Original Article

Nationwide analysis of COVID-19 death rate throughout the pandemic in Italy

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Background: No definitive epidemiological evidence is available on SARS-CoV-2 lethality during the surge of different variants of concern (VoCs) and coronavirus disease 2019 (COVID-19) vaccination in relation to common flu fatality.

Methods: We collected and longitudinally analyzed official data about new COVID-19 cases and COVID-9 related deaths throughout the pandemic in Italy, which were then compared with the recent influenza virus-related fatality rate.

Results: The mortality rate of COVID-19 has declined from 3.53% during predominance of the ancestral SARS-CoV-2 strain to 0.26–0.21% after surge of the new Omicron sublineages BA.1/2 and BA.4/5, when the nationwide COVID-19 vaccine coverage with primary cycle and booster doses has been concomitantly extended to 90.2% and 84.5% of the general population aged ≥12 years, respectively. The death rate of COVID-19 was approximately 11-fold higher than that of common flu (i.e., 3.53% versus 0.32%) at the beginning of the pandemic, but has then become 36% lower than that caused by the Influenza virus after widespread COVID-19 vaccine coverage, acquisition of natural immunity and surge of Omicron sublineages BA.4/5.

Conclusions: Although our findings underpin a reassuring epidemiological scenario, with death rate of COVID-19 currently lower than that of Influenza virus in Italy, we reemphasize the importance of preventing further surge of aggressiveness (and potential lethality) of SARS-CoV-2, especially in the most vulnerable parts of the population.

Keywords: Severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2); coronavirus disease 2019 (COVID-19); mortality; vaccines; variants

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Introduction

Coronavirus disease 2019 (COVID-19), a respiratory infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2), has been first identified in the Chinese town of Wuhan in November 2019, and has since been declared pandemic by the World Health Organization (WHO) in March 2020 (1), becoming the seven most deadly pandemics throughout the reported

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human history (2). The clinical course of this infectious disease has changed substantially over time, due to a number of biological and clinical aspects that have contributed to attenuate the impact of the virus on human health (3).

It is now undeniable that the major knowledge that we have progressively garnered on the pathogenesis of COVID-19, which might potentially become a life-threatening systemic disorder (i.e., thus causing injuries to a vast array of human organs and tissues) rather than remaining an isolated pulmonary disease (4), has enabled to considerably ameliorate the managed care of patients with SARS-CoV-2 infection, by adopting an ample armamentarium of conventional, innovative and even revolutionary medications, encompassing antiviral agents (i.e., anti-SARS-CoV-2 monoclonal antibodies, convalescent plasma, intravenous immune globulins, virucidal agents), anti-inflammatory and immunosuppressive drugs, anticoagulants (e.g., heparin and direct oral anticoagulants) and supportive treatments (i.e., supplemental oxygen, prone position), among others (5).

Three other aspects that have enormously contributed to mitigate the clinical and social burden of SARS-CoV-2 infection encompass the organization of widespread COVID-19 vaccination campaigns in several countries, acquisition of natural (herd) immunity and accumulation of less lethal mutations within the single-stranded RNA viral genome of SARS-CoV-2 (6). As concerns the former aspect, a huge number of COVID-19 vaccines (mRNA-based, protein-based, adenoviral, attenuated) have now become commercially available or are nearly ready to be approved (7), with some of these that have already progressed towards their "second" generation, being constructed with sequences of the original prototype SARS-CoV-2 virus combined with those of the recent Omicron BA.4/5 sublineages (i.e., the so-called "bivalent vaccines") (8). Although the number of human lives that COVID-19 vaccines have helped to save throughout the pandemic cannot be definitely established, and will probably remain incalculable forever, it has been estimated that over 60% of SARS-CoV-2 related deaths could have been saved during the first year of COVID-19 vaccination, worldwide (9). A landscape of genomic mutations have also gradually accumulated over time in the RNA sequence of SARS-CoV-2, especially in that of the spike protein and its receptor biding domain (RBD) (10). Reliable evidence has now been provided that most of these genetic polymorphisms have rendered the original virus more fit to infect its human host, concomitantly expressing a globally less pathogenetic potential on human cells (11,12). It is hence not surprising that widespread perception is gaining momentum that the clinical severity of the disease caused by the currently predominant SARS-CoV-2 Omicron sublineages may be comparable to that caused by common flu (13).

