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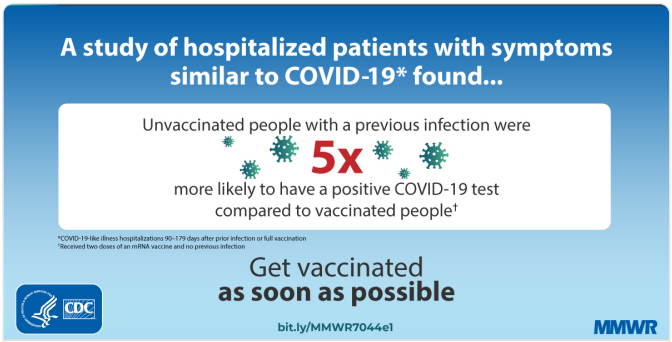

Laboratory-Confirmed COVID-19 Among Adults Hospitalized ...

This report describes mRNA COVID-19 vaccine recipients as having greater immunity from COVID-19 infection than previously infected, unvaccinated persons.

https://www.cdc.gov/mmwr/volumes/70/wr/mm7044e1.htm

This MMWR article is a confluence of methodological flaws, that amplify to serve the predetermined message of the CDC. This 🧵 will summarize my appraisals.

2a/ On a high-level, they utilize “adjusted” odds ratios to dramatize the result. The ACTUAL raw difference between PI and Vax is actually small: 8.7% PI vs. 5.1% Vax in HOSPITALIZED PATIENTS with C19-like symptoms. 3.6%. That is a SMALL difference in a very SPECIFIC population.

2b/ On ABSOLUTE TERMS this is rather small, and can easily created by subtle selection bias. If they could find 53 fewer PI infxns or 228 vax infxms out of 201, 000 eligible patients --- the ORs would “break even”.

2c/ Weirdly, authors define pop based on a hospitalization endpoint, and search bckwrds for PI vs. Vax. This is peculiar, because most other studies identify PI and Vax first, and then look forward for outcome (“longitudinal” observation). This is suspicious.

3a/ DEFINITIONS: Exposure groups are narrowly constrained. First, limited to HOSP pts only, a very small subset of sickest C19. Both PI and Vax protect against hospitalization, EXCLUDING MOST PEOPLE.

3b/Definition of exposure groups very constrained. PI group with prior infection btwn 14-90 days prior to hospitalization were excluded – the strongest naturally immune

polymerase chain reaction) performed before mRNA vaccination and ≥14 days before admission; testing performed after February 2020 was primarily within network partners' medical facilities. Adults were considered unvaccinated with a previous SARS-CoV-2 infection if no COVID-19 vaccine doses were received and if the most recent positive SARS-CoV-2 test result occurred ≥90 days before hospitalization. Adults were considered fully vaccinated with an mRNA COVID-19 vaccine with no previous documented infection if the second dose of Pfizer-BioNTech (BNT162b2) or Moderna (mRNA-1273) mRNA vaccine was received ≥14 days before the index test date[§] and if they had been tested since February 1, 2020, and had no positive test results ≥14 days before hospitalization. Patients were excluded if they had received 1 mRNA

3c/ Primary analysis looked at PI or Vax 90-179 days prior (3-6mos) Why? This avoids Pfizer's WANING tendency after 6 mos. It also biases Vax group to a more elderly population vs PI group. This will be important in "matching" the groups (more later).

4a/EXCLUSIONS: Of 201,000 hospitalized pts with C19-like illness originally identified, only 7,300 met criteria ! Only 1,020 with PI. They excluded so many people, but then derived a conclusion based on only 414 infections! A small shift in inclusions could change entire result.

4b/ Children <18 yo excluded (reasonable), but cannot apply conclusions to children. J&J also excluded, the weakest vax. If J&J was beneficial to their analysis, you KNOW they would have included it.

5a/ Matching and : The above definitions and exclusions creates a highly MISMATCHED PI and vax group. Age, geography, hospitalization period, and time from PI/Vax are all different in both groups!

