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Estimation of SARS-CoV-2 Infection Fatality Rate by Age and Comorbidity Status Using Antibody Screening of Blood Donors During the COVID-19 Epidemic in Denmark

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Background. Studies presenting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection fatality rate (IFR) for healthy individuals are warranted. We estimate IFR by age and comorbidity status using data from a large serosurvey among Danish blood donors and nationwide data on coronavirus disease 2019 (COVID-19) mortality.

Methods. Danish blood donors aged 17–69 years donating blood October 2020–February 2021 were tested with a commercial SARS-CoV-2 total antibody assay. IFR was estimated for weeks 11 to 42, 2020 and week 43, 2020 to week 6, 2021, representing the first 2 waves of COVID-19 epidemic in Denmark.

Results. In total, 84 944 blood donors were tested for antibodies. The seroprevalence was 2% in October 2020 and 7% in February 2021. Among 3 898 039 Danish residents aged 17–69 years, 249 deaths were recorded. The IFR was low for people < 51 years without comorbidity during the 2 waves (combined IFR = 3.36 per 100 000 infections). The IFR was below 3‰ for people aged 61–69 years without comorbidity. IFR increased with age and comorbidity but declined from the first to second wave.

Conclusions. In this nationwide study, the IFR was very low among people < 51 years without comorbidity.

Keywords. SARS-CoV-2; seroprevalence; infection fatality rate; blood donors.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected countries worldwide since the beginning of 2020 [1]. Throughout the pandemic, SARS-CoV-2 serosurveys have been carried out in several populations [2–6] and still constitute an important tool to monitor the pandemic and to provide information on the number of SARS-CoV-2 vaccinated individuals [7]. Hence, many of the published serosurveys are now visualized on the regularly updated SeroTracker Dashboard, illustrating wide variation in seroprevalences between countries [8, 9].

From a public health perspective, seroprevalence surveys are useful because they may provide reliable estimates of the accumulated number of SARS-CoV-2 infected in the underlying population. Estimates of seroprevalence can be used to estimate the infection fatality rate (IFR) when combined with population mortality. The IFR is essential in coronavirus disease 2019 (COVID-19) surveillance and risk assessment as it takes into account also mild and asymptomatic infections. Like seroprevalence, reported IFRs have varied widely between countries [10, 11]. Extensive research has demonstrated a higher IFR with increasing age [12–14] and comorbidity [15].

Not many studies have presented IFR for otherwise healthy people. Additionally, timely age-stratified IFRs are important, as the IFR can vary over time reflecting changes in age distributions of infections during an epidemic [16]. In spring 2020, we estimated an IFR of 89 per 100 000 infections for people aged 17 to 69 years in Denmark using results of a quick-test serosurvey among Danish blood donors [17]. We repeated this study design and now present SARS-CoV-2 seroprevalence among Danish blood donors during 2 time periods corresponding to

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the first 2 waves of the epidemic in Denmark. We used these data to estimate the ratio of confirmed SARS-CoV-2 cases to estimated number of SARS-CoV-2 seropositives and the IFR. Uniquely, we moreover stratify IFR by age, comorbidity, and by IFR estimated with both 30- and 60-day mortality rates.

METHODS

The COVID-19 Epidemic in Denmark

Briefly, the first known case of COVID-19 in Denmark was diagnosed on 27 February 2020 [18], after which the first wave took place during March and April 2020. The daily number of patients admitted to hospital due to COVID-19 peaked at approximately 550 during this period. A range of preventive measures were introduced by 9 March 2020 against further spread of COVID-19, which successfully decreased transmission rates. These preventive measures were gradually lifted around summertime, but were gradually reintroduced during autumn and winter, when the incidence of new infections started to increase stepwise from November 2020, peaking in December. The highest daily number of admitted cases was approximately 980 [19]. As of 25 July 2021, 311 520 confirmed cases of COVID-19 have been registered in addition to 15 960 admissions and 2542 deaths with COVID-19 [20].

Different test strategies have been used for testing the Danish population for SARS-CoV-2 during the epidemic. The per capita rate of testing for SARS-CoV-2 in Denmark is among the highest in the world [21].

