The test report for an increased risk of mortality or a cardiovascular event following the corona vaccine in Israel

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1. Executive summary

Following various scientific publications, which examined whether there is an increased risk of mortality and/or cardiovascular events following the corona vaccine, and most of them did not find any connection with the exception of one single report, the Ministry of Health decided to examine this question in Israel as well. The current study focused on the question of an increased risk of mortality or a cardiovascular event in the 30 days after receiving the Pfizer vaccine (second dose) compared to the 30 days after.

The chosen research format, similar to the previous report that found an increased risk, is: controlled-Self SCCS, case series, which included all those who received a second vaccination against Corona in the period between January 11, 2021 and the end of October, 2021 and also had one of the above results. The source of the data was (a) the database of those vaccinated against COVID-19; (b) the death file; (c) the database of

The hospitalizations.

The results regarding mortality indicated a possible bias, known as the vaccinee healthy effect, which results from the fact that people who got vaccinated were relatively healthy (both empirically and in light of the guidelines) compared to those who were not vaccinated at the same time, and because of this it was not possible to determine whether or not there was an increased risk of mortality 30 day after the vaccination. The results regarding cardiovascular events close to the vaccination did not indicate an excess risk 30 days after the vaccination: the risk (odds) (in the first period (up to 30 days after the vaccination)) in relation to the second (between 31 and 60 days after the vaccination) is 0.95 (which indicates a risk lower in the first period) with a confidence interval of 95% (0.90-1.01) which is not statistically significant (p-value=0.12)

Our conclusion is that it is not possible to check in this study format an excess risk of mortality, but in relation to acute cardiovascular hospitalizations, no evidence of an increased risk was found in the time period of 30 days after the second corona vaccine compared to the time period of 31 - 60 days.

2. Introduction

Various scientific publications have referred to the possibility of cardiovascular complications or even death from these causes, in close proximity to the administration of Pfizer's and Moderna's mRNA vaccine against the new corona virus -2CoV-SARS. A French study of the self-controlled case series (SCCS) series that examined the incidence of acute cardiovascular events in the three weeks after administration of the mRNA vaccine compared to other time periods in 74-18 year olds did not find any difference [1]. Similar from Hong Kong, which focused on people with known heart disease and examined the incidence of major cardiovascular events 0 - 13 days and 14 - 27 days after vaccination

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mRNA for COVID-19, he also did not find an increased risk [2]. However, a report published by the Florida Department of Health Services [3] that focused on mortality following the corona vaccine, indicated an increase in the risk of mortality from a cardiac cause in the 28 days after vaccination compared to other time periods in those aged 18 and over (95% confidence, RI = 1.07, Incidence Relative (interval, 1.03 - 1.12 CI). The risk was observed in all age groups examined (18-24, 25-, 39-60) except for the age group 40-59 years. However, no similar increase in mortality from all causes was observed in any age group [3 [.

The Ministry of Health decided to examine the relationship between the administration of Pfizer vaccines against COVID-19 and mortality or acute cardiovascular events in Israel as well, using a similar research method. Since the breakdown of the causes of death for those who died in the years 2021 - 2022 is not yet available in Israel, we examined in this work whether among recipients of a second Pfizer vaccine dose there is an increased risk of (i) mortality from all causes; ii) An acute cardiovascular event that caused hospitalization.

3. Methods

The research format we used is called: series case controlled-self. In this research design, the study population includes only those vaccinated (with a second vaccine dose) with the desired event (death or hospitalization due to a cardiovascular event). An acute cardiovascular event was defined as an event of myocardial infarction, stroke or new thromboembolic event.

The study focused on the period between January 11, 2021 and the end of October 2021. The source of the data was (a) the database of those vaccinated against COVID-19; (b) the death file; (c) the database of

The hospitalizations.

The analysis method was based on the fact that each vaccinator in the second vaccine dose has a follow-up period of 60 days from the day of vaccination. The follow-up period is divided into 2 periods:

ÿ First period (1 - 30 days), the risk period: according to the hypothesis, it has an increased risk due to its proximity to the vaccination date.

