Estimating real-world COVID-19 vaccine effectiveness in Israel using aggregated counts

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Abstract

The vaccination roll-out of the COVID-19 vaccines in Israel has been highly successful. By February 9th, approximately 39% of the population has already been administered at least one dose of the BNT162b2 vaccine. Efforts to estimate the true real-world effectiveness of the vaccine have been hampered by disease dynamics and social-economic discrepancies. Here, using counts of positive and hospitalized cases of vaccinated individuals, we conduct a sensitivity analysis of the vaccine effectiveness. Under conservative assumptions about possible systemic differences between vaccinating and non-vaccinating people, on the second week after the second dose we observe effectiveness of 72% in reducing SARS-CoV-2 positive cases (symptomatic and asymptomatic), 83% reduction of COVID-19 hospitalizations and 86% reduction in severe cases in 60 years and older individuals. On week 3-4 after the second dose we observe vaccine effectiveness of 95%+, however cases may still accumulate. Our analysis suggests that high effectiveness of the vaccine only starts after three weeks, which coincides with the administration of the second dose. As more granular data will be available, it will be possible to extract more exact estimates; however, the emerging evidence suggest that the vaccine is highly effective in reducing cases, hospitalizations and deaths.

Introduction

Vaccination rollout in Israel of the COVID-19 vaccines started on December 20, 2020. By February 5th, 39% and 25% of the population had already received the first dose and second dose, respectively, by the BNT162b2 vaccine developed by BioNTech and Pfizer. The vaccination campaign coincided with the beginning of a "3rd wave" of infections, and by mid-January SARS-CoV2 positive cases and hospitalizations more than doubled. To mitigate this increase in cases, on January 8 a strict lockdown was imposed. However, cases and hospitalizations did not drop as expected and as observed in previous waves. There was some frustration in the public and by government officials, and doubts were raised whether the vaccines are effective.[1]

Estimating real-world effectiveness of vaccinations is complicated compared to randomized, controlled and double-blinded clinical trial. First, in real-world there is no control group. With the protection from the vaccine cases are eliminated, and the general population incidence does not represent the incidence rate with no vaccinations. Second, in real-world there is no randomization. Israel has seen significant discrepancies between socio-economic and demographics groups in vaccination uptake.[2] Additionally, COVID-19 disproportionately stroked individuals of lower socio-economic status. Third, the real-world vaccination is not blinded. Behavioral aspects of those immunized may affect the number of encounters and chances of infection. In summary, while in the clinical trial the disease dynamics, socio-economic differences and behavioral aspects are less of an issue, in real-world, it is not possible to accurately tease out those confounding factors.

Here, using publicly available data of COVID-19 dynamics and SARS-CoV2 positive and hospitalizations of those that were vaccinated, we provide estimates using different scenarios of the effectiveness of the vaccines in reducing cases and severe cases. All data and code are available at https://github.com/dviraran/covid_analyses.

Methods

Daily SARS-CoV2 positive cases and numbers of severe or critical hospitalization were downloaded from the Israeli Ministry of Health (MOH) COVID-19 public database.[3] Number of positives cases, hospitalizations and severe or critical hospitalizations of vaccinated individuals was provided by the MOH on February 10th, 2021, for all cases up to February 9th, 2021. The counts are stratified by ages 60 years and above (60+) and below 60 years (60-), and five groups according to number of days from the vaccination – between day 0 to 13 of the first dose (group 1), between day 14 to 20 of the first dose (group 2), between day 0 to 6 of the second dose (group 3), from day 7-13 of the second dose (group 4), and from the 14+ (group 5).

To calculate vaccine effectiveness (VE), we first estimate the expected number of cases or hospitalizations (**Supplementary Figure 1**). To achieve this, we count the number of the cumulative vaccinated individuals on each day that are eligible in each group. We call this vector V. We then calculate the daily incidence rate of cases in the whole population. Naively, that is the number of cases divided by the population size. However, the daily incidence is affected by the effectiveness of the vaccine, as there are cases that are eliminated by the vaccination. The number of observed cases per day is available, and we divide that number to two sums – the number of cases from those vaccinated after the second dose ('protected') and those not vaccinated or before second dose. Those vaccinated are multiplied by 1 minus the VE. Finally, since incidence rates of the vaccinated cohort are different from the general population, we use a sensitivity parameter β to adjust for the incidence rates. Based on all this, the formula for the VE is as below:

$$(1)\ VE(g,\beta) = 1 - \frac{O(g)}{V_i \cdot d_i \cdot \beta}$$

And d_i can be calculated by S_i^1 (number of cases from 'protected' individuals and S_i^2(number of cases from all others):

$$(2)\ S_i^1(\beta, VE) = V'_i \cdot d_i \cdot (1 - VE) \cdot \beta$$
$$(3)\ S_i^2 = (H - V'_i) \cdot d_i$$
$$(4)\ S_i(\beta, VE) = S_1 + S_2$$

Where $O(g)$ is the observed number of cases in the relevant group; S_i is the number of cases on day i; V'_i is the number of vaccinated individuals after the second dose on day i; d_i is the daily incidence; VE is the effectiveness of the vaccine; β is the sensitivity parameter; and H is the population size (1,428,000 for >60 years old, 7,539,000 for <60 years old).