Data Overview

Four data sources were used to perform this study: (1) seroprevalence among blood donors for each of the 5 administrative regions in Denmark; data were available from week 41 (5 October 2020) to week 8 (28 February 2021); (2) SARS-CoV-2 RNA-positive cases measured by real-time polymerase chain reaction (RT-PCR) in oropharyngeal swabs from Danish residents; data were obtained from the Danish Microbiological Database [22] and available from week 9, 2020 to week 10, 2021; (3) population of Danish residents by region with associated comorbidity status. The population numbers were based on the part of the population in Denmark that have been invited for a SARS-CoV-2 vaccination corresponding to the Danish population [23]; data were extracted from the Danish Civil Registration System [24] and calculated on 23 April 2021; and (4) the number of deceased individuals with COVID-19 among Danish residents with associated comorbidity status. The date of death was obtained from the National Cause of Death Register [25], and data were available from weeks 11 to 42, 2020 and week 11, 2020 to week 6, 2021.

Information on comorbidity was obtained from the Danish National Patient Register [26] and is defined below. The Danish Civil Registration System was used as a link between registers and provided information on region of residence. Besides blood donor data, all other data were aggregated data obtained from Statens Serum Institut [27]. Each data set was restricted to people aged 17 to 69 years.

Serological Testing of Blood Donors

Since the local COVID-19 outbreak in March 2020, blood donors have been used in monitoring the Danish epidemic. Annually, approximately 270 000 blood donations are made by 17 to 69-year-old donors. All governmental blood donation facilities in Denmark participated in this survey. In spring 2020, we conducted a serosurvey by SARS-CoV-2 antibody screening of Danish blood donors using a SARS-CoV-2 lateral flow test. The antibody screening took place from 6 April to 3 May 2020 [17]. In autumn 2020, just before the second wave, routine antibody screening was resumed. From 5 October 2020 to 28 February 2021, a total of 121 110 blood samples were collected from 84 944 donors. Experienced staff in the 5 regional establishments tested undiluted EDTA plasma for total antibodies to the SARS-CoV-2 receptor-binding domain using a commercial SARS-CoV-2 total antibody enzyme-linked immunosorbent assay (ELISA, Wantai Biological Pharmacy Enterprise, Co, Ltd) according to the manufacturer's instructions. The method has previously been described in detail [28]. The assay has a sensitivity of 96.7% and a specificity of 99.5%; it had the highest sensitivity among 16 validated SARS-CoV-2 immunoassays in a Danish national validation study. No cross-reactivity was observed. The sensitivity of the assay was validated using 150 samples from SARS-CoV-2 RNA-positive cases measured by RT-PCR. The cases were mainly not hospitalized (79.1%) [29]. Additionally, the sensitivity was verified in a study including healthcare and administrative employees in Central Denmark Region: 98% of the participants previously tested positive by RT-PCR had a positive test for SARS-CoV-2 antibodies using this assay. Only actively working staff were included and thus previous severe infection was improbable, as in the current study [28].

Comorbidity

Comorbidities were classified by using specified diagnostic codes in the Danish National Patient Register [26]. Diagnostic information was based on the International Classification of Diseases, Tenth Revision (ICD-10) [30]. Comorbidity was defined as having a hospital contact due to any of 25 groups of diseases including diabetes, cancer, chronic lung disease, cardiovascular disease, and hematological disease. The definition of comorbidity was similar to the definition used in the Danish surveillance system of COVID-19 [27]. The specific diagnostic codes are available in the Supplementary Material.

For population numbers, comorbidity was defined as a hospital contact within 5 years before the date of the first SARS-CoV-2 vaccination and, if not vaccinated, before 27 December 2020. For deceased individuals with COVID-19, comorbidity

was defined as a hospital contact within 5 years before the date of either the first negative RT-PCR test or the first positive RT-PCR test. Age was calculated on the date of RT-PCR testing.

Statistics

The ratio of confirmed cases to estimated number of seropositives was estimated during 2 time periods: weeks 9 to 40, 2020 and week 41, 2020 to week 4, 2021 representing the seroprevalence after the first and second epidemic wave, respectively. Similarly, IFR was estimated during weeks 11 to 42, 2020 and week 43, 2020 to week 6, 2021, representing the first and second epidemic wave, respectively. Aggregated numbers of deceased individuals with COVID-19 were available only for these 2 time periods, explaining the discrepancy between the periods for the ratio of estimated number of seropositives to confirmed cases and the IFR.