ÿ Second period (31 - 60 days), the control period: serves as a comparison period. According to the hypothesis, the risk in this period is lower than the risk in the first period because of the distance in time from the day of vaccination.

It is possible to divide the total number of vaccinators as in Table 1. As previously stated, in this type of study only the vaccinators who had an event during the follow-up period are included, therefore all those who are in slot A (generally the majority of the population of vaccinators) are not included.

According to the null hypothesis, there is no difference in risk between the two periods, so the events will be uniformly distributed over the duration of the follow-up. Conversely, if there are more events in the first period, the alternative hypothesis that there is an increased risk of an event in the period close to the administration of the vaccine will be supported.

Table 1: Distribution of those vaccinated according to the time of the event

התפלגות	לא היה אירוע בתקופה ראשונה	היה אירוע בתקופה ראשונה
לא היה אירוע בתקופה השנייה	A	B
היה אירוע בתקופה השנייה	C	D

Only the events in slots B and C contribute information to the research hypothesis. If there are more vaccinated in slot B (event during the risk period) compared to C (event during the control period) in a significant way, the hypothesis is supported that there is a higher risk of the event in the vicinity of the vaccine. To test the hypothesis, conditional logistic regression is used when the dependent variable is dichotomous: was the event in the first period (=1) or in the second period (=0).

In events that cannot happen twice during the follow-up period, such as death, there is a certain bias in this method, since all those who were supposed to be slotted in D (events in the 2 periods), actually move to slot B (an event in the first period, which prevents the possibility of another event in the second period) But since this is a rare event, there could not have been many people in slot D anyway, even if it were possible to experience two events, so the bias is small.

An important advantage of the SCCS method is that it neutralizes possible differences between the vaccinated and non-vaccinated population as well as variables that may affect the results, such as background morbidity and behavioral differences. The actual comparison is given that the vaccinated had an event, and the estimated variable is whether the event was in the first period (the risk period) or the second (the control period).

4. Results 4.1
Mortality

All those vaccinated in two doses until the end of October 2021 (before the start of the micron wave) who died during the 60-day follow-up from the vaccination and who were not positive for corona (1815 cases) were included. Figure 1 shows the distribution of the number of deaths according to the duration of the vaccination.

Chart 1: Distribution of deaths according to the number of days from the day of vaccination
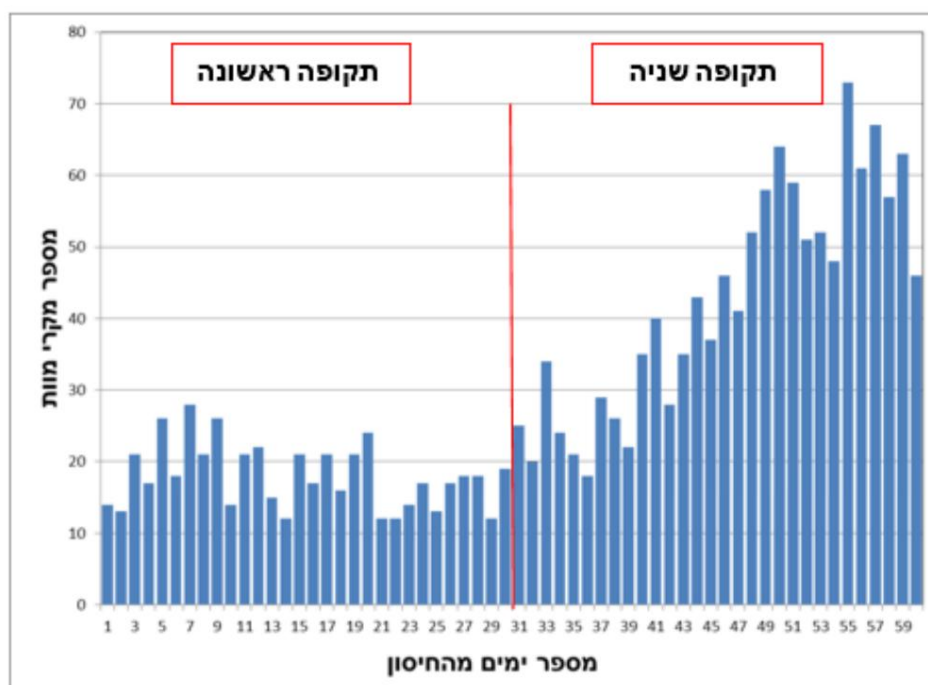
In the diagram, it appears that there are far fewer deaths in the first period (540) compared to the second period (1,275). The explanation for this phenomenon is probably related to a bias called the vaccinee healthy effect [4]. Those who get vaccinated are apparently healthier compared to the general population. People who do not feel well are hospitalized or those who are in a life-threatening condition do not come to be vaccinated, and there was even a clear directive to the public about this. Therefore, in the first days after vaccination, it is likely that we will see less mortality than usual among those who are vaccinated. Because of this bias, we could not actually prove the research hypotheses. Appendix 1 shows the distribution of mortality among the population The study is up to 200 days

