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Research Article

Time-varying associations between daily SARS-CoV-2 positive rates, positive deaths, and total deaths in Germany

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ABSTRACT

Background: Highly aggregated ecologic SARS-CoV-2 statistics about positive cases and positive deaths were used to make predictions and to decree public health control measures. Daily death counts correlated with daily positive rates 10 to 30 days earlier, worldwide. In Germany, this lagged association revealed a distinct temporal clustering suggesting uncontrolled determinants of key pandemic metrics. Ignoring the secular mortality upward-trend in Germany, scientists, official institutions, and the media compared the total deaths in 2020 with the average deaths from 2016 to 2019 and, thereby, overestimated COVID-19 excess deaths. Ad hoc corona metrics and statistics, predictions, and control measures based on this have been called into question.

Methods: The German Robert-Koch Institute reported daily SARS-CoV-2 positive cases and daily positive deaths until 5/26/2021, and the number of tests performed per week until 5/23/2021. The German Statistisches Bundesamt documented annual and daily deaths from 1990 until 5/16/2021. The optimum lag between positive rate and positive deaths was determined as the lag maximizing Spearman rank correlation. Inverse variance weighted (generalized) linear regression, Poisson regression, and logistic regression served to analyse the associations between positive rate, positive deaths, and total deaths with emphasis on the temporal developments of these associations.

Results: The estimated optimum lag between positive rate and positive deaths was 16.9 (11.1, 23.1) days, with a rank correlation of 0.927 (0.913, 0.939). The association between positive deaths and 17d-lagged positive rates showed a distinct four-phasic temporal clustering. The annual deaths per 1000 population in Germany from 1990 to 2019 followed a cubic logistic trend, which the deaths in 2020 exceeded by 1.3% equivalent to 12 667 (-20 886, 45 115) total excess cases, p-value 0.4543.

Conclusion: The association between positive rate and positive deaths revealed a significant temporal clustering, and the preliminary total deaths in Germany in 2020 did not significantly deviate from the secular trend from 1990 to 2019. These findings indicate potential deficits in SARS-CoV-2 metrics and statistics possibly due to unknown pandemic determinants and non-representative data generation. Characterization and control of the pandemic should be based on clearly defined, representative, and population-specific testing strategies of cases and deaths.

Keywords: Covid-19, excess deaths, optimum time lag, secular trend in total deaths, temporal clustering

ABBREVIATIONS

95%-CI or (. , .): 95%-confidence interval; Chi^2 : Chi-squared distributed test statistic; COVID-19: Coronavirus disease 2019; CW: Calendar Week; DESTATIS: Statistisches Bundesamt, Germany; DF: Degree of freedom; GLM: Generalized linear model; IFR: Infection Fatality Rate; OR: Odds Ratio; OWID: Our World in Data; RKI: Robert Koch-Institute; SAS: Statistical Analysis System, software produced by SAS Institute Inc; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SE: Standard Error; UK: United Kingdom; VIF: Variance Inflation Factor.

INTRODUCTION

The assessment of COVID-19 prevalence, incidence, and risk depends on ecological ad-hoc data reported on the coronavirus pandemic. Despite their highly aggregated preliminary nature, daily data on SARS-CoV-2 positive persons and positive deaths are employed for the estimation of indicators such as the reproduction rate (R), the case fatality rate (CFR), the infection fatality rate (IFR), the mortality rate (MR), and years of life lost (YLL). Ioannidis presented a global perspective of COVID-19 epidemiology [1]. Since COVID-19 metrics and statistics depend on differing definitions and reporting rules, the general conceptual and technical quality, validity, and stability of COVID-19 related metrics and statistics play a key role in the subjective and scientific perception as well as in the administration of the pandemic [2]. Pre-analytical factors, such as specimen selection and collection, are crucial for RT-PCR, and any suboptimal collection may contribute to false results [3]. Recent large national and international cohorts described the input characteristics and outcome of hospitalized patients with COVID-19, but these reports were limited in detail [4]. Petti and Cowling emphasized the ecologic nature of COVID-19 mortality statistics. They recommended, e.g., influenza mortality as a predictor for multivariable COVID-19 mortality prediction models since influenza and COVID-19 mortality rates were significantly associated [5].

