Journal of Infection and Public Health 18 (2025) 102698

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: www.elsevier.com/locate/jiph

Original Article

COVID-19 Fallsterblichkeitsrate und Infektionssterblichkeitsrate von 2020 bis 2023: Bundesweite Analyse in Österreich

COVID-19 case fatality rate and infection fatality rate from 2020 to 2023: Nationwide analysis in Austria

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ARTICLE INFO

Article history:
Received 24 July 2024
Received in revised form 4 February 2025
Accepted 6 February 2025

Keywords:
SARS-CoV-2
COVID-19
Case fatality rate
Infection fatality rate
Austria
Nationwide

ABSTRACT

Background: Comprehensive analyses of COVID-19 case fatality rates (CFRs) and infection fatality rates (IFRs) that span the entire pandemic are not yet available but critical to retrospectively evaluate the COVID-19 disease burden and its related public health policies. We used nationwide individual participant data from Austria, the continental country with the highest SARS-CoV-2 testing rate per capita, to calculate COVID-19 CFR and estimate IFR covering the entire pandemic.

Methods: This retrospective observational study included all Austrian residents and covered the time from February 2020 to May 2023, examining CFRs overall, monthly, and during dominant SARS-CoV-2 variant periods. CFRs were calculated for the whole population and stratified according to immunization status (presence of previous vaccination and/or infection), age, gender and nursing home residency. We additionally estimated the IFRs based on estimations of undocumented infections using a test positivity model.

Results: The overall CFR of 30-day COVID-19 mortality was 0.31 % but varied depending on month, with the highest being 5.9 % in April 2020 and the lowest 0.07 % in January 2022. The variant periods reflected this trend of decreasing CFR, with the highest for Wuhan-Hu-1 (2.05 %) and the lowest for BA.1 (0.08 %). Overall CFRs were particularly high in the group without any previous immunizing event (0.67 %), the elderly (85 + year group: 7.88 %) and in nursing home residents (7.92 %). Nursing home residents accounted for 30.82 % of all COVID-19 deaths while representing only 1.22 % of diagnosed infections. Total SARS-CoV-2 infections were estimated to be 47 % higher than confirmed cases with a corresponding overall IFR of 0.16 %.

Conclusion: This estimation of nationwide CFR and IFR across the entirety of the SARS-CoV-2 pandemic gives crucial insights into the period-dependent variability of the severity of diagnosed COVID-19 cases and its risk factors. Our findings further underline the disproportionate severity of COVID-19 among the elderly and especially nursing home residents.

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https://doi.org/10.1016/j.jiph.2025.102698

Introduction

The SARS-CoV-2 pandemic was a major health crisis [1,2]. Various public health measures were implemented to reduce the disease burden. However, there is an ongoing scientific debate on the effect and justification of some of these measures [3,4]. To retrospectively evaluate policies as well as prepare for future pandemics, we first and foremost need to understand the actual severity of the COVID-19 pandemic overall and across its different variant periods.

Case fatality rate (CFR) can provide an estimate of the disease severity by dividing the number of COVID-19 deaths by the number of documented infections. Previous studies on COVID-19 CFR have estimated values that differ between countries and have high variability over the pandemic's course [5–7]. Possible reasons for this include the over or under attribution of deaths due to COVID-19 [8], changes in dominant SARS-CoV-2 variants [6], differences in health care systems and protection by natural and/or vaccine based immunity [9]. Importantly, differences between countries in the underestimation of SARS-CoV-2 infections strongly contributed to heterogeneous CFRs [10]. Seroprevalence studies have shown, that the vast majority of SARS-CoV-2 infections worldwide were not diagnosed or officially registered [11–13].

The percentage of undocumented infections may be especially high in COVID-19 as many SARS-CoV-2 infections, by the end of the pandemic probably the large majority, were asymptomatic [14]. Thus, estimating undocumented cases via seroprevalence studies [11,15] and mathematical modeling [16] is a crucial component for calculating the infection fatality rate (IFR). The IFR, obtained by dividing COVID-19 deaths by the total number of infections, provides a more comprehensive picture of disease severity than CFR. Existing IFR estimates vary by country and age, primarily focusing on pre-vaccination periods [17–20]. For example, while an earlier study reported a median IFR of 0.506 % for the 60–70 age group and 0.0003 % for 0–19 year olds (with IFR steadily increasing with age) [19], research suggests lower IFRs in later pandemic waves [21–23]. National assessments of IFR that span close to two years have been performed in Italy [24] and England [25,26] and reported on relatively high IFRs in 2020 that decreased with time. However, nationwide studies investigating CFR and IFR across the entire pandemic are lacking, but required to retrospectively assess the disease burden of COVID-19 [5,7,17,21]. As Austria had the highest SARS-CoV-2 testing rate per capita of any non-island country in the world (on average more than 21 tests per capita over the duration of the pandemic), it is an instructive country for evaluating the COVID-19 severity regarding CFR and IFR [27].

We calculated CFR and estimated IFR using an Austrian nationwide dataset of SARS-CoV-2 infections and their COVID-19 mortality [28,29]. We calculated overall and monthly CFRs as well as CFRs based on periods of dominant variants across the entire pandemic (February 2020 to May 2023). We additionally stratified by age, gender and nursing home residency and immunization (previous vaccination, documented infection, both or neither). Finally, we applied a previously published model to estimate undocumented infections and calculate overall, monthly and dominant variant period IFRs [16].

