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Short Report

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SARS-CoV-2 pandemic: on its way to becoming an endemic disease?

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Abstract

We analysed the impact of Alpha, Delta and Omicron SARS-CoV-2 lineages throughout the three sequential waves of these variants in the UK. In summary, the cumulative vaccination rate increased by over 12-fold throughout the study period, while the odds of coronavirus disease 2019 (COVID-19) related hospitalizations declined by 78% and 83% from Alpha to Delta and Alpha to Omicron periods. Likewise, COVID-19 related deaths declined by 93% and 95% from Alpha to Delta and Alpha to Omicron periods. Widespread vaccination and SARS-CoV-2 mutation seem thus to have combined to modify the scenario, with early signs of endemicity.

Keywords: SARS-CoV-2; COVID-19; Omicron; Variants, Vaccine
1. Introduction

Although the number of cumulative deaths remains considerably lower than those caused by the Spanish flu pandemic in 1918-1919 (i.e., around 50 millions) [1], the ongoing worldwide outbreak sustained by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is causing unprecedented consequences on healthcare, society and economy. As observed in the past for other infective agents, deadly pandemics have emerged throughout the recorded human history, but have then disappeared or have become endemic disease over time by concurrent impact of herd immunity (which can be achieved by either natural infection or vaccination) and virus attenuation [2]. Influenza A virus H1N1 is a paradigmatic example of a pathogen that has so much mutated its genome (by introducing over 300 non-synonymous changes, i.e., around 7% of all codons) [3], such that it has now become endemic, whilst SARS-CoV(-1) and Middle East respiratory syndrome coronavirus (MERS-CoV) have instead progressively disappeared [4].

Predicting the future trajectories of coronavirus disease 2019 (COVID-19) remains a strenuous and almost unpredictable enterprise, as demonstrated by the recent emergence of the Omicron (B.1.1.529) variant. Nonetheless, recent evidence is accumulating that the pathogenicity and lethality of the latest globally dominant SARS-CoV-2 Omicron variant may have some intrinsic attenuation, that combined with an increasing rate of COVID-19 vaccinations, may have opened a new chapter in the COVID-19 pandemic [5]. To investigate further, we analysed here the clinical impact of COVID-19 in three different periods of 2021 in the UK, characterized by predominance of three distinct SARS-CoV-2 lineages.

2. Materials and Methods
We carried out an electronic search in the official UK Government website for data and insights on coronavirus (COVID-19) [6], to retrieve official information on nationwide volume of SARS-CoV-2 testing, numbers of new SARS-CoV-2 daily cases, COVID-19 related daily hospitalizations and daily deaths, along with the cumulative number of COVID-19 vaccinations, comparing three different and representative weeks of the year 2021 (9-15 January 2021, 17-25 June 2021 and 25-31 December 2021), since they reflect three different “waves” of SARS-CoV-2 attributable to three distinct variants. Information on the prevalence of SARS-CoV-2 lineages was accessed from the UK website for COVID-19 Genomic Surveillance of the Sanger Institute [7], which provides real-time monitoring of genomes of SARS-CoV-2 samples across the country and combines statistical and computational expertise for detecting new variants and providing weekly updated statistics. The different endpoints (number of new weekly diagnosis of SARS-CoV-2 infections, new COVID-19 related weekly hospitalizations and deaths) were compared among the three periods by estimating the odds ratio (OR) with 95% confidence interval (95%CI), using MedCalc (Version 20.015; MedCalc Software Ltd., Ostend, Belgium). Statistical significance was set at p<0.05. The study was carried out in accordance with Helsinki Declaration, under terms of relevant local legislation. This research was based on publicly available data, thus Ethical Committee approval was unnecessary.