The rate of positive individuals (positive rate) is a central, however imprecise measure. Its interpretation depends among others on the clinical false positive rate, e.g., due to unspecific signals [6, 7], the number of PCR cycles and contaminations of laboratory equipment [8], as well as the composition of individuals tested in relation to the accuracy of the tests employed (PCR vs. antigen vs. antibody tests) [9, 10]. Backhaus discussed several pitfalls about the interpretation of corona data [11]. Kennedy and Yam investigated at the international level the possibility of uncovering fabrication of COVID-19 case figures employing statistical methods [12].

Although considerable scientific efforts concerning detection of the virus, diagnosis of COVID-19 disease, and the optimization of pandemic control have been undertaken globally [13-20], simple notorious unresolved problems remain. The distinction between 'died with corona' vs. 'died due to corona' is a big issue and may distort findings and burden the entire narrative [21, 22]. The CDC emphasized 'Getting high-quality cause-of-death information can be challenging, especially during emergencies. Certifiers may be faced with heavy workloads, may not have access to complete information about the death, or may not be well trained in how to prepare good quality cause-of-death statements.' [23]. From these perspectives it is problematic that in Germany the attribution to death from COVID-19 may be based on the positivity of a PCR test alone: 'The infection with SARS-CoV-2 presents itself with a broad but unspecific spectrum of symptoms so that the virological diagnosis is the mainstay in the context of the detection of the infection, the reporting and the control of measures' [24].

In several countries considered, SARS-CoV-2 positive deaths were correlated with lagged positive rates. In Germany, this correlation was subject to a distinct temporal clustering in the period from February 2020 to January 2021 [25]. Because of their preliminary and aggregated nature, epidemiologic pandemic descriptors should be subject to continuous quality and validity control [26-28]. Observations of established associations, e.g., between infection and death [29], or between lagged positive rate and positive deaths [25] provide opportunities for monitoring of pandemic metrics and control measures. Using publicly available OWID data [30] from December 2019 to August 2020 it was found that globally as well as for selected countries the daily SARS-CoV-2 positive rates showed delays to proportional counts of positive deaths as follows: World 20.6 days with 95%-CI (8.4, 32.8), USA 19.8 (9.3, 30.4), Germany 18.8 (6.1, 31.6), and Italy 2.4 (-10.2, 15.0) [25]. Employing the most recent German data from 2/24/2020 until 5/26/2021, the present article updates and scrutinizes the association between optimum lagged daily positive rate, positive deaths, and total deaths for temporal stability or heterogeneity. Data from India and the United States were considered for comparison.

Schreiner et al. observed a median delay from symptom onset to death of 11 days with high variability across European countries including the UK. For Germany, this delay was 11.2 days [29]. Scherb estimated a delay of 15.7 (10.8, 19.8) days between the reporting of positivity and the reporting of death [25]. Considering reporting delays for cases and deaths of up to one week, these both observations fit together. Despite the drawbacks of the involved corona metrics and statistics emphasized above, the association between positive deaths and lagged positive rate, taken at its face value, provides an opportunity for continuous outcome monitoring and plausibility checks.

Morfeld and Erren [31] and Morfeld et al. [32] emphasized the necessity of considering the mortality in 2020 in the context of preceding years. Giattino et al. cautioned against under- or overestimation of the excess with decreasing or increasing mortality trends: 'For instance, for countries that have an increasing trend in mortality like the US and South Korea the five-year average will overestimate excess deaths; while for countries that have a decreasing trend in mortality like Russia it will underestimate excess deaths' [33]. Scherb noted: '… the total deaths in Germany in 2020 are in line with the previous upward trend from 2005-2019' [25]. Therefore, the provisional deaths per 1000 population in Germany in 2020 reported by DESTATIS were compared with the expected deaths deduced from an optimum cubic trend from 1990 through 2019. The purpose of this was (1) to estimate the likely excess deaths in 2020 and (2) to investigate whether the daily positive deaths reported by the RKI are consistent with the total deaths of the year 2020 reported by DESTATIS [34,35].

