Letter to Editor

Early Exposure to SARS-CoV-2 in 2019 Not Reflected in All-Cause Mortality Data

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Introduction

Much of the literature and scientific research has focused on whether SARS-CoV-2 emerged as a result of a laboratory event or natural recombination. Comparatively few studies have attempted to empirically determine when the virus is most likely to have emerged, such as through wastewater-based epidemiology. Although this area has been largely neglected, there is a growing body of evidence indicating that the virus was much more widespread in 2019 than is generally accepted [1]. However, early indications of viral presence are not reflected in excess mortality statistics.

Evidence from Italy, France, and Brazil

Based on molecular clock inference and epidemiological simulations, *Pekar, et al.* concluded that the plausible interval during which SARS-CoV-2 emerged in the Hubei province, China, was between mid-October and mid-November 2019 [2]. The study did not support the hypothesis that the virus emerged in the Hubei province prior to October.

In contrast, there is growing evidence that SARS-CoV-2 was widespread in Italy in September 2019. If true, this would be evidence that the virus may not have emerged in China. For example, using 959 samples from a prospective lung cancer screening trial, *Apolone, et al.* in Tumori found IgG and/or IgM antibodies to SARS-CoV-2 in 111 samples [3]. A total of 14.2% of the samples were positive in September 2019, 16.3% in October, 9.5% in November, 7.5% in December, 2.8% in January, and 20% in February. Participants in the trial came from each of Italy's 13 regions.

These findings are complemented by an important paper by *Amendola, et al.* They found anti-SARS-CoV-2 antibodies (IgG and IgM) and SARS-CoV-2 RNA in urine and serum samples collected from an 8-month-old boy in Milan on September 12, 2019 [4]. They also obtained sequences of SARS-CoV-2 RNA from samples collected in Lombardy in October 2019. These contained mutations characteristic of B.1 strains. They concluded that the strains were at least six mutations removed from the SARS-CoV-2 progenitor strain, suggesting a possible emergence between late June and late July 2019.

There is also evidence that infections were symptomatic as early as September 2019. *Amendola, et al.* concluded that the virus produced a measles-like syndrome. In addition, a paper by *Lippi, et al.* in Tumori analyzed Google Trends data for the keywords fever, cough, and cold. They found a statistically significant increase in the Lombardy region beginning in the first week of September [5]. The increase could not be attributed to influenza.

Apart from Italy, there is evidence that the virus has been circulating undetected in France since early November 2019. From a collection of serum samples from 9,144 adults in France, *Carrat, et al.* showed that samples from the first week of November 2019 were positive for anti-SARS-CoV-2 antibodies (IgG) as well as positive for neutralizing antibodies (SN) [6]. They didn't test samples from earlier than November. Several participants who tested positive for both SN and IgG antibodies had symptoms similar to those of COVID-19 at the time of sample collection or had been in contact with symptomatic individuals.

Officially, SARS-CoV-2 arrived in Brazil at the end of February 2020. However, a paper by *Fongaro, et al.* detected a β mutation of the virus in a sewage sample from Florianópolis dated November 27, 2019. The study concluded that SARS-CoV-2 appeared to have been "circulating unnoticed" for some months before a pandemic was declared by the WHO [7].

Excess Mortality in Brazil, Italy, and France

Given the evidence that SARS-CoV-2 began to spread earlier than the official timeline suggests, it is possible that COVID-associated mortality began in 2019, but there is no evidence of this from weekly all-cause mortality data. In Brazil, for example, excess mortality began in March 2020, even though it had been circulating unnoticed without any preventive measures [8].