Overall, the estimated number of seropositives was estimated by multiplying the donor seroprevalence with the population of Danish residents. To estimate the number of seropositives during the 2 time periods, the blood donor seroprevalence and the number of seropositives for each region in Denmark for each age strata (17–35, 36–50, 51–60, and 61–69 years) were estimated at two 4-week intervals: weeks 41 to 44, 2020 and weeks 5 to 8, 2021. We used the first blood sample during the 2 time intervals when estimating the seroprevalence. Convalescent plasma donors and donations, and SARS-CoV-2 vaccinated donors were not included.

The increase in seroprevalence after the second wave was estimated as the difference in adjusted seroprevalence between the first and second wave periods. By assuming a blood donor seroprevalence of zero in week 9, 2020, we were able to estimate the ratio of confirmed cases to estimated number of seropositives and the IFR during the first wave even though antibody measurements among the blood donors were available from week 41, 2020.

Donors are required a 4-week deferral period when tested positive for SARS-CoV-2. Thus, the estimated number of seropositives in weeks 41 to 44, 2020 represents the estimated number of seropositives through week 40, 2020. Similarly, the estimated number of seropositives in weeks 5 to 8, 2021 represents the estimated number of seropositives through week 4, 2021.

Exact number of seropositive donors in region and age strata were used to estimate the number of seropositives. However, due to low numbers in specific strata, only total numbers and seroprevalences are presented.

The ratio of confirmed cases to estimated number of seropositives was derived by dividing the number of RT-PCR positives by estimated number of seropositives. To allow for an extra 2-week lag time between detectable virus and antibody development [31], the numbers of cumulated RT-PCR positives were calculated 2 weeks prior to the median date for the 2 time intervals (weeks 41 to 44, 2020 and weeks 5 to 8, 2021).

The IFR was estimated by dividing the number of deceased individuals with COVID-19 by the estimated number of seropositives. IFR was stratified by age, comorbidity status, and by IFR estimated with both 30- and 60-day mortality rates. Subanalyses with further stratification for biological sex in older age strata were performed.

The Rogan Gladen estimate was used to calculate the true prevalence by adjusting for assay sensitivity and specificity. Confidence intervals (CIs) were derived by 10^6-sample percentile bootstrapping independently sampling sensitivity, specificity, and apparent prevalence using posterior binomial distributions.

χ^2 tests were used to compare categorical variables. A 10^6-fold Monte Carlo simulation test was used to compare ratios of confirmed cases to estimated number of seropositives and IFRs. Only comparisons for strata with sufficient statistical power were done. Results are reported numbers and percentages with 95% CIs. A *P* value below .05 was considered statistically significant. Adjusted IFRs per 100 000 infections using 30-day mortality rate are presented unless otherwise specified. Statistical analyses were performed in R version 4.0.0 (R Foundation for Statistical Computing).

Ethics

SARS-CoV-2 antibody testing was performed as a routine screening of all blood donations. Only consenting donors were tested and informed about their result. The Regional Scientific Ethical Committees for the Zealand Region of Denmark approved the investigation as a register project (SJ-740), and the study was approved by the Danish Data Protection Agency (P-2019-99).

Furthermore, we used administrative register data. According to Danish law, ethics approval is exempt for such research. The Danish Data Protection Agency, which is a dedicated ethics and legal oversight body, thus waives ethical approval for the use of administrative register data when no individual contact of participants is necessary and only aggregate results are included as findings. The study is therefore fully compliant with all legal and ethical requirements. All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

RESULTS

From week 41 to week 44, 2020, a total of 23 934 blood samples were tested for SARS-CoV-2 antibodies and 2% were seropositive. When using the first blood sample for each donor during this period, 22 690 donors were included. The corresponding numbers for weeks 5 to 8, 2021 were 21 656 samples and 20 398 blood donors with 7% seropositive.

The number of SARS-CoV-2 RT-PCR–positive cases in Denmark and the seroprevalence among the Danish blood donors between week 41, 2020 and week 8, 2021 are illustrated

in Figure 1. An increase in the number of RT-PCR–positive cases followed by a corresponding increase in donor seroprevalence with 4 to 5 weeks' delay was observed.

Table 1 shows the regional stratification of the serological status and seroprevalence among blood donors for weeks 41 to 44, 2020 and weeks 5 to 8, 2021. Table 2 shows the same data stratified according to age. The highest seroprevalence was observed in the Capital Region and among blood donors aged 17 to 35 years in weeks 5 to 8, 2021 ($P \leq .001$ for effect of both region and age).

