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Peer Review File

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Reviewer Comments

Events associated with COVID-19 vaccination in the context of a tertiary hospital. This protocol is proposed in the context of a Singapore tertiary vaccination centre, but it is unclear whether a similar set-up would work as effectively in smaller hospitals, in different cultures, and possibly with fewer resources. This caveat needs to be clearly acknowledged if the authors were to submit a revised manuscript. I am also unsure from the content of the paper, the extent to which the protocol was trialled at the hospital. Authors mention that a 'simulated' scenario and 'internal audits' were carried out, but do not describe the outcome of these investigations. It is unclear whether authors carried out any objective examination of the efficacy of the protocol in action. There are also several places within the main body of text where the language, grammar and wording are not clear. These issues would also need to be addressed in any future version of the paper. My recommendation at present is for the manuscript to be revised (as per my suggestions and those of further reviewers) and then resubmitted for a second round of reviewing. I am happy to review a revised version of this manuscript.

Originality – adding to currently published literature: This manuscript proposes a novel protocol for response to emergencies associated with COVID-19 vaccination, which has not appeared in previous published literature.

Research question clearly defined and appropriately answered: The manuscript would benefit from clearly defining the purpose of the paper sooner into the article, rather than midway through. While starting with some history of the need for COVID-19 vaccination is useful, the idea of adverse events and the need for standardised methods of managing these effects, should be brought in within the first few sentences of the article. Authors provide a good rationale for the need for in-site emergency response within vaccine centres and they describe their proposed protocol in an acceptable level of detail. Nevertheless, it is not clear in the current version of the paper as to whether the protocol was objectively successful in the context of the Singapore hospital.

Importance of work to general readers : The proposed protocol does have relevance to a wide range of audiences, but particularly clinicians and managerial staff within hospitals. This protocol was trialled in a Singapore tertiary hospital – so we cannot

infer the extent to which its success would generalise to smaller less-specialised hospitals in different cultures, and perhaps with fewer resources available. The authors need to add these caveats as limitations.

References up to date and relevant: References are appropriate and formatted consistently.

Line-by-Line Comments:
·Initial paragraph: Please clearly define rationale and research question in the first paragraph.
Reply: We have added the rationale and research questions in line 107-110

Changes in the text: "This paper will outline the importance of COVID 19 vaccination, the need to ensure swift and effective emergency medical response at a COVID-19 vaccination centre and the key steps taken at the vaccination center in a large tertiary hospital in Singapore to do so."

·104: 'Spectrum' should read 'The spectrum'.
Reply: We have changed the word to "The spectrum" in line 113

Changes in the text: "The spectrum of pharmacotherapy to treat COVID-19 is evolving rapidly after 2 years into the pandemic."

·108: 'for global pandemic' should read 'for the global pandemic'
Reply: We have changed the phrase to "the pandemic" in line 114

Changes in the text: "The spectrum of pharmacotherapy to treat COVID-19 is evolving rapidly after 2 years into the pandemic."

·109: 'evidently, recent Delta variant' should read 'evidently, the recent Delta variant'.
Reply: We have changed the phrase to "The Delta variant" in line 102

Changes in the text: "The Delta variant has shown to be deadlier than the previous variants, while preliminary data suggested that the mutations identified in Omicron, the prevailing SARS-CoV2 Variant of Concern, could confer increased infectivity."

·119: 'receiving booster dose' should read 'receiving a booster dose'.
Reply: We have changed the phrase to "receiving a booster dose" in line 124

Changes in the text: "Similarly, Arbel et al concluded that vaccination participants receiving a booster dose after at least 5 months from the 2nd dose had 90% lower mortality due to COVID-19 than those who did not."

·124: 'received booster vaccination' should read 'received a booster vaccination'.
Reply: We have changed the phrase to "received a booster vaccination" in line 142

Changes in the text: "The national vaccination campaign in Singapore kick-started on 14 December 2020 and as of, 13 March 2022, 91% of Singapore population are fully vaccinated against COVID-19 vaccination and 70% have received a booster vaccination."

·129: 'following implementation' should read 'following the implementation'.
Reply: We have changed it to "following the implementation" in line 130

Changes in the text: "Following the implementation of mass vaccination, however, severe allergic and anaphylactic reactions though rare, have been reported."

