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LETTER TO THE EDITOR

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SARS-CoV-2 pandemic, influenza, and influenza-like illness epidemics: Allies or enemies?

A current major issue not yet resolved is the relationship between the SARS-CoV-2 pandemic and seasonal outbreaks of influenza and other respiratory viruses, as suggested by Zeng et al.[1] In the 2019/2020 flu season, Italy reached the epidemic pick of influenza-like illness (ILI), with a level equal to about 13 cases per thousand assisted (around 30% of which were caused by influenza viruses), immediately before the start of SARS-CoV-2 outbreak.[2] After the first wave of the pandemic, (1) the observation that severe COVID-19 patients reported ILI-related symptoms in the weeks before contagion, (2) the evidence that some respiratory viruses could cause host SARS-CoV-2 receptor modulation, and (3) the suspect that viral coinfection in SARS-CoV-2 patients could potentially influence COVID-19 outcome, induce scientists to speculate that previous ILIs could represent a Trojan horse facilitating a subsequent severe SARS-CoV-2 infection.[3,4] Based on this hypothesis and given the unavailability of a SARS-CoV-2 vaccine at the time, a large flu vaccine campaign was supported by the Italian Ministry of Health in the fall of 2020 to avoid a possible 2020/2021 influenza outbreak complicating the SARS-CoV-2 pandemic. Similarly, this strategy was adopted in many European countries. The aggressiveness of the flu vaccination campaign, the extensive use of the face mask, and the "social distancing" strategy changed the curve of the 2020/2021 flu season beyond the expected[5]: in fact, in the period in which generally the incidence of ILI gradually increased until reaching the epidemic peak, the number of ILI cases remained high below the expected threshold with about 1.2 cases per thousand assisted (Figure 1).[2] Despite this result and differently from what was expected, the impact of the SARS-CoV-2 pandemic did not decline, and a third severe wave was observed. From a public health perspective, this period was characterized by the closure of schools with distance learning, by an extensive adoption of smart working, and by careful use of social distancing and individual protection measures against SARS-CoV-2. Moreover, vaccination against SARS-CoV-2 was made available in late December 2020.

A similar strategy against ILI was also adopted in the 2021/2022 season when most of the population had been fully vaccinated against SARS-CoV-2.[6] Anyway, in this case, the schools remained open, smart working was limited, and the adoption of prophylactic measures was less stringent. The result was that the ILI curve was intermediate between the epidemic peak of 2019/2020 and the very low diffusion of 2020/2021 (Figure 1). In the same period, Italy has been hit by a new major SARS-CoV-2 wave characterized by a high number of cases and by the significant spread of the omicron variant.[6]

These epidemiological data seem to support the hypothesis that social distancing, lockdowns, and prophylactic measures (in addition to the benefit of vaccination) may represent the key factors in explaining the dramatic reduction of ILI incidence observed in the 2020/2021 season. Nevertheless, it remains to be explained how the same containment strategies may have had nonhomogeneous effects on the epidemiological curves of the spread of ILI and SARS-CoV-2, especially during the second pandemic wave. One possible interpretation could be the higher probability of SARS-CoV-2 finding susceptible hosts. In fact, the population at that time had a clearly lower immunological protection for COVID-19 compared to ILI, towards which there was already an immune memory linked to the cyclical annual outbreaks and previous influenza vaccinations. Furthermore, the high frequency of asymptomatic or paucisymptomatic infections due to SARS-CoV-2 and ILI[7,8] could have led to neglect of prophylactic measures: anyway, under the same conditions of insufficient prevention, it is likely that people were more susceptible to SARS-CoV-2, the pathogen for which they had less immunological protection.

Finally, although prophylactic behaviors and immune factors have certainly limited the spread of ILI, the hypothesis of a direct contribution to the SARS-CoV-2 pandemic cannot be excluded.[9,10] In fact, a number of epidemiological studies showed that simultaneous viral infections could drive viral interference and respiratory viruses could compete with each other in a way that means one virus can suppress the spread of another.[10] Although extensive research are not currently available on the topic, early epidemiological observations confirmed that respiratory viruses and SARS-CoV-2 coinfections are uncommon events, suggesting a possible viral interference between ILI pathogens and SARS-CoV-2.[11,12] In particular, Nowak et al.[13] reported that an ILI pathogen was isolated in 13% of cases in the absence of SARS-CoV-2 co-infection, while only in 3% in the presence of COVID in the population with respiratory symptoms, despite the chronological overlap of the two epidemic curves during the first pandemic wave. Similarly, Sapra et al.[14] reported that viral coinfections are significantly lower among COVID-19-positive patients as compared to COVID-19-negative individuals (4.6% vs. 24.5%). This was supposed to be possible due to viral interference and the competitive advantage of SARS-CoV-2 in modulating the host immunity. In this sense, the third pandemic wave could be somehow linked to competitiveness between SARS-CoV-2 and ILI pathogens, with the latter losing in the evolutionary struggle for the infection of the natural host.

