

A Note on the COVID-19 Pandemic Evolution Debate: What is Next?

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ABSTRACT

The recent surge in COVID-19 cases and the reopening of borders in China has brought the debate on the evolution of the pandemic back to the forefront. Should we expect a new variant of concern (VOC), other than Omicron, to appear unexpectedly and spread worldwide? What should be done to prevent this occurrence? This note addresses these questions, highlighting the zoonotic and zoonoanthropotic nature of the transmission of the SARS-CoV-2 virus and the need for continuous surveillance of the global ecosystem, which remains affected by inequalities in vaccine distribution between the North and South countries.

Keywords: SARS-CoV-2; COVID-19 Pandemic; Zoonosis; Zoonoanthroposis; New Variants of Concern (VOCs)

Abbreviations: VOC: Variant of Concern; TAG-VE: Technical Advisory Group on Virus Evolution; IHR: International Health Regulations; PHEIC: Public Health Emergency of International Concern; PHSM: Public Health and Social Measures

Introduction

The debate on the evolution of the COVID-19 pandemic [1] has resurged after the recent increase in infections [2] in China, most likely due to the lifting of its strict 'zero-COVID' policy; the reopening of the border and the prediction [3] that new epidemic waves may occur in the coming months also fuels this debate. Thus, global public attention is drawn to the complex question of if and when a new variant of concern (VOC) of SARS-CoV-2 other than Omicron will arise and whether it will eventually spread worldwide. The Technical Advisory Group on Virus Evolution (TAG-VE), in a statement [4] released on January 4, 2023, informed the World Organization (W.H.O.) that "no new variant or mutation of known significance is noted in the publicly available sequence data" provided by Chinese authorities. On January 14, 2023, the W.H.O. asked in a follow-up meeting with Chinese authorities that "further sequences be shared with open access databases such as GISAID for deeper phylogenetic analyses, and for continued collaboration with technical groups working on virus evolution, clinical care, and beyond" [5].

In a more recent statement on January 30, 2023, [6] the W.H.O. Director-General, while presenting the report of the fourteenth meeting of the International Health Regulations (2005) (IHR)

Emergency Committee regarding the coronavirus 2019 disease (COVID-19) pandemic, agreed that:

- The COVID-19 pandemic remains a Public Health Emergency of International Concern (PHEIC); and
- The pandemic is likely at a transition point.

The W.H.O. Director-General then issued a set of temporary recommendations, among which the most important are:

The urgent need to:

- a) "Maintain momentum for Covid-19 vaccination to achieve 100% coverage of high priority groups by evolving SAGE recommendations on the use of booster doses";
- b) "Improve reporting of SARS-CoV-2 surveillance data to WHO (better data are needed to detect, assess and monitor emerging variants, identify significant changes to Covid-19 epidemiology and understand the burden of Covid-19 in all regions)";
- c) "Maintain strong national response capacity and prepare for future events to avoid the occurrence of panic-neglect cycle. State Parties should consider how to strengthen country readiness to respond to outbreaks including attention to health workforce

capacity, infection prevention and control”;

- d) “Continue working with communities and their leaders to address the infodemic and to effectively implement the risk-based public health and social measures (PHSM)”;
- e) “Continue to adjust any remaining international travel-related measures, based on risk assessment”;
- f) “Continue to support research for improved vaccines that reduce transmission and have broad applicability, as well as research to understand the full spectrum, incidence and impact of post COVID-19 condition, and to develop relevant integrated care pathways”.

In summary, in his recent statements, the W.H.O. Director-General suggests that even if the COVID-19 pandemic is at a transition point, it has not yet concluded and the evolution of the pandemic in China will be of fundamental importance. At this stage, two questions arise: considering the forecasts regarding the evolution of the COVID-19 pandemic in China and the country’s reopening of borders, should we be worried about the possible emergence and spread of new VOCs, and what should be done about this potential threat? Answers to both of these questions are provided in the subsequent paragraphs.

Table 1: Number of COVID-19 cases per 100,000 residents in Europe overall and Italy in January 2022 and January 2023.