Methods

Study design and population

We conducted a retrospective cohort analysis of COVID-19 deaths in the entire population of Austria (9,104,772 as of 1 January 2023). As in previous publications, we analyzed national health data provided by the Austrian Agency for Health and Food Safety (German: Österreichische Agentur für Gesundheit und Ernährungssicherheit; AGES) and acquired through the Austrian epidemiological reporting system (German: Epidemiologisches Meldesystem; EMS) [28,29]. Unique personal identifiers were used to match the EMS data with individual vaccination data provided by the national COVID-19 vaccine registry. The original dataset included individual participant data on all Austrian residents with confirmed SARS-CoV-2 infections up to June 30, 2023. Records contained COVID-19 deaths, SARS-CoV-2 positive test results, date of vaccination and vaccine product used in the study population, age, sex and nursing home residency. Data on the number of daily performed SARS-CoV-2 tests in Austria were publicly available in aggregate form [30]. COVID-19 deaths were classified as recorded by the local public health offices [28]. We previously published findings based on this dataset [29,31] and a subset limited to individuals with available all-cause mortality data [28]. We calculated both 30-day and 60-day COVID-19 fatality rates, i.e. excluding deaths that occurred either more than 30 or more than 60 days after a person's last recorded infection [21]. Additionally, we accounted for time lags between infections and deaths by handling deaths as if they occurred on the first day of the last recorded SARS-CoV-2 infection.

As the study included the entire Austrian population, we did not perform a sample size estimation. We followed the procedural suggestions of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist (Table S1). The study was approved by the ethics committee at the Medical University of Graz (no. 33–144 ex 20/21).

Statistical analysis

The CFR was calculated for documented infections that occurred from February 2020, the month of the first detected SARS-CoV-2 infections in Austria, to May 30 2023, when the World Health Organization (WHO) declared an end of this pandemic [2]. We calculated 95 % confidence intervals (CIs) estimates for the CFR based on the Jeffrey's prior distribution. This was calculated for the entire pandemic (overall), monthly and periods of dominant virus variants. We additionally calculated CFRs stratified by immunization status (according to previous documented vaccination and/or infection), age groups, gender (binary) and nursing home residency (binary) and combinations thereof. Immunization status was categorized into no immunity, vaccine induced immunity, natural immunity (after any previous documented SARS-CoV-2 infection) and hybrid immunity (after any previous documented SARS-CoV-2 infection and vaccination) (Figure S1). Vaccination was counted if it occurred at least 14 days before the infection. Reinfection was defined as a positive test 90 days or more after a previous positive test, so that group allocation to natural or hybrid immunity was assigned after 90 days of the first positive test result of the first SARS-CoV-2 infection. We did not differentiate between number of vaccine doses or previous documented infections, as research suggests strong and long-lasting protection against severe COVID-19 cases and mortality, even after a single vaccine dose or previous infection [32]. Examined age groups were 0–19, 20–39, 40–59, 60–74, 75–84 and 85 + years old. We defined variant dominant periods as timeframes in which more than 50 % of the reported samples were attributed to a specific variant or sub-variant. Analyzed dominant variants were Wuhan-Hu-1, Alpha, Delta, and Omicron sub-variants BA.1, BA.2 and BA.5. Their respective dominant timeframes were retrieved from AGES (Table S2).

Additionally, we calculated the overall, monthly and dominant variant period IFRs by dividing COVID-19 deaths by the number of SARS-CoV-2 infections. Infection prevalence estimates were based on a previously published approach, that estimated infection prevalence in Austria from April 2020 to December 2022 [16]. Accordingly, we used the described test positivity model (POS) which estimates prevalence based on testing rate and reported cases. The POS model showed comparable results to those of models utilizing

infection fatality rates and wastewater monitoring data for estimating true infections [16].

The model makes two assumptions: First, the error is larger when the number of tests is smaller. Specifically, that the test positivity rate is associated with the prevalence of undocumented infected persons by a time-dependent factor (b). Second, the bias factor b is inversely related to the testing rate (Tests/Population) by some factor f ($0 \leq f \leq 1$). These assumptions lead to the following formulation:

$$\boldsymbol{I_u}(\boldsymbol{t} + \boldsymbol{t_{lead}}) = \boldsymbol{N_{INF}}(\boldsymbol{t})^{*}\boldsymbol{N_{TEST}^{f-1}}(\boldsymbol{t})^{*}\boldsymbol{N^{1-f}}$$

Such that the number of undocumented infected persons (I_u) can be calculated from the number of daily infected (N_{INF}), number of tested (N_{Test}), size of the population (N) and an estimated ratio (f), while accounting for time shift in the estimates (t_{lead}). For a detailed formulation see the Supplementary Methods.

We calculated estimates of unidentified infections from May 1 2020 to May 31 2023, as data on testing rates were not available before April 2020 and the earliest possible estimations were for late April 2020. Estimations are based on all cases and are not further stratified by age, immunization status, or gender. IFR estimates are also provided for community-dwelling individuals, excluding deaths of nursing home residents and assuming 1 % of infections to be in the nursing home population (an approximation, based on them representing 0.94 % of the population [33]). Details on the model and implementation are given in the Supplementary Methods and the original publication [16].

