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MEDIA RELEASE

COVID mRNA VACCINES POSE HIGHER RISK OF HOSPITALISATION THAN A COVID INFECTION

OCTOBER 25, 2022

1. **1 in 800 risk of serious adverse health event from mRNA Covid vaccines, a value that significantly exceeds the stated risk interpreted from randomised controlled trials conducted by Pfizer and Moderna prior to provisional approval;**
2. **20% increase in out-of-hospital cardiac arrest ambulance call-outs in the UK during 2021 compared to 2019;**
3. **25% increase in acute coronary syndrome and cardiac arrest calls in 16 to 39 year old Israelis, specifically associated with the first and second dose of Covid vaccination, not actual Covid infection.**

Recent papers present mounting evidence of unacceptable risks of the mRNA Covid vaccines. These peer review and published studies (see attached) appear to confirm serious adverse reactions arising from these vaccines are far greater than presented by the pharmaceutical companies that manufacture and profit from mRNA vaccines.

A recent peer reviewed study published in the Vaccine Journal (August 2022) indicates that mRNA Covid vaccines have a greater risk of causing a serious adverse reaction, resulting in hospitalisation and/or disability, than being hospitalised from Covid infection.

The statement in Point 3 above is critical, as the pharmaceutical industry and many Australian politicians and media outlets claimed that the increased coronary incidents were related to "Long Covid", not from adverse reactions to Covid vaccine. This was possibly a blatant untruth.

Never before has a vaccine remained on the market with such high incidence of adverse reactions (1:800). Other vaccines have been pulled with far lower risks, such as Swine Flu vaccine: 1:100,000, or Rotavirus vaccine: 1:10,000.

It is now widely accepted that the Covid vaccine (or its boosters) cannot prevent infection nor transmission. Further, Pfizer has now publically admitted their mRNA vaccines were never tested for these critical benefits. More careful analysis of the recently released study data that led to approval of the Pfizer mRNA Covid vaccine, that claimed a 95% risk reduction in infection, was in fact a relative risk reduction. This analysis now confirms that the absolute risk reduction (ARR) was 0.84% (i.e. for every 119 individuals vaccinated, only one would be protected from Covid infection; source The Lancet 2021). Yet these vaccines were widely promoted by most politicians and their "health" advisors on the basis that vaccination would prevent infection and the spread of Covid. Remember the "don't kill granny" campaigns? Such false claims were not supported by any evidence, and again, were highly likely to be blatant untruths.

It seems quite clear the Covid vaccine was only ever justified for the small population group of elderly with serious co-morbidities, where the initial ancestral strain of SARS-CoV-2 (Covid)

indicated a possible mortality rate of 6%. There was no data or evidence to support the widespread and often mandated vaccination of any other population group, particularly when the original serious adverse reaction data from Pfizer and Moderna actually confirmed a higher level of adverse reaction health risk and hospitalisation for the much larger lower risk population group when exposed to the mRNA vaccine.

Any Australian politician that promoted and mandated Covid vaccination removed informed consent to a risky procedure from the vast majority of the population, which also impacted on employment, natural constitutional freedoms of expression and movement. These actions have in effect broken many Australian laws, its constitution, and could leave such politicians potentially liable to prosecution. Further, those employers that effectively terminated any employee for failing to be vaccinated with what were clearly dangerous and ineffective experimental vaccines are probably liable to unfair dismissal actions.

PCS warns of the many dubious "fact checking" groups, particularly their motives and allegiances, that consistently deny the mounting evidence of Covid vaccine harm with any excuse or criticism.

Accordingly, PCS calls on all Australian media to start serious investigation and honest reporting on the actual safety and efficacy of Covid vaccines, and the Australian laws that are likely to have been broken over the past two years by government Ministers, their health officers and many employers. The media must also resist the temptation of censored reporting on this subject due to political affiliations or simply because of a fear of advertising revenue loss.

Accurate and unbiased assessment of Covid vaccine risks is now overdue, as suspension of further Covid vaccination programs may offer a preferable health outcome for most Australians.

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Attachments:

- Malhortra-JIR-Covid Vaccine Misinformation-Sept 2022
- Fraiman el al-Vaccine-Serious adverse events mRNA Covid vaccines-Sept 2022
- Sun-Increased cardiovascular events in under 40 population-Israel-Covid vaccine-2022
- The Lancet-Covid 19 vaccine efficacy and effectiveness-ARR 0.84%-Vol 2, July 2021

Journal of Insulin Resistance
ISSN: (Online) 2519-7533, (Print) 2412-2785

Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine - Part 1

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Dates:
Received: 10 June 2022
Accepted: 01 Sept. 2022
Published: 26 Sept. 2022

How to cite this article:
Malhotra A. Curing the pandemic of misinformation on COVID-19 mRNA vaccines through real evidence-based medicine - Part 1. J. insul. resist. 2022;5(1), a71. https://doi.org/10.4102/jir.v5i1.71

Background: In response to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), several new pharmaceutical agents have been administered to billions of people worldwide, including the young and healthy at little risk from the virus. Considerable leeway has been afforded in terms of the pre-clinical and clinical testing of these agents, despite an entirely novel mechanism of action and concerning biodistribution characteristics.

Aim: To gain a better understanding of the true benefits and potential harms of the messenger ribonucleic acid (mRNA) coronavirus disease (COVID) vaccines.

Methods: A narrative review of the evidence from randomised trials and real world data of the COVID mRNA products with special emphasis on BionTech/Pfizer vaccine.

Results: In the non-elderly population the "number needed to treat" to prevent a single death runs into the thousands. Re-analysis of randomised controlled trials using the messenger ribonucleic acid (mRNA) technology suggests a greater risk of serious adverse events from the vaccines than being hospitalised from COVID-19. Pharmacovigilance systems and real-world safety data, coupled with plausible mechanisms of harm, are deeply concerning, especially in relation to cardiovascular safety. Mirroring a potential signal from the Pfizer Phase 3 trial, a significant rise in cardiac arrest calls to ambulances in England was seen in 2021, with similar data emerging from Israel in the 16–39-year-old age group.

Conclusion: It cannot be said that the consent to receive these agents was fully informed, as is required ethically and legally. A pause and reappraisal of global vaccination policies for COVID-19 is long overdue.

Contribution: This article highlights the importance of addressing metabolic health to reduce chronic disease and that insulin resistance is also a major risk factor for poor outcomes from COVID-19.

Keywords: COVID-19; mRNA vaccine; cardiac arrests; real evidence-based medicine; shared decision-making.

Vaccines save lives

The development of safe and highly effective vaccines during the latter half of the 20th century has been one of medicine's greatest achievements. The prominent scars on my left arm are a constant reminder of the success of our ability to curb some of the deadliest diseases such as smallpox, tuberculosis (TB), measles, mumps and rubella to name but a few. Collectively, traditional vaccines are estimated to save approximately 4–5 million lives per year.[1] The greatest success of vaccination was the global eradication of smallpox, which had a 30% mortality rate.[2]

In other words, almost one in three people who contracted it died. The development of a safe and effective vaccine after much trial and error resulted in 95 out of 100 individuals being protected from symptomatic infection from smallpox with immunity lasting five years, which by the 1970s resulted in complete eradication of the virus. Similarly, one dose of the measles vaccine is said to be '95% effective'. What is meant by this? What most people would assume is that 95 out of 100 who take the inoculation are protected from symptomatic infection, transmission and also have long-lasting immunity. Similarly, if exposed to chickenpox, only five out of 100 vaccinated children will catch it.

Vaccines are also some of the safest interventions in the world when compared to most drugs used in chronic disease management, as indeed we should expect, given that they are being administered to prevent something in healthy people, not treat an illness. It was therefore welcome

news that in the summer of 2020, several drug companies including both Pfizer and Moderna announced the results of their 2-month randomised controlled trial that they had developed a vaccine with more than '95% effectiveness' at preventing infection from what at the time was the predominantly circulating strain of the coronavirus disease 2019 (COVID-19).

A doctor's experience

Volunteering in a vaccine centre, I was one of the first to receive two doses of Pfizer's messenger ribonucleic acid (mRNA) vaccine, at the end of January 2021. Although I knew my individual risk was small from COVID-19 at age 43 with optimal metabolic health, the main reason I took the jab was to prevent transmission of the virus to my vulnerable patients. During early 2021, I was both surprised and concerned by a number of my vaccine-hesitant patients and people in my social network who were asking me to comment on what I regarded at the time as merely 'anti-vax' propaganda.

I was asked to appear on *Good Morning Britain* after a previously vaccine-hesitant film director Gurinder Chadha, Order of the British Empire (OBE), who was also interviewed, explained that I convinced her to take the jab.

But a very unexpected and extremely harrowing personal tragedy was to happen a few months later that would be the start of my own journey into what would ultimately prove to be a revelatory and eye-opening experience so profound that after six months of critically appraising the data myself, speaking to eminent scientists involved in COVID-19 research, vaccine safety and development, and two investigative medical journalists, I have slowly and reluctantly concluded that contrary to my own initial dogmatic beliefs, Pfizer's mRNA vaccine is far from being as safe and effective as we first thought. This critical appraisal is based upon the analytical framework for practicing and teaching evidence-based medicine, specifically utilising individual clinical expertise and/or experience with use of the best available evidence and taking into consideration patient preferences and values.

A case study

Case studies are a useful way of conveying complex clinical information and can elicit useful data that would be lost or not be made apparent in the summary results of a clinical trial.

On 26 July 2021, my father, Dr Kailash Chand OBE, former deputy chair of the British Medical Association (BMA) and its honorary vice president (who had also taken both doses of the Pfizer mRNA vaccine six months earlier) suffered a cardiac arrest at home after experiencing chest pain. A subsequent inquiry revealed that a significant ambulance delay likely contributed to his death.[3] But his post-mortem findings are what I found particularly shocking and inexplicable. Two of his three major arteries had severe blockages: 90% blockage in his left anterior descending artery and a 75% blockage in his right coronary. Given that he was an extremely fit and active 73-year-old man, having walked an average of 10–15 000 steps/day during the whole of lockdown, this was a shock to everyone who knew him, but most of all to me. I knew his medical history and lifestyle habits in great detail. My father who had been a keen sportsman all his life, was fitter than the overwhelming majority of men his age. Since the previous heart scans (a few years earlier, which had revealed no significant problems with perfect blood flow throughout his arteries and only mild furring), he had quit sugar, lost belly fat, reduced the dose of his blood pressure pills, started regular meditation, reversed his prediabetes and even massively dropped his blood triglycerides, significantly improving his cholesterol profile.

I couldn't explain his post-mortem findings, especially as there was no evidence of an actual heart attack but with severe blockages. This was precisely my own special area of research. That is, how to delay progression of heart disease and even potentially reverse it. In fact, in my own clinic, I successfully prescribe a lifestyle protocol to my patients on the best available evidence on how to achieve this. I've even co-authored a high-impact peer-reviewed paper with two internationally reputed cardiologists (both editors of medical journals) on shifting the paradigm on how to most effectively prevent heart disease through lifestyle changes.[4] We emphasised the fact that coronary artery disease is a chronic inflammatory condition that is exacerbated by insulin resistance. Then, in November 2021, I was made aware of a peer-reviewed abstract published in *Circulation*, with concerning findings. In over 500 middle-aged patients under regular follow up, using a predictive score model based on inflammatory markers that are strongly correlated with risk of heart attack, the mRNA vaccine was associated with significantly increasing the risk of a coronary event within five years from 11% pre-mRNA vaccine to 25% 2–10 weeks post mRNA vaccine. An early and relevant criticism of the validity of the findings was that there was no control group, but nevertheless, even if partially correct, that would mean that there would be a large acceleration in progression of coronary artery disease, and more importantly heart attack risk, within months of taking the jab.[5] I wondered whether my father's Pfizer vaccination, which he received six months earlier, could have contributed to his unexplained premature death and so I began to critically appraise the data.

Questioning the data

I recalled a cardiologist colleague of mine informing me, to my astonishment at the time, that he had made a decision not to take the vaccine for a number of reasons, including his personal low background COVID-19 risk (see Table 1)[6] and concerns regarding unknown short- and longer-term harms. One thing that alarmed him about Pfizer's pivotal mRNA trial published in *The New England Journal of Medicine* was the data in the supplementary appendix, specifically that there were four cardiac arrests in those who took the vaccine versus only one in the placebo group.[7] These figures were

TABLE 1: Infection fatality rate of ancestral variants of COVID-19 pre-vaccination by age.

Age	Median IFR %	Median IFR (absolute)	Survival rate estimate (%)
0–19	0.0027	1 in 37 037	99.9973
20–29	0.0140	1 in 7143	99.9860
30–39	0.0310	1 in 3225	99.9690
40–49	0.0820	1 in 1220	99.9180
50–59	0.2700	1 in 370	99.7300
60–69	0.5900	1 in 169	99.4100
> 70 community	2.4000	1 in 42	97.6000
> 70 overall	5.5000	1 in 18	94.5000

Source: Adapted from Axfors C, Ioannidis JPA. Infection fatality rate of COVID-19 in community-dwelling elderly populations. Eur J Epidemiol. In press 2022;37(3):235–249. https://doi.org/10.1007/s10654-022-00853-w

IFR, infection fatality rate.

TABLE 2: Deaths prevented, and number needed to vaccinate to prevent a death based on death rates and case fatality rates from UKHSA data for England during Delta wave.

Age	Deaths prevented (in England) based on differences in death rates per 100 000	Number needed to vaccinate per death prevented based on differences in death rates per 100 000
< 18	-0.1	Negative
18–29	70	93 000
30–39	240	27 000
40–49	640	10 000
50–59	2740	2600
60–69	4580	1300
70–79	9100	520
80+	11 900	230
Total	**29 270**	**-**

Source: Adapted from HART. How many injections to prevent one covid death? [homepage on the Internet]. No date. Available from: https://www.hartgroup.org/number-needed-to-vaccinate/

UKHSA, United Kingdom Health Security Agency.

small in absolute terms and did not reach statistical significance in the trial, suggesting that it may just be coincidence, but without further studies it was not possible to rule out this being a genuinely causal relationship (especially without access to the raw data), in which case it could have the effect of causing a surge in cardiac arrests once the vaccine was rolled out to tens of millions of people across the globe.

