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Methodological and Ethical Concerns in a Study on Effect of COVID-19 Vaccine among Health Care Workers in a Medical College of India

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Abstract

A critical look into the nature of observational data from a study on effect of COVID-19 vaccine of health care workers points out some methodological and ethical concerns. Further analysis with relative and absolute risk reductions indicate that the effect size was lower, at times not significant and even negative when one tried to compare fully vaccinated with single dose, or tried to use person days (rather than number of health care workers) to account for differences in exposure. This, on the one hand, calls for caution in the media while reporting such results, and on the other hand, it calls for transparency and sharing of information in the public domain to facilitate wider scrutiny and informed debate.

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Conflict of Interest: None

1. Introduction

In a recent publication (Victor, et al. 2021), the effect of emergency use authorization vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to minimize or pre-empt adverse impact from coronavirus disease 2019 (COVID-19) among health care workers in a medical college of India, has been studied by comparing those who have either been vaccinated with a single dose or are fully vaccinated (that is, two weeks after second dose) with those who are unvaccinated. The comparison based on relative risk and its positive effect or relative risk reduction (additive inverse of relative risk from one) adds to our understanding. However, immediately after the availability of the uncorrected proof there was generalization of the results and its widespread dispersal in social media, (Mascarenhas 2021) (News18 2021) (The Wire Staff 2021), which is also not in sync with the policies of the medical college (Pulla 2021), and needs caution (Patnaik, Rath and Mishra 2020). The purpose of the current exercise is to point out some methodological and ethical concerns that have implications for individual and public policy decisions.

2. Material and Methods

There are two sources of data in this current exercise. One is from the recent observational study on effect of COVID-19 vaccines on health care workers in a medical college during the second wave of the pandemic (Victor, et al. 2021). From the 10,600 health care workers in the medical college, 8,991 (93.4%) received either a single or two doses of vaccination during 21 January-30 April 2021 (a 100-days period), and 1,350 (12.7%) were symptomatic and tested positive for COVID-19 during 21 February-19 May 2021 (an 88-days period) in the second wave of the pandemic. To begin with, we propose to replicate the relative risk reduction exercise. In addition, we plan to compute absolute risk reduction, compare fully vaccinated with single dose, and also normalize the relative and absolute effects for person days with some restrictive but reasonable assumptions.

Now, we further elaborate the notations and formula for calculating relative and absolute risk reductions and their confidence intervals (CIs). Let $i, j = U, V, W, F$ represent unvaccinated, vaccinated with single dose, double dose vaccinated but not completed 14 days after second dose, and fully vaccinated or those who have completed 14 days after second dose, respectively, where$i \neq j$ and i represents a higher vaccination status but we would also use i in the generic sense also. Now, if N_i and n_i (or, N_j and n_j) denote population and those suffering (or, with different levels of suffering) from COVOD-19 from that population, respectively, such that α_i (or, α_j) is the proportion of that population suffering from the ailment (or, with additional adverse health effects that might require hospitalization, oxygen therapy (O_2 Therapy), or admission in intensive care unit (ICU)) then relative risk of i over j is

(1) $r_{ij} = \alpha_i/\alpha_j.$

Relative risk reduction of i over j is,

(2) $R_{ij} = 1 - r_{ij},$

R_{ij}'s 95% confidence interval (CI) is $1 - exp^{Ln(\alpha_i/\alpha_j) \pm 1.96 * SE_{r_{ij}}}$ where $SE_{r_{ij}} = \sqrt{(1-\alpha_i)/\alpha_i N_i + (1-\alpha_j)/\alpha_j N_j}.$

Absolute risk reduction of i over j is,

(3) $A_{ij} = \alpha_j - \alpha_i.$

And, its 95% CI is $A_{ij} \pm 1.96 * SE_{A_{ij}}$ where $SE_{A_{ij}} = \sqrt{\alpha_i(1-\alpha_i)/N_i + \alpha_j(1-\alpha_j)/N_j}$.

