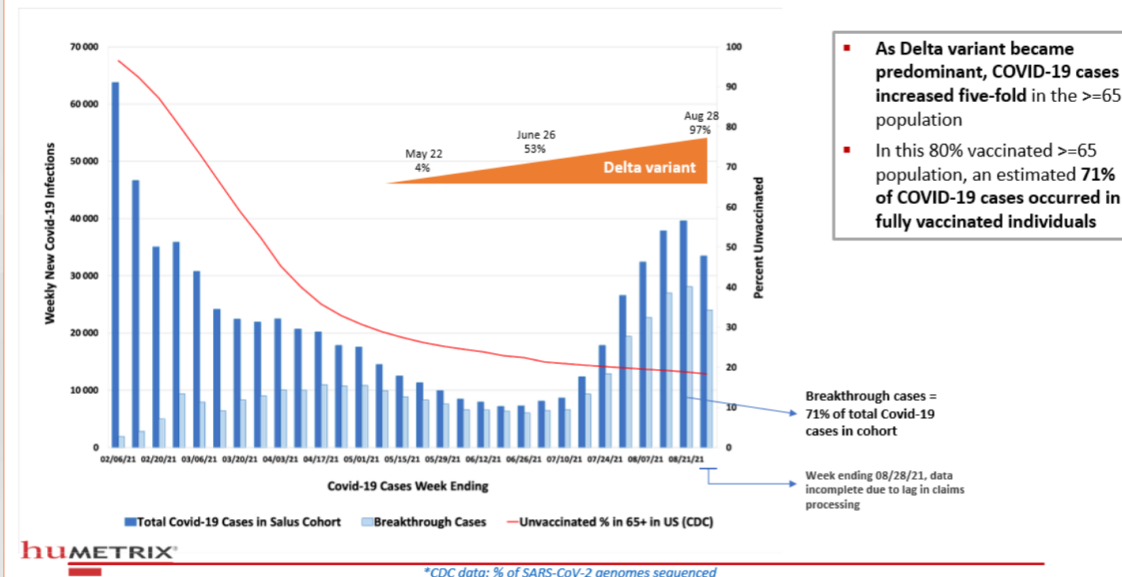
Key Breakthrough vs. Pre-Vaccination COVID-19 Metrics

Among 5.6M fully vaccine immunized Salus cohort members aged 65 and older (2.7M Pfizer and 2.9M Moderna), as of September 10, 2021:

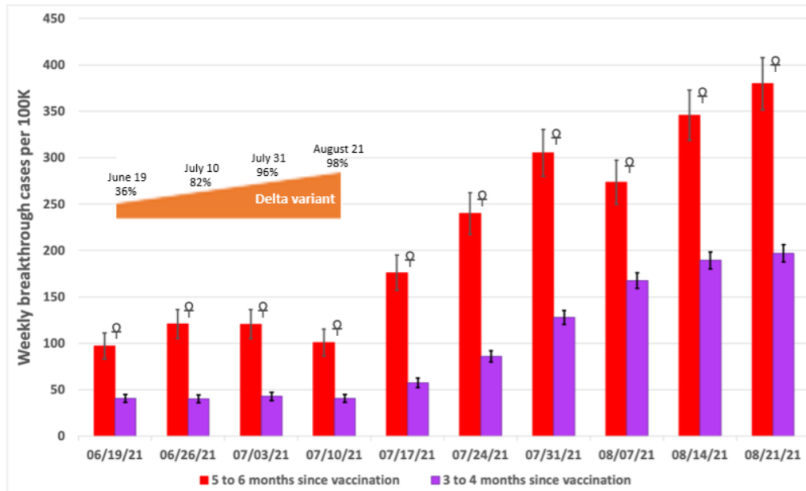
- **2.9% cumulative breakthrough rate**
- **21% hospitalization rate** in breakthrough infections, reduced by one third of 32% hospitalization rate March – December 2020
- **31% breakthrough hospitalizations include ICU care**, equivalent to 32% ICU rate March – December 2020
- **2.1% death rate** in breakthrough infections, reduced six-fold from 12% death rate March – December 2020



Total & Breakthrough Cases in the 65 Years and Older Salus Cohort



Is mRNA Vaccine Effectiveness Against Delta Breakthrough Infection Waning Over Time in 65 Years and Older Salus Cohort?



