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RESEARCH ARTICLE

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Evaluation of antibody response to SARS-CoV-2 variants after 2 doses of mRNA COVID-19 vaccine in a correctional facility

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ABSTRACT

The SARS-CoV-2 pandemic has posed a challenge for correctional facilities worldwide. People in such settings are more vulnerable to severe forms of infection and it is impossible to completely isolate inmates from the outside world. This study aimed to assess the antibody-mediated immune response in terms of neutralizing antibodies against Alpha, Beta, Gamma and Omicron (sub-lineage BA.1) variants of concern after two doses of mRNA vaccine in correctional officers and inmates from an Italian correctional facility. Most of the correctional officers (56.5%) and inmates (52.3% and 63.6%) retained their neutralizing activity toward the Alpha and Gamma variants, respectively. By contrast, the most striking reduction in comparison with the ancestral virus was found in the antibody response toward the Beta and Omicron variants, in both correctional officers (91.2% and 93.9%) and inmates (85.1% and 92.8%). In addition, subjects who had undergone primary vaccination and had previously been naturally infected had higher neutralizing antibody titers toward the 4 variants than negative subjects. Overall, our findings indicate that primary mRNA vaccination is able to induce neutralizing antibodies toward the ancestral virus, while titers toward variants may vary, depending on the mutations harboring by the variants. Although the correctional setting is often considered distinct or isolated from the wider society and sanitary system, the health of correctional workers and prisoners is inexorably linked to the public health of the country as a whole and it is of paramount importance to monitor the antibody response in these settings.

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Introduction

Coronavirus Disease (COVID-19), which is caused by SARS-CoV-2, has posed a challenge for correctional facilities worldwide. Of the more than 8 million prison inmates in the world, 50,900 are in Italy,[1] which has one of the most overcrowded prison systems in Europe, with an occupation rate of 120%.[2,3] Although the World Health Organization (WHO) has issued guidelines on "preparedness, prevention and control of COVID-19 in prisons and other places of detention,"[4] people in such settings are more vulnerable to severe forms of infection for several reasons. Firstly, the average level of health, prior to entry into prison, is lower than that of the general population, making these subjects more vulnerable and fragile. In addition, detainees often have comorbidities and high rates of substance abuse.[5,6] In community settings such as prisons, it is almost impossible to respect measures aimed at limiting the spread of the virus, owing to overcrowding, limited access to hand sanitizers and face masks and poor ventilation. Indeed, it has been estimated that the incidence of COVID-19 among prisoners is nearly six times higher than among non-incarcerated subjects and increased crowding is associated with an increased incidence rate of COVID-19.[7–9]

As prisons are not a closed system, it is impossible to completely isolate inmates from the outside world; indeed, visitors, prison staff, such as directors, administrative workers, healthcare personnel and correctional officers (CO), come and go daily, increasing the risk of bringing the virus into the facility.[10,11] The most part of correctional workers, in fact, have been considered essential personnel during the COVID-19 response, and their jobs bring them into direct daily contact with a high-risk population. Apart of sharing all the risks of the physical environment as listed above, the CO are additionally exposed through uncontrolled physical contacts, moving prisoners or engaging in altercations, and the medical staff perform physical examinations and medical procedures. Because of transmission of COVID-19 through asymptomatic patients is nearly inevitable, and because conditions strongly favor contagion inside the institution, most correctional facilities will amplify the COVID-19 pandemic and act as a reservoir of illness to the wider community.[12]

Vaccination has proved to be the most valuable and cost-effective healthcare intervention in the fight against SARS-CoV-2. Even if scientists and public health experts have recommended prioritization of prison and jail populations for deployment of COVID-19 vaccines, detainees have not been included in vaccine trial population.[13] Vaccines rollout has varied across prisons and countries, and only in some of them detainees and prison staff were among the priority targets of vaccination, resulting in lower infection rates among the former.[14] However, few studies have evaluated vaccination coverage in prisons.[14–16]

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The most commonly used COVID-19 vaccines are the mRNA-based vaccines (BNT162b2 and mRNA-1273), both of which are more than 90% effective against COVID-19.[14,15]

