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# Epidemiological trends in Covid-19 pandemic: critical appraisal of observations from six countries



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# Epidemiological trends in Covid-19 pandemic: critical appraisal of observations from six countries

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## ABSTRACT

**Introduction:** Europe was the epicentre of the Coronavirus disease 2019 (Covid-19) pandemic in March 2020, with the highest number of cases and deaths between March and April. In May, the infection numbers registered a fall followed by a second new rise, not proportionally reflected by an increase in the number of deaths. We aimed to investigate the relationship between disease prevalence and outcomes over time, to develop a predictive model, as well as appraising the potential contributing factors underpinning this complex relationship.

**Methods:** A prospective epidemiological study using data from six countries collected between 10th March and 4th September. Data on the number of daily hospital and intensive care unit (ICU) admissions with Covid-19 were gathered, and the infection fatality rate and the prevalence were calculated. Trends over time were analysed. A linear regression model was used to determine the association between the fatality rates and the number of admissions.

**Findings:** The prediction model confirmed the linear association between the fatality rates and the numbers of ICU and hospital admissions. The exception was during the peak of the Covid-19 pandemic when the model underestimated the fatalities indicating that a substantial number of deaths occurred outside of the hospitals. The fatality rates decreased in all countries from May until September regardless of the trends in prevalence, differences in healthcare systems or strategic variations in handling the pandemic.

**Interpretation:** The observed gradual reduction in Covid-19 fatality rates over time despite varying disease prevalence and public health measures across multiple countries warrants search for a biological explanation. Whilst our understanding of this novel virus grows, hospital and ICU admission rates remain effective predictors of patient outcomes which can be used as early warning signs for escalation of public health measures.


## ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Comprehensive data on mortality, hospital and ICU admissions were gathered from 6 countries from March to September 2020 on a daily basis
- Our data were verified from multiple sources for each country to ensure accuracy and consistency
- The analysis was adjusted for the number of Covid-19 tests performed to remove the confounding influence of variations in test numbers over time and between countries
- Different countries use different testing technology which may have different diagnostic accuracy
- There were variations in reporting between countries especially when multiple tests were done on the same individual

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan (Hubei province, China) on 31 December 2019 and has emerged as a new zoonotic infectious disease, leading the World Health Organization (WHO) to declare, in early March, a global health emergency.(1) The SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavisurs-2), which is similar to other previously described coronaviruses, i.e. SARS-CoV-1 (Severe Acute Respiratory Syndrome Coronavisurs-1) and MERS-CoV (Middle East Respiratory Syndrome coronavirus), was identified as the pathogenic agent of COVID-19.(1) Initial studies have shown the SARS-CoV-2 to have higher transmissibility, but lower pathogenicity than that of SARS-CoV-1 and MERS-CoV .(1,2) About 81% of the COVID-19 symptomatic patients develop mild symptoms, such as headache, dry cough and fatigue. However, more severe cases can develop respiratory distress, sepsis, severe neurologic symptoms and multi-organ failure.(2) On 13$^{th}$ of March 2020, the WHO declared Europe the epicentre of the pandemic with more reported cases and deaths than the rest of the world combined, apart from the People's Republic of China. In Europe, a record number of new cases and deaths caused by Covid-19 occurred between March and beginning of April. This urged most of the European countries to adopt national lockdown measures in March, with the highest stringency levels worldwide.(1) The number of new cases and deaths consequently registered a fall, although by the end of May the distribution of new cases began to rise again. However, the trend in deaths continued downwards, indicating that the increase in cases was not leading to proportional increased mortality.(2)

To better understand these divergent trends, we analysed the data from five of the most severely affected European countries (Spain, Italy, France, Germany and the United Kingdom). Additionally, we studied data from the USA given the impact of Covid-19 on this country and its significantly different healthcare system from those in Europe. Using the data available, we estimated and compared the distribution of the infection fatality rates (IFR) over time and the prevalence for each country. We included in our study the numbers of intensive care unit (ICU) and hospital admissions and developed a predictive model for outcomes using these two parameters. We also discussed the potential explanations for the observed trends.

## METHODS

### Search strategy

Data on Covid-19 for each country were acquired from the Statistics and Research Coronavirus Pandemic section on *Our World in Data* website (www.ourworldindata.org) as the first step. All data were then further verified with the official publicly available sources: for Spain, from the Spanish Ministry of Health daily reports (www.mscbs.gob.es), and the Science and Innovation Institute Carlos III (www.iscii.es), which made available datasets for public use about the number of tests and both hospital and ICU admission numbers; for Italy, from the Italian Ministry of Health (www.salute.gov.it), with detailed datasets published by the Presidency of the Council of Ministers - Department of Civil Protection (www.dati-covid.italia.it); for Germany, from data published in the daily epidemiological bulletin from the Robert Koch Institute (www.RKI.de); for France, from datasets accessed from the French Public Health website (www.satepublique.fr); for UK, from datasets from the official governmental website (www.gov.uk); for USA, from the Centre of Disease Control and Prevention COVID Data Tracker website and US Department of Health and Human Services. Where contradictory information was found for a given variable, Ministry of Health or official data were given priority over other sources.

The process for Covid-19 case reporting underwent continuous change, and case notifications developed into more standardised procedures from May, when surveillance platforms, such as SiViES in Spain, NHS Test and Trace in the UK, SI-DEP in France and the internationally adopted contact tracing measures were implemented. Consistent data were available from 10th March and were collected from this date until 4th September 2020. For most countries, the number of tests refers to the number of Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) tests performed. The RT-PCR is widely used as the reference standard for the diagnosis of Covid-19. The WHO published its first guidance on laboratory testing on 17th January(3) and further released a more comprehensive document on 19th March.(4)

Serological tests have also been used as an alternative or complement to RT-PCR in the diagnosis of acute infection. In some countries, such as the USA, serological tests have also

been included in the total number of tests,(5) while others have reported their results separately as in the UK.

**Data variables**

The variables included in our data analysis were the number of Covid-19 cases (new and cumulative), the number of deaths (new and cumulative), the number of tests (per day and cumulative), the daily number of confirmed Covid-19 hospitalised individuals, and the daily number of individuals admitted in the ICU diagnosed with Covid-19. The data collected were homogenous for each country, except for Spain, where the numbers displayed for ICU and hospital admissions were cumulative values; therefore, the analysis was performed without the linear regression.

The number of daily tests included in our calculations represent the tests that were reported during that day. Delays in case notification were up to nine days(6) and retrospective corrections were conducted regularly in all countries and amended in the subsequent epidemiological bulletins.(6–8) The approach for reporting multiple tests done on the same individual was not uniform for all countries and detailed information on how this was addressed was inconsistent; when available, the algorithm consisted of first positive or negative RT-PCR test being declared if there were similar results, and the first positive test declared if the results were contradictory.(6) As a result, overestimation of the number of individuals that were tested in each country can vary.

Worldwide testing capacity has improved with time and this was reflected in the daily number of tests performed. We estimated the prevalence as a proportion of positive individuals from the total tested, and this was adjusted for the number of tests, as a correction for testing fluctuations.(Figure 1) In order to measure disease severity, infection fatality rate was preferred over the case fatality rate, and was calculated as the proportion of new deaths from the disease out of the estimated number of infected individuals, based on WHO definition(9):

$$\textit{Infection fatality rate ( IFR, \%)} = \frac{Number\ of\ deaths\ from\ disease}{Number\ of\ infected\ individuals} \text{ X } 100$$

Multiple methods have been described for the calculation of the IFRs; some studies have included the RT-PCR positive tests, while others have used the seroprevalence results. A systematic review of the published data on IFRs concluded that there was a high

heterogeneity among the estimates of IFRs, the calculation of which remains a challenging task.(10) Also, estimates made on seroprevalence surveys are likely to deliver slightly lower fatality rates when compared with those that are inferred from other forms of testing.(10) We have based our calculations on the number of RT-PCR tests given the more consistent availability of these data across the countries studied.

**Statistical analysis**

Data analysis was carried out using IBM SPSS®. Parametric tests were applied, and Pearson's correlation calculated to determine the strength of the association between the IFR and the number of ICU and hospital admissions. The three parameters were examined using a multivariate linear regression, and an IFR prediction model was developed based on the results. Sample size was considered adequate to support the regression. A stepwise model was built for each country, with the regression equation calculated based on the results:

$$\textit{Infection Fatality Rate} = \text{intercept} + (b_1 \times X) + (b_2 \times Y)$$

Where the analysis revealed better estimates for univariate regression, the best predictor was included in the model. If a bivariate regression was calculated, the model was examined for collinearity. The strength of the association in the model was assessed by calculating the effect size using *Cohen's f*. The linear regression was not validated in order to preserve the sample size. The epidemic curves including the course estimate of the IFR (observed and mean of predicted) and prevalence were plotted, and demographic characteristics were summarised for each country.

**RESULTS**

We developed the regression models based on the estimated values of the IFR and the prevalence. The fatality rate and the regression mean curves are displayed in Figures 2 and 3 and their trends compared with the estimated prevalence.

The analysis for Germany showed a strong positive association with IFR for both ICU admissions (r(157)=0.912, *P*<0.001) and hospital admissions (r(154)=0.771, *P*<0.001). The number of ICU admissions was included as best predictor, and the regression showed the highest value for the determination coefficient ($R^2$=0.830) with the univariate model. Table 1 summarises the descriptive statistics and analysis results. The high effect size (*f* = 1.7) validates the linear association between the two variables. The strong prediction model results in the overlapping of the fatality rate curves during the entire time frame (Figure 2).

Table 1. Linear regression analysis for each country, with results of the regression for ICU and/or hospital admissions. The results were included in the prediction model equation of the IFR.
(b, unstandardised beta coefficient; SE, standard error; $\beta$, standardised beta coefficient)
Note: Germany, $R^2$=0.830; France, $R^2$ =0.205; Italy, $R^2$= 0.634; UK, $R^2$=0.696; USA, $R^2$ =0.327.

| **Germany** | | | | |
|---|---|---|---|---|
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | **P value** |
| Intercept | -0.001 (-0.001, -222.0E-6) | 197.0E-6 | | <0.05 |
| ICU admissions | 4.23E-06 (4.0E-6, 5.0E-6) | 1.5419E-07 | 0.911 | <0.001 |
| **France** | | | | |
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | -0.053 (-0.094, -0.011) | 0.021 | | <0.05 |
| Hospital admissions | 8.41E-06 (6.0E-6, 11.0E-6) | 1.0E-6 | 0.452 | <0.001 |
| **Italy** | | | | |
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | 424.0E-6 (90.0E-6, 758.0E-6) | 169.0E-6 | | <0.05 |
| ICU admissions | -2.27E-06 (-3.0E-6, -1.0E-6) | 4.81E-07 | -1.145 | <0.001 |
| Hospital admissions | 4.13E-07(3.079E-7, 5.1834E-7) | 5.33E-08 | 1.886 | <0.001 |
| **UK** | | | | |
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | -0.005 (-0.008, -0.002) | 0.002 | | <0.05 |
| Hospital admissions | 3.28E-06 (3.0E-6, 4.0E-6) | 1.75E-07 | 0.834 | <0.001 |
| **USA** | | | | |
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | 459.0E-6 (-0.001, 0.002) | 0.001 | | 0.616 |
| ICU admissions | 2.19E-06 (2.0E-6, 3.0E-6) | 2.49E-07 | 0.572 | <0.001 |

For France, a moderate association was found between the IFR and the ICU admissions (r(169)=0.400, *P*<0.001) as well as the hospital admissions (r(169)=0.452, *P*<0.001). The correlation coefficients accounted for a medium but statistically significant effect size. The number of hospital admissions was the best predictor ($R^2$= 0.205, *f* =0.5) (Table 1). When

plotted, the modest prediction strength of the number of the hospital admissions in France was more evident from 16th May and explained the gap between the rapid decrease of the IFR within a short interval and the gradual normalisation of both ICU and hospital admissions (Figure 2).

Data from Italy showed a strong association between the IFR and ICU (r(159)=0.703, *P*<0.001) and the hospital admissions (r(159)=0.763, *P*<0.001). The bivariate regression showed the highest determination coefficient ($R^2$= 0.634, *f* =1.3), and both variables were included in the equation (Table 1). Except for the interval between 4th April and 2nd May, corresponding with the peak of the ICU and hospital admissions, all parameters decreased at comparable rates, consistent with the prediction of the model (Figure 3).

Analogous results were found in the UK, with significant correlation of both ICU( r(154)=0.843, P<0.001) and hospital admissions (r(154)=0.834, P<0.001) with IFR. The number of hospital admissions was included in the model and the regression found a good predictive strength ($R^2$=0.696) and a high effect size (*f* = 1.4) (Table 1). When compared with the observed values, the regression underestimated the IFR until 20th April, although the interval corresponded to the period with the highest number of hospital admissions, after which the curves diverged again, as the fatality rates dropped faster than the number of hospitalised individuals.

