

Myocarditis in Malta in the COVID-19 vaccination era – a population-based study

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BACKGROUND

Vaccination against COVID-19 is crucial for controlling this scourge. COVID/vaccination deniers often rationalise their unfounded fears by citing rare vaccination side-effects. One of the most frequently cited side effects is myocarditis, especially in younger persons. Malta has very high vaccination rates. This study was carried out to ascertain whether admissions to hospital for myocarditis changed during the vaccination rollout, up to October 2021, when 83.4% of Malta's population of circa half a million had had their first 1st dose.

METHODS

Malta is served by one large regional hospital (Mater Dei Hospital). Anonymous data for admissions with a diagnosis of myocarditis (ICD I40, I41, I51.4) were obtained for 01/2016-10/2021. Myocarditis discharges and 95% confidence intervals were plotted for 2016-2020. Myocarditis discharges for Jan-Oct 2021 were plotted separately.

RESULTS

There were no outlier values for myocarditis discharges in either direction for any age for either sex.

CONCLUSION

Myocarditis, independent of vaccination, is commonest in young males, half resolving and some developing dilated cardiomyopathy, possibly leading to transplantation or death. The ongoing mass vaccination with novel messenger RNA vaccines resulted in reports of myocarditis in male teens, this being a rare side effect. The lack of significantly increased rates of myocarditis admission in any age/sex group in Malta confirms that only rarely, myocarditis may be temporally associated with COVID vaccination which almost invariably runs a benign course and that this risk is very low, far lower than myocarditis due to actual COVID infection.

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INTRODUCTION

The COVID-19 pandemic continues to ravage the globe at the time of writing and non-pharmaceutical interventions,¹ a handful of treatments,² and vaccination,³ appear to be the mainstays in controlling this scourge, now and in the future.⁴

COVID/vaccination deniers often rationalise their unfounded fears by citing rare vaccination side-effects. This fuels their own vaccination hesitancy as well as that of others.⁵ One of the most frequently cited side effects is that of myocarditis, especially in younger persons.⁶ This is defined by the Dallas criteria as an inflammatory disorder of the myocardium that is characterized by lymphocytic and monocytic infiltrates, myocyte degeneration, and non-ischaemic necrosis.⁷ Myocarditis is predominantly viral induced by primary cardiotropic viruses such as adenoviruses and enteroviruses (e.g. coxsackie A, B viruses and echoviruses), although other viruses may also cause this condition and these include vasculotropic viruses such as parvovirus B19, lymphotropic viruses such as herpesvirus 6 (HHV6), Epstein–Barr virus, and cytomegalovirus. Viruses may also indirectly precipitate myocarditis by immune system activation, and these include the HIV, hepatitis C, influenza A B viruses and coronaviruses such as Middle East respiratory syndrome coronavirus (MERS-CoV), severe acute respiratory syndrome coronavirus (SARS-CoV) and SARS-CoV-2. Bacteria (e.g., *Borrelia spp.*), protozoa (e.g., *Trypanosoma cruzi*) and fungi have also been implicated. Non-infectious aetiologies like toxins, drugs and systemic auto-immune conditions have also been described. The individual response/reaction to these agents is extremely heterogenous, making it impossible to predict the development of myocarditis after exposure.⁸

Malta is an island nation in the centre of the Mediterranean, part of the European Union and just 60 miles south of Sicily. The population is circa half a million and the country is served by one large regional hospital (Mater Dei Hospital) on the larger island of Malta and one smaller district general hospital on the island of Gozo.

Vaccination rollout has accelerated in many countries, including in Malta which has very high vaccination rates.⁹ This study was carried out to ascertain whether admissions to hospital for myocarditis had changed in any way during vaccination rollout, up to October 2021.

MATERIALS AND METHODS

Anonymous data for admissions to Mater Dei Hospital with a recorded diagnosis of myocarditis (ICD I40, I41, I51.4) were obtained from the Hospital Activity Analysis of Mater Dei Hospital for the period January 2016 to October 2021. Myocarditis discharges and 95% confidence intervals were plotted for 2016-2020. Myocarditis discharges for Jan-Oct 2021 were plotted separately.