In terms of efficacy, headlines around the world made very bold claims of 95% effectiveness, the interchangeable use of 'efficacy' and 'effectiveness' glossing over the big difference between controlled trial and real-world conditions.[8] It would be understandable for the lay public and doctors to interpret this that if 100 people are vaccinated then 95% of people would be protected from getting the infection. Even the Centers of Disease Control (CDC) director Rochelle Walensky recently admitted in an interview that it was initial news from CNN that made her optimistic that the vaccine would significantly stop transmission and infection, but this was later to be proved far from true for the COVID-19 vaccines.[9] The original trial revealed that a person was 95% 'less likely' to catch the autumn 2020 variant of COVID-19. This is known in medical speak as relative risk reduction, but to know the true value of any treatment one needs to understand for that person, by how much is their individual risk reduced by the intervention – that is, the *absolute individual risk reduction*.

Importantly, it turns out that the trial results suggest that the vaccine was only preventing a person from having a symptomatic positive test, and the absolute risk reduction for this was 0.84% (0.88% reduced to 0.04%). In other words, if 10 000 people had been vaccinated and 10 000 had not, for every 10 000 people vaccinated in trial 4 would have tested positive with symptoms compared to 88 who were unvaccinated. Even in the unvaccinated group, 9912 of the 10 000 (over 99%) would not have tested positive during the trial period. Another way of expressing this is that you would need to vaccinate 119 people to prevent one such symptomatic positive test (assumed to be indicative of an infection, which, in itself, is potentially misleading but beyond the scope of this article).[10]

This absolute risk reduction figure (0.84%) is extremely important for doctors and patients to know but how many of them were told this when they received the shot? Transparent communication of risk and benefit of any intervention is a core principle of ethical evidence-based medical practice and informed consent.[11]

The Academy of Medical Royal Colleges made this clear in a paper published in the *BMJ* in 2015.[12] A co-author at the time was also the then chair of the General Medical Council. In fact, in a 2009 World Health Organization (WHO) bulletin Gerd Gigerenzer, the director of the Max Planck institute stated, 'It's an ethical imperative that every doctor and patient understand the difference between relative and absolute risks to protect patients against unnecessary anxiety and manipulation'.[13]

Contrary to popular belief, what the trial did not show was any statistically significant reduction in serious illness or COVID-19 mortality from the vaccine over the 6-month period of the trial, but the actual numbers of deaths (attributed to COVID-19) are still important to note. There were only two deaths from COVID-19 in the placebo group and one death from COVID-19 in the vaccine group. Looking at all-cause mortality over a longer period, there were actually slightly more deaths[14] in the vaccine group (19 deaths) than in the placebo group (17 deaths). Also of note was the extremely low rate of COVID-19 illness classed as severe in the placebo group (nine severe cases out of 21 686 subjects, 0.04%), reflecting a very low risk of severe illness even in regions chosen for the trial because of perceived high prevalence of infection.

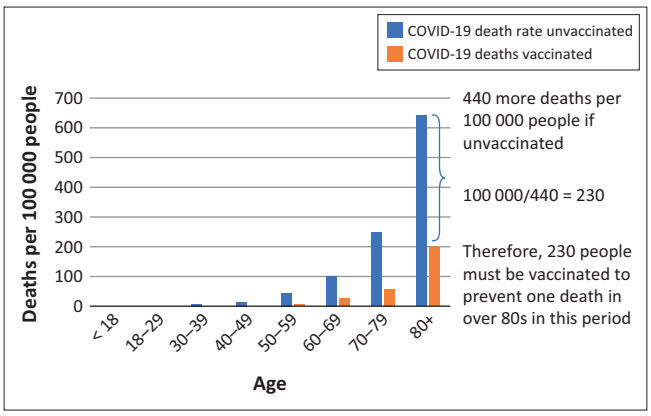
Finally, the trials in children did not even show a reduction in symptomatic infections but instead used the surrogate measure of antibody levels in the blood to define efficacy, even though the relationship between Wuhan-spike vaccine-induced antibody levels and protection from infection is tenuous, at best. The Food and Drug Administration's (FDAs) own website states that:

> [*R*]esults from currently authorised SARS-COV-2 antibody tests should not be used to evaluate a person's level of immunity or protection from COVID-19 at any time, and especially after the person received a COVID-19 vaccination.[15]

Now that we know what the published trial did and did not show in terms of the vaccine efficacy, we can attempt to extrapolate what the effect of the vaccine would be in reducing mortality or any other adverse outcome from the virus. If there is a 1 in 119 chance the vaccine protects you from getting symptomatic infection from ancestral variants, then to find the protection against death, this figure ($n = 119$) must be multiplied by the number of infections that lead to a single death for each age group. This would give (for up to two months after the inoculation) the absolute risk reduction (for death) from the vaccine. For example, if my risk at age 44 from dying from Delta (should I get infected with it) is 1 in 3000, then the absolute risk reduction from the vaccine protecting me from death is 1 over 3000 multiplied by 119, that is, 1 per 357 000.

Of course, even for those people who do become infected the vaccination may provide some protection against death. From observational data it is possible to calculate the number who would need to be vaccinated to prevent a COVID-19 death. For example, comparing the population death rates[16] during the Delta wave gives 230 for people over 80s needing to be vaccinated to prevent a single death in that period with that number rising to 520 for people in their 70s and 10 000 for people in their 40s (see Table 2 and Figure 1[17]). However, these figures will be distorted by inaccuracies in the measure of the size of the unvaccinated population. As also pointed out in a recent editorial by John Ioannidis in *BMJ* evidence-based medicine the inferred efficacy of the vaccine from non-randomised studies may be 'spurious', with bias being generated by 'pre-existing immunity, vaccination misclassification, exposure differences, testing, disease risk factor confounding, hospital admission decision, treatment use differences and death attribution'.[18]

These numbers are for the whole population of England and do not necessarily apply to the healthy; more than 95% of deaths were in people with pre-existing conditions.[19] It is also important to note that the vaccinated and unvaccinated populations are different in other ways, which could bias the death data. For example, the unvaccinated are more likely to be from a lower socioeconomic demographic, which puts them at a greater risk of severe illness or death should they be infected.



Source: Fraiman J, Erviti J, Jones M, et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. Vaccine. 2022 Aug 30:S0264-410X(22)01028-3. https://doi.org/10.1016/j.vaccine.2022.08.036

Note: Difference between proportion of unvaccinated and vaccinated population dying with COVID-19 from 27 Aug to 16 Dec 2021.

UKHSA, United Kingdom Health Security Agency.

FIGURE 1: Calculation of number needed to be vaccinated from COVID-19 death rates in vaccinated and unvaccinated from UKHSA data for England during the Delta wave. The difference between the deaths that occurred in the vaccinated and that would have occurred if they had the same rate as the unvaccinated was used to calculate the number of people who would need to be vaccinated to prevent a single death.

Professor Carl Heneghan, the director of the Centre of Evidence Based Medicine in Oxford, has explained his own clinical experience of healthy user bias. Some of his own patients who ended up in intensive care unit (ICU) with COVID-19 (classified as unvaccinated) did not take the vaccine because they were already suffering from terminal illness.

Given these limitations, the above figures are likely an overestimate of the individual benefit of vaccination; the open and frank discussion of such uncertainties is an essential component of shared decision-making.

What should be part of the shared decision-making informed consent discussion when any member of the public is considering taking the shot is something along these lines: Depending on your age, several hundreds or thousands of people like you would need to be injected in order to prevent one person from dying from the Delta variant of COVID-19 over a period of around three months. For the over 80s, this figure is at least 230, but it rises the younger you are, reaching at least 2600 for people in their 50s, 10 000 for those in their 40s, and 93 000 for those between 18 and 29 years. For omicron, which has been shown to be 30% – 50% less lethal, meaning significantly more people would need to be vaccinated to prevent one death. How long any protection actually lasts for is unknown; boosters are currently being recommended after as short a period as 4 months in some countries.

But how many people have had a conversation that even approaches an explanation similar to that? This is before we get into the known, unknown and as yet to be fully quantified harms.

Although many have proposed that omicron is intrinsically less lethal (supported by observed molecular differences between omicron and the Wuhan-type virus) immunity built up by prior exposure protecting against severe illness is likely to be relevant to some extent as well. The critical point to note that, whether it is a viral or immune-related phenomenon, the milder nature of omicron is evident in the unvaccinated and therefore the reduction in mortality should not be attributed to vaccines. ≤

What are the harms?

Concerns have already been raised about the under-reporting of adverse events in the clinical trials for the COVID-19 vaccines. Investigative medical reporter Maryanne Demasi analysed the various ways that the pivotal mRNA trials failed to account for serious harms.[20] Not only were trial participants limited to the type of

adverse event they could report on their digital apps, but some participants who were hospitalised after inoculation were withdrawn from the trial and not reported in the final results. After two months into the pivotal trials, the FDA allowed vaccine companies to offer the vaccine to subjects in the placebo group, essentially torpedoing any chance of properly recording adverse events from that point on, forcing a reliance of pharmacovigilance data.

Such data have shown that one of the most common mRNA COVID-19 vaccine-induced harms is myocarditis. A study across several Nordic countries showed an increased risk from mRNA vaccination over background, especially in young males.[21] Authorities have repeatedly maintained that myocarditis is more common after COVID-19 infection than after vaccination.[22] However, trial data demonstrating that vaccination reduces the risk of myocarditis in subsequent infection is elusive, and in fact the risks may be additive. Incidence of myocarditis rocketed from spring 2021 when vaccines were rolled out to the younger cohorts having remained within normal levels for the full year prior, despite COVID-19,[23] with the most up-to-date evidence, a paper from Israel[24] found that the infection itself, prior to roll-out of the vaccine, conferred no increase in the risks of either myocarditis or pericarditis from COVID-19, strongly suggesting that the increases observed in earlier studies were because of the mRNA vaccines, with or without COVID-19 infections as an additional risk in the vaccinated.[24]

Indeed, this reflects my own clinical experience of advising and managing several patients in the community who presented with a clear suggestion from the history of myocarditis post mRNA vaccination but aren't necessarily unwell enough to require hospital admission. A very fit lady in her 50s developed fatigue and shortness of breath on exertion a few weeks after her second Pfizer injection. An echocardiogram revealed severe impairment of her left ventricular function. Another lady in her 30s experienced similar symptoms with distressing palpitations within a few days of her second shot; mild left ventricular impairment was also present on echo and a subsequent cardiac MRI scan revealed several areas of *late gadolinium enhancement*, a feature seen on the scan, which is consistent with damaged heart tissue, and given that heart cells cannot be replaced this is likely to have a long-term impact.

Although vaccine-induced myocarditis is not often fatal in young adults, MRI scans reveal that, of the ones admitted to hospital, approximately 80% have some degree of myocardial damage.[25,26] It is like suffering a small heart attack and sustaining some – likely permanent – heart muscle injury. It is uncertain how this will play out in the longer-term, including if, and to what degree, it will increase the risk of poor quality of life or potentially more serious heart rhythm disturbances in the future.

A number of reports have produced concerning rates of myocarditis, depending on age, ranging from 1 in 6000 in Israel[27] to 1 in 2700 in a Hong Kong study in male children and adolescents aged 12–17 years.[28] Most of the epidemiology studies that have been carried out have measured myocarditis cases that have been diagnosed in a hospital setting, and do not claim to be a comprehensive measure of more mild cases (from which long-term harm cannot be ruled out). In addition, under-reporting of adverse events is the scourge of pharmacovigilance data.[29]

The United Kingdom relies on the Medicines and Health Regulatory Agency's (MHRAs) 'Yellow Card' reporting system,[30] which is far from adequate to cope with a rapid roll-out of a brand new product. It only detected the clotting problems that resulted in the withdrawal of the AstraZeneca product in April 2021 for younger people after 9.7 million doses had been given in the United Kingdom[31]; in contrast, Denmark detected the problem after only 150 000 doses had been administered.[32]

In the United Kingdom, since the vaccine roll-out there have been almost 500 000 adverse event reports recorded (via the Yellow Card system) in association with the mRNA COVID-19 vaccinations involving over 150 000 individuals. In terms of the number of reports per person (i.e. having received at least one dose), the MHRA figures show around 1 in 120 suffering a likely adverse event that is beyond mild.[30] However, the MHRA are unclear about the rate and furthermore do not separate out the serious adverse events. Nevertheless, this level of reporting is unprecedented in the modern medical era and equals the total number of reports received in the first 40 years of the Yellow Card reporting system (for all medicines – not just vaccines) up to 2020.[33] In comparison, for the measles, mumps and rubella (MMR) vaccine, the number of reports per person vaccinated was around 1 in 4000, more than thirty times less frequent than the 1 in 120 Yellow Card reports for COVID-19 vaccine recipients.[34] Norway does separate out the reported serious adverse reactions and has shown a rate of approximately 1 in 1000 after two doses of BioNTech/Pfizer mRNA product that result in hospitalisation or are life changing.[35]

Another, and more useful, source of information (because of the level of detail for each report made available to the public) is the United States (US) Vaccine Adverse Effect Reporting System (VAERS). As with the UK's system, the level of reports – including serious ones – associated with COVID-19 vaccines is completely unprecedented. For example, over 24 000 deaths have now been recorded in VAERS as of 02 March 2022; 29% of these occurred within 48 h of injection, and half within two weeks. The average reporting rate prior to 2020 was less than 300 deaths per annum. One explanation often given for this is that the COVID-19 vaccine roll-out is unprecedented in scope; however, this is not valid, since (for the last decade at any rate) the United States has administered 150 million – 200 million vaccinations annually. Another criticism of VAERS is that 'anyone can make an entry', yet, in fact, an analysis of a sample of 250 early deaths suggested that the vast majority are hospital or physician

entries,[36] and knowingly filing a false VAERS report is a violation of Federal law punishable by fine and imprisonment.[37]

Given that VAERS was set up to generate early signals of potential harm for new vaccines, and was instrumental in doing so for several products, it seems perverse to only now criticise it as unreliable when there seem to have been no changes in the way it operates.