Analyses were pre-specified and agreed among authors before any data were analyzed. The statistical analysis was conducted using R (version 4.4.0)[34].

Results

Between February 2020, and May 2023, 5,998,260 SARS-CoV-2 infections were recorded, and 20,966 deaths were attributed to COVID-19. Of these deaths, 18,727 and 20,283 occurred within 30 and 60 days after the first positive SARS-CoV-2 test result, respectively. The 30-day and 60-day COVID-19 mortality was highly correlated and close in scale (Table 1); therefore, we only present the 30-day COVID-19 mortality (Figures S31-S35 and Tables S31-S34**)**. Outcomes of the 60-day COVID-19 mortality can be found in the Supplements (Figures S61-S65 and Tables S61-S66**)**. Confidence intervals are omitted from the results section but are presented in tables. Overall CFR during the entire pandemic in Austria was 0.31 %. Monthly CFRs are presented in Fig. 1 and Table S31. Among all COVID-19 deaths the median (25th to 75th percentile) age was 83 (76–89) years and 47.09 % were women.

Previous immunization

Among all documented infections, 4,006,347 (66.79 %) were previously immunized by either a vaccination (52.45 %), a prior documented infection (5.14 %) or both (9.2 %). At the time of SARS-CoV-2 infection the median age (25th to 75th percentile) in years of groups with no previous immunization, natural immunity, vaccine induced immunity and hybrid immunity was 31 (13–49), 31 (14–44), 43 (29–58) and 39 (27–52), respectively. Overall CFR (95 % CI) of the non-immunized group was 0.67 % (0.66 % – 0.68 %), while those with natural immunity, vaccine induced immunity and hybrid immunity had a CFR of 0.03 % (0.03 % – 0.04 %), 0.16 % (0.15 % – 0.16 %) and 0.05 % (0.05 % – 0.06 %), respectively. The CFR of the non-immunized group was 0.38 % for infections after 2020, when vaccinations first started (Table 1). The monthly analysis further confirmed this trend. CFRs were consistently higher in the non-immunized group compared to the other groups (Fig. 2**a**), except for early 2021, where the distribution of SARS-CoV-2 infected individuals in the previously vaccinated and hybrid immunity groups was shifted towards higher age (Figs. 2**b**, 2**c**, 3 and S1). Of note, the high CFR of documented previously infected individuals in February 2021 is based on only two deaths (Table S32a).

Table 1
Overall CFRs, IFRs, infections and population for all subgroups calculated from 30- and 60-day mortality.

	Population[a]	Infections	Deaths (30-day mortality)	30-day mortality in percent (95 confidence interval)	Deaths (60-day mortality)	60-day mortality in percent (95 confidence interval)
Overall CFR	9,104,772	5,998,260	18,720	0.31 (0.31–0.32)	20,276	0.34 (0.33–0.34)
Immunization						
No Immunization		1,991,913	13,351	0.67 (0.66–0.68)	14,529	0.73 (0.72–0.74)
No Immunization; after 1. Jan 21		1,631,562	6152	0.38 (0.37–0.39)	6707	0.41 (0.4–0.42)
Prior Documented Infection		308,632	95	0.03 (0.03–0.04)	101	0.03 (0.03–0.04)
Prior Vaccination		3,145,999	4972	0.16 (0.15–0.16)	5317	0.17 (0.16–0.17)
Hybrid Immunity		551,716	302	0.05 (0.05–0.06)	329	0.06 (0.05–0.07)
Gender						
Female	4,619,957	3,154,190	8816	0.28 (0.27–0.29)	9440	0.3 (0.29–0.31)
Male	4,484,815	2,844,070	9904	0.35 (0.34–0.36)	10,836	0.38 (0.37–0.39)
Age (years)						
< 20	1,761,561	1,188,601	11	0.001 (0.0005–0.002)	14	0.001 (0.001–0.002)
20–39	2,353,741	1,897,735	71	0.004 (0.003–0.005)	82	0.004 (0.003–0.01)
40–59	2,577,991	1,862,756	727	0.04 (0.04–0.04)	892	0.05 (0.04–0.05)
60–74	1,544,467	688,900	3371	0.49 (0.47–0.51)	3838	0.56 (0.54–0.57)
75–84	644,578	256,067	6332	2.47 (2.41–2.53)	6786	2.65 (2.59–2.71)
85 +	222,434	104,201	8208	7.88 (7.71–8.04)	8664	8.31 (8.15–8.48)
Nursing home residency						
Yes	85,462	72,892	5770	7.92 (7.72–8.11)	6114	8.39 (8.19–8.59)
No	9,019,310	5,925,368	12,950	0.22 (0.21–0.22)	14,162	0.24 (0.24–0.24)
Overall IFR		11,234,074[c]		0.16 (0.16–0.16)		0.18 (0.18–0.18)
Overall IFR excluding nursing homes[b]		11,121,734[c]		0.12 (0.11–0.12)		0.13 (0.13–0.13)

Prior infection was defined as a positive SARS-CoV-2 test result at least 90 days before a current SARS-CoV-2 (re-)infection.
[a] as of January 1st, 2023. Taken from [33] and [35].
[b] calculation excludes deaths of nursing home residents and assumes approximately 1 % of infections were in nursing homes.
[c] estimates.