Characteristic	SARS-CoV-2 infection	previous documented infection	proportion difference**
All hospitalizations with COVID-19–like illness	1,020 (100)	6,328 (100)	NA
SARS-CoV-2 test result associated with COVID-19–like illness hospitalization			
Positive	89 (9)	324 (5)	0.14
Negative	931 (91)	6,004 (95)	
Sex			
Male	405 (40)	2,905 (46)	0.13
Female	615 (60)	3,423 (54)	
Age group, yrs			
18–49	313 (31)	560 (9)	0.74
50–64	241 (24)	[illegible] (19)	
65–74	203 (20)	[illegible]7 (28)	
75–84	172 (17)	[illegible]018 (32)	
≥85	80 (8)	[illegible]28 (18)	

Characteristic	No. (column %) Unvaccinated with previous SARS-CoV-2 infection	Fully vaccinated[§] without previous documented infection	Standardized mean or proportion difference**
Site			
Columbia University	53 (5)	238 (4)	0.73
HealthPartners	22 (2)	94 (1)	
Intermountain Healthcare	117 (11)	45[illegible]	
Kaiser Permanente Northern California	254 (25)	3,614 (57)	
Kaiser Permanente Northwest	30 (3)	25[illegible]	
Regenstrief Institute	390 (38)	1,145 (18)	
University of Colorado	154 (15)	533 (8)	
Unknown	136 (13)	1,114 (18)	
Month of index test date†			
January	11 (1)	0 (—)	2.10
February	41 (4)	0 (—)	
March	114 (11)	0 (—)	
April	245 (24)	6 (0)	
May	294 (29)	235 (4)	
June	184 (18)	1,300 (21)	
July	99 (10)	2,731 (43)	
August	31 (3)	2,049 (32)	
September	1 (0)	7 (0)	

See table footnotes on the next page.

Time since either previous SARS-CoV-2 infection or full mRNA vaccination until COVID-19–like illness index test date, days			
90–119	367 (36)	3,325 (53)	0.42
120–149	353 (35)	2,107 (33)	
150–179	300 (29)	902 (14)	

5b/ Age in particular is very mismatched, with PI having a younger bias, and vax having an elderly bias. This stems from using the 90-179 day window, and the elderly were vaxed earlier.

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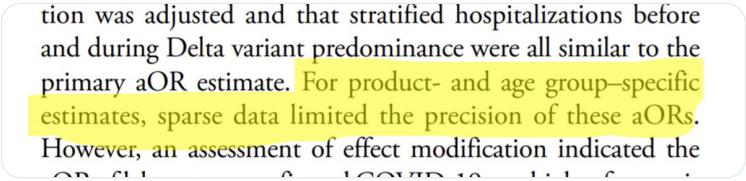
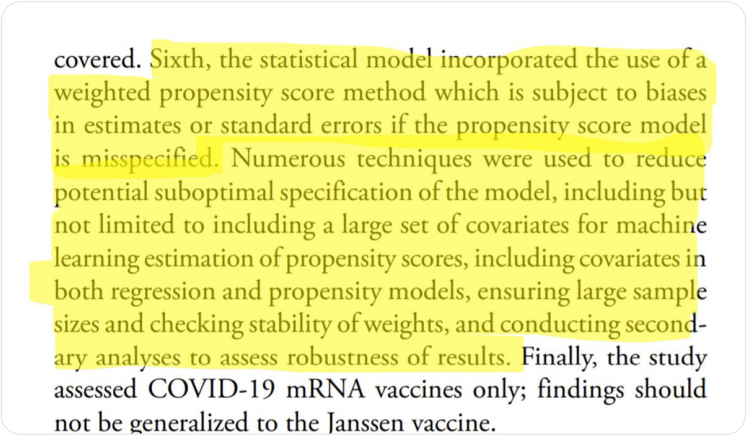
5c/ Because of these mismatches, the authors have to rely heavily on adjustment. However, the data was not robust enough to provide reliable adjustment by authors own description, particularly on age.