To solve VE we find the minimum VE that solves the following function:

$$(5)\ argmin_{VE} \left| 1 - VE(g,\beta) - \frac{O(g)}{\sum \frac{\beta \cdot S_i(\beta,p) \cdot V_i}{H + V'_i(-1 + \beta - \beta \cdot VE(g,\beta)}} \right|$$

To estimate β for each group, we hypothesized that by day 13 of the first dose, there should not be an observed effect of the vaccine.

Results

Between December 20, 2020 and February 9th, 2021, there were 3,623,573 individuals vaccinated in Israel by the first dose of the BNT162b2 vaccine, of them, 1,255,966 over the age of 60. By that date, 2,263,178 have already received their second dose of the vaccine. Of all those vaccinated, 43,889 individuals have tested positive for SARS-CoV2, 2,778 have been hospitalized due to COVID-19 and 1,911 were hospitalized with severe or critical conditions or have died (**Table 1**).

Table 1. Number of cases as reported by the Ministry of Health.

	Positive cases (>60y)	*Positive cases (<60y)*	*Hospitalization*	*Severe / critical / death cases*
1st dose, day 0-13	7,438	19,793	1,535	1060
1st dose, day 14-20	5,262	6,552	862	589
2nd dose, day 0-6	1,199	1,182	171	128
2nd dose, day 7+	1,202	779	183	118

Based on daily numbers of vaccinations and rates of general incidence we estimated expected numbers of SARS-CoV-2 positive cases, COVID-19 hospitalizations and severe cases. We correct our estimation to two confounding factors. First, the incidence rates of those that were vaccinated early are not similar to the general population, as previous analyses have shown that older populations have lower incidence and lower socio-economic groups have higher incidence.[4] Therefore, we perform a sensitivity analysis by adjusting incidence rates using different levels of beta values. Second, the general incidence rate is affected by the vaccinations, as individuals that have been vaccinated would have been infected without the vaccine. Therefore, we derived a formula to estimates the daily incidence rate by adding eliminated cases as a function of the VE (Methods).