METHODS

On 5/26/2021, the Robert Koch Institute (RKI) published on the internet the following cumulative SARS-CoV-2 related counts. Daily positive cases: 3,656,177, daily deaths: 87,726 and weekly performed tests until 5/23/2021: 60,408,571. Daily test counts were derived by linearly interpolating weekly counts (reported on Wednesdays for the week before). The total of the estimated/interpolated daily tests through 5/23/2021of 60,418,862 is practically identical to the total official weekly counts [34]. The deviation is only 0.02%. Table 1

Table 1. SARS-CoV-2 in Germany 2/24/20 through 5/26/2021 by calendar week: deaths, positive deaths, positive tested persons, number of tests, positive rate and positive rate lagged 17 days; daily data aggregated by calendar week; last week incomplete.

Week in 2020 or 2021*		Calendar week	Total deaths	Positive deaths	Positive tested persons	Number of tests	Positive rate	Positive rate lagged 17 days
From	To							
2020-02-24	2020-03-01	9	19,507	0	117	na	na	na
2020-03-02	2020-03-08	10	19,656	0	785	69,493	0.0113	na
2020-03-09	2020-03-15	11	19,901	12	3,936	129,291	0.0304	0.0025
2020-03-16	2020-03-22	12	19,752	43	13,772	374,534	0.0368	0.0103
2020-03-23	2020-03-29	13	19,719	334	33,937	377,599	0.0899	0.0210
2020-03-30	2020-04-05	14	20,661	953	39,167	417,646	0.0938	0.0320
2020-04-06	2020-04-12	15	20,523	1,331	28,765	386,241	0.0745	0.0678
2020-04-13	2020-04-19	16	19,289	1,621	19,418	339,983	0.0571	0.0924
2020-04-20	2020-04-26	17	18,563	1,346	14,278	363,659	0.0393	0.0868
2020-04-27	2020-05-03	18	17,923	1,009	8,321	327,799	0.0254	0.0618
2020-05-04	2020-05-10	19	17,644	746	6,722	385,638	0.0174	0.0498
2020-05-11	2020-05-17	20	17,000	519	5,137	431,682	0.0119	0.0323
2020-05-18	2020-05-24	21	17,166	333	3,926	356,489	0.0110	0.0193
2020-05-25	2020-05-31	22	16,769	253	3,201	408,078	0.0078	0.0149
2020-06-01	2020-06-07	23	17,275	168	2,497	342,328	0.0073	0.0116
2020-06-08	2020-06-14	24	16,609	119	2,290	327,980	0.0070	0.0077
2020-06-15	2020-06-21	25	16,399	95	3,553	384,834	0.0092	0.0082
2020-06-22	2020-06-28	26	17,297	75	3,677	472,823	0.0078	0.0079
2020-06-29	2020-07-05	27	16,452	55	2,836	512,969	0.0055	0.0065
2020-07-06	2020-07-12	28	16,168	51	2,469	513,572	0.0048	0.0099
2020-07-13	2020-07-19	29	16,532	21	2,770	544,219	0.0051	0.0064
2020-07-20	2020-07-26	30	16,910	34	3,695	556,634	0.0066	0.0050
2020-07-27	2020-08-02	31	17,415	23	4,624	589,201	0.0078	0.0047
2020-08-03	2020-08-09	32	17,488	55	5,998	719,476	0.0083	0.0056
2020-08-10	2020-08-16	33	19,696	35	7,562	871,191	0.0087	0.0078
2020-08-17	2020-08-23	34	17,560	38	9,411	1,034,449	0.0091	0.0079
2020-08-24	2020-08-30	35	16,642	26	8,907	1,133,623	0.0079	0.0086
2020-08-31	2020-09-06	36	16,734	30	8,214	1,052,942	0.0078	0.0090
2020-09-07	2020-09-13	37	17,105	24	9,443	1,148,465	0.0082	0.0085
2020-09-14	2020-09-20	38	17,544	37	11,987	1,147,879	0.0104	0.0076
2020-09-21	2020-09-27	39	17,400	71	12,725	1,220,279	0.0104	0.0083
2020-09-28	2020-10-04	40	17,594	72	15,097	1,129,127	0.0134	0.0091
2020-10-05	2020-10-11	41	17,466	86	23,627	1,218,988	0.0194	0.0103
2020-10-12	2020-10-18	42	17,725	162	39,110	1,284,349	0.0305	0.0117
2020-10-19	2020-10-25	43	18,574	255	67,207	1,445,463	0.0465	0.0156
2020-10-26	2020-11-01	44	18,577	449	103,749	1,663,992	0.0623	0.0247
2020-11-02	2020-11-08	45	19,064	808	125,575	1,634,729	0.0768	0.0369
2020-11-09	2020-11-15	46	19,753	1,196	131,998	1,467,454	0.0900	0.0567
2020-11-16	2020-11-22	47	20,202	1,537	127,766	1,400,145	0.0913	0.0708
2020-11-23	2020-11-29	48	21,294	2,101	124,431	1,381,117	0.0901	0.0844
2020-11-30	2020-12-06	49	22,661	2,649	128,623	1,395,790	0.0922	0.0898
2020-12-07	2020-12-13	50	23,962	3,015	149,393	1,516,038	0.0985	0.0919
2020-12-14	2020-12-20	51	24,726	4,262	173,293	1,672,033	0.1036	0.0887
2020-12-21	2020-12-27	52	25,499	3,729	146,849	1,090,372	0.1347	0.0925
2020-12-28	2021-01-03	53	25,421	4,494	124,808	845,729	0.1476	0.1021
2021-01-04	2021-01-10	1	24,769	6,071	142,861	1,231,405	0.1160	0.1351
2021-01-11	2021-01-17	2	24,424	6,076	124,991	1,187,564	0.1052	0.1395
2021-01-18	2021-01-24	3	24,019	5,451	101,418	1,113,690	0.0911	0.1082
2021-01-25	2021-01-31	4	22,552	5,075	81,427	1,151,633	0.0707	0.1190
2021-02-01	2021-02-07	5	21,639	4,572	67,647	1,101,499	0.0614	0.0959
2021-02-08	2021-02-14	6	20,824	3,443	50,551	1,060,602	0.0477	0.0796
2021-02-15	2021-02-21	7	20,351	2,881	51,998	1,103,231	0.0471	0.0652
2021-02-22	2021-02-28	8	18,825	2,204	55,777	1,171,798	0.0476	0.0540
2021-03-01	2021-03-07	9	18,298	1,855	57,846	1,153,270	0.0502	0.0464
2021-03-08	2021-03-14	10	18,476	1,471	69,063	1,280,050	0.0540	0.0473