It has been estimated that serious adverse effects that are officially reported are actually a gross underestimate, and this should be borne in mind when the above comments in relation to VAERS reports are considered. For example, a paper by David Kessler (a former FDA Commissioner) cites data suggesting that as few as 1% of serious adverse events are reported to the FDA.[38] Similarly in relation to the Yellow Card scheme in the United Kingdom, it has been estimated that only 10% of serious adverse effects are reported.[39,40] A recent pre-print publication co-authored by some of the most trusted medical scientists in the world in relation to data transparency adds validity to pharmacovigilance data. Accessing data from the FDA and health Canada websites and combining results from journal articles that published the Pfizer and Moderna trials, the authors concluded that the absolute risk of a serious adverse event from the mRNA vaccines (a rate of one in 800) significantly exceeded the risk of COVID-19 hospitalisation in randomised controlled trials.[17]

What VAERS and other reporting systems (including the yet to be accessed and independently evaluated raw data from randomised controlled trials) will miss are potential medium to longer term harms that neither patients nor doctors will automatically attribute to the drug. For example, if the mRNA vaccine increases the risk of a coronary event within a few months (in what was a likely contributory factor in my father's sudden cardiac death), then this would increase event rates well beyond the first few weeks of the jab yet linking it back to the vaccine, and thus reporting it is highly unlikely to occur later on.

It is instructive to note that according to ambulance service data, in 2021 (the year of the vaccine roll-out), there were approximately an extra 20 000 (~20% increase) out-of-hospital cardiac arrest calls compared to 2019, and approximately 14 000 more than in 2020. Data obtained under Freedom of Information laws from one of the largest ambulance trusts in England suggest that there was no increase from November 2020 to March 2021, and thereafter the rise has been seen disproportionately in the young.[41] This is a huge signal that surely needs investigating with some urgency.[42]

Similarly, a recent paper in *Nature* revealed a 25% increase in both acute coronary syndrome and cardiac arrest calls in the 16- to 39-year-old age groups significantly associated with administration with the first and second doses of the mRNA vaccines but no association with COVID-19 infection.[43] The authors state that:

> [*T*]he findings raise concerns regarding vaccine-induced undetected severe cardiovascular side effects and underscore the already established causal relationship between vaccines and myocarditis, a frequent cause of unexpected cardiac arrest in young individuals. (p. 1)

The disturbing findings in this paper have resulted in calls for a retraction. In the past, scientists with a different view of how data should be analysed would have published a paper with differing assumptions and interpretation for discussion. Now they try to censor.

Many other concerns have been raised about potential harms from the vaccines in the mid- to long-term. Although some of these concerns remain hypothetical, it may be a grave mistake to focus only on what can be measured and not on the wider picture, especially for the young.

What could be the mechanism of harm?

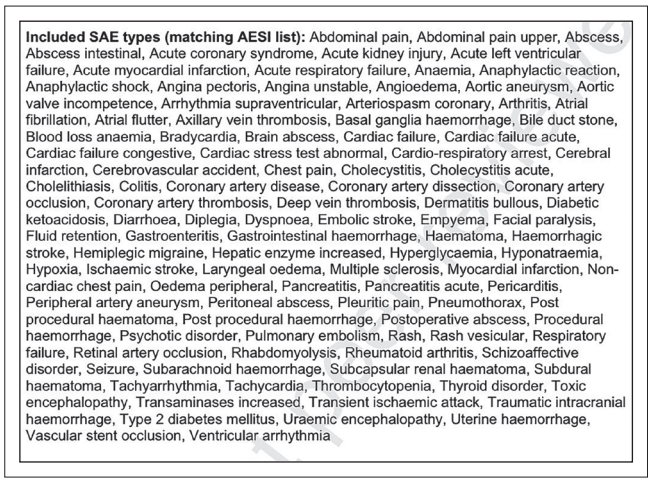
For 'conventional vaccines', an inert part of the bacteria or virus is used to 'educate' the immune system. The immune stimulus is limited, localised and short-lived. For the COVID-19 vaccines, spike protein has been shown to be produced continuously (and in unpredictable amounts) for at least four months after vaccination[44] and is distributed throughout the body after intramuscular injection.[45] For the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines, the spike protein was chosen, possibly because it enables cell entry. However, this protein is not inert, but rather it is the source of much of the pathology associated with severe COVID-19, including endothelial damage,[46] clotting abnormalities[47] and lung damage. It is instructive to note that prior to roll-out of the mRNA products, the WHO endorsed a priority list of potential serious adverse events of special interest that may occur as a direct result of COVID-19 vaccines. The list was based upon the specific vaccine platform, adverse events associated with prior vaccines in general, theoretical associations based upon animal models and COVID-19-specific immunopathogenesis[40] (see Figure 2).

Is the vaccine doing more harm than good?

The most objective determinant of whether the benefits of the vaccines outweigh the harms is by analysing its effects on 'all-cause mortality'. This gets round the thorny issue as to what should be classified as a COVID-19 death, and also takes full account of any negative effects of the vaccine. It would be surprising – to say the least – if during an apparently deadly pandemic, an effective vaccine could not clearly and unequivocally be shown to reduce all-cause mortality.

Pfizer's pivotal mRNA trial in adults did not show any statistically significant reduction in all-cause mortality, and in absolute terms there were actually slightly more deaths in the treatment arm versus in the placebo.

Work by Fenton et al. showed an unusual spike in mortality in each age group of the unvaccinated population, which



Source: Fraiman J, Erviti J, Jones M, et al. Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. Vaccine. 2022 Aug 30:S0264-410X(22)01028-3. https://doi.org/10.1016/j.vaccine.2022.08.036.

SAE, serious adverse events; AESI, adverse events of special interest.

FIGURE 2: World Health Organization endorsed a list of adverse events of special interest associated with COVID-19 vaccinations.

coincides with the vaccine roll-out for each age group.[48] The rapid shrinking in the size of this population means a small-time lag could theoretically produce this effect artifactually. Alternative explanations must include the (more likely) possibility that a rise in mortality after vaccination was misattributed to the unvaccinated population: in other words, those counted as 'unvaccinated deaths' would in fact be those who had died within 14 days of being vaccinated (a freedom of information [FOI] request has now confirmed that authorities in Sweden were indeed categorising deaths within 14 days of dosing as unvaccinated, creating a misleading picture of efficacy vs death).

One has to raise the possibility that the excess cardiac arrests and continuing pressures on hospitals in 2021/2022 from non-COVID-19 admissions may all be signalling a non-COVID-19 health crisis exacerbated by interventions, which would of course also include lockdowns and/or vaccines.

Given these observations, and reappraisal of the randomised controlled trial data of mRNA products, it seems difficult to argue that the vaccine roll-out has been net beneficial in all age groups. While a case can be made that the vaccines may have saved some lives in the elderly or otherwise vulnerable groups, that case seems tenuous at best in other sections of the population, and when the possible short-, medium- and unknown longer-term harms are considered (especially for multiple injections, robust safety data for which simply does not exist), the roll-out into the entire population seems, at best, a reckless gamble. It's important to acknowledge that the risks of adverse events from the vaccine remain constant, whereas the benefits reduce over time, as new variants are (1) less virulent and (2) not targeted by an outdated product. Having appraised the data, it remains a real possibility that my father's sudden cardiac death was related to the vaccine. A pause and reappraisal of vaccination Policies for COVID-19 is long overdue.

Acknowledgements

The author thanks Dr Clare Craig for edits and data analysis, and Alex Starling for comments and suggestions. The author is also grateful for the assistance of a scientist who wishes to remain anonymous due to career pressure.

Competing interests

The author declares that he/she has no financial or personal relationships that may have inappropriately influenced them in writing this article.

Author's contribution

A.M. is the sole author of this article.

Ethical considerations

This article followed all ethical standards for research without direct contact with human or animal subjects.

Funding information

This research received no specific grant from any funding agency in the public , commercial or not-for-profit sectors.

Data availability

Data sharing is not applicable to this article, as no new data were created or analysed in this study.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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Vaccine 40 (2022) 5798–5805

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults

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ARTICLE INFO

Article history:
Received 31 May 2022
Received in revised form 21 July 2022
Accepted 1 August 2022
Available online 31 August 2022

Keywords:
SARS-CoV-2
COVID-19
Vaccines
COVID-19 vaccines
mRNA vaccines
Pfizer-BioNTech COVID-19 vaccine
BNT162b2
Moderna COVID-19 vaccine mRNA-1273
NCT04368728
NCT04470427
Serious adverse events
Adverse events of special interest
Brighton Collaboration
Coalition for Epidemic Preparedness Innovations
Safety Platform for Emergency vACcines

ABSTRACT

Introduction: In 2020, prior to COVID-19 vaccine rollout, the Brighton Collaboration created a priority list, endorsed by the World Health Organization, of potential adverse events relevant to COVID-19 vaccines. We adapted the Brighton Collaboration list to evaluate serious adverse events of special interest observed in mRNA COVID-19 vaccine trials.

Methods: Secondary analysis of serious adverse events reported in the placebo-controlled, phase III randomized clinical trials of Pfizer and Moderna mRNA COVID-19 vaccines in adults (NCT04368728 and NCT04470427), focusing analysis on Brighton Collaboration adverse events of special interest.

Results: Pfizer and Moderna mRNA COVID-19 vaccines were associated with an excess risk of serious adverse events of special interest of 10.1 and 15.1 per 10,000 vaccinated over placebo baselines of 17.6 and 42.2 (95 % CI −0.4 to 20.6 and −3.6 to 33.8), respectively. Combined, the mRNA vaccines were associated with an excess risk of serious adverse events of special interest of 12.5 per 10,000 vaccinated (95 % CI 2.1 to 22.9); risk ratio 1.43 (95 % CI 1.07 to 1.92). The Pfizer trial exhibited a 36 % higher risk of serious adverse events in the vaccine group; risk difference 18.0 per 10,000 vaccinated (95 % CI 1.2 to 34.9); risk ratio 1.36 (95 % CI 1.02 to 1.83). The Moderna trial exhibited a 6 % higher risk of serious adverse events in the vaccine group: risk difference 7.1 per 10,000 (95 % CI –23.2 to 37.4); risk ratio 1.06 (95 % CI 0.84 to 1.33). Combined, there was a 16 % higher risk of serious adverse events in mRNA vaccine recipients: risk difference 13.2 (95 % CI −3.2 to 29.6); risk ratio 1.16 (95 % CI 0.97 to 1.39).

Discussion: The excess risk of serious adverse events found in our study points to the need for formal harm-benefit analyses, particularly those that are stratified according to risk of serious COVID-19 outcomes. These analyses will require public release of participant level datasets.

1. Introduction

In March 2020, the Brighton Collaboration and the Coalition for Epidemic Preparedness Innovations partnership, Safety Platform for Emergency vACcines (SPEAC), created and subsequently updated a "priority list of potential adverse events of special interest relevant to COVID-19 vaccine trials." [1] The list comprises adverse events of special interest (AESIs) based on the specific vaccine platform, adverse events associated with prior vaccines in general, theoretical associations based on animal models, and COVID-19 specific immunopathogenesis. [1] The Brighton Collaboration is a global authority on the topic of vaccine safety and in May 2020, the World Health Organization's Global Advisory Committee on Vaccine Safety endorsed and recommended the reporting of AESIs based on this priority list. To our knowledge, however, the list has not been applied to serious adverse events in randomized trial data.

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https://doi.org/10.1016/j.vaccine.2022.08.036
0264-410X/

We sought to investigate the association between FDA-authorized mRNA COVID-19 vaccines and serious adverse events identified by the Brighton Collaboration, using data from the phase III randomized, placebo-controlled clinical trials on which authorization was based. We consider these trial data against findings from post-authorization observational safety data. Our study was not designed to evaluate the overall harm-benefit of vaccination programs so far. To put our safety results in context, we conducted a simple comparison of harms with benefits to illustrate the need for formal harm-benefit analyses of the vaccines that are stratified according to risk of serious COVID-19 outcomes. Our analysis is restricted to the randomized trial data, and does not consider data on post-authorization vaccination program impact. It does however show the need for public release of participant level trial datasets.

2. Methods

Pfizer and Moderna each submitted the results of one phase III randomized trial in support of the FDA's emergency use authorization of their vaccines in adults. Two reviewers (PD and RK) searched journal publications and trial data on the FDA's and Health Canada's websites to locate serious adverse event results tables for these trials. The Pfizer and Moderna trials are expected to follow participants for two years. Within weeks of the emergency authorization, however, the sponsors began a process of unblinding all participants who elected to be unblinded. In addition, those who received placebo were offered the vaccine. These self-selection processes may have introduced nonrandom differences between vaccinated and unvaccinated participants, thus rendering the post-authorization data less reliable. Therefore, to preserve randomization, we used the interim datasets that were the basis for emergency authorization in December 2020, approximately 4 months after trials commenced.

The definition of a serious adverse event (SAE) was provided in each trial's study protocol and included in the supplemental material of the trial's publication. [2–4] Pfizer and Moderna used nearly identical definitions, consistent with regulatory expectations. An SAE was defined as an adverse event that results in any of the following conditions: death; life-threatening at the time of the event; inpatient hospitalization or prolongation of existing hospitalization; persistent or significant disability/incapacity; a congenital anomaly/birth defect; medically important event, based on medical judgment.

In addition to journal publications, we searched the websites of the FDA (for advisory committee meeting materials) and Health Canada (for sections of the dossier submitted by sponsors to the regulator). [5] For the FDA website, we considered presentations by both the FDA and the sponsors. [6] Within each of these sources, we searched for SAE results tables that presented information by specific SAE type; we chose the most recent SAE table corresponding to the FDA's requirement for a safety median follow-up time of at least 2 months after dose 2.

For each trial, we prepared blinded SAE tables (containing SAE types without results data). Using these blinded SAE tables, two clinician reviewers (JF and JE) independently judged whether each SAE type was an AESI. SAE types that matched an AESI term verbatim, or were an alternative diagnostic name for an AESI term, were included as an AESI. For all other SAE types, the reviewers independently judged whether that SAE type was likely to have been caused by a vaccine-induced AESI, based on a judgment considering the disease course, causative mechanism, and likelihood of the AESI to cause the SAE type. Disagreements were resolved through consensus; if consensus could not be reached, a third clinician reviewer (PW) was used to create a majority opinion. For each included SAE, we recorded the corresponding Brighton Collaboration AESI category and organ system. When multiple AESIs could potentially cause the same SAE, the reviewers selected the AESI that they judged to be the most likely cause based on classical clinical presentation of the AESI.