In USA, a moderate but significant association was found for the ICU admissions (r(160)=0.572, P<0.001) and a modest one with the hospital admissions (r(160)=0.333, P<0.001) and the IFR. The number of ICU admissions was included in the regression, but the strength of the prediction model was relatively low with a moderate effect size ($R^2$ =0.327, *f*=0.7) (Table 1). The intercept contribution to the model was not significant and was excluded from the equation. Notably, the hospital admissions curve revealed a second peak in August that was not reflected in a significant increase in ICU admissions as was recorded in April, and instead corresponded with the highest estimated prevalence. This finding opposed the assumption of a parallel distribution between the numbers of ICU and hospital admissions generally observed in the previous months. Thus, the regression curve predicted lower fatality rates until May, and higher values until September. Another notable finding was that the estimated prevalence continued to increase from March until August and only started declining gradually towards September (Figure 3).

According to our calculations, France recorded the highest fatality rate (May) among all countries (0.216% vs. 0.204% ,95% CI 0.135 - 0.334), and also the highest ICU daily occupancy (7,019), followed by UK (April) (0.089% vs. 0.062%, 95%CI 0.049-0.074) and Spain (April) (0.047%). The highest fatality rates for the USA (0.026% vs. 0.015%, 95% CI 0.014, 0.021), Germany (0.012% vs. 0.010% , 95% CI 0.010 - 0.013) and Italy (0.006% vs.0.008% , 95% CI -0.001, 0.012) occurred in April. The fatality rates decreased with more than 90% in all countries until plateauing around June, with only small fluctuations towards September.

The estimates for prevalence showed the highest value in Spain (4.88%) in May, preceded by Italy (2.76%) in April (Table 2). The largest interval between the first reported cases and the peak of the prevalence (2.22%) was registered in France. The prevalence had a continuous decline in Italy (2.76%) and UK (0.05%) throughout the entire period, and in September, UK had the lowest prevalence (0.01%) among all countries. In USA the prevalence continued to increase from April (0.02%) until August (0.07%), with a gradual decline in September (0.05%). From June in Germany and France, and July in Spain (Figure 2) the prevalence curves showed a gradual upturn with increasing values until September. At the point of upturn, the prevalence figures had declined in Spain by 76% (to 1.25%), in France by 61% (to 0.88%) and in Germany by 54% (to 1.16%) compared to the peak. Figures 2 and 3 depict the different trends of both prevalence and IFR and highlight the changes in their association when compared with the first and most affected months. All countries experienced a significant decrease of the fatality rates in May, which remained low from June until September, regardless of the course of prevalence.

**Table 2**. Summary of the upper and lower values of the estimated Infection Fatality Rate, prevalence, ICU and hospital admissions, and demographic characteristics of each country.

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Germany** | | | | **Hospital beds /1000** | **8** | **Population** | **83,783,945** |
| *Infection Fatality Rate per 10.000 population* | | *Prevalence* | | *ICU admissions* | | *Hospital admissions* | |
| 07/06/2020 | 2.17 | 14/06/2020 | 1.16 | 09/08/2020 | 222 | 12/07/2020 | 252 |
| 19/04/2020 | 122.60 | 12/04/2020 | 2.61 | 26/04/2020 | 2,777 | 12/04/2020 | 5,704 |
| **France** | | | | **Hospital beds /1000** | **5.98** | **Population** | **65,273,512** |
| *Infection Fatality Rate per 10.000 population* | | *Prevalence* | | *ICU admissions* | | *Hospital admissions* | |
| 13/06/2020 | 18.65 | 21/03/2020 | 0.61 | 01/08/2020 | 358 | 29/08/2020 | 4,579 |
| 02/05/2020 | 2160.00 | 23/05/2020 | 2.22 | 11/04/2020 | 7,019 | 18/04/2020 | 31,446 |
| **Italy** | | | | **Hospital beds /1000** | **3.18** | **Population** | **60,461,828** |
| *Infection Fatality Rate per 10.000 population* | | *Prevalence* | | *ICU admissions* | | *Hospital admissions* | |
| 02/09/2020 | 2.79 | 19/08/2020 | 0.02 | 06/08/2020 | 42 | 30/07/2020 | 773 |
| 16/04/2020 | 67.31 | 02/04/2020 | 2.76 | 02/04/2020 | 3,976 | 09/04/2020 | 32,615 |
| **UK** | | | | **Hospital beds /1000** | **2.54** | **Population** | **67,886,004** |
| *Infection Fatality Rate per 10.000 population* | | *Prevalence* | | *ICU admissions* | | *Hospital admissions* | |
| 31/07/2020 | 0.58 | 03/04/2020 | 0.01 | 28/08/2020 | 68 | 04/09/2020 | 447 |
| 03/04/2020 | 887.57 | 29/05/2020 | 0.05 | 17/04/2020 | 3,243 | 17/04/2020 | 19,221 |
| **USA** | | | | **Hospital beds /1000** | **2.77** | **Population** | **331,002,647** |
| *Infection Fatality Rate per 10.000 population* | | *Prevalence* | | *ICU admissions* | | *Hospital admissions* | |
| 17/07/2020 | 32.67 | 31/03/2020 | 0.02 | 31/03/2020 | 211 | 31/03/2020 | 9,480 |
| 14/04/2020 | 255.70 | 28/07/2020 | 0.07 | 12/05/2020 | 6,323 | 28/07/2020 | 59,026 |
| **Spain** | | | | **Hospital beds /1000** | **2.97** | **Population** | **46,754,783** |
| *Infection Fatality Rate per 10.000 population* | | *Prevalence* | | | | | |
| 26/07/2020 | 2.14 | 05/07/2020 | 1.25 | | | | |
| 19/04/2020 | 473.39 | 03/05/2020 | 4.88 | | | | |

## DISCUSSION

This study was aimed at assessing the pattern of change in prevalence and estimated IFR of Covid-19 over time using data from 6 countries as well as establishing a predictive model for fatality based on hospital and ICU admissions. Our findings show that at the peak of the pandemic, the model underestimated IFR based on hospital and ICU admissions, and that the predictive value increased gradually thereafter until September. One plausible explanation here could be the surge of cases at the peak which generally exceeded the capacity to accommodate and treat by the public health services, leading to fatalities outside the hospitals in venues such as residential and nursing homes. Once healthcare capacities were improved, hospital and/ or ICU admissions became much better predictors of IFR, providing a useful tool to foresee outcomes. Our findings also show a reduction in IFR over time across all countries regardless of variations and differences in prevalence, health care systems and Covid-19 management strategies (Figures 2, 3), prompting discussion on possible explanations for the apparent reduced aggressiveness of the virus. Before exploring these further, however, a note needs to be added on the potential confounding effect of Covid-19 test availability on our observation. In the early stages of the pandemic the lack of diagnostic resources and the need to prioritise tests was recognised as one of the major challenges.(11) Consequently, testing among the symptomatic individuals prevailed over the detection of asymptomatic cases. The gradual increase in the number of daily tests (Figure 1), enabling testing of asymptomatic/ mildly symptomatic patients can lead to underestimation of the IFR. To address this, therefore, our data has been adjusted for the number of tests.

### Testing and public health explanations

Since the beginning of the Covid-19 pandemic, laboratories have used the RT-PCR assays as gold standard, but diagnostic development landscape is dynamic and moving rapidly towards antigen rapid detection tests(Ag-RDT).(12) Sero-epidemiological surveys are now widely used to quantify the extent of SARS-CoV-2 transmission in the population. Many of these studies are small or based on non-random sampling of participants and thus cannot provide precise

estimates for the general population. Multiple surveys worldwide are currently ongoing, however preliminary data has been made available with seroprevalence estimates for various countries.(15-17) As previously mentioned, the detection of asymptomatic SARS-CoV-2 infections might explain the apparent reduced pathogenicity of Covid-19. Several studies estimated a third of all infected individuals to be asymptomatic. A meta-analysis which included prediction models put the percentage of asymptomatic cases at 9.2% - 69%.(13) In our study, however, the pattern of reduced IFR regardless of prevalence over time was maintained even when data were adjusted for the increased number of tests.

In terms of public health measures, the first preventive steps were taken early in March, with a rapid progression towards national lockdown by the end of the month. A systematic review which included data from previous SARS-CoV-1 and MERS-CoV outbreaks, concluded that despite the limited evidence in favour of quarantine to control SARS-CoV-2, the available studies supported the benefits of public health measures.(14) In Europe, the lockdown did impact the viral transmission rate, and this was reflected in the general decline in the number of new cases and deaths, as well as the number of hospitalised individuals. The governmental strategies varied between countries, with high stringency levels generally maintained in USA and the UK , while others adopted a more permissive policy from May.(1) Despite the variations in the public health policy and patterns of prevalence, the IFR has continued to remain low thereafter. Therefore, the theory that slowing the spread of COVID-19 reduces the fatality rates by preventing hospitals from being overrun and thus allowing better and lifesaving care would not solely explain the persistence of low mortality rates.

The demographic characteristics of the affected population are also relevant and have been constantly changing, with a shift towards an increased incidence among the younger age groups. In France, this has been observed from July, with the highest incidence corresponding to 15 to 44-year olds. In Spain, the median age in July was 44, 38 in August and 39 in September. In Germany, the median age in July was 36, 32 in August with a slight increase to 35 in September. The median age in Italy decreased from 40 in July to 28 in August, and 40 towards September. In USA, the median age declined from 46 in May to 37 in July and 38 in August. In the UK, case positivity was the highest amongst older age groups until September;

thereafter the highest incidence was seen among individuals aged 15-44 years old. In spite of the increased relative prevalence amongst the younger age groups, overall since July, the prevalence has been increasing in all age groups without a significant proportional increase in IFR, suggesting that other factors may also play an important role here.

**Biological explanations**

The relationship between the viral load and the likelihood of developing the disease has only been partly explored. As a result of the public health measures such as social distancing or wearing face masks, the individuals are likely to be exposed to lower viral loads. This may not decrease the spread of the virus across the affected population but has potentially an impact on the ability of the immune system to respond and the subsequent disease evolution in the infected individuals. Currently there is only limited evidence regarding reduced viral loads in asymptomatic versus symptomatic individuals, as well as reduced seroconversion among the asymptomatic population,(18,19) to suggest a positive association between viral load and disease severity.

The mechanisms underlying the differences in Covid-19 susceptibility and disease presentation are currently unknown, although viral and host genetic variants are probable factors influencing both disease severity and immune response outcomes. Host genetic variation may result in different susceptibility to SARS-CoV-2. Although this may account for the broad spectrum of the symptoms and disease severity associated with Covid-19, it cannot explain the observed improved fatality rates in the population, as the interval required for human genome mutations to occur is incomparably high ($10^{-8}$ per site per generation)(20).

Alterations in the viral genome are another possible explanation for the apparent reduced pathogenicity. The single-stranded RNA viruses accumulate mutations at a rate of $10^{-6}$-$10^{-4}$ per replication cycle and might result in enhanced abilities to escape the host immune system or cause increased virulence.(21) The mutation rate in the SARS-CoV-1 genome was estimated to be $0.80 – 2.38 \times 10^{-3}$ nucleotides/genome/year, which is in the same order of magnitude as

other RNA viruses.(22) For SARS-CoV-2 the mutation rate has been found to be approximately $6 \times 10^{-4}$ nucleotides/genome/year.(23) The frequency at which the mutations are found in a viral population is different from the mutation rate, and depends on several other processes such as natural selection, random genetic drift, host immune responses, and recombination amongst others.(21) Natural selection acts on individual alleles based on their mutational fitness effect (MFE). A positive MFE results in fixation of beneficial alleles, whereas deleterious and lethal alleles are removed from the population by negative selection.(21) The zoonotic origin of the SARS-CoV-2 implies the filtering of a multitude of viral strains of different strengths during its transition to a human host, allowing for the least lethal to efficiently replicate. The rate at which the environment of a virus population changes has been found to be closely related with the dynamics of the RNA evolution.(25) Thus, a faster changing environment would prompt rapid evolutionary changes, such as the case of Influenza.