Therefore, since no definitive epidemiological evidence has been published about the mutated SARS-CoV-2 lethality due to variant of concerns (VoCs) predominance and COVID-19 vaccination in relation to Influenza virus fatality to the best of our knowledge, we provide here an updated analysis of the COVID-19 death rate throughout the pandemic in Italy.

Highlight box

Key findings

- Although our findings underpin a reassuring epidemiological scenario, with death rate for coronavirus disease 2019 (COVID-19) currently lower than that for common flu, active surveillance should be maintaining for preventing further surge of aggressiveness of SARS-CoV-2.

What is known and what is new?

- Mortality for COVID-19 has gradually declined over time, due to the combined effect of virus mitigation and herd (natural or vaccine-elicited) immunity.
- In this work, we estimated that the current death rate of COVID-19 is around 0.2%, thus lower than that of common flu (i.e., around 0.3%).

What is the implication, and what should change now?

- Some restrictive measures could be relieved, provided that active epidemiologic surveillance is maintained to intercept future hazards.

Methods

The number of new SARS-CoV-2 infections and COVID-19 related deaths was collected from official data reported by the WHO in its Coronavirus (COVID-19) Dashboard between February 2020 (when the first indigenous case was diagnosed in Italy) and present time (i.e., up to November 11, 2022), after setting the geographical location to Italy (14). Data on SARS-CoV-2 VoCs predominance and roll out of COVID-19 vaccination in Italy (encompassing both the primary cycle and booster doses administration) were accessed from the official website of the Italian National Institute of Health (15). As concerns influenza infections and mortality

Table 1 Epidemiological evolution of SARS-CoV-2 variants of concern and COVID-19 vaccination throughout the COVID-19 pandemic in Italy

SARS-CoV-2 VoC	Vaccination	Period	Duration (days)	COVID-19				
				Total cases	Daily cases	Attributable deaths	Daily attributable deaths	Death rate
Ancestral	No	February 2020 to December 2020	314	2,083,698	6,636	73,604	234	3.53%
Ancestral	Primary cycle	January 2020 to January 2021	50	458,085	9,162	14,675	294	3.20%
Alpha	Primary cycle	February 2021 to June 2021	150	1,717,350	11,449	39,263	262	2.29%
Delta	Primary cycle	July 2021 to September 2021	92	409,128	4,447	3,328	36	0.81%
Delta	Booster	October 2021 to December 2021	92	1,186,167	12,893	6,221	68	0.52%
Omicron BA.1/BA.2	Booster	January 2022 to May 2022	150	11,542,295	76,949	29,540	197	0.26%
Omicron BA.4/BA.5	Booster	June 2022 to present	165	6,245,288	37,850	12,805	78	0.21%

SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; VoC, variant of concern.

in the country, information was retrieved from the Italian National Institute of Health report published by Rosano *et al.* in 2019 (16), relative to the influenza seasons 2013/14 to 2016/17. Raw data were imported into a Microsoft Excel worksheet (Microsoft, Redmond, WA, United States), were they were graphically plotted, with calculation of the death rate for both COVID-19 and common flu. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This analysis was based on electronic searches in open and publicly available repositories, so that no informed consent or approvals from ethical committee were necessary.

Results

The progressive genetic evolution of SARS-CoV-2, with appearance of the four leading VoCs that have become predominant in Italy since the beginning of the COVID-19 pandemic is summarized in *Table 1*, compounded by the progression of COVID-19 primary vaccination and booster dose administration. Thus, not less than seven different periods could be identified by combining the surge of SARS-CoV-2 VoCs and the progression of the COVID-19 vaccination. The number of new diagnosed COVID-19 cases, COVID-19 attributable deaths and the resulting death rate is also reported in *Table 1*. Although a dramatic increase of new COVID-19 cases can be noted during the Omicron surge, as a result of the growth advantage of these compared to former SARS-CoV-2 VoCs in Italy and in most other countries (17), the COVID-19 death rate has instead exhibited a dramatic decline since the diagnosis of the first Italian case, in February 2020. Specifically, the mortality rate has declined from 3.53% during the ancestral SARS-CoV-2 strain predominance to 0.26% and 0.21% after surge of Omicron sublineages BA.1/2 and BA.4/5, respectively, when COVID-19 vaccine coverage (primary cycle) has also been extended to 90.2% of the national population aged 12 years of older, with 84.5% of these also receiving at least one COVID-19 vaccine booster dose (18).