from the vaccine.

4.2 Hospitalization due to an acute cardiovascular event

All vaccinators until the end of October 2021 (before the start of the micron wave) who were hospitalized due to an acute cardiovascular event (myocardial infarction, stroke, thromboembolic event) within 60 days of vaccination and who were not positive for corona (4163 cases) were included. We did not include myocarditis events because it had already been found that the vaccine increases the risk of this, especially in young men [5]. Those who had an event in both periods are considered as if they only had an event in the first period because it is likely that the event in the second period, which is adjacent to the first, is a kind of continuation of the first event. For this reason, we also did not include in the data analysis those who were vaccinated who had an event 60 days or less before the day of vaccination.

The distribution of the number of events according to the length of time since the vaccination is shown in Figure 2. On the first day there were few cases, perhaps due to the bias of healthy vaccinators as explained regarding mortality, but for a very short period of time. Therefore, for the sake of comparison, we removed the first day from the first period and at the same time - in order to balance the follow-up time - the last day from the second period.

Chart 2: Distribution of the number of cardiovascular events according to the number of days from the day of vaccination
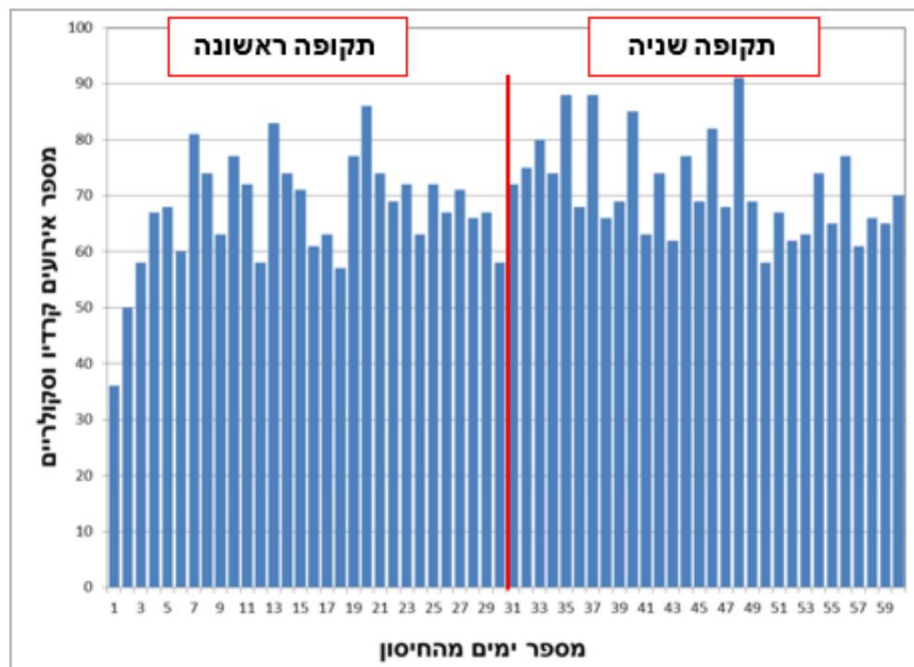
Out of 4057 cases, 1979 occurred in the first period compared to 2078 in the second. The risk (Odds) in the first period in relation to the second is 0.95 (an index that indicates a lower risk in the first period) with a 95% confidence interval (0.90 - 1.01) which is not statistically significant (p = -0.12 value). We fitted a conditional logistic regression model to test the effect of the following variables on the difference between the two periods: sex, age group (divided into 0 - 29, 30 - 59, 60 - 79 and +80) and whether there was a previous sudden cardiovascular event In the last 10 years. In addition, we controlled for the season (winter versus the rest of the year). The effects of all the above variables were not significant at a significance level of >5% (Table 2).