The SARS-CoV-2 genome alignment can be considered as broken into a large Open Reading Frame (ORF) encoding non-structural proteins, E gene (envelope protein), M gene (membrane protein), S gene (spike protein), and N gene (nucleocapsid protein) that are common to coronaviruses , and a set of small accessory genes (ORF 3a, 6, 7a, 7b and 8). Among the non-structural proteins, the Main protease (Mpro) encoded by ORF 1a and 1b, plays an essential role in controlling the replication, and the RNA-dependent RNA polymerase, (RdRp) catalyses the replication of RNA.(23,24) A single mutation in the S protein appears to significantly increase the transmissibility of SARS-CoV-2 , and the strains containing this mutation spread fast through Europe and the USA; other recurrent mutations were found proximal to a potential antiviral binding site in the RdRp or in the receptor-binding-domain(RBD) of the S protein on a strain from India, which might alter the SARS-CoV-2 ACE2 specific receptor binding affinity and thus viral behaviour.(20) Therefore, continued surveillance for mutations and understanding their impact on the biology of the virus remain crucial. A recent study which analysed the single nucleotide polymorphisms(SNPs) of 31,421 SARS-CoV-2 genome isolates worldwide, found multiple mutations on the COVID-19 RT-PCR diagnostic targets, including those designated by the US CDC, with the targets of the E gene and RdRP based primers exhibiting fewer mutations than the N gene.(27)

SARS-CoV-2 as well as SARS-CoV-1 and MERS-CoV all display increased pathogenicity when compared with the seasonal coronaviruses. A proposed theory that has been investigated for Dengue virus, HIV, Ebola and other respiratory viruses is the Antibody Dependent Enhancement (ADE) of the infection, where poorly neutralising antibodies elicited by a previous contact with the virus facilitate the viral entry resulting in severe forms of disease.(29) Other studies dispute the cross-reactivity with other coronaviruses, and suggest the increased pathogenicity as a result of humans' serologically naivety to SARS-CoV-2.(28,29) Nonetheless, when compared with recent novel virus outbreaks, such as SARS and MERS, the mortality rate is significantly lower with Covid-19. SARS accounted for 8098 laboratory confirmed cases between 2002-2004 and 774 deaths, whilst MERS led to 2,494 confirmed cases and 858 associated deaths in 2012.(30) Similarly, a total of 28,616 Ebola cases were reported between 2014-2016 with 11,310 deaths.(26) As of 7th September, there were 26,763,217 SARS-CoV-2 cases and 876,616 deaths reported worldwide. The overall lower fatality potential of Covid-19 compared to these other novel viruses combined with its rapid spread across the world since March, may have provided further evolutionary opportunity in favour of a less virulent but more infectious virus, manifesting in reduced fatality rates over time.

Covid-19 is a novel virus and there is much to learn about its biology and behaviour. Since early 2020, the virus has spread fast with catastrophic loss of life and impact on the society. Nonetheless our data shows a gradual but significant reduction in the virus-related mortality over time which is difficult to wholly explain by public health measures. Understanding the basic biology of the virus and how it interacts with host's immune system and leveraging that knowledge might ultimately hold the key to defeating this disease. Till then our results show the hospital and ICU admission rates to be useful predictors of patient outcomes and could be used as early warning signs for escalation of public health measures.

**Figure legend**

Figure 1. Monthly test rate changes for all countries, expressed in percentages from the maximum recorded value.

Figure 2. Weekly distribution of the estimated prevalence and the Infection Fatality Rate (IFR, observed and predicted) for Germany, France and Spain. Weekly distribution of ICU and hospital admissions for Germany and France.

Figure 3. Weekly distribution of prevalence and Infection Fatality Rate (IFR, observed and predicted) for Italy, the UK and USA. Weekly distribution of ICU and hospital admissions in the same order.

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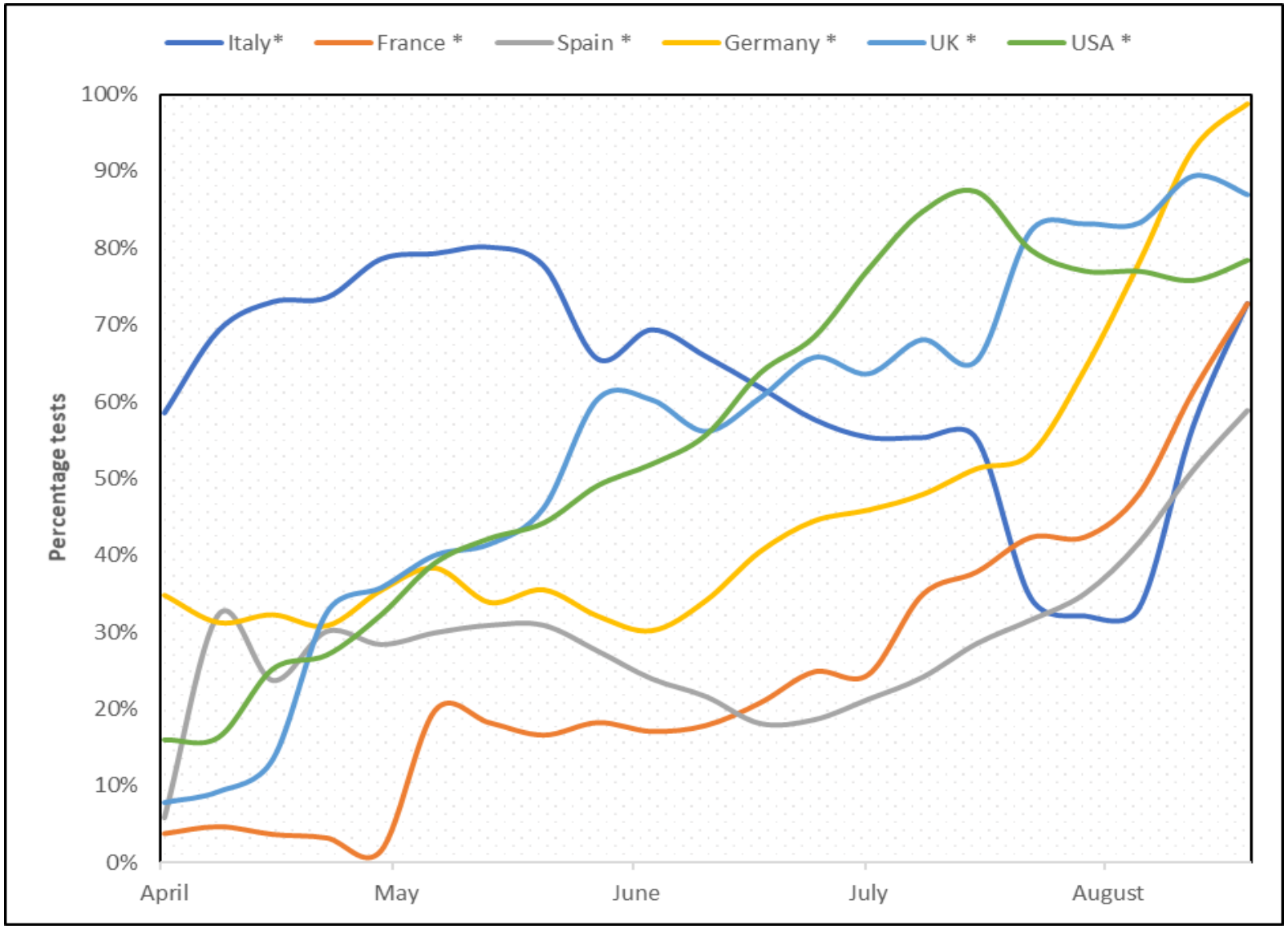


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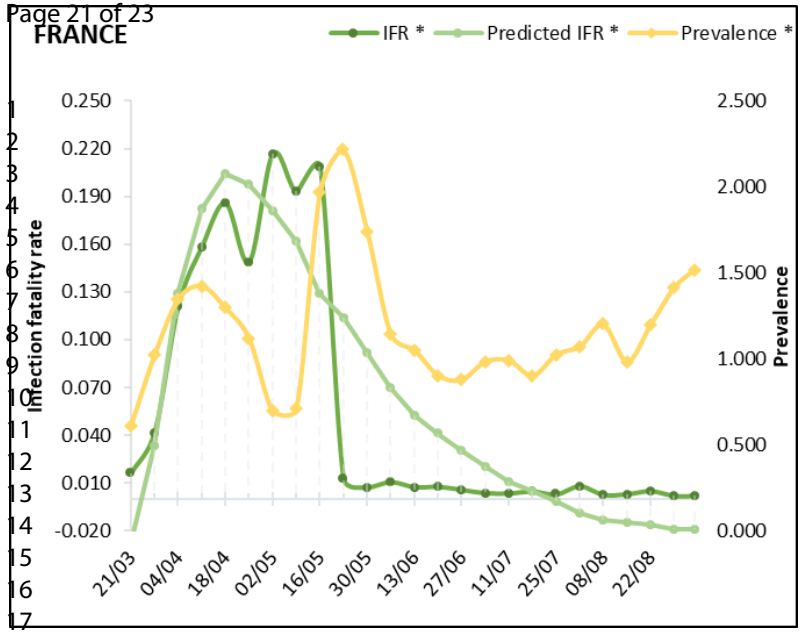