The mRNA-based vaccines were developed by encoding the spike (S) protein of the virus circulating early in the pandemic. Since then, however, several variants, some defined by the WHO as variants of concern (VOCs), have emerged worldwide, raising concerns regarding vaccine effectiveness. So far, five VOCs have emerged: Alpha (Pango lineage B.1.1.7), Beta (Pango lineage B.1.351), Gamma (Pango lineage P.1), Delta (Pango lineage B.1.617.2) and Omicron (Pango lineage B.1.1.529).[17] The Alpha variant, first documented in the United Kingdom in September 2020, harbored 17 mutations/deletions in the viral genome, including eight in the S protein, and was associated with a 50% increase in transmission and an increased risk of death. The Beta variant was isolated in South Africa in May 2020 and caused an increase in hospitalizations and deaths. The Gamma variant, first isolated in Brazil in November 2020, shared common mutations in the S protein with the Beta variant, increasing the possibility of evasion of the humoral response and enhancing transmissibility. The Delta variant emerged in India in October 2020 and rapidly became predominant throughout the world. This variant harbored 23 mutations compared to the Alpha variant, 12 of which in the S protein, allegedly making it the most transmissible variant. The currently circulating variant is Omicron, which is considered the most divergent; in November 2021, it was documented in many countries.[17–20] Omicron harbors more than 50 mutations, 30 of which in the S protein, and is able to escape the immunity elicited by vaccination and/or natural infection.[17–19–21,22] So far, many sub-lineages of the Omicron variant have emerged.

This study aimed to assess the antibody-mediated immune response in terms of neutralizing antibodies against Alpha, Beta, Gamma and Omicron (sub-lineage BA.1) VOCs after two doses of mRNA vaccine in CO and inmates from an Italian correctional facility.

Materials and methods

Study population

A total of 342 serum samples were collected at the Bari correctional facility (Apulia, Italy) 21 days after the 2nd dose (primary vaccination) of mRNA vaccine (BNT162b2). One hundred forty-seven (147) serum samples were from CO and 195 from inmates.[23] Subjects were recruited on a voluntary basis and provided informed consent to participate in the study and data processing prior to the start of the study and after receiving a briefing on the study by medical personnel. All subjects were informed about the results of the study and received two doses of BNT162b2 vaccine. All subjects included in the study were administered by adequately trained medical staff a questionnaire on the general characteristics, work activity, and the recent and remote pathological history. The same day of the administration of the questionnaire a blood sampling was collected by adequately trained medical staff.

All samples were tested by means of commercial ELISAs for the detection of antibodies against the S protein and the nucleoprotein (NP), which is indicative of previous infection. Samples were further tested in duplicate by means of the virus neutralization (VN) assay, using authentic live viruses.

The research protocol was approved by the Ethics Committee of the University Hospital of Bari (n. 6955, prot. N. 0067544–02082021).

ELISAs

A double-antigen ELISA kit was used to detect antibodies against the SARS-CoV- 2 NP and S proteins in human serum samples. IgG antibodies binding to the SARS-CoV-2 NP protein were determined by means of the ERADIKIT COVID-19 MULTISPECIES (In3diagnostic, Turin, Italy). The results were defined according to the calculated ratio described in the following formula, and expressed as a percentage: PR (%) = (OD test sample – OD negative control)/(OD positive control – OD negative control). Values ≥20% were considered positive for the presence of antibodies against SARS-CoV-2. IgG antibodies binding to the SARS-CoV-2 S protein were determined by using the IDK anti-SARS-CoV-2 IgG ELISA kit (Immundiagnostik AG, Bensheim, Germany). The results were defined by using a linear ordinate for OD and a logarithmic abscissa for concentration. The numbers obtained were multiplied by the dilution factor of 101 to get the actual concentrations in ng/mL. Values ≥175 ng/mL were considered positive for the presence of antibodies against the SARS-CoV-2 S protein.

Viruses

Authentic ancestral SARS-CoV-2 2019 (2019-nCov/Italy-INMI1 strain) virus (hereinafter referred to as ancestral or Wuhan virus) was purchased from the European Virus Archive goes Global (EVAg, Spallanzani Institute, Rome). The Alpha variant, named England/MIG457/2020, and the Beta variant, named hCoV-19/Netherlands/NoordHolland_10159/2021, next strain clade 20 H, wild-type viruses were purchased from EVAg. The Gamma variant (next strain 20J/501Y.V3) (lineage B.1.1.28.1) was kindly provided by the University of Siena, Department of Medical Biotechnology. The live Omicron SARS-CoV-2 variant, sub-lineage BA.1, was kindly provided by Prof. Piet Maes, NRC UZ/KU Leuven (Leuven, Belgium). The Omicron sequence has been deposited on GISAID with the following ID: EPI_ISL_6794907.