According to the official statistics of the Italian National Institute of Health (16), the number of estimated influenza-like illness cases was 21.3 million between the seasons 2013/14 and 2016/17, causing 68,068 attributable deaths, and thus yielding a crude death rate of 0.32% (Influenza virus vaccine coverage was between 50–65% during the same period) (16). Thus, the death rate of COVID-19 was approximately 11-fold higher than that of common flu at the beginning of the pandemic, but has now instead become nearly 36% lower after widespread COVID-19 vaccination and surge of Omicron sublineages BA.4/5 (*Figure 1*).

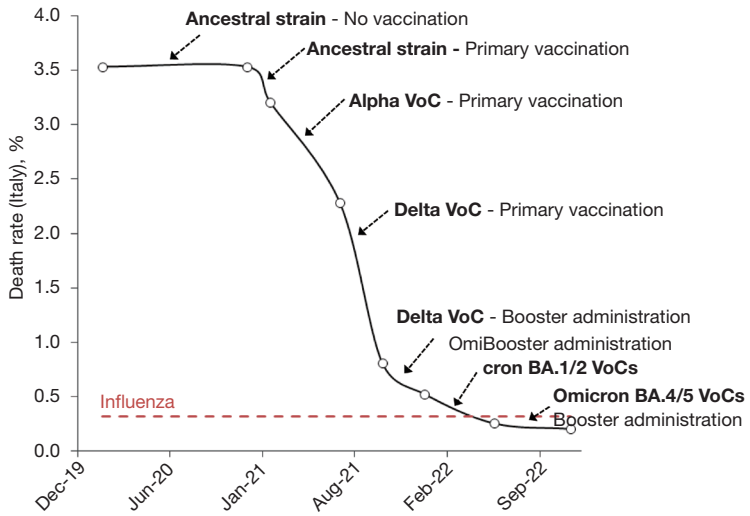

Figure 1 Epidemiological evolution of SARS-CoV-2 variants of concern, COVID-19 vaccination and death rate of COVID-19 throughout the COVID-19 pandemic in Italy. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019.

Discussion

There is now consolidated perception that after we have holistically learnt to live with common flu, it is very likely that we will now need to finally learn to live with SARS-CoV-2 as well, since this new coronavirus is on its way to become an(other) endemic human pathogen (19). Nonetheless, underrating the potentially detrimental clinical consequences of SARS-CoV-2 infections, or reclassifying COVID-19 "just like the flu" (13), may turn out to be paramount (even irreversible) mistakes, provided that reliable epidemiological data will be brought in support of this "attenuation and mitigation" thesis.

The evidence emerged from the analysis of Italian data about the progressive surge of SARS-CoV-2 VoCs combined with the progression of the nationwide COVID-19 vaccination campaign clearly attests that the lethality of COVID-19 had inexorably declined over time in the country (*Figure 1*), becoming over 17-fold lower in November 2022 than at the beginning of the national outbreak, nearly three years before (i.e., 0.21% *vs.* 3.53%). Notably, we have decided to arbitrarily limit our analysis to a single country (i.e., Italy), since the nationwide COVID-19 vaccination campaigns and the emergence and spread of new SARS-CoV-2 VoCs are both dramatically heterogeneous all around the world, thus precluding the possibility to pool data and obtain reliable information on these two different aspects on a global scale.

Looking at the temporal trend reported in *Figure 1*, it becomes evident that the initiation of the primary COVID-19 nationwide vaccination campaign in December 2020 in Italy has determined the sharpest decrease of the fatality rate, with continuation of such favorable trend when SARS-CoV-2 Alpha and Delta VoCs replaced the ancestral strain derived from the prototype virus firstly identified in Wuhan and bearing the lethal D614G polymorphism. At that point in time, the mortality rate had already declined to 0.81%. The effectiveness of the COVID-19 vaccine boosters administration has then maintained this favorable trend, being associated with a further reduction of the death rate by 1.36 folds (i.e., from 0.81% to 0.52%). Yet, such variation is not comparable to the magnitude of clinical benefits probably generated by the primary COVID-19 vaccination, which contributed to lower the mortality rate by over 4 folds between December 2020 and September 2021 (i.e., from 3.53% to 0.81%). This is in keeping with recent evidence showing that booster doses of COVID-19 vaccines may be effective to reduce the likelihood of developing acute SARS-CoV-2 infection by boosting humoral immunity, whilst both immunological memory (20) and cellular immunity (21,22) developed after primary vaccination remain almost unvaried (23), thus preserving part of their original potential to produce a marked anti-viral response that will ultimately prevent an unfavorable disease progression, including death (24).