In Italy, there was a prolonged mortality deficit beginning in week 31 of 2019 (Figure 1). This lasted until the first lockdown was imposed in week 9 of 2020, which covered multiple municipalities (Figure 2), [9-11]. The lockdown was soon after extended to the entire country. The lack of excess mortality in Italy despite widespread exposure to the virus in September raises questions that need to be addressed. Why did the virus seemingly not impact mortality statistics for months, but only after containment measures were introduced? Based on transmission dynamics, it has been argued that it is unlikely that there was significant transmission as far back as November, let alone September [12]. The argument is that the waves of COVID-associated morbidity and mortality would have occurred much earlier. Research is needed to clarify whether current data on transmission dynamics are compatible with the data from Italy.
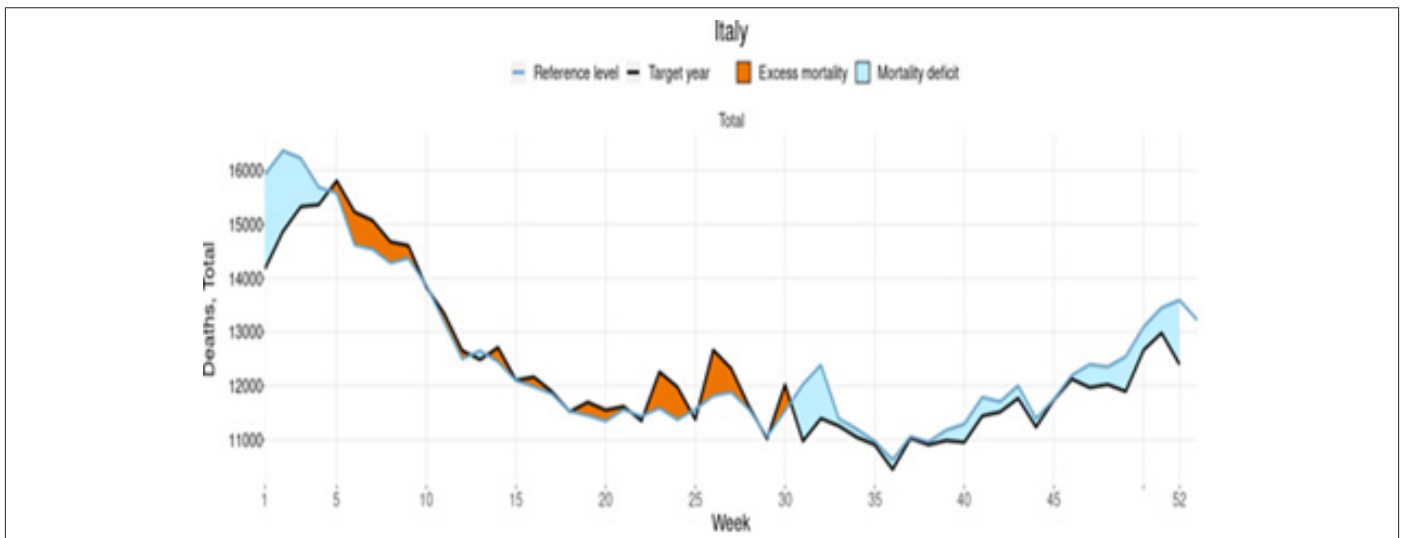

Figure 1: Weekly all-cause mortality in Italy in 2019 vs. projected mortality based on the period 2014-2018.
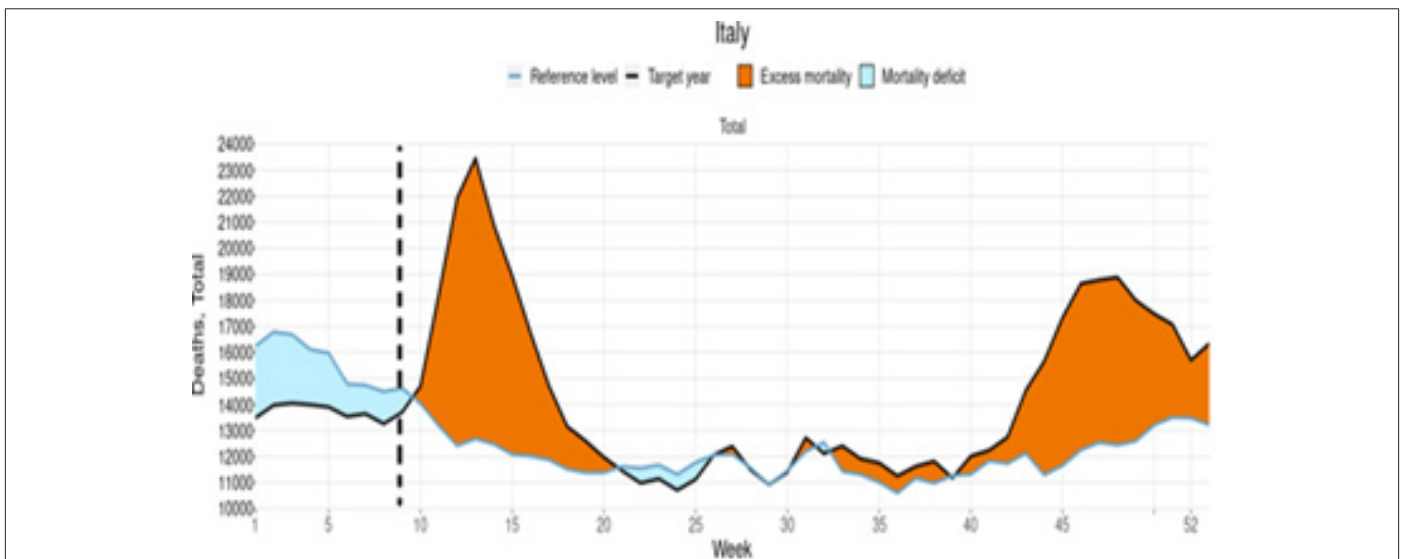

Figure 2: Weekly all-cause mortality in Italy in 2020 vs. projected mortality based on the period 2015-2019. The vertical dashed line indicates the approximate time of the first lockdown in week 9.

