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Covid-19 Vaccine Efficacy: Accuracy Assessment, Comparison, and Caveats

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Abstract

Vaccine efficacy is a key index to evaluate vaccines in initial clinical trials during the development of vaccines. In particular, it plays a crucial role in authorizing Covid-19 vaccines. It has been reported that Covid-19 vaccine efficacy varies with a number of factors, including demographics of population, time after vaccine administration, and virus strains. By examining clinical trial data of three Covid-19 vaccine studies, we find that current approach to evaluating vaccines with an overall efficacy does not provide desired accuracy. It requires no time frame during which a candidate vaccine is evaluated, and is subject to misuse, resulting in potential misleading information and interpretation. In particular, we illustrate with clinical trial data that the variability of vaccine efficacy is underestimated. We demonstrate that a new method may help to address these caveats. It leads to accurate estimation of the variation of efficacy, provides useful information to define a reasonable time frame to evaluate vaccines, and avoids misuse of vaccine efficacy and misleading information.

Keywords *confidence interval; efficacy curve; loess smoothing; time window; weekly efficacy*

1 Introduction

Vaccination is crucial in blocking fast spread of deadly infectious diseases, such as the highly contagious Covid-19, especially when effective treatment or cure of the diseases does not exist. Even if treatments are available, vaccines are still preferred for primary prevention of long term effects of the diseases. Efficacy is one of the key indices to evaluate vaccines. It measures the effect of vaccination by calculating the percentage reduction of risk of disease infection among the vaccinated subjects out of the unvaccinated in a double-blind placebo-controlled randomized clinical trial (CDC, 2000; FDA, 2020a,b).

Studies on the effectiveness of Covid-19 vaccines have reported that the effectiveness may vary with a number of factors, including subject's demographic and preclinical conditions, virus strains, and time after the vaccine administration. Feikin et al. (2022) conducted a systematic review of the duration of effectiveness of vaccines against SARS-CoV-2 infection and Covid-19 disease. Using a random-effects meta-regression model, they estimated the average change in

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vaccine efficacy or effectiveness and found a sharp decrease in 1–6 months after full vaccination. Specifically, they reported a significant decrease of 24.9 percentage points against symptomatic Covid-19 in people of all ages and a significant decrease of 32.0 percentage points in older people (50 years and older), as well as a significant decrease of 10.0 percentage points of vaccine efficacy against severe Covid-19 disease in people of all ages and a significant decrease of 9.5 percentage points in older people. On the neutralization and resistance of Covid-19 viruses, Wang et al. (2021) reported antibody resistance of SARS-Cov-2 variants. Liu et al. (2021) studied reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescence serum. Abu-Raddad et al. (2021) and Bernal et al. (2021) reported reduction of vaccine effectiveness against variants of Covid-19 viruses. Kim et al. (2022) conducted a simulation study to evaluate the interactions between the speed of distribution and efficacy against infection of multiple vaccines and to assess the level of infection attack rate when variants emerge using a comprehensive susceptible-infected-recovered-deceased model, and reported the crucial importance of distribution speed of vaccines against the emergence of new variants. Lin et al. (2022) studied the effectiveness of Covid-19 vaccines and the increase of post vaccination infection over a 9-month period in North Carolina, and found that the waning protection of the vaccines against infection over time was due to both declinining immunity and the emergence of the delta variant. Wright et al. (2022) conducted a large scale case-control study of hospitalization of Covid-19 cases from April to October of 2021 and controls in the same period of time, and reported declines of overall vaccine efficacy over time of three vaccines by Pfizer-BioNTech, Moderna, and Janssen.

It is also worthwhile to note, in particular, that the Janssen vaccine received authorization for emergency use in February 2021 by the US Food and Drug Administration (FDA) (FDA (2021a)), which was revised in May 2022 for limited use to certain individuals due to various reasons (FDA (2022a)), including adverse events, after the lift of its recommended pause in April 2021 (FDA (2021b)), though the advantage of its single shot administration over other vaccines requiring administration of two shots was favored by many people who clinically prefer fewer or no shot. Overall, solid evidence suggests declines of Covid-19 vaccine effectiveness over time. Some key questions in this regards are

1) Is such decline or variation observable in the initial clinical trials during the development of vaccines before authorization of the vaccines? To our best knowledge, no such observations have been reported in the literature.

2) If the above variation is observable in initial trials, should vaccine authorization take it into consideration? And how?