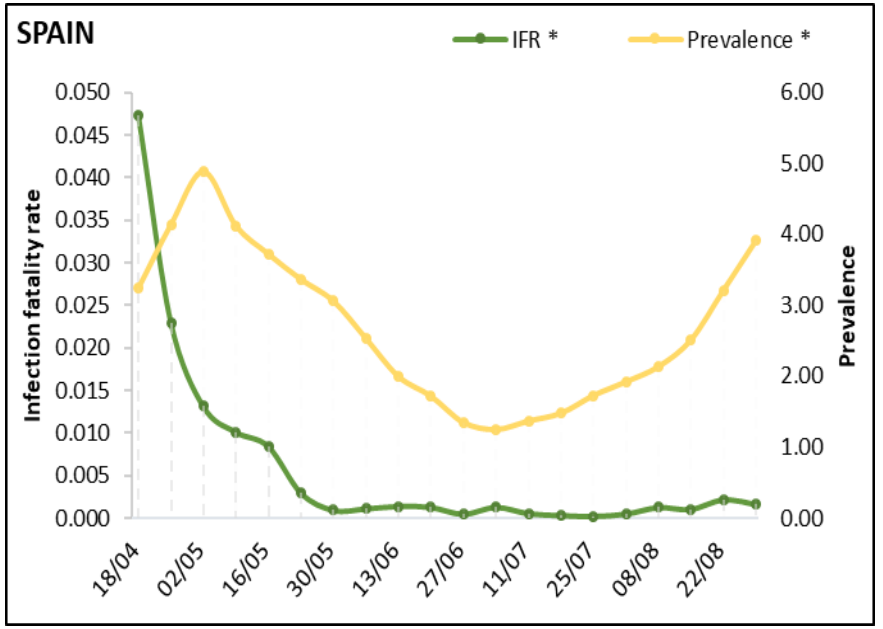


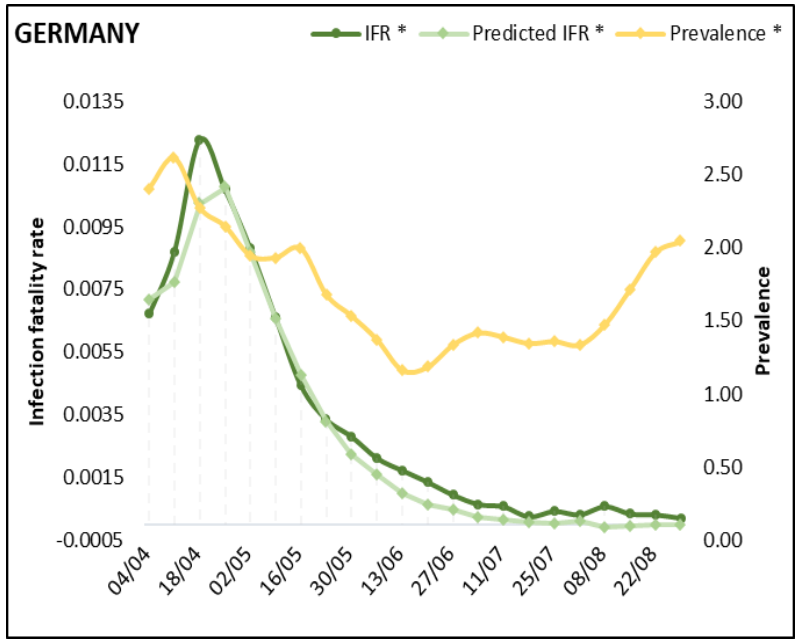


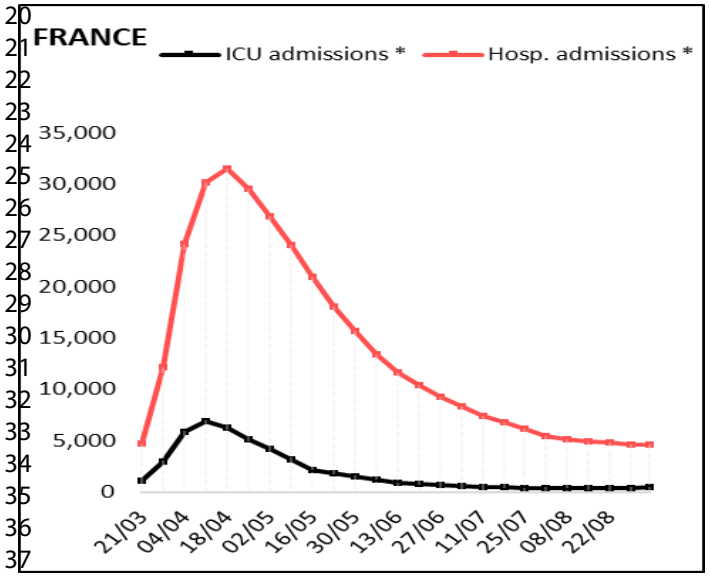


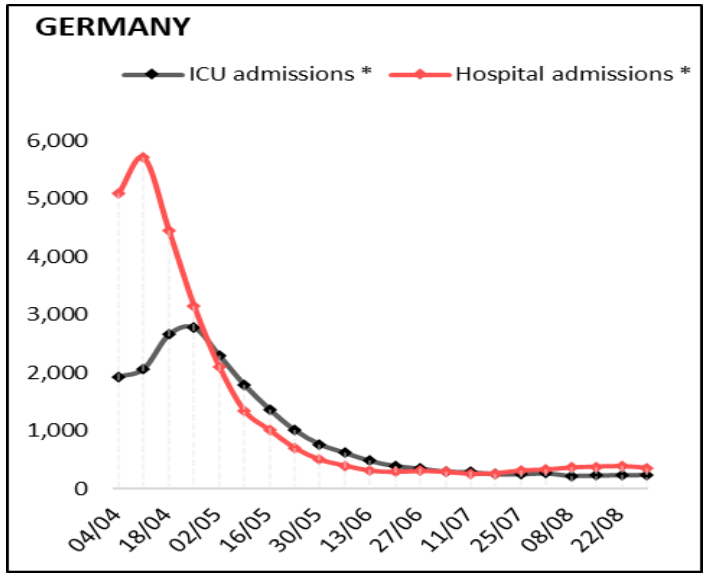




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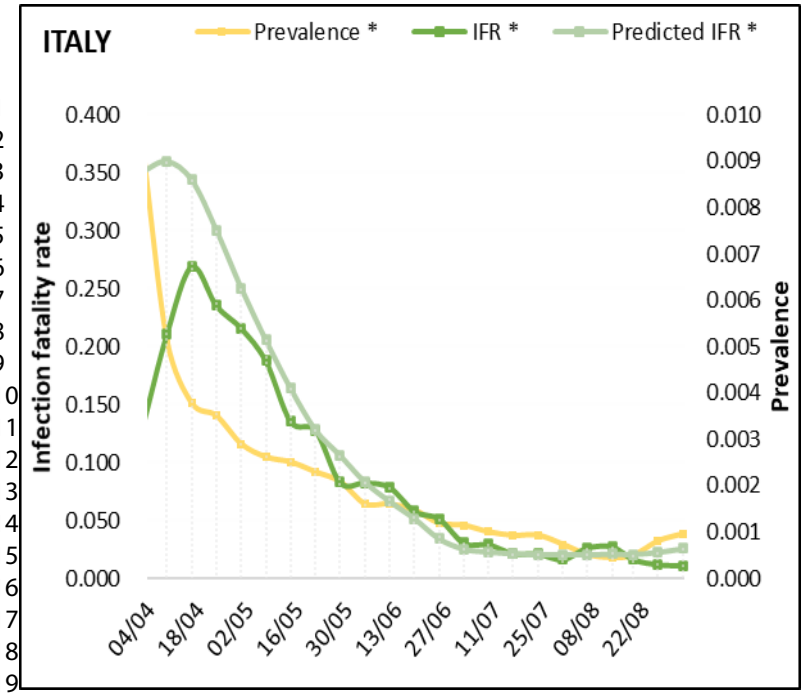


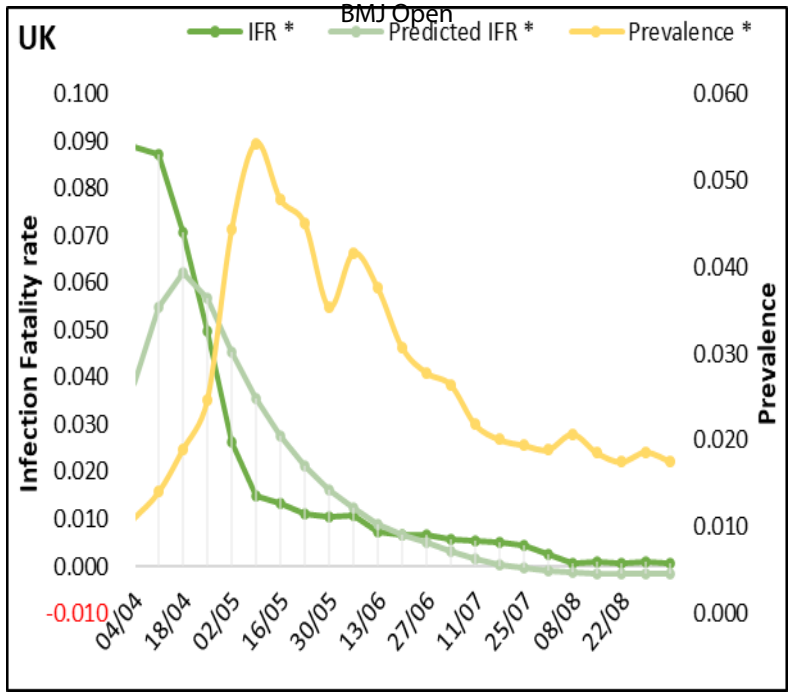


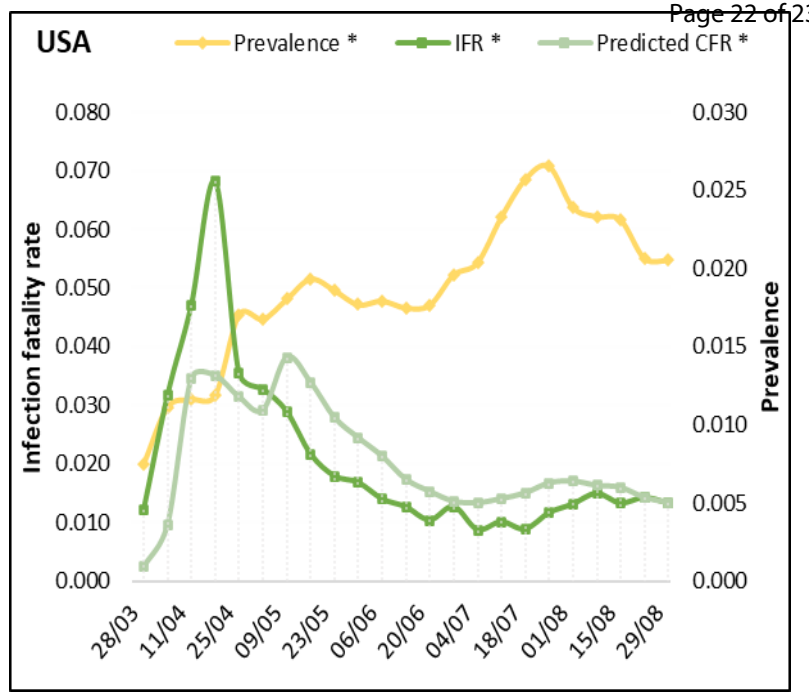


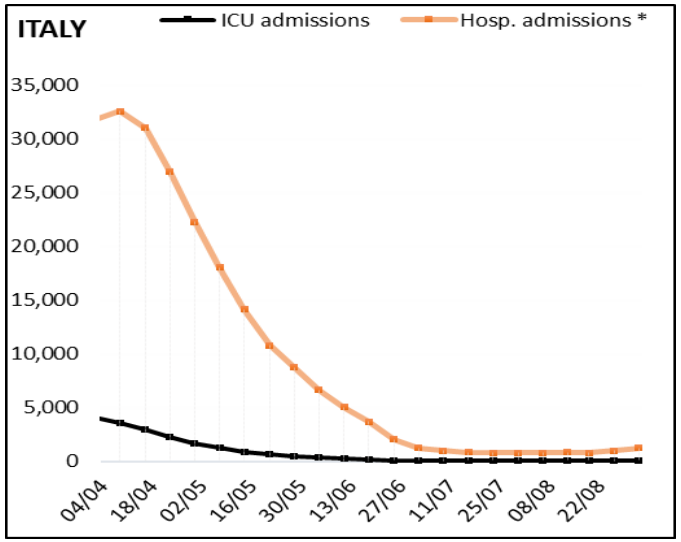


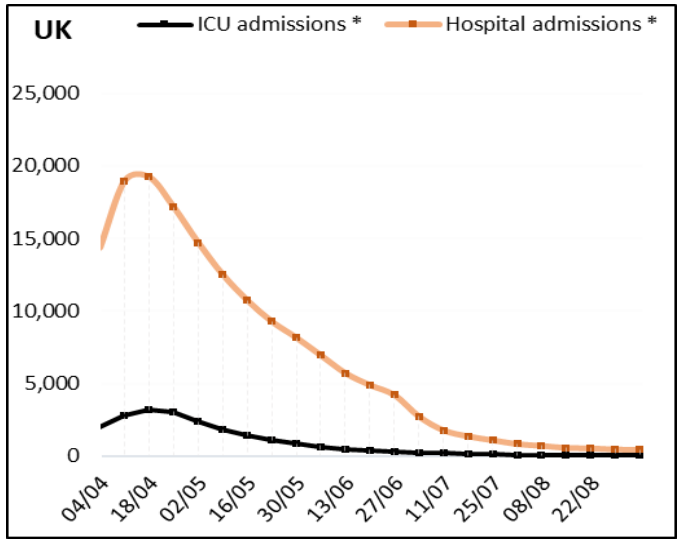


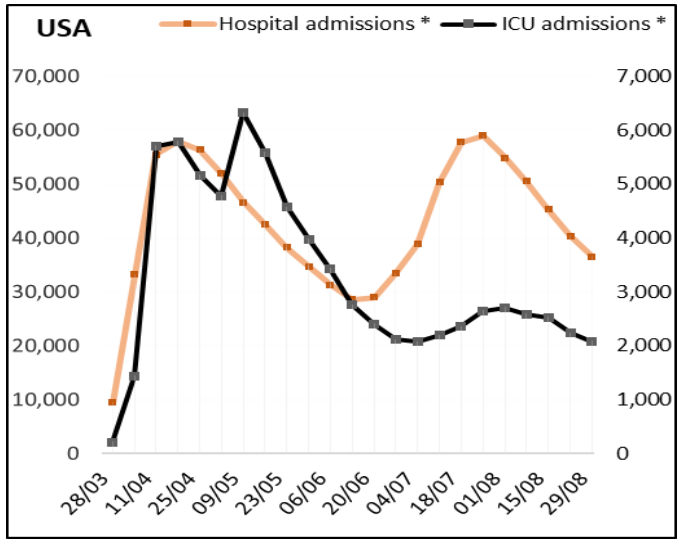


Figure 3. Weekly distribution of prevalence and Infection Fatality Rate (IFR, observed and predicted) for Italy, the UK and USA. Weekly distribution of ICU and hospital admissions in the same order.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5,6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5,6 |
| Study size | 10 | Explain how the study size was arrived at | 3,4 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | 4,5 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 7,8,9 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 7,8,9 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 9 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 11,12,13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 12,13,14, 15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 16 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# Epidemiological trends in Covid-19 pandemic: prospective critical appraisal of observations from six countries in Europe and America



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# Epidemiological trends in Covid-19 pandemic: prospective critical appraisal of observations from six countries in Europe and America

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Running Title: Epidemiological trends in Covid-19 pandemic

**Keywords**: COVID-19, SARS-CoV2, Prevalence, Infection Fatality Rate, Epidemiology

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## ABSTRACT

**Introduction:** Europe was the epicentre of the Coronavirus disease 2019 (Covid-19) pandemic in March 2020, with the highest number of cases and deaths between March and April. In May, the infection numbers registered a fall followed by a second new rise, not proportionally reflected by an increase in the number of deaths. We aimed to investigate the relationship between disease prevalence and infection fatality rate, and the number of intensive care unit (ICU) and hospital admissions over time, to develop a predictive model, as well as appraising the potential contributing factors underpinning this complex relationship.

**Methods:** A prospective epidemiological study using data from six countries collected between 10th March and 4th September. Data on the number of daily hospital and ICU admissions with Covid-19 were gathered, and the infection fatality rate and the prevalence were calculated. Trends over time were analysed. A linear regression model was used to determine the association between the fatality rates and the number of admissions.