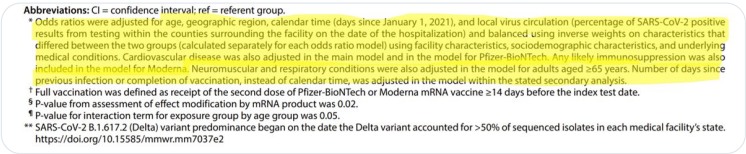
tion was adjusted and that stratified hospitalizations before and during Delta variant predominance were all similar to the primary aOR estimate. For product- and age group–specific estimates, sparse data limited the precision of these aORs. However, an assessment of effect modification indicated the

6a/ Adjustments: The authors use a "propensity score matching" method to "adjust" for above mismatches. This method is very nuanced, and can lead to wrong conclusions if misapplied. In fact, authors actually concede this too in their limitations (see fig).



covered. Sixth, the statistical model incorporated the use of a weighted propensity score method which is subject to biases in estimates or standard errors if the propensity score model is misspecified. Numerous techniques were used to reduce potential suboptimal specification of the model, including but not limited to including a large set of covariates for machine learning estimation of propensity scores, including covariates in both regression and propensity models, ensuring large sample sizes and checking stability of weights, and conducting secondary analyses to assess robustness of results. Finally, the study assessed COVID-19 mRNA vaccines only; findings should not be generalized to the Janssen vaccine.

6b/ There appears to be a lot of adjustment processes – so much so that little appears to come from SMALL NUMBERS in the actual data, and more comes from the adjusting! Of course, we never see the adjustment metadata, so it is NOT TRANSPARENT.



Abbreviations: CI = confidence interval; ref = referent group.

* Odds ratios were adjusted for age, geographic region, calendar time (days since January 1, 2021), and local virus circulation (percentage of SARS-CoV-2 positive results from testing within the counties surrounding the facility on the date of the hospitalization) and balanced using inverse weights on characteristics that differed between the two groups (calculated separately for each odds ratio model) using facility characteristics, sociodemographic characteristics, and underlying medical conditions. Cardiovascular disease was also adjusted in the main model and in the model for Pfizer-BioNTech. Any likely immunosuppression was also included in the model for Moderna. Neuromuscular and respiratory conditions were also adjusted in the model for adults aged ≥65 years. Number of days since previous infection or completion of vaccination, instead of calendar time, was adjusted in the model within the stated secondary analysis.

† Full vaccination was defined as receipt of the second dose of Pfizer-BioNTech or Moderna mRNA vaccine ≥14 days before the index test date.

§ P-value from assessment of effect modification by mRNA product was 0.02.

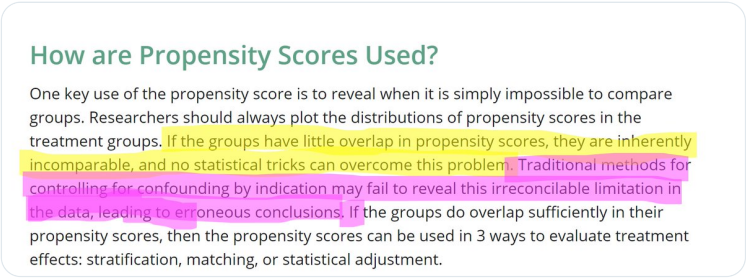
¶ P-value for interaction term for exposure group by age group was 0.05.

** SARS-CoV-2 B.1.617.2 (Delta) variant predominance began on the date the Delta variant accounted for >50% of sequenced isolates in each medical facility's state.

https://doi.org/10.15585/mmwr.mm7037e2

6c/ Apparently they correct for comorbidities, BUT never publish the differences in comorbidities in each group for reader to dissect. Large differences in comorbidities (as we would now expect) would further mismatch the groups.

6d/ https://onlinelibrary.wiley.com/doi/full/10.1016/j.pmrj.2012.07.002 If two groups are do not overlap very well, propensity score matching method can lead to erroneous conclusions.



How are Propensity Scores Used?

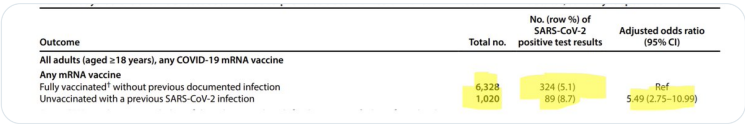
One key use of the propensity score is to reveal when it is simply impossible to compare groups. Researchers should always plot the distributions of propensity scores in the treatment groups. If the groups have little overlap in propensity scores, they are inherently incomparable, and no statistical tricks can overcome this problem. Traditional methods for controlling for confounding by indication may fail to reveal this irreconcilable limitation in the data, leading to erroneous conclusions. If the groups do overlap sufficiently in their propensity scores, then the propensity scores can be used in 3 ways to evaluate treatment effects: stratification, matching, or statistical adjustment.