In this paper, we answer these questions and emphasize the importance from a technical point of view by examining the efficacy of those vaccines approved for Covid-19 emergency use in the US, including the vaccines developed by Pfizer-BioNTech, Janssen (Johnson & Johnson or J&J), and Novavax. We examine the variation of the efficacy using data reported in the initial clinical trials, compare their efficacy, and identify caveats of current evaluation method. We conclude that the current method using an overall efficacy may not be a good criterion for vaccine evaluation, and further suggest a multiple (weekly) efficacy approach for improved evaluation. We leave detailed procedures of the new approach in a separate paper.

2 Methods

2.1 Vaccine Efficacy and Estimation

In examining vaccine efficacy, a double-blind placebo-controlled clinical trial is often conducted, as reported by Pfizer-BioNTech, Moderna, J&J, and Novavax (FDA, 2020c,d, 2021a, 2022b). In

such trials, a moderate or large number of participants are recruited over a period of months and randomly assigned to one of two trial groups (or two arms) to ensure the comparability of subjects between groups. One group is called treatment group and its subjects receive the study vaccine. The other group is called control group and its subjects receive placebo with no generic study medication, mimicking the population in the communities who would receive no vaccine treatment. The efficacy is then calculated to be $(1 - RR)$, with RR being the risk ratio, a ratio of the disease rates of the vaccine group R_v to the control group R_u. Hence, the smaller the rate among the vaccinated relative to the unvaccinated (R_v/R_u), the higher the efficacy $(1 - RR)$ (CDC (2000)).

The Covid-19 vaccines developed by Pfizer-BioNTech, Moderna, and Novavax require two doses with 3–4 weeks in between and achieve above 94% overall efficacy. In contrast, Janssen vaccine requires a single dose and achieves above 66% overall efficacy. All these vaccines have been authorized by the US Food and Drug Administration (FDA) for emergency use (FDA, 2020c,d, 2021a, 2022b). Since Janssen vaccine requires only one dose, it may potentially offer rapid prevention against the disease more timely than the two dose vaccines in expediting mass vaccination, if it achieves a high enough level of efficacy as early as the others, making it desirable to compare vaccine efficacies based on the clinical trial data.

Choosing a vaccine based on one's preference from multiple vaccines after their approval may depend on a number of factors, including the efficacy, safety, adverse effects, and how soon the protection against infection starts. Hence a fair comparison is helpful for decision-making. The advantages of the single shot Janssen vaccine may weigh more to certain people who are more concerned about receiving vaccine shots than other factors, meanwhile adverse effects may make other people to choose vaccines with milder or lesser symptoms after the administration. While these are by all means important factors in choosing vaccines, they are personal preferences, and thus make it difficult for fair comparison. In this paper, we focus on vaccine efficacy and the time window of vaccine protection, the two important factors that all vaccines are evaluated based upon.

2.2 Study Data

To study the efficacies and compare them among vaccines, we examine the clinical data from the corresponding initial trials. For this purpose, we take the following into consideration, time after the administration of the first dose, weekly population exposure, and weekly number of cases in each trial group, derived from the reported cumulative population exposure and cumulative number of cases of each trial group.

The data in this study are obtained from publicly available briefing documents submitted to the FDA for the panel discussions as listed in Table 1. Since Moderna has reported weekly number of exposed populations, but no case counts except for a plot, analysis of its vaccine trial data is excluded from this study.

Since these clinical trials were conducted among different populations in different countries, it is difficult to make comparison adjusting for the population effects. Since the comparison needs to be made within the scope of available data, we thus treat all populations equal for the purpose of comparison, though it is not ideal. One may argue vaccine efficacy varies with population, however, the efficacy results are still valid for efficacy assessment and vaccine authorization. Albeit, these study results were examined and the vaccines received emergency authorization by the FDA with no adjustment of population effect.

Table 1: Efficacy and clincal trial data source by vaccine.

Vaccine	Efficacy (%)*	Sample size**	Page info	Briefing Document
Pfizer-BioNTech	95.0 (90.3, 97.6)	(21314, 21258)	Figure 13, P.58	FDA (2020c)
Moderna	92.1 (68.8, 99.1)	(14312, 14370)	Figure 2, P.28	FDA (2020d)
Janssen	66.7 (55.6, 75.2)	(19744, 19822)	Figure 1, P.31	FDA (2021a)
Novavax	86.1 (78.6, 90.9)	(19714, 9868)	Figure 1, P.26	FDA (2022b)

* Estimate of efficacy and 95% confidence interval
** (number of subjects in vaccine group, number of subjects in placebo group)

2.3 Statistical Methods

Although each study reported high efficacy achieved among study populations as listed in Table 1, the efficacy has been reported to vary with time, such as before and after 21 days, as discussed in the above. Often the efficacy is calculated based on the trial data starting at a certain number of days after the vaccine administration to the end of trial, with no standard time window, making it susceptible to large variation and inaccurate estimation. To address this issue, we suggest a new approach to evaluating the efficacy with a varying time window, examining its performance over time.

