Increased Incidence of Adverse Cardiovascular Events Among Under-40 Population During COVID-19 Vaccine Rollout in Israel

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Abstract

Background: Cardiovascular adverse conditions (e.g., myocarditis, cardiac arrest, and acute coronary syndrome) can be caused by COVID-19 infections and were also reported as side-effects of the COVID-19 vaccines.

Objective: To evaluate the association between cardiac arrest and acute coronary syndrome incidents in the 16-39-year-old population, and two potential causal factors, COVID-19 infection rates and COVID-19 vaccine rollout.

Methods: This study uses a unique dataset from Israel National Emergency Medical Services, which includes all emergency calls for cardiac arrest and acute coronary syndrome events between January 1st, 2019, and June 20th, 2021. These data are combined with data on weekly counts of COVID-19 infections and administered 1st and 2nd doses of the COVID-19 BNT162b2 vaccine, to explore their association with weekly changes in the respective emergency call volume via Negative Binomial regression models.

Results: The study detected an increase of over 25% in both cardiac arrest and acute coronary syndrome calls among people of age 16-39 that occurred in Israel during the vaccination campaign (January-May, 2021), compared with the years 2019-2020. The weekly emergency call counts have statistically significant association with the rates of 1st and 2nd vaccine doses administered to this age group (adjusted incidence rate ratio: 2.12 [95% confidence interval: 1.05 to 4.22]; $P<0.05$), but are not significantly associated with COVID-19 infection rates.

Conclusions: The findings raise concerns regarding COVID-19 vaccine-induced undetected severe cardiovascular side-effects among young people and underscore the already established causal relationship between the vaccine and myocarditis. Further investigation of this relationship should be promptly pursued.

Keywords: COVID-19; BNT162b2 Vaccine; Vaccination side effects; Cardiac arrest; Acute coronary syndrome; Myocarditis; Emergency Medical Services; Health Policy

Abbreviations: CA ≡ Cardiac Arrest; ACS ≡ Acute Coronary Syndrome; VAERS ≡ Vaccine Adverse events Reporting System; CDC ≡ Center of Disease Control; IEMS ≡ Israel National Emergency Medical Services; BIC ≡ Bayesian information criterion; CI ≡ Confidence Intervals; IRR ≡ adjusted incidence rate ratios

Introduction

Cardiovascular comorbidities, such as hypertension and heart failure are associated with increased risk of severe cases of COVID-19 infections, and cardiovascular adverse outcomes, such as blood clotting, acute coronary syndrome and myocarditis were identified in COVID-19 patients(1,2). Similarly, data from self-reporting systems, including the Vaccine Adverse events Reporting System (VAERS) in the US(3), the Yellow Card System in the UK(4) and the EudraVigilance system in Europe(5), associate similar cardiovascular side-effects(6-10) with a number of COVID-19 vaccines currently in use.

More recently, several studies established probable causal relationship between the mRNA vaccines of BNT162b2 and mRNA-1273 and increased risk of myocarditis in children and young adults(8,11). The initial study originated from Israel that has one of the highest vaccination rates in the world, and currently is embarking on a campaign to vaccinate children of age 12-15. The study by the Ministry of Health in Israel assesses the risk of myocarditis after receiving the 2^{nd} vaccine dose to be between 1 in 3,000 to 1 in 6,000 in men of age 16-24 and 1 in 120,000 in men under 30(8-10).

A follow up study by the US Center of Disease Control (CDC) based on the VAERS and V-Safe reporting systems(12) further confirms these findings(13). The study estimates a 200-fold increased risk of myocarditis in young men after the 2^{nd} dose of the mRNA vaccines. The CDC has recently posted a warning regarding a vaccine-related risk of myocarditis, but still kept its recommendation to vaccinate young individuals and children over 12(4).

Assessing the connection between myocarditis and other potential cardiovascular conditions, and the COVID-19 vaccines is challenging. First, self-reporting systems(14) of adverse events are known to have biased and under reporting problems(15-17). Even the study from Israel that is based on more proactive data collection mentions that some of the potentially relevant cases were not fully investigated.

Second, myocarditis is an insidious disease that is usually asymptomatic and likely to be underdiagnosed(18,19). For example, there is vast literature that highlights frequent cases in which myocarditis is misdiagnosed as acute coronary syndrome (ACS) (20-22). Moreover, several comprehensive studies demonstrate that myocarditis is a major cause of sudden, unexpected deaths in adults less than 40 years of age, and assess that it is responsible for 12%-20% of these deaths(18,23-25). Thus, it is a plausible concern that increased rates of myocarditis among young people could lead to increase in other severe adverse events, such as cardiac arrest (CA) and ACS.

Third, the fact that COVID-19 vaccine campaigns often take place with background community COVID-19 infections, creates additional challenges. Specifically, myocarditis could result from a viral infection, an autoimmune mechanism or a toxin(18). As a result, it could be challenging to identify whether increased incidence of myocarditis and related cardiovascular conditions, such as CA and ACS is driven by COVID-19 infections, induced by COVID-19 vaccines, or perhaps caused by other underlying causal mechanisms, for example, patients delaying seeking emergent care because of fear of the pandemic and lockdowns(26).

This study aims to explore the association between CA and ACS incidents in the 16-39-year-old population, and two potential causal factors, COVID-19 infection rates and COVID-19 vaccine rollout. The study leverages the Israel National Emergency Medical Services (IEMS) data system and analyzes all calls related to CA and ACS events over two and half years, from January 1st, 2019, throughout June 20th, 2021.

