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ORIGINAL ARTICLE

The efficacy of SARS-CoV-2 booster dose on SARS-CoV-2 inpatient epidemiology
an overview on disease severity and mortality

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Background
The world is moving into the 3rd year of the SARS-CoV-2 pandemic. There is no doubt that vaccination has been crucial in significantly reducing the impact of the pandemic. Given the novelty of the SARS-CoV-2 vaccines and the waning immunity over time, data is required to determine the efficacy of SARS-CoV-2 booster doses.

Methods
The comparative observational study included 451 eligible inpatients at Mater Dei Hospital, Malta. Hospital software and bed management databases were used to extract cases of confirmed infection in patients aged 17 years and older. Patients were stratified into two study arms: boosted and non-boosted cohorts. Disease severity was calculated based on clinical criteria and the Modified Chest X-Ray Score. A Pearson-Chi square test of independence was then used to analyse the data to acquire and compare rates of disease severity and mortality between the two groups.

Results
5.6% of non-boosted patients required intensive care unit admission compared to 0% of the boosted population. 8.8% of non-boosted patients developed severe illness compared to 5.5% of the boosted group. The study also found higher rates of ARDS and mortality in non-boosted inpatients, with a higher male predominance.

Conclusion
This study underpins the superior protection offered by a booster dose of SARS-CoV-2. It also points to a time-dependent waning in immunity, highlighting the importance of robust vaccination programmes.

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Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) infection has caused havoc in healthcare systems and international socioeconomics.[1] Vaccination against SARS-CoV-2 has been observed to significantly reduce both the morbidity and mortality in various countries.[2-4] In Malta, the national vaccination programme was initiated in December 2020, with a booster dose programme starting in September 2021. The population was vaccinated using one of the EMA-approved vaccines i.e Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine), Janssen (Ad26. COV2.S), the Moderna COVID-19 (mRNA-1273) vaccine and the Pfizer BioNTech (BNT162b2) COVID-19 vaccine. Janssen (Ad26.COV2.S) vaccine consisted of one dose whereas the others required two doses for completion. In the booster programme, only Moderna (mRNA-1273) and the Pfizer BioNTech (BNT162b2) COVID-19 vaccines were utilised.

In both programmes, the elderly and immunocompromised populations were given priority. By the start of September 2021, approximately 94.5% of the total eligible population of 438,321 people had received two doses of the vaccine.[5,6], with 67% of people aged over 18 having received their first booster shot by January 2022.[7]

Unfortunately, new spikes in case numbers were observed in autumn and winter of 2021 with the emergence of viral variants such as the Delta variant and Omicron variant. With growing evidence of waning vaccine immunity overtime, as well as the heightened infectivity of the variants.[8], a national booster programme was introduced. It was postulated that the booster provided protection from infection and even reduction in disease severity in cases of infection [9,10] The aim of this study was to analyse the efficacy of SARS-CoV-2 first booster vaccine dose in reducing disease severity and mortality rate in Malta.

METHOD

Study Design

A comparative observational study was performed, looking at the vaccination status of all in-patients with symptomatic SARS-CoV-2-related illness hospitalised at Mater Dei Hospital, Malta between October 2021 and mid-January 2022. This included patients who tested positive for SARS-CoV-2 in the community, patients who swabbed positive for SARS-CoV-2 through routine hospital admission swabbing and eventually developed symptomatic SARS-CoV-2-related illness and patients who tested SARS-CoV-2 positive and developed SARS-CoV-2-related symptoms during their hospital stay. A nasopharyngeal PCR swab was utilized throughout the study. The study population was limited to patients aged 17 years and over. The eligible cohort was split into two arms: Non-boosted arm i.e fully-vaccinated patients without a booster dose and Boosted arm i.e fully-vaccinated patients with an addition of a booster dose. Exclusion criteria for this study were unvaccinated patients, immunocompromised patients, patients who were ineligible for booster dose (that is patients who had swabbed positive for SARS-CoV-2 less than 3 months after SARS-CoV-2 vaccine completion) and patients on whom we had incomplete data.

Data protection and legal approval were obtained from the Data Protection Manager and legal office respectively at MDH. Ethical approval was obtained from the Health Ethics Committee within the Directorate for Health Information and Research of Malta.

All patient data was anonymised. SARS-CoV-2 patients were flagged through the hospital's Bed Management notifications and hospital software, iSoft Clinical Manager (iCM) and Patient Dashboard (PD), with data being gathetered retrospectively and in real time by the authors of the study. Demographic data including age, gender, date, duration of admission and mortality was collected from iCM. The reasons for hospital admission, admissions to Intensive Therapy Unit (ITU), as well as respiratory status (hypoxia, low oxygen saturations, shortness of breath) and immune status (immunocompetent vs immunocompromise) of patients were obtained from patients' electronic discharge summaries, patient administration system (CPAS), iCM, medical notes and visit histories.