Virus neutralization assay

The VN assay was performed as previously described.[24] Briefly, a 2-fold serial dilution of heat-inactivated serum samples was prepared and mixed with an equal volume of SARS-CoV-2 viral solution containing 100 tissue culture infective dose 50% (TCID50) of each virus. After 1 hour of incubation at room temperature, 100 µL of virus – serum mixture was added to a 96-well plate containing an 80% confluent Vero E6 cell monolayer. Plates were incubated for 72 hours (ancestral virus) and 96 hours (Alpha, Beta, Gamma and Omicron

variants) at 37°C and 5% CO_2 in a humidified atmosphere and then checked for presence/absence of cytopathic effect (CPE) by means of an inverted optical microscope. A CPE higher than 50% indicated infection.

The VN titer was expressed as the reciprocal of the highest serum dilution showing protection from viral infection and CPE.

Statistical analysis

Median VN titers were calculated along with their interquartile range (IQR). For each variant, a decrease in median VN titers in comparison with the Wuhan strain was calculated as a reduction factor (RF). Comparisons between median VN titers were performed by using the Friedman test or Kruskal-Wallis test with Dunn's correction for multiple comparisons. Statistical significance was set at $p < .05$, two tailed. All statistical analyses were performed by means of GraphPad Prism version 9.0 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com).

Results

The 147 CO had a median age of 53.9 years (range 23.9–72.2 years); 34 (23.1%) were female and 113 (76.9%) were male. Eighteen (18) (12.2%) had at least one disease (cancer, transplants, HIV, hepatitis C or hepatitis B virus chronic infection, diabetes, autoimmune disease) and/or were on immunosuppressive therapy. The 195 inmates had a median age of 46.3 years (range 20.0–81.2 years) and were all male. Twenty-seven (27) (13.85%) had at least one disease and/or were drug users and/or were on immunosuppressive therapy.

A median time of 21 days after the 2nd dose of mRNA vaccine, 98.6% of CO and 99.0% of inmates had antibodies against the S protein.

Figure 1 shows individual VN titers against the Wuhan strain in CO (Figure 1a) and inmates (Figure 1b). Among CO, the median VN titer against the Wuhan strain was 40.0 (IQR 20.0–80.0); 8 subjects (5.4%) were negative. Among inmates, the median VN titer against the Wuhan strain was 40.0 (IQR 14.1–80.0), with 14 subjects (7.2%) negative. On comparing median VN titers against the Wuhan strain, no differences were found between CO and inmates.

When tested for Alpha, Beta, Gamma, and Omicron BA.1 variants (Figure 1c,d, Tables 1 and 2), a significant decrease in median VN titers was observed ($p < .0001$ for both CO and inmates).

Among CO, the median VN titer was 20.0 (IQR 10.0–40.0, RF of 2.0) toward the Alpha variant, with 43.5% of subjects showing a ≥ 2-fold reduction in the median VN titer; 10.0 (IQR 5–14.1, RF of 4.0) toward the Beta variant, with 91.2% of subjects showing a ≥