Since weekly data are available from all studies except for the Moderna trial, we calculate weekly efficacy for Pfizer-BioNTech, Janssen, and Novavax vaccines, ensuring comparison across vaccines within the same time windows. Two biweekly time windows are used to calculate Novavax vaccine efficacy during the last 4 weeks because no cases were reported in the control group in two separate weeks, making the corresponding weekly risk ratio to be infinity and an invalid efficacy. For the same reason, efficacies of the last week of Pfizer-BioNTech vaccine and last five weeks of Janssen vaccine were not calculated, either.

For a given week, the population exposure of the current week is calculated to be 7 days multiplied by the number of people exposed at the end of the current week, plus 3.5 days multiplied by those people who were present at the end of last week but lost before the end of the current week, including those cases reported in the current week. The biweekly population exposure is calculated to be the sum of two weekly exposures. The disease risk of vaccine group R_v and control group R_u is then calculated with the number of cases reported in the current week divided by the population exposure of the week. And the vaccine efficacy of a given week is calculated to be Efficacy $= 1 - RR = 1 - R_v/R_u$.

Each vaccine is presented with a curve of weekly efficacy starting day 7 after the first dose. An empirical estimate of efficacy is calculated to be the mean of all weekly efficacies 28 days after the first dose. An empirical variance, which is used as an estimate of the variance of vaccine efficacy, is calculated to be the sample variance of all weekly efficacies 28 days after the first dose. Its square root is the empirical standard deviation (ESD), and is used to form the empirical 95% confidence interval (CI) for the vaccine efficacy by Efficacy $\pm$ 1.96ESD, assuming independence of cases over time and normality of the weekly efficacies of each vaccine, for which the former is valid by the independence of individual study subjects and the latter can be examined with a QQnorm plot of standardized weekly efficacies, as shown in Figure 1. For the QQnorm plot, the weekly efficacies (E_t) with $t = 1, \ldots, T$ are standardized as follows with the mean efficacy $\overline{E_T}$ and the ESD

$$(E_t - \overline{E_T})/\text{ESD}\,.$$

Notice that we are evaluating the variation of the efficacy and use 1.96(standard deviation) to gauge the 95% of the weekly efficacy data, instead of constructing a 95% CI of the mean efficacy, for which the latter requires correction of the standard deviation (ESD/$\sqrt{T}$) with the square-root of the sample size T.

This approach to the efficacy estimation largely differs from the reported estimate of the vaccine efficacy, which often is calculated to be the highest possible value of efficacy by arbitrarily selecting one starting time to an ending time or the end of the study trial, for which no regulation is available, making it susceptible to misuse.

Although each weekly efficacy is an estimate of true efficacy in that week with uncertainty and a sample size varying over time, the weekly efficacies collectively constitute a sample of true efficacy over time, present an important efficacy profile along time, and need to be studied.

3 Results

3.1 Variation of Efficacy Over Time

We examine the weekly efficacy of the Pfizer-BioNTech, Janssen, and Novavax vaccines in Figure 2 based on the reported weekly number of cases and population exposure. It is shown that all three vaccines start with a low efficacy from day 7, achieve a relatively high efficacy around day 21, and then fluctuate at a relatively high level, which varies with vaccines. The Janssen vaccine efficacy stays around 66% up to 70 days following the administration and then moves up and down dramatically after that, potentially due to relatively small number of population exposure after many participants dropped out. The Novavax vaccine efficacy stays around 80% before 100 days and then varies largely after that. The Pfizer-BioNTech vaccine efficacy stays steadily around 94% through 105 days without large variation. Such variation suggests a reasonable time frame to reliably evaluate vaccines, for example, a time window of 28–105 days for Pfizer-BioNTech vaccine, 28–70 days for Janssen vaccine, and 28–98 days for Novavax vaccine. Outside the time window, especially after the window, the vaccine performance may become unstable, and possible reasons may include waning effect of vaccines due to loss of strength, for which, a booster shot may be helpful.

3.2 Reported Efficacy and Confidence Interval

We further examine the reported efficacy and 95% CI, and compare with the weekly efficacies. It is shown in Figure 2 that the reported overall efficacies are within the range of the weekly efficacies after 21 days for all vaccines, but the 95% CIs seem to be narrow, leaving a relatively large proportion of weekly efficacies outside the CI for all three vaccines, as shown in Figure 2 (a-c). This indicates that the current CI fails to reflect accurate variation of the efficacy, and needs to be corrected. Furthermore, it has been shown that the CI of vaccine efficacy for some subpopulations cannot be calculated or carry a negative confidence limit for a large and positive efficacy value due to methodological limitation (FDA, 2020c,d, 2022b). All these prompt for an alternative method to accurately estimate the variation and construct a CI of the vaccine efficacy.