Methods

Study design

This retrospective population-based study aims to explore the association between CA and ACS incidents in the population of age 16-39, and two potential causal factors, COVID-19 infection rates and

COVID-19 vaccination rates. The study leverages the IEMS data system and analyzes all calls related to CA and ACS events over two and half years, from January 1st, 2019, to June 20th, 2021. The IEMS call data are coupled with data on COVID-19 infection rates, as well as the respective vaccination rates over the same period of time.

The study's time period spans 14 months of a 'normal period' prior to the COVID-19 pandemic and vaccine rollout, about 10 months of a 'pandemic period' with two waves of the pandemic, and about 6 months of a 'pandemic and vaccination period', during which Israel launched its vaccination campaign parallel to a third wave of the COVID-19 pandemic. Thus, it allows to study how CA and ACS call counts change over time with different background conditions and potentially highlight factors that are associated with the observed temporal changes.

This study was deemed exempt from review by the Massachusetts Institute of Technology Institutional Review Board. The study was also approved by the research committee of the IEMS.

Data sources and study population

CA and ACS call data

The IEMS data system includes records of all the calls received through the Israel's national emergency telephone number (1-0-1). Note that the IEMS is a national organization that manages all EMS calls in Israel. Each record contains multiple fields of information, including the retrospective verified call-type as determined by the EMS team, date, relevant response characteristics (e.g., if resuscitation was required during the response), and the patient's age and gender.

The study's dataset includes all non-cancelled calls with reported patient age and a verified call-type of either CA that is defined as a sudden electrical malfunction of the heart resulting in collapse of a patient, or ACS that is defined as conditions associated with reduced blood flow to the heart (e.g., myocardial infarction).

The call codes are determined by the EMS teams based on defined protocols of the IEMS. The Supplemental Methods describe the IEMS call data fields and call type codes in further detail.

Vaccination and COVID-19 infection cases

Data on the vaccinations and COVID-19 cases were obtained from the online Israel Government Database Portal (https://info.data.gov.il/datagov/home/). These data include the number of daily administered 1st and 2nd vaccination doses by age group(27), as well as the weekly number of new confirmed COVID-19 cases by age group, across all of Israel(28). The age groups consist of bins of 20 years starting with 0-19. Population counts by similar age groups were also collected from publicly accessible data used to complement these datasets(29). Note that Israel administered only BNT162b2 vaccines for which the lag between the 1st and 2nd dose is three weeks, and that during January-May 2021, the vaccines were administered to individuals of age 16 and over.

<u>Data and statistical analyses</u>

Trends in CA and ACS call volume

For each pair of a diagnosis (CA or ACS) and an age group (16-39, over-40 or all-ages), the year-to-year absolute and relative change and the respective statistical significance of the change based on two-tailed Poisson E-test(30), were calculated. This was done separately with respect to the full calendar year (2019-2020) and the months January-May (2019-2021).

To visualize the temporal trends of CA and ACS call volume and potential relationship to COVID-19 infection rates and vaccination rates, graphs were created for CA and ACS, respectively. Each graph overlays several moving-average time-series over the study period. These include the five-week centered moving-average of weekly CA/ACS call counts for the age group 16-39, and the three-week centered moving-average counts of new COVID-19 infection cases and administered 1^{st} and 2^{nd} vaccine doses, respectively. The graphs also include the periods of the three national COVID-19-related public health lockdown advisories in Israel(31).

Focusing on the period of time of the third pandemic wave, during which Israel also launched its vaccination campaign, 'zoom-in' graphs were created for the time-period October 18^{th}, 2020, through June 20^{th}, 2021. The zoom-in graphs have the additional time-series of the three-week moving-average of the administered 2^{nd} vaccine doses shifted backwards in time by three weeks. This time-series captures the expected pattern of the 1^{st} vaccine doses under an 'ideal scenario' in which the three-week gap recommended by Pfizer between the two vaccine doses is followed exactly. Additionally, the zoom-in graph includes important dates in Israel vaccination campaign.

Graphs for the above-40 and all-ages groups are shown in Online Figures 1-4.

Association of Year-to-Year call count trends with COVID-19 Infections and vaccine administration

To check whether the observed year-to-year trends in weekly counts of CA and ACS calls among the 16-39 age group are associated with either COVID-19 infections or vaccine administration, the following weekly time-series are considered over the entire study period: CA weekly call counts, respectively, for patients in age groups 16-39 and over-40; ACS weekly call counts of patients in age group 16-39; bi-weekly (current and prior week) cumulative counts of 1^{st} and 2^{nd} vaccine doses administered, respectively, in age groups 16-39, over-40, and all-ages; and cumulative three-week (current and prior two weeks) new COVID-19 infection counts in age groups 16-39 (approximated by age group 0-39), over-40, and all-ages groups, respectively. Note that the COVID-19 infection dataset(28) only includes aggregated data for the age grouping 0-39 and thus overestimates the number of COVID-19 infections for the age group 16-39.

The choice of bi-weekly counts of 1st and 2nd vaccine doses is motivated by studies that suggest myocarditis typically appears within two weeks from vaccination(13). The choice of three-week cumulative counts of new COVID-19 infections is motivated by the fact that acute symptoms of COVID-19 are typically observed within three weeks of infection onset(13). Since the impact of COVID-19 might be variable, some of the analysis described below was conducted also with different COVID-19 new infection counts varying the counting period from one to six weeks.