The second source of information is daily incidence of COVID-19 in the district where the medical college is located (available at covid19india.org, as accessed on 16 June 2021) and its distribution over the 88-days period under analysis (21 February-19 May 2021) as a proxy for spread of COVID-19 among health care workers in a medical college in the district. In the absence of information on the date of their transition to their vaccination status, the distribution would also be used in indirectly computing the person days exposed or not exposed prior to being infected, which are important components in different stages of their vaccination before they reach their vaccination status that is under analysis. For instance, the fully vaccinated before being in the stage of fully vaccinated, would have passed through the stage of double dose vaccinated but not completed 14 days after second dose, and before that they would have been vaccinated with a single dose for at least a month, and prior to that they would have been unvaccinated.

For simplification, we further assume the following.

- For all those vaccinated with a single dose, we assume that the administration of the first dose was equally distributed over 30 days during 1-30 April 2021 (the last 30 days from the 100 days of vaccination under analysis). The 30 days being equally distributed, on an average, a person would be unvaccinated for 15 days during this period and also for 35 days prior to that and these two together add up to 54 person days. If not infected, they would be vaccinated with single dose for 34 person days, which includes the remaining 15 days from the 30-day period and another 19 days after that.

- For all those with two doses of vaccination, we assume that the administration of the first dose was completed before testing of symptomatic cases began on 21 February 2021 and that the administration of the second dose was equally distributed over 40 days during 21 February-1 April 2021. The 40 days period being equally distributed, on an average, a person would remain as vaccinated with single dose for 20 person days, and then after excluding two weeks or 14 person days after second dose of vaccination as a cooling-off period, the remaining 20 days and an additional 34 days or a total of 54 person days can be considered as fully vaccinated for those not infected.
- For those infected within 14 days after second dose, we assume that their infections were equally distributed, which means that they had seven person days prior to infections, and the remaining seven person days would get added to another 54 person days to give us 61 person days after infection, while 20 person days, as in the previous scenario, would be their prior status as vaccinated with single dose.

For the vaccinated with a single dose or the fully vaccinated who got infected, the 34 person days in the former case and the 54 person days in the latter case would get further dived into person days exposed (prior to infection) and not exposed (after infection) to the virus by a method, which we now elaborate.

Let $t = 1, \dots, \tau_i, \dots, T$ denote the t^{th} day during the 88-day period under analysis when symptomatic health care workers in the medical college were tested for COVID-19, τ_i is given and depends on the vaccination status, $i = U, V, F$, and , s_t is share of positive COVID-19 on t^{th} day in the district where the medical college is located from all days under analysis such that $\sum_{t=\tau_i}^{T} s_t = 1$. If a person is infected on day t then the person days exposed and not exposed would be $\theta_t = t - \tau_i$, and $\vartheta_t = T - (t-1)$, respectively. Given s_t, the values of relevance for being exposed and not exposed will be $s_t\theta_t$ and $s_t\vartheta_t$, respectively. The sum of the two series gives us, on an average, the number of person days that an infected person would have been exposed to the virus prior to their infection, $\sum_{t=\tau_i}^{T} s_t\theta_t$, or not exposed to the virus any more as they are already infected, $\sum_{t=\tau_i}^{T} s_t\vartheta_t$, respectively.

In this exercise, $\tau_U = 1$ for the unvaccinated, $\tau_V = 40$ for the vaccinated with a single dose, and $\tau_F = 15$ for the fully vaccinated, and it follows that the total number of days for each of these three categories of vaccination status will be, $\beta_i = T - (\tau_i - 1)$, that is, 88 days, 49 days, and 74 days, respectively. These days can also be divided into two sub-periods, γ_i, the sub-period during vaccination, and δ_i, the sub-period after vaccination. For the period during vaccination because of the assumption of equal distribution the average days of exposure per health care worker in the medical college will be $\gamma_i/2$, and the total number of adjusted person days for each of the three categories will be $\varphi_i = \gamma_i/2 + \delta_i$, (or, $\varphi_U = 88, \varphi_V = 34, \varphi_F = 54$) which gives us an adjustment factor, $\omega_i = \varphi_i/\beta_i$. And, with this, the adjusted number of person days that an infected person would have been exposed (prior to infection) or not exposed (post infection) to the virus will be $\omega_i \sum_{t=\tau_i}^{T} s_t\theta_t$ and $\omega_i \sum_{t=\tau_i}^{T} s_t\vartheta_t$, respectively.