We used an AESI list derived from the work of Brighton Collaboration's Safety Platform for Emergency vACcines (SPEAC) Project. This project created an AESI list which categorizes AESIs into three categories: those included because they are seen with COVID-19, those with a proven or theoretical association with vaccines in general, and those with proven or theoretical associations with specific vaccine platforms. The first version was produced in March 2020 based on experience from China. Following the second update (May 2020), the WHO Global Advisory Committee on Vaccine Safety (GACVS) adopted the list, and Brighton commenced a systematic review process "to ensure an ongoing understanding of the full spectrum of COVID-19 disease and modification of the AESI list accordingly." [7] This resulted in three additional AESIs being added to the list in December 2020. The subsequent (and most recent fourth) update did not result in any additional AESIs being added to the list. [1].

We matched SAEs recorded in the trial against an expanded list of AESIs created by combining Brighton's SPEAC COVID-19 AESI list with a list of 29 clinical diagnoses Brighton identified as "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list." [7] Sensitivity analysis was used to determine whether use of the original versus expanded list altered our results.

Risk ratios and risk differences between vaccine and placebo groups were calculated for the incidence of AESIs and SAEs. We excluded SAEs that were known efficacy outcomes (i.e. COVID-19), consistent with the approach Pfizer (but not Moderna) used in recording SAE data. The Pfizer study trial protocol states that COVID-19 illnesses and their sequelae consistent with the clinical endpoint definition were not to be reported as adverse events, "even though the event may meet the definition of an SAE." [8] For unspecified reasons, Moderna included efficacy outcomes in their SAE tables, effectively reporting an all-cause SAE result. Because we did not have access to individual participant data, to account for the occasional multiple SAEs within single participants, we reduced the effective sample size by multiplying standard errors in the combined SAE analyses by the square root of the ratio of the number of SAEs to the number of patients with an SAE. This adjustment increased standard errors by 10 % (Pfizer) and 18 % (Moderna), thus expanding the interval estimates. We estimated combined risk ratios and risk differences for the two mRNA vaccines by averaging over the risks using logistic regression models which included indicators for trial and treatment group.

We used a simple harm-benefit framework to place our results in context, comparing risks of excess serious AESIs against reductions in COVID-19 hospitalization.

3. Results

Serious adverse event tables were located for each of the vaccine trials submitted for EUA in adults (age 16 + for Pfizer, 18 + for Moderna) in the United States: Pfizer-BioNTech COVID-19 vaccine BNT162b2 (NCT04368728) [2,9,10] and Moderna COVID-19 vaccine mRNA-1273 (NCT04470427). [3,11,12] (Table 1).

3.1. Reporting windows and serious adverse events

Moderna reported SAEs from dose 1 whereas Pfizer limited reporting from dose 1 to 1 month after dose 2. Both studies

Table 1
Data sources for phase III trials.

Trial	Data cutoff date	Journal articles	FDA sources	Health Canada sources
Pfizer trial in ages 16 and above (NCT04368728)	14 Nov 2020 (supported Dec 2020 EUA)	Aggregate data only	**Table 23 in sponsor briefing document**	**Table 55 in sponsor document C4591001 Final Analysis Interim Report Body**
Moderna trial in ages 18 and above (NCT04470427)	25 Nov 2020 (supported Dec 2020 EUA)	Table S11 in publication	Table 27 in sponsor briefing document	**Table 14.3.1.13.3 in sponsor document mRNA-1273-P301 Unblinded Safety Tables Batch 1 (DS2)**

Note: bolded font indicates dataset chosen for analysis; EUA = Emergency Use Authorization.

reported all data at the time of data cutoff (14 Nov 2020 for Pfizer, 25 Nov 2020 for Moderna). 17 SAEs that were efficacy endpoints were removed from the Moderna trial (16 "COVID-19" SAEs and 1 "COVID-19 pneumonia" SAE). One such efficacy endpoint meeting the definition of a SAE was removed from the Pfizer trial ("SARS-CoV-2 test positive" SAE).

The Pfizer trial exhibited a 36 % higher risk of serious adverse events in vaccinated participants in comparison to placebo recipients: 67.5 per 10,000 versus 49.5 per 10,000; risk difference 18.0 per 10,000 vaccinated participants (95 % compatibility[1] interval 1.2 to 34.9); risk ratio 1.36 (95 % CI 1.02 to 1.83). The Moderna trial exhibited a 6 % higher risk of SAEs in vaccinated individuals compared to those receiving placebo: 136 per 10,000 versus 129 per 10,000; risk difference 7.1 per 10,000 (95 % CI −23.2 to 37.4); risk ratio 1.06 (95 % CI 0.84 to 1.33). Combined, there was a 16 % higher risk of SAEs in mRNA vaccine recipients than placebo recipients: 98 per 10,000 versus 85 per 10,000; risk difference 13.2 (95 % CI −3.2 to 29.6); risk ratio 1.16 (95 % CI 0.97 to 1.39). **(**Table 2**)**.

3.2. Serious adverse events of special interest

Regarding whether each SAE type was included on the SPEAC derived AESI list, agreement between the two independent clinician reviewers was 86 % (281/325); 40 of the 44 disagreements were resolved through consensus, and only four disagreements necessitated a third clinician reviewer. **Supplemental** Table 1 includes a full list of included and excluded SAEs across both trials.

In the Pfizer trial, 52 serious AESI (27.7 per 10,000) were reported in the vaccine group and 33 (17.6 per 10,000) in the placebo group. This difference corresponds to a 57 % higher risk of serious AESI (RR 1.57 95 % CI 0.98 to 2.54) and a risk difference of 10.1 serious AESI per 10,000 vaccinated participants (95 % CI −0.4 to 20.6). In the Moderna trial, 87 serious AESI (57.3 per 10,000) were reported in the vaccine group and 64 (42.2 per 10,000) in the placebo group. This difference corresponds to a 36 % higher risk of serious AESI (RR 1.36 95 % CI 0.93 to 1.99) and a risk difference of 15.1 serious AESI per 10,000 vaccinated participants (95 % CI −3.6 to 33.8). Combining the trials, there was a 43 % higher risk of serious AESI (RR 1.43; 95 % CI 1.07 to 1.92) and a risk difference of 12.5 serious AESI per 10,000 vaccinated participants (95 % CI 2.1 to 22.9). **(**Table 2**)**.

Of the 236 serious AESIs occurring across the Pfizer and Moderna trials, 97 % (230/236) were adverse event types included as AESIs because they are seen with COVID-19. In both Pfizer and Moderna trials, the largest excess risk occurred amongst the Brighton category of coagulation disorders. Cardiac disorders have been of central concern for mRNA vaccines; in the Pfizer trial more cardiovascular AESIs occurred in the vaccine group than in the placebo group, but in the Moderna trial the groups differed by only 1 case. **(**Tables 3 and 4**)**.

[1] A compatibility interval is identical to a confidence interval, but relabeled to emphasize that it is not a Bayesian posterior interval (as is improperly suggested by the "confidence" label).[13,14].

3.3. Sensitivity analysis

As a sensitivity analysis, we restricted the serious AESI analysis to those AESIs listed in SPEAC's COVID-19 AESI list (i.e. separating out Brighton's list of 29 clinical diagnoses "known to have been reported but not in sufficient numbers to merit inclusion on the AESI list.") This reduced the total number of AESIs across the two trials by 48 (35 vaccine group, 13 placebo group). There was still a higher risk of serious AESI when limited to the SPEAC COVID-19 AESI list, but the magnitude of the excess (in both relative and absolute terms) was smaller than when using the larger AESI list. **(Supplemental** Table 2**)**.

3.4. Harm-benefit considerations

In the Moderna trial, the excess risk of serious AESIs (15.1 per 10,000 participants) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (6.4 per 10,000 participants). [3] In the Pfizer trial, the excess risk of serious AESIs (10.1 per 10,000) was higher than the risk reduction for COVID-19 hospitalization relative to the placebo group (2.3 per 10,000 participants).

4. Comparison with FDA reviews

In their review of SAEs supporting the authorization of the Pfizer and Moderna vaccines, the FDA concluded that SAEs were, for Pfizer, "balanced between treatment groups," [15] and for Moderna, were "without meaningful imbalances between study arms." [16] In contrast to the FDA analysis, we found an excess risk of SAEs in the Pfizer trial. Our analysis of Moderna was compatible with FDA's analysis, finding no meaningful SAE imbalance between groups.

The difference in findings for the Pfizer trial, between our SAE analysis and the FDA's, may in part be explained by the fact that the FDA analyzed the total number of participants experiencing any SAE, whereas our analysis was based on the total number of SAE events. Given that approximately twice as many individuals in the vaccine group than in the placebo group experienced multiple SAEs (there were 24 more events than participants in the vaccine group, compared to 13 in the placebo group), FDA's analysis of only the incidence of participants experiencing any SAE would not reflect the observed excess of multiple SAEs in the vaccine group.

A more important factor, however, may be that FDA's review of non-fatal SAEs used a different analysis population with different follow-up windows. The FDA reported 126 of 21,621 (0.6 %) of vaccinated participants experienced at least one SAE at data cutoff compared to 111 of 21,631 (0.5 %) of placebo participants. In contrast, our analysis found 127 SAEs among 18,801 vaccine recipients versus 93 SAEs among 18,785 placebo recipients. [15] While summary results for the population we analyzed was provided in a table, FDA did not report an analysis of them. The substantially larger denominators in FDA's analysis (5,666 more participants) reflect the fact that their analysis included all individuals receiving at least one dose (minus 196 HIV-positive participants), irrespec-

Table 2
Serious adverse events.

Trial	Total events (events per 10,000 participants)[a] Vaccine	Placebo	Risk difference per 10,000 participants (95 % CI)[e]	Risk ratio (95 % CI)[e]
Serious adverse events				
Pfizer[b]	127 (67.5)	93 (49.5)	18.0 (1.2 to 34.9)	1.36 (1.02 to 1.83)
Moderna[c,d]	206 (135.7)	195 (128.6)	7.1 (−23.2 to 37.4)	1.06 (0.84 to 1.33)
Combined[f]	333 (98.0)	288 (84.8)	13.2 (-3.2 to 29.6)	1.16 (0.97 to 1.39)
Serious adverse events of special interest				
Pfizer	52 (27.7)	33 (17.6)	10.1 (-0.4 to 20.6)	1.57 (0.98 to 2.54)
Moderna	87 (57.3)	64 (42.2)	15.1 (-3.6 to 33.8)	1.36 (0.93 to 1.99)
Combined[f]	139 (40.9)	97 (28.6)	12.5 (2.1 to 22.9)	1.43 (1.07 to 1.92)

[a] Denominators for Pfizer were 18,801 in the vaccine group and 18,785 in the placebo group, and for Moderna were 15,185 in the vaccine group and 15,166 in the placebo group.
[b] Pfizer excluded efficacy outcomes from its SAE table (COVID-19 illnesses and their sequelae meeting the definition of an SAE). However, at least one SAE appears to have been inadvertently included, which we removed from our calculations (“SARS-CoV-2 test positive”: 0 vaccine group; 1 placebo group).
[c] Moderna included efficacy outcomes in its SAE table (COVID-19 illnesses and their sequelae meeting the definition of an SAE). We removed efficacy SAEs outcomes that could be identified: “COVID-19” and “COVID-19 pneumonia.” Lacking access to participant level data, SAEs that were sequelae of serious COVID-19 could not be identified and therefore remain included in this analysis.
[d] “All SAEs” for Moderna was calculated using the “Number of serious AEs” row in Moderna’s submission to FDA.[11].
[e] Standard errors used to estimate 95% CIs were inflated by the factor $\sqrt{}$[#SAE]/[#patients with SAE] to account for multiple SAE within patients.
[f] The combined risk differences and risk ratios were computed from the fitted logistic regression models and so may not exactly equal comparisons computed from the first two columns.

Table 3
Serious AESIs, Pfizer trial.

Brighton category	Vaccine	Placebo	Vaccine events per 10,000	Placebo events per 10,000	Difference in events per 10,000	Risk ratio
Association with immunization in general						
Anaphylaxis	1	1	0.5	0.5	0.0	1.00
Association with specific vaccine platform(s)						
Encephalitis/encephalomyelitis	0	2	0.0	1.1	−1.1	0.00
Seen with COVID-19						
Acute kidney injury	2	0	1.1	0.0	1.1	N/A
Acute liver injury	0	1	0.0	0.5	−0.5	0.00
Acute respiratory distress syndrome	2	1	1.1	0.5	0.5	2.00
Coagulation disorder	16	10	8.5	5.3	3.2	1.60
Myocarditis/pericarditis	2	1	1.1	0.5	0.5	2.00
Other forms of acute cardiac injury	16	12	8.5	6.4	2.1	1.33
Subtotal	39	28	20.7	14.9	5.8	1.39
Brighton list of 29 clinical diagnoses seen with COVID-19						
Abscess	4	1	2.1	0.5	1.6	4.00
Cholecystitis	4	2	2.1	1.1	1.1	2.00
Colitis/Enteritis	1	1	0.5	0.5	0.0	1.00
Diarrhea	1	0	0.5	0.0	0.5	N/A
Hyperglycemia	1	1	0.5	0.5	0.0	1.00
Pancreatitis	1	0	0.5	0.0	0.5	N/A
Psychosis	1	0	0.5	0.0	0.5	N/A
Subtotal	13	5	6.9	2.7	4.3	2.60
Total	**52**	**33**	**27.7**	**17.6**	**10.1**	**1.57**

tive of the duration of post-injection follow-up time. In contrast, our analysis was based on the study population with median follow-up $\geq$ 2 months after dose 2 (minus 120 HIV-positive participants), of which 98.1 % had received both doses. [2,17] The FDA’s analysis of SAEs thus included thousands of additional participants with very little follow-up, of which the large majority had only received 1 dose.