The Spearman rank correlation was calculated between the time-series of CA weekly call counts for the age group 16-39 and the time-series of the vaccination dose counts for the same age group. Similarly, the rank correlation was calculated between the time-series of the CA weekly call counts and the time-series of the three-week new COVID-19 infection counts. The same was calculated for the sum of the time-series of respective CA and ACS weekly call counts (i.e., correlation with the respective time-series of vaccine dose and new COVID-19 infection counts). Finally, the same analysis was repeated with respect to the time-series of new COVID-19 infections count but varying the count period from one to six weeks.

Negative Binomial Regression Models

To further study the potential association between weekly CA and ACS counts, vaccine administration and COVID-19 infections, and control for cross interactions and other factors, two Negative Binomial regression models(32) were developed.

The first model, hereinafter referred to as *Model 1*, regresses the respective time-series of the CA weekly call counts and the ACS weekly call counts in the age group 16-39 (the dependent variable), against the time-series of vaccine dose counts and new COVID-19 infection counts, both in age group 16-39 normalized by the respective population size (independent variables). The model also controls for the different diagnoses (CA versus ACS), for weeks included in periods of national public health lockdown, as well as year-to-year (2019-2020) variations (e.g., due to population growth) in calls through respective dummy variables.

Similarly, the second model, hereinafter referred to as *Model 2*, regresses the respective time-series of CA weekly counts of age groups 16-39 and over-40 (the dependent variable) against the time-series of vaccine dose counts and new COVID-19 infection counts in the respective age groups, again normalized by the respective population size (independent variables). Additionally, instead of the dummy variable used in Model 1 above to capture the different diagnosis groups, Model 2 introduces a dummy variable to capture the different age groups (16-39 and over-40).

To identify the most statistically significant predictors, the models use bidirectional stepwise feature selection based on the model's Bayesian information criterion (BIC). The BIC metric summarizes the model's goodness of fit while penalizing the number of variables selected to avoid overfitting(33). During each step of the selection algorithm, features are tested to be added or removed to minimize the model's BIC. The adjusted incidence rate ratios (IRR) and 95% confidence intervals (CI), representing the estimated change in weekly calls per unit change of each predictor variable, were reported both for the final model after stepwise BIC selection and the full model without variable selection. Model development was performed using R version 4.0.2.

Sensitivity analysis

As robustness check of the associations determined by Models 1 and 2, the analysis was repeated while considering the one to six-week count time-series of new COVID-19 infections in the respective age groups.

Results

<u>General descriptive results</u>

Of the 30,262 cardiac arrest and 60,398 ACS calls included in the study population (see Supplemental Results for details), 945 (3.1%) and 3,945 (6.5%) calls were for patients of age 16-39, respectively. Of the 834,573 confirmed COVID-19 cases during the study period, 5,506,398 patients receiving their 1st vaccination dose, 5,152,417 patients receiving their 2nd vaccination dose, 572,435 (68.6%), 2,382,864 (43.3%) and 2,176,172 (32.2%) patients were of age 16-39, respectively.

Year-to-year changes in CA and ACS call volume

Table 1 below summarizes the year-to-year changes in CA and ACS call volume. The results highlight a statistically significant increase of over 25% in both CA (25.7%, P<0.05) and ACS (26.0%, P<0.001) calls for patients of ages 16-39 during January-May 2021, compared to the same period in 2020. Interestingly, for CA, there is no statistically significant difference in the respective call volume from 2019 to 2020. For ACS there is a statistically significant increase between 2019 and 2020 ([11.5%, P<0.01] for the full year and [15.1%, P<0.05] for January-May), but yet an even a larger increase from 2020 to 2021 ([26.0%, P<0.001] for January-May). A similar pattern exists for the over 40-age group but with more modest increases of 4.5% (P<0.05) and 14.2% (P<0.001) for CA and ACS calls, respectively.

Association between CA and ACS calls to COVID-19 infections and vaccine administration

Considering the age group 16-39, the Spearman rank correlation between the CA weekly call counts and the cumulative bi-weekly (current and prior week) 1st and 2nd doses count is 0.209 (P<0.05). The correlation factor of the sum of the weekly CA and ACS call counts with the same vaccine count time-series is 0.164 (P<0.01). In contrast, the time-series of the cumulative three-week (current and two prior weeks) new COVID-19 infections count was not significantly correlated to either the CA weekly call count time-series (0.047, P=0.600) or the time-series sum of CA and ACS weekly call counts (0.117, P=0.061), respectively. The same patterns hold when the COVID-19 infection count period is varied between one to six weeks (Online Table 1).

These findings are emphasized by the Figure 1-3 that present the graphs described in the Methods Section for both CA and ACS, CA only, and ACS only, respectively. Both the CA and ACS call counts (red curve) start increasing early January 2021 and seem to track closely the 2nd dose curve (solid blue curve). They peak around early March and then decrease during March and the first part of April (Figures 2B and 3B). The graphs also highlight the lack of association between the COVID-19 infection counts (grey curve) and the CA and ACS call counts, which is most clearly seen during the first two major infection waves in 2020.

A second increase is observed starting around April 18th. Interestingly, this second increase seems to track closely the increased gap, starting on April 11th, between the 1st vaccine dose count (purple curve) and the three-week backed 2nd vaccine dose count (the dashed blue curve). This gap could suggest an increased number of people who receive only one vaccine dose. Indeed, in early March the Israel Ministry of Health approved the vaccination of individuals of age 16 and over, who recovered from a COVID-19 infection, with only one vaccine dose, as long as three months elapsed from their recovery(34). As can be seen from the COVID-19 infection counts, the peak of the third wave among people under 40 occurred around January 11th. This could explain the potential increase in one-dose vaccination observed starting April 11th.