Immunocompromise was defined as all those patients on immunosuppressive or immunomodulatory biological treatments, chemotherapy, radical radiotherapy, steroids for at least a month, solid organ transplant recipients, human immunodeficiency virus infection, haematological malignancy or history of such malignancy, and genetic disorders affecting the immune system.[11]

Patients in the two arms of the study group were stratified according to disease severity based on a combination of clinical and radiological criteria as per Table 1 below.

Mild disease was defined as the presence of SARS-CoV-2 symptoms with/without mild SARS-CoV-2 radiological changes without the presence of hypoxia. Moderate disease was defined as presence of COVID-19 symptoms with mild SARS-CoV-2 radiological changes and hypoxia (oxygen saturations of less than 94% on room air on arterial blood gas testing or bedside pulse oximetry) or moderate SARS-CoV-2 radiological changes without hypoxia. Severe disease was defined as the presence of SARS-CoV-2 symptoms with moderate/severe SARS-CoV-2 radiological changes and hypoxia. Critical disease was defined as patients requiring high flow nasal oxygen (HFNO) or endotracheal intubation secondary to SARS-CoV-2.

Chest imaging was reviewed through Picture Archiving and Communication System (PACS) imaging software with the degree of radiological changes being stratified according to the Modified Chest X-Ray scoring system.[12] The scoring was calculated by drawing two horizontal lines, dividing the lungs into 6 regions, with each region scoring between 0-2 (0 being normal, 1 infiltrates/consolidations less than 50% of the regions and 2 infiltrates/consolidations of more than 50%) giving a final score from 0-12, mild being score of 1-4, moderate being score of 5-8, severe being score of 9-12, as depicted in **Table 1** above.

Details regarding vaccination status were obtained from the PD and discharge summaries. This included the number of doses, dates of vaccination and vaccination brands received by patients against SARS-CoV-2. Vaccination status was considered to be valid if the last dose of the vaccine (either second dose or booster or first dose of Janssen (Ad26.COV2.S) was taken not less than 2 weeks prior to the patient testing positive for SARS-CoV-2.

Comparison was drawn between the rate of severe and critical illness in patients who received a booster vaccine dose at least 14 days prior to testing positive for SARS-CoV-2 and those who were not boosted. Comparison was also made between SARS-CoV-2 acute respiratory distress syndrome (ARDS)-related in hospital mortality rate in patients who received a booster vaccine dose at least 14 days prior to testing positive for SARS-CoV-2 and those who were not boosted.

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software (version 23) was used for statistical analysis. A p value of less than 0.05 was considered to indicate statistical significance.

A one-sample Kolmogorov-Smirnov test was performed to analyse test distribution. Test-distribution was found to be normal (**Digital Supplement File 1**).

A Pearson Chi-square test of independence was used to analyse the relation between not receiving a SARS-CoV-2 booster and hospitalisation with severe or critical SARS-CoV-2 illness. The null hypothesis was that there is no relationship between not receiving a SARS-CoV-2 booster and severe or critical SARS-CoV-2 illness. The alternative hypothesis was that there is a statistically significant association between these two variables.

Table 1 *Stratification of SARS-CoV-2 Disease using Clinical and Radiological Criteria*

Severity of SARS-CoV-2 Disease	Clinical Criteria	Radiological criteria - Modified Chest X-Ray Scoring System
Mild	SARS-CoV-2 symptoms **without** hypoxia	Normal (score 0) or Mild i.e (score 1-4)
Moderate	SARS-CoV-2 symptoms **without** hypoxia	Moderate (score 5-8)
	SARS-CoV-2 symptoms with hypoxia	Mild (score 1-4)
Severe	SARS-CoV-2 symptoms **with** hypoxia	Moderate (score 5-8) or Severe (score 9-12)
Critical	SARS-CoV-2 symptoms with hypoxia **requiring HFNO or intubation**	Moderate (score 5-8) or Severe (score 9-12