3. Results

The main outcome of our analysis is shown in Table 1. In the three considered weeks of the year 2021, three genetically distinct SARS-CoV-2 lineages were largely prevalent in the UK. More specifically, the Alpha variant (B1.1.7; 83.2%) was prevalent between 9-15 January 2021, the Delta variant (B.1.617.2 + AY4.2; 99.0%) between 17-25 June 2021, whilst the Omicron variant (B.1.1.529; 95.8%) between 25-31 December
2021. The number of cumulative COVID-19 vaccinations increased consistently throughout the study period, from 5320, to 65576 and finally to 77041 per 100,000 in the three different periods (Table 1 and Figure 1). With respect to the clinical endpoints, the SARS-CoV-2 positivity rate of testing was 10.7% in the SARS-CoV-2 Alpha prevalent period, decreasing to 1.7% in the SARS-CoV-2 Delta prevalent period, but then increasing to 11.7% in the SARS-CoV-2 Omicron prevalent period. Such trend of SARS-CoV-2 positivity was not mirrored by the rate of COVID-19 related hospital admissions and deaths, as shown in Table 2. More specifically, the odds of COVID-19 related hospitalizations declined by 78% and 83% from Alpha to Delta and from Alpha to Omicron prevalence periods, respectively, decreasing also by 22% from the Delta to Omicron periods (Figure 1). A similar trend could be noted for COVID-19 related deaths, which declined by 93% and 95% from Alpha to Delta and from Alpha to Omicron periods, respectively, also decreasing by 24% between the Delta and Omicron periods (Figure 1).

4. Discussion

The results of our analysis pave the way to some important reflections. The first and perhaps most important consideration is that both COVID-19 related hospitalizations and deaths have dramatically declined (by over 90%) over time in the 2021. This trend truthfully mirrors the increased of nationwide vaccinations (i.e., augmented by nearly 15-fold between January and December 2021) over a period of gradual replacement of former SARS-CoV-2 strains with new and diverging lineages (Alpha → Delta → Omicron). As concerns the recently emerged Omicron (B.1.1.529) variant, which has become endemic at the end of 2021 throughout UK and Europe, our analysis confirm that it apparently retains moderately higher infectivity compared to the Alpha lineage (+10%), though its spread has been associated with considerably
enhanced (up to 8-fold) rate of positive SARS-CoV-2 tests compared to the rate found during the Delta strain prevalence. This finding confirms previous evidence that have attributed a considerably enhanced reproduction number (between 3 to 4 higher) to this new strain compared to the formerly endemic Delta lineage [8,9]. Nonetheless, such increased infectivity has not been mirrored by exponential increase of COVID-19 related hospitalizations and deaths in the UK, which were actually found to be 83% and 95% lower compared to the Alpha variant period, but also 22% and 24% lower compared to the Delta strain period. These findings are in keeping with recently published evidence, which would seemingly portrait the Omicron lineage as a less pathogenic virus compared with the Delta variant despite its immune escape capacity. Garrett et al. recently reported that the rate of asymptomatic SARS-CoV-2 cases among persons living in South Africa was over 12-fold higher during the recent Omicron outbreak compared to the former Delta wave [10]. In accordance with these findings, Maslo et al. explored the clinical outcome of South African patients hospitalized for COVID-19 during the Omicron wave [11], revealing that the number of patients needing oxygen therapy, mechanical ventilation, intensive care and even the death rate progressively declined over time, becoming the lowest during the period of prevalence of the Omicron strain. Similar data were preliminary reported in Canada by Ulloa et al. [12], who evidence an over 50% reduction of COVID-19 related hospitalizations and deaths in patients testing positive for the Omicron lineage compared to those with infection sustained by Delta variant. Additional preliminary evidence comes from a Californian study carried out by Lewnard et al. [13], who concluded that the number of COVID-19 related hospitalizations, intensive care unit (ICU) admissions and deaths decreased by 50-90% by comparing Omicron and Delta variant infections.

The fact that infection with the highly mutated SARS-CoV-2 Omicron variant (this lineage has accumulated over 30 non-synonymous mutations in the spike protein,
of which within the receptor binding domain) [14] is seemingly less severe than with other strains (i.e., Alpha or Delta) fits with early scientific findings regarding its intrinsic viral properties. Evidence attests that this lineage seems to have magnified affinity for its human host cell receptor (i.e., angiotensin converting enzyme 2; ACE2) [15], while more prevalently infecting and more efficiently replicating in the upper respiratory tract [16-17], thus having attenuated pulmonary and systemic virulence.