The population numbers of Danish residents are presented in Supplementary Table 1. The estimated number of seropositives for week 9 to 40, 2020 and week 9, 2020 to week 4, 2021 is presented in Supplementary Table 2. The ratios of confirmed cases to estimated number of seropositives for both waves are presented in Table 3. The adjusted ratio was lower

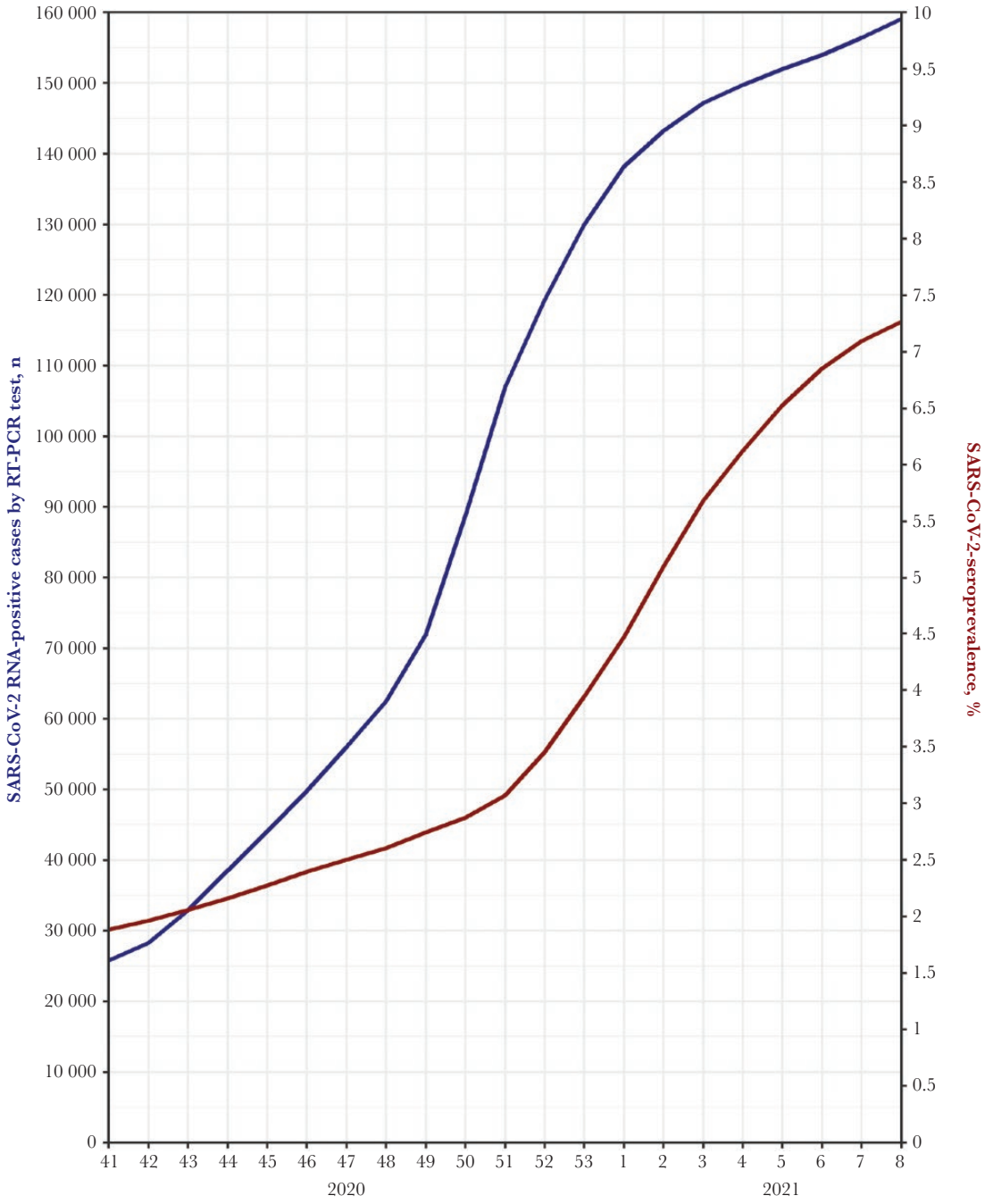

Figure 1. Cumulative number of SARS-CoV-2 RT-PCR–positive cases in the Danish population and SARS-CoV-2 seroprevalence among Danish blood donors by calendar period, week 41, 2020 to week 8, 2021. Data were restricted to people aged 17 to 69 years. Cumulative numbers and percentages are presented. Abbreviations: RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 1. Serological Status and Seroprevalence Among Danish Blood Donors by Region in Denmark