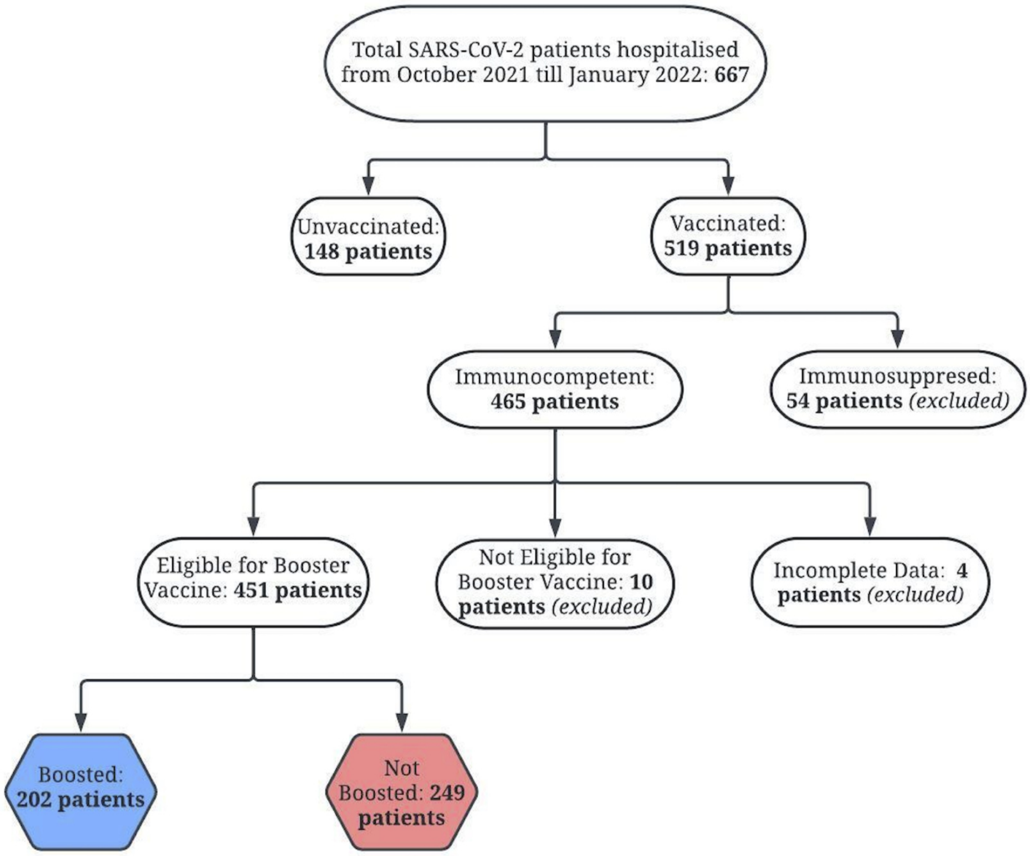

Figure 1 *Study population*

A Pearson Chi-square test of independence was used to analyse the relation between not receiving a SARS-CoV-2 booster and SARS-CoV-2 ARDS-related deaths. The null hypothesis was that there is no relationship between not receiving a SARS-CoV-2 booster with SARS-CoV-2 ARDS-related deaths. The alternative hypothesis was that there is a statistically significant association between these two variables.

A simple linear regression model analysis was performed to analyse potential variables that effected significantly SARS-CoV-2-related admissions to ITU (as the dependent variable).

RESULTS

Out of a total of 667 patients testing positive for SARS-CoV-2 during the study period. 451 patients satisfied the inclusion criteria, of which 202 patients were included in the boosted group and 249 patients in the non-boosted group (Figure 1).

When comparing gender and age, the boosted group was noted to have a higher proportion of female patients compared to the non-boosted group (52% vs 47%) as well as significantly more patients over the age of 70 years (73% vs 29% respectively) (Table 2).

The study population was vaccinated with the following SARS-CoV-2 vaccines: 72.7% received Pfizer BioNTech (BNT162b2), 20.9% received Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine, 3.1% received Janssen (Ad26.COV2.S) and 2.9% received Moderna COVID-19 (mRNA-1273) . 77.7% of the boosted arm received Pfizer BioNTech (BNT162b2) as a booster vaccine whilst 21.8% received Moderna COVID-19 (mRNA-1273) (Table 3).

Importantly, there were zero patients classified as critical in the boosted group as compared to 6.4% in the non-boosted group (predominantly between the age of 41 and 80 years), (Table 2, Table 4). The latter correlates with admission to ITU, 0% vs 5.6% in the boosted group and non-boosted group, respectively. 12 patients (86%) of the non-boosted group that required ITU admission secondary to SARS-CoV-2 pneumonia were males.

The study found significantly more non-boosted patients with severe/critical SARS-CoV-2 related illness compared to the boosted population (boosted group: 5.4% vs non-boosted group: 18.0%, $p = 0.001$). Furthermore, a simple linear regression model demonstrated that the booster/vaccination status was a statistically significant independent variable to SARS-CoV-2 related admissions to ITU ($p < 0.001$) (Digital Supplement File 2).