According to this and other previous evidence, SARS-CoV-2 may have started a (predictably long) journey to gradually becoming an endemic disease, with which humanity will need to for better or worse must live with [18]. However, the position of Omicron is the progressive evolution of the virus has yet to be fully understood and the future remains unpredictable, especially with much of the world still unvaccinated, leaving high potential for emergence of new variants. Moreover, the potential individual and population health impacts of Omicron on post-acute sequelae of COVID-19 and long COVID remain to be seen and the consequences of endemicity remain unknown.

Irrespective of the ostensibly lower pathogenicity attributed to the SARS-CoV-2 Omicron lineage compared to previous variants, it is noteworthy that the exiting evidence garnered so far on the so-called “Omicron wave” around the world, including that provided in this UK-based study, has emerged from highly vaccinated populations. It is hence not easy to discriminate to what extent the considerable decline observed in the number of COVID-19 hospitalizations and deaths may be attributed to SARS-CoV-2 mutations versus widespread vaccination, since the efficacy of COVID-19 vaccines against the risk of developing a vast array of COVID-19 related complications needing hospital care is now almost unquestionable [19-20]. Although the Omicron variant appears more resistant versus antibody-mediated neutralization (e.g., neutralization can be however efficiently restored by administering COVID-19 vaccine booster doses)
Thus, the most likely scenario encompasses that both increasing population immunity and changes in intrinsic viral properties may have combined to modify the current pandemic scenario. Thus, the path to a future where SARS-CoV-2 is endemic may be occurring. Regardless of the pathogenic attenuation, Omicron is still associated with substantial morbidity and mortality and widespread transmission could potentially lead to further mutation and variant emergence, thus physical preventive measures and widespread vaccination and boosters must still be advocated, especially in developing countries, as nobody should forget that we are still facing one of the worst pandemics in human history.

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AUTHOR CONTRIBUTIONS
Camilla Mattiuzzi: Conceptualization; data curation; methodology, article revision.
Brandon M. Henry: Conceptualization; formal analysis; methodology, supervision.
Giuseppe Lippi: Conceptualization; investigation; formal analysis; methodology; article writing.

CONFLICT OF INTEREST
The authors have no conflicts of interest relevant to this article to disclose.

DATA AVAILABILITY STATEMENT
Research data are available upon request to the corresponding author.
References

1. Sampath S, Khedr A, Qamar S, Tekin A, Singh R, Green R, Kashyap R. Pandemics Throughout the History. Cureus 2021;13:e18136.

2. Telenti A, Arvin A, Corey L, Corti D, Diamond MS, García-Sastre A, Garry RF, Holmes EC, Pang PS, Virgin HW. After the pandemic: perspectives on the future trajectory of COVID-19. Nature 2021;596:495-504.

3. Carter RW, Sanford JC. A new look at an old virus: patterns of mutation accumulation in the human H1N1 influenza virus since 1918. Theor Biol Med Model 2012;9:42.

4. Barth RF, Buja LM, Barth AL, Carpenter DE, Parwani AV. A Comparison of the Clinical, Viral, Pathologic, and Immunologic Features of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Coronavirus 2019 (COVID-19) Diseases. Arch Pathol Lab Med 2021;145:1194-1211.

5. Karim SSA, Karim QA. Omicron SARS-CoV-2 variant: a new chapter in the COVID-19 pandemic. Lancet 2021;398:2126-2128.

6. UK Government. UK Coronavirus Dashboard. Available at: https://coronavirus.data.gov.uk/. Last accessed: January 14, 2022.

7. Sanger Institute. COVID-19 Genomic Surveillance. Available at: https://covid19.sanger.ac.uk/lineages/raw. Last accessed: January 14, 2022.

8. Nishiura H, Ito K, Anzai A, Kobayashi T, Piantham C, Rodriguez-Morales AJ. Relative Reproduction Number of SARS-CoV-2 Omicron (B.1.1.529) Compared with Delta Variant in South Africa. J Clin Med 2021 23;11:30.