We construct an empirical 95% CI using the empirical mean efficacy of all weekly efficacies 28 days and more after the first shot and the empirical standard deviation. It is shown in Figure 2 that the empirical CI contains almost all weekly efficacies, and thus serves the purpose of accurately quantifying the efficacy variation, while the reported efficacy and CI only contains

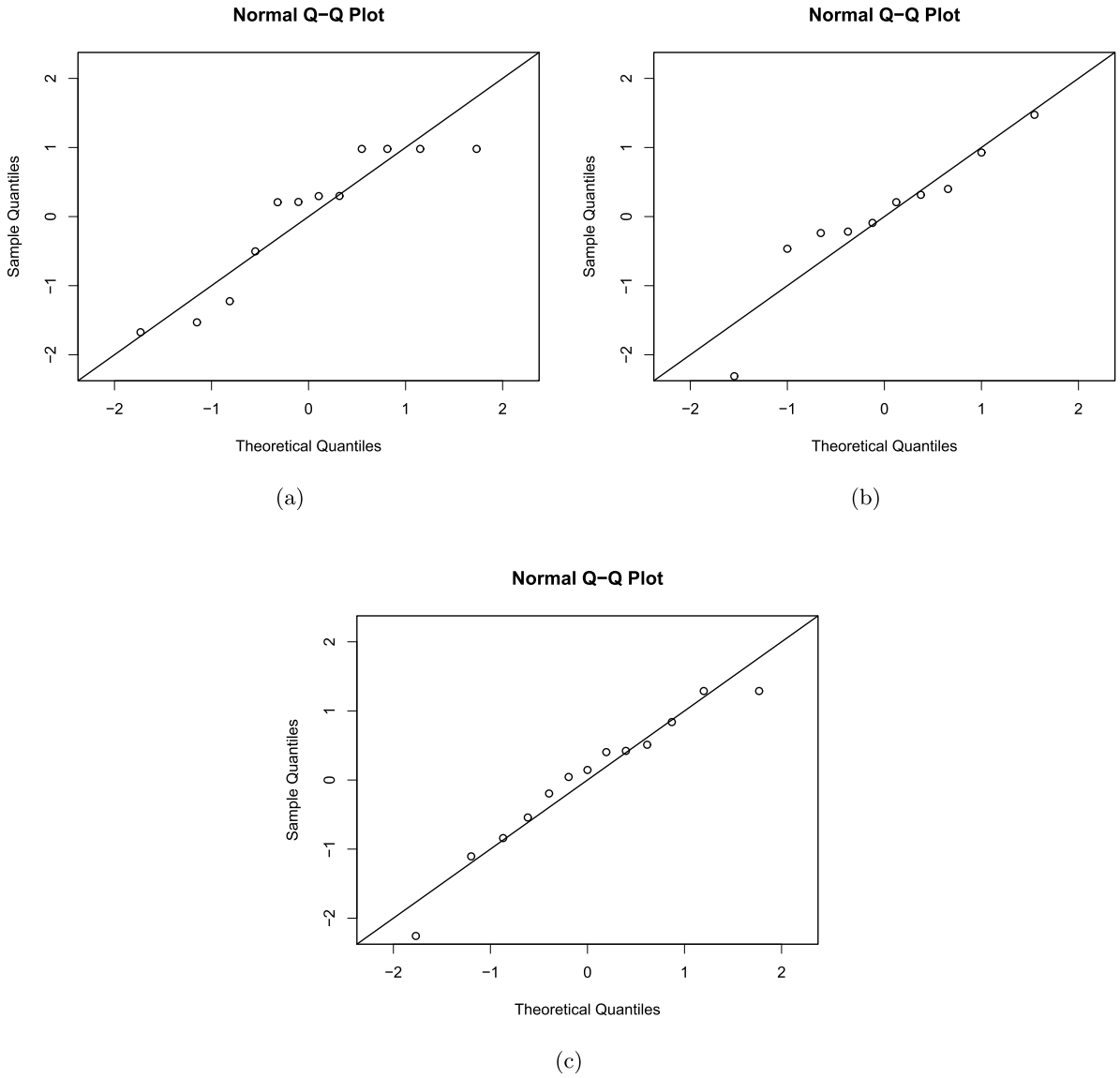

Figure 1: QQnorm plots for normality assumption of standardized weekly efficacies. (a) Pfizer-BioNTech vaccine; (b) Janssen vaccine; (c) Novavax vaccine.

a small proportion of the weekly efficacies, leaving many outside the CI. This is especially true in Figure 2 (a) and (c), for the Pfizer-BioNTech and Novavax vaccines, respectively. In contrast, Figure 2 (b) presents large variation of the weekly efficacies of the Janssen vaccine close to the end of the trial, which increases the width of the empirical CI for the overall efficacy and makes its lower bound lower than 20% ($< .20$), indicating potentially low overall efficacy.