RESULTS

As vaccines became available in the last quarter of 2020 and approved by the European Medicines Authority, Malta was able to acquire sufficient vaccines to cover the entire population, purchasing vaccines from all suppliers including 830,000 doses from Pfizer and Moderna combined, one million doses from AstraZeneca and 250,000 doses from Johnson and Johnson. The manufacturer's recommended dosing schedules were strictly adhered to with second doses for Pfizer being given after 3 weeks, Moderna after 4 weeks and AstraZeneca after 10 weeks. Vaccination hubs were set up throughout the Island,¹⁰ such that by the end

of Oct 2021, 83.4% of the population had received at least one vaccine dose.¹¹

There were no outlier values for myocarditis discharges in either direction for any age for any of

the two sexes (figures 1 and 2). Table 1 shows admission rates per 100,000 population by age group in acute public and private hospitals in Malta from 2016-2020.

Figure 1 Male myocarditis admissions by age for 2016-2020 (with 95% CI) and for Jan-Oct 2021

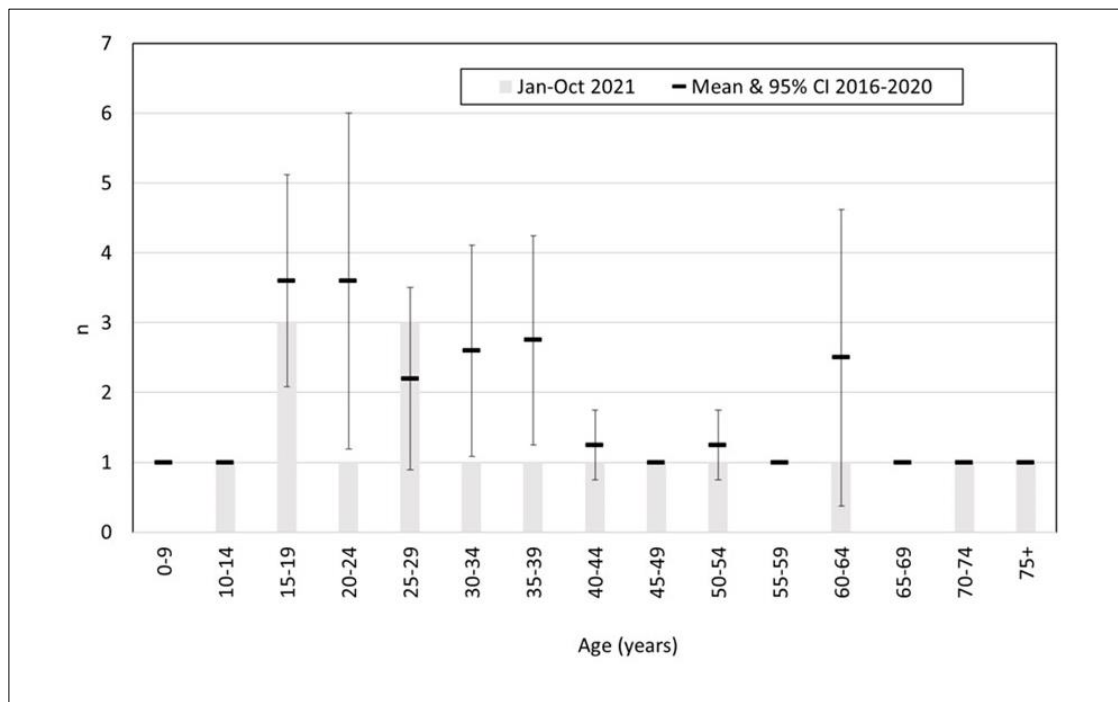


Figure 2 Female myocarditis admissions by age for 2016-2020 (with 95% CI) and for Jan-Oct 2021

