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Letter to the Editor

Timeline analysis of clinical severity of COVID-19 in the general population

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Dear editor

We read with interest the recent article of Giacomelli et al. [1], who showed that the main characteristics of patients hospitalised with coronavirus disease 2019 (COVID-19) have substantially evolved throughout the course of the ongoing pandemic, reporting a significant increase of patients with milder clinical phenotype. This finding has exceptional importance for influencing future healthcare policies, though it does not reliably mirror the evolution of clinical severity of COVID-19 within the general population.

To provide a reliable picture of the clinical impact of COVID-19 in the entire Italian population over time, we accessed the official data of the Italian Institute of Health (Istituto Superiore di Sanità, ISS), made available on its COVID-19 dashboard [2], and containing updated statistics on the total number of COVID-19 cases, home isolations, COVID-19 hospitalizations with symptoms, COVID-19 hospitalizations in intensive care unit (ICU), and timeline of prevalence of different SARS-CoV-2 variants (first available bulletin: May 19, 2021). The data were imported within a Microsoft Excel worksheet, were they were graphically plotted. This analysis encompassed electronic searches in open and publicly available scientific repositories, so that no informed consent or Ethical Committee approval were necessary.

The results of our analysis are shown in Fig. 1. According to the Italian Institute of Health, the timeline of SARS-CoV-2 variants (i.e., major prevalence in sequenced specimens) since the first available bulletin reporting data on nationwide sequencing was as follows: pre-Alpha variants: up to February 1, 2021; Alpha (α; B.1.1.7) variant: up to June 28, 2021; Delta (δ; B.1.167.2) variant: up to January 3, 2022; Omicron (θ; B.1.1.529) BA.1 sublineage: up to March 14, 2022; Omicron (θ; B.1.1.529) BA.2 sublineage: up to June 20, 2022; Omicron (θ; B.1.1.529) BA.5 sublineage: up to November 28, 2022; and Omicron (θ; B.1.1.529) BQ.1 sublineage: up to present time (i.e., 9/12/2022). The evolution of clinical severity in patients with an official diagnosis of COVID-19 has considerably changed over time, decreasing from the pre-Alpha period to Omicron BA.1 predominance by ~5-fold (from 4.53% to 0.84%) for hospitalizations with symptoms and by ~10-fold (from 0.50% to 0.05%) for hospitalizations in ICU, respectively. Accordingly, the number of home isolations, thus reflecting milder disease, has increased from 94.97% to 99.10% during the same period. An inversion of such favourable trend could be noted after the Omicron BA.5 and (especially) BQ.1 sublineages become prevalent, since hospitalizations with symptoms and hospitalizations in ICU increased to 1.67% and 0.06% at the end of our observation period (i.e., by 1.5- and 1.8-fold, respectively) compared to the initial Omicron BA.1 period.

The results of this analysis based on nationwide Italian COVID-19 data leads the way to two important considerations. First, we can confirm that the clinical burden of COVID-19 has remarkably decreased over time as earlier emphasized by Giacomelli et al. [1], with nearly 3- and 8-fold decline of hospitalizations with symptoms and hospitalizations in ICU, respectively. The reasons for this advantageous pattern are certainly many and multifaceted, mostly encompassing more efficient and timely diagnosis of SARS-CoV-2 infection, increased availability of healthcare resources (both human and technical), improved prevention and therapeutic management of COVID-19, spread of natural (i.e., infection-triggered) or vaccine-elicited immunity and, last but not least, mitigation of SARS-CoV-2 aggressiveness and pathogenicity over time [3]. Nonetheless, our data are also seemingly showing that this pandemic is not over yet, either epidemiologically or clinically. According to the Italian Institute of Health, the number of new COVID-19 diagnoses is still as high as 30,000 per day in December 2022 [2], whilst the recent surge of the Omicron BQ.1 and XBB.1 sublineages should be considered another important threat, since both natural and vaccine-elicited immunity against these new subvariants seems considerably impaired, as shown by recent studies [4,5]. This is mostly due to accumulation of additional escape mutations in the genotypes of these sublineages, that may boost their widespread diffusion and characterize higher aggressiveness in vivo.