▪ Breakthrough infection rates 5-6 months post vaccination are twice as high as 3-4 months post vaccination

| 95% CI

♀ Breakthrough infection rates 5-6 months since vaccination > 3-4 months since vaccination
P < 0.001

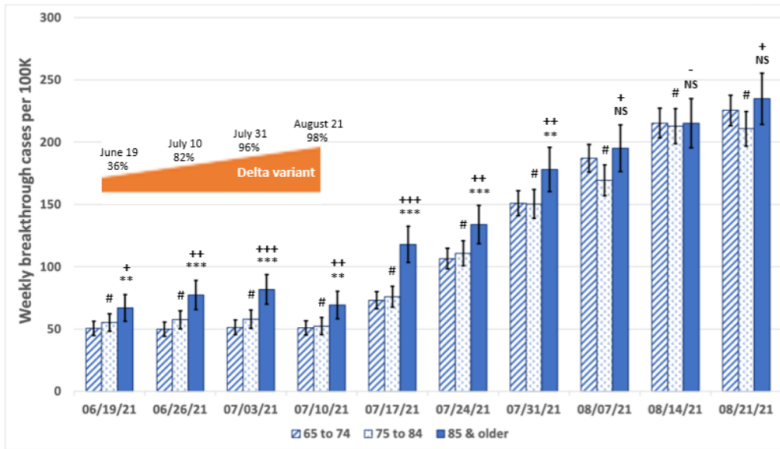
Age Distribution of Vaccinated Groups in the 65 Years and Older Cohort

Vaccinee Group		
5-6 months post vaccination		
age groups	65 to 74	24%
	75 to 84	33%
	85 & older	43%
3-4 months post vaccination		
age groups	65 to 74	51%
	75 to 84	35%
	85 & older	14%

▪ Could higher proportion of 85 years and older members in first vaccinated group explain reduced VE?



Does Age Affect Vaccine Effectiveness Against Breakthrough Infections in the 65 Years and Older Cohort?

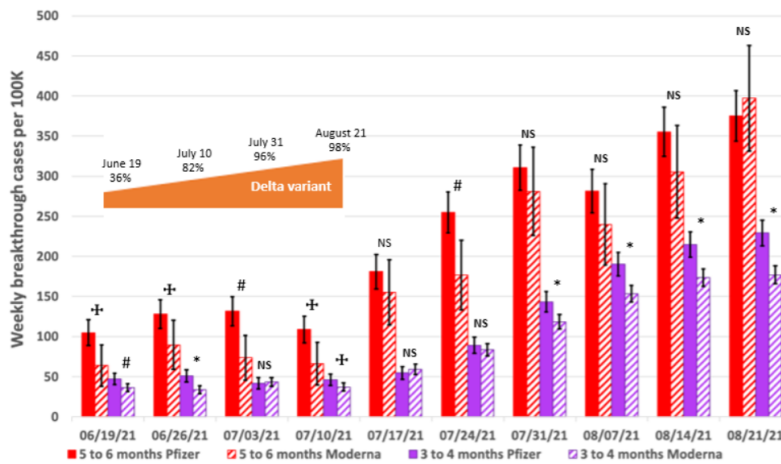


• Age has a minor contribution to the reduced vaccine protection seen in the group vaccinated 5-6 months ago

	Over 85 > 75 to 84	Over 85 > 65 to 74	75 to 84 > 65 to 74
P < 0.001	+++	***	none
P < 0.01	++	**	none
P < 0.05	+	none	none
P > 0.05	-	NS	#



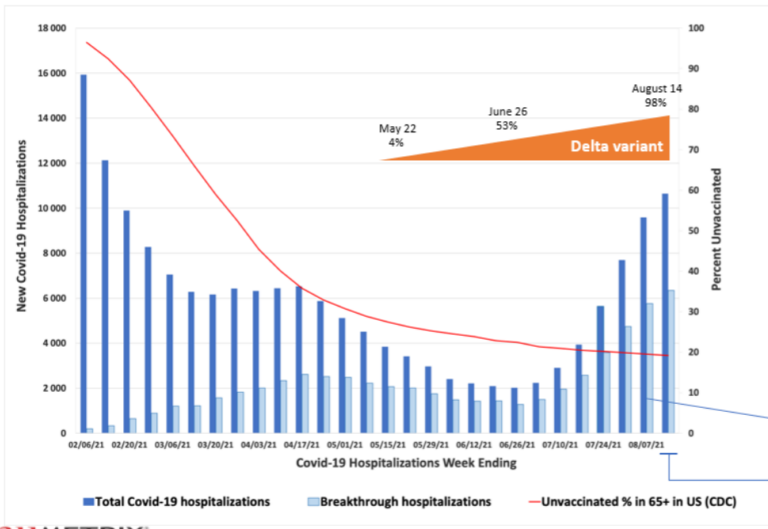
Are There Differences in Waning Effectiveness Between Pfizer-BioNTech and Moderna Vaccines in the 65 Years and Older Cohort?



