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Immediate reinfection with Omicron variant after clearance of a previous SARS-CoV-2 infection



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ABSTRACT

SARS-CoV-2 Omicron variant is spreading worldwide, causing unprecedented epidemic peaks due to its transmissibility and immune evasion. We searched in the archive of the Regional Microbiology Laboratory (Umbria, Italy) for immediate reinfection (i.e. infection occurring 25–60 days from primary infection) among 454,764 RT-PCR tests from 261,217 individuals. Lineage heterogeneity was assessed by S gene target failure phenomenon or whole genome sequencing. We found that BA.1 Omicron variant may cause immediate reinfection of patients just recovered from Delta infection. Immediate reinfection was not observed for any other combination of variants, including Delta over Alpha variant and BA.2 over BA.1 Omicron lineage.

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Text

The SARS-CoV-2 Omicron variant swiftly spread in many countries after first identification in November 2021 [1]. Different Omicron lineages have been described, causing unprecedented epidemic peaks in countries with both high and low vaccination coverage [<https://www.who.int/activities/tracking-SARS-CoV-2-variants>]. In Italy, the first case of BA.1 lineage infection was identified in November 2021 [2]. In Umbria region, the first case was identified in December 13, 2021 by whole genome sequencing (WGS), followed by an exponential increase in the number of cases. The national surveys documented that Delta variant was the only variant present in Umbria in November 2021, but it was rapidly overtaken by Omicron BA.1 thereafter (Fig. 1a). In February 3, 2022, the first BA.2 lineage was identified, reaching 96 % prevalence in May (not shown).

Previous evidence on SARS-CoV-2 variants different from Omicron indicated that reinfection was a possible, although rare and time-dependent phenomenon [3–5]. Cumulative incidence of reinfection has been reported to be less than 1 % of all infected cases

[6]. However, preliminary evidence indicates that the risk of reinfection is increased for the Omicron variant [7,8].

We show that the Omicron variant can cause an immediate reinfection of patients just recovered from a previous infection by another variant (Delta). This was not observed for other combination of variants, including Delta over Alpha variant and BA.2 over BA.1 Omicron variant. We looked for cases of reinfection over a period spanning from 25 to 60 days after diagnosis (immediate reinfection) in the archive of the Regional Reference Microbiology Laboratory, using the commercial RT-PCR assay TaqPath by Thermo Fisher Scientific for molecular diagnosis of infection, revealing the S gene target failure (SGTF) phenomenon [9]. The time span chosen correlates with protection, since anti-SARS-CoV-2 neutralizing antibodies peak about 25 days after symptoms onset and start to decrease after 60 days [10]. Reinfection was defined as a sequence of positive, negative and newly positive RT-PCR test result due to a different viral lineage. We searched for reinfection among 258,598 RT-PCR tests from 148,539 individuals (32,950 positive), in the period October 6, 2021 to May 30, 2022.

Lineage heterogeneity was assessed by SGTF over the period October 6, 2021 to January 25, 2022, in which only Delta variant (SGTF negative) or Omicron BA.1 lineage (SGTF positive) were circulating, and by WGS after January 26, 2022, when also BA.2 Omicron lineage (SGTF negative) was present.

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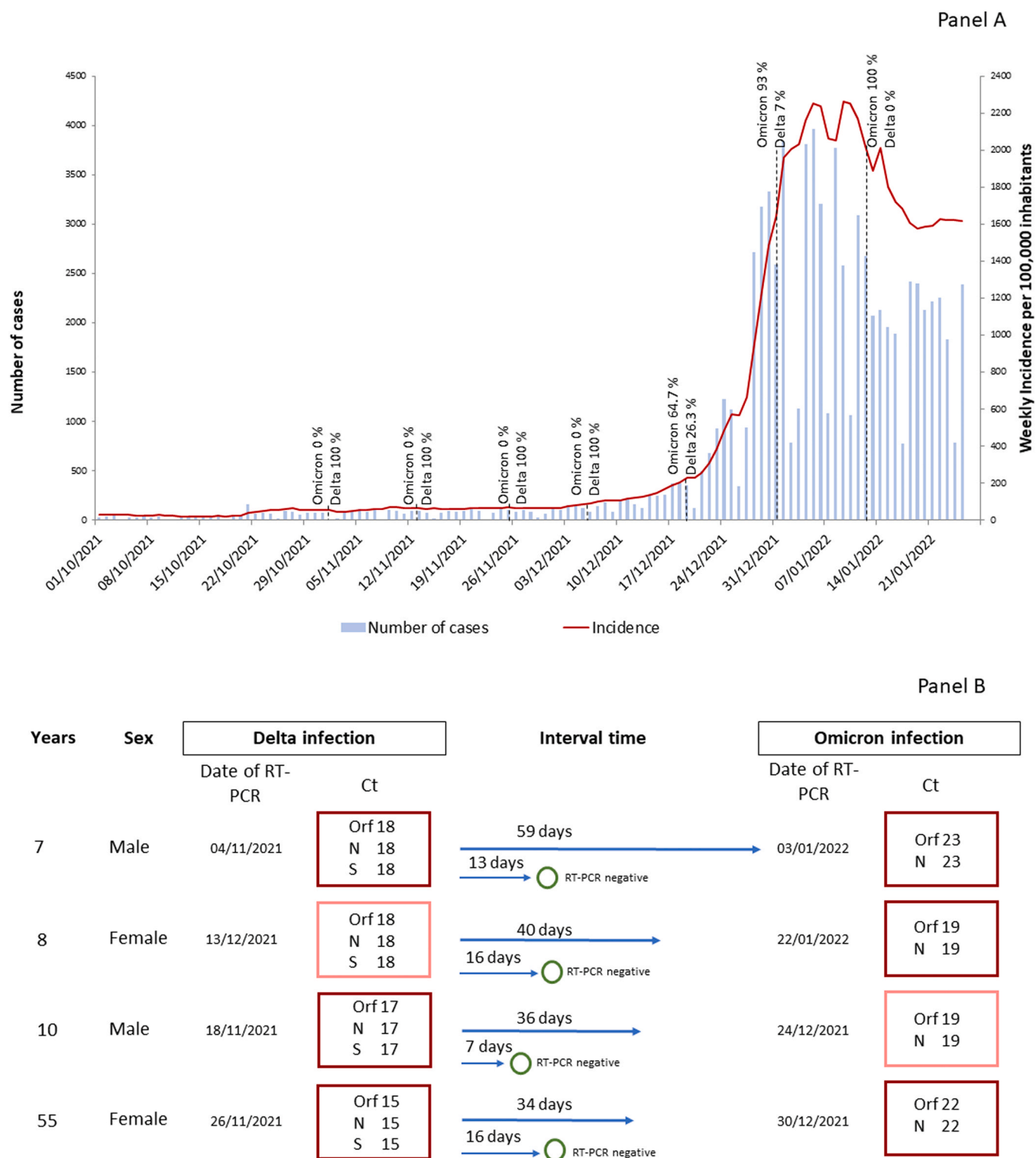