Negative Binomial regression models results

Table 2 below shows the results for Model 1 described in the Methods Section (the dependent variable: time-series of CA weekly call counts the ACS weekly call counts, both in age group 16-39). With BIC feature selection, the bi-weekly cumulative counts of 1st and 2nd vaccine doses in the age group 16-39 (normalized by the respective population size), was selected as statistically significant predictor with a positive relationship to the dependent variables (IRR: 3.33, [95% CI: 2.14-5.14]). That is, increased rates of vaccination in the respective age group are associated with increased number of CA and ACS weekly call counts. In contrast, the three-week cumulative new COVID-19 infection counts among the age group 16-39 (normalized by the respective population size) was not selected as a predictor of the call counts time-series. That is, the model did not detect a statistically significant association between the COVID-19 infection rates and the CA and ACS weekly call counts.

Similar results are obtained without feature selection. The time-series of vaccine dose counts still had a statistically significant positive relationship with the CA and ACS weekly call counts (IRR: 2.12, [95% CI: 1.05-4.22]), while the time-series of new COVID-19 infection counts did not have statistical significance. Additionally, national public health lockdown periods did not have statistical significance. The adjusted R^2 was 0.874 and 0.876 with and without feature selection, respectively.

Table 3 shows the results for Model 2 described in the Methods Section (the dependent variable: the time-series of CA weekly call counts of the respective age groups 16-39 and over-40). Like in the analysis of Model 1 above, with the BIC feature selection, the time-series of vaccine doses was selected as a statistically significant with positive associated with the dependent variable of CA weekly call counts (IRR: 1.79, 95% CI: [1.43-2.25]), whereas the time-series of the new COVID-19 infection counts was not selected. Without feature selection, the time-series of vaccine dose counts remained statistically significant and positive (IRR: 1.92, 95% CI: [1.34-2.76]) and the time-series of new COVID-19 infection counts did not have statistical significance. The national public health lockdown periods were also not statistically significant. The adjusted R^2 was 0.930 and 0.932 for the with and without feature selection models, respectively.

Sensitivity analysis

For each model, the new COVID-19 infection normalized counts time-series is never selected as a significant variable, even when the count period is varied between one to six weeks. At the same time the vaccine doses normalized counts time-series is always selected as a statistically significant variable with positive association (see Online Tables 2-5).

Discussion

This study leverages a unique dataset of all EMS CA and ACS calls in Israel over two and half years that span 14 months prior to the start of the COVID-19 pandemic, 10 months that include two waves of the COVID-19 pandemic, and 6 months with a third wave of the pandemic parallel to massive vaccination campaign among the 16-year-old and over population. Thus, it provides a unique perspective to explore the association between trends in CA and ACS call volume over the study period and different factors, such as COVID-19 infection rates and vaccination rates.

Moreover, because the IEMS is a national organization the data provide a rather comprehensive access to the respective incidence of the conditions being studied. For example, for CA incidence, it is reasonable to assume that the IEMS data includes almost all of the relevant events, since CA events always involve calling EMS services. For ACS, it is reasonable to assume that at least most of the severe events are included, but of course one has to account for the hospital walk-in patients that did not use EMS services (about 50% of all events based IEMS data). This stands in contrast to the known very partial and biased access provided by adverse event self-reporting surveillance systems(15-17), and highlights the importance of incorporating additional data sources into these systems.

The main finding of this study concerns with an increase of over 25%, compared with the years 2019-2020, both in the number of CA calls and ACS calls of people in the 16-39 age group during the COVID-19 vaccination campaign in Israel (January-May, 2021). Moreover, there is a robust and statistically significant association between the weekly CA and ACS call counts, and the rates of 1st and 2nd vaccine doses administered to this age group. At the same time there is no observed statistically significant association between COVID-19 infection rates and the CA and ACS call counts.

The visuals in the Figures 1-3 support and reinforce these findings. The increase in CA and ACS calls starting early January 2021 seems to track closely the administration of 2nd dose vaccines. This observation is consistent with prior findings that associated more significant adverse events, including myocarditis to the 2nd dose of the vaccine(13). A second increase in the CA and ACS call counts is observed starting April 18th, 2021, which seems to track an increase of single-dose vaccination to individuals who recovered from COVID-19 infections. This is consistent with prior findings that suggest that the immune response generated by a single dose on recovered individuals is generally stronger than the response to the 2nd vaccine dose in individuals, who were not exposed to COVID-19 infection(35). Additionally, the graphs emphasize the absence of correlation between the call counts and COVID-19 infection counts, which is most clearly seen during the two major pandemic waves in 2020.

The large increase in the incidence of CA and ACS events in the population of age 16-39 parallel to the vaccination rollout and its association with the vaccination rates is consistent with the known causal relationship between the mRNA vaccines and incidents of myocarditis in young people(11,13), as well as the facts that myocarditis is often misdiagnosed as ACS(20-22), and that asymptotic myocarditis is a frequent cause for unexplained sudden death among young adults from CA(18,23-25).

Limitations

It is important to note the main limitation of this study, which is that it relies on aggregated data that do not include specific information regarding the affected patients and their vaccination status or whether they were infected by the COVID-19 virus. Such data are critical to determine the exact nature of the observed increase in CA and ACS calls in young people, and what the underlying causal factors are.

Additionally, the IEMS data do not include hospital outcomes of EMS cases and information regarding the medical background of the different cases. The Israel Ministry of Health and the large HMOs have access to such data, which should be investigated in detail.