▪ Waning immunity are seen with both Pfizer-BioNTech and Moderna vaccines during Delta phase of the pandemic
 ▪ Moderna vaccine offers better protection than Pfizer vaccine for individuals vaccinated 4 months prior for weeks ending after July 31

Breakthrough infection rate Pfizer > Moderna	
P < 0.001	*
P < 0.01	#
P < 0.05	+/-
P > 0.05	NS

Total & Breakthrough Hospitalizations in the 65 Years and Older Cohort

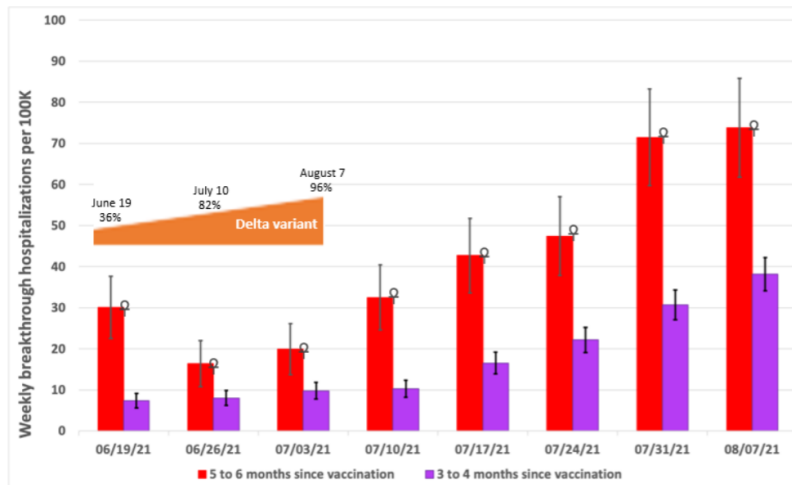


- As Delta variant surged to over 50% in June, COVID-19 hospitalizations more than doubled, reversing the prior trend of decreasing hospitalizations since April
- In this 80% vaccinated 65+ population, an estimated 60% of COVID-19 hospitalizations occurred in fully vaccinated individuals in the week ending August 7th

60% of COVID-19 hospitalizations are in vaccinated individuals

On 08/14/21, data incomplete due to lag in claims processing

Is Vaccine Protection Against Breakthrough Hospitalization Waning Over Time in the 65 Years and Older Cohort?



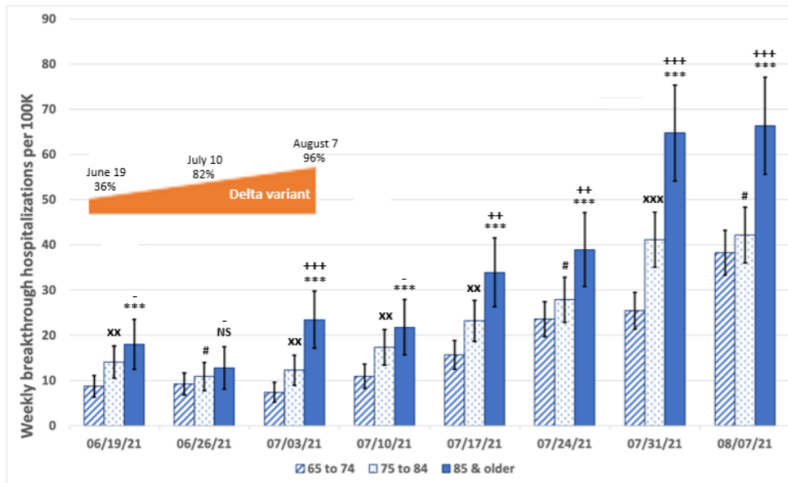
- VE against breakthrough hospitalization is significantly lower 5-6 months post vaccination than 3-4 months post vaccination

95% CI

♀ Breakthrough hospitalization rate for 5-6 months since vaccination > 3-4 months
P < 0.001



Are there Age Differences in Vaccine Protection Against Breakthrough Hospitalizations in the 65 Years and Older Cohort?



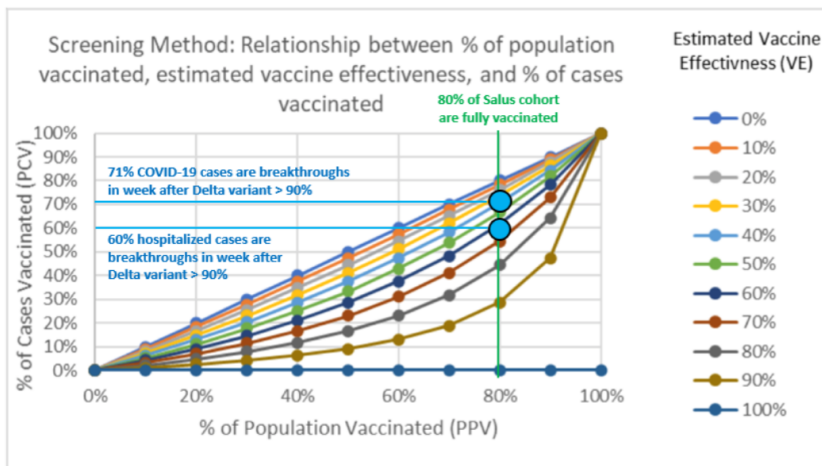
Older age associated with increased breakthrough hospitalization rates