It is also shown in Figure 2(b) and (c) that the empirical CI moves down much lower than the reported CI. This is partly due to the fact that the efficacy becomes unstable with large variability due to the drop of the population exposure and the consequently unstable small number of cases in each week close to the end of the clinical trial. The reported CI does not reflect such large variance, but the weekly efficacy approach does. Such unstable efficacy estimates close

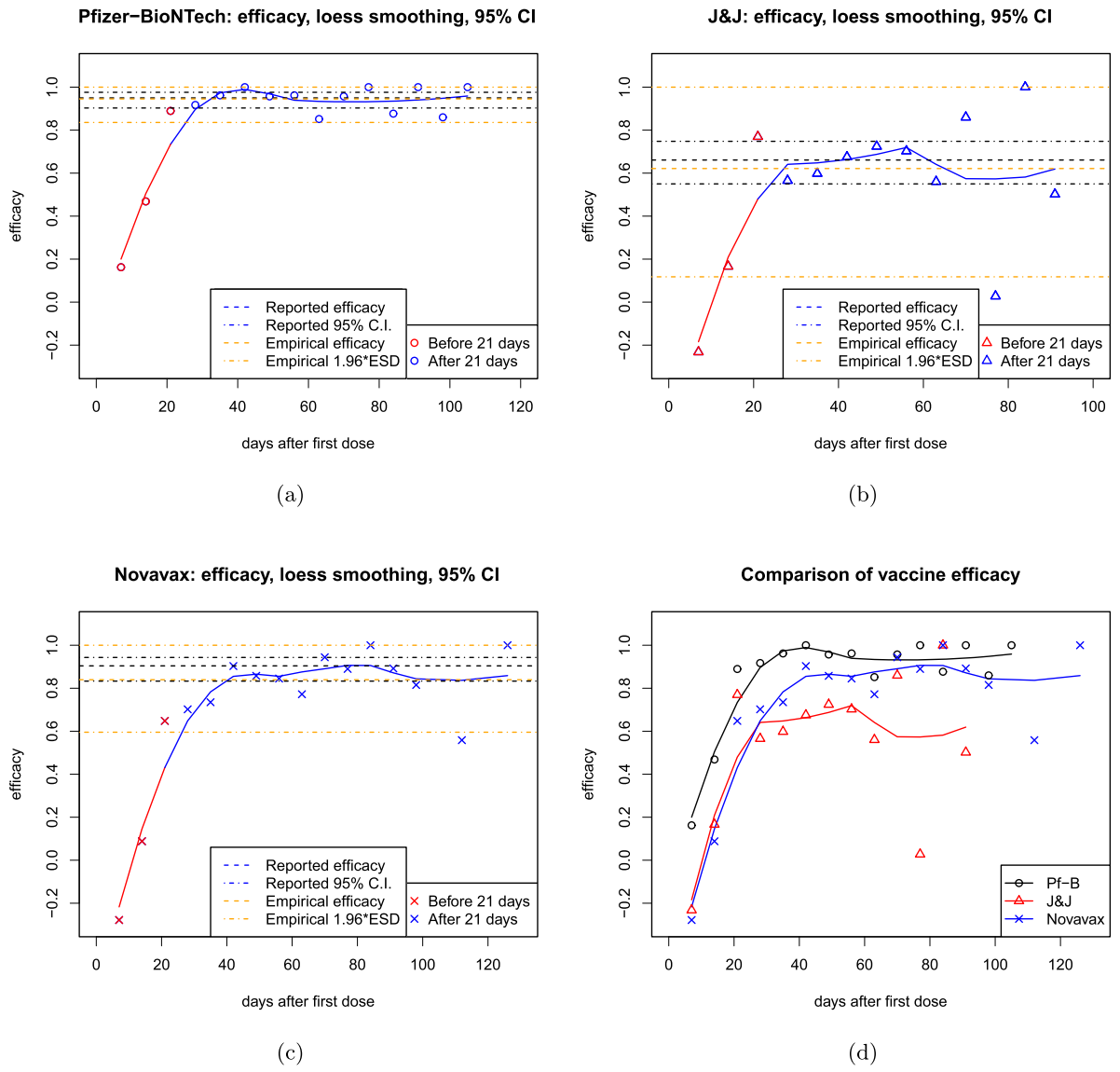

Figure 2: Weekly efficacy, loess smoothing curve, reported efficacy with 95% CI, and empirical estimate of efficacy with 95% CI (empirical estimate $\pm$ 1.96ESD). The blue dashed lines are the reported overall efficacy and 95% CI. The orange dashed lines are the empirical efficacy and 95% CI. It is seen that a relatively large proportion of weekly efficacies falls outside of the reported 95% CI. (a) Pfizer-BioNTech vaccine; (b) Janssen (J&J) vaccine; (c) Novavax vaccine; (d) Comparison of efficacies of the three vaccines.

