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Article

Epidemiological and clinical features of SARS-CoV-2 variants circulating between April-December 2021 in Italy

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Abstract: SARS-CoV-2 is constantly evolving leading to new variants. We analysed data from 4,400 SARS-CoV-2-positive samples in order to continue variant surveillance in Italy to evaluate their epidemiological and relative impact on public health in the period April-December 2021.

The main circulating strain (76.2%) was Delta followed by Alpha (13.3%), Omicron (5.3%) and Gamma variants (2.9%). B.1.1 lineages, Eta, Beta, Iota, Mu and Kappa variants represented around 1% of cases. Overall, 48.2% of subjects were not vaccinated with a lower median age compared to vaccinated subjects (47 *vs.* 61 years). An increasing number of infections in vaccinated subjects was observed overtime, with the highest proportion in November (85.2%). Variants correlated with clinical status; the largest proportion of symptomatic patients (59.6%) was observed among Delta variant, while subjects harboring Gamma variant showed the highest proportion of asymptomatics

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(21.6%), albeit also of deaths (5.4%). The Omicron variant was only found in vaccinated subjects, of which 47% were hospitalized.
Diffusivity and pathogenicity associated with the different SARS-CoV-2 variants are likely to have relevant public health implications, both at national and international level. Our study provides data on the rapid changes in the epidemiological landscape of SARS-CoV-2 variants in Italy.

Keywords: variants circulation; SARS-CoV-2; Italy; epidemiology

1. Introduction

The ongoing global Coronavirus disease 2019 (COVID-19) pandemic has caused significant mortality and morbidity [1], requiring unprecedented efforts to develop novel vaccines and strategies for treating COVID-19. Despite its limited intrinsic genetic variability, the huge number of infections led to SARS-CoV-2 evolution in an expanding array of new variants. While the driver of this evolution is certainly immune escape, the new emerging variants may differ from those previously circulating also in terms of increased transmissibility and virulence. These variations can affect diagnostic detection, available treatments and vaccine efficacy [2, 3]. Currently, the spike (S) protein is the region mostly affected by mutation, and the circulating SARS-CoV-2 variants are classified on the basis of variations in S protein, compared to ancestral strain [4]. Among the growing number of SARS-CoV-2 variants documented worldwide during the pandemic, previously classified variants of concern (VOCs) such as Alpha (B.1.1.7/20I), Beta (B.1.351/20H), Gamma (B.1.1.28/P1) and Delta (B.1.617.2) were associated with increased transmissibility, mortality, or decreased susceptibility to neutralising antibodies induced by vaccination or previous infection [2, 3, 5-8].

Among these, the Beta variant resulted significantly more resistant to neutralization by sera of convalescent or vaccinated person, mainly because the presence of E484K mutation [9]. The P.1 and Delta variants were related to increase transmissibility, virulence, and reduced sensibility to neutralizing antibodies [10-13]. The Delta variant showed additional mutations in the spike protein such as P681R, E484Q, and L452R, with the last two associated to immune escape [14]. Different sub-lineages previously classified as variants of interest (VOI), i.e. Kappa (B.1.617.1/21B), Iota (B.1.526/21F), Lambda (C.37/21G) and Mu (B.1.621/21H), and also previous prevalent VOCs were de-escalated as they became “extinct” and ceased to impact on the overall epidemiological situation (https://www.who.int/activities/tracking-SARS-CoV-2-variants).

Currently, Omicron is the only present VOC representing the predominant worldwide circulating variant (www.gisaid.com) largely causing breakthrough infections [15].

In light of the its widespread transmission worldwide and its observed viral diversity, WHO added a new category to the variant tracking system, termed “Omicron subvariants under monitoring" (VUM) in order to alert public health authorities globally, on which of them may require prioritized attention and monitoring (BA.4, BA.5, BA.2.12.1, BA.2.9.1, BA.2.11, BA.2.13 and BA.2.75). Currently there are no VUMs (https://www.who.int/activities/tracking-SARS-CoV-2-variants).

Our previous analysis [16], reported data obtained in several Italian regions involved in the SARS-CoV-2 variant monitoring in the period October 2020-March 2021. The aim of the present study is to continue the surveillance in Italy by evaluating COVID-19 epidemiology and clinical data of subjects in the subsequent period, ranging from April to December 2021.