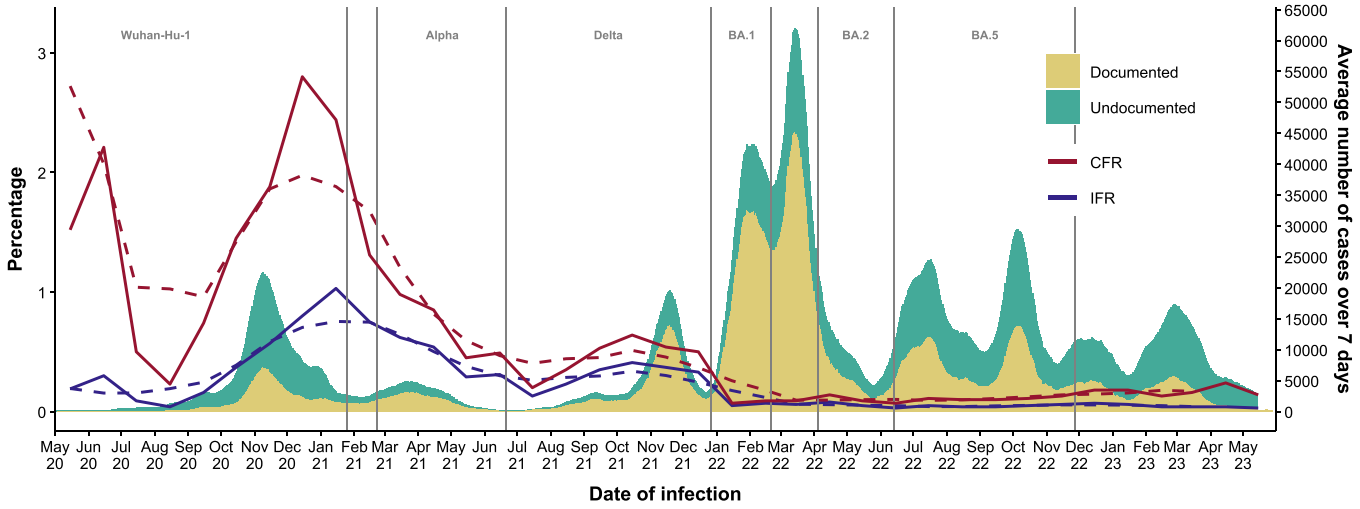

Fig. 1. COVID-19 case fatality rates, infection fatality rates (left scale) and seven-day average number of confirmed (documented) SARS-CoV-2 cases and estimated (undocumented) infections (right scale) from May 2020 onward. Estimation of undocumented cases are based on [16]. Note a steep increase in testing in early 2021 leading to a decrease in estimated undocumented cases. Dashed lines represent 5 months moving average for CFR and IFR respectively. This approach shows less abrupt fluctuations over time and takes into account that some of the testing data in late 2020 and early 2021 are implausible, as detailed in the Supplements.

Age groups

The overall CFRs (95 % CI) were highest in the 85 + year age group (7.88 %; 7.71 % – 8.04 %), followed by the 75–84 (2.47 %; 2.41 % – 2.53 %), 60–74 (0.49 %; 0.47 % – 0.51 %), 40–59 (0.04 %; 0.04 % – 0.04 %), 20–39 (0.004 %; 0.003 % – 0.005 %) and < 20 (0.001 %; 0.0005 % – 0.002 %) age groups. This pattern was consistent in all immunization groups (Figure S31, Table S33). Monthly analysis showed decreasing CFRs later in the pandemic, irrespective of age group (Figure S31).

Gender

CFR (95 % CI) in men (0.35 %; 0.34 % – 0.36 %) was higher than in women (0.28 %; 0.27 % – 0.29 %). This relative difference was present throughout the whole pandemic, even in later stages when CFRs were generally very low (Figure S33, Table S34).

Nursing home residency

During the entire pandemic, 30.82 % of all COVID-19 deaths were recorded in nursing home residents, even though nursing home residents were only a small part (n = 72.892, 1.22 %) of all SARS-CoV-2 infected individuals. Overall CFR (95 % CI) for nursing home residents was 7.92 % (7.72 % – 8.04 %), but only 0.22 % (0.21 % – 0.22 %) for non-nursing home residents (Table 1). Nursing home residents were older than the remainder population, but nursing home residency was still an indicator for increased fatality when stratifying by age (Table 2) and immunization status (Figure S32). Especially in the age group 60–74, nursing home residents had 11-fold higher CFR than others (4.86 % (4.46 % – 5.3 %) versus 0.42 % (0.41 % – 0.44 %)).

Periods of variant dominance

The highest CFR (95 % CI) of 2.05 % (2.01 % – 2.09 %) was detected in the Wuhan-Hu-1 variant, followed by Alpha (0.87 %; 0.83 % – 0.91 %), Delta (0.54 %; 0.52 % – 0.56 %), BA.2 (0.11 %; 0.1 % – 0.12 %), BA.5 (0.1 %; 0.1 % – 0.11 %) and BA.1 (0.08 %; 0.07 % – 0.08 %) (Table 3). Older individuals, and residents of nursing homes had much higher CFRs irrespective of variant (Table 3). These risk increases were especially high during early variant periods (Figure S32 and S33, Table S33).