Number of Covid-19 Cases (Per 100k Residents)	January 2022	January 2023
Europe	121,700	29,158
Italy	1823	65

Note: (Sources: For Europe - Eurostat Covid-19 - European Commission. Available online at <https://covid-statistics.jrc.ec.europa.eu/Home/Dashboard> and at <https://covidstatistics.jrc.ec.europa.eu/> and for Italy: Epicentro- Istituto Superiore della Sanità <https://www.epicentro.iss.it/coronavirus/sars-cov-2-dashboard> and Ministry of Health

<https://www.salute.gov.it/portale/nuovocoronavirus/archivioNotizieNuovoCoronavirus.jsp?lingua=italiano&tipo=Report+settimanale+Covid-19&btnCerca=cerca>)

Southern Countries

SARS-Cov-2: The Current Situation

The SARS-CoV-2 virus and the COVID-19 vaccination campaign have once again highlighted the differences between North and South countries, i.e., between high-income countries (where 75% of the population is vaccinated) and low-income countries (where only 19% of the population is vaccinated) [7-9] and the greater or lesser efficiency of the public health policy and of the National Health Systems according to the presence or absence of democratic institutions in the evaluated countries [10].

Northern Countries

Focusing on European countries, particularly Italy, the decreasing trend in the number of COVID-19 cases (see Table 1) between 2022 and 2023 facilitates cautious optimism. In particular, in Italy, as of January 27, 2023, the infection rate is 65 per 100,000 residents (significantly lower than the rate when 1823 individuals were infected on the same day in January 2022); additionally, the vaccination campaign has resulted in over 84% of the population receiving several doses, thus achieving near immunity. Similarly, there was a significant drop in the number of infected individuals between January 2022 (121,700) and January 2023 (29,158) in Europe overall.

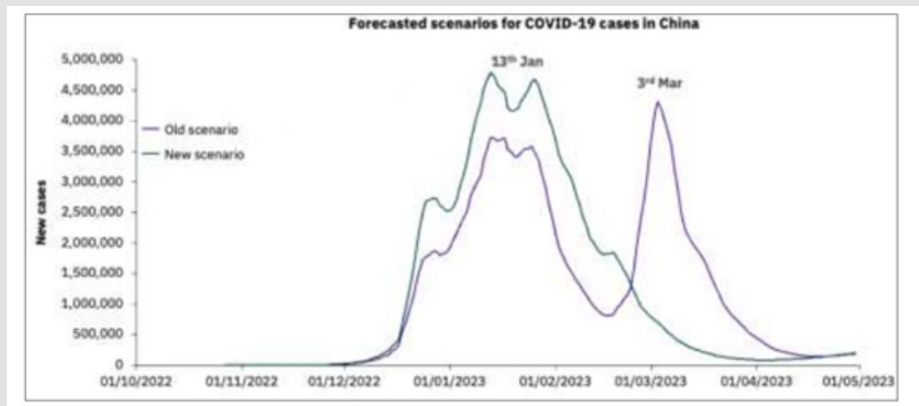


Figure 1: The Airinfinity model initially (Old scenario) estimated that the number of Covid cases would reach 3.7 million per day during the January peak (on Jan 13.) and 4.2 million a day by March 3, 2023. An updated version of the Airinfinity model (New scenario) estimates that the number of cases could peak at 4.8 million per day, with 62 million infections between January 13 and 27, 2023 (overrunning the health care system), before falling. (Source: Model of the UK health analytics from Airfinity, available online at: <https://www.airfinity.com/articles/china-to-see-one-longer-more-severecovid-wave-as-lunar-festival-fuels>).

In Europe, Italy and the so-called Western world (in particular North America), the epidemiological situation appears to be improving [11], and the pandemic [12] is under control [13]; however, in other countries, such as those in Africa (where National Health Systems are nonexistent or inefficient, and the vaccination rate is very low), the virus is less controlled and its potential to mutate is higher. China is a large country with a population in the billions, a high real GDP growth rate, and a distinct pandemic status. Chinese authorities have generally failed to adequately control the COVID-19 pandemic, particularly regarding the abandonment of the 'zero COVID' policy [14] and the resulting reopening of the borders and massive rate of travelers entering and leaving China over the New Year (Sunday, January 22, 2023) [15]. Furthermore, the Chinese government, which has always been reluctant to reveal the real number of infections and deaths due to COVID-19, has stopped mass testing and changed its approach to counting the number of cases and deaths [16]; thus, China's statistics are considered highly unreliable by international observers. As a result, the only source of information consists of unofficial estimates [17] (Figure 1); these estimates indicate that COVID cases will likely double [18] by mid-January 2023, and a new wave with 4.2 million cases per day is forecasted by March 2023 [19,20], putting the Chinese health system under strain.