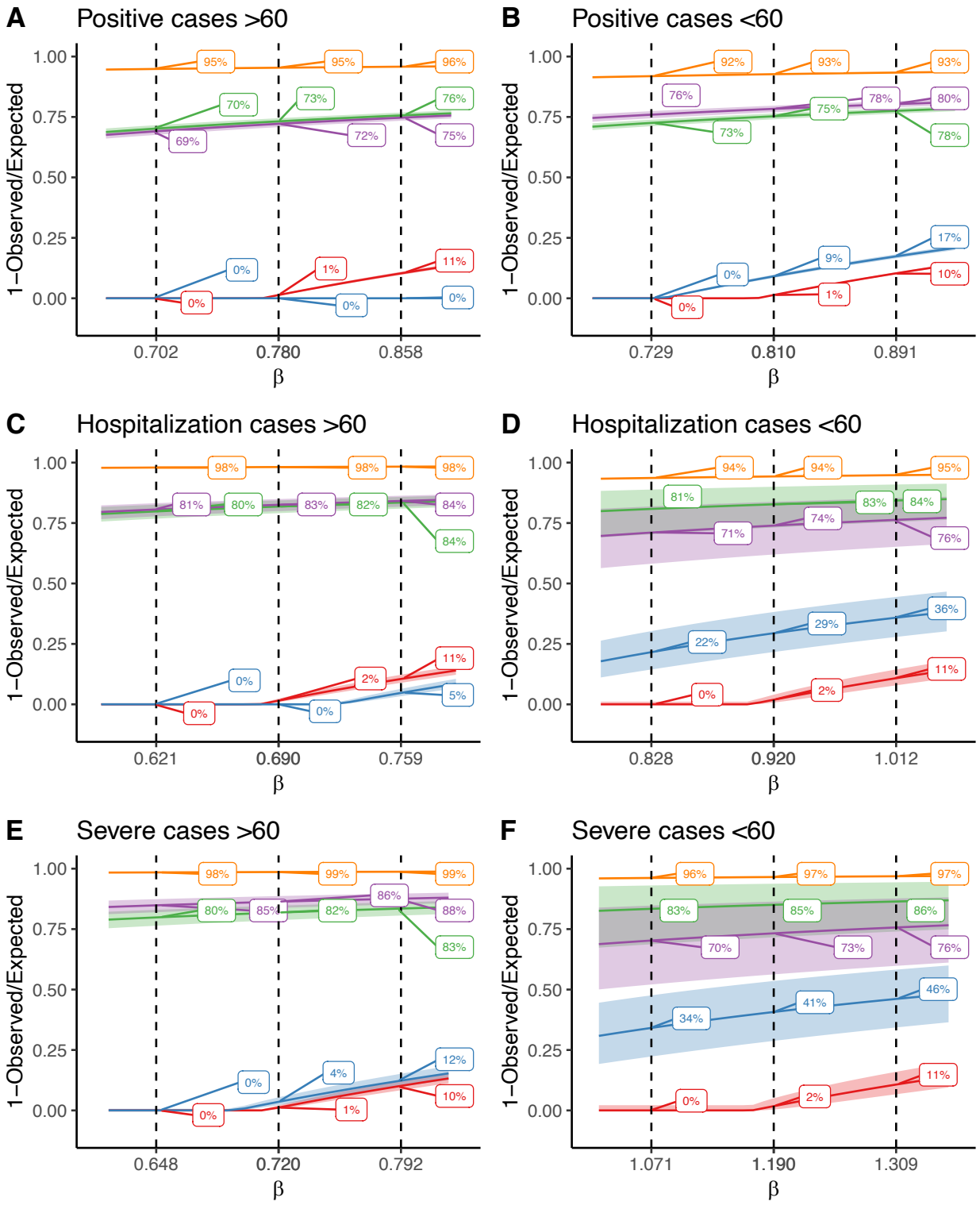

Figure 1. Effectiveness rate estimations of the vaccination by different levels of beta values. *Each plot shows the estimated effectiveness (y-axis) as a function of β. Dashed lines are for empirical β value, and +-10% from the β value. 95% Confidence intervals are in shade.*

For positive cases, which are a combination of symptomatic and asymptomatic individuals, in ages 60 years and above, we find the empirical β to be 0.78, which implies that the vaccinated population are expected to have 78% the cases of the general 60+ population. Strikingly, the analysis suggests no effect at all by day 20 of the first dose. However, on the 4th week, after the second dose, we observe a reduction of 73% in cases before day 7, 72% reduction in week 5, and 95% reduction from 14+ days and above. For individuals aged below 60 years, the empirical beta values are 0.81. Here we see reduction 75% after the second dose, 78% reduction in week 5, and 93% reduction from 14+ days and above.

Similarly, we perform the analysis for hospitalizations and severe cases, stratified by the age groups. For hospitalizations in 60+ our analysis suggests beta values of 0.69. Similarly, we do not observe any effect by day 20. After the second dose we find 82-83% reduction in hospitalizations, which increase to 98% reduction two weeks after the second dose. For severe case we estimate the β values to be between 0.72 and 4.2. Up to day 20 we find -8% to 19% reduction in severe cases, and after the second dose we observe a reduction of 82-86% in the first two weeks and 99% after day 14. It is important to note, that while positive cases may already have been counted, severe cases may deteriorate later and the number of cases is expected to increase, which in turn will reduce the estimation of the VE. In those below age 60, the number of hospitalization and severe cases have been too low for a reliable estimation, with high confidence intervals.

Discussion

The randomized clinical trial (RCT) of BNT162b2 has suggested efficacy of 95% a week after the second dose and unclear efficacy earlier.[5] It also suggested differences between the older and younger population, but with large standard errors due to relatively small sample sizes. In addition, the clinical trial was performed on a relatively small population; in contrast, by February 5th, in Israel alone 155-fold more individuals have been vaccinated compared to the trial. Therefore, real-world data effectiveness is of high interest and important for decision-makers and mobilizing individuals to get the vaccine. Our sensitivity analysis provides an estimate for the effectiveness of the vaccine in reducing positive cases, hospitalizations and severe cases. While this estimates are lower than the efficacy of the RCT, it is still substantive and provides reassurance for the vaccine efficacy.

Our sensitivity analysis provides estimate of the effectiveness of the vaccine under different scenarios. Our empirical approach to identify the beta values, which combine demographic, socio-economic and additional behavioral aspects, provides lower and upper bound estimate of the effectiveness. We report here that in the first two weeks after the second dose the VE is 72% in reducing positive cases in individuals older than 60 years, effectiveness of 78% for individuals younger than 60 years, 83-85% reduction in hospitalizations and in preventing severe cases. This numbers increase towards over 90% later on.