3. Results and Discussion

In this we will indicate the results and discuss them and in the process raise some methodological and ethical concerns. We elucidate eleven points of concerns.

First, for 1,350 health care workers of the medical college who were symptomatic and tested positive for COVID-19 during an 88 days period (21 Feb-19 May 2021), the relative risk reductions, R_{ij}'s, computed in the study show a positive effect from those vaccinated with a single dose (0.61, 95% CI: 0.54, 0.66) or fully vaccinated (0.65, 95% CI: 0.61, 0.68) when compared with unvaccinated (Victor, et al. 2021). This is a positive result. However, using the same logic, if one compares fully vaccinated with those vaccinated with a single dose then R_{ij} result indicates a much lower positive effect (0.10, 95% CI: −0.05, 0.22), which is also not statistically significant, Table 1. This means that the health care workers who have been fully vaccinated are not necessarily better off than those who have taken a single dose of vaccination. From an ethical perspective, it is important that this result was also indicated, even if the result was somewhat counter intuitive. More so, as the vaccines administered are under emergency use authorization.

Second, if those vaccinated with a single dose are better off than the unvaccinated then why did the study exclude 33 cases of COVID-19 infection among health care workers who were infected within 14 days after receiving their second dose. If the reason is that the vaccine is only effective after 14 days of the second dose and that they might have not developed antibodies then should those vaccinated with a single dose be also considered as unvaccinated. Independent of that, even if one excludes them from a comparative exercise, in an ongoing pandemic it would add to our understanding if additional information regarding those among the 33 cases who needed hospitalization, oxygen therapy, or admission in intensive care unit would have been provided. This information even in the form of a footnote in the table would have added value.

Third, the time period for the reference population is not comparable across the three categories (unvaccinated, vaccinated with a single dose, and fully vaccinated). For instance, each unvaccinated individual has been exposed to possible infection for all the 88 days under analysis, but it is lower for the other two categories and this exposure to possible infection is also limited by those who have been infected earlier. To address this once could consider person days, which for all 10,600 health care workers after excluding 120,475 person days on account being infected and two week window after second dose gives us the total person days of possible exposure as 235,120 for the unvaccinated, 203,712 for the vaccinated with a single dose, and 373,493 for the fully vaccinated (Table 2). Now, if one calculates the revised R_{ij}'s with total person days as the reference population (as against number of health care workers) then the effect size for reducing infection for single dose (0.47, 95% CI: 0.38, 0.55) or fully vaccinated (0.02, 95% CI: −0.11, 0.13) when compared with unvaccinated is relatively lower and not significant for the latter, Table 1. Besides, the effect of fully vaccinated with single dose is now negative and significant (−0.86, 95% CI: −1.18, −0.59).

Fourth, in the calculation of person days we relied on certain assumptions and the incidence of COVID-19 infection in the district where the medical college is located (Figure 1), as we did not have access to the actual person days. Nevertheless, we have reasons to believe that our person days are likely to be underestimates for the unvaccinated (for instance, those who received their second dose had not completed their first dose by 21 February 2021 but it continued even after that), overestimates for the fully vaccinated (for instance, the second dose of the vaccine did not get completed in 40 days but went much beyond that), and can go either way for the vaccinated with a single dose. This means that the result for those fully vaccinated in comparison to the unvaccinated will further weaken, but the result for the vaccinated with a single dose in comparison to the unvaccinated could either get strengthened or weakened.

Fifth, the actual person days for each category of vaccination status are likely to differ. And, even if one gets the correct person days, they would still represent different time periods and may not be appropriate for a comparative exercise. A possible comparison could be the positive COVID-19 tests during May 2021. Further, if one has access to data with other confounding factors, one could compute hazard ratios, as has been done for health care workers in England (Hall, et al. 2021), or even explore spatial statistics to address possible interdependence (Cressie 1993). The moot point is that in matters of immense public importance, unit level micro data of these studies should be made available after anonymizing them and with appropriate safeguards for protecting privacy.