·120-130: It would be useful to include a sentence to explicitly state (rather than just state statistics) that these anaphylactic reactions are indeed very rare – otherwise this paragraph begins with a tone that might promote anti-vaccine responses.
Reply: We have included that the severe allergic and anaphylaxis reactions are rare in lines 130-134. The authors have referenced a study looking at adverse reactions post-mRNA vaccinations and have included the word "rare" in the statement.

Changes in the text: "Following the implementation of mass vaccination, however, severe allergic and anaphylactic reactions though rare, have been reported. The COVID-19 Citizen Science Study, an online cohort study reported that allergic reactions or anaphylaxis was reported in 0.3% after 1 dose of the Pfizer/BioNTech or Moderna vaccine, 0.2% after 2 doses of the Pfizer/BioNTech or Moderna vaccine. Such reactions, though rare, can have a negative rippling effect on vaccination uptake, thus hindering the progress of the vaccination exercise."

·131-133: If the authors wish to refer to the vaccine mechanism (e.g. mRNA) then they really need to include a simple explanation of the key differences in mechanism between the most popular COVID-19 vaccines.
Reply: We have included a simple explanation on the key differences in vaccine mechanisms from lines 145-150

Changes in the text: "Moderna are messenger ribonucleic acid (mRNA) vaccines which contain the genetic material from the SARS-CoV-2. After its inoculation, such material will signal the body to make a protein that triggers a protective immune response against COVID-19. On the other hand, Sinovac-Coronovac and Sinopharm are inactivated vaccines that utilise unreactive SARS-CoV-2 particles to stimulate the immune system to make antibodies against the virus."

·144-151: Authors need to mention how this operation was funded and staffed.
Reply: We have included how the operation was staffed in lines 168-176
Changes in the text: There were a total of 11 nurses, 2 doctors and 10 administrative staffs funded by our institution's Staff Vaccination Programme under the support and guidance from Singapore's Ministry of Health (MOH) COVID-19 Vaccination Taskforce. These staffs were deployed to the vaccination centre full-time to ensure smooth running of the operation. A nurse clinician was appointed to oversee the vaccine workflow and tally the stock. 11 nurses (including 2 nurse clinicians) who are familiar with vaccination procedures were deployed from the travel clinic and other departments. In addition, the doctors were residents from the Division of Medicine competent of performing medical resuscitation. Administrative staffs were temporary staffs recruited by the institution for this vaccination programme to aid with administrative work.

·151-152: Authors stated that 98.1% of staff had been vaccinated by 28/11/221 – but with which kind of vaccine and what was the rate, severity, and duration of any adverse events?
Reply: We have included the types of vaccination and the rate of anaphylaxis in lines 259-269

Changes in the text: "As of 28 November 2021, 98.1% of our eligible staffs have received at least 2 Pfizer - BioNTech vaccine doses and 30.3% have received a Pfizer - BioNTech booster dose. All vaccinees with vaccine-related reactions were promptly attended to by our on-site medical team within 5 minutes of the development of their symptoms. 26 cases that were sent to ED due to their severe reactions requiring closer monitoring. The overall rate of anaphylaxis was 0.02% with 4 anaphylaxis cases in the 23,006 vaccine doses administered. The 4 anaphylaxis cases were admitted for closer monitoring and discharge well after a period of observation. Those who were not eligible for Pfizer–BioNtech vaccine were eventually enrolled into another vaccination programme with the use of the Sinovac-Coronovac vaccine. As the number of this group is small, we have not included the rate of vaccination and

vaccine-related reactions of this group."

·154-161: Authors mention the use of screening for potential allergic/anaphylactic response prior to administering the vaccine. Absolute contraindications to the vaccine are described, but authors should also list any other inclusion criteria too – exactly what criteria were needed for a patient to be classed as high risk?
Reply: We have included the criteria for high risk in lines 193-195

Changes in the text: "Patients with a history of atopy or a history of allergic reactions to any drug or vaccine were classified as higher risk of developing allergic reactions post-vaccination".