Our analysis suggest that the vaccine does not provide substantial protection in days 14-20 after the first dose, as we only observe substantive effectiveness in days 0-6 of the second dose, which is administered in Israel on the 21st day after the first dose of the vaccine. We cannot differentiate here between the possibility that the first dose is effective but only after three weeks, or that the vaccine is only protective following the second dose of the vaccine. However, there is some preliminary evidence to support that the single dose is effective after three weeks.[6]

In Israel, individuals may get tested for SARS-CoV-2 for any reason, not just due to symptoms. Thus, the positive cases come from both symptomatic and asymptomatic individuals. This is different from the clinical trial, where only symptomatic individuals with suspected COVID-19 where tested. It might

explain some of the difference in effectiveness we observe in Israel regarding positive cases. However, the lower effectiveness we observe for hospitalization and severe cases is alarming.

It is important to note that our estimates of effectiveness in reducing the disease should not be confused with effectiveness in reducing transmission. As noted, we cannot exclude the possibility that vaccinated individuals may still get infected by SARS-CoV-2 and stay asymptomatic or with mild symptoms and will therefore not get tested. However, other studies have shown reduction in Ct values of the PCR test due to the vaccination, suggesting lower viral load, and in turn reduced transmission.[7]

Our analysis suffers from many limitations. First, all analyses are performed on aggregated counts, which limits the possibilities to make individual-level inferences. Second, hospitalizations and severe cases may accumulate with time, as some of the patients will deteriorate later on. The number of new vaccinated individuals have been relatively low in the last week of our study, therefore this issue should not have a major effect on our estimates. Third, in Israel there is an incentive to get tested if you are required to be in isolation due to contact with an infected individual, and as noted above some asymptomatic individuals are thus identified. However, this incentive is reduced for people who are 7 days after the second dose, as the Israeli MOH regulations now exempts these people from mandated isolation. Thus, there is a difference in testing rates of asymptomatic individuals between groups. It is reassuring to see that there are relatively similar levels of effectiveness of those 7 days after the second dose to those before those 7 days, suggesting that this testing incentive has only a marginal effect. Fourth, the general population incidence is also affected by the vaccination roll-out, as more individuals are vaccinated, the incidence is expected to be affected by the vaccination; thus, the real effectiveness might be higher than our estimates.

Other attempts to identify the impact of the vaccination campaign in Israel are underway. Chodik et al. compared cases in vaccinated individuals on days 13-24 after the first dose with vaccinated individuals in days 0-12.[8] Rossman et al. used a natural experiment approach to compare early and late vaccinated cities and differences in the prioritization for the vaccine between age groups.[4] Our contribution here is the use of the general population as a control group to assess the effectiveness rather than vaccine impact.

In conclusion, this study provides estimate the effectiveness of the BNT162b2 vaccine on a population level compared to the general population. Our analysis provides strong reassurance that the vaccine is highly effective. With more data that will be shared with the public we believe that more accurate estimation can be calculated.

Data and code availability

All data is public and can be downloaded from https://data.gov.il/dataset/covid-19 or Ministry of Health press releases. Data and code used in the analyses was deposited in https://github.com/dviraran/covid_analyses. In addition, we provide an interactive shiny app, which will be updated as more data is available by the Ministry of Health - https://dviraran.shinyapps.io/VaccineEffectIsrael/.

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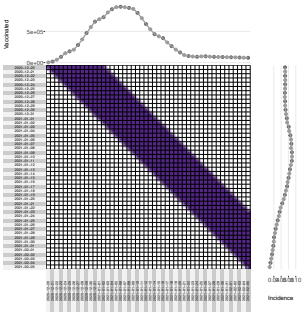
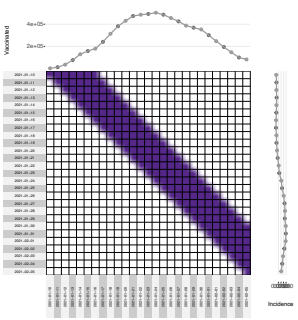
Supplementary Figures

Supplementary Figure 1. Visualization of expected case counts model. Days counted from vaccination. Columns are days of vaccination; Rows are days of possible infection. A cell is blue if the vaccinated individual is counted in the relevant group. The distribution on the top is the sum of each column (the number of vaccinated individuals that are counted for that date). The distribution on the right is the infection rate in Israel on the relevant date.

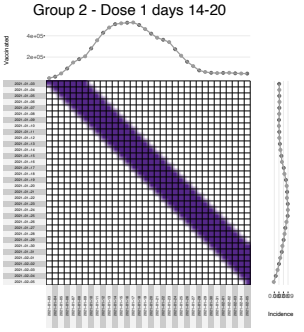
Group 1 - Dose 1 days 0-13



Group 3 - Dose 2 days 0-6



Group 2 - Dose 1 days 14-20



Group 4 - Dose 2 days 7+