4.1. Comparison with post-authorization studies

Although the randomized trials offer high level evidence for evaluating causal effects, the sparsity of their data necessitates that harm-benefit analyses also consider observational studies. Since their emergency authorization in December 2020, hundreds of millions of doses of Pfizer and Moderna COVID-19 vaccines have been administered and post-authorization observational data offer a complementary opportunity to study AESIs. Post-authorization observational safety studies include cohort studies (which make use of medical claims or electronic health records) and disproportionality analyses (which use spontaneous adverse event reporting systems). In July 2021, the FDA reported detecting four potential adverse events of interest: pulmonary embolism, acute myocardial infarction, immune thrombocytopenia, and disseminated intravascular coagulation following Pfizer’s vaccine based on medical claims data in older Americans. [18] Three of these four serious adverse event types would be categorized as coagulation disorders, which is the Brighton AESI category that exhibited the largest excess risk in the vaccine group in both the Pfizer and Moderna trials. FDA stated it would further investigate the findings but at the time of our writing has not issued an update. Similarly, spontaneous-reporting systems have registered serious adverse reactions including anaphylaxis (all COVID-19 vaccines), thrombocytopenia syndrome among premenopausal females (Janssen vaccine), and myocarditis and pericarditis among younger males (Pfizer and Moderna vaccines). [19,20].

Using data from three postmarketing safety databases for vaccines (VAERS, EudraVigilance, and VigiBase), disproportionality studies have reported excess risks for many of the same SAE types as in

Table 4
Serious AESIs, Moderna trial.

Brighton category	Vaccine	Placebo	Vaccine events per 10,000	Placebo events per 10,000	Difference in events per 10,000	Risk ratio
Association with specific vaccine platform(s)						
Bell's Palsy	1	0	0.7	0.0	0.7	N/A
Encephalitis/encephalomyelitis	1	0	0.7	0.0	0.7	N/A
Seen with COVID-19						
Acute kidney injury	1	3	0.7	2.0	−1.3	0.33
Acute liver injury	1	0	0.7	0.0	0.7	N/A
Acute respiratory distress syndrome	7	4	4.6	2.6	2.0	1.75
Angioedema	0	2	0.0	1.3	−1.3	0.00
Coagulation disorder	20	13	13.2	8.6	4.6	1.54
Generalized Convulsions	2	0	1.3	0.0	1.3	N/A
Myelitis	0	1	0.0	0.7	−0.7	0.00
Myocarditis/pericarditis	4	5	2.6	3.3	−0.7	0.80
Other forms of acute cardiac injury	26	26	17.1	17.1	0.0	1.00
Other rash	1	1	0.7	0.7	0.0	1.00
Rhabdomyolysis	0	1	0.0	0.7	−0.7	0.00
Single Organ Cutaneous Vasculitis	1	0	0.7	0.0	0.7	N/A
Subtotal	65	56	42.8	36.9	5.9	1.16
Brighton list of 29 clinical diagnoses seen with COVID-19						
Abscess	1	0	0.7	0.0	0.7	N/A
Arthritis	3	1	2.0	0.7	1.3	3.00
Cholecystitis	4	0	2.6	0.0	2.6	N/A
Colitis/Enteritis	6	3	4.0	2.0	2.0	2.00
Diarrhea	2	1	1.3	0.7	0.7	2.00
Hyperglycemia	1	0	0.7	0.0	0.7	N/A
Hyponatremia	1	1	0.7	0.7	0.0	1.00
Pancreatitis	2	0	1.3	0.0	1.3	N/A
Pneumothorax	0	1	0.0	0.7	−0.7	0.00
Psychosis	1	1	0.7	0.7	0.0	1.00
Thyroiditis	1	0	0.7	0.0	0.7	N/A
Subtotal	22	8	14.5	5.3	9.2	2.75
Total	**87**	**64**	**57.3**	**42.2**	**15.1**	**1.36**

the present study. [21–23] For example, a study using VAERS and EudraVigilance comparing the disproportionality of adverse event reports between the influenza vaccine versus the mRNA COVID-19 vaccines reported excess risks for the following Brighton AESIs: cardiovascular events, coagulation events, hemorrhages, gastrointestinal events, and thromboses. [22] While CDC published a protocol[24] in early 2021 for using proportional reporting ratios for signal detection in the VAERS database, results from the study have not yet been reported. [25] Among self-controlled case series, one reported a rate ratio of 1.38 (95 % CI 1.12–1.71) for hemorrhagic stroke following Pfizer vaccine, [26] another reported 0.97 (95 % CI 0.81–1.15), [27] while a cohort study[28] reported 0.84 (95 % CI 0.54–1.27).

5. Discussion

Using a prespecified list of AESI identified by the Brighton Collaboration, higher risk of serious AESI was observed in the mRNA COVID-19 vaccine group relative to placebo in both the Pfizer and Moderna adult phase III trials, with 10.1 (Pfizer) and 15.1 (Moderna) additional events for every 10,000 individuals vaccinated. Combined, there was a risk difference of 12.5 serious AESIs per 10,000 individuals vaccinated (95 % CI 2.1 to 22.9). These results raise concerns that mRNA vaccines are associated with more harm than initially estimated at the time of emergency authorization. In addition, our analysis identified a 36 % higher risk of serious adverse events in vaccinated participants in the Pfizer trial: 18.0 additional SAEs per 10,000 vaccinated (95 % CI 1.2 to 34.9). Consistent with the FDA evaluation, our analysis found no clear difference in SAEs between groups in the Moderna trial.

Results between the Pfizer and Moderna trials were similar for the AESI analysis but exhibited substantial variation in the SAE analysis. Caution is needed in interpreting this variation as it may be substantially explained by differences in SAE recording practices in the trials rather than differences in actual vaccine harm profiles. For reasons that are not documented in the trial protocol, Moderna included efficacy outcomes in its SAE tabulations, while Pfizer excluded them. As a result, Moderna's SAE table did not present a traditional SAE analysis but rather an all-cause SAE analysis. The FDA analysis of the Moderna trial presented an all-cause SAE analysis, which estimates total vaccine effects on SAEs, including effects transmitted via effects on COVID-19. It did not however present a traditional SAE analysis with efficacy endpoints removed, which attempts to estimate only the direct effects on SAEs. While our analysis attempted to perform a traditional SAE analysis by excluding efficacy SAEs (serious COVID-19 and its sequelae), our effort was hindered because we did not have access to patient level data. Easily recognizable efficacy SAEs ("COVID-19", "COVID-19 pneumonia," and "SARS-CoV-2 test positive") could be removed, but many participants who experienced a COVID-19 SAE likely experienced multiple other SAEs (e.g. pneumonia, hypoxia, and thrombotic events) which could not be identified and therefore remain included in our analysis. Of 17 total efficacy SAEs (16 "COVID-19" and 1 "COVID-19 pneumonia") removed from our analysis of the Moderna trial, 16 were in the placebo arm. As a consequence, the background SAE risk (risk in absence of COVID-19) would be overestimated by the Moderna placebo group, resulting in underestimation of the actual risk of SAEs and AESIs attributable to the vaccine in the Moderna comparisons as well as in the combined analysis. Access to patient-level data would allow adjustments for this problem.

Rational policy formation should consider potential harms alongside potential benefits. [29] To illustrate this need in the present context, we conducted a simple harm-benefit comparison using the trial data comparing excess risk of serious AESI against reductions in COVID-19 hospitalization. We found excess risk of serious AESIs to exceed the reduction in COVID-19 hospitalizations in both Pfizer and Moderna trials.

This analysis has the limitations inherent in most harm-benefit comparisons. First, benefits and harms are rarely exact equivalents, and there can be great variability in the degree of severity within both benefit and harm endpoints. For example, intubation and short hospital stay are not equivalent but both are counted in "hospitalization"; similarly, serious diarrhea and serious stroke are not equivalent but both are counted in "SAE." Second, individuals value different endpoints differently. Third, without individual participant data, we could only compare the number of individuals hospitalized for COVID-19 against the number of serious AESI events, not the number of participants experiencing any serious AESI. Some individuals experienced multiple SAEs whereas hospitalized COVID-19 participants were likely only hospitalized once, biasing the analysis towards exhibiting net harm. To gauge the extent of this bias, we considered that there were 20 % (Pfizer) and 34 % (Moderna) more SAEs than participants experiencing any SAE. As a rough sensitivity calculation, if we divide the Pfizer excess serious AESI risk of 10.1 by 1.20 it becomes 8.4 compared to a COVID-19 hospitalization risk reduction of 2.3; if we divide the Moderna excess serious AESI risk of 15.1 by 1.34 it becomes 11.3 compared to a COVID-19 hospitalization risk reduction of 6.4.

Harm-benefit ratios will be different for populations at different risk for serious COVID-19 and observation periods that differ from those studied in the trials. Presumably, larger reductions in COVID-19 hospitalizations would have been recorded if trial follow-up were longer, more SARS-CoV-2 was circulating, or if participants had been at higher risk of serious COVID-19 outcomes, shifting harm-benefit ratios toward benefit. Conversely, harm-benefit ratios would presumably shift towards harm for those with lower risk of serious COVID-19 outcomes--such as those with natural immunity, younger age or no comorbidities. Similarly, waning vaccine effectiveness, decreased viral virulence, and increasing degree of immune escape from vaccines might further shift the harm-benefit ratio toward harm. Large, randomized trials in contemporary populations could robustly answer these questions. Absent definitive trials, however, synthesis of multiple lines of evidence will be essential. [30,48,49].

Adverse events detected in the post-marketing period have led to the withdrawal of several vaccines. An example is intussusception following one brand of rotavirus vaccine: around 1 million children were vaccinated before identification of intussusception, which occurred in around 1 per 10,000 vaccinees. [31] Despite the unprecedented scale of COVID-19 vaccine administration, the AESI types identified in our study may still be challenging to detect with observational methods. Most observational analyses are based on comparing the risks of adverse events "observed" against a background (or "expected") risk, which inevitably display great variation, by database, age group, and sex. [32] If the actual risk ratio for the effect was 1.4 (the risk ratio of the combined AESI analysis), it could be quite difficult to unambiguously replicate it with observational data given concerns about systematic as well as random errors. [33–35].

In addition, disproportionality analyses following COVID-19 vaccination also have limitations, particularly with respect to the type of adverse events seen in our study. The majority of SAEs that contributed to our results are relatively common events, such as ischemic stroke, acute coronary syndrome, and brain hemorrhage. This complicates signal detection because clinical suspicion of an adverse vaccine reaction following an event commonly seen in clinical practice will be lower than for SAEs like myocarditis.[50] For this reason, clinical suspicion leading to the filing of an individual case safety report--may be far less common in the post-authorization setting than in the trials. At the same time, heightened awareness about COVID-19 vaccine SAEs can result in under and overreporting. Public health messages assuring vaccine safety may lower clinical suspicion of potential causal relationships, whereas messages about potential harms can conversely stimulate reports that otherwise may not have been made. These factors can lead to bias both directions, further complicating interpretation. In contrast to these problems, in the randomized trials used in this analysis, all SAEs were to be recorded, irrespective of clinical judgment regarding potential causality.

Although our analysis is secondary, reanalyses of clinical trial data have led to the detection of adverse events well after the market entry of major drugs such as rofecoxib and rosiglitazone. [36,37] Our analysis has an advantage over postmarketing observational studies in that the data are from blinded, placebo-controlled randomized trials vetted by the FDA, which were matched against a list of adverse events created before the availability of the clinical-trial results and designed for use in COVID-19 vaccine trials.

Our study has several important limitations. First, Pfizer's trial did not report SAEs occurring past 1 month after dose 2. This reporting threshold may have led to an undercounting of serious AESIs in the Pfizer trial. Second, for both studies, the limited follow up time prevented an analysis of harm-benefit over a longer period. Third, all SAEs in our analysis met the regulatory definition of a serious adverse event, but many adverse event types which a patient may themselves judge as serious may not meet this regulatory threshold. Fourth, decisions about which SAEs to include or exclude as AESIs requires subjective, clinical judgements in the absence of detailed clinical information about the actual SAEs. We encourage third party replication of our study, with access to complete SAE case narratives, to determine the degree to which these decisions affected our findings. For additional sensitivity analyses, such replication studies could also make use of other AESI lists, such as those prepared by FDA, [38–41] CDC, [24], Pfizer, [42], or a *de novo* AESI list derived from a list of COVID-19 complications understood to be induced via SARS-CoV-2's spike protein. [43,44].

A fifth important limitation is our lack of access to individual participant data, which forced us to use a conservative adjustment to the standard errors. The 95 % CIs[13,14] calculated are therefore only approximate because we do not know which patients had multiple events. Finally, as described above, in the Moderna analysis, the SAEs that were sequelae of serious COVID-19 could not be identified and therefore remain included in our calculations. Because the vaccines prevent SAEs from COVID-19 while adding SAE risks of their own, this inclusion makes it impossible to separately estimate SAEs due to the vaccine from SAEs due to COVID-19 in the available Moderna data, as must be done to extrapolate harm-benefit to other populations. These study limitations all stem from the fact that the raw data from COVID-19 vaccine clinical trials are not publicly available. [45,46].

We emphasize that our investigation is preliminary, to point to the need for more involved analysis. The risks of serious AESIs in the trials represent only group averages. SAEs are unlikely to be distributed equally across the demographic subgroups enrolled in the trial, and the risks may be substantially less in some groups compared to others. Thus, knowing the actual demographics of those who experienced an increase in serious AESI in the vaccine group is necessary for a proper harm-benefit analysis. In addition, clinical studies are needed to see if particular SAEs can be linked to particular vaccine ingredients as opposed to unavoidable consequences of exposure to spike protein, as future vaccines could then be modified accordingly or sensitivities can be tested for in advance. In parallel, a systematic review and meta-analysis using individual participant data should be undertaken to address questions of harm-benefit in various demographic subgroups, particularly in those at low risk of serious complications from COVID-19. Finally, there is a pressing need for comparison of SAEs and harm-benefit for different vaccine types; some initial work has already begun in this direction. [47].

Full transparency of the COVID-19 vaccine clinical trial data is needed to properly evaluate these questions. Unfortunately, as we approach 2 years after release of COVID-19 vaccines, participant level data remain inaccessible. [45,46].