2. Materials and Methods

2.1 Sample collection and study design

This retrospective observational study included 4,400 SARS-CoV-2-positive nasopharyngeal-swabs obtained from COVID-19 positive patients referred to Italian Centers participating to the SCIRE (SARS-CoV-2 Italian Research Enterprise) collaborative group during the period of April 1st to December 31st, 2021. Distribution of samples through the

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different months was as follow: 357 (April), 267 (May), 184 (June), 304 (July), 443 (August), 409 (September), 323 (October), 764 (November) and 1,349 (December).

All the genotypic data, demographic, epidemiological and clinical data used for the analyses were collected at each center as part of routine variant surveillance or for research purpose.

This study was conducted in accordance with the principles of the 1964 Declaration of Helsinki and approved by the ethic committee of the Sacco Hospital (prot. n. 47866, 09-09-2020).

2.2 Virus amplification and sequencing

Genotypic data were obtained by using different methods: RT-PCR variant screening assays (n=2,535), spike Sanger (n=938) and Next Generation Sequencing (NGS, n=46), and Whole Genome Sequencing (WGS, n=881). These data, stratified according to different methodologies used for the variant monitoring and months of sampling collection, are shown in Table 1.

Table 1. Description of analysed data.

	April (n=357)	May (n=267)	June (n=184)	July (n=304)	August (n=443)	September (n=409)	October (n=323)	November (n=764)	December (1,349)	Total (n=4,400)
RT-PCR	162	57	25	118	248	219	211	514	981	2,535
NGS WG	134	149	81	59	109	77	32	76	164	881
NGS Spike	42	1	0	0	0	0	0	0	3	46
Sanger Spike	19	60	78	127	86	113	80	174	201	938

RT-PCR: Real-Time PCR
NGS: Next Generation Sequencing
WGS: Whole Genome Sequencing

SARS-CoV-2 swabs were collected from the respiratory tract of individuals who were either hospitalized or tested in screening programs. Viral RNA was extracted using different commercial kits such as the Kit QIAsymphony DSP Virus/Pathogen Midi kit on the QIAsymphony automated platform (QIAGEN, Hilden, Germany), the NucleoMag 96 Virus (Macherey-Nagel, Dueren, Germany) on automated KingFisherTM ml Magnetic Particle Processors (Thermo Fisher Scientific, Waltham, MA, USA) and manually with QIAamp Viral RNA Mini Kit (QIAGEN, Hilden, Germany). RT-PCR genotyping assays were performed using TaqPath COVID-19 test (Thermo Fisher Scientific, USA), COVID-19 Ultra Variant Catcher (Clonit srl, Milan, Italy), Allplex SARS-CoV-2 Variants (Arrow Diagnostics srl, Genoa, Italy), multiplexed RT-qPCR developed by English consortium (https:// www. proto cols. io/ view/multi plexed- rt- qpcr- to- screen- for- sars- cov-2- b-1- 1-br9vm 966? versi on_ warni ng= no) or home–made protocols. Spike sequences were obtained using home-made protocols. Full genome sequences were obtained with different protocols, by a modified version of Artic Protocol (https://artic.netwo rk/ ncov- 2019) using Illumina DNA Prep and IDT ILMN DNA/RNA Index kit (Illumina), or by CleanPlex® SARS-CoV-2 Panel (Paragon Genomics Inc, Hayward, CA, USA). Sequencing was performed on Illumina iSeq (n=99), Miseq (n=644) and Nextseq (n=138) platforms for all samples. The results were mapped and aligned to the reference genome obtained from GISAID, (https://www.gisaid.org/, accession ID: EPI_ISL_406800) using Geneious Prime software v. 11.1 (http://www.geneious.com, Biomatters, Auckland, New Zealand) or BWA-mem and rescued using Samtools alignment/Map (Hinxton, UK) (v. 1.9).

SARS-CoV-2 lineage was attributed to all sequences using the Pangolin COVID-19 Lineage Assigner v. 4.1.1 (https://pango lin. cog- uk. io/) and Nextclade v. 2.4.1 (https://clades. nexts train. org/). Mutations were identified using Nextclade.