Conclusion

The significant increases in CA calls and ACS calls among the 16-39 age population during the COVID-19 vaccination rollout underscores the urgency for a rapid and thorough investigation of these concerning data, and the apparent association between COVID-19 vaccine administration and adverse cardiovascular outcomes among young adults. Israel and other countries should immediately collect the data necessary to determine whether such association indeed exists, including thorough investigation of individual CA and ACS cases in young adults, and their potential connection to the vaccine or other factors. This would be critical to better understanding the risk-benefits of the vaccine and informing related public policy. In the interim, it is vital that following vaccination, patients should be instructed to seek appropriate emergency care if they are experiencing symptoms of myocarditis, such as chest discomfort and shortness of breath, as well as consider avoiding strenuous physical activity following the vaccination that may induce severe adverse cardiac events.

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Figure Captions

Figure 1. Weekly counts of both cardiac arrest and acute coronary syndrome calls (five-week centered moving-average), COVID-19 cases (three-week centered moving-average), and vaccination doses (three-week centered moving-average) for those between 16-39 during A) the study period (January 1st, 2019, to June 20th, 2021) and B) the third COVID-19 wave and vaccination distribution period (October 18th, 2020, to June 20th, 2021). The figure highlights how the cardiac arrest and acute coronary syndrome calls closely track the administration of 2nd dose vaccines, a second increase in the call counts during April 2021 that seems to track an increase of single-dose vaccination to individuals who recovered from COVID-19 infections, and the lack of correlation between the call counts and COVID-19 infections, which is most clearly seen during the first two major infection waves in 2020. Figures 2 and 3 show these trends for the cardiac arrest and acute coronary syndrome calls, separately.

Figure 2. Weekly counts of cardiac arrest calls (five-week centered moving-average), COVID-19 cases (three-week centered moving-average), and vaccination doses (three-week centered moving-average) for those between 16-39 during A) the study period (January 1st, 2019, to June 20th, 2021) and B) the third COVID-19 wave and vaccination distribution period (October 18th, 2020, to June 20th, 2021).

Figure 3. Weekly counts of acute coronary syndrome calls (five-week centered moving-average), COVID-19 cases (three-week centered moving-average), and vaccination doses (three-week centered moving-average) for those between 16-39 during A) the study period (January 1st, 2019, to June 20th, 2021) and B) the third COVID-19 wave and vaccination distribution period (October 18th, 2020, to June 20th, 2021).

Tables

Age Group	Cardiac Arrest, Counts (Percent change relative to previous year; P-value)					Acute Coronary Syndrome, Counts (Percent change relative to previous year; P-value)				
	Full year		January – May			Full year		January – May		
	2019	**2020**	**2019**	**2020**	**2021**	**2019**	**2020**	**2019**	**2020**	**2021**
Overall	11,149 (-)	12,325 (10.6; P<0.001)	5,003 (-)	5,347 (6.9; P<0.001)	5,622 (5.1; P<0.01)	23,116 (-)	23,475 (1.6; P=0.096)	9,217 (-)	9,708 (5.3; P<0.001)	11,159 (15.0; P<0.001)
16-39	371 (-)	350 (-5.7; P=0.435)	142 (-)	152 (7.0; P=0.561)	191 (25.7; P<0.05)	1,405 (-)	1,566 (11.5; P<0.01)	545 (-)	627 (15.1; P<0.05)	790 (26.0; P<0.001)
Over 40	10,778 (-)	11,975 (11.1; P<0.001)	4,861 (-)	5,195 (6.9; P<0.001)	5,431 (4.5; P<0.05)	21,711 (-)	21,909 (0.9; P=0.343)	8,672 (-)	9,081 (4.7; P<0.01)	10,369 (14.2; P<0.001)

Table 1. Year-to-year absolute and relative changes in the counts of cardiac arrest and acute coronary syndrome calls by age group. Each cell shows the counts of calls during the respective time period and age group with the relative percent change in counts to the previous year shown in the parenthesis (e.g., relative change from 2020 to 2021). For counts during 2019, no relative change is reported.

Variable	With Stepwise BIC selection		Without Feature Selection	
	Adjusted incidence rate ratio (95% CI)	P-Value	Adjusted incidence rate ratio (95% CI)	P-Value
The bi-weekly cumulative counts of 1st and 2nd vaccine doses in the age group 16-39, normalized by the respective population size	3.33 (2.14 - 5.14)	<0.001	2.12 (1.05 - 4.22)	<0.05
The three-week cumulative new COVID-19 infection count among the age group 16-39, normalized by the respective population size	-	-	27.37 (0.05 - 13,177.26)	0.295
Call type: Acute Coronary Syndrome	1 [Reference]	-	1 [Reference]	-
Call type: Cardiac arrest	0.24 (0.22 - 0.26)	<0.001	0.24 (0.22 - 0.26)	<0.001
Week not during a COVID-19 public health advisory	1 [Reference]	-	1 [Reference]	-
Week during a COVID-19 public health advisory	-	-	0.94 (0.85 - 1.04)	0.233
Year: 2019	0.89 (0.83 - 0.94)	<0.001	0.82 (0.74 - 0.91)	<0.001
Year: 2020	-	-	0.92 (0.83 - 1.03)	0.146
Year: 2021	1 [Reference]	-	1 [Reference]	-

Table 2. Associations with cardiac arrest and acute coronary syndrome calls among those aged 16-39 using a negative binomial regression model, with and without stepwise BIC feature selection.