**Findings:** The prediction model confirmed the linear association between the fatality rates and the numbers of ICU and hospital admissions. The exception was during the peak of the Covid-19 pandemic when the model underestimated the fatalities indicating that a substantial number of deaths occurred outside of the hospitals. The fatality rates decreased in all countries from May until September regardless of the trends in prevalence, differences in healthcare systems or strategic variations in handling the pandemic.

**Interpretation:** The observed gradual reduction in Covid-19 fatality rates over time despite varying disease prevalence and public health measures across multiple countries warrants search for a biological explanation. Whilst our understanding of this novel virus grows, hospital and ICU admission rates remain effective predictors of patient outcomes which can be used as early warning signs for escalation of public health measures.


## ARTICLE SUMMARY

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Comprehensive data on mortality, hospital and ICU admissions were gathered from 6 countries from March to September 2020 on a daily basis
- Our data were verified from multiple sources for each country to ensure accuracy and consistency
- The analysis was adjusted for the number of Covid-19 tests performed to remove the confounding influence of variations in test numbers over time and between countries
- Different countries use different testing technology which may have different diagnostic accuracy

- There were variations in reporting between countries especially when multiple tests were done on the same individual

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first reported in Wuhan (Hubei province, China) on 31 December 2019 and has emerged as a new zoonotic infectious disease, leading the World Health Organization (WHO) to declare, in early March, a global health emergency.(1) The SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavisurs-2), which is similar to other previously described coronaviruses, i.e. SARS-CoV-1 (Severe Acute Respiratory Syndrome Coronavisurs-1) and MERS-CoV (Middle East Respiratory Syndrome coronavirus), was identified as the pathogenic agent of COVID-19.(1) Initial studies have shown the SARS-CoV-2 to have higher transmissibility, but lower pathogenicity than that of SARS-CoV-1 and MERS-CoV .(1,2) About 81% of the COVID-19 symptomatic patients develop mild symptoms, such as headache, dry cough and fatigue. However, more severe cases can develop respiratory distress, sepsis, severe neurologic symptoms and multi-organ failure.(2) On 13$^{th}$ of March 2020, the WHO declared Europe the epicentre of the pandemic with more reported cases and deaths than the rest of the world combined, apart from the People's Republic of China. In Europe, a record number of new cases and deaths caused by Covid-19 occurred between March and beginning of April. This urged most of the European countries to adopt national lockdown measures in March, with the highest stringency levels worldwide.(1) The number of new cases and deaths consequently registered a fall, although by the end of May the distribution of new cases began to rise again. However, the trend in deaths continued downwards, indicating that the increase in cases was not leading to proportional increased mortality.(2)

To better understand these divergent trends, we analysed the data from five of the most severely affected European countries (Spain, Italy, France, Germany, and the United Kingdom). Additionally, we studied data from the USA given the impact of Covid-19 on this country and its significantly different healthcare system from those in Europe. Using the data available, we estimated and compared the distribution of the infection fatality rates (IFR) over time and the prevalence for each country. We included in our study the numbers of intensive

care unit (ICU) and hospital admissions and developed a predictive model for outcomes using these two parameters. We also discussed the potential explanations for the observed trends.

## METHODS

### Search strategy

Data on Covid-19 for each country were acquired from the Statistics and Research Coronavirus Pandemic section on *Our World in Data* website (3) as the first step. All data were then further verified with the official publicly available sources: for Spain, from the Spanish Ministry of Health daily reports,(4) and the Science and Innovation Institute Carlos III,(5) which made available datasets for public use about the number of tests and both hospital and ICU admission numbers; for Italy, from the Italian Ministry of Health,(6) with detailed datasets published by the Presidency of the Council of Ministers - Department of Civil Protection;(7) for Germany, from data published in the daily epidemiological bulletin from the Robert Koch Institute;(8) for France, from datasets accessed from the French Public Health website;(9) for UK, from datasets from the official governmental website;(10) for USA, from the Centre of Disease Control and Prevention COVID Data Tracker website and US Department of Health and Human Services. Where contradictory information was found for a given variable, Ministry of Health or official data were given priority over other sources.

The process for Covid-19 case reporting underwent continuous change, and case notifications developed into more standardised procedures from May, when surveillance platforms, such as SiViES in Spain, NHS Test and Trace in the UK, SI-DEP in France and the internationally adopted contact tracing measures were implemented. Consistent data were available from 10th March and were collected from this date until 4th September 2020. For most countries, the number of tests refers to the number of Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) tests performed. The RT-PCR is widely used as the reference standard for the diagnosis of Covid-19. The WHO published its first guidance on laboratory testing on 17th January(11) and further released a more comprehensive document on 19th March.(12)

Serological tests have also been used as an alternative or complement to RT-PCR in the diagnosis of acute infection. In some countries, such as the USA, serological tests have also been included in the total number of tests,(13) while others have reported their results separately as in the UK.

**Patient and public involvement:** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Data variables**

The variables included in our data analysis were the number of Covid-19 cases (new and cumulative), the number of deaths (new and cumulative), the number of tests (per day and cumulative), the daily number of confirmed Covid-19 hospitalised individuals, and the daily number of individuals admitted in the ICU diagnosed with Covid-19. The data collected were homogenous for each country, except for Spain, where the numbers displayed for ICU and hospital admissions were cumulative values; therefore, the analysis was performed without the linear regression.

The number of daily tests included in our calculations represent the tests that were reported during that day. Delays in case notification were up to nine days,(14) and retrospective corrections were conducted regularly in all countries and amended in the subsequent epidemiological bulletins.(14–16) The approach for reporting multiple tests done on the same individual was not uniform for all countries, and detailed information on how this was addressed was inconsistent; when available, the algorithm consisted of first positive or negative RT-PCR test being declared if there were similar results, and the first positive test declared if the results were contradictory.(14) As a result, overestimation of the number of individuals that were tested in each country can vary.

Worldwide testing capacity has improved with time and this was reflected in the daily number of tests performed. We estimated the prevalence as a proportion of positive individuals from the total tested, and this was adjusted for the number of tests, as a correction for testing fluctuations.(Figure 1) Among the measures used to assess the proportion of individuals with fatal outcomes, infection fatality rate was preferred over the case fatality rate, and was

calculated as the proportion of new deaths from the disease out of the estimated number of infected individuals, based on WHO definition(17):

$$\textit{Infection fatality rate ( IFR, \%)} = \frac{Number\ of\ deaths\ from\ disease}{Number\ of\ infected\ individuals} \text{ X } 100$$

Multiple methods have been described for the calculation of the IFRs; some studies have included the RT-PCR positive tests, while others have used the seroprevalence results. A systematic review of the published data on IFRs concluded that there was a high heterogeneity among the estimates of IFRs, the calculation of which remains a challenging task.(18) Also, estimates made on seroprevalence surveys are likely to deliver slightly lower fatality rates when compared with those that are inferred from other forms of testing.(18) We have based our calculations on the number of RT-PCR tests given the more consistent availability of these data across the countries studied.

**Statistical analysis**

Data analysis was carried out using IBM SPSS®. Parametric tests were applied, and Pearson's correlation calculated to determine the strength of the association between the IFR and the number of ICU and hospital admissions. The three parameters were examined using a multivariate linear regression, and an IFR prediction model was developed based on the results. Sample size was considered adequate to support the regression. A stepwise model was built for each country, with the regression equation calculated based on the results:

$$\textit{Infection Fatality Rate} = \text{intercept} + (b_1 \times X) + (b_2 \times Y)$$

Where the analysis revealed better estimates for univariate regression, the best predictor was included in the model. If a bivariate regression was calculated, the model was examined for collinearity. The strength of the association in the model was assessed by calculating the effect size using *Cohen's f*. The linear regression was not validated in order to preserve the sample size. The epidemic curves including the course estimate of the IFR (observed and mean of predicted) and prevalence were plotted, and demographic characteristics were summarised for each country.

A final analysis of data heterogeneity has been performed using the method proposed by Wang et al. (19) for the determination of spatial stratified heterogeneity(q) and its probability density function(F). The q statistic has been used as a tool for the assessment of the within and between countries heterogeneity. Data for each variable has been compared among the six countries during three consecutive periods corresponding to equally distributed time intervals from March until September. The variables included in the analysis were the numbers of daily new tests and deaths, the ICU and hospital admissions, and the IFR and prevalence.

**RESULTS**

We developed the regression models based on the estimated values of the IFR and the prevalence. The fatality rate and the regression mean curves are displayed in Figures 2 and 3 and their trends compared with the estimated prevalence.

The analysis for Germany showed a strong positive association with IFR for both ICU admissions (r(157)=0.912, $P$<0.001) and hospital admissions (r(154)=0.771, $P$<0.001). The number of ICU admissions was included as best predictor, and the regression showed the highest value for the determination coefficient ($R^2$=0.830) with the univariate model. Table 1 summarises the descriptive statistics and analysis results. The high effect size ($f$ = 1.7) validates the linear association between the two variables. The strong prediction model results in the overlapping of the fatality rate curves during the entire time frame (Figure 2).

Table 1. Linear regression analysis for each country, with results of the regression for ICU and/or hospital admissions. The results were included in the prediction model equation of the IFR.
(b, unstandardised beta coefficient; SE, standard error; $\boldsymbol{\beta}$, standardised beta coefficient)
Note: Germany, $R^2$=0.830; France, $R^2$ =0.205; Italy, $R^2$= 0.634; UK, $R^2$=0.696; USA, $R^2$ =0.327.

| Germany | | | | |
|---|---|---|---|---|
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | **P value** |
| Intercept | -0.001 (-0.001, -222.0E-6) | 197.0E-6 | | <0.05 |
| ICU admissions | 4.23E-06 (4.0E-6, 5.0E-6) | 1.5419E-07 | 0.911 | <0.001 |

| France | | | | |
|---|---|---|---|---|
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | -0.053 (-0.094, -0.011) | 0.021 | | <0.05 |
| Hospital admissions | 8.41E-06 (6.0E-6, 11.0E-6) | 1.0E-6 | 0.452 | <0.001 |

| Italy | | | | |
|---|---|---|---|---|
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | 424.0E-6 (90.0E-6, 758.0E-6) | 169.0E-6 | | <0.05 |
| ICU admissions | -2.27E-06 (-3.0E-6, -1.0E-6) | 4.81E-07 | -1.145 | <0.001 |
| Hospital admissions | 4.13E-07(3.079E-7, 5.1834E-7) | 5.33E-08 | 1.886 | <0.001 |

| UK | | | | |
|---|---|---|---|---|
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | -0.005 (-0.008, -0.002) | 0.002 | | <0.05 |
| Hospital admissions | 3.28E-06 (3.0E-6, 4.0E-6) | 1.75E-07 | 0.834 | <0.001 |

| USA | | | | |
|---|---|---|---|---|
| ***Predictor*** | ***b (95%CI)*** | ***SE B*** | ***β*** | ***P value*** |
| Intercept | 459.0E-6 (-0.001, 0.002) | 0.001 | | 0.616 |
| ICU admissions | 2.19E-06 (2.0E-6, 3.0E-6) | 2.49E-07 | 0.572 | <0.001 |

For France, a moderate association was found between the IFR and the ICU admissions (r(169)=0.400, *P*<0.001) as well as the hospital admissions (r(169)=0.452, *P*<0.001). The correlation coefficients accounted for a medium but statistically significant effect size. The number of hospital admissions was the best predictor ($R^2$= 0.205, *f*=0.5) (Table 1). When plotted, the modest prediction strength of the number of the hospital admissions in France was more evident from 16th May and explained the gap between the rapid decrease of the IFR within a short interval and the gradual normalisation of both ICU and hospital admissions (Figure 2).

Data from Italy showed a strong association between the IFR and ICU (r(159)=0.703, *P*<0.001) and the hospital admissions (r(159)=0.763, *P*<0.001). The bivariate regression showed the highest determination coefficient ($R^2$= 0.634, *f* =1.3), and both variables were included in the equation (Table 1). Except for the interval between 4th April and 2nd May, corresponding with the peak of the ICU and hospital admissions, all parameters decreased at comparable rates, consistent with the prediction of the model (Figure 3).

Analogous results were found in the UK, with significant correlation of both ICU( r(154)=0.843, P<0.001) and hospital admissions (r(154)=0.834, P<0.001) with IFR. The number of hospital admissions was included in the model and the regression found a good predictive strength ($R^2$=0.696) and a high effect size (*f* = 1.4) (Table 1). When compared with the observed values, the regression underestimated the IFR until 20th April, although the interval corresponded to the period with the highest number of hospital admissions, after which the curves diverged again, as the fatality rates dropped faster than the number of hospitalised individuals.