2.3 Statistical analysis

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Descriptive analyses of demographic and clinical data are presented as median and Inter-Quartile Range (IQR) when continuous and as frequency and proportion (%) when categorical. To compare normally distributed, non-normally distributed continuous, and categorical variables, parametric tests (t test and ANOVA), nonparametric tests (Mann–Whitney and Kruskal–Wallis) and the Pearson $\chi 2$ test (or Fisher exact test, when necessary) were used, respectively. Significance was established at $p < 0.05$. A data analysis was performed using the IBM SPSS Statistics version 25.

3. Results

3.1 Characteristics of the study population

Samples were collected from several Italian centers located in Apulia (n=85), Liguria (n=375), Campania (n=56), Calabria (n=25), Lombardy (n=1,145), Basilicata (n=13), Umbria (n=144), Marche (n=2,311), Lazio (n=192), Veneto (n=53) and also Republic of San Marino (n=1). Females were a slight majority (51.4%, 1,582/3,078) and the median age was 47 years (IQR: 29-63). Significant differences were observed in the median age over different months (*p<.001*), with the lowest median age reported in July (35 yo, IQR: 22-55) and the highest in April (57 yo, IQR: 35-72).

Among subjects with available data, 51.9% (n=507/979) received at least one dose of COVID-19 vaccine and 2.3% (n=12/532) reported previous exposure to SARS-CoV-2.

At the time of testing, mild infections were the most prevalent (2,330/2,965, 78.6%), followed by moderate/severe infections requiring hospitalization (474/2,965, 16%). Only 4.7% (138/2,965) of patients were asymptomatic. Deaths were reported in 23 patients among subjects with known outcome (0.8%).

Among patients with different age ranges, statistically significant differences in clinical status, were observed between subjects aged < and ≥ 60. Globally, proportions of hospitalized (44.2% *vs.* 55.7%; *p<.001*) and deaths subjects (14.4% *vs.* 85.7%; *p<.001*) resulted higher in aged patients compared to youngest. Of note, asymptomatic status was prevalent in subjects under the age of 60 while deaths were observed only in patients aged over 60, with the exception of 2 unvaccinated patients and 1 patients vaccinated with one dose in September and November, respectively.

3.2 Lineages and clades

Overall, the main circulating variant, representing more than 76.2% of total sequences (3,333/4,375), was Delta, B.1.617.2 lineage (60.5%, n= 2,648) together with its descendants (15.7%,n=685, including AY.4, AY.4.1, AY.4.2, AY.4.2.1, AY.4.2.3, AY.4.3, AY.4.6, AY.4.7, AY.4.9, AY.5, AY.5.4, AY.9, AY.9.1, AY.9.2, AY.10, AY.20, AY.23, AY.25, AY.26, AY.33, AY.34, AY.34.1, AY.36, AY.39, AY.42, AY.43, AY.44, AY.46.4, AY.46.6, AY.46.6.1, AY.48, AY.51, AY.53, AY.54, AY.58, AY.61, AY.68, AY.71, AY.73, AY.75, AY.82, AY.92, AY.91.1, AY.98, AY.98.1, AY.102, AY.103, AY.106, AY.112, AY.112.2, AY.118, AY.116, AY.119.2, AY.120, AY.122, AY.122.2, AY.122.3, AY.124, AY.124.1, AY.125, AY.126, AY.127 and AY.129) followed by Alpha variant (B.1.1.7 lineage, 13.3%, n=583) and Omicron (B.1.1.529 lineage, 5.3%, n=230) with its sub-lineages BA.1 (n=219), BA.1.1 (n=3) and BA.1.17.2 (n=8).

A proportion of 2.9% (n=127) of samples were Gamma variant including P.1 (n=79), P.1.1 (n=36), P.1.15 (n=2) and P.1.6 (n=10). About 1% of samples were of lineage B.1.1 and its descendant (n=47), Eta variant (n=10, B.1.525), Beta variant (n=12, B.1.351), Iota variant (n=8, B.1.526), Mu variant (n=10, B.1.621) and Kappa variant (n=1, B.1.617.1). Five cases of XF recombinants were also observed.

Considering clade classification (n=2,109), the most prevalent were 21J (n=756, 35.8%) and 20I (n=583, 27.6%) followed by 21A (n=267, 12.7%) and 21K (n=235, 11.1%). Clade 21I showed a prevalence of 2.4% (n=51) while clades 20A (n=8), 20B (n=16), 20D (n=16), 20E.EU1 (n=9), 20H (n=12), 21B (n=1), 21D (n=10), 21F (n=8) and 21H (n=10) had a prevalence of less than 1%.