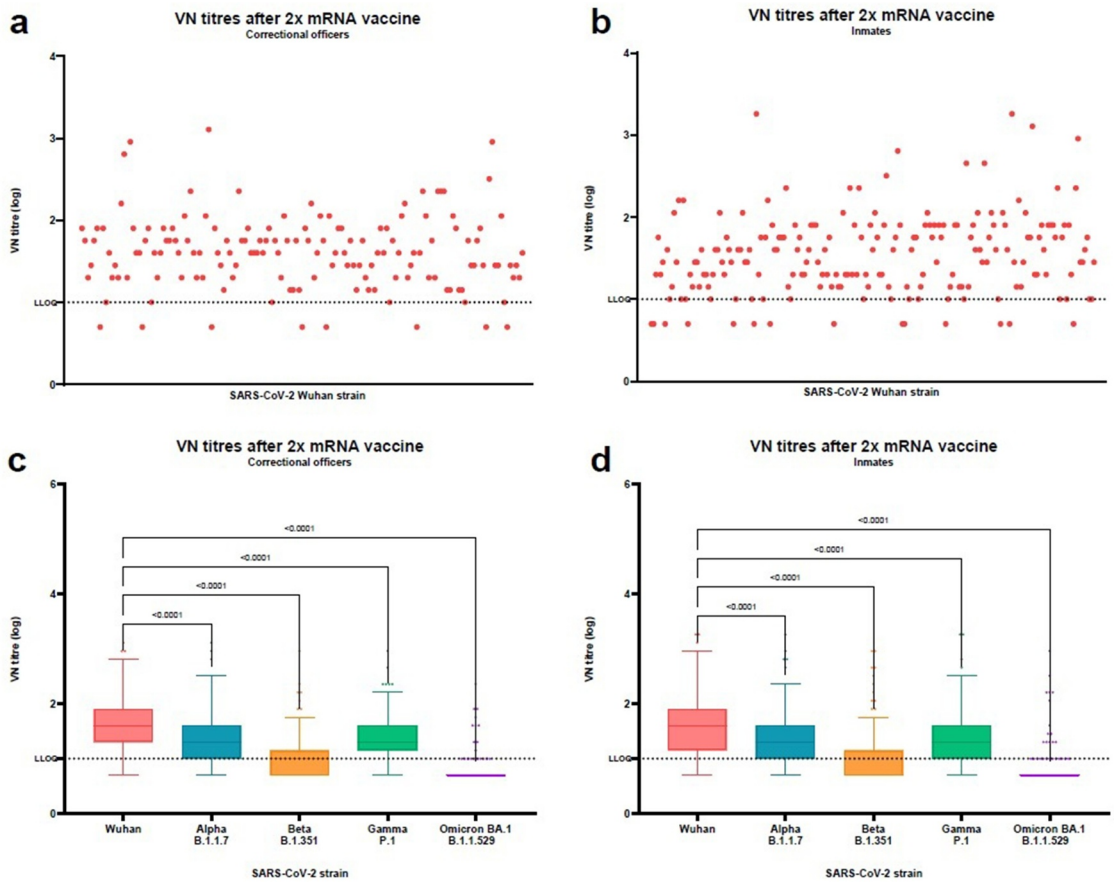

Figure 1. Virus neutralization (VN) titers to SARS-CoV-2 virus after 2 doses of mRNA vaccine in correctional officers and inmates. Panel a: VN titers against Wuhan strain in correctional officers; Panel b: VN titers against Wuhan strain in inmates; Panel c: VN titers against Wuhan and Alpha, Beta, Gamma, and Omicron BA.1 variants in correctional officers; Panel d: VN titers against Wuhan and Alpha, Beta, Gamma, and Omicron BA.1 variants in inmates. Dot plots show individual values. Tukey boxplots show outlier values (dots), medians (middle line), third and first quartiles (boxes), while the whiskers display the minimum and maximum values. Horizontal dashed line represents the Lower Limit of Quantification (LLOQ) of VN assay. Statistically significant differences were analyzed by Friedman and Dunn's multiple comparisons test ($p < .05$).

Table 1. Fold decrease in virus neutralization titers to SARS-CoV-2 variants with respect to Wuhan strain in correctional officers, by variant.

Correctional officers								
Variant	Alpha		Beta		Gamma		Omicron BA.1	
Decrease	N	%	N	%	N	%	N	%
-	83	56.5	13	8.8	83	56.5	9	6.1
2-fold	40	27.2	45	30.6	48	32.6	17	11.6
4-fold	21	14.3	53	36.1	15	10.2	44	29.9
>4-fold	3	2.0	36	24.5	1	0.7	77	52.4
From 2 to >4-fold	**64**	**43.5**	**134**	**91.2**	**64**	**43.5**	**138**	**93.9**
Total	**147**	**100.0**	**147**	**100.0**	**147**	**100.0**	**147**	**100.0**

Table 2. Fold decrease in virus neutralization titers to SARS-CoV-2 variants with respect to Wuhan strain in inmates, by variant.