to the end of the trial would be excluded should robust estimation of vaccine efficacy be required. To do so, a proper time window is required to be reported for the estimation, which is crucially important and needs to be considered in future work on efficacy assessment. Once a proper time window is selected, the CI may move up and become narrower, but within a shorter time window, such as 28–63 days and 28–98 days, for the Janssen and Novavax vaccines, respectively.

3.3 Comparison of Efficacy Among Vaccines

We compare the efficacies of the three vaccines by examining their weekly efficacies and loess smoothing curve in Figure 2(d). It is shown that the efficacies of all three vaccines increase fast before 28 days, then slow down and plateau (Pfizer-BioNTech, and Novavax), or even decrease slightly as in the case of Janssen vaccine. Furthermore, it is shown clearly that the Janssen efficacy is constantly lower than that of Pfizer-BioNTech and Novavax vaccines after 28 days, except for one time point, where it is greater than Pfizer-BioNTech on day 84 when the Janssen efficacy has a large variability with an unstable efficacy estimation.

Such comparison of weekly efficacy helps facilitate vaccine selection, if a selection based solely on the efficacy is desirable. Furthermore, vaccines with a short peak time, such as an overall low efficacy with a decline after the peak in a short period of time, as shown for the Janssen vaccine with a peak time from 42 to 56 days, can be easily identified by a weekly efficacy profile, and a decision is readily made and explained with ease.

3.4 Misuse of Vaccine Efficacy

Since current definition of vaccine efficacy does not have well defined time frame in which the collected data are used for efficacy estimation, it leaves room for arbitrary selection of time window for vaccine efficacy estimation and reporting, leading to potentially misleading information and interpretation.

We find that in the published Janssen clinical trial study (Sadoff et al. (2021)), two efficacies at a level above 63%, one 14 days and the other 28 days after the administration, are reported in the same table (Table 2 of Sadoff et al. (2021)) for a subpopulation of 18–59 years old participants. Given that other Covid-19 vaccines requiring second dose on 21 or 28 days after the first dose, reporting an efficacy 28 days after the administration of a single dose makes a good competitor. However, reporting in the same table side-by-side with another efficacy of above 63% after 14 days makes it more promising and an even better competitor with the earliest start of protection against the disease. But a careful examination of the data shows that it is a stretch and misleading. Why? As it no doubt leads to the interpretation that the vaccine achieves good performance of at least 63% efficacy not only 28 days after the shot, but also as early as 14 days after, and thus may offer sought-after protection. Such results of the clinical study have been praised as "a game changer" as described in Cohen (2021), which also stated "Some protection was seen as early as 14 days after the dose, and by day 28, the overall efficacy against COVID-19 cases with any noticeable symptoms was 72% among trial participants in the United States, 66% in Latin America, and 57% in South Africa".

Is the early protection starting 14 days after the administration correct? The answer is no. To ensure the extension of protection with 63% efficacy from 28 days after the single dose to as early as 14 days after, one would expect the protection is valid with the same efficacy between 14 days and 27 days. However, our calculation based on the reported weekly clinical data shows that the protection for the specific subpopulation of 18–59 years old is very low with an efficacy of 22.1% (see Table 2 for details), indicating no protection between 14 and 27 days by the FDA standard of at least 50% efficacy for the emergency authorization. This spurious high efficacy is a result of choosing arbitrary time points to calculate the efficacy by including all data after 14 days, ignoring the fact that the efficacy is extremely low between 14 and 27 days.

Had the standard of efficacy reporting required a proper time frame, or reporting weekly or biweekly efficacies, such misleading information would not be published and no misleading

Table 2: Cases, exposure (person-year) and efficacy of Janssen vaccine 14–27 days after one dose.

Category	Group	Ad26.COV2.S*		Placebo*		Efficacy
		Cases	Exposure	Cases	Exposure	(%)
Moderate – Severe	Overall	50	14.6	155	25.4	43.9
critical Covid-19	18–59 years	43	9.2	108	18.0	22.1
	$\geqslant$ 60 years	7	5.4	47	7.6	79.0

* The cases and exposures during 14–27 days were calculated with those of the period 14 days after the single dose minus those of period 28 days after in Sadoff et al. (2021).