3.3 Lineages and clades over time

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During the study period, the prevalence of the Alpha variant (B.1.1.7/20I) significantly (*p<.001*) decreased from 77.8% (n=273) in April 2021 to 0.7% (n=3) in August 2021 until its disappearance. Only 1 isolated case was reported in November 2021 in Lombardy.

Gamma variant (P.1 and it descendant/20J) remained stable in the first three months with a prevalence of 12.5% (n=44), 17.1% (n=45) and 19% (n=35), in April, May and June, respectively. The last cases were observed in July (n=3), one of these (lineage P.1.15) was identified in a 25 years old hospitalized patient, traveling from Argentina to Apulia.

Previously circulating lineages B.1.1 and its descendants were present at low prevalence only until August 2021, decreasing from 6.8% in April (n=24) to 0.7% (n=2) in July. One case of B.1.177 (20E.EU1) was observed in August in Lombardy.

The last case of Beta variant (B.1.351/20H) was identified in August, never reaching a prevalence above 2%.

Only few cases of Eta variant (B.1.525/21D) were reported until June in Marche when it reached the highest prevalence (2.7%, n=5). Two cases of Iota variant (B.1.526/21F) were detected in April in Marche and Liguria, with additional 6 cases in May and June in Liguria.

Mu variant (B.1.621/21H) was firstly detected in Marche (n=1) in April; a limited number of cases was reported until July reaching the highest proportion in June (3.2%; n=6) in Marche. A single case of Kappa variant (B.1.617.1/21B) was observed in May in Liguria in a young (25 years old) asymptomatic subject.

Starting from the middle of June, Delta variant (B.1.617.2) was firstly observed in the following Regions: Liguria, Lazio, Veneto and Marche (9.7%; n=18) together with 19 (10.3%) sub-lineages (AY.42, AY.61, AY.106 and AY.122) identified in Liguria, Apulia, Campania and Marche. Among these, a hospitalized subject reported a recent trip to Afghanistan. The prevalence of Delta variant and its sub-lineages rapidly increased reaching the totality of cases in September and October. However, while in June and July clades 21A and 21J showed similar proportions (8.2% *vs.* 10.9% in June and 44% *vs.* 32.7% in July), in the following months clade 21J became prevalent. The prevalence of clade 21J significantly increased overtime (*p<.001*), remaining around 70% from August (74.1%, 140/189) to November (72.5%; 140/193), while decreasing in December (45.6%; 239/524). Otherwise, clade 21I maintained low prevalence over time, with a higher proportion (9.5%; n=16) reported in July.

The first cases of Omicron variant (B.1.1.529/21K) were detected in Lombardy (n=4), with the first sequence reported in the city of Cremona (Lombardy) on November 5th, 2021. Its prevalence reached 16.8% of cases in December 2021.

Of note, its prevalence during the month of December increased steadily: 0.4% (November 29- December 5), 0.5% (December 6-12), 5% (December 13-19), 16.8% (December 20-26) to 61.7% (December 27-31). In this month, in addition to the BA.1 lineage (n=215), we observed the presence of sub-lineages BA.1.1 (n=3) and BA.1.17.2 (n=8).

Five cases of XF recombinants were identified in December in the Marche Region predominantly in vaccinated and hospitalized subjects (80%). Figure 1 shows the main viral variants and clades overtime.