BIC = Bayesian information criterion

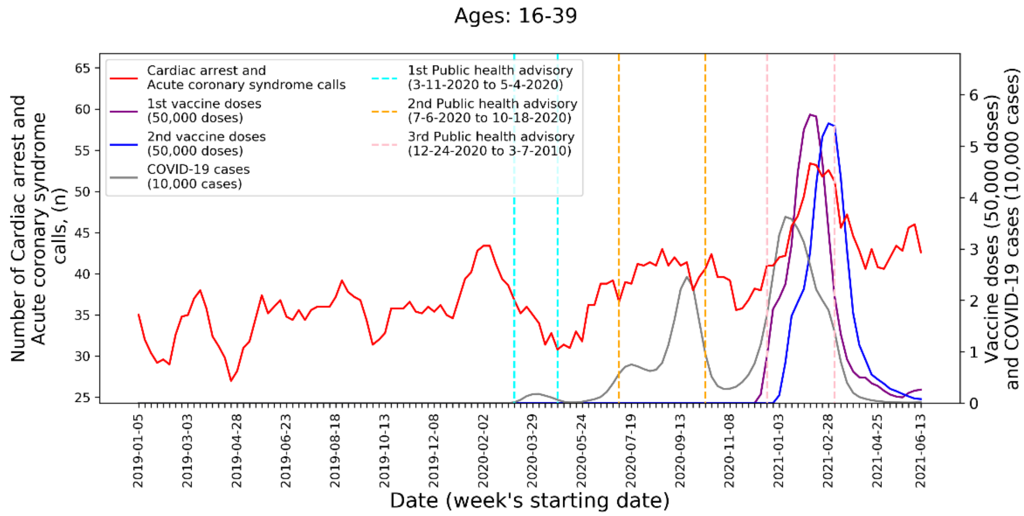
Variable	With Stepwise BIC selection		Without Feature Selection	
	Adjusted incidence rate ratio (95% CI)	P-Value	Adjusted incidence rate ratio (95% CI)	P-Value
The bi-weekly cumulative counts of 1st and 2nd vaccine doses per age group, normalized by the respective population size	1.79 (1.43 - 2.25)	<0.001	1.92 (1.34 - 2.76)	<0.001
The three-week cumulative new COVID-19 infection count per age group, normalized by the respective population size	-	-	6.21 (0.001 - 24,098.97)	0.668
Age Group: Below 40	1 [Reference]	-	1 [Reference]	-
Age Group: 40 and above	30.95 (28.89 - 33.21)	<0.001	31.05 (28.90 - 33.41)	<0.001
Week not during a COVID-19 public health advisory	1 [Reference]	-	1 [Reference]	-
Week during a COVID-19 public health advisory	-	-	0.98 (0.92 - 1.05)	0.639
Year: 2019	0.90 (0.86 - 0.94)	<0.001	0.93 (0.87 - 0.99)	<0.05
Year: 2020	-	-	1.04 (0.97 - 1.12)	0.233
Year: 2021	1 [Reference]	-	1 [Reference]	-

Table 3. Associations with cardiac arrest calls among all ages using a negative binomial regression model, with and without stepwise BIC feature selection.

BIC = Bayesian information criterion

Figures

A



B

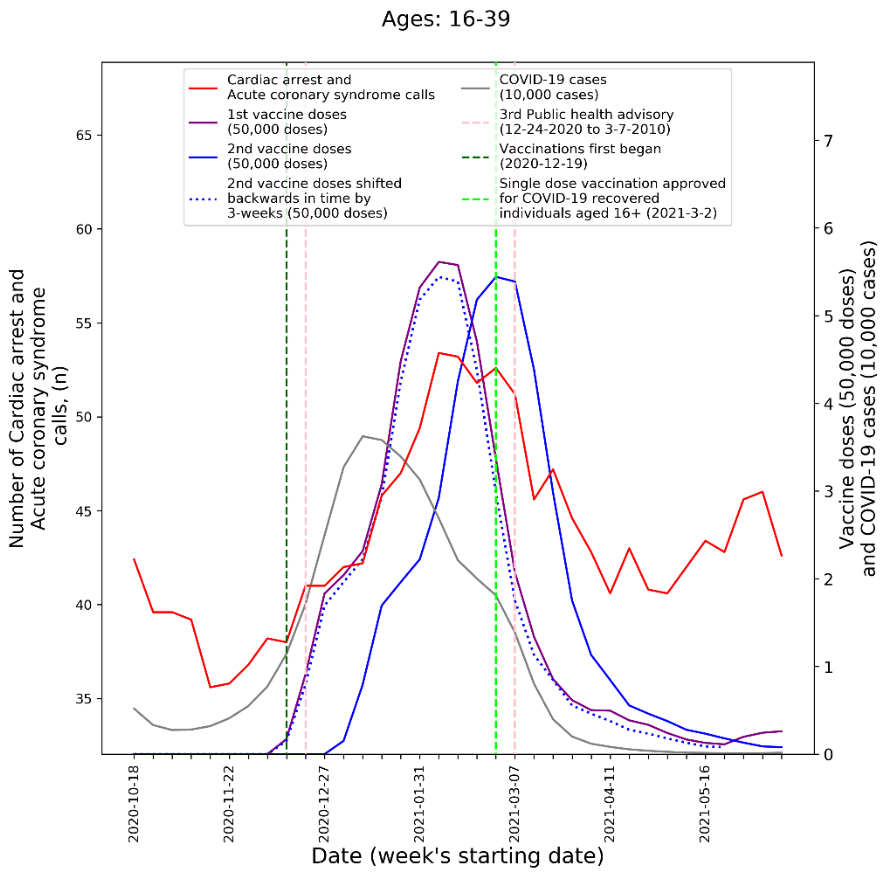
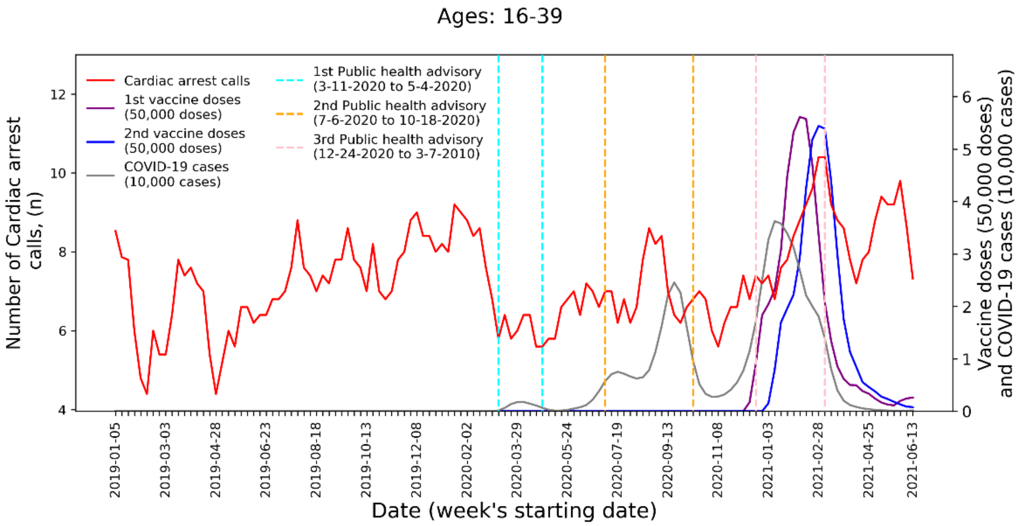