Table 2: The odds ratio for a sudden cardiovascular event between the first and the second time period - multiple conditional logistic regression

מובהקות	דרגות חופש	χ^2	יחס הסיכויים (OR) ורווח סמך של 95%	משתנה
0.07	1	3.24	0.89 (0.73 - 1.09)	תקופה (ראשונה לעומת שנייה)
0.68	1	0.17	1.04 (0.86 – 1.27)	עונה (חורף לעומת השאר)
0.31	3	3.61		קבוצת גיל
			1.75 (0.82 – 3.72)	0-29
			1.12 (0.95 – 1.31)	30-59
			1.00 (קטגוריית יחס)	60-79
			1.03 (0.88 – 1.21)	80+
0.63	1	0.24	1.03 (0.91 – 1.18)	מין (נשים לעומת גברים)
0.29	1	1.11	0.93 (0.81 – 1.06)	אירוע קודם בעשור האחרון

The research hypothesis was also tested stratified by age: we estimated the risk of the first period compared to the second for each age group. The findings appear in Table 3. There is no indication of an increased risk in the first period in any age group. Although in the younger age group there seems to be a high point estimate (1.7=Odds), but the numbers are very small, 20 events in the first period compared to 12 in the second period, and there is no statistical significance. Also, there seems to be a reduced risk in the first period in the age group of 60 - .79

Table 3: The odds ratio for a sudden cardiovascular event between the first and the second time period stratified by age groups - multiple conditional logistic regression

מובהקות	רווח סמך של 95%	הסיכון (Odds) בין התקופות*	קבוצת גיל
0.20	0.77 – 3.46	1.64	0-29
0.68	0.90 – 1.17	1.03	30-59
0.04	0.84 – 0.99	0.91	60-79
0.38	0.83 – 1.07	0.95	80+

* ערך גדול מ 1 מצביע על סיכון יתר בתקופה הראשונה

Sensitivity analysis

Three sensitivity tests were done. In the first, the model was adapted only to those vaccinated who did not have a heart attack in the last 10 years. In the second, the risk was examined starting from the first vaccination with a follow-up of 100 days in total (divided into two periods, each period of 50 days). In both analyzes no increased risk was found in the first period and the findings are similar to those presented in this report. From previous studies [5], an increased risk of the event was found in the first period compared to the second period, in the younger age group (the distribution is shown in Figure 4 in Appendix 2).

5. Summary

In light of the previous published studies, including the report from Florida and questions raised by the public, we tested whether there is an increase in the risk of an acute cardiovascular event requiring hospitalization after vaccination with the second corona vaccine using the series case controlled-self research method. No indication of an increased risk was found in the 30-day post-vaccination time period compared to the 31-60 day time period, nor in additional sensitivity analyses.

We also tried to check if there is an increase in the risk of mortality, but due to a built-in bias (the healthy vaccinator effect), according to which vaccinators are in a better state of health than those who get vaccinated around the time of vaccination, we could not check this.