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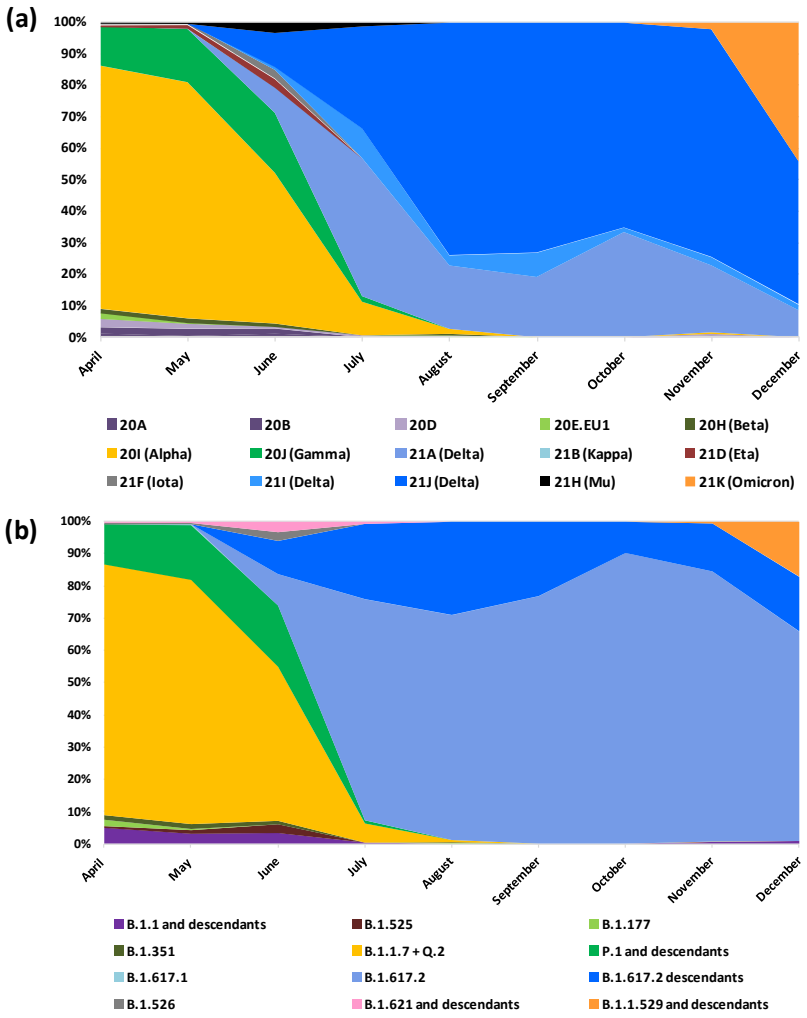

Figure 1. Dynamics of the SARS-CoV-2 epidemic in Italy. (**a**) Variants prevalence in terms of clades; (**b**) Variants prevalence in terms of lineages.

3.4 Vaccinated vs. unvaccinated

We observed a significantly ($p<.001$) increased proportion of subjects receiving at least one dose of COVID-19 vaccine from 15.8% to 73.2% over the study period, with the highest proportion reached in November (85.2%, 115/135) (Figure 2).

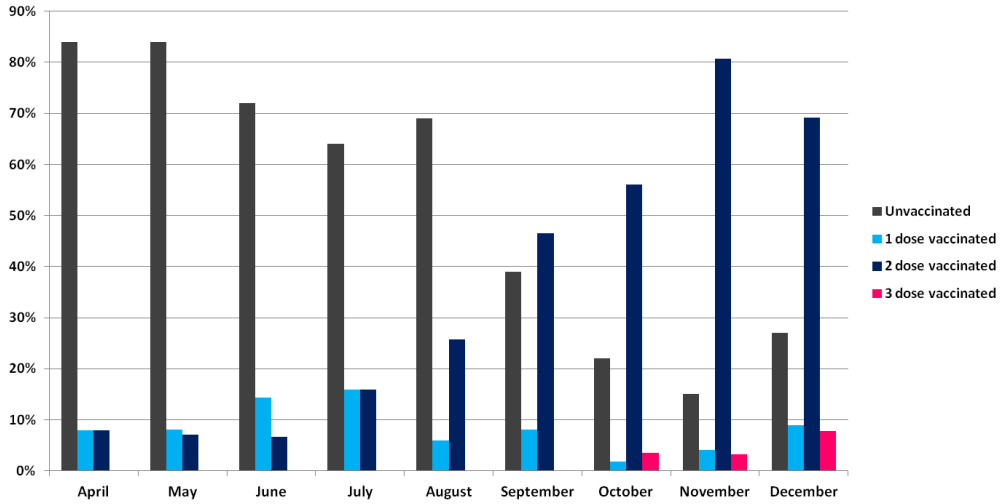

Figure 2. Proportion of unvaccinated and vaccinated subjects overtime.