Inmates								
Variant	Alpha		Beta		Gamma		Omicron BA.1	
Decrease	N	%	N	%	N	%	N	%
-	102	52.3	29	14.9	124	63.6	14	7.2
2-fold	63	32.3	67	34.3	57	29.2	44	22.6
4-fold	27	13.9	63	32.3	11	5.7	51	26.1
>4-fold	3	1.5	36	18.5	3	1.5	86	44.1
From 2 to >4-fold	**93**	**47.7**	**166**	**85.1**	**71**	**36.4**	**181**	**92.8**
Total	**195**	**100.0**	**195**	**100.0**	**195**	**100.0**	**195**	**100.0**

2-fold reduction in the median VN titer; 20.0 (IQR 14.1–40.0, RF of 2.0) toward the Gamma variant, with 43.5% of subjects showing a ≥ 2-fold reduction in the median VN titer; and 5.0 (IQR 5–5, RF of 8.0) toward the Omicron BA.1 variant, with 93.9% of subjects showing a ≥ 2-fold reduction in the median VN titer. Among inmates, the median VN titer was 20.0 (IQR 10.0–40.0, RF of 2.0) toward the Alpha variant, with 47.7% of subjects showing a ≥ 2-fold reduction in the median VN titer; 5.0 (IQR 5–14.1, RF of 8.0) toward the Beta variant, with 85.1% of subjects showing a ≥ 2-fold reduction in the median VN titer; 20.0 (IQR 10.0–40.0, RF of 2.0) toward the Gamma variant, with 36.4% of subjects showing a ≥ 2-fold reduction in the median VN titer; and 5.0 (IQR 5–5, RF of 8.0) toward the Omicron BA.1 variant, with 92.8% of subjects showing a ≥ 2-fold reduction in the median VN titer. No differences were observed between CO and inmates on comparing median VN titer toward the same strain.

1Fifteen (15) (4.4%) subjects among CO and inmates tested positive to ELISA antibodies against the NP. Subjects were divided according to their NP ELISA results, as shown in Figure 2. Among NP-positive subjects, the median VN titer against the Wuhan strain was 640.0 (IQR 226.3–1280.0); this was significantly higher than the median VN titer among NP negatives (40.0, IQR 20.0–566, $p = .0007$). On comparing median VN titers between NP-positive and NP-negative subjects, differences were significant for all the variants tested ($p < .0001$).

While the decrease in median VN titers toward all the variants tested was significant ($p < .0001$) in NP-negative subjects, in NP-positive subjects the decrease was significant toward the Beta (median VN titer 160.0, IQR 80.0–452.5, $p = .0081$) and Omicron BA.1 (median VN titer 80.0, IQR 28.3–160.0, $p < .0001$) variants, but not toward the Alpha (median VN titer 452.5, IQR 160.0–905.1) and Gamma (median VN titer 226.3, IQR 226.3–640.0) variants.

No differences were found comparing NP-positive CO and NP-positive inmates toward the Wuhan strain (median VN titer 772.5, IQR 198.0–998.8 for CO and median VN titer 640.0, IQR 216.6–1545.0 for inmates) and all the variants tested.

Discussion

Since the beginning of the SARS-CoV-2 pandemic, on 11 March 2020, 5 VOCs harboring mutations in the S protein have emerged, which may jeopardize current vaccine effectiveness.

In this study, we evaluated the antibody response in terms of neutralizing antibodies toward the Alpha, Beta, Gamma and Omicron (sub-lineage BA.1) variants in 342 serum samples collected from CO and inmates at the Bari correctional facility (Apulia, Italy) 21 days after the 2nd dose of mRNA vaccine (BNT162b2).

Vaccination in correctional facilities has specific challenges, such as the coordination of the administration of the second and the booster doses among inmates, without loss to follow up, considering the high turnover of inmates, often with individuals being released in the community before their second or third dose is due.[25] In addition, incarcerated subjects are at high risk for COVID-19 transmission and severe disease, they have higher rates of many physical and mental health comorbidities, usually more common than in community subjects of similar age. Studies aimed at evaluating the antibody response in correctional settings provide the opportunity to increase data on the effectiveness of the vaccination strategy in a context different from the general population and potentially to identify susceptible cohorts to COVID-19.