In USA, a moderate but significant association was found for the ICU admissions (r(160)=0.572, P<0.001) and a modest one with the hospital admissions (r(160)=0.333, P<0.001) and the IFR. The number of ICU admissions was included in the regression, but the strength of the prediction model was relatively low with a moderate effect size ($R^2$ =0.327, *f*=0.7) (Table 1). The intercept contribution to the model was not significant and was excluded from the equation. Notably, the hospital admissions curve revealed a second peak in August that was not reflected in a significant increase in ICU admissions as was recorded in April, and instead corresponded with the highest estimated prevalence. This finding opposed the assumption of a parallel distribution between the numbers of ICU and hospital admissions generally observed in the previous months. Thus, the regression curve predicted lower fatality rates until May, and higher values until September. Another notable finding was that the estimated prevalence continued to increase from March until August and only started declining gradually towards September (Figure 3).

According to our calculations, France recorded the highest fatality rate (May) among all countries (0.216% vs. 0.204% ,95% CI 0.135 - 0.334), and also the highest ICU daily occupancy (7,019), followed by UK (April) (0.089% vs. 0.062%, 95%CI 0.049 - 0.074) and Spain (April) (0.047%). The highest fatality rates for the USA (0.026% vs. 0.015%, 95% CI 0.014 - 0.021), Germany (0.012% vs. 0.010%, 95% CI 0.010 - 0.013) and Italy (0.006% vs.0.008%, 95% CI 0.001 - 0.012) occurred in April. The fatality rates decreased with more than 90% in all countries until plateauing around June, with only small fluctuations towards September.

The estimates for prevalence showed the highest value in Spain (4.88%) in May, preceded by Italy (2.76%) in April (Table 2). The largest interval between the first reported cases and the peak of the prevalence (2.22%) was registered in France. The prevalence had a continuous decline in Italy (2.76%) and UK (0.05%) throughout the entire period, and in September, UK

had the lowest prevalence (0.01%) among all countries. In USA, the prevalence continued to increase from April (0.02%) until August (0.07%), with a gradual decline in September (0.05%). From June in Germany and France, and July in Spain (Figure 2) the prevalence curves showed a gradual upturn with increasing values until September. At the point of upturn, the prevalence figures had declined in Spain by 76% (to 1.25%), in France by 61% (to 0.88%) and in Germany by 54% (to 1.16%) compared to the peak. Figures 2 and 3 depict the different trends of both prevalence and IFR and highlight the changes in their association when compared with the first and most affected months. All countries experienced a significant decrease of the fatality rates in May, which remained low from June until September, regardless of the course of prevalence.



**Table 2**. Summary of the upper and lower values of the estimated Infection Fatality Rate, prevalence, ICU and hospital admissions, and demographic characteristics of each country.

| **Germany** | | | | **Hospital beds /1000** | **8** | **Population** | **83,783,945** |
|---|---|---|---|---|---|---|---|
| ***Infection Fatality Rate per 10.000 population*** | | ***Prevalence*** | | ***ICU admissions*** | | ***Hospital admissions*** | |
| 07/06/2020 | 2.17 | 14/06/2020 | 1.16 | 09/08/2020 | 222 | 12/07/2020 | 252 |
| 19/04/2020 | 122.60 | 12/04/2020 | 2.61 | 26/04/2020 | 2,777 | 12/04/2020 | 5,704 |
| **France** | | | | **Hospital beds /1000** | **5.98** | **Population** | **65,273,512** |
| ***Infection Fatality Rate per 10.000 population*** | | ***Prevalence*** | | ***ICU admissions*** | | ***Hospital admissions*** | |
| 13/06/2020 | 18.65 | 21/03/2020 | 0.61 | 01/08/2020 | 358 | 29/08/2020 | 4,579 |
| 02/05/2020 | 2160.00 | 23/05/2020 | 2.22 | 11/04/2020 | 7,019 | 18/04/2020 | 31,446 |
| **Italy** | | | | **Hospital beds /1000** | **3.18** | **Population** | **60,461,828** |
| ***Infection Fatality Rate per 10.000 population*** | | ***Prevalence*** | | ***ICU admissions*** | | ***Hospital admissions*** | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 02/09/2020 | 2.79 | 19/08/2020 | 0.02 | 06/08/2020 | 42 | 30/07/2020 | 773 |
| 16/04/2020 | 67.31 | 02/04/2020 | 2.76 | 02/04/2020 | 3,976 | 09/04/2020 | 32,615 |
| **UK** | | | | **Hospital beds /1000** | **2.54** | **Population** | **67,886,004** |
| ***Infection Fatality Rate per 10.000 population*** | | ***Prevalence*** | | ***ICU admissions*** | | ***Hospital admissions*** | |
| 31/07/2020 | 0.58 | 03/04/2020 | 0.01 | 28/08/2020 | 68 | 04/09/2020 | 447 |
| 03/04/2020 | 887.57 | 29/05/2020 | 0.05 | 17/04/2020 | 3,243 | 17/04/2020 | 19,221 |
| **USA** | | | | **Hospital beds /1000** | **2.77** | **Population** | **331,002,647** |
| ***Infection Fatality Rate per 10.000 population*** | | ***Prevalence*** | | ***ICU admissions*** | | ***Hospital admissions*** | |
| 17/07/2020 | 32.67 | 31/03/2020 | 0.02 | 31/03/2020 | 211 | 31/03/2020 | 9,480 |
| 14/04/2020 | 255.70 | 28/07/2020 | 0.07 | 12/05/2020 | 6,323 | 28/07/2020 | 59,026 |
| **Spain** | | | | **Hospital beds /1000** | **2.97** | **Population** | **46,754,783** |
| ***Infection Fatality Rate per 10.000 population*** | | ***Prevalence*** | | | | | |
| 26/07/2020 | 2.14 | 05/07/2020 | 1.25 | | | | |
| 19/04/2020 | 473.39 | 03/05/2020 | 4.88 | | | | |

When examined for heterogeneity, the analysis has shown that there is significant heterogeneity within the data records of each country and for all variables, with higher q statistic values reflecting the within country and not the between countries heterogeneity for the variable analysed ($F_\alpha$ calculated for $\alpha$=0.05). Overall, the analysis shows an increasing within country heterogeneity of the data towards September for the numbers of daily new deaths, ICU and hospital admissions, whereas for the number of daily tests, prevalence and IFR, the last period shows a trend towards less heterogenous data. The increased q statistic values towards September for the explanatory variables, and decreased for the outcome variables, are in accordance with the maintained low IFR across all countries during the time interval between July and September.

## DISCUSSION

This study was aimed at assessing the pattern of change in prevalence and estimated IFR of Covid-19 over time using data from 6 countries as well as establishing a predictive model for fatality based on hospital and ICU admissions. Our findings show that at the peak of the pandemic, the model underestimated IFR based on hospital and ICU admissions, and that the predictive value increased gradually thereafter until September. One plausible explanation here could be the surge of cases at the peak which generally exceeded the capacity to accommodate and treat by the public health services, leading to fatalities outside the hospitals in venues such as residential and nursing homes. Once healthcare capacities were improved, hospital and/ or ICU admissions became much better predictors of IFR, providing a useful tool to foresee outcomes. Our findings also show a reduction in IFR over time across all countries regardless of variations and differences in prevalence, health care systems and Covid-19 management strategies (Figures 2, 3), prompting discussion on possible explanations for the apparent reduced aggressiveness of the virus. Before exploring these further, however, a note needs to be added on the potential confounding effect of Covid-19 test availability on our observation. In the early stages of the pandemic the lack of diagnostic resources and the need to prioritise tests was recognised as one of the major challenges.(20) Consequently, testing among the symptomatic individuals prevailed over the detection of asymptomatic cases. The gradual increase in the number of daily tests (Figure 1), enabling testing of asymptomatic/ mildly symptomatic patients, can lead to underestimation of the IFR. To address this, therefore, our data has been adjusted for the number of tests.

**Testing and public health explanations**

Since the beginning of the Covid-19 pandemic, laboratories have used the RT-PCR assays as gold standard, but diagnostic development landscape is dynamic and moving rapidly towards antigen rapid detection tests(Ag-RDT).(21) Sero-epidemiological surveys are now widely used to quantify the extent of SARS-CoV-2 transmission in the population. Many of these studies are small or based on non-random sampling of participants and thus cannot provide precise estimates for the general population. Multiple surveys worldwide are currently ongoing, however preliminary data has been made available with seroprevalence estimates for various

countries.(22-24) As previously mentioned, the detection of asymptomatic SARS-CoV-2 infections might explain the apparent reduced pathogenicity of Covid-19. Several studies estimated a third of all infected individuals to be asymptomatic. A meta-analysis which included prediction models put the percentage of asymptomatic cases at 9.2% - 69%.(25) In our study, however, the pattern of reduced IFR regardless of prevalence over time was maintained even when data were adjusted for the increased number of tests.

In terms of public health measures, the first preventive steps were taken early in March, with a rapid progression towards national lockdown by the end of the month. A systematic review which included data from previous SARS-CoV-1 and MERS-CoV outbreaks, concluded that despite the limited evidence in favour of quarantine to control SARS-CoV-2, the available studies supported the benefits of public health measures.(26) In Europe, the lockdown did impact the viral transmission rate, and this was reflected in the general decline in the number of new cases and deaths, as well as the number of hospitalised individuals. The governmental strategies varied between countries, with high stringency levels generally maintained in USA and the UK , while others adopted a more permissive policy from May.(1) Despite the variations in the public health policy and patterns of prevalence, the IFR has continued to remain low thereafter. Therefore, the theory that slowing the spread of COVID-19 reduces the fatality rates by preventing hospitals from being overrun and thus allowing better and lifesaving care would not solely explain the persistence of low mortality rates.

The demographic characteristics of the affected population are also relevant and have been constantly changing, with a shift towards an increased incidence among the younger age groups. In France, this has been observed from July, with the highest incidence corresponding to 15- to 44-year-olds. In Spain, the median age in July was 44, 38 in August and 39 in September. In Germany, the median age in July was 36, 32 in August with a slight increase to 35 in September. The median age in Italy decreased from 40 in July to 28 in August, and 40 towards September. In USA, the median age declined from 46 in May to 37 in July and 38 in August. In the UK, case positivity was the highest amongst older age groups until September; thereafter the highest incidence was seen among individuals aged 15-44 years old. In spite of the increased relative prevalence amongst the younger age groups, overall since July, the

prevalence has been increasing in all age groups without a significant proportional increase in IFR, suggesting that other factors may also play an important role here.

**Biological explanations**

The relationship between the viral load and the likelihood of developing the disease has only been partly explored. As a result of the public health measures such as social distancing or wearing face masks, the individuals are likely to be exposed to lower viral loads. This may not decrease the spread of the virus across the affected population but has potentially an impact on the ability of the immune system to respond and the subsequent disease evolution in the infected individuals. Currently there is only limited evidence regarding reduced viral loads in asymptomatic versus symptomatic individuals, as well as reduced seroconversion among the asymptomatic population,(27,28) to suggest a positive association between viral load and disease severity.

The mechanisms underlying the differences in Covid-19 susceptibility and disease presentation are currently unknown, although viral and host genetic variants are probable factors influencing both disease severity and immune response outcomes. Host genetic variation may result in different susceptibility to SARS-CoV-2. Although this may account for the broad spectrum of the symptoms and disease severity associated with Covid-19, it cannot explain the observed improved fatality rates in the population, as the interval required for human genome mutations to occur is incomparably high ($10^{-8}$ per site per generation).(29)

Alterations in the viral genome are another possible explanation for the apparent reduced pathogenicity. The single-stranded RNA viruses accumulate mutations at a rate of $10^{-6}$-$10^{-4}$ per replication cycle and might result in enhanced abilities to escape the host immune system or cause increased virulence.(30) The mutation rate in the SARS-CoV-1 genome was estimated to be $0.80 – 2.38 \times 10^{-3}$ nucleotides/genome/year, which is in the same order of magnitude as other RNA viruses.(31) For SARS-CoV-2 the mutation rate has been found to be approximately $6 \times 10^{-4}$ nucleotides/genome/year.(32) The frequency at which the mutations are found in a

viral population is different from the mutation rate, and depends on several other processes such as natural selection, random genetic drift, host immune responses, and recombination amongst others.(30) Natural selection acts on individual alleles based on their mutational fitness effect (MFE). A positive MFE results in fixation of beneficial alleles, whereas deleterious and lethal alleles are removed from the population by negative selection.(30) The zoonotic origin of the SARS-CoV-2 implies the filtering of a multitude of viral strains of different strengths during its transition to a human host, allowing for the least lethal to efficiently replicate. The rate at which the environment of a virus population changes has been found to be closely related with the dynamics of the RNA evolution.(33) Thus, a faster changing environment would prompt rapid evolutionary changes, such as the case of Influenza. A recent mutation in the spike protein appears to have significantly increased the transmissibility of SARS-CoV-2 , and the strains containing this mutation are spreading fast through Europe and the USA.(29) Therefore, continued surveillance for mutations and understanding their impact on the biology of the virus remain crucial.