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Overall, 48.2% (472/979) of infected subjects were not vaccinated with a lower median age compared to vaccinated subjects (47 *vs.* 61 years). Most vaccinated subjects reported to have received 2 doses (78.4%, 366/467) of which 50.7% with BNT162b2 vaccine, followed by 17.4% (n=80) of vaccinated with a single dose (60% with BNT162b2 vaccine). Only 21 subjects (4.5%) had received 3 doses (42.8% of which with the BNT162b2 vaccine), and their proportion increased from October (n=2, 0.4%) to December (n=15, 3.2%). The median time from vaccination to SARS-CoV-2 infection was 28 (IQR: 12-120), 150 (IQR: 120-180) and 13,5 days (IQR: 6-41.2) for subjects who had received one, two and three doses of vaccine, respectively.

The median age of patients who had received three doses of vaccine resulted significantly (*p=.018*) higher compared to that of those who had received one and two doses (70, IQR: 57.5-82 *vs.* 60, IQR: 45-77 and 59 years, IQR: 39-69).

Twelve patients experienced a documented re-infection, 11 were diagnosed among unvaccinated subjects while the remaining one occurred in a subjects who received a single dose of vaccine. They had a median age of 54 years (IQR: 41-63) and three of them were hospitalized. Re-infections were distributed as follow: 3, 3, 1, 2, 1, 1, 1 in April, May, June, July, August, September and December, respectively. Until June, all patients were re-infected with Alpha variant while from August Delta variant (21J) re-infections were reported.

Among subjects with known vaccination status (n=881), no differences were observed between vaccinated and unvaccinated concerning clinical status (Figure 3) (12.7% *vs.* 11.8%, 53.3% *vs.* 49.7%, 31.6% *vs.* 35.9% and 0.2% *vs.* 0.3% for asymptomatic, symptomatic, hospitalized and dead subjects, respectively).

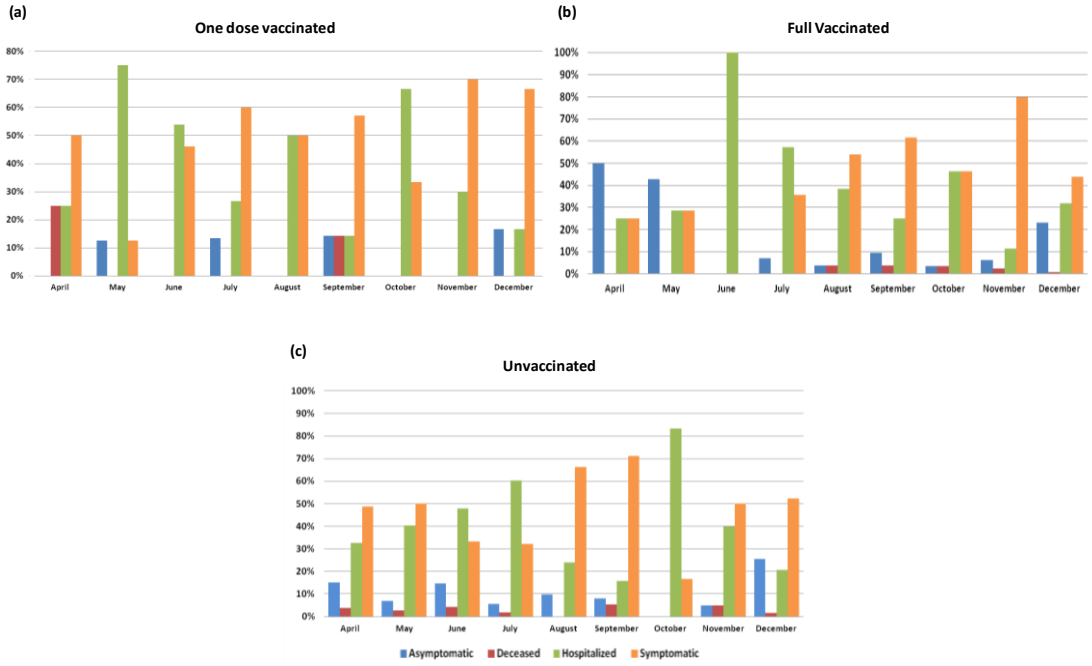

Figure 3. Clinical status/outcome in (**a**) subjects vaccinated with one dose, (**b**) subjects vaccinated with two or three doses and (**c**) unvaccinated subjects during the study period.