In the correctional facility under study, the prevalence of inmates that have received two vaccine doses was similar to that observed in the Italian general population, whereas the percentage of those receiving the third dose was lower.[16]

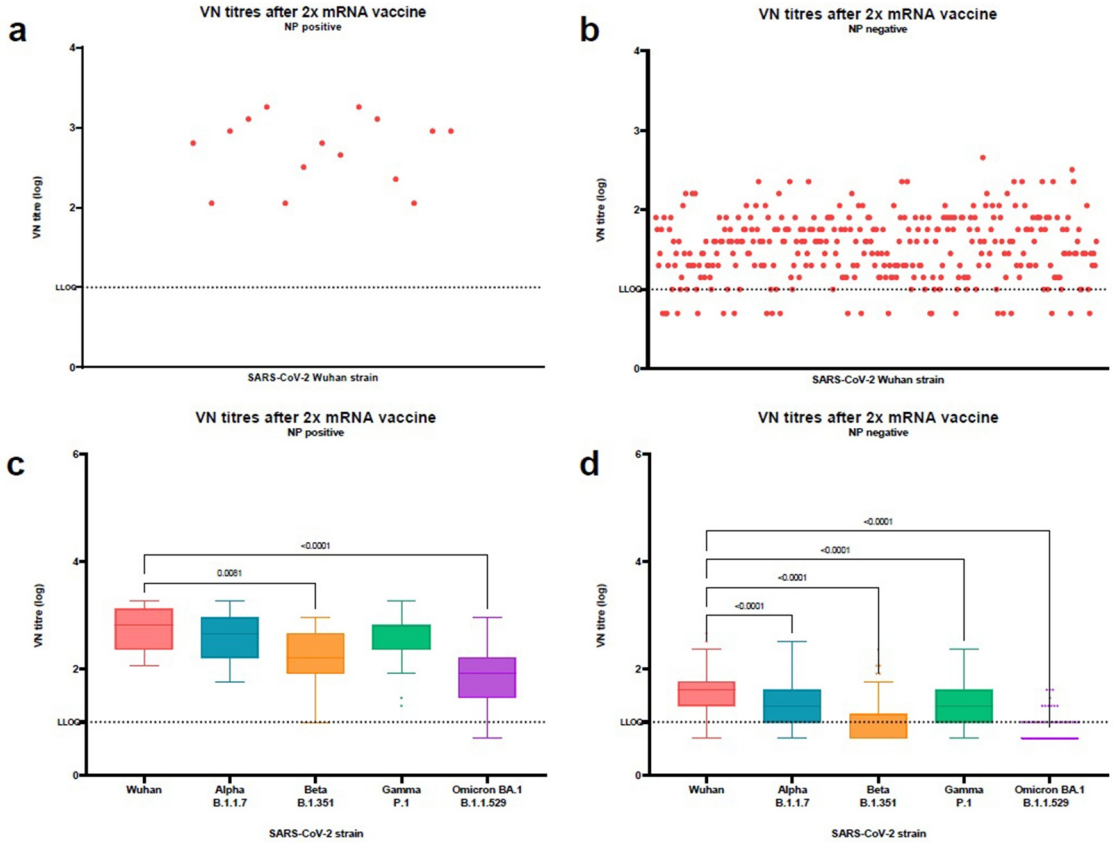

Figure 2. Virus neutralization (VN) titers to SARS-CoV-2 virus after 2 doses of mRNA vaccine in nucleoprotein (NP) positive and NP negative subjects. Panel a: VN titers against Wuhan strain in NP positive subjects; Panel b: VN titers against Wuhan strain in NP negative subjects; Panel c: VN titers against Wuhan and Alpha, Beta, Gamma, and Omicron BA.1 variants in NP positive subjects; Panel d: VN titers against Wuhan and Alpha, Beta, Gamma, and Omicron BA.1 variants in NP negative subjects. Dot plots show individual values. Tukey boxplots show outlier values (dots), medians (middle line), third and first quartiles (boxes), while the whiskers display the minimum and maximum values. Horizontal dashed line represents the Lower Limit of Quantification (LLOQ) of VN assay. Statistically significant differences were analyzed by Friedman and Dunn's multiple comparisons test ($p < .05$).