Author contributions

All authors had full access to all of the data in the study (available at https://doi.org/10.5281/zenodo.6564402), and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.
Acquisition of data: Doshi.
Analysis and interpretation: All authors.
Statistical analysis: Jones, Greenland.
Drafting of the manuscript: Fraiman, Doshi.
Critical revision of the manuscript for important intellectual content: All authors.

Data availability

All of the data in the study is available at https://doi.org/10.5281/zenodo.6564402

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank Jean Rees for help identifying sources of data.

Funding

This study had no funding support.

Ethical review statement

This research was confirmed to be Not Human Subjects Research (NHSR) by University of Maryland, Baltimore (HP-00102561).

Conflicts of interest

JF, JE, MJ, SG, PW, RK: none to declare. PD has received travel funds from the European Respiratory Society (2012) and Uppsala Monitoring Center (2018); grants from the FDA (through University of Maryland M-CERSI; 2020), Laura and John Arnold Foundation (2017-22), American Association of Colleges of Pharmacy (2015), Patient-Centered Outcomes Research Institute (2014-16), Cochrane Methods Innovations Fund (2016-18), and UK National Institute for Health Research (2011-14); was an unpaid IMEDS steering committee member at the Reagan-Udall Foundation for the FDA (2016-2020) and is an editor at The BMJ. The views expressed here are those of the authors and do not necessarily reflect those of their employers.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2022.08.036.

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Increased emergency cardiovascular events among under-40 population in Israel during vaccine rollout and third COVID-19 wave

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Cardiovascular adverse conditions are caused by coronavirus disease 2019 (COVID-19) infections and reported as side-effects of the COVID-19 vaccines. Enriching current vaccine safety surveillance systems with additional data sources may improve the understanding of COVID-19 vaccine safety. Using a unique dataset from Israel National Emergency Medical Services (EMS) from 2019 to 2021, the study aims to evaluate the association between the volume of cardiac arrest and acute coronary syndrome EMS calls in the 16–39-year-old population with potential factors including COVID-19 infection and vaccination rates. An increase of over 25% was detected in both call types during January–May 2021, compared with the years 2019–2020. Using Negative Binomial regression models, the weekly emergency call counts were significantly associated with the rates of 1st and 2nd vaccine doses administered to this age group but were not with COVID-19 infection rates. While not establishing causal relationships, the findings raise concerns regarding vaccine-induced undetected severe cardiovascular side-effects and underscore the already established causal relationship between vaccines and myocarditis, a frequent cause of unexpected cardiac arrest in young individuals. Surveillance of potential vaccine side-effects and COVID-19 outcomes should incorporate EMS and other health data to identify public health trends (e.g., increased in EMS calls), and promptly investigate potential underlying causes.

Cardiovascular adverse outcomes such as blood clotting (e.g., coronary artery thrombosis), acute coronary syndrome, cardiac arrest and myocarditis have been identified as consequences of coronavirus disease 2019 (COVID-19) infection[1–5]. Similarly, data from regulatory surveillance and self-reporting systems, including the Vaccine Adverse events Reporting System (VAERS) in the United States (US)[6], the Yellow Card System in the United Kingdom[7] and the EudraVigilance system in Europe[8], associate similar cardiovascular side-effects[9–13] with a number of COVID-19 vaccines currently in use.

More recently, several studies established probable causal relationship between the messenger RNA (mRNA) vaccines of BNT162b2 and mRNA-1273[11,14–16] as well as adenovirus (ChAdOx1) vaccines[17] with myocarditis, primarily in children, young and middle-age adults. The study by the Ministry of Health in Israel, a country with one of the highest vaccination rates in the world, assesses the risk of myocarditis after receiving the 2nd vaccine dose to be between 1 in 3000 to 1 in 6000 in men of age 16–24 and 1 in 120,000 in men under 30[11–13]. A follow up study by the US Center of Disease Control (CDC) based on the VAERS and V-Safe self-reporting systems[18] further confirms these findings[19]. The CDC has recently posted a warning regarding a vaccine-related risk of myocarditis, but still maintained their recommendation to vaccinate young individuals and children over 12[7]. Similar concerns are reflected in the recent Food and Drug Administration approval to the Pfizer vaccine that requires several follow studies on the short and long terms effects of myocarditis in young individuals[20].

While the benefits of COVID-19 vaccination are clear, especially for populations at great risk of developing serious and potentially life-threatening illness[15,21], it is important to better understand the potential risks to

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minimize potential harm. However, assessing the connection between myocarditis and other potential cardiovascular conditions, and the COVID-19 vaccines is challenging. First, self-reporting systems[22] of adverse events are known to have self-reporting bias and both under and over-reporting problems[23–25]. 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 a particularly insidious disease with multiple reported manifestations. There is vast literature that highlights asymptomatic cases of myocarditis, which are often underdiagnosed[26,27], as well as cases in which myocarditis can possibly be misdiagnosed as acute coronary syndrome (ACS)[28–30]. 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[26,31–33]. Thus, it is a plausible concern that increased rates of myocarditis among young people could lead to an increase in other severe cardiovascular adverse events, such as cardiac arrest (CA) and ACS. Anecdotal evidence suggests that this might not be only a theoretical concern[16].

Third, myocardial injury and myocarditis is prevalent among patients with COVID-19 infection[26,34]. As COVID-19 vaccine rollouts often take place with background community COVID-19 infections, 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 or induced by COVID-19 vaccines. Moreover, such increases may even be caused by other underlying causal mechanisms indirectly related to COVID-19, for example, patients delaying seeking emergent care because of fear of the pandemic and lockdowns[35].

This study aims to explore how additional data sources, such as those from emergency medical services (EMS), can complement self-reporting vaccine surveillance systems in identifying COVID-19 related public health trends. More specially, the study examines 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 EMS (IEMS) data system and analyzes all calls related to CA and ACS events over two and a half years, from January 1st, 2019, throughout June 20th, 2021.

Methods

Study design. This retrospective population-based study leverages the IEMS data system and analyzes all calls related to CA and ACS events over two and a 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 (1/2019–2/2020), about 10 months of a 'pandemic period' with two waves of the pandemic (3/2020–12/2020), and about 6 months of a 'pandemic and vaccination period' (1/2021–6/2021), during which Israel launched its vaccination rollout 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 (E-3300). 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 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 (as opposed to the initial call classification), date, relevant response characteristics (e.g., death on scene and whether 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 or ACS. CA calls were defined as a sudden electrical malfunction of the heart of presumed cardiac or medical etiology, resulting in collapse of a patient, excluding CAs related to trauma, drug overdose, or suicide. ACS calls were defined as conditions where the patients experience a reduction in blood flow to the heart that is associated with myocardial infarction.

The call codes used to identify CA and ACS calls are determined by the EMS teams based on defined protocols of the IEMS. CA diagnosis was made based on the circumstances of collapse as described by the caller to the dispatch team, the CA victim's electrocardiogram (ECG) as obtained through an automated external defibrillator, and common indicators of CA as observed by the responding paramedics (e.g., patient unresponsiveness, agonal breathing). CAs due or obviously related to trauma, drug overdose, or suicide were excluded in this call code and from the study. ACS diagnosis was made based on the patient's 12-lead ECG (a 12-lead ECG was performed on all patients suspected of ACS to confirm the diagnosis), symptoms (e.g., chest pain, shortness of breath), medical history, and physical examination, as obtained by the responding paramedics. Importantly, these protocol and diagnoses were the same throughout the entire study period (2019–2021), allowing for a consistent comparison between the call counts during the baseline, pandemic, and vaccination periods.

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[36], as well as the weekly number of new confirmed COVID-19 cases by age group, across all of Israel[37]. 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[38]. 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.

Data and statistical analyses. *Trends in CA and ACS calls.* For each pair of a diagnosis (CA or ACS), age group (16–39, over-40 or all-ages), and gender (male, female, or both genders) the year-to-year absolute and relative changes in calls were calculated. The respective statistical significance of these changes were based on the two-tailed Poisson E-test[39]. These changes were calculated separately with respect to the full calendar year (2019–2020) and from January 1st to May 31st (2019–2021). January–May time period was used for comparison as it corresponds with the administration of vaccinations among the 16–39 age group in 2021[36]. The full calendar year comparisons were calculated to examine the changes in calls when COVID-19 infections were prevalent, but no vaccinations were administered among the 16–39 age group. Additional analyses describing the percent of CA calls where the patient died on scene (i.e., death declared prior to hospital arrival) and received resuscitation (i.e., patient received defibrillation or cardiopulmonary resuscitation) are outlined in the Appendix.

To visualize the temporal trends of CA and ACS call volume and potential relationship to COVID-19 infection rates and vaccination rates for the 16–39 age group, graphs were created for CA and ACS calls, respectively. Each graph overlays several moving-average time-series over the study period. These include the five-week centered moving-average of the respective weekly EMS call counts, as well as the three-week centered moving-average counts of new COVID-19 infection cases, administered 1st vaccine doses, and administered 2nd vaccine doses. The graphs also indicate the periods of the three national COVID-19-related public health lockdown advisories in Israel[40].

To improve the understanding these trends during the third pandemic wave and vaccination rollout, 'zoom-in' graphs were similarly created for the time-period October 18th, 2020, through June 20th, 2021. The zoom-in graphs also highlight estimates of the number of individuals who only received one vaccination dose during this time. This was done by plotting an additional time-series of the three-week moving-average of the administered 2nd vaccine doses shifted backwards in time by three weeks. More precisely, the difference between the number of 1st vaccine doses and the number of 2nd vaccine doses shifted backwards in time by three weeks shows the estimated number of patients that only received their 1st dose following Pzifer's vaccination administration recommendations (i.e., the estimated number of patients who did not received a 2nd vaccine dose after a 3-week period following 1st vaccine dose administration). This difference is also used to estimated number of single doses administered to individuals who had recovered from COVID-19 infections, which was plotted from April 1st, 2021, onwards (April 1st 2021 was shortly after the Israel Ministry of Health approved vaccination for this population[41]).

Graphs for the above-40 and all-ages groups are shown in Supplemental Figs. 1–4.

Time-series data processing for CA and ACS call, vaccination administration, and COVID-19 infection counts. 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 were calculated and 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 1st and 2nd vaccine doses administered, respectively, in age groups 16–39 and over-40; 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) and over-40, respectively. Note that the COVID-19 infection dataset[37] 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[19]. 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[19]. 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 (i.e., cumulative counts between one, two, three, four, five and six weeks).

Association of year-to-year call count trends with COVID-19 infections and vaccine administration. 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 bi-weekly (current and prior week) cumulative counts of 1st and 2nd vaccine doses administered 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 cumulative three-week (current and prior two weeks) new COVID-19 infection counts. The same was calculated for the sum of the time-series of CA and ACS weekly call counts for the 16–39 age group (i.e., correlation with the respective time-series of vaccine dose and new COVID-19 infection counts). As mentioned previously, the bi-weekly and three-week cumulative counts for the vaccinations and COVID-19 infections, respectively, were determined based on prior literature suggesting adverse events occur within those respective durations of time[19]. A post hoc power analysis was also performed using G*Power (version 3.1.9.7)[42] to determine the statistical power (i.e., the probability of rejecting the null hypothesis, concluding an effect is found, and avoiding a Type II error, when an effect truly exists) of the correlation analyses. Finally, since the impact of COVID-19 might occur across a variable period of time, the same analysis was repeated with respect to the time-series of new COVID-19 infections count but varying the cumulative count period from the original three-weeks to a range between one to six weeks.

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[43] were developed. Negative binomial regression models are commonly used to model count data and allows for the analysis of cases where the outcome variable counts are over-dispersed (variance of the count data is larger than the mean)[43,44]. Such models can also be designed to use cumulative historical count data as features to estimate outcome counts during a given current time period[35,45,46].

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 the bi-weekly cumulative vaccine dose counts and three-week cumulative 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 the bi-weekly cumulative vaccine dose counts and three-week cumulative 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[47]. 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.

Patient and public involvement. The formal involvement of the public and patients was not feasible under the time and resources constraints of this research project. However, this work has been informed by dialogue with those working in healthcare systems and public policy.

Ethical approval. This study was deemed exempt from review by the Massachusetts Institute of Technology Institutional Review Board(E-3300). The study was also approved by the research committee of the IEMS.

Results

General descriptive results. 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 3945 (6.5%) calls were for patients of age 16–39, respectively, from a population of close to 3.5 million people in this age group[38]. Of the 834,573 confirmed COVID-19 cases during the study period, 572,435 (68.6%) cases were from individuals of age 16–39. Among the 5,506,398 patients receiving their 1st vaccination dose and 5,152,417 patients receiving their 2nd vaccination dose, 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 calls. Table 1 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 across the full year (January–December) from 2019 to 2020 (relative decrease of − 2.4% [$P = 0.740$]), prior to the vaccination rollout and third COVID-19 wave in this age group. Similarly, for ACS, the increase across the full year from 2019 and 2020 (significant relative increase of 15.8% [$P < 0.001$]) was followed by an even a larger increase in the January to May period from 2020 to 2021 (significant relative increase of 26.0% [$P < 0.001$]), which was during the third COVID-19 wave and vaccination rollout. Both genders in the 16–39 age group experienced increases in CA and ACS calls from 2020 to 2021 for January–May. Among males, CA calls increased by 25.0% ($P = 0.073$) and ACS calls increased significantly by 21.3% ($P < 0.01$). Among females, CA calls increased by 31.4% ($P = 0.224$) and ACS calls instead significantly by 40.8% ($P < 0.01$).

Supplemental Table 1 shows the year-to-year percent of CA patients who died on scene (i.e., prior to hospital arrival) for the same time periods. Among the 16–39 age group, the percent of CA patients that died prior to hospital arrival increased significantly from 2019 to 2020 during the full year (52.8–60.5%; $P < 0.001$). This percent remained elevated during January–May of 2021 and no significant differences were found between same period in 2020 (65.1–61.3% $P = 0.460$). Similarly, Supplemental Table 2 shows that in the 16–39 age group, resuscitation (i.e., patient received defibrillation or cardiopulmonary resuscitation delivery) rates for CA calls increased from 2019 to 2020 during the full year (41.5–54.4%; $P < 0.001$). These higher rates of resuscitation persisted during January–May 2021, with no significant difference compared to the same period in 2020 (54.6–53.9%; $P = 0.900$).