Stratifying patients according to age, a statistically significant higher proportions of hospitalizations and deaths were observed in vaccinated subjects over 60 years (76.5% and 88.9%, *p<.001*) while only deaths were significantly higher in unvaccinated (81.8%, *p<.001*). Of note, at the end of data collection (April 2022), 91% (n=429) of unvaccinated subjects had not received any dose yet.

3.5 Clinical status and vaccination according to variants

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The median age of subjects carrying different viral variants significantly differed ($p<.001$) resulting lower in those infected by Omicron variant (40 years, IQR:24-58) compared to all others lineages and sub-lineages (Alpha: 51 years, IQR: 32-67; Gamma: 51 years, IQR: 40-64; Delta: 46 years, IQR: 29-61; Delta descendants: 49 years, IQR: 29-68).

Viral variants resulted also significantly correlated to clinical status in the total cohort ($p=.001$). Symptomatic patients were observed more frequently (59.5%) amongst those infected by Delta variant. Subjects harboring Gamma variant showed the highest frequency of asymptomatic status (21.6%) but, oddly also of death (5.4%).

In the subset with known vaccination and clinical status, significant differences were observed only among vaccinated ($p<.001$) subjects according to viral variant. Vaccinated symptomatic patients were more prevalent (61.1%) among those with Delta variant infection while the hospitalized subjects were more prevalent in those infected with the Alpha variant (55.6%). As already observed in the whole cohort, vaccinated subjects with Gamma variant presented the highest proportion of asymptomatic status (41.7%) but also of death (8.3%). No deaths were observed in vaccinated subjects carrying Alpha and Omicron variants (Figure 4).

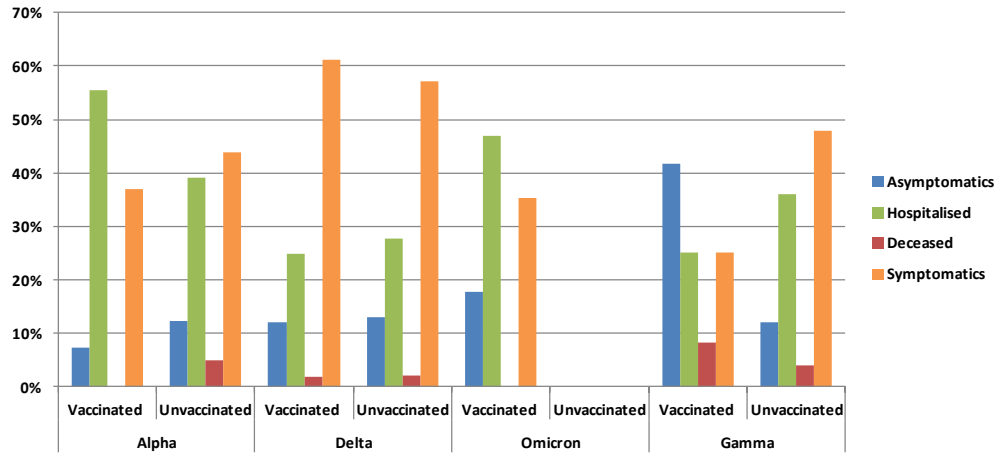

Figure 4. Proportion of clinical status in vaccinated and unvaccinated subjects infected with different variants.

The Omicron variant was only observed in vaccinated subjects, of which 47% were hospitalized.

Concerning vaccination status, the majority of subjects (63%) with Alpha variant were vaccinated with one dose, while 58.3%, 76.5% and 83.5% of those with Gamma, Omicron and Delta variants, respectively, had received two doses. Only 11.8% and 3.7% of subjects carrying Omicron and Delta variants, respectively, reported a booster dose. A similar proportion of deaths was associated to Alpha and Gamma variants (4.9% and 4%).

4. Discussion

In this study, based on the characterization of the SARS-CoV-2 strains circulating in Italy, complemented by demographics and, partially, by clinical information, we provided a clear view of the spread of SARS-CoV-2 variants in the Italian territory, highlighting how the replacement of the previously dominant variants of concern has dictated the subsequent epidemic waves in the country.

The timing of this study mostly overlaps the emergence and spread of the Delta variant and its descendants throughout Italy at the beginning of summer 2021 and offers a unique and well characterised cohort of hospitalised and non-hospitalised patients covering all the Italian territory with the exclusion of the islands.