9. Ito K, Piantham C, Nishiura H. Relative instantaneous reproduction number of Omicron SARS-CoV-2 variant with respect to the Delta variant in Denmark. J Med Virol. 2021 Dec 30. doi: 10.1002/jmv.27560. Epub ahead of print.
10. Garrett N, Tapley A, Andriesen J, Seocharan I, Fisher LH, Bunts L, Espy N, Wallis C, Randhawa AK, Goga A, Bekker LG, Gray GE, Corey L. High Rate of Asymptomatic Carriage Associated with Variant Strain Omicron. MedRxiv 2021.12.20.21268130; doi: https://doi.org/10.1101/2021.12.20.21268130.

11. Maslo C, Friedland R, Toubkin M, Laubscher A, Akaloo T, Kama B. Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves. JAMA 2021:e2124868.

12. Ulloa AC, Buchan SA, Daneman N, Brown KA. Early estimates of SARS-CoV-2 Omicron variant severity based on a matched cohort study, Ontario, Canada. MedRxiv 2021.12.24.21268382; doi: https://doi.org/10.1101/2021.12.24.21268382.

13. Lewnard JA, Hong VX, Patel MM, Kahn R, Lipsitch M, Tartof SY. Clinical outcomes among patients infected with Omicron (B.1.1.529) SARS-CoV-2 variant in southern California. MedRxiv 2022.01.11.22269045; doi: https://doi.org/10.1101/2022.01.11.22269045.

14. Lippi G, Mattiuzzi C, Henry BM. Updated picture of SARS-CoV-2 variants and mutations. Diagnosis (Berl). 2021 Dec 23. doi: 10.1515/dx-2021-0149. Epub ahead of print.

15. Lupala CS, Ye Y, Chen H, Su XD, Liu H. Mutations on RBD of SARS-CoV-2 Omicron variant result in stronger binding to human ACE2 receptor. Biochem Biophys Res Commun 2021;590:34-41.

16. Zhao H, Lu L, Peng Z, Chen LL, Meng X, Zhang C, Ip JD, Chan WM, Chu AW, Chan KH, Jin DY, Chen H, Yuen KY, To KK. SARS-CoV-2 Omicron variant shows less efficient replication and fusion activity when compared with delta variant in TMPRSS2-expressed cells. Emerg Microbes Infect. 2021 Dec 24:1-18. doi: 10.1080/22221751.2021.2023329. Epub ahead of print.
17. Diamond M, Halfmann P, Maemura T, Iwatsuki-Horimoto K, Iida S, Kiso M, Scheaffer S, Darling T, Joshi A, Loeber S, Foster S, Ying B, Whitener B, Floyd K, Ujie M, Nakajima N, Ito M, Wright R, Uraki R, Li R, Sakai Y, Liu Y, Larson D, Osorio J, Hernandez-Ortiz J, Āòiuoderis K, Florek K, Patel M, Bateman A, Odle A, Wong LY, Wang Z, Edara VV, Chong Z, Thackray L, Ueki H, Yamayoshi S, Imai M, Perlman S, Webby R, Seder R, Suthar M, Garcia-Sastre A, Schotsaert M, Suzuki T, Boon A, Kawaoka Y, Douek D, Moliva J, Sullivan N, Gagne M, Ransier A, Case J, Jeevan T, Franks J, Fabrizio T, DeBeauchamp J, Kercher L, Seiler P, Singh G, Warang P, Gonzalez-Reiche AS, Sordillo E, van Bakel H, Simon V. The SARS-CoV-2 B.1.1.529 Omicron virus causes attenuated infection and disease in mice and hamsters. Res Sq [Preprint]. 2021 Dec 29:rs.3.rs-1211792. doi: 10.21203/rs.3.rs-1211792/v1.

18. Ledford H. How severe are Omicron infections? Nature 2021;600:577-578.

19. Rubin EJ, Longo DL. Covid-19 mRNA Vaccines - Six of One, Half a Dozen of the Other. N Engl J Med 2022;386:183-185.

20. Mattiuzzi C, Lippi G. Primary COVID-19 vaccine cycle and booster doses efficacy: analysis of Italian nationwide vaccination campaign. Eur J Public Health. 2022 Jan 3:ckab220. doi: 10.1093/eurpub/ckab220. Epub ahead of print.