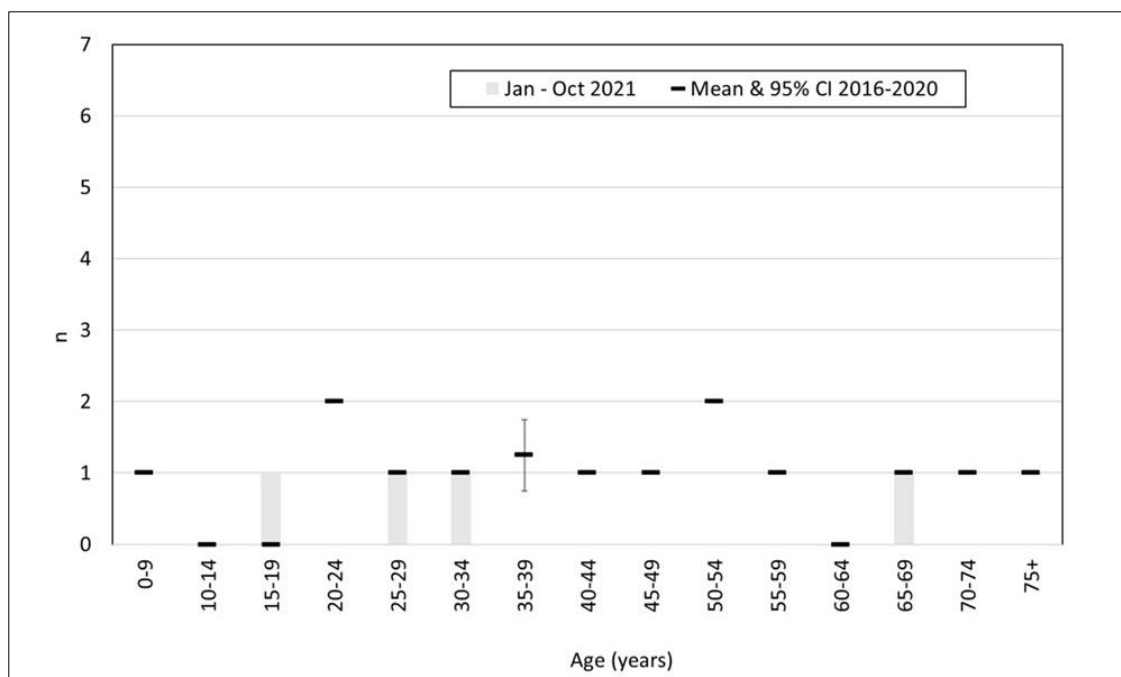


Table 1 Myocarditis Admission rates per 100,000 population by age group from 2016-2020

Age group in years	2016 Myocarditis Admission rate per 100,000 pop	2017 Myocarditis Admission rate per 100,000 pop	2018 Myocarditis Admission rate per 100,000 pop	2019 Myocarditis Admission rate per 100,000 pop	2020 Myocarditis Admission rate per 100,000 pop
0-4	0.00	0.00	0.00	4.22	0.00
5-9	4.83	4.51	0.00	0.00	0.00
10-14	0.00	4.84	0.00	4.64	0.00
15-19	8.60	21.71	8.89	17.99	22.96
20-24	10.38	16.21	3.17	6.17	28.43
25-29	15.15	5.19	4.78	4.46	8.78
30-34	15.37	5.36	4.96	9.01	4.23
35-39	12.71	8.47	7.93	4.92	11.72
40-44	3.43	6.20	2.92	8.21	0.00
45-49	3.92	0.00	3.42	3.22	0.00
50-54	3.62	10.72	7.18	7.11	3.53
55-59	0.00	0.00	0.00	6.46	6.58
60-64	0.00	0.00	3.30	12.95	3.20
65-69	0.00	0.00	3.45	3.50	0.00
70-74	0.00	0.00	3.67	0.00	7.03
75-79	6.87	0.00	7.02	0.00	5.70
80-84	9.61	0.00	0.00	0.00	0.00
85+	0.00	0.00	0.00	0.00	0.00
Total	5.71	5.13	3.71	5.75	6.21

Source: National Hospitals Information System, Directorate for Health Information & Research

STUDY LIMITATIONS

- a. A proportion of pericarditis which is by far commoner to myocarditis.
- b. Vaccination roll out in adolescents was far slower than in adults and this may have somewhat skewed the data as there may have been limited myocarditis cases in the younger age brackets given that they had not yet been vaccinated at the time of study.