Infection fatality rate

Estimated SARS-CoV-2 infections between May 2020 and May 2023 were 11,234,074 (Fig. 1). This indicates that 47 % of infections in Austria were undetected during this period. Increased testing in late 2021 and early 2022 led to lower estimated undetected infections when compared to earlier and later periods of the pandemic (Fig. 1). Both the CFR and IFR show some evidence of seasonality, with decreasing values in the summers of 2020, 2021, and 2022 and upticks in the subsequent cold season periods. Monthly IFRs show a downward trend after a peak in early 2021, comparable with the CFRs (Fig. 1, Table S31). For the Wuhan-Hu-1, Alpha, Delta, BA.1, BA.2 and BA.5 variants, the estimated IFRs (95 % CI) were 0.61 % (0.6 % – 0.63 %), 0.55 % (0.52 % – 0.58 %), 0.37 % (0.35 % – 0.38 %), 0.06 % (0.05 % – 0.06 %), 0.06 % (0.06 % – 0.07 %) and 0.05 % (0.04 % – 0.05 %) respectively (Table 3). Excluding the nursing home populations, the estimated IFRs in the community-dwelling people were 0.12 % (0.11 % – 0.12 %) overall (Table 1), as well as 0.36 % (0.35 % – 0.37 %), 0.51 % (0.49 % – 0.54 %), 0.31 % (0.3 % – 0.32 %), 0.04 % (0.03 % – 0.04 %), 0.05 % (0.04 % – 0.05 %), and 0.04 % (0.03 % – 0.04 %), for Wuhan-Hu-1, Alpha, Delta, BA.1, BA.2 and BA.5 variants respectively.

Discussion

During the entirety of the COVID-19 pandemic in Austria, the nationwide CFR was 0.31 %. Based on our estimate 47 % of SARS-CoV-2 infections were undetected. The corresponding IFR was 0.16 % overall and 0.12 % among community-dwelling people. These rates were highest in late 2020 and early 2021, decreasing steadily thereafter. With the onset of the Omicron variant at the beginning of 2022, rates dropped significantly with nationwide IFRs consistently much below 0.1 % until the end of the pandemic. COVID-19 fatality rates increased steeply with age. Compared to community dwelling persons, nursing home residents had significantly increased COVID-19 fatality rates and made up 30.82 % of all COVID-19 deaths. Men had consistently slightly higher fatality rates than women. When stratified by age, individuals with prior immunity through vaccination, past infection or both, exhibited lower COVID-19 fatality rates compared to those without any prior immune conferring event.

This investigation is, to our knowledge, the first to calculate nationwide COVID-19 CFRs and IFRs throughout the pandemic. It also considers major risk factors of CFR including nursing home