Weekly all-cause mortality in France was also lower than the projected levels in the period before the restrictions (Figures 3-4). Research is needed to clarify the cause of this mortality deficit. Significant excess mortality occurred shortly after restrictions were imposed [13]. Restrictions were imposed in week 9 and culminated in the first lockdown in week 12.
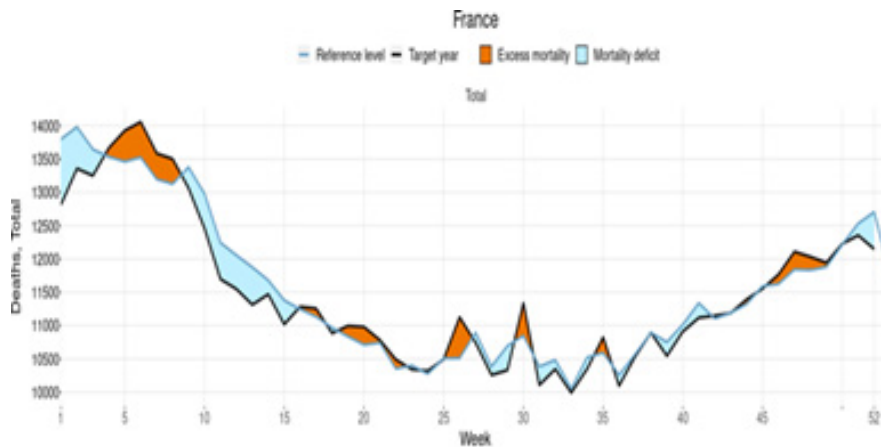
Figure 3: Weekly all-cause mortality in France in 2019 vs. projected mortality based on the period 2014-2018.
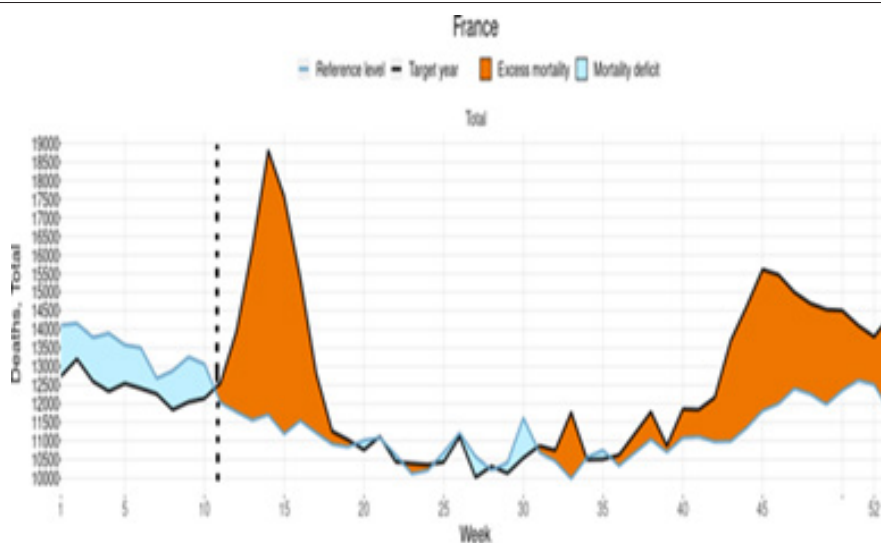

Figure 4: Weekly all-cause mortality in France in 2020 vs. projected mortality based on the period 2015-2019. The vertical dashed line indicates the approximate time at which the first lockdown was imposed in week 12.

Conclusions

The scientific community is encouraged to investigate these inconsistencies and look for further evidence of SARS-CoV-2 in pre-2020 wastewater samples and stored biological material. In particular, the sequence features of the 2019 strains should be compared with those circulating during periods of excess mortality in 2020. If sequence features cannot explain the excess mortality, then it is urgent to find out what can.

Conflict of Interest

The author declares that he has no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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