95% CI

	Over 85 > 75 to 84	Over 85 > 65 to 74	75 to 84 > 65 to 74
P < 0.001	+++	***	xxx
P < 0.01	++	none	xx
P < 0.05	+	none	x
P > 0.05	-	NS	#



What is the Vaccine Effectiveness Against the Delta Variant in the Salus Cohort? – Using the CDC Screening Approach



41% calculated VE against infection

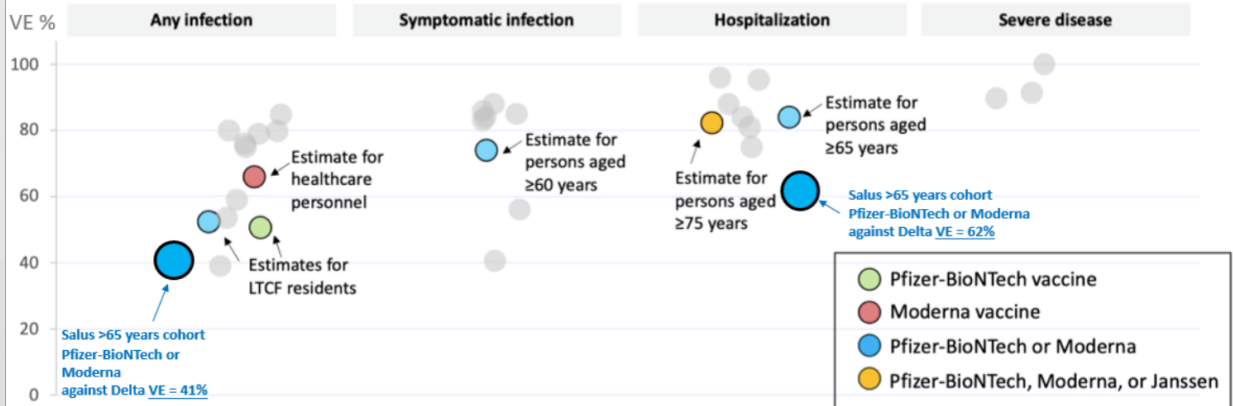
62% calculated VE against hospitalization

VE Screening method
 $VE = 1 - [(PCV / (1 - PCV)) / ((1 - PPV) / PPV)]$
 PCV = proportion cases vaccinated
 PPV = proportion population vaccinated

Graphic adapted from CDC Presentation July 30, 2021
 Improving communication around vaccine breakthrough and vaccine effectiveness



How Does mRNA Vaccine Effectiveness in 65+ Salus Cohort with 5.6M Vaccinees Compared to Published Estimates?

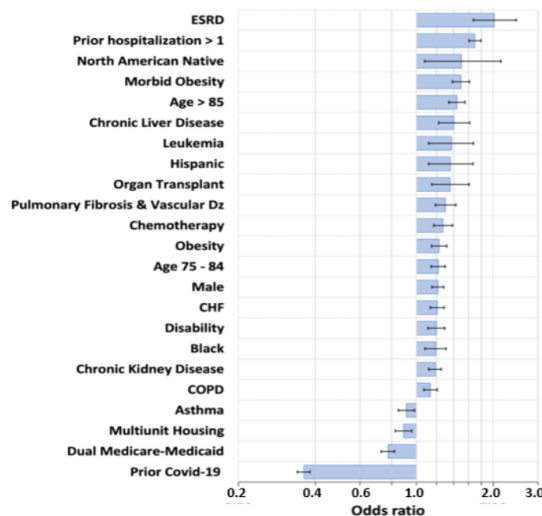


- VE of both mRNA vaccines in this 65+ cohort is lower than previously reported in smaller study sizes for both COVID-19 infection and hospitalization
- VE for mRNA vaccines is higher against hospitalization than against infection

huMETRIX® Graphic adapted from CDC Presentation ACIP Meeting August 30, 2021, Oliver, S. Framework for Booster Doses of COVID-19 Vaccines



Risk Model for Breakthrough Hospitalization



- Risk of breakthrough hospitalization increases with time elapsed since mRNA vaccination with odds ratio increasing to 2.5 at 6 months post vaccination
- Prior COVID-19 infection has a major protective effect against breakthrough hospitalization
- There is a step up in risk in the 75-84 and again in the over 85 age categories compared to the 65-74 category
- Risk model can be used to stratify the over 65 population to best select those in most need of booster vaccine dose

Logistic Regression Model performance:
AUROC 0.73, balanced accuracy 0.67