As reported in other studies,[16–36] the most striking reduction in comparison with the ancestral virus was found in the antibody response toward the Beta and Omicron variants, in both CO and inmates. Indeed, 91.2% and 93.9% of CO and 85.1% and 92.8% of inmates showed a ≥ 2-fold reduction in the median VN titer against the Beta and Omicron variants, respectively. The Beta variant, like the Gamma, harbors 3 mutations in the RBD region of the S protein, which may enable these variants to evade the neutralizing antibodies against the ancestral virus. The Omicron variant, which is derived from the Alpha lineage, is characterized by several mutations in the S protein; these mutations, and especially those at the top of the protein, in regions accessible to antibodies, may increase the likelihood of immune evasion.[27,34,36] Together, the mutations carried by the variants that have emerged may enable these variants to evade the antibodies induced by primary vaccination.[37–41] These findings suggest that two doses of mRNA could be insufficient to provide adequate levels of protection against variants with critical mutations. Thus, a booster dose could enhance the immune response, as reported for the Omicron variant.[29]

By contrast, 56.5% of CO and 52.3% and 63.6% of inmates retained their neutralizing activity toward the Alpha and Gamma variants, respectively. Our findings regarding the Alpha variant are consistent with previous observations that mutations carried by this variant have little or no effect on neutralizing activity in samples from vaccinated subjects.[42–45] Moreover, neutralization of the Gamma variant was not compromised, since most of the vaccinated subjects retained an antibody titer similar to that against the ancestral virus, as reported in other studies.[30,46,47]

However, no significant difference was observed between CO and inmates, indicating that the latter does not seem to have a different response to the vaccine as neutralizing activity.

Furthermore, we evaluated the antibody response toward the 4 VOCs on considering positivity to the NP protein, which is indicative of previous infection. Our findings showed that subjects who had undergone primary vaccination and had previously been naturally infected had higher neutralizing antibody titers toward the 4 variants than negative subjects. These NP-positive subjects had also developed an immune response against the Omicron variant. Consistently with previous reports, our results provide evidence that previous exposure to SARS-CoV-2 enhances the production of neutralizing antibodies in vaccinated individuals against both the ancestral virus and VOCs.[26,29,34,48]

These findings taken together support the need for a rapid and synchronized widespread deployment of additional mRNA vaccine doses as public health preventive measure to increase the protection of inmates and correctional workers

against COVID-19. Notably, all these subjects are at risk to contract the COVID-19 infection and therefore, it is of paramount importance to monitor the antibody response in these settings.

A key strength of this study was the use of a VN assay with authentic live viruses rather than a surrogate neutralization assay. A long assay incubation time of the virus-sample mixture in cell cultures can enable us to identify more precisely the antibody titer that best correlates with real protection, since this titer is based on the complete inhibition of CPE in the cell monolayer.

This study also has some limitations. Firstly, we did not evaluate the same serum samples after the third dose. Secondly, gender distribution was not balanced, since most of the subjects enrolled were male. Thirdly, we did not evaluate the antibody response against the Delta variant. Lastly, we did not evaluate other branches of immunity, such as T-cell responses, which could contribute to protection even if neutralizing antibodies are absent or reduced. In addition, it might be interesting to evaluate the antibody response and adverse events after breakthrough infection after a longer period of time.

Overall, our findings indicate that primary mRNA vaccination is able to induce neutralizing antibodies toward the ancestral virus, while titers toward variants may vary, depending on the mutations harboring by the variants. Critical mutations may lead to an almost complete loss of neutralizing activity in some cases, such as that of the Omicron variant. However, additional exposure to viral antigens through natural infection increases and enhances neutralizing activity even against the most divergent variant.

In conclusion, although the correctional setting is often considered distinct or isolated from the wider society and sanitary system, the health of correctional workers and prisoners is inexorably linked to the public health of the country as a whole. The finding of this study highlights that completing the vaccination course by administering a booster dose in particular settings such as prisons must be considered as an essential and effective measure for the COVID-19 prevention.

Disclosure statement

C.M.T. is an external consultant of VisMederi Research srl.
M.L. is an employee of VisMederi Research srl.
E.M. is an external consultant and Chief Scientific Officer of VisMederi srl and VisMederi Research srl.
The other authors declare no competing interests to declare.

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Author's contributions

Conceptualization: C.M.T., N.D., P.L.; Formal Analysis: S.M.; Investigation: C.M.T., S.M., M.L., E.L.; Resources: C.M.T., A.S., N.B., N. D., P.L.; Writing – original draft preparation: C.M.T.; Writing – review and editing: S.M., M.L., N.B., A.S., E.L., E.M., N.D., P.L.; Visualization: S. M.; Supervision: C.M.T. and P.L.; Project administration: C.M.T., N.D., P. L.; Funding acquisition. C.M.T., N.D., P.L.

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