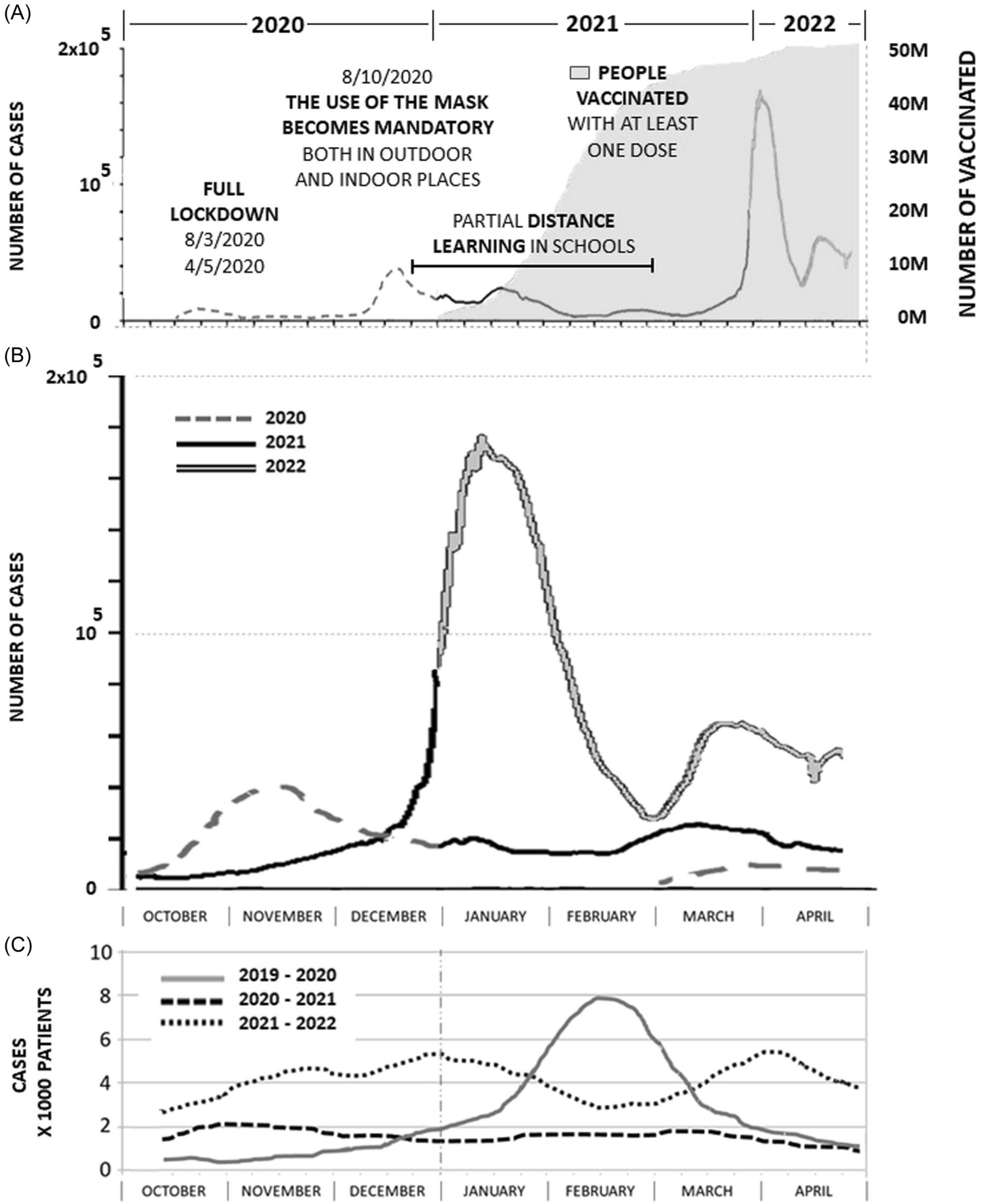

FIGURE 1 Overall curve of the SARS-CoV-2 pandemic in Italy, key preventive interventions* and vaccinations from 2020 to 2022 (A); comparison between the incidence of SARS-CoV-2 (B) and ILI (C) in Italy (seasons from 2019/2020 to 2021/2022). *A summary of the preventive interventions and regulations adopted in Italy during the pandemic is available at https://www.governo.it/it/coronavirus-misure-del-governo (accessed on 16/8/2022).

Interestingly, in apparent contrast with this hypothesis, some studies reported high levels of viral coinfections, in particular with influenza A, in hospitalized COVID patients during the early time of the SARS-CoV-2 pandemic.[15–17] In these cases, several factors may have influenced the difference reported in the frequency of coinfections: for example, the seasonal and geographic variability in respiratory pathogens, the strength of the preventive measures used in each country, the average age of the population analyzed, the selection of hospitalized patients, the type of analysis adopted. Finally, another possible reason for the low co-infections in COVID-19 patients might be due to the quick identification methods available for COVID-19 patients, which can allow the COVID-19 patients to be identified and isolated in the very early period before the patients have a chance to be infected by other respiratory viruses.[18,19]

In light of the clinical and epidemiological relevance of the topic and of the current knowledge gaps, additional studies are needed to establish whether simultaneous/succeeding ILI pathogen infection in SARS-CoV-2 patients could potentially drive some viral interference and impact the spread of the pandemic. In this regard, we note that the new generation of vaccines plans to raise immunity with a single shot comprising antigens against flu and SARS-COV-2. It would be interesting to evaluate the epidemiological and clinical data after such shots to gain a better understanding of the interference between the viruses.

AUTHOR CONTRIBUTIONS

Giancarlo Ceccarelli: Conceptualization, writing – original draft, drawing of the figure; **Silvia Fabris**: Conceptualization, review of scientific literature; **Gabriele d'Ettorre**: conceptualization, review of scientific literature; **Alessandro Russo**: Conceptualization, critical revision; **Massimo Ciccozzi**: Conceptualization, critical revision; **Gabriella d'Ettorre:** Conceptualization, critical revision.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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