Table 2 *Demographics and clinical characteristics of the Study Population*

	Unvaccinated n %	Boosted-Group n %	Non-Boosted Group n %
Sex			
Male	69 46.6%	97 48.0%	132 53%
Female	79 53.4%	105 52.0%	117 47%
Age-distribution			
17 – 30 years	27 18.2%	2 1%	32 12.9%
31 – 40 years	27 18.2%	2 1%	38 15.2%
41 – 50 years	16 10.8%	10 5.0%	42 16.9%
51 – 60 years	22 14.9%	16 8.0%	24 9.6%
61 – 70 years	25 16.9%	24 11.9%	42 16.9%
71 – 80 years	15 10.2%	63 31.1%	40 16.1%
>80 years	16 10.8%	85 42%	31 12.4%
Severity of SARS-CoV-2 Illness			
Asymptomatic	41 27.7%	61 30.2%	63 25.3%
Mild	47 31.8%	98 48.5%	114 45.8%
Moderate	17 11.5%	32 15.8%	34 13.7%
Severe	28 18.9%	11 5.5%	22 8.8%
Critical	15 10.1%	0 0%	16 6.4%
SARS-CoV-2 related ITU admissions			
ITU admissions	11 7.4%	0 0%	14 5.6%
Non-ITU admissions	137 92.6%	202 100%	235 94.4%
Mortality			
ARDS-related deaths	7 4.7%	2 1%	11 4.4%
Males	4 57.1%	2 100%	7 63.6%
Females	3 42.9%	0 0%	4 36.4%
17 – 30 years	0	0	0
31 – 40 years	1	0	0
41 – 50 years	0	0	1
51 – 60 years	0	0	2
61 – 70 years	2	0	0
71 – 80 years	2	0	3
>80 years	2	2	5
Non-ARDS related deaths	6	17	6

Table 3 *Vaccine/booster brands administered to the study group*

		No of patients	%
Vaccine Brand	Pfizer BioNTech (BNT162b2)	328	72.7%
	Moderna COVID-19 (mRNA-1273)	13	2.9%
	Oxford/AstraZeneca (ChAdOx1-S [recombinant] vaccine)	94	20.9%
	Janssen (Ad26.COV2.S)	14	3.1%
	Missing data	2	0.4%
Booster Brand	Pfizer BioNTech (BNT162b2)	157	77.7%
	Moderna COVID-19 (mRNA-1273)	44	21.8%
	Missing data	1	0.05%

Table 4 *Stratification of SARS-CoV-2 Disease according to age groups in Boosted vs non-Boosted groups*

Age years	Asymptomatic count (%)	Mild count (%)	Moderate count (%)	Severe count (%)	Critical count (%)
Boosted Group					
17 - 30	0 (0%)	1 (1%)	1 (3.1%)	0 (0%)	0 (0%)
31 - 40	2 (3.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
41 - 50	2 (3.3%)	8 (8.2%)	0 (0%)	0 (0%)	0 (0%)
51 - 60	9 (14.8%)	7 (7.1%)	0 (0%)	0 (0%)	0 (0%)
61 - 70	8 (13.1%)	13 (13.3%)	2 (6.2%)	1 (9.1%)	0 (0%)
71 - 80	24 (39.3%)	26 (26.5%)	10 (31.3%)	3 (27.3%)	0 (0%)
>80	16 (26.2%)	43 (43.9%)	19 (59.4%)	7 (63.6%)	0 (0%)
Non-Boosted Group					
17 - 30	11 (17.5%)	20 (17.5%)	1 (2.9%)	0 (0%)	0 (0%)
31 - 40	19 (30.2%)	15 (13.2%)	2 (5.9%)	1 (4.5%)	1 (6.2%)
41 - 50	7 (11.1%)	22 (19.3%)	9 (26.5%)	1 (4.5%)	3 (18.8%)
51 - 60	4 (6.3%)	10 (8.7%)	1 (2.9%)	5 (22.7%)	4 (25.0%)
61 - 70	8 (12.7%)	19 (16.7%)	6 (17.6%)	6 (27.3%)	3 (18.8%)
71 - 80	5 (7.9%)	15 (13.2%)	12 (35.3%)	5 (22.7%)	3 (18.8%)
>80	9 (14.3%)	13 (11.4%)	3 (8.8%)	4 (18.2%)	2 (12.5%)

5.5% of the boosted group (all over the age of 60years) had severe SARS-CoV-2 related illness as compared to 8.8% of the non-boosted group (predominantly within the age range of 51-80 years), however, this difference did not reach statistical significance (p=0.116) .