Among the variants rapidly causing concern, B.1.1.7 (Alpha clade) and B.1.351 (Beta clade)/P.1 (Gamma clade) emerged in our country in December 2020 and January 2021 [16], respectively, while first cases of B.1.617.2 (Delta clade) were described in June 2021

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reaching a prevalence of 20.1% in this same month, as also reported in a national survey [17].

All these variants were clearly characterised by an increased transmissibility compared with the preceding lineages, starting with the original lineage which was detected at very low levels (<1% of total sequences) in the study period. As a consequence, B.1.617.2 + AY was the most prevalent variant in our population followed by B.1.1.7 (76.2% and 13.3%). Most of the epidemiological success of these new variants can be attributed to their ability to overcame previous natural or vaccine-induced herd immunity, in addition to an intrinsic increase in their transmissibility.

The SARS-CoV-2 most recent VOC Omicron has rapidly replaced SARS-CoV-2 Delta variant in most European countries including Italy starting from December 2021. Omicron, with its potential to evade the host's immune response stimulated by previous infections or vaccination, is considered more adapted and transmissible than its predecessors. Immunity acquired after previous infection or vaccination is less effective against Omicron than against other variants, but the risk of severe COVID-19 remains low [18].

Despite our study interrupted its analysis at the end of December when only the first sub-lineage of Omicron (BA.1) was present, such lineage was only observed in vaccinated subjects mostly with asymptomatic or mild disease (53%).

The first detection of Omicron variant in our country dated at the beginning of November 2021 in Lombardy followed by its rapid wide diffusion in December (from 0.4% to 61.7% in 4 weeks).

On December 20th 2021, data of the institutional "flash survey" conducted in Italy showed that the Delta variant was still predominant, and the prevalence of the Omicron variant was 21.0% (18), in line with our data indicating a prevalence of 16.8%.

Our data confirmed that old aged increased the risk of sever COVID-19 clinical course and death, also in vaccinate individuals, as reported in several studies [19, 20].

Surprisingly, our results did not reveal differences between vaccinated and unvaccinated subjects concerning their clinical status. This is certainly due to the fact that the population was not randomly selected among infected subjects, but most subjects were included as patients referring to hospitals (and therefore with some kind of clinical problem that needed attention), which excluded most mild/asymptomatic infections. In fact, the study population showed a low proportion of mild/asymptomatic infections (12% in our data). By contrast, a significant association was found between SARS-CoV-2 lineages and COVID-19 presentation, even if for some variants a low number of cases was considered.

Significant associations were found only in vaccinated subjects: specifically, hospitalization and death displayed a higher incidence in those aged over 60 and in subjects with Alpha and Gamma variant, respectively.

This could probably be explained by the fact that when these variants circulated most of vaccinated patients had received only a single dose.

This study presents some limitations. Our study does not analyse the course and the outcome of the infections, and does not consider the Ct (cycle threshold of real time PCR) levels at diagnosis. Albeit a large number of samples were included in the study, these are not proportionally distributed among regions in relation to their total populations and related number of confirmed cases. Moreover, data were missing for many subjects, particularly concerning vaccination.

The COVID-19 pandemic continues to represent a global health crisis. Analyses of the characteristics and clinical outcomes associated with SARS-CoV-2 variants are likely to have important public health implications, both nationally and internationally. Our report complements previous analyses by providing further data on the rapid change in the epidemiological landscape of SARS-CoV-2 variants in Italy revealing that, in addition to known variants of concern, other minor variants circulate and contribute to the epidemics.

Our study provides strong evidence consolidating the notion that since the beginning of the epidemic sustained local lineage replacements is associated to new local epidemic waves [16, 21].

Our data also reveal that, during each main variant epidemic wave, the expansion of minor variants (descendant lineages) contributes significantly to the epidemics, creating "sub-waves" that probably extend the epidemic course of their parent lineage, and, independently of where they were generated, may lead to other geographical areas with a potential to reverberate globally. In this context, the role of a continuous SARS-CoV-2 genomic monitoring to follow local viral evolution in real time appears of the utmost importance.

In addition, the association between genomic and clinical data allowed us to evaluate the role of viral variants in vaccinated people with respect to severity of disease.

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