The European Centre for Disease Control and Prevention (ECDC) has estimated that over 80% of all SARS-CoV-2 infections will be caused by the Omicron BQ.1/BQ.1.1 and/or XBB.1 sublineages in early 2023 [6]. Thus, considering that healthcare will now be also challenged by a predictable surge of emergency care admissions and constrained bed capacity caused by other respiratory infections (due to declined immunity against other viruses and lifting of most non-pharmaceutical

Abbreviations: COVID-19, Coronavirus Disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; ICU, Intensive Care Unit.

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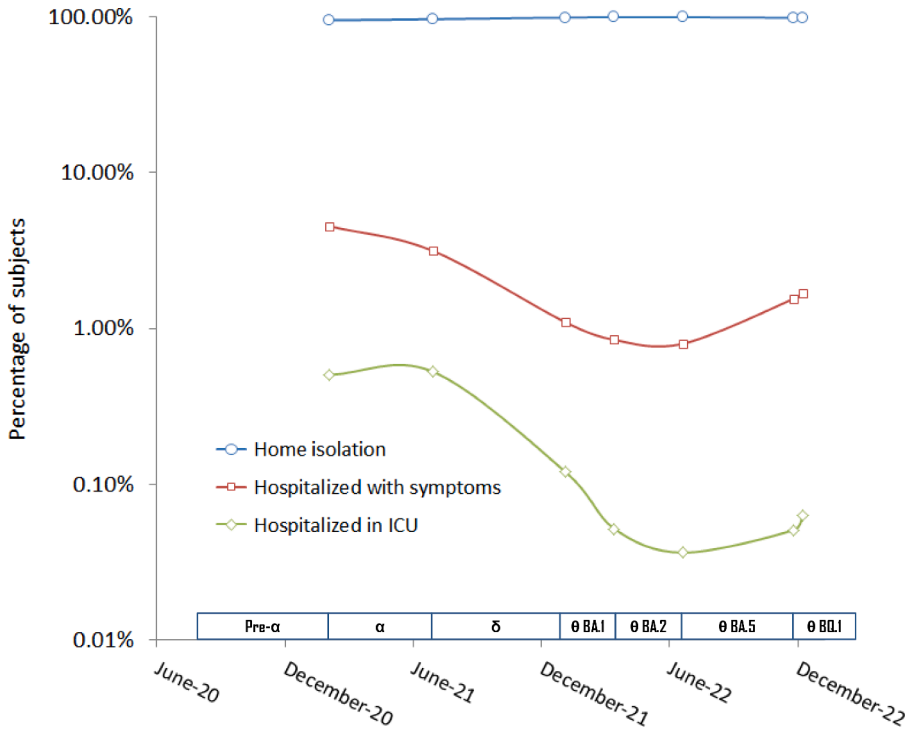

Fig. 1. Percentage of home isolations, coronavirus disease 2019 (COVID-19) hospitalizations with symptoms, COVID-19 hospitalizations in intensive care unit (ICU) and timeline of prevalence (i.e., ≥50% in sequenced specimens) of different SARS-CoV-2 variants in Italy, from February 1, 2021 to December 7, 2022.

preventive measures), continuous epidemiological monitoring of diffusion and clinical burden of new SARS-CoV-2 variants will become more vital than ever for preventing the deleterious consequences of a mixed COVID-19, Influenza and perhaps even Respiratory Syncytial Virus "triple wave" in the narrower future [7].

Authors' contributions

GL and CM designed the study; GL was responsible for the statistical analysis. GF prepared a preliminary draft of the manuscript, which was critically reviewed by CM. All of the authors have read and approved the final manuscript.

Data availability statement

The complete dataset will be provided in txt format upon reasonable request to the corresponding author.

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Declaration of Competing Interest

The authors have no conflict of interest relating to this study.

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