Gender was shown to be an independent variable to SARS-CoV-2-related admissions to ITU, irrelevant of their booster status as per simple linear regression model equation (**Digital Supplement File 2**).

The mortality rate of hospitalised and non-immunocompromised SARS-CoV-2 patients (deaths attributed to acute respiratory distress syndrome (ARDS) secondary to SARS-CoV-2 pneumonia and not underlying chronic comorbid diseases) was 4.4% in the non-boosted population when compared to 1% in the boosted group. It seems that the non-boosted patients had a higher risk of ARDS-related death than the boosted patients (Boosted group 1% vs non-boosted group: 4.4%, p = 0.031). A male predominance was noted amongst the ARDS-related deaths, 2 patients (100%) in the boosted group and 7 patients (64%) in the non-boosted group, as shown in **Table 2**.

Of interest, 14 (87.5%) of the critical admissions in the non-boosted group tested positive for SARS-CoV-2 and required hospitalisation beyond 5 months after completing their SARS-CoV-2 vaccination regimen.

DISCUSSION

Various studies have shown that SARS-CoV-2 vaccine immunity wanes over time and a booster dose seems to restore this immune decline resulting in a decrease in disease severity and mortality.[3,13] Our study similarly seems to show a significant decrease in severe and critical SARS-CoV-2 disease in the boosted. In fact, zero patients with critical SARS-CoV-2-related disease were documented in the boosted arm of the study. Our study also demonstrates a statistically significant decrease in in hospital mortality in the boosted arm.

Malta with a population of approximately 516,000[6] has one major acute hospital, Mater Dei hospital (MDH). Virtually all SARS-CoV-2-related hospitalisations during the study period were admitted to this major 1000 bed hospital. The only exception being a small number of elderly patients who contacted SARS-CoV-2 whilst residing in one long term hospital facility and were deemed not eligible for escalation of treatment and thus were managed in the said hospital without being transferred to MDH. The fact that virtually all SARS-CoV-2 positive patients were managed at MDH meant that the management of these patients was standardized and data collection was facilitated, possibly giving more power to our study.

Potential sources of bias include; the relatively small numbers in our cohort and the use of different vaccine brands during the vaccination and booster programmes. However, one notes that the majority of eligible patients (approximately 70%) received the Pfizer BioNTech (BNT162b2) vaccine for their primary vaccination and booster dosing.

We would like to highlight that even though we report 0 critical patients in the boosted arm, there were 2 ARDS-related deaths in severely comorbid boosted patients, in whom escalation of treatment/ITU admission was deemed medically futile and thus did not meet the criteria to include in the critical disease cohort.

Of interest was the observation that the proportion of non-boosted patients with critical disease included significantly more males than females. In fact, the male gender was deemed to be an independent risk for SARS-CoV-2-related admission to ITU in our simple linear regression model above.

The study also shows that there was a trend to younger age for the non-boosted arm of the cohort. This reflects one facet of vaccine/booster hesitancy, a phenomenon which seems to be more prevalent amongst the younger population.

One other observation that emerged from the study was that a sound majority of the critical admissions to ITU in the non-boosted arm had received their primary vaccination more than 5 months prior to their illness. This points towards waning immunity which has been observed by other studies [14-16] thus underpinning the importance of timely boosting of the primary vaccination regimens.

The emergence of variants during the pandemic, with their different propensity towards increased infectivity and different disease severity, meant that during our study period the epidemiology changed from a majority prevalence of Delta variant (98% in October-November 2021) on to the emergence of the Omicron variant (85% Omicron BA.1 in December 2021: 82% Omicron BA.1, 12% Omicron BA.1.1 and 5% Omicron BA.2 in January 2022 as per verbal communication with/data collected by the Molecular Diagnostics Department in Mater Dei Hospital). To try to mitigate the bias potentially created by this changing epidemiology, we extended our study period to try to cover both the Delta high prevalence period and the Omicron high prevalence period in approximately equal periods.

CONCLUSIONS

At the time of submission, it was envisaged that another SARS-CoV-2 booster (4th dose) was going to be required in the near future. This came at a time of increasing vaccine hesitancy and pandemic fatigue. Our study indicates that a booster dose in the general immunocompetent adult population significantly reduces the chances of critical SARS-CoV-2-associated diseases. Although SARS-CoV-2 is nowadays, no longer considered a public health emergency, our study highlights the importance and role of vaccination strategies in curbtailing disease-severity in pandemics.

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