21. Lippi G, Mattiuzzi C, Henry BM. Neutralizing potency of COVID-19 vaccines against the SARS-CoV-2 Omicron (B.1.1.529) variant. J Med Virol. 2022 Jan 5. doi: 10.1002/jmv.27575. Epub ahead of print.

22. May DH, Rubin BER, Dalai SC, Patel K, Shafiani S, Elyanow R, Noakes MT, Snyder TM, Robins HS. Immunosequencing and epitope mapping reveal substantial preservation of the T cell immune response to Omicron generated by SARS-CoV-2 vaccines. MedRxiv 2021.12.20.21267877; doi: https://doi.org/10.1101/2021.12.20.21267877.
Table 1. Cumulative vaccination coverage, volume of laboratory testing and clinical impact of coronavirus disease 2019 (COVID-19) in the UK across three different periods characterized by prevalence of three distinct SARS-CoV-2 variants.

| Variable                        | Alpha Prevalent | Delta Prevalent | Omicron Prevalent |
|---------------------------------|-----------------|-----------------|-------------------|
| Period                          | 9-15 Jan 2021   | 17-25 Jun 2021  | 25-31 Dec 2022    |
| SARS-CoV-2 variant              |                 |                 |                   |
| - Alpha (B.1.1.7)               | 83.2%           | 1.0%            | 0.0%              |
| - B                             | 2.4%            | 0.0%            | 0.0%              |
| - B.1.177                       | 14.4%           | 0.0%            | 0.0%              |
| - Delta (B.1.617.2 + AY4.2)     | 0%              | 99.0%           | 4.2%              |
| - Omicron (B.1.1.529)           | 0%              | 0.0%            | 95.8%             |
| Vaccination                     |                 |                 |                   |
| - Cumulative number             | 3576263         | 44080358        | 51786768          |
| - Cumulative rate (per 100,000) | 5320            | 65576           | 77041             |
| Total SARS-CoV-2 tests (number) | 4228427         | 7274282         | 10933860          |
| New weekly diagnoses            |                 |                 |                   |
| - Number                        | 452245          | 120967          | 1277529           |
| - Per tests performed           | 10.7%           | 1.7%            | 11.7%             |
| New weekly hospitalizations     |                 |                 |                   |
| - Number                        | 31965           | 1955            | 16236             |
| - Rate (per 100,000 positives)  | 7068            | 1616            | 1271              |
| New weekly deaths               |                 |                 |                   |
| - Number                        | 7195            | 140             | 1119              |
| - Rate (per 100,000 positives)  | 1591            | 116             | 88                |
Table 2. Clinical impact of coronavirus disease 2019 (COVID-19) in the UK across three different periods characterized by prevalence of three distinct SARS-CoV-2 variants. Results are shown as odds ratio (OR) and 95% confidence interval (95%CI).

| Prevalence period     | New diagnoses     | New hospitalizations | New deaths         |
|-----------------------|-------------------|----------------------|--------------------|
| Delta vs. Alpha       | 0.14 (0.14-0.14;  | 0.22 (0.21-0.23;    | 0.07 (0.06-0.08;   |
|                       | p<0001)           | p<0.001)             | p<0.001)           |
| Omicron vs. Alpha     | 1.10 (1.10-1.11;  | 0.17 (0.17-0.17;    | 0.05 (0.05-0.06;   |
|                       | p<0.001)          | p<0.001)             | p<0.001)           |
| Omicron vs. Delta     | 7.82 (7.78-7.87;  | 0.78 (0.75-0.82;    | 0.76 (0.63-0.90;   |
|                       | p<0.001)          | p<0.001)             | p=0.001)           |
Figure 1. Cumulative vaccination coverage and clinical impact of coronavirus disease 2019 (COVID-19) in the UK across three different periods characterized by prevalence of three distinct SARS-CoV-2 variants.