Table 3: Comparison of empirical mean and ESD of weekly efficacies in time windows.

Vaccine	Selected time-window (days after 1st shot)	Empirical mean and SD selected time-window	Empirical mean and SD open-end window (28+ days)
Janssen	28–63 days	(0.638, 0.072)	(0.621, 0.257)
Novavax	28–98 days	(0.851, 0.089)	(0.840, 0.125)
Pfizer-BioNTech	28–98 days	(0.945, 0.056)	(0.945, 0.056)

interpretation would be made in this regards. Unfortunately, the FDA Development and Licensure of Vaccines to Present COVID-19 Guidance for Industry (FDA (2020a)) requires no time frame of clinical data for evaluation, but only specifies in part E on Statistical Consideration

> "To ensure that a widely deployed COVID–19 vaccine is effective, the primary efficacy endpoint point estimate for a placebo-controlled efficacy trial should be at least 50%, and the statistical success criterion should be that the lower bound of the appropriately alpha-adjusted confidence interval around the primary efficacy endpoint point estimate is $> 30\%$."

Furthermore, proper selection of the time window will not only make the efficacy estimate stable and reliable, but also achieve high accuracy. We illustrate with the weekly efficacy data of all three vaccines. It is shown in Figure 2(b) that the weekly efficacy of Janssen vaccine remains stable in the time window of 28 to 63 days, but unstable after 63 days. Similarly, the weekly efficacy of Novavax vaccine remains stable between 28 and 98 days, and becomes unstable after 98 days. We calculate the empirical standard deviation of the weekly efficacies in the selected time window and compare it with that of the weekly efficacy in the open-end time window from 28 days to the end of the trials. Table 3 compares the empirical mean and standard deviation in the selected time window with the open-end time window for all three vaccines. It is shown that the empirical means of the two windows do not differ much, while the empirical standard deviations are much smaller in the selected time window than the open-end time window for both Janssen and Novavax vaccines, achieving higher accuracy. Since the Pfizer–BioNTech vaccine presents stable weekly efficacy after 28 days, the selected time window covers the entire range of time, hence the empirical mean and standard deviation remain the same.

The above evidence and analysis clearly indicate the crucial importance of selecting a reliable time window of clinical data to evaluate vaccine efficacies, which helps to prevent arbitrary selection and misleading conclusion and interpretation.

4 Conclusion and Discussion

Vaccine efficacy is crucially important in evaluating candidate vaccines and decision-making for vaccine authorization. Although current vaccine efficacy has a simple and easy-to-understand form, and provides an estimate that is readily calculated with two-armed placebo-controlled clinical trial data, the facts that the efficacy varies over time and a few other factors, and its waning effect after a peak value make it less accurate to reflect true performance of vaccines.

In this paper, we examine the performance of three Covid-19 vaccines using initial clinical trial data. We have found a number of caveats in the current approach to assessing vaccine performance.

1) Vaccine performance varies over time as the protection does not stay at the same strength, indicating needs of boosting. Hence it is crucially important to consider the sustainability of the vaccine protection, and take a time frame into consideration in evaluating vaccine efficacy.

2) Current approach to evaluating vaccine efficacy does not provide a good assessment of its variation. The 95% CI aims to assess the accuracy of the mean efficacy estimate, but not the variation of the efficacy itself. It leaves a relatively large proportion of weekly efficacies outside, indicating the needs for improvement.

3) Current efficacy does not define a time frame in evaluating vaccine performance, leaving room for arbitrary choice. It is noted that though vaccines for different diseases may have different time frames for the evaluation, similar time frame should be required for a given disease. Early onset and sustained long protection are desirable and should be considered for vaccine evaluation and authorization as well. Hence, vaccine efficacy reporting needs to be standardized and regulated.

4) Misleading results on vaccine efficacy with arbitrary choice of time window should be discouraged and avoided, if all possible.

To address the above caveats of the current efficacy approach, we suggest to examine vaccine efficacy with a proper varying time window, such as weekly, biweekly, or monthly efficacies, so that accurate estimation of vaccine efficacy, its variation, and a reasonable time frame can be made and presented for proper interpretation and scientifically sound decision-making.