Serological Status and Seroprevalence	Weeks 41 to 44, 2020	Weeks 5 to 8, 2021
SARS-CoV-2 serological status		
Seronegative, n (%)		
Capital	6419 (29)	5395 (29)
Central Denmark	5255 (24)	4919 (26)
North Denmark	2361 (11)	1991 (11)
South Denmark	4905 (22)	3825 (20)
Zealand	3191 (14)	2759 (15)
Total	22 131 (100)	18 889 (100)
Seropositive, n (%)		
Capital	288 (52)	706 (47)
Central Denmark	99 (18)	317 (21)
North Denmark	29 (5)	118 (8)
South Denmark	89 (16)	161 (11)
Zealand	54 (10)	207 (14)
Total	559 (100)	1509 (100)
Donor seroprevalence		
Unadjusted seroprevalence, %		
Capital	4.29	11.6
Central Denmark	1.85	6.05
North Denmark	1.21	5.60
South Denmark	1.78	4.04
Zealand	1.66	6.98
Total	2.46	7.40
Adjusted seroprevalence, % (95% CI)[a]		
Capital	3.98 (2.99–4.61)	11.6 (10.4–12.6)
Central Denmark	1.44 (.48–1.95)	5.81 (4.75–6.60)
North Denmark	0.78 (.00–1.38)	5.34 (4.06–6.47)
South Denmark	1.37 (.41–1.88)	3.72 (2.66–4.46)
Zealand	1.25 (.27–1.83)	6.77 (5.54–7.85)
Total	2.08 (1.17–2.47)	7.21 (6.30–7.78)

Serological status and seroprevalence among Danish blood donors stratified by region for weeks 41 to 44, 2020 and weeks 5 to 8, 2021. The exact numbers stratified by region and age were used in the estimation of the number of SARS-CoV-2 seropositives. However, due to the low number of seropositives in specific age strata for some regions, only total numbers and seroprevalences per region are presented.

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Seroprevalence adjusted for assay sensitivity and specificity.

during the first wave compared to the second wave (0.29 vs 0.64, $P = .007$).

The adjusted IFRs for both waves are presented in Figure 2 stratified by comorbidity and age. Both unadjusted and adjusted rates are furthermore presented in Supplementary Table 3. The IFR was very low among people younger than 51 years without comorbidity during the 2 waves (combined IFR = 3.36 per 100 000 infections). The IFR increased with age (281 per 100 000 for people aged 61 to 69 years without comorbidity; $P \leq .01$ for effect of age). The IFR was higher for people with comorbidities than for people without comorbidities for ages 51 and older during the 2 waves ($P < .001$). When comparing the 2 waves, IFRs were lower during the second wave compared to the first wave for people aged 51 to 69 years without comorbidity ($P = .04$). In subanalyses estimating IFRs for women and men in older age strata without comorbidity, the IFR for men was 3.8-fold and 2.9-fold higher than for women aged 61 to 69 years during the first and second wave, respectively ($P \leq .01$ for effect of sex in both waves; Supplementary Table 4).

DISCUSSION

This is the first nationwide study to assess the COVID-19 IFR among citizens without comorbidity. We used the seroprevalence among Danish blood donors to assess the ratio of confirmed cases to estimated number of seropositives and the IFR during the first 2 waves of the epidemic in Denmark. The seroprevalence differed between regions and was higher in younger age strata, similar to findings in a large serosurvey among blood donors in the United States [32].

According to Worldometer, only 2 other countries have a higher test rate per capita than Denmark [21]. However, we found a ratio of confirmed cases to estimated number of seropositives of 0.29 and 0.64 during the first the second wave, respectively. This corresponds to an estimated 71% undiagnosed