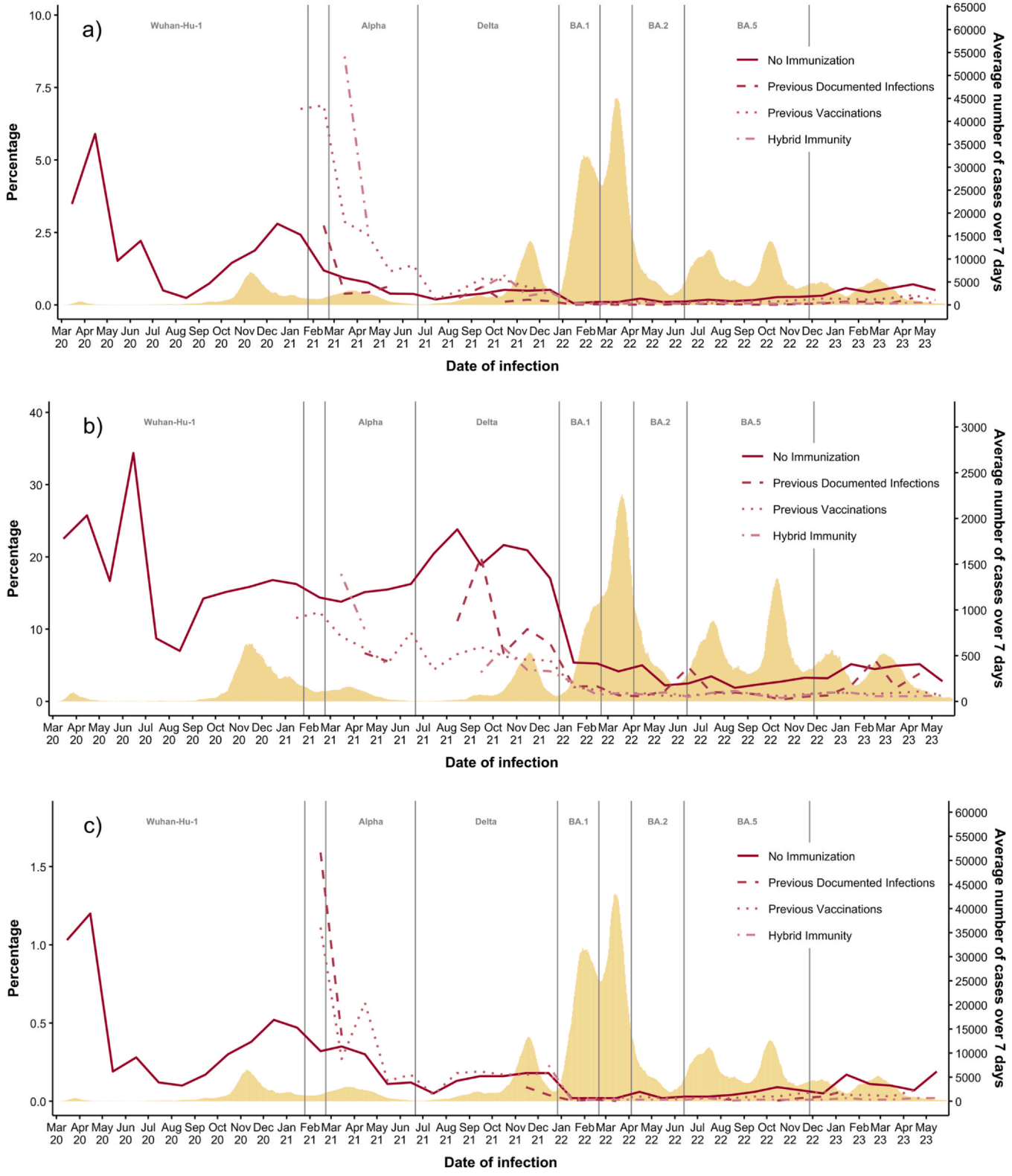

Fig. 2. Monthly COVID-19 case fatality rate (CFR) with confirmed primary SARS-CoV-2 infections, stratified by immunization status and seven-day average numbers of documented SARS-CoV-2 cases. Shown for all age groups (in years) (a), all people 75 and older (b) and all people under 75 (c).

residency, which is likely the strongest predictor of COVID-19 fatality beyond age. Austria's healthcare infrastructure, demographic distribution, and socio-economic factors share similarities with many European and other Western countries, thus supporting its likely applicability to other high-income nations. Though our results have to be interpreted in view of Austria's rapid and intensive pandemic response in terms of e.g., early restrictive measures and mass vaccinations.

Our results are generally in line with previous studies [6,7,19,21,35]. We confirmed previous findings on higher COVID-19 fatality risks for non-immunized, elderly, males and nursing home residents [36,37]. Our calculated CFRs were lower than in most

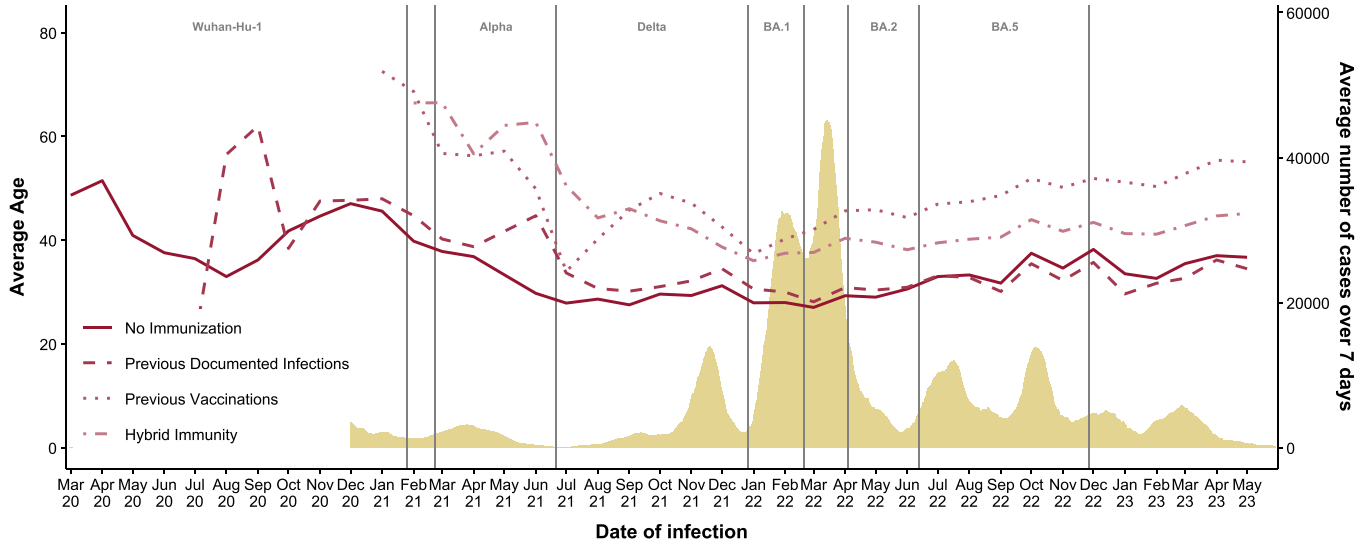

Fig. 3. Average age (in years) of newly infected persons by month, stratified by immunization status and seven-day average numbers of documented SARS-CoV-2 cases.

Table 2
Age and Nursing home residency stratified infections and CFRs.

Age group	Nursing home residency			
	No		Yes	
	documented infections	CFR (95 % CI)	documented infections	CFR (95 % CI)
< 20	1,188,601	0.001 (0.0005–0.002)	0	no deaths
20–39	1,897,735	0.004 (0.003–0.005)	0	no deaths
40–59	1,862,756	0.04 (0.04–0.04)	0	no deaths
60–74	678,866	0.42 (0.41–0.44)	10,034	4.86 (4.46–5.3)
75–84	231,568	2.01 (1.95–2.06)	24,499	6.89 (6.58–7.21)
85 +	65,842	7.01 (6.81–7.2)	38,359	9.37 (9.08–9.66)

Table 3
Variant period CFRs for all subgroups and IFRs in % (30-day COVID-19 mortality).