6e/ We never see this complex adjustment model, for which the authors heavily rely on to achieve their top line conclusions. RED FLAG! ►►

7a/ Other biases: Vaxed people are less likely to get tested, seek medical attention, and/or get admitted. Therefore, Vaxed persons that may be infected, never make it to this analysis. Also, majority of vax comes from 1 center, vs. PI come from 7 centers.

7b/ While they grossly match time from prior infection/vaccination, there does not appear to be a direct time adjustment. Incidences are generally reported in events/person-time. Methodology seems avoid robust time methods.

8a/ Results: The top line result, is that within hospitalized patients, PI/Unvaxxed has a 5.49x odds of infection compared to Fully vaxxed.



Outcome	Total no.	No. (row %) of SARS-CoV-2 positive test results	Adjusted odds ratio (95% CI)
All adults (aged ≥18 years), any COVID-19 mRNA vaccine			
Any mRNA vaccine			
Fully vaccinated† without previous documented infection	6,328	324 (5.1)	Ref
Unvaccinated with a previous SARS-CoV-2 infection	1,020	89 (8.7)	5.49 (2.75–10.99)

8b/The absolute result demonstrates a small difference in attack rate, PI 8.7% vs. Vax 5.1% (in a hospitalized population with COVID-like symptoms). This absolute difference would likely be smaller, if included non-hospitalized patients as well.

8c/ The "odds" for PI is 91.3/8.7=10.5; for vax: 94.9/5.1=18.6. The RAW OR should be 18.6/10.5= 1.77 ; however, they report 5.49 AFTER ADJUSTMENT.

Tripling the ODDS ratio by "adjustment" seems rather EXCESSIVE. This can be explained by an unstable adjustment method.

8d/ While not as dramatic, other adjusted ORs vary quite a bit from their raw ORs. But persons AGED over >65 had an aOR of ~20x ! Age mismatch likely had a large role in adjustment.

There could be other significant adjustments, but we don't know because its not presented

8e/ Bottom line on results: While the raw results were based on small numbers within a small SELECTIVE subset, the intensive and hidden ADJUSTMENT processes based on imprecise models likely introduced ERROR.

9A/ OTHER THOUGHTS: Why did they limit analysis to PI/UnVax and Vax/Never Infected only? Based on database, they could have EASILY pulled the UnVax/Never Infected (UV/NI) group for comparison.

9B/ If they presented the UV/NI group, it would show relative differences between PI and Vax group were comparable. By only comparing PI to Vax, it focuses on small differences.

9C/ Authors conclude all pers should get vaxed, including those w/PI. They make this statement WITHOUT presenting data on vaccination effect on previously infected! This is not a scientific conclusion based on their study, but a POLICY statement.

10a/ CONCLUSION: It appears that this study was specifically designed to derive a result favorable to the CDC narrative. The design and methods are peculiar and seem constructed in a deliberate manner different than other studies on the same topic.

10b/ By looking at hospitalized patients only , then applying definitions/time filters/exclusions, created highly mismatched comparison groups. Not all mismatched variables are even presented

10c/ They then relied on an opaque and hidden adjustment process to “correct” for this mismatch, which is never presented, and cannot be directly challenged.

10d/ They focus on the small differences between PI/Unvaxxed and the Never Infected/Vaxed. They neglect presenting the NeverInfected/Unvaxed (when they easily could have) , which would likely show substantially similar protection.

11a/ FINAL THOUGHTS: It is important for a public institution, like the CDC, to provide objective scientific analysis, without any pre-determined conclusions.

11b/ When highly contorted and opaque methods are utilized instead of simple and straightforward longitudinal comparisons, it seems methods were designed to achieve the desired result.

11c/ The study populations seem highly selected, and the adjustments (which we never see) seem much stronger than the raw effect.

11d/ I hope I am wrong. I would respectfully request the @CDCgov and @CDCMMWR to fully publish their dataset, & all adjustment and propensity score models, for PUBLIC review. This is the only way we can reach an honest conclusion. Let's do what is RIGHT, not what is POLITICAL

@CDCgov @CDCMMWR 11e/ As always, thank you for reading. There is always more detail than I can include in a tweet, so apoligize for the technospeak. I am open to comments/ corrections/ concerns.