Fig. 1. Frequency of SARS-CoV-2 infection and Omicron BA.1 lineage reinfection in Umbria. Panel A, incidence of SARS-CoV-2 infection with circulating variants from the National Flash Surveys. These Surveys of the Italian Institute of Health are carried out every 2 weeks by WGS on a random sample of cases. Panel B, features of the four cases of reinfection identified during the October 2021 - January 2022 period, corresponding to the surge of Omicron BA.1 cases.

Four cases of immediate Omicron BA.1 reinfection over Delta (BA.1/D) infection were identified (Fig. 1b), showing amplification of ORF1ab, N, and S target genes at first infection and of ORF1ab and N genes at reinfection. No patient was immunocompromised or reported comorbidities. Three out of four patients were not-vaccinated children, and the adult patient received the second dose of ChAdOx1 nCoV-19 vaccine, six months before Delta primary infection. The

majority of patients suffered mild symptoms (fever, cough, pharyngodynia, and headache), both in the first and second episode.

The Alpha B.1.1.7 variant (SGTF positive) was first identified in Umbria in January 8, 2021 and was replaced by the Delta B.1.617.2, in the August 8, 2021 national survey. Alpha and Gamma B.1.1.28.1 variant co-circulated in the period February-August 2021. Thus, we were able to search for reinfections of Alpha variant over the original

Wuhan virus or over the Gamma variant (both SGTf negative) and, conversely, reinfections by Gamma or Delta variants over Alpha previous infection. Among 196,166 RT-PCR tests, from 112,678 individuals (14,148 positive), from October 1, 2020 to August 30, 2021, covering the entire period of Alpha circulation, no case of reinfection was identified.

Our findings indicate that immediate reinfection is likely to be a much more frequent phenomenon when a patient previously infected with Delta is exposed to the Omicron variant. In fact, Omicron, accumulating a number of mutations, including fifteen mutations in the receptor-binding domain, presents substantial change if compared to the original Wuhan virus and to the other variants [11]. This feature is the basis for the evasion of both natural and vaccine-induced humoral immunity, and for reduced neutralizing ability of several monoclonal antibodies [11,12].

Although Omicron over Omicron reinfections are emerging, immediate reinfections are uncommon [8]. We investigated the occurrence of immediate reinfection by different Omicron lineages. We found three cases of Omicron BA.2 infection over a previous BA.1 (BA.2/BA.1) primary infection, all after 90 days. The lineage of these samples was confirmed by NGS analysis using Illumina COVIDSeq RUO Kits, analyzed by DRAGEN software and confirmed by Global Initiative on Sharing Avian Influenza Data (GISAID) platform as: BA.2, BA.2 and BA.2.9 lineage (genome sequences and associated metadata are published in GISAID's EpiCoV database: EP1_ISL_12570891, EP1_ISL_12399662, EP1_ISL_12399663 respectively).

It is difficult to assess the relevance of our observation based on a limited number of cases and further research is needed. Guidelines tend to exclude from reinfections newly positive RT-PCR results observed within 90 days, and comparable data for variants not exhibiting the SGTf phenomenon are scarce. Indeed, we did not find neither immediate reinfections by variants circulating before BA.1 Omicron, nor BA.2/BA.1 immediate reinfections. This could be due to the similarity between Omicron lineages and consequent better immune protection afforded, if compared to the less affine Delta variant. Thus, the finding of four cases of immediate BA.1/D reinfection represents an important and distinctive phenomenon proper of the Omicron variant over a non-Omicron one. Our observation that three out of four reinfections occurred in children may reflect high viral circulation in this age group and low vaccination coverage in children [13].

Our study has limitations. Data are not population based even if the RT-PCR database is by far the largest of the region. Immediate reinfection was likely underestimated when cases were diagnosed by rapid antigenic test without RT-PCR confirmation. Finally, WGS of viral isolates from immediate reinfections would have added

evidence to our findings, but sequencing, limited to randomly selected cases, was not available for study cases. However, both the epidemiological context and RT-PCR data indicate that study cases were primarily infected with SARS-CoV-2 Delta variant and, shortly after, reinfected with the Omicron BA.1 lineage.

In conclusion, this report highlights that the Omicron variant can produce immediate infection in patients which have just recovered from Delta SARS-CoV-2 infection. Moreover, immediate reinfection is much less frequent with other variants or between different Omicron lineages.

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