	Wuhan-Hu-1	Alpha	Delta	BA.1	BA.2	BA.5
Overall CFR	2.05 (2.01–2.09)	0.87 (0.83–0.91)	0.54 (0.52–0.56)	0.08 (0.07–0.08)	0.11 (0.1–0.12)	0.1 (0.1–0.11)
Immunization						
No Immunization	2.05 (2.01–2.09)	0.81 (0.77–0.85)	0.48 (0.46–0.5)	0.08 (0.07–0.09)	0.18 (0.15–0.22)	0.19 (0.16–0.21)
Prior Documented Infection	1.47 (0.16–6.67)	0.56 (0.19–1.32)	0.2 (0.12–0.31)	0.02 (0.01–0.03)	0.005 (0.001–0.02)	0.02 (0.01–0.03)
Prior Vaccination	14.04 (6.87–24.74)	2.16 (1.86–2.49)	0.65 (0.62–0.69)	0.09 (0.08–0.09)	0.11 (0.1–0.12)	0.12 (0.11–0.13)
Hybrid Immunity		3.08 (1.05–7.15)	0.51 (0.28–0.86)	0.04 (0.03–0.07)	0.06 (0.04–0.1)	0.05 (0.04–0.06)
Gender						
Female	1.94 (1.88–2)	0.72 (0.67–0.78)	0.49 (0.47–0.52)	0.08 (0.07–0.09)	0.1 (0.09–0.12)	0.09 (0.08–0.1)
Male	2.17 (2.11–2.24)	1 (0.94–1.07)	0.59 (0.56–0.62)	0.08 (0.07–0.09)	0.13 (0.11–0.14)	0.12 (0.11–0.13)
Age (years)						
< 20	0.002 (0.0002–0.01)	0.01 (0.002–0.02)	0.001 (0.0002–0.004)	no deaths	no deaths	0.003 (0.001–0.01)
20–39	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.01 (0.01–0.02)	0.001 (0.0002–0.002)	0.001 (0.0001–0.004)	0.003 (0.001–0.005)
40–59	0.17 (0.15–0.19)	0.17 (0.14–0.21)	0.12 (0.1–0.13)	0.01 (0.01–0.01)	0.01 (0.01–0.02)	0.01 (0.01–0.02)
60–74	2.55 (2.41–2.69)	2.32 (2.12–2.54)	1.39 (1.3–1.5)	0.2 (0.18–0.24)	0.13 (0.1–0.16)	0.11 (0.09–0.12)
75–84	11.58 (11.18–11.98)	9.45 (8.76–10.18)	6.17 (5.82–6.53)	1.26 (1.12–1.41)	0.69 (0.58–0.8)	0.6 (0.54–0.66)
85 +	23.5 (22.86–24.14)	20.73 (19.22–22.31)	19.12 (18.17–20.09)	4.73 (4.32–5.18)	2.59 (2.25–2.96)	2.41 (2.22–2.61)
Nursing home residency						
Yes	19.81 (19.22–20.4)	11.05 (9.35–12.95)	18.07 (16.69–19.51)	4.62 (4.16–5.12)	2.57 (2.16–3.03)	2.59 (2.31–2.89)
No	1.23 (1.2–1.27)	0.81 (0.77–0.85)	0.46 (0.44–0.47)	0.05 (0.05–0.05)	0.08 (0.07–0.09)	0.08 (0.08–0.09)
Overall IFR	0.61 (0.6–0.63)	0.55 (0.52–0.58)	0.37 (0.35–0.38)	0.06 (0.05–0.06)	0.06 (0.06–0.07)	0.05 (0.04–0.05)
Overall IFR excluding nursing homes*	0.36 (0.35–0.37)	0.51 (0.49–0.54)	0.31 (0.3–0.32)	0.04 (0.03–0.04)	0.05 (0.04–0.05)	0.04 (0.03–0.04)

95 % confidence intervals in brackets
Note that immunization stratified CFRs might be misleading when not accounting for age differences between groups (Table S33).
* calculation excludes deaths of nursing home residents and assumes approximately 1 % of infections were in nursing homes.

previous studies [6,7,35], which is likely due to the inclusion of longer stretches of low-CFR Omicron periods in our investigation, in combination with the extraordinary high rates of testing in Austria. IFR magnitude was comparable to previous nationwide investigations that focused on shorter time periods in France [20], Italy [24], and England [25,26].

While overall, the CFR of non-immunized individuals was significantly higher than that of groups with any kind of immunization, monthly CFRs in early 2021 and early variants seem to indicate higher fatality rates for vaccinated and sometimes hybrid immunity groups. This may be explained by the vaccination policy in Austria, which focused on the oldest citizens first, reflected in the differences in the average age of new infections based on immunization status (Fig. 3). The age stratified analyses indicate that immunization was the leading factor in the decrease in CFRs throughout 2021, as age stratified individuals without immunization yielded no significant decrease before the onset of Omicron (Figure S31, Table S33). Importantly, lower CFRs, among vaccinated compared with unvaccinated may be at least partially explained by healthy vaccinee bias, or better underlying health among the vaccinated, which has previously been documented in Austria [28]. Differences in average age of infected persons may also help explain the CFR decrease of the non-immunized between the Alpha and Delta wave (Table 3), as no such decreases are found in the age stratified CFRs (Figure S31, Table S33).