Sixth, the estimates of absolute risk reduction, A_{ij}, tell a different story, which is an important parameter for public policy decisions, as indicated in a study discussing phase 3 trials data of five COVID-19 vaccines (Olliaro, Torreele and Vaillant 2021). The effect sizes seen through A_{ij} for infections are much lower and are also negative for the fully vaccinated when compared with the vaccinated with a single dose (−0.0008, 95% CI: −0.001, −0.0007). This is also the case for the hospitalized who have required oxygen therapy (−0.06, 95% CI: −0.12, −0.003) or needed admission in intensive care unit (ICU) (−0.03, 95% CI: −0.07, 0.01) because there have been no instances of these among the vaccinated with a single dose. The absence of any hospitalization or admission in intensive care unit call for caution in interpreting the results, and this caution also holds when one would compare and point out the advantages of the vaccinated with a single dose over the unvaccinated.

Seventh, one should also be cautious in estimating and reporting of R_{ij} for the only death of a health care worker in the medical college in the entire pandemic who happened to be unvaccinated and with multiple co-morbidities, as this case of death during the study's reference period could be an outlier. It is quite possible that because of the medical condition the person was perhaps advised to or did not give consent for administration of a vaccination under emergency use authorization.

Eighth, it is possible that a health care worker is unvaccinated or has single dose because the person got infected before being administered the first or second dose, respectively. In such cases, their vaccination status has been influenced by their infection and they also should have been excluded from the exercise.

Ninth, as earlier infection could foster immunity (Radbruch and Chang 2021), information about health care workers who were infected and cured before the start of vaccination (that is, before 21 January 2021) and their current vaccination status will have implications for statistical inference (Cressie 1993).

Tenth, it is also important to note that the comparison between vaccinated (single dose or fully vaccinated) and unvaccinated health care workers in the medical college is an observational study and that it is not a randomized control trial. Besides, the study is neither single blind (each health care worker knows her status of vaccination) nor double blind (in addition to health care workers knowing their vaccination status, those who are administering and also perhaps the authors of the study know the vaccination status of health care workers). There was no prior design to the study as vaccination was being rolled out. It is a post-facto analysis of available information necessitated by the second wave that provided the opportunity for a natural experiment, which has its own merits, but calls for caution by the media while reporting these.

And, finally, somewhat related to the tenth, the authors of the paper are the Director of the medical college as lead/first author, Associate Director of the medical college as corresponding author, and all other contributing authors are either the chairperson or members of hospital infection control committee. This means that the authors, between themselves, would have not only been involved in taking the decision to vaccinate health care workers in the medical college, but would have also been involved in designing the protocols for prioritization/sequencing of vaccination among health care workers in the medical college. This means that a particular health care workers vaccination status is not an independent outcome, but dependent on the above decisions and on each other. Their interdependence would impact their statistical significance, as standard errors are likely to be higher (Cressie 1993). In any case, a study concomitant on the authors' decision as administrators on designing, prioritizing and sequencing vaccines to health care workers needs to be mentioned under conflict of interest.

4. Conclusion

To sum up, the paper raises some methodological and ethical concerns in a study on effect of COVID-19 vaccine on health care workers in a medical college during the second wave of the pandemic. It shows that the fully vaccinated are not necessarily better off than those with single dose, observes that bringing in person days (instead of number of health care workers) as a reference population lowers the positive effect and strengthens the negative effects, indicates on the limits of comparability because of different time frames for different category of vaccination status, points out the interdependence of observations that will affect statistical significance, and cautions against generalizations by the media. Further, the paper also estimates an important policy parameter of absolute risk reduction where effect sizes are much lower, suggests that the death of a health care worker with other underlying co-morbidities should have been treated as an outlier, requests further information on 33 health care workers who were infected within two weeks of second dose, specifies that infection itself can influence the status of vaccination for other categories, and also requests exploring links with prior infection for natural immunity. In the end, the paper also argues out a case for adding a caveat on administrative decisions having a bearing on the vaccination status of the health care workers.