Figure 1.

A


Ages: 16-39
Cardiac arrest calls
1st vaccine doses (50,000 doses)
2nd vaccine doses (50,000 doses)
COVID-19 cases (10,000 cases)
1st Public health advisory (3-11-2020 to 5-4-2020)
2nd Public health advisory (7-6-2020 to 10-18-2020)
3rd Public health advisory (12-24-2020 to 3-7-2010)
Number of Cardiac arrest calls, (n)
Vaccine doses (50,000 doses) and COVID-19 cases (10,000 cases)
Date (week's starting date)

B

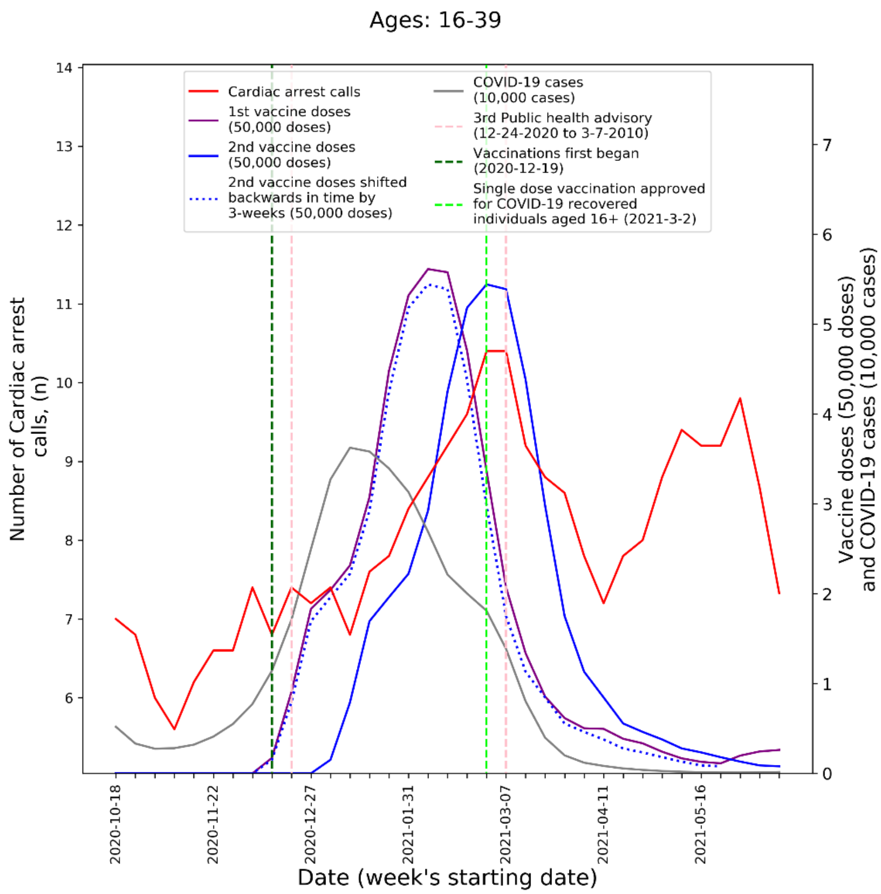

Ages: 16-39
Cardiac arrest calls
1st vaccine doses (50,000 doses)
2nd vaccine doses (50,000 doses)
2nd vaccine doses shifted backwards in time by 3-weeks (50,000 doses)
COVID-19 cases (10,000 cases)
3rd Public health advisory (12-24-2020 to 3-7-2010)
Vaccinations first began (2020-12-19)
Single dose vaccination approved for COVID-19 recovered individuals aged 16+ (2021-3-2)
Number of Cardiac arrest calls, (n)
Vaccine doses (50,000 doses) and COVID-19 cases (10,000 cases)
Date (week's starting date)

Figure 2.