·Figure 1: this is a useful pictorial representation of the proposed centre layout. It would be useful to include an explanation for colour choice – especially in the seating area. I am assuming the green dots in the pose-vaccination section are for patients at high risk of a reaction.
Reply: We have included the explanation in lines 199-206

Changes in the text: "Prospective vaccinees without contraindication who were eligible to be vaccinated but deemed to be at a higher risk of developing adverse or allergic reactions were asked to sit in the front rows of the post-vaccination observation area (green dots in Figure 1) during the 30-minutes mandatory monitoring period. Such central location allowed full visibility of this group of vaccines by the nurse stationed in front of the post-vaccination observation areas. This arrangement allowed the healthcare providers to monitor and attend to them swiftly in the event they develop adverse or allergic reactions. Other low risk vaccinees were free to sit on any chair indicated by the red-dots"

·167-168: Nice rationale provided for why the patients at higher risk were on the front row of the post-vaccine seating area – but what else can the authors include in their description of the centre layout/protocol that can highlight any other benefits to patient care and staff response?
Reply: We have highlighted other benefits in lines in 202-206

Changes in the text: "Such central location allowed full visibility of this group of vaccines by the nurse stationed in front of the post-vaccination observation areas. This arrangement allowed our healthcare providers to monitor and attend to such vaccinees swiftly in the event they develop adverse or allergic reactions. Other low risk

vaccinees were free to sit on any chair indicated by the red dots"

·195: 'once stabilised, patient will be transferred' should read 'once stabilised, the patient will be transferred'.
Reply: We have modified the text accordingly in line 236 to read "Stabilised vaccinees"

Changes in the text: "Stabilised vaccinees with residual symptoms would be transferred to Emergency Department (ED) for continuity of care."

·194-195: Authors mention transport to ED after being stabilised post-anaphylaxis. They claim this is to provide 'continuity of care' – though ED is normally one of the busiest places in the hospital and it may make more sense for the patient to be transferred to a ward. This idea should at least be considered in this part of the paper.
Reply: We have included an explanation in lines 237-242

Changes in the text: "This was possible due to the prior arrangement with the ED and their close proximity with our centre, and the fact that most of the allergic reactions were expected to be mild which most did not require subsequent inpatient care after being attended to and further monitored at the ED. Coupled with a next day outpatient allergist review, this reduced the need for admission which would stress our institution's high bed occupancy rate."

·Table 1: Table 1 provides a detailed overview of the protocol's pathway. It would be useful for authors to reflect on some of the potential barriers to these principles, in the protocol were to be rolled out in a different hospital setting.
Reply: We have included the potential barriers in lines 280 to 284 under the Section D) The limitations and caveats to adopting our model of care

Changes in the text: "Though this programme was a success, it required multi-faceted and comprehensive team effort involving different medical specialties, nursing, administrative and auxiliary support and it was resource intensive. It also necessitated the need for a strategic location where such a layout could be implemented. Such requirements may post as a barrier to the implementation of such a programme in a smaller hospital with relatively fewer resources."

·197: Authors mention that the processes in the protocol were carried out in a simulated scenario so that staff could be aware of how the pathway would work. What was the outcome of this simulated scenario? Were there any difficulties encountered?

If so, how were they addressed? What did staff think of the workflow?
Reply: We have included the details of the simulation assessments in lines 247-256 under the subsection iv) Competency assessments:

Changes in the text: "A total of 3 simulation exercises involving vaccinees with severe anaphylactic reactions were independently conducted by the medical team from the Department of Respiratory and Critical Care on separate days to ensure that the resuscitation procedures were performed competently. During each exercise, the reviewers used a checklist to detail steps of the resuscitation workflow which were expected to be carried out. A debrief was also held after each session to highlight the important learning points. Such exercises ensured that the on-site medical team and the various medical, nursing, and auxiliary teams involved were familiar with the workflow and gave us the opportunities to identify potential challenges that could arise. The finalized and refined workflow based on these simulation exercises was displayed on the wall of the resuscitation area for easy reference."

·200: Authors also mention having carried out internal audits of their proposed processes. What was the outcome of this audit process?
Reply: We have removed the statement on internal audits.

·201-209: The authors address impact in this final paragraph in terms of the importance of having such a protocol in place, and the implications for patient mortality and vaccine hesitancy. Reply: Authors really need to add a sentence in here as to how and why their proposed protocol is of specific benefit to these issues though – i.e. is there any evidence that the protocol worked?
Reply: The authors have included, in lines 259-277 under the subsection v) "Our results"