In an ongoing pandemic, an observational study in a prestigious medical journal can have important implications for decision by individuals as also for public policy with immediate effect, which might not have been anticipated, and hence, could have unintended consequences. Hence, on the one hand, it calls for caution in the media while reporting such results, and on the other hand, it calls for transparency and sharing of information in the public domain to facilitate wider scrutiny and informed debate.

Table 1: Effects through relative risk reduction and absolute risk reduction while comparing single dose (V) and fully vaccinated (X) with unvaccinated (U) and comparing X with V among health care workers in a medical college of India during 88 days (21 Feb-19 May 2021)[a] in the second wave of the pandemic

Intervention over Earlier Status (Adverse Health Effect among Reference Population)[b]	Intervention		Earlier Status		Relative Risk Reduction (R_{ij})[c]			Absolute Risk Reduction (A_{ij})[c]		
	Health Effect (n_i)	Popula-tion (N_i)	Health Effect (n_j)	Popula-tion (N_j)	R_{ij} Effect Size	R_{ij} 95% CI Lower	R_{ij} 95% CI Upper	A_{ij} Effect Size	A_{ij} 95% CI Lower	A_{ij} 95% CI Upper
V / U-(Infected/HCWs)	200	1878	438	1609	0.609	0.544	0.664	0.1657	0.1399	0.1916
X / U-(Infected/HCWs)	679	7080	438	1609	0.648	0.608	0.684	0.1763	0.1535	0.1991
X / V-(Infected/HCWs)	679	7080	200	1878	0.099	-0.045	0.224	0.0106	-0.0050	0.0261
V / U-(Infected/Person days)[d]	200	203712	438	235120	0.473	0.377	0.554	0.0009	0.0007	0.0011
X / U-(Infected/Person days)[d]	679	373493	438	235120	0.024	-0.100	0.134	0.0000	-0.0002	0.0003
X / V-(Infected/Person days)[d]	679	373493	200	203712	-0.852	-1.168	-0.582	-0.0008	-0.0010	-0.0006
V / U-(Hospitalized/Infected)	22	200	64	438	0.247	-0.186	0.522	0.0361	-0.0184	0.0907
X / U-(Hospitalized/Infected)	64	679	64	438	0.355	0.107	0.534	0.0519	0.0121	0.0916
X / V-(Hospitalized/Infected)	64	679	22	200	0.143	-0.355	0.458	0.0157	-0.0329	0.0644
V / U-(O_2Therapy/Hospitalized)	0	22	11	64	1.000	[e]	[e]	0.1719	0.0794	0.2643
X / U-(O_2Therapy/Hospitalized)	4	64	11	64	0.636	-0.082	0.878	0.1094	-0.0004	0.2192
FV/SD-(O_2Therapy/Hospitalized)	4	64	0	22	[e]	[e]	[e]	-0.0625	-0.1218	-0.0032
V / U-(ICU/Hospitalized)	0	22	8	64	1.000	[e]	[e]	0.1250	0.0440	0.2060
X / U-(ICU/Hospitalized)	2	64	8	64	0.75	-0.132	0.945	0.0938	0.0022	0.1853
X / V-(ICU/Hospitalized)	2	64	0	22	[e]	[e]	[e]	-0.0313	-0.0739	0.0114