Interestingly, the subsequent appearance and spread of the Omicron sublineages has then been associated with further reduction of the fatality rate, by exactly 2-fold during Omicron BA.1/2 preponderance (i.e., 0.26% versus 0.52% during the former Delta VoC wave) and by further 1.5-fold during the period of Omicron BA.4/5 surge (0.21% versus 0.26% during the former Omicron BA.1/2 wave), respectively. This epidemiological data are in keeping with the many biological studies published so far, reporting that the new Omicron sublineages are characterized by lower lethal potential on their human host, prevalently infecting the cells of the upper respiratory tract but exhibiting lower capacity to infect alveolar and inflammatory cells (25-28). Overall, our epidemiological results are also aligned to those earlier published by Lauring *et al.* in the US (29), who demonstrated that the clinical severity of COVID-19 has progressively declined over time across the country due to the combined effect of COVID-19 vaccination and virus attenuation.

Confronting the data garnered from our analysis with the recent death rate of common flu in that same country (i.e., 0.32%), it is then evident that SARS-CoV-2 was over tenfold more lethal than the Influenza virus at the beginning of the pandemic, but COVID-19 has now paradoxically become 36% less fatal than common flu at the beginning of November 2022 (*Figure 1*). Importantly, several lines of evidence attest that the efficacy of COVID-19 vaccination against symptomatic and severe COVID-19 illness slowly but progressively wanes over time (30), while the potential risk that more virulent and aggressive SARS-CoV-2 variants will emerge in the future cannot be discounted (31). Moreover, even if the clinical consequences of SARS-CoV-2 reinfection are milder than those caused by a primary infection, they are not clinically negligible, being associated with twofold higher risk of hospitalization and death compared to patients without reinfection (32). Irrespective of the favorable trend exhibited by the COVID-19 death rate recorded during the past three years, we hence proffer that it may be too premature to declass this new pathology to an influenza-like disease.

Conclusions

Although our data seem to underline a currently reassuring scenario in terms of COVID-19 death rate, we reemphasize the importance of preventing further surge of aggressiveness (and potential lethality) of SARS-CoV-2, especially in the most vulnerable parts of the population, which especially include unvaccinated, fragile and/or immunocompromised patients.

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Footnote

Data Sharing Statement: Available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-75/dss

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-22-75/coif). GL serves as the Editor-in-Chief of *Journal of Laboratory and Precision Medicine*. The other author has no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This analysis was based on electronic searches in open and publicly available repositories, so that no informed consent or approvals from ethical committee were necessary.

References

1. Cucinotta D, Vanelli M. WHO Declares COVID-19 a Pandemic. Acta Biomed 2020;91:157-60.
2. Sampath S, Khedr A, Qamar S, et al. Pandemics Throughout the History. Cureus 2021;13:e18136.
3. Li Wan Po A. Omicron variant as nature's solution to the