Gender: 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 counts		January–May counts			Full year counts		January–May counts		
	2019	2020 (Percent change relative to 2019; P-value)	2019	2020 (Percent change relative to January–May 2019; P-value)	2021 (Percent change relative to January–May 2020; P-value)	2019	2020 (Percent change relative to 2019; P-value)	2019	2020 (Percent change relative to January–May 2019; P-value)	2021 (Percent change relative to January–May 2020; P-value)
All: overall*	11,149 (–)	12,792 (14.7; P < 0.001)	5003 (–)	5347 (6.9; P < 0.001)	5622 (5.1; P < 0.01)	23,116 (–)	24,345 (5.3; P < 0.001)	9217 (–)	9708 (5.3; P < 0.001)	11,159 (15.0; P < 0.001)
All: 16–39*	371 (–)	362 (–2.4; P = 0.740)	142 (–)	152 (7.0; P = 0.561)	191 (25.7; P < 0.05)	1405 (–)	1627 (15.8; P < 0.001)	545 (–)	627 (15.1; P < 0.05)	790 (26.0; P < 0.001)
All: over 40*	10,778 (–)	12,430 (15.3; P < 0.001)	4861 (–)	5195 (6.9; P < 0.001)	5431 (4.5; P < 0.05)	21,711 (–)	22,718 (4.6; P < 0.001)	8672 (–)	9081 (4.7; P < 0.01)	10,369 (14.2; P < 0.001)
Female: overall	5492 (–)	6254 (13.9; P < 0.001)	2521 (–)	2629 (4.3; P = 0.132)	2756 (4.8; P = 0.084)	7877 (–)	8714 (10.6; P < 0.001)	3164 (–)	3473 (9.8; P < 0.001)	4118 (18.6; P < 0.001)
Female: 16–39	108 (–)	81 (–25.0; P < 0.05)	39 (–)	35 (–10.3; P = 0.648)	46 (31.4; P = 0.224)	304 (–)	408 (34.2; P < 0.001)	112 (–)	152 (35.7; P < 0.05)	214 (40.8; P < 0.01)
Female: over 40	5384 (–)	6173 (14.7; P < 0.001)	2482 (–)	2594 (4.5; P = 0.116)	2710 (4.5; P = 0.111)	7573 (–)	8306 (9.7; P < 0.001)	3052 (–)	3321 (8.8; P < 0.001)	3904 (17.6; P < 0.001)
Male: overall	5636 (–)	6537 (16.0; P < 0.001)	2473 (–)	2717 (9.9; P < 0.001)	2866 (5.5; P < 0.05)	15,137 (–)	15,630 (3.3; P < 0.01)	5993 (–)	6235 (4.0; P < 0.05)	7041 (12.9; P < 0.001)
Male: 16–39	260 (–)	280 (7.7; P = 0.390)	102 (–)	116 (13.7; P = 0.344)	145 (25.0; P = 0.073)	1095 (–)	1219 (11.3; P < 0.01)	430 (–)	475 (10.5; P = 0.135)	576 (21.3; P < 0.01)
Male: over 40	5376 (–)	6257 (16.4; P < 0.001)	2371 (–)	2601 (9.7; P < 0.01)	2721 (4.6; P = 0.100)	14,042 (–)	14,411 (2.6; P < 0.05)	5563 (–)	5760 (3.5; P = 0.064)	6465 (12.2; 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 and gender. Each cell shows the counts of calls during the respective time period, age group, and gender with the relative percent change in counts to the previous year shown in the parenthesis (e.g., relative change from 2019 to 2020, and then from 2020 to 2021). The relative percent changes were calculated across the same duration per year (i.e., either across the full year or across the January–May period). For counts during 2019, no relative change is reported. *Counts in the All category includes calls with missing gender variable values. Number of calls with missing gender values: Cardiac arrest: N = 119 and Acute Coronary syndrome: N = 183.

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 ($P < 0.01$). The post hoc power analysis found that the statistical power for a significance level of 0.05 were both 1.00 for the correlation between vaccination doses and CA weekly call counts, and sum of CA and ACS weekly call counts, respectively. 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 post hoc power analysis found that the statistical power for a significance level of 0.05 was 0.94 and 1.00 for the correlation between COVID-19 infection and CA weekly call counts, and sum of CA and ACS weekly call counts, respectively. The same patterns hold when the COVID-19 infection count period is varied between one to six weeks (Supplemental Table 3).

These findings are emphasized by Figs. 1 and 2 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 (Figs. 1B and 2B). 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 estimated number of single doses delivered for individuals who recovered from COVID-19 (green line), starting on April 11th. 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[41]. 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]).

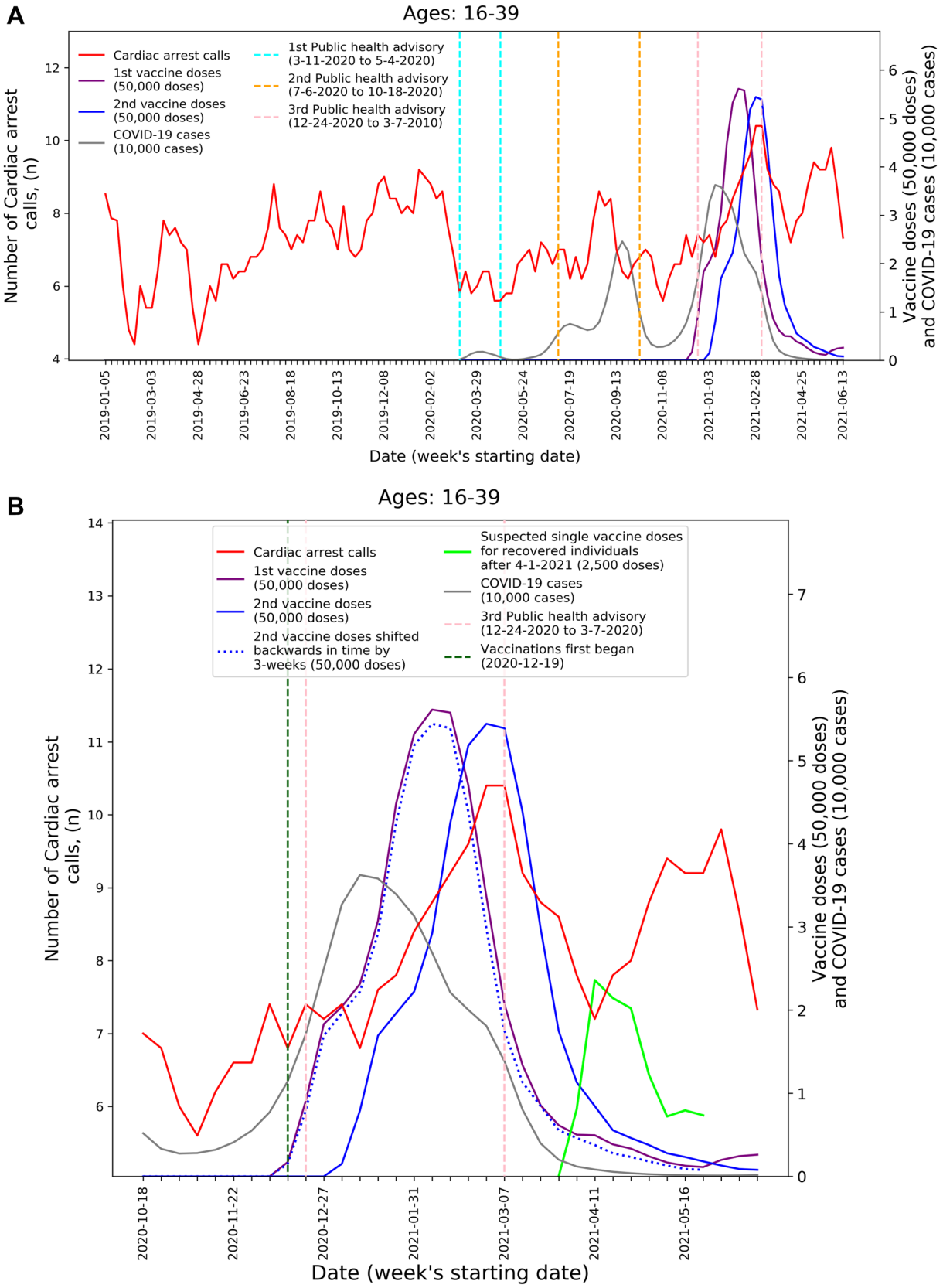

Figure 1. Weekly counts of cardiac arrest calls (five-week centered moving-average), COVID-19 cases (three-week centered moving-average), and vaccination doses (three-week centered moving-average) for those between 16 and 39 during: A) the study period (January 1st, 2019, to June 20th, 2021) and B) the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

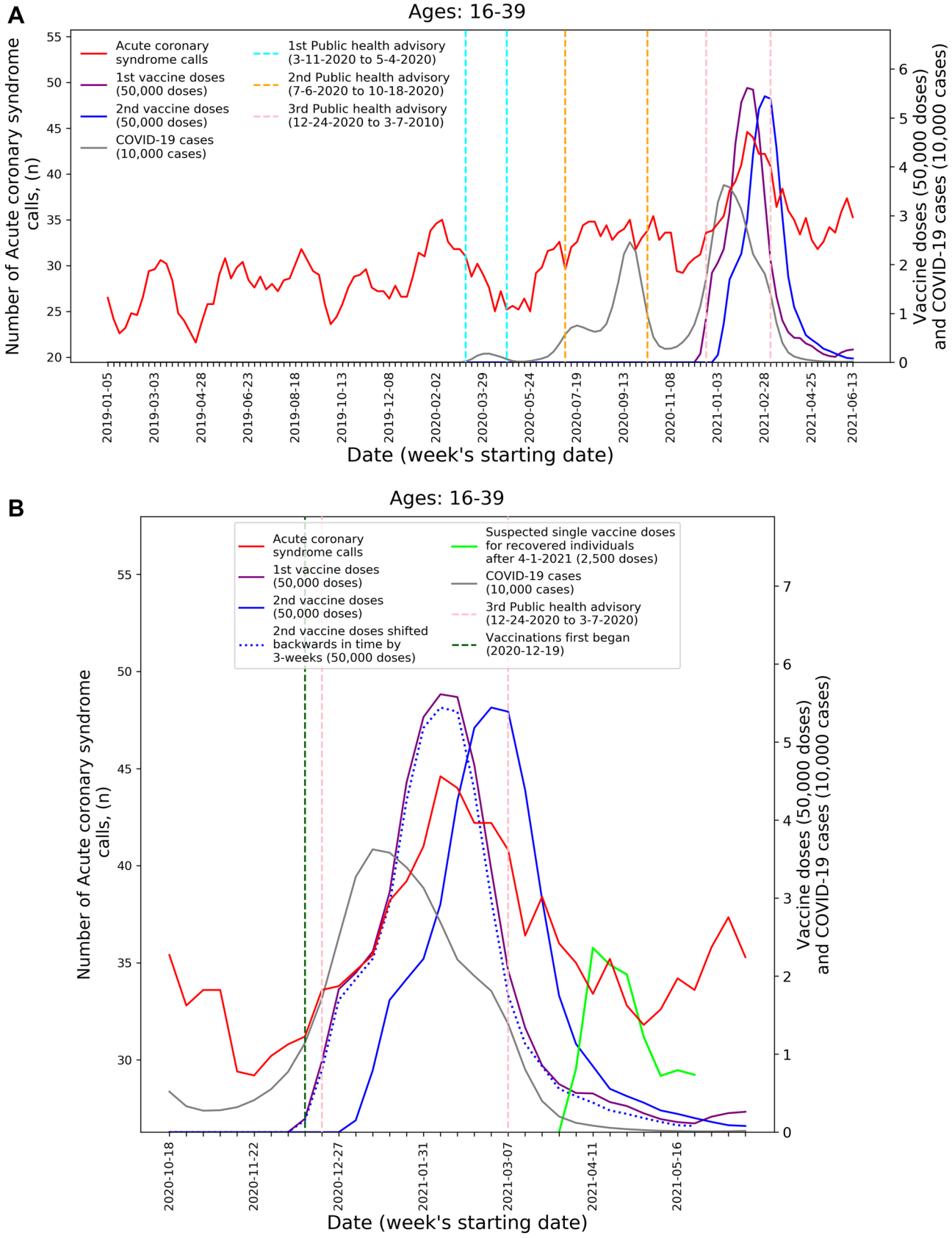

Figure 2. Weekly counts of acute coronary syndrome calls (five-week centered moving-average), COVID-19 cases (three-week centered moving-average), and vaccination doses (three-week centered moving-average) for those between 16 and 39 during: A) the study period (January 1st, 2019, to June 20th, 2021)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

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, *CI* confidence interval, *COVID-19* coronavirus disease 2019.

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, *CI* confidence interval, *COVID-19* coronavirus disease 2019.

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 Supplemental Tables 4–7).

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 the vaccination rollout 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 more comprehensive access to the respective incidence of the conditions being studied. This stands in contrast to the known very partial and biased access provided by adverse event self-reporting surveillance systems[23–25], and highlights the importance of incorporating additional data sources into these systems[48]. However, it is important to highlight several significant differences between the CA and ACS EMS calls. For CA events, it is reasonable to assume that the IEMS data includes almost all of the relevant events, since CA events almost always involve calling EMS services. Moreover, the diagnosis of CA is relatively more straightforward. In contrast, for ACS events, while EMS calls capture a significant fraction of the respective incidents, direct hospital walk-in will not be accounted for in the EMS data. In Israel this is estimated to be 50% of all events. Additionally, the diagnosis of ACS events is more involved, and while EMS protocols during the study period did not change, it is reasonable to assume a higher rate of diagnosis error.