Table 2. Serological Status and Seroprevalence Among Danish Blood Donors by Age

Serological Status and Seroprevalence	Weeks 41 to 44, 2020	Weeks 5 to 8, 2021
SARS-CoV-2 serological status		
Seronegative, age, y, n (%)		
17–35	8217 (37)	7066 (37)
36–50	6971 (31)	5846 (31)
51–60	4651 (21)	3994 (21)
61–69	2292 (10)	1983 (10)
Total	22 131 (100)	18 889 (100)
Seropositive, age, y, n (%)		
17–35	255 (46)	735 (49)
36–50	161 (29)	422 (28)
51–60	111 (20)	257 (17)
61–69	32 (6)	95 (6)
Total	559 (100)	1509 (100)
Donor seroprevalence		
Unadjusted seroprevalence, age, y, %		
17–35	3.01	9.42
36–50	2.26	6.73
51–60	2.33	6.05
61–69	1.38	4.57
Total	2.46	7.40
Adjusted seroprevalence, age, y, % (95% CI)[a]		
17–35	2.65 (1.70–3.16)	9.31 (8.27–10.15)
36–50	1.87 (.91–2.36)	6.52 (5.47–7.29)
51–60	1.94 (.96–2.51)	5.80 (4.70–6.66)
61–69	0.95 (.00–1.58)	4.27 (3.05–5.32)
Total	2.08 (1.16–2.47)	7.21 (6.30–7.78)

Serological status and seroprevalence among Danish blood donors stratified by age for week 41 to 44, 2020 and week 5 to 8, 2021. The exact numbers stratified by region and age were used in the estimation of the number of SARS-CoV-2 seropositives. However, due to low numbers of seropositives in specific age strata for some regions, only total numbers and seroprevalences per age strata are presented.

Abbreviations: CI, confidence interval; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Seroprevalence adjusted for assay sensitivity and specificity.

Table 3. The Ratio of Confirmed SARS-CoV-2 Cases to Estimated Number of SARS-CoV-2 Seropositives

Measure of SARS-CoV-2 Case Numbers	Value
Estimated number of seropositives weeks 9 to 40, 2020	
Unadjusted, n	97 172
Adjusted, n (95% CI)[a]	82 523 (50 377–100 413)
Estimated number of seropositives week 41, 2020 to week 4, 2021	
Unadjusted, n	189 780
Adjusted, n (95% CI)[a]	197 048 (183 514–215 328)
Confirmed cases by RT-PCR, n	
Weeks 9 to 40, 2020	23 691
Week 41, 2020 to week 4, 2021	126 023
Ratio of confirmed cases to estimated number of seropositives, weeks 9 to 40, 2020	
Unadjusted	0.24 (.22–.26)
Adjusted (95% CI)[a]	0.29 (.24–.47)
Ratio of confirmed cases to estimated number of seropositives, week 41, 2020 to week 4, 2021	
Unadjusted	0.66 (.61–.73)
Adjusted (95% CI)[a]	0.64 (.59–.69)

The ratio of confirmed cases to estimated number of seropositives, weeks 9 to 40, 2020 and week 41, 2020 to week 4, 2021. The number of estimated seropositives and RT-PCR–positive cases used in the estimation were additionally specified.

Abbreviations: CI, confidence interval; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Seroprevalence adjusted for assay sensitivity and specificity.

cases during the first wave, while only 36% were undiagnosed during the second wave.

Our findings showed that IFR was very low among people younger than 51 years without comorbidity but increased with age and having comorbidities. However, IFR was below 3‰ for people aged 61 to 69 years without comorbidity. People older than 50 years without comorbidity had a lower IFR during the second wave compared to the first wave. In subanalyses estimating IFRs for women and men in older age strata without comorbidity, we observed an up to 3.8-fold higher IFR for men compared to women. The changing test strategy and the lower test capacity during the first wave, may explain the higher number of undiagnosed cases. We speculate, that the lower IFR during the second wave was a result of better treatment and better protection of the particularly vulnerable.

As mentioned above, we found a seroprevalence of 1.9% (95% CI, .8%–2.3%) among 20 640 Danish blood donors in April 2020. At that time, the ratio of confirmed cases to estimated number of seropositives was 0.06 (95% CI, .05–.09) and the IFR for people aged 17 to 69 years was 89 (95% CI, 72–211) per 100 000 infections using a quick test [17]. In June 2020, we found an IFR of 5400 (95% CI, 2700–6400) per 100 000 infections among elderly Danes older than 69 years, based on a SARS-CoV-2 seroprevalence among 1201 elderly retired blood donors using the same assay as in this study [33].

Our findings support another recent study based on Danish SARS-CoV-2 antibody test results from TestCenter Denmark, a public national test facility system [34]. The study, based on 34 081 participants, reported a ratio of confirmed cases to estimated number of seropositives of 0.38 in December 2020. The IFR was zero among people aged 18 to 39 years, 80 per 100 000 infections among people aged 40 to 64, and 3800 per 100 000 infections among people aged 65 years or older. No comorbidity-specific IFR was estimated in the study. Furthermore, the participation rate was low compared to our study. Similarly, Sweden reported an IFR of 0.09% for people aged 0–69 years in spring 2020 [35].