SARS-CoV-2 as well as SARS-CoV-1 and MERS-CoV all display increased pathogenicity when compared with the seasonal coronaviruses. A proposed theory that has been investigated for Dengue virus, HIV, Ebola and other respiratory viruses is the Antibody Dependent Enhancement (ADE) of the infection, where poorly neutralising antibodies elicited by a previous contact with the virus facilitate the viral entry resulting in severe forms of disease.(34) Other studies dispute the cross-reactivity with other coronaviruses, and suggest the increased pathogenicity as a result of humans' serologically naivety to SARS-CoV-2.(34,35) Nonetheless, when compared with recent novel virus outbreaks, such as SARS and MERS, the mortality rate is significantly lower with Covid-19. SARS accounted for 8098 laboratory confirmed cases between 2002-2004 and 774 deaths, whilst MERS led to 2,494 confirmed cases and 858 associated deaths in 2012.(36) Similarly, a total of 28,616 Ebola cases were reported between 2014-2016 with 11,310 deaths.(37) As of 7$^{th}$ September, there were 26,763,217 SARS-CoV-2 cases and 876,616 deaths reported worldwide. The overall lower fatality potential of Covid-19 compared to these other novel viruses combined with its rapid spread across the world since March, may have provided further evolutionary opportunity in

favour of a less virulent but more infectious virus, manifesting in reduced fatality rates over time.

**Limitations**

One of the main limitations of our study related to the variations in the testing technology both between different countries and also over time in the same country. Furthermore, the way test results were reported was not always consistent, especially when multiple tests were performed in the same individuals. By using data from multiple sources in each country, we aimed to minimise the effect of these confounding factors.

**Conclusions**

Covid-19 is a novel virus and there is much to learn about its biology and behaviour. Since early 2020, the virus has spread fast with catastrophic loss of life and impact on the society. Nonetheless our data shows a gradual but significant reduction in the virus-related mortality over time which is difficult to wholly explain by public health measures. Understanding the basic biology of the virus and how it interacts with host's immune system and leveraging that knowledge might ultimately hold the key to defeating this disease. Till then our results show the hospital and ICU admission rates to be useful predictors of patient outcomes and could be used as early warning signs for escalation of public health measures.

**Figure legend**

Figure 1. Monthly test rate changes for all countries, expressed in percentages from the maximum recorded value.

Figure 2. Weekly distribution of the estimated prevalence and the Infection Fatality Rate (IFR, observed and predicted) for Germany, France and Spain. Weekly distribution of ICU and hospital admissions for Germany and France.

Figure 3. Weekly distribution of prevalence and Infection Fatality Rate (IFR, observed and predicted) for Italy, the UK and USA. Weekly distribution of ICU and hospital admissions in the same order.

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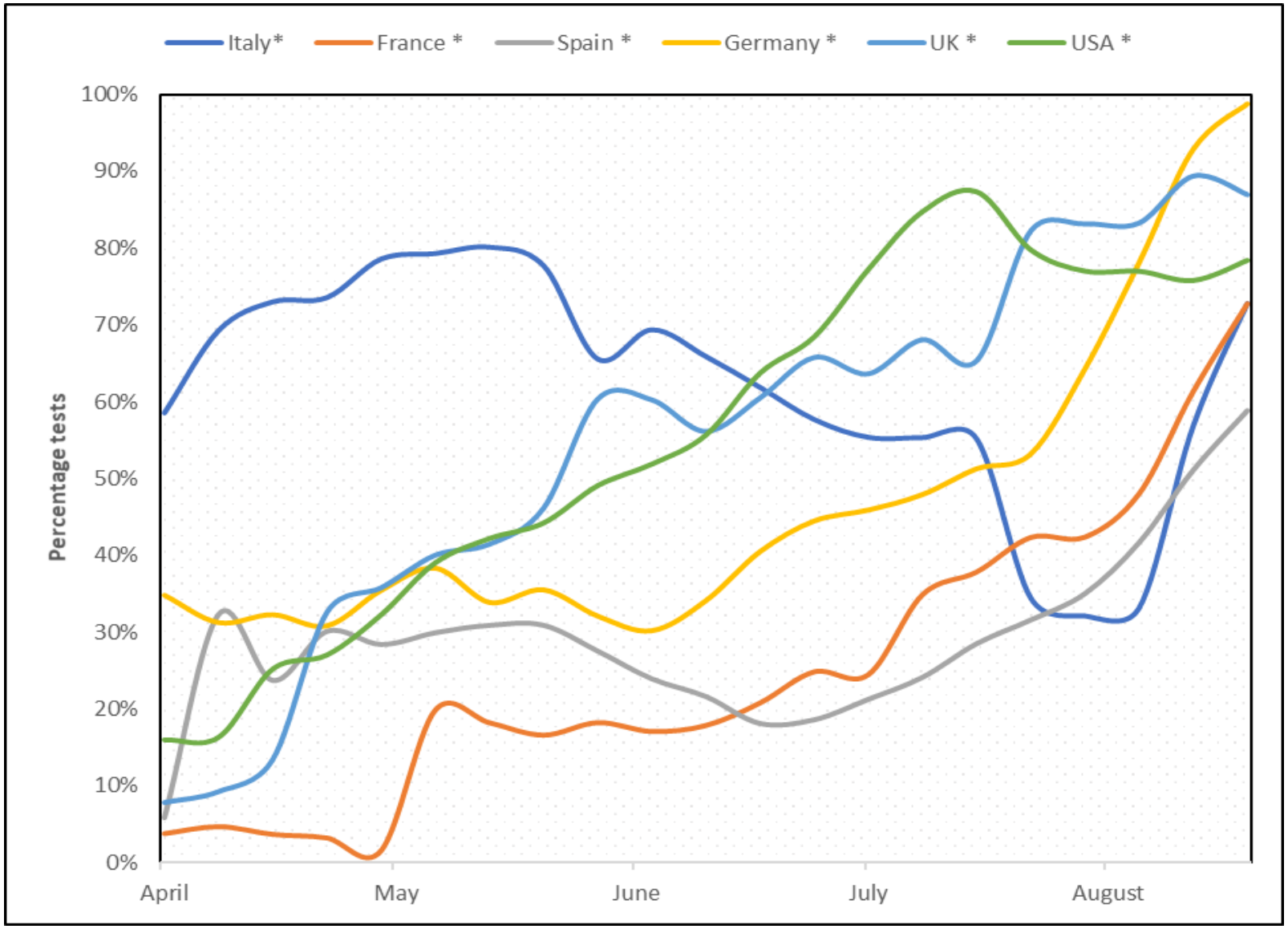
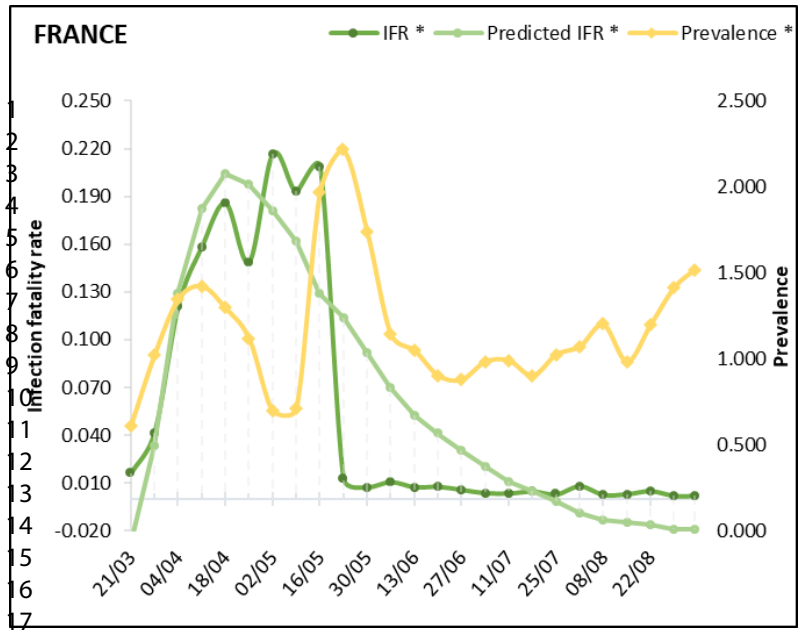
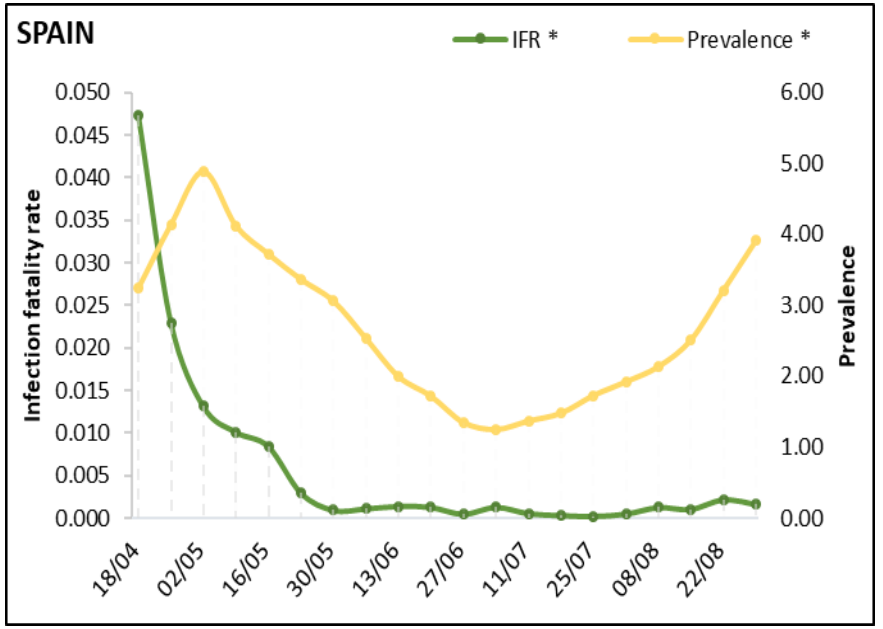
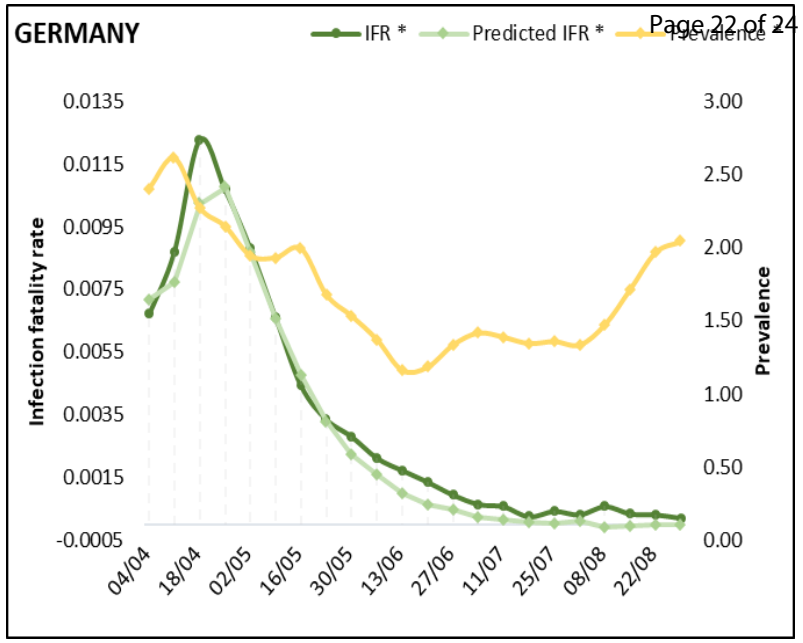
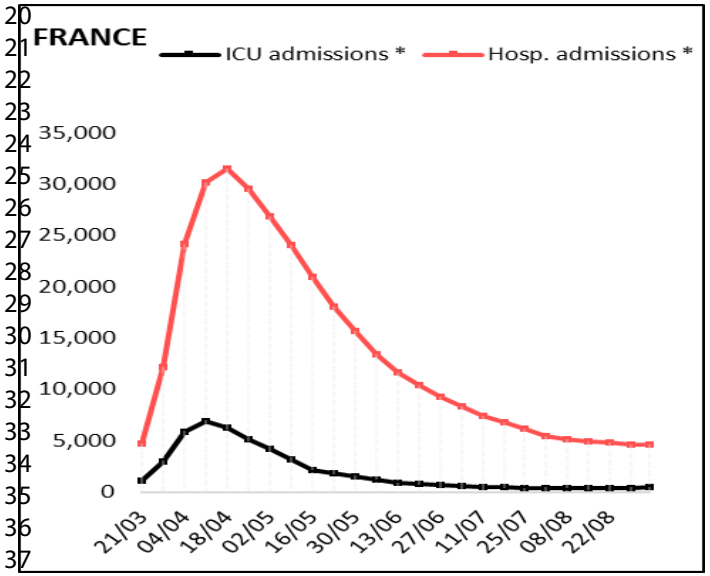



Figure 1. Monthly test rate changes for all countries, expressed in percentages from the maximum recorded value.