The main finding of this study concerns with increases of over 25% in both the number of CA calls and ACS calls of people in the 16–39 age group during the COVID-19 vaccination rollout in Israel (January–May, 2021), compared with the same period of time in prior years (2019 and 2020), as shown in Table 1. 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. This result is aligned with previous findings which show increases in overall CA incidence were not always associated with higher COVID-19 infections rates at a population level[35,49,50], as well as the stability of hospitalization rates related to myocardial infarction throughout the initial COVID-19 wave compared to pre-pandemic baselines in Israel[51]. These results also are mirrored by a report of increased emergency department visits with cardiovascular complaints during the vaccination rollout in Germany[52] as well as increased EMS calls for cardiac incidents in Scotland[53].

The visuals in Figs. 1 and 2 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[19]. 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[54]. 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.

While increased CA incidence was not observed among the 16–39 age group in 2020, there was a significant increase in the proportion of CA patients that died on scene during 2020, relative to 2019 (Supplemental Table 1), emphasizing the potential direct and indirect harmful effects of the pandemic[35,49,55] on out-of-hospital CA patient outcomes. The percent of patients that died on scene remained elevated in 2021.

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 could be consistent with the known causal relationship between the mRNA vaccines and incidents of myocarditis in young people[14,17,19,56], as well as the fact that myocarditis is often misdiagnosed as ACS[28–30], and that asymptomatic myocarditis is a frequent cause for unexplained sudden death among young adults from CA[26,31–33]. This is further supported by more anecdotal reports describing sudden cardiac death following COVID-19 vaccination[16,57]. While vaccine-induced myocarditis was predominantly reported in males[14,19] it is interesting to note that the relative increases of CA and ACS events (Table 1) was larger in females. This may suggest the potential underdiagnosis or under-self-reporting of myocarditis in females, or other unique patterns, which is consistent with the ongoing challenge of gender-related differences related to cardiovascular disease diagnosis and care[15,58].

The paper suggests several important policy implications. First, it is important that surveillance programs of potential vaccine side-effects and COVID-19 infection outcomes incorporate EMS and other health data to identify public health trends and promptly investigate potential underlying causes. Specifically, prompt investigation is needed to better understand the potential underlying causes of the observed increase in cardiac-related EMS calls, including vaccine and COVID-19 infection related factors, as well as additional factors, such as reduced willingness to seek hospital or EMS care, reduced access to care, and increased public awareness to post-vaccination adverse events. Second, it is essential to raise awareness among patients and clinicians with respect to related symptoms (e.g., chest discomfort and shortness of breath) following vaccination or COVID-19 infection to ensure that potential harm is minimized. This is especially important among the younger population and particularly young females, who often receive less diagnostic evaluation for adverse cardiac events compared to males[15]. These implications are further underscored by the continued administration of additional vaccine booster doses to the public because of the waning vaccine immunity against COVID-19 variants (e.g., delta variant) after the 2nd vaccine dose[59]. Moreover, recent studies have also demonstrated the association of increased risk of myocarditis with the administration of adenovirus-based vaccines (i.e., ChAdOx1)[17], in addition to mRNA vaccinations, increasing the number of individuals that could be susceptible potential vaccine side-effects as well that can benefit from enhanced vaccine surveillance programs.

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, including hospital outcomes, underlying comorbidities as well as vaccination and COVID-19 positive status. Such related 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. Notably, recent studies have found vaccination induced myocardial injury has differentiating features, such as histopathology[60], compared to typical myocarditis, which can further support identification of possible drivers of these cardiac events. The Israel Ministry of Health and the large HMOs have access to such data, which should be investigated in detail. Additionally, the CA examined in the study included those of both cardiac and medical etiology as data discerning these differences were not available, increasing the importance of further investigation of these patients. However, previous literature has estimated that the vast majority, approximately 84–92%, of non-traumatic cardiac arrest cases stem from cardiac origins[61]. For example, among other potential causes of CA, approximately 2–9% and 2% of cardiac arrests stem from pulmonary embolism[62,63] and acute cerebrovascular events (e.g. subarachnoid hemorrhage)[64], respectively. Therefore, it is likely that the observed changes in incidence can primarily be attributed to CAs of cardiac etiology.

The significant increases in CA calls and ACS calls among the 16–39 age population during the COVID-19 vaccination rollout highlights the value of additional data sources, such as those from EMS systems, that can supplement self-reporting surveillance systems in identifying concerning public health trends. Moreover, it underscores the need for the thorough investigation of 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 to inform related public policy and prevent potentially avoidable patient harm. In the interim, it is vital that following vaccination, patients should be instructed to seek appropriate emergency care if they are experiencing symptoms potentially associated with 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.

Data availability

The COVID-19 and vaccination rate datasets generated and analysed during the current study are available at https://data.gov.il/dataset/covid-19. EMS call count data are not publicly available as they are derived from national clinical records. Due to national and organizational data privacy regulations this data cannot be shared openly.

Received: 30 November 2021; Accepted: 14 April 2022
Published online: 28 April 2022

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Acknowledgements
The authors would like to acknowledge that this study represents the individual views of the authors and do not represent the views of the respective institutions that they are affiliated with. The authors also would like to thank Professor Amos Adler, Professor Shoshana Altuvia and Dr. Yoav Yecheszkeli for many constructive comments that helped improve the exposition of this paper.

Author contributions
E.J., R.L., and C.S., were responsible for the study concept and design. R.L. and C.S., were responsible for the literature search. E.J., R.L., C.S. were responsible for acquisition of data. E.J., R.L., and C.S. were responsible for analysis and interpretation of data. R.L. and C.S. were responsible for drafting of the manuscript. E.J., R.L., and C.S. were responsible for critical revision of the manuscript for important intellectual content. R.L. and C.S. were responsible for statistical analysis. R.L. and C.S. were responsible for figures. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding
Author CS is partially funded by a postdoctoral fellowship from Massachusetts General Hospital, Boston, MA and a Canadian Institutes of Health Research Fellowship.

Competing interests
Author CS has been partially funded by a postdoctoral fellowship from Massachusetts General Hospital, Boston, MA and a Canadian Institutes of Health Research Fellowship for unrelated work within the last three years. Author RL has been received grants and contracts (all made to his primary institution: MIT) from Walmart Foundation, World Wildlife Foundation, Massachusetts General Hospital, Food and Drug Administration, Target Inc., as well as consulting fees from Israel Defense Forces and U.S. Securities and Exchange Commission, and honoraria for a lecture at Pepsico for unrelated work within the last three years.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-10928-z.

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Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room

Published Online
April 20, 2021
https://doi.org/10.1016/S2666-5247(21)00069-0

This online publication has been corrected. The corrected version first appeared at thelancet.com/microbe on June 11, 2021

Approximately 96 COVID-19 vaccines are at various stages of clinical development.[1] At present, we have the interim results of four studies published in scientific journals (on the Pfizer–BioNTech BNT162b2 mRNA vaccine,[2] the Moderna–US National Institutes of Health [NIH] mRNA-1273 vaccine,[3] the AstraZeneca–Oxford ChAdOx1 nCov-19 vaccine,[4] and the Gamaleya GamCovidVac [Sputnik V] vaccine)[5] and three studies through the US Food and Drug Administration (FDA) briefing documents (on the Pfizer–BioNTech,[6] Moderna–NIH,[7] and Johnson & Johnson [J&J] Ad26.COV2.S vaccines).[8] Furthermore, excerpts of these results have been widely communicated and debated through press releases and media, sometimes in misleading ways.[9] Although attention has focused on vaccine efficacy and comparing the reduction of the number of symptomatic cases, fully understanding the efficacy and effectiveness of vaccines is less straightforward than it might seem. Depending on how the effect size is expressed, a quite different picture might emerge (figure; appendix).

Vaccine efficacy is generally reported as a relative risk reduction (RRR). It uses the relative risk (RR)—ie, the ratio of attack rates with and without a vaccine—which is expressed as 1–RR. Ranking by reported efficacy gives relative risk reductions of 95% for the Pfizer–BioNTech, 94% for the Moderna–NIH, 91% for the Gamaleya, 67% for the J&J, and 67% for the AstraZeneca–Oxford vaccines. However, RRR should be seen against the background risk of being infected and becoming ill with COVID-19, which varies between populations and over time. Although the RRR considers only participants who could benefit from the vaccine, the absolute risk reduction (ARR), which is the difference between attack rates with and without a vaccine, considers the whole population. ARRs tend to be ignored because they give a much less impressive effect size than RRRs: 1·3% for the AstraZeneca–Oxford, 1·2% for the Moderna–NIH, 1·2% for the J&J, 0·93% for the Gamaleya, and 0·84% for the Pfizer–BioNTech vaccines.

ARR is also used to derive an estimate of vaccine effectiveness, which is the number needed to vaccinate (NNV) to prevent one more case of COVID-19 as 1/ARR. NNVs bring a different perspective: 81 for the Moderna–NIH, 78 for the AstraZeneca–Oxford, 108 for the Gamaleya, 84 for the J&J, and 119 for the Pfizer–BioNTech vaccines. The explanation lies in the combination of vaccine efficacy and different background risks of COVID-19 across studies: 0·9% for the Pfizer–BioNTech, 1% for the Gamaleya, 1·4% for the Moderna–NIH, 1·8% for the J&J, and 1·9% for the AstraZeneca–Oxford vaccines.

ARR (and NNV) are sensitive to background risk—the higher the risk, the higher the effectiveness—as exemplified by the analyses of the J&J's vaccine on centrally confirmed cases compared with all cases:[8] both the numerator and denominator change, RRR does not change (66–67%), but the one-third increase in attack rates in the unvaccinated group (from 1·8% to 2·4%) translates in a one-fourth decrease in NNV (from 84 to 64).

See Online for appendix

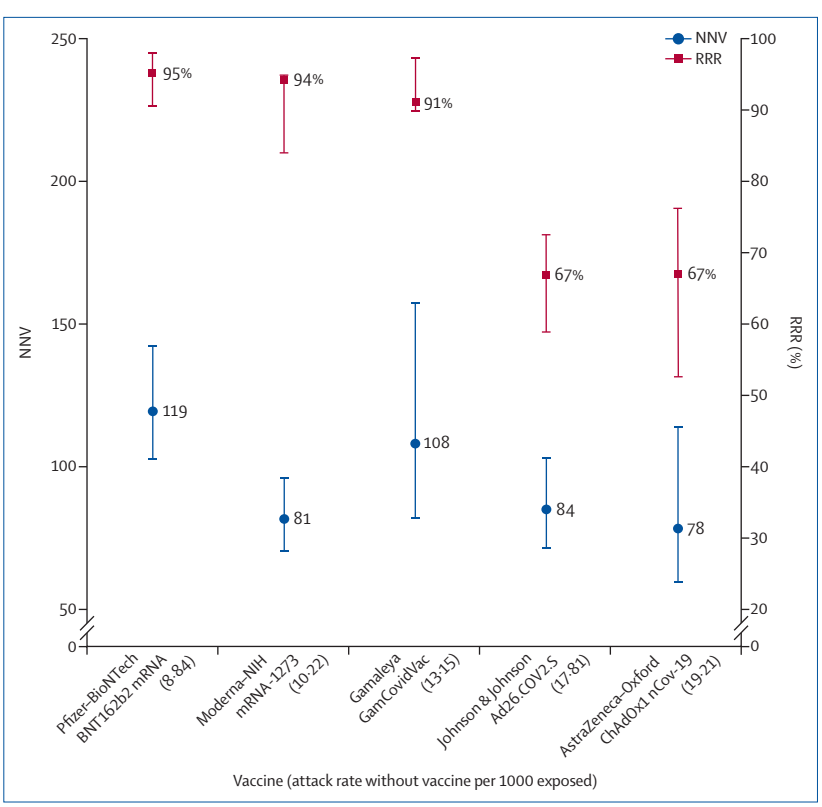

Figure: **RRR and NNV with 95% CI ranked by attack rate in the unvaccinated (placebo) group for five COVID-19 vaccines**
The lower the NNV and the higher the RRR, the better the vaccine efficacy. Details are in the appendix (p 3). RRR=relative risk reduction. NNV=numbers needed to vaccinate. NIH=US National Institutes of Health.

There are many lessons to learn from the way studies are conducted and results are presented. With the use of only RRRs, and omitting ARRs, reporting bias is introduced, which affects the interpretation of vaccine efficacy.[10] When communicating about vaccine efficacy, especially for public health decisions such as choosing the type of vaccines to purchase and deploy, having a full picture of what the data actually show is important, and ensuring comparisons are based on the combined evidence that puts vaccine trial results in context and not just looking at one summary measure, is also important. Such decisions should be properly informed by detailed understanding of study results, requiring access to full datasets and independent scrutiny and analyses.

Unfortunately, comparing vaccines on the basis of currently available trial (interim) data is made even more difficult by disparate study protocols, including primary endpoints (such as what is considered a COVID-19 case, and when is this assessed), types of placebo, study populations, background risks of COVID-19 during the study, duration of exposure, and different definitions of populations for analyses both within and between studies, as well as definitions of endpoints and statistical methods for efficacy. Importantly, we are left with the unanswered question as to whether a vaccine with a given efficacy in the study population will have the same efficacy in another population with different levels of background risk of COVID-19. This is not a trivial question because transmission intensity varies between countries, affected by factors such as public health interventions and virus variants. The only reported indication of vaccine effectiveness is the Israeli mass vaccination campaign using the Pfizer–BioNTech product. Although the design and methodology are radically different from the randomised trial,[2] Dagan and colleagues[11] report an RRR of 94%, which is essentially the same as the RRR of the phase 3 trial (95%) but with an ARR of 0·46%, which translates into an NNV of 217 (when the ARR was 0·84% and the NNV was 119 in the phase 3 trial). This means in a real-life setting, 1·8 times more subjects might need to be vaccinated to prevent one more case of COVID-19 than predicted in the corresponding clinical trial.

Uncoordinated phase 3 trials do not satisfy public health requirements; platform trials designed to address public health relevant questions with a common protocol will allow decisions to be made, informed by common criteria and uniform assessment. These considerations on efficacy and effectiveness are based on studies measuring prevention of mild to moderate COVID-19 infection; they were not designed to conclude on prevention of hospitalisation, severe disease, or death, or on prevention of infection and transmission potential. Assessing the suitability of vaccines must consider all indicators, and involve safety, deployability, availability, and costs.

We declare no competing interests.

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