To our knowledge, no other studies have reported comorbidity-specific IFRs. While we conclude that the IFR is higher among people with comorbidity, we expect their true IFR to be higher. Thus, a recent study showed seroprevalence of SARS-CoV-2 antibodies among blood donors to be several-fold higher (1.9%) than among patients with chronic rheumatic

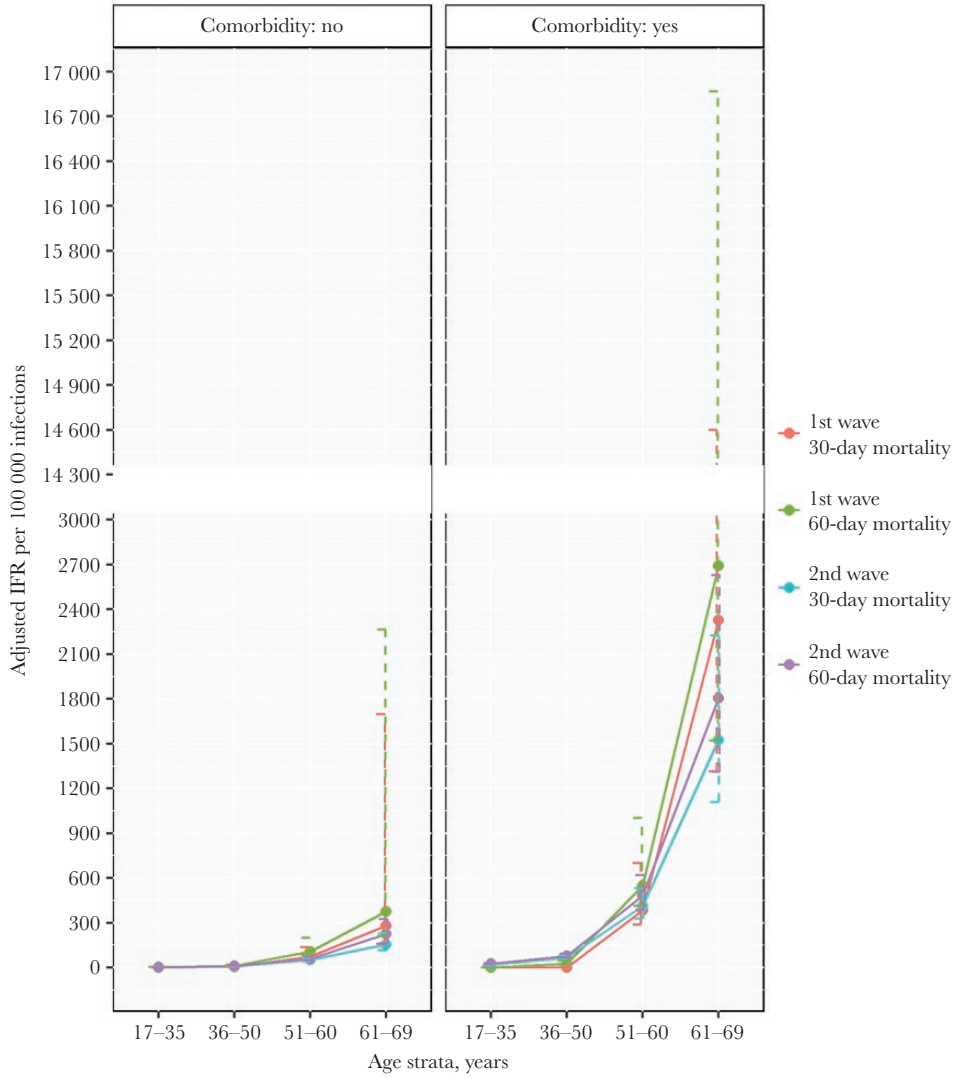

Figure 2. Adjusted infection fatality rate (IFR) for weeks 11 to 42, 2020 representing the first wave and week 43, 2020 to week 6, 2021 representing the second wave of the epidemic in Denmark. The IFR was stratified by comorbidity status, age, and by using 30- and 60-day mortality rates. Dots with error bars represent numbers per 100 000 infections with 95% confidence intervals. The seroprevalence used in this estimation was adjusted for assay sensitivity and specificity.

diseases (0.3%). Thus, we speculate that the risk of infection was lower among people with preexisting disease [36]. Plausible mechanisms to explain this include increased compliance regarding social distancing and self-isolating after exposure to close encounters of COVID-19 cases. Under our hypothesis, we would overestimate the prevalence of SARS-CoV-2 in comorbid individuals and consequently underestimate the IFR for people with comorbidity, leaving us with some uncertainty when interpreting IFRs for this subgroup.