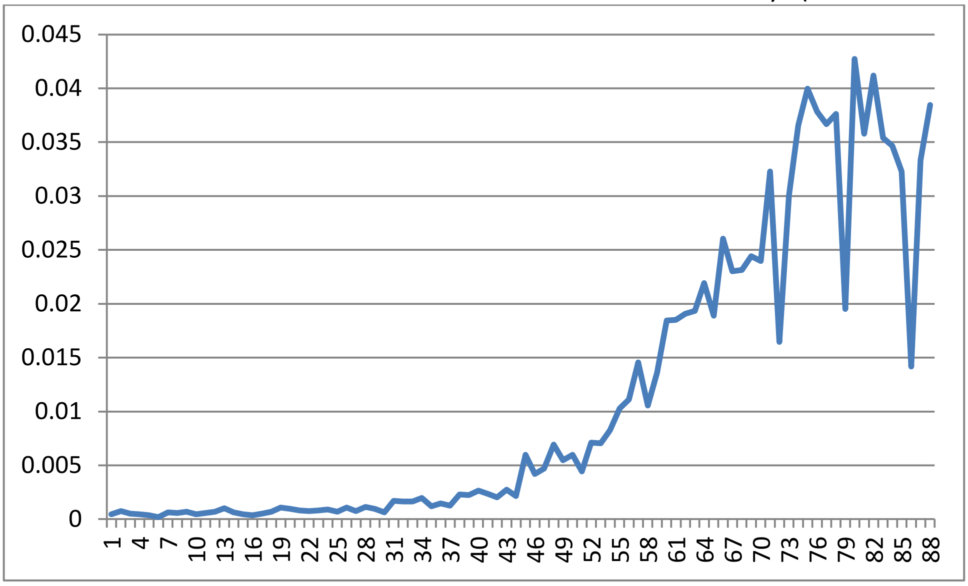
Notes: [a] The basic information were taken from an observational study in a medical college of India (Victor, et al. 2021). [b] V / U denotes intervention in single dose over earlier status in unvaccinated. Similarly, for X / U (fully vaccinated over unvaccinated) and X / V (fully vaccinated over single dose). Infected/HCWs denotes health effect in infected among HCWs (health care workers). Similarly, for infected among person days, hospitalized among infected, those requiring O_2 Therapy (oxygen therapy) among hospitalized, and need admission in ICU (intensive care unit) among hospitalized. [c] See text in material and methods for notations, formula for calculation relative risk reduction, R_{ij}, and absolute risk reduction, A_{ij}, and their confidence interval (CI). [d] Calculation of person days is discussed in material and methods and also in Table 2 and Figure 1. [e] Not calculable because for the infected among vaccinated with a single dose who were hospitalized there were no cases that required O_2Therapy or admission to ICU.

Table 2: Person days per healthcare worker (HCW) and person days by vaccination status of HCW and their stages of vaccination during 88 days (21 Feb-19 May 2021) when COVID-19 tests have been reported for HCWs in a medical college of India.[a]

Vaccination status of HCW	Number of HCWs	Stages of vaccination (person days per HCW)					
		Not yet vaccinated	After first but not yet taken second dose	After full vaccination	Within two weeks after second dose	After infection	Total
Unvaccinated, not infected	1171	88	-	-	-	-	88
Unvaccinated, infected	438	70	-	-	-	18	88
Single dose, not infected	1678	54	34	-	-	-	88
Single dose, infected	200	54	22	-	-	12	88
Two doses, fully vaccinated, not infected	6401	-	20	54	14	-	88
Two doses, fully vaccinated, infected	679	-	20	41	14	13	88
Two doses, not fully vaccinated, infected	33	-	20	-	7	61	88
Total number of HCWs/person days	10600 [b]	235120 [c]	203712 [c]	373493 [c]	99351 [c]	21124 [c]	932800 [c]

Notes: [a] The basic information were taken from an observational study in a medical college of India, (Victor, et al. 2021). For details of calculation, see material and methods in text. [b] This is the total number of health care workers. [c] For each stage of vaccination the person days per health care worker is multiplied with number of health care workers for that vaccination status and then this multiplied value is summed over vaccination status to give us the total person days for that stage of vaccination.

Figure 1: Distribution of confirmed COVID-19 cases in the district for 88 days (21 Feb-19 May 2021)



Note: Based on data available at covid19india.org (accessed on 16 June 2021). In X-axis we have $t = 1, \dots, T$ (where $T = 88$), which denotes the t^{th} day during the 88-day period under analysis. In Y-axis we have s_t, which denotes the share of infection from COVID-19 in the district where the medical college is located for the t^{th} day from the 88 days such that $\sum_{t=1}^{T} s_t = 1$.

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