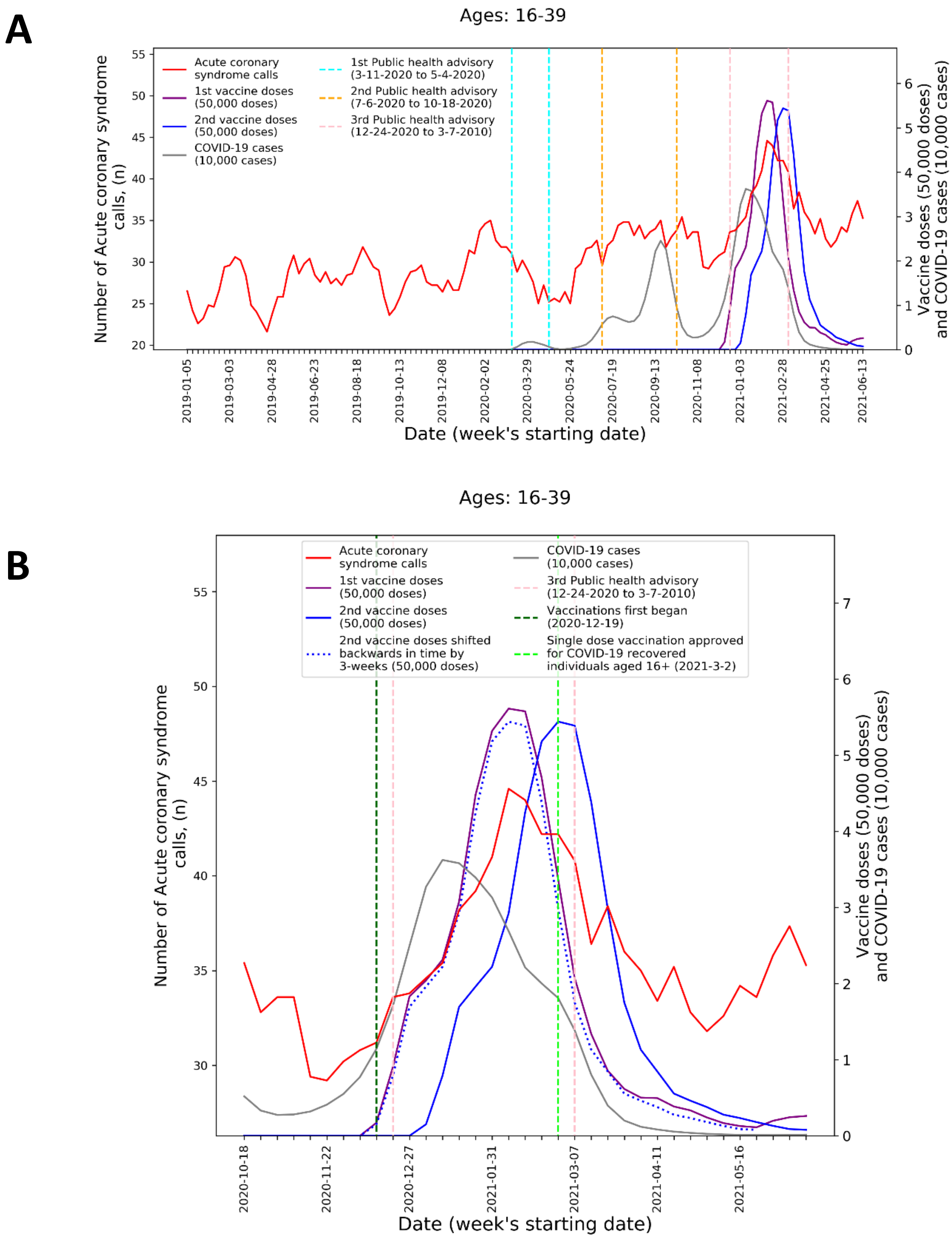

A
Ages: 16-39
Acute coronary syndrome calls
1st vaccine doses (50,000 doses)
2nd vaccine doses (50,000 doses)
COVID-19 cases (10,000 cases)
1st Public health advisory (3-11-2020 to 5-4-2020)
2nd Public health advisory (7-6-2020 to 10-18-2020)
3rd Public health advisory (12-24-2020 to 3-7-2010)
Number of Acute coronary syndrome calls, (n)
Vaccine doses (50,000 doses) and COVID-19 cases (10,000 cases)
Date (week's starting date)
2019-01-05
2019-03-03
2019-04-28
2019-06-23
2019-08-18
2019-10-13
2019-12-08
2020-02-02
2020-03-29
2020-05-24
2020-07-19
2020-09-13
2020-11-08
2021-01-03
2021-02-28
2021-04-25
2021-06-13
B
Ages: 16-39
Acute coronary syndrome calls
1st vaccine doses (50,000 doses)
2nd vaccine doses (50,000 doses)
2nd vaccine doses shifted backwards in time by 3-weeks (50,000 doses)
COVID-19 cases (10,000 cases)
3rd Public health advisory (12-24-2020 to 3-7-2010)
Vaccinations first began (2020-12-19)
Single dose vaccination approved for COVID-19 recovered individuals aged 16+ (2021-3-2)
Number of Acute coronary syndrome calls, (n)
Vaccine doses (50,000 doses) and COVID-19 cases (10,000 cases)
Date (week's starting date)
2020-10-18
2020-11-22
2020-12-27
2021-01-31
2021-03-07
2021-04-11
2021-05-16

Figure 3.