Although we used absolute nationwide numbers of COVID-19 mortality in our calculation, a very low number of deceased individuals were observed in all age strata, endowing our estimates with statistical imprecision. The number of deceased individuals with COVID-19 was low compared to other countries [21].

We estimated the IFR using both 30- and 60-day mortality. To our knowledge no other studies have addressed IFRs using 60-day mortality. It is increasingly common to use 60-day mortality rates to avoid exclusion of COVID-19–related deaths [37, 38]. On the other hand, an overestimation of the IFR is possible when using 60-day mortality rate.

This study has strengths and limitations. Serosurveys are useful to estimate the cumulative number of previously infected individuals in the general population taking into account also undiagnosed cases. The blood bank infrastructure has been used for serosurveillance in several countries [17, 32, 33, 39]. It is a strength that blood donors comprise a large subset of the Danish population, that is blood donors comprise approximately 4.7% of Danish residents aged 17 to 69 years [40]. Geographical coverage is good with blood donations taking place in most areas of the country. Additionally, the blood donor population is stable over time with nearly all donors consenting to antibody testing. This contrasts with studies in the general population where the

participation rate is much lower and varies over time [34]. Our data showed a 4 to 5-week delay in the increase in donor seroprevalence compared to RT-PCR–positive cases (Figure 1).

Conversely, it is a limitation that blood donors are healthier than the background population and must fulfill strict criteria to donate. All-cause mortality among blood donors is lower than in the background population [41]. However, in the current study we assume this allows us to achieve an accurate seroprevalence and thereby IFR among people without comorbidity. As described above, we might, however, have overestimated the seroprevalence and thus underestimated the IFR among citizens with comorbidity.

In this study, we used nationwide Danish health registers. The registers retain high-quality and routinely collected data, assuring adequate completeness. The effect measurements in this study are thus objectively measured and as precise as possible; for example, comorbidities were based on diagnostic codes recorded in The Danish National Patient Register. This register has been validated as a tool for epidemiological research [42]. However, it is a limitation that comorbidities not requiring hospital-based treatment, for example, obesity, are not included in this study. Furthermore, the low numbers of deceased individuals did not allow us to explore the influence of specific comorbidities.

In this study, IFR was impacted by age and comorbidity. Several other factors, for example, genetic differences, immunity from exposure to other coronaviruses, and socioeconomic status, may also impact IFR and were not considered here [43]. Thus, IFR may vary substantially across locations and populations.

CONCLUSION

This is the first large nationwide study to assess the COVID-19 IFR among citizens without comorbidity. We used the seroprevalence among Danish blood donors to estimate the ratio of confirmed SARS-CoV-2 cases to estimated number of SARS-CoV-2 seropositives and IFR during the 2 first waves of the COVID-19 epidemic in Denmark. Denmark now has one of the world's highest per capita SARS-CoV-2 viral RNA test rates and the percentage of undiagnosed cases decreased from 71% during the first wave to 36% during the second wave. For people aged 17 to 50 years without comorbidities, the combined IFR for the 2 waves was 3.36 per 100 000 infections. The IFR increased with age and having comorbidities. Among people older than 50 years without comorbidity, the IFR decreased from the first to the second wave, and the IFR was higher for men than for women. Blood donor serosurveys are useful for risk assessment of epidemics, making further studies using this population advantageous.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Author contributions. K. A. K. and C. E. drafted the manuscript. K. A. K., L. H., J. K. B., L. V., A. S. N. B., I. R. M. H., and C. E. designed the study. L. H. and J. K. B. performed the statistical analyses. K. A. K. , L. H., J. K. B., L. V., A. S. N. B., I. R. M. H., H. H., T. G. K., H. H., H. U., O. B. V., S. R. O., and C. E. interpreted the data. S. M., D. K. H., A. C. N., S. G. S., E. S., L. H. H., B. A., S. T. L., C. S. J., H. U., O. B. V. P., S. R. O., and C. E. planned and analyzed laboratory analyses. All authors were involved in critically revising the manuscript and approved the final version before submission.

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