Despite the recent statement from the W.H.O. Director-General indicating that the pandemic is near its final phase, there remain some uncertainties in the scientific community regarding what will happen. These uncertainties are not trivial; according to the W.H.O., a new VOC is a variant that is much more transmissible, better at evading the immune system, causes a more severe disease than the currently circulating variant, and may represent a major turning point in the pandemic. Therefore, fears related to the emergence of new VOCs in 2023 in areas with a substantial Chinese population are well-founded, particularly in Europe and in Italy [21], whose government has ordered antigenic swabs and viral sequencing for all travelers coming from China and quarantine for travelers who test positive.

New VOCs: What to Expect and What to Do

SARS-CoV-2 is the causative agent of COVID-19, whose impact on the world population in terms of the number of infections and deaths and the resulting economic and social crisis demonstrates [22] the devastating effects of a zoonosis [18-20], i.e. an infectious disease [23,24] transmissible from vertebrate animals to humans or from humans to animals (in the latter case, the disease is named a zoonoanthroposis or a reverse zoonosis) [25]. In the case of the COVID-19 pandemic, SARS-CoV-2, a positive single-stranded RNA coronavirus belonging to the family Coronaviridae of the order Nidovirales, emerged as the result of multiple cross species transmission events from live wild animals into humans, likely during November and December of 2019 at the Huanan Seafood Wholesale Market in Wuhan, China. Globalization and the level of travel from China to the rest of the world, particularly Italy, the European country most affected by the virus, spread the infection worldwide in multiple same-species transmission events among humans.

Although the mechanism that determines the emergence of new VOCs, such as Omicron [26,27], remains unknown, it is clear that the virus is transmitted via infected individuals and replicates within their organs, giving rise to mutations in the SARS-CoV-2 genome. Only a few mutations can enhance the virus's functions and its degree of infectivity (i.e., the capacity of the virus to enter human host cells), transmissibility (the capacity of the virus to move from one host to another) and immune escape, giving rise to VOCs. Currently, only five SARS-CoV-2 variants have been declared VOCs by the W.H.O. and have become dominant either regionally or globally. These VOCs are Alpha (Pango lineage B.1.1.7), Beta (B.1.351) and Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529). The latest mutants that have emerged from the currently circulating SARS-CoV-2 variant, Omicron, are XBB.1.5, XBB, BQ1, BN1, and CH1.1 [28]; to date, none of these have been declared VOCs by the W.H.O. Where do new VOCs come from? Unfortunately, there is no single answer to that fundamental question. There are, however, different hypotheses regarding VOC origin [29]:

- a) VOCs may not have been identified initially as they circulate in undersampled geographical areas;
- b) Hidden circulation within an animal reservoir infected via an initial reverse zoonosis event;
- c) The result of the evolution of a chronic infection in one or more immunosuppressed human hosts.

Currently, the 'chronic infection hypothesis' is best supported by evidence and as recent research [30,31] suggests, extensive monitoring of chronic infections is needed to understand the origin of VOCs.

Concluding Remarks

The mechanism of SARS-CoV-2 replication and dissemination is neither fully understood nor reproducible; thus, the ability to predict the future trend of its evolution is limited, as are the tools available (the most important of which is the vaccine) to counter its spread. The 'chronic infection' hypothesis seems the most promising, and further research is required to 'predict the unpredictable'. Decreasing the likelihood of the emergence of new pandemics is also critical, especially COVID-19 outbreaks. Given the zoonotic origin of SARS-CoV-2, the study of the drivers of zoonotic emergence may become an important tool. Determining the animals that are a common source of zoonotic viruses may become critical in counteracting future pandemics.

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