Estimated undocumented cases, and thus the differences between CFRs and IFRs, were relatively high in early and late parts of the COVID-19 pandemic, as testing was either not as readily available or not as strictly enforced as in the Delta variant and early Omicron subvariants (Fig. 1). The downward trend in IFRs over the course of the COVID-19 pandemic is likely multifactorial. Contributing factors may include natural and vaccine-induced immunity, improved treatment guidelines [5], decreased pathogenicity of dominant variants (e.g. with the onset of Omicron in early 2022), decreasing average age of the infected non-previously immunized people after 2020, and better protection of nursing homes after the initial waves with decreasing proportion of deaths accounted by nursing home residents (Table S35).

In line with the downward trend of COVID-19 fatality, variant CFRs were highest at the start of the pandemic, decreasing with time, reaching its lowest point during BA.1, and slightly increasing again in the following BA.2 and BA.5 periods, though these increases seem to be due to decreases in SARS-CoV-2 detection rates, and were thus not found in the IFRs (Table 3). Importantly, across all variant time periods individuals without immunization had a lower average infection age than vaccinated and hybrid immunized individuals (Fig. 3 and S2). This may partially explain why some variant period CFRs of the non-immunization group are lower than the respective CFRs of the vaccination group (Table 3 and S1). Our results in the pre-Omicron period additionally suggest a seasonal trend in IFRs with peaks in winter. This is potentially explained by a rise in incidental COVID-19 deaths during winter months and by beneficial effects of summer months related to solar radiation or higher ambient temperature [38,39].

Potential seasonality in CFR and IFR may reflect different age distributions and vulnerability in patients infected in summer versus winter months, less pressure on health systems and thus better outcomes during the summer months or/and also genuine lower fatality potential of SARS-CoV-2 variants circulating during the summer months.

Limitations

One significant limitation of calculating CFR from observational data is the potential for reporting bias and inconsistencies in data collection. Misattributed COVID-19 deaths and variations in testing capacity and criteria over time can lead to fluctuations in the number of reported cases and deaths, impacting the accuracy of both CFR and IFR calculations. In particular, underreporting of asymptomatic and mild cases, which are less likely to be tested, can result in an overestimation of the CFR and thus COVID-19 disease severity. On the other hand, non-immunized CFR may be underestimated because many individuals in this group had previously undetected infections. Thus, we consider it as a main strength of our work that we used the national data of Austria, the continental country with the highest SARS-CoV-2 testing rate to calculate CFRs [27]. Additionally, we also investigated the IFR by estimating undocumented infections with a model that accounts for the variability in testing rate and yielded similar results as a wastewater monitoring based model [16]. While the rate of testing was high, another limitation is that age stratified testing data is currently not available.

CFRs presented for certain time periods (e.g. monthly CFRs) are prone to potential bias by edges of time windows related to accurate recording of infections and COVID-19 deaths and their case definitions. As we had access to individual participant data of the date of SARS-CoV-2 infection and the date of COVID-19 deaths we used the straightforward cohort method to calculate CFRs rather than some other more sophisticated approaches [26].

We did not account for confidence intervals in the POS models reported by Rauch and colleagues [16], as the intervals were very small which would add complexity with miniscule impact on outcomes.

The IFR interpretation is additionally limited by its inability to provide estimates before May 2020, the period in which we would suspect the biggest percentage of undocumented cases [40,41]. This is due to the lack of testing data prior to April 2020 and additional data averaging for estimation and backcasting of undocumented active infections used to estimate new daily infections (see Supplements). Model estimates may still be more unreliable in 2020 and 2023, when testing was not as comprehensive as in 2021–2022.

Conclusion

This investigation shows a comprehensive overview on the COVID-19 mortality related disease burden and its risk factors throughout the whole pandemic in Austria, thus providing a basis to further model the impact of time-varying COVID-19 related health policies including vaccinations and restrictions. It may also be used for future cost-effectiveness analyses of these interventions in order to learn from this past experience for future pandemics.

List of abbreviation

AGES Austrian agency for health and food safety
CFR Case fatality rate
CI Confidence interval
COVID-19 Coronavirus disease 2019
EMS Austrian epidemiological reporting system
HR Hazard ratio
IFR Infection fatality rate
POS Test positivity model
SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2
STROBE Strengthening the reporting of observational studies in epidemiology
WHO World health organization

Funding

This work is funded by the Austrian Science Fund (FWF) KLI 1188.

Data availability

The data that support the findings of this study are available upon request with approval needed from the Austrian Agency for Health and Food Safety (AGES), Vienna, Austria. The data are not publicly available due to restrictions pertaining to contained information that could compromise the privacy of patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors thank all persons and organizations involved in data collection.

Contributors

UR and SP conceptualized the study with contributions on the analytical plan by JPAI and TBH. UR wrote the original draft of the manuscript and performed the formal analyses with contributions of WR. AC and LR were involved in data curation. All authors contributed to supervision, writing, reviewing, and editing the manuscript, and approved the final version before submission.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jiph.2025.102698.

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