DISCUSSION

The precise mechanisms whereby SARS-CoV-2 affects the heart are thus far unknown.⁸ It is, nonetheless, a known indirect effect of several coronavirus infections (including MERS-CoV, SARS-CoV and SARS-CoV-2) all of which have Angiotensin Converting Enzyme 2 (ACE2) affinity, thus potentially mediating myocardial injury. Studies quantifying the risk of myocarditis have varied, possibly due to the varying ascertainment of asymptomatic cases – with figures varying from 450

per million infected individuals¹² to 5% of infected individuals.⁸

Myocarditis, independent of vaccination, occurs most commonly in young males. More than half of cases resolve while some fail to recover and develop dilated cardiomyopathy, possibly leading to transplantation or death.⁸ The ongoing mass vaccination with novel messenger RNA vaccines resulted in reports of myocarditis in male teens, this being a rare side effect.

Specifically, one report defined myocarditis using the Brighton Collaboration criteria and found 136 definite/probable cases of suspected post-vaccination myocarditis in >5 million vaccinees, with 95% resolving benignly and one reported death. The rate ratio for myocarditis vaccinated:unvaccinated was reported as 2.35 in Israel, with the rate in the vaccinated being 0.78 per million person-days and the baseline rate in unvaccinated being 0.33 per million person-days, the highest risk being in young males aged 16-19 years (around 5 per million person-days).¹³ A second report using CDC myocarditis criteria found 54 cases in >2.5 million vaccinees and all had a benign outcome including one case who initially developed cardiogenic shock. The highest was also in young males as above, with an overall myocarditis incidence of 2.13/100,000 persons.¹⁴ Yet another report seeking hospital admission or death from myocarditis/pericarditis/cardiac arrhythmias analysed 38,615,491 vaccine doses and compared these with 3,028,867 COVID positive individuals. The risk of myocarditis ranged from an extra 1 to 10 events per million vaccinees (varying with 1st/2nd doses and type of vaccine) versus an extra 40 myocarditis events/million for COVID positive

individuals. This study also found elevated risks for pericarditis and arrhythmias in COVID positive individuals while none were found after vaccination other than an increased risk of arrhythmia following a second dose of mRNA-1273. The increased risk of myocarditis associated with vaccination was only present in those aged <40.⁶

Table 1 shows that myocarditis admission rates per 100,000 pop in 2020 for the age bracket 15-24 were rather elevated. These age groups have been traditionally associated with the highest COVID infection rates throughout this epidemic. That said, further research would be warranted to determine whether these contemporaneous events could have been associated or not.

The lack of significantly increased rates of myocarditis admission in 2021 in any age/sex groups in Malta confirms the take-home messages that rarely, myocarditis may be temporally associated with COVID vaccination which almost invariably runs a benign course and that this risk is very low, far lower than myocarditis due to actual COVID infection. It has also been averred that vaccination-associated myocarditis may reflect an adjuvant effect that promoted/reactivated/accelerated naturally occurring myocarditis due to viral/immune-mediated causes.¹⁵ In addition, the paediatric dose is lower than the adult dose, a third in fact for the Pfizer vaccine at 10 µg instead of 30 µg,¹⁶ and still 90.7% effective at preventing symptomatic COVID.¹⁷ This lower dose may be behind the substantially lower risk of myocarditis reported by CDC amongst 5-11 year olds (1.1 per million doses)¹⁸ compared even to the risk among 12-16 year olds reported 6 months ago (34 per million doses), which was already quite low.¹⁹

CONCLUSION

The authors acknowledge that further research regarding the temporal association between diagnosis of myocarditis and time of vaccination as well as the manufacturer of the vaccine is necessary. That being said, the evidence presented should allay public fear of myocarditis as a reason for vaccine hesitancy, especially among the young.

SUMMARY

What is already known about this subject?

- Vaccination appears to be part of the mainstay in controlling COVID-19, now and in the future

- One of the most frequently cited side effects is that of myocarditis, especially in younger persons.

What are the new findings?

- There were no significantly increased rates of myocarditis admission in Malta.
- Myocarditis may be temporally associated with COVID vaccination but this risk far lower than myocarditis due to actual COVID infection.
- These findings should allay public fear of myocarditis as a reason for vaccine hesitancy, especially among the young.

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