6. References

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Appendix: 1 Distribution of mortality up to 200 days after vaccination

Figure 3 shows the distribution of the number of deaths as in Figure 1, but with follow-up up to 200 days after the
vaccination. Due to the bias resulting from the fact that those vaccinated were generally healthier at the time of
vaccination (as explained above) excess risk cannot be ruled out in the first days. In the diagram it appears that the
bias disappears approximately after 50 days. After that there are waves that do not seem suitable for a significant long-
term effect of the vaccine. Waves These are not explained by the normal seasonality of the year as estimated
from 2019. They may be related to the corona waves and the burdens on the health care system.

Chart 3: Distribution of deaths according to the number of days from the day of vaccination to 200 days
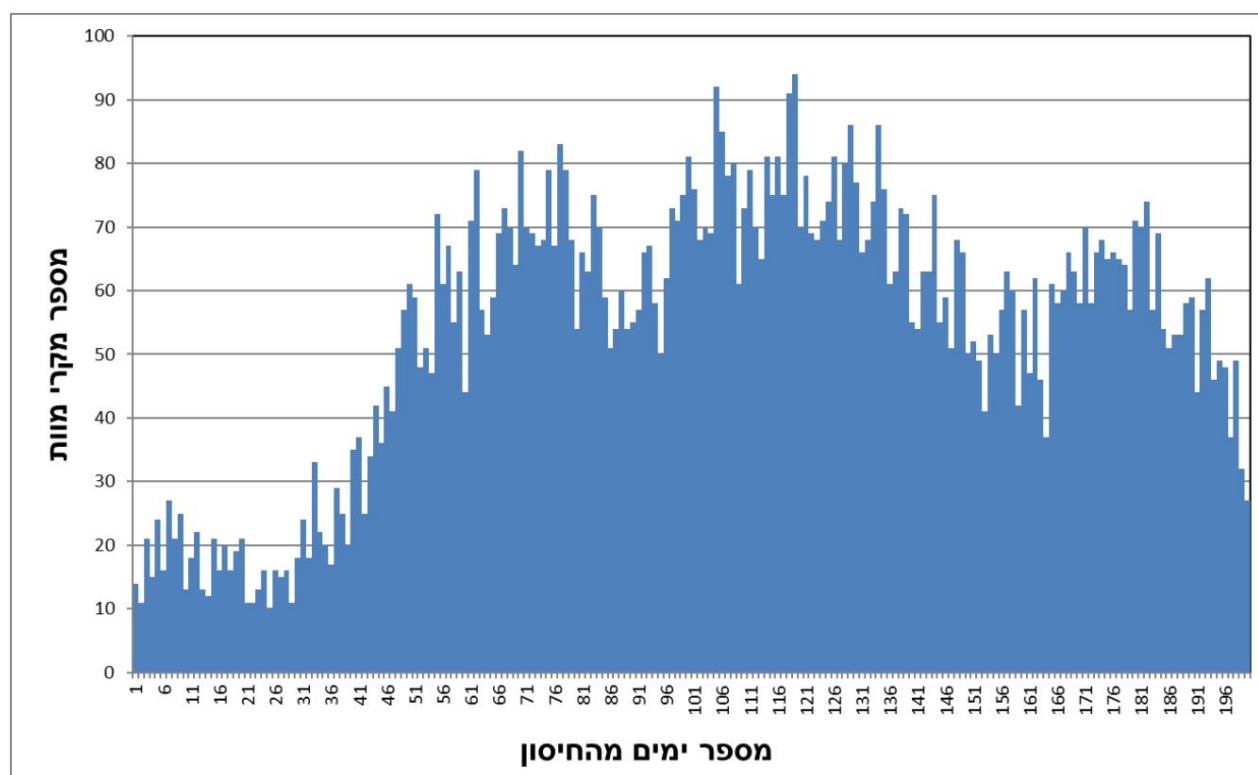
Appendix 2: The sensitivity test of the findings with the inclusion of myocarditis cases

Chart 4: Distribution of the number of cardiovascular events according to the number of days from the day

of vaccination in the younger age group