Supplementary Material

The datasets and R code used for this project can be found at https://github.com/Wenjiangfu/JDS-Weekly-vaccine-efficacy/blob/main/Eff_comp.R

References

Abu-Raddad LJ, Chemaitelly H, Butt AA, Vaccinati NSGC (2021). Effectiveness of the BNT162b2 COVID-19 vaccine against the B.1.1.7 and B.1.351 variants. *New England Journal of Medicine*, 385(2): 187–189. https://doi.org/10.1056/NEJMc2104974

Bernal JL, Andrews N, Gower C, Gallagher E, Simmons R, Thelwall S, et al. (2021). Effectiveness of COVID-19 Vaccines against the B.1.617.2. *(Delta) Variant. New England Journal of Medicine*, 385(7): 585–594. https://doi.org/10.1056/NEJMoa2108891

CDC (2000). *Principles of Epidemiology in Public Health Practice - An Introduction to Epidemiology and Biostatistics, 3rd ed.* Center for Disease Control and Prevention, Office of Workforce and Career Development, https://www.cdc.gov/csels/dsepd/ss1978/index.html.

Cohen J (2021). One–dose COVID-19 vaccine offers solid protection against severe disease — Johnson & Johnson candidate provides new weapon in vaccine arsenal that could significantly expand world's supply. *Science News Scienceinsider*. https://doi.org/10.1126/science.abg7115

FDA (2020a). Development and Licensure of Vaccines to Prevent COVID-19 Guidance for Industry. Food and Drug Administration, https://www.fda.gov/media/139638/download.

FDA (2020b). Emergency Use Authorization for Vaccines to Prevent COVID-19. Food and Drug Administration, https://www.fda.gov/media/142749/download.

FDA (2020c). FDA Briefing Document: Pfizer and BioNTech COVID-19 Vaccine (BNT162, PF-07302048). Food and Drug Administration, https://www.fda.gov/media/144246/download.

FDA (2020d). FDA Briefing Document: Moderna COVID-19 Vaccine. Food and Drug Administration, https://www.fda.gov/media/144434/download.

FDA (2021a). FDA Briefing Document: Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19. Food and Drug Administration, https://www.fda.gov/media/146217/download.

FDA (2021b). FDA and CDC Lift Recommended Pause on Johnson & Johnson (Janssen) COVID-19 Vaccine Use Following Thorough Safety Review. Food and Drug Administration, https://www.fda.gov/news-events/press-announcements/fda-and-cdc-lift-recommended-pause-johnson-johnson-janssen-covid-19-vaccine-use-following-thorough.

FDA (2022a). Coronavirus (COVID-19) Update: FDA Limites Use of Janssen COVID-19 to Certain Individuals. Food and Drug Administration, https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-limits-use-janssen-covid-19-vaccine-certain-individuals.

FDA (2022b). FDA Briefing Document: Novavax COVID-19 Vaccine. Food and Drug Administration, https://www.fda.gov/media/158912/download.

Feikin DR, Higdon MM, Abu-Raddad LJ, Andrews N, Araos R, Goldberg Y, et al. (2022). Duration of effectiveness of vaccines against SARS-Cov-2 infection and COVID-19 disease: Results of a systematic review and meta-regression. *The Lancet*, 399(10328): 924–944. https://doi.org/10.1016/S0140-6736(22)00152-0

Kim D, Keskinocak P, Pelin P, Yildirim I (2022). The balancing role of distribution speed against varying efficacy levels of COVID-19 vaccines under variants. *Scientific Reports*, 12: 7493. https://doi.org/10.1038/s41598-022-11060-8

Lin DY, Gu Y, Wheeler B, Young H, Holloway S, Sunny SK, et al. (2022). Effectiveness of COVID-19 vaccines over a 9-month period in North Carolina. *New England Journal of Medicine*, 386: 933–941. https://doi.org/10.1056/NEJMoa2117128

Liu C, Ginn HM, Dejnirattisai W, Supasa P, Wang B, Tuekprakhon A, et al. (2021). Reduced neutralization of SARS-CoV-2 B.1.617 by vaccine and convalescent serum. *Cell*, 184(16): 4220–4236. https://doi.org/10.1016/j.cell.2021.06.020

Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. (2021). Safety and efficacy of single-dose Ad26.COV2.S vaccine against COVID-19. *New England Journal of Medicine*, 384: 2187–2201. https://doi.org/10.1056/NEJMoa2101544

Wang P, Nair MS, Liu L, Iketani S, Luo Y, Guo Y, et al. (2021). Antibody resistance of SARS-CoV-2 variants B.1.351 and B.1.1.7. *Nature*, 593(7857): 130–135. https://doi.org/10.1038/s41586-021-03398-2

Wright BJ, Tideman S, Diaz V, French T, Parsons GT, Robicsek A (2022). Comparative vaccine effectiveness against severe COVID-19 over time in US hospital administrative data: A case-control study. *Lancet Respiratory Medicine*, 10(6): 557–565. https://doi.org/10.1016/S2213-2600(22)00042-X