COVID-19 pandemic. J Clin Pharm Ther 2022;47:3-5.
4. Lippi G, Sanchis-Gomar F, Henry BM. COVID-19: unravelling the clinical progression of nature's virtually perfect biological weapon. Ann Transl Med 2020;8:693.
5. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [Internet]. Bethesda (MD): National Institutes of Health (US), 2021 Apr 21–2022 Sep 30.
6. Mattiuzzi C, Henry BM, Lippi G. COVID-19 vaccination and SARS-CoV-2 Omicron (B.1.1.529) variant: a light at the end of the tunnel? Int J Infect Dis 2022;118:167-8.
7. Barouch DH. Covid-19 Vaccines - Immunity, Variants, Boosters. N Engl J Med 2022;387:1011-20.
8. Lippi G, Mattiuzzi C. Bilavent vaccines against COVID-19. Biochim Clin 2022. doi: 10.19186/BC_2022.076.
9. Watson OJ, Barnsley G, Toor J, et al. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. Lancet Infect Dis 2022;22:1293-302.
10. Lippi G, Henry BM. The landscape of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) genomic mutations. J Lab Precis Med 2022;7:10.
11. Mattiuzzi C, Henry BM, Lippi G. Regional Association between Mean Air Temperature and Case Numbers of Multiple SARS-CoV-2 Lineages throughout the Pandemic. Viruses 2022;14:1913
12. Fan Y, Li X, Zhang L, et al. SARS-CoV-2 Omicron variant: recent progress and future perspectives. Signal Transduct Target Ther 2022;7:141.
13. Stokel-Walker C; . How similar is covid-19 to the flu? BMJ 2022;379:o2625.
14. World Health Organization. Coronavirus (COVID-19) Dashboard. Available online: https://covid19.who.int/region/euro/country/it, last accessed November 11, 2022.
15. Istituto Superiore di Sanità. COVID-19 integrated surveillance: key national data. Available online: https://www.epicentro.iss.it/en/coronavirus/sars-cov-2-integrated-surveillance-data, last accessed November 11, 2022.
16. Rosano A, Bella A, Gesualdo F, et al. Investigating the impact of influenza on excess mortality in all ages in Italy during recent seasons (2013/14-2016/17 seasons). Int J Infect Dis 2019;88:127-34.
17. Stefanelli P, Trentini F, Petrone D, et al. Tracking the progressive spread of the SARS-CoV-2 Omicron variant in Italy, December 2021 to January 2022. Euro Surveill 2022.
18. Italian Ministry of Health. COVID-19 Vaccines Report. Available online: https://www.governo.it/it/cscovid19/report-vaccini/, last accessed November 11, 2022.
19. Lippi G, Mattiuzzi C, Henry BM. Updated picture of SARS-CoV-2 variants and mutations. Diagnosis (Berl) 2021;9:11-7.
20. Kuse N, Zhang Y, Chikata T, et al. Long-term memory CD8(+) T cells specific for SARS-CoV-2 in individuals who received the BNT162b2 mRNA vaccine. Nat Commun 2022;13:5251.
21. Takeuchi JS, Fukunaga A, Yamamoto S, et al. SARS-CoV-2 specific T cell and humoral immune responses upon vaccination with BNT162b2: a 9 months longitudinal study. Sci Rep 2022;12:15447.
22. Oliver MA, Meredith RT, Smith BR, et al. Longitudinal T Cell Responses against Ancestral, Delta, and Omicron SARS-CoV-2 Variants Determined by Rapid Cytokine Release Assay in Whole Blood. Immunohorizons 2022;6:398-407.
23. Maringer Y, Nelde A, Schroeder SM, et al. Durable spike-specific T-cell responses after different COVID-19 vaccination regimens are not further enhanced by booster vaccination. Sci Immunol 2022. [Epub ahead of print]. doi: 10.1126/sciimmunol.add3899.
24. Lippi G, Mattiuzzi C, Henry BM. Is cellular immunity the future key for deciphering and monitoring COVID-19 vaccines efficacy? J Lab Precis Med 2022;7:18.
25. Hui KPY, Ng KC, Ho JCW, et al. Replication of SARS-CoV-2 Omicron BA.2 variant in ex vivo cultures of the human upper and lower respiratory tract. EBioMedicine 2022;83:104232.
26. Armando F, Beythien G, Kaiser FK, et al. SARS-CoV-2 Omicron variant causes mild pathology in the upper and lower respiratory tract of hamsters. Nat Commun 2022;13:3519.
27. McMahan K, Giffin V, Tostanoski LH, et al. Reduced pathogenicity of the SARS-CoV-2 omicron variant in hamsters. Med (N Y) 2022;3:262-268.e4.
28. Granerud BK, Ueland T, Lind A, et al. Omicron Variant Generates a Higher and More Sustained Viral Load in Nasopharynx and Saliva Than the Delta Variant of SARS-CoV-2. Viruses 2022.
29. Lauring AS, Tenforde MW, Chappell JD, et al. Clinical severity of, and effectiveness of mRNA vaccines against, covid-19 from omicron, delta, and alpha SARS-CoV-2 variants in the United States: prospective observational study. BMJ 2022;376:e069761.
30. Ferdinands JM, Rao S, Dixon BE, et al. Waning of vaccine effectiveness against moderate and severe covid-19 among adults in the US from the VISION network: test negative,

case-control study. BMJ 2022;379:e072141.
31. Caputo E, Mandrich L. SARS-CoV-2: Searching for the Missing Variants. Viruses 2022;14:2364.
32. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. Nat Med 2022;28:2398-405.

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