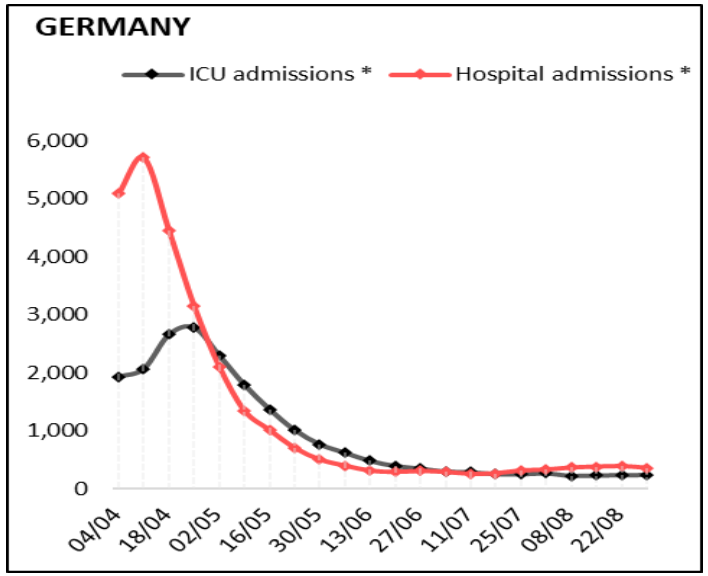
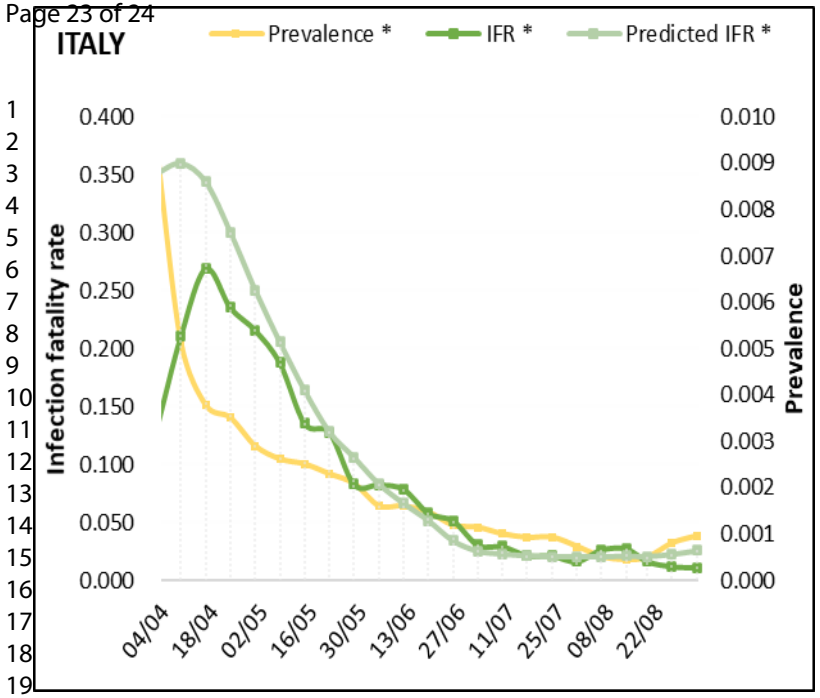
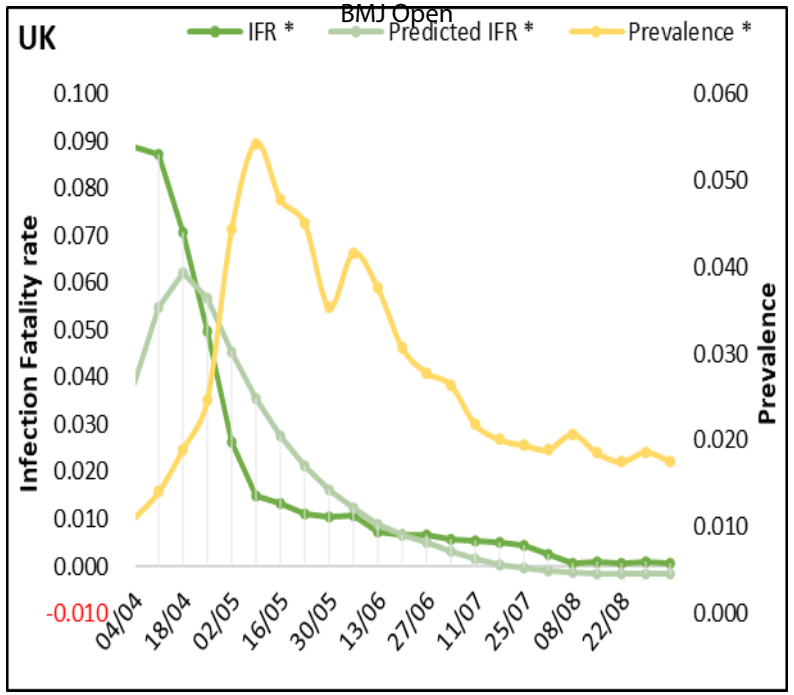
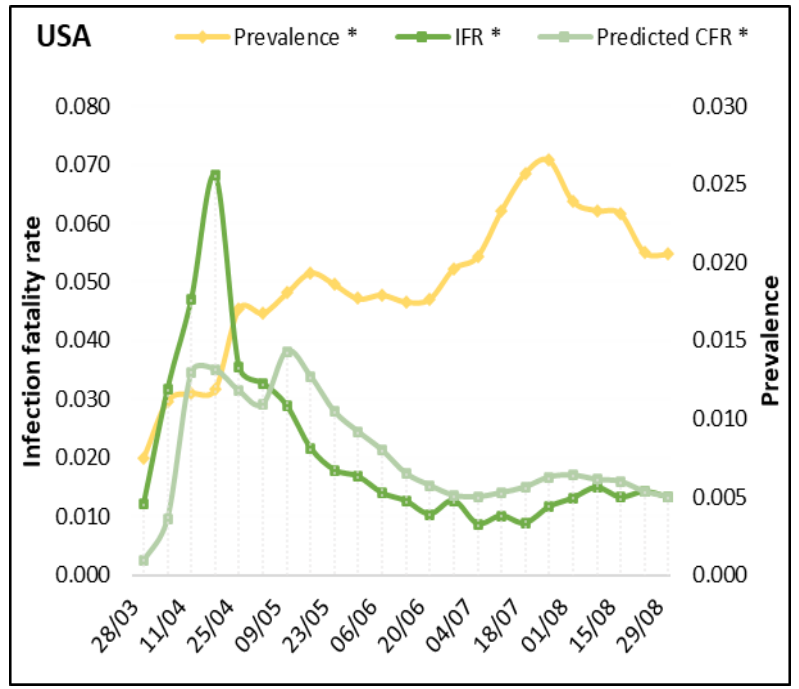



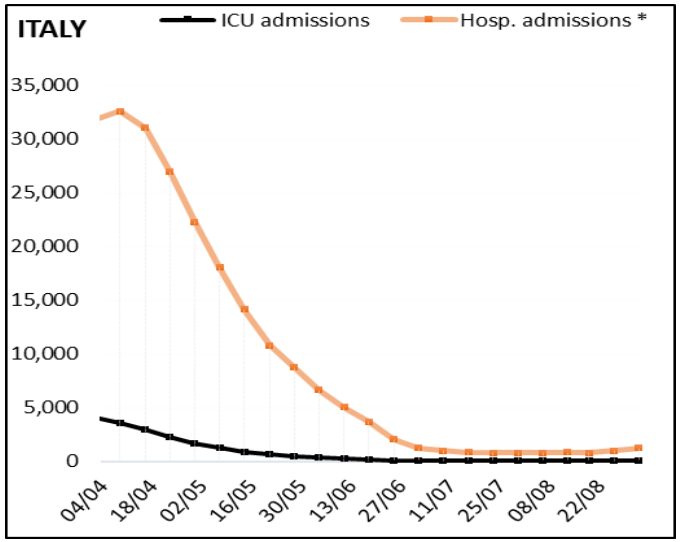


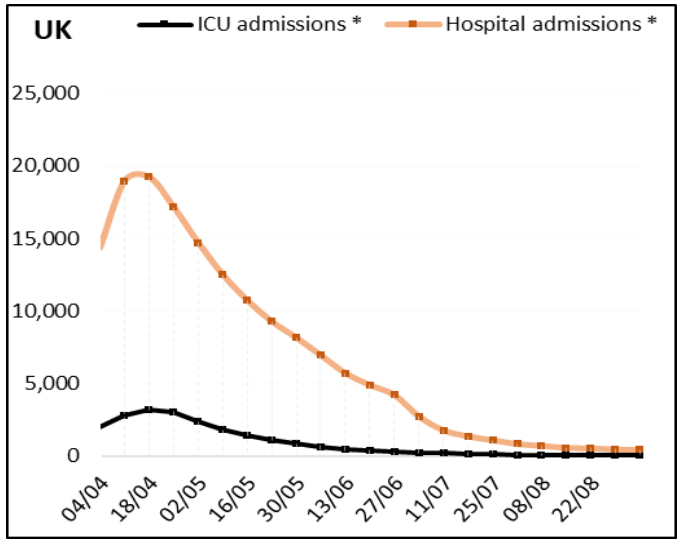

Figure 2. Weekly distribution of the estimated prevalence and the Infection Fatality Rate (IFR, observed and predicted) for Germany, France and Spain. Weekly distribution of the ICU and hospital admissions for Germany and France.



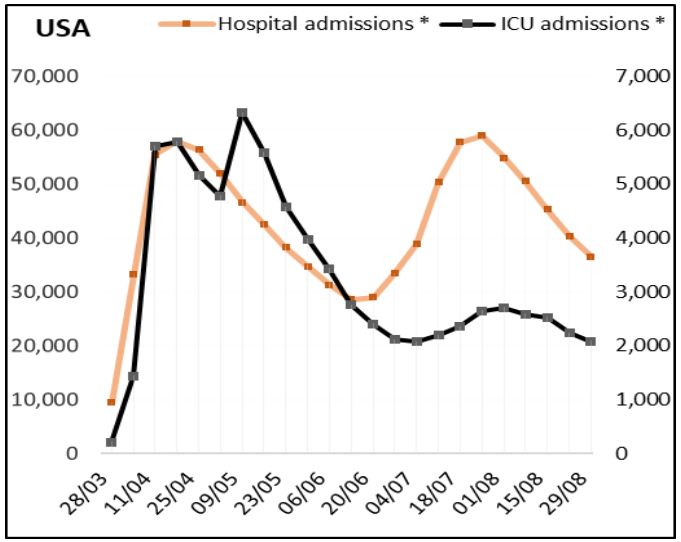




Figure 3. Weekly distribution of prevalence and Infection Fatality Rate (IFR, observed and predicted) for Italy, the UK and USA. Weekly distribution of ICU and hospital admissions in the same order.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation | Page No |
|---|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract | 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found | 2 |
| **Introduction** | | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported | 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses | 3 |
| **Methods** | | | |
| Study design | 4 | Present key elements of study design early in the paper | 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 4 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up | 4 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed | |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 5,6 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 4,5 |
| Bias | 9 | Describe any efforts to address potential sources of bias | 5,6 |
| Study size | 10 | Explain how the study size was arrived at | 3,4 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding | 6 |
| | | (*b*) Describe any methods used to examine subgroups and interactions | 6 |
| | | (*c*) Explain how missing data were addressed | 4,5 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed | |
| | | (*e*) Describe any sensitivity analyses | |
| **Results** | | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | |
| | | (b) Give reasons for non-participation at each stage | |
| | | (c) Consider use of a flow diagram | |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders | |
| | | (b) Indicate number of participants with missing data for each variable of interest | |
| | | (c) Summarise follow-up time (eg, average and total amount) | |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time | 7,8,9 |

| | | | |
|---|---|---|---|
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included<br>(*b*) Report category boundaries when continuous variables were categorized<br>(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 7,8,9 |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses | 9 |
| **Discussion** | | | |
| Key results | 18 | Summarise key results with reference to study objectives | 11 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 11,12,13 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 12,13,14, 15 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results | 15 |
| **Other information** | | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 16 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.