2021-03-15	2021-03-21	11	18,141	1,293	90,271	1,367,247	0.0660	0.0493
2021-03-22	2021-03-28	12	18,225	1,206	112,885	1,415,220	0.0798	0.0498
2021-03-29	2021-04-04	13	18,325	1,093	112,985	1,178,378	0.0959	0.0596
2021-04-05	2021-04-11	14	18,633	1,390	112,882	1,169,510	0.0965	0.0724
2021-04-12	2021-04-18	15	18,919	1,561	143,994	1,312,602	0.1097	0.0938
2021-04-19	2021-04-25	16	19,093	1,650	145,156	1,427,668	0.1017	0.0833
2021-04-26	2021-05-02	17	19,355	1,628	129,404	1,360,960	0.0951	0.1140
2021-05-03	2021-05-09	18	18,916	1,583	103,507	1,251,817	0.0827	0.1047
2021-05-10	2021-05-16	19	18,324	1,321	73,105	1,088,421	0.0672	0.1004
2021-05-17	2021-05-23	20	na	1,284	55,524	1,195,684	0.0464	0.0895
2021-05-24	2021-05-26	21	na	346	7,219	na	0.0479	0.0796
Total or overall rate			**1,229,925**	**87,726**	**3,656,177**	**60,408,571**	**0.0605**	**0.0607**

* last week incomplete, included for the exact to the day documentation of the totals

Table 2. Population and total deaths in Germany 1990 to 2020; deaths per 1000 population and expected deaths per 1000 population according to a cubic logistic regression model; for a graphical representation see Figure 4.

Year	Population	Total deaths	Deaths per 1000 population	*Expected deaths per 1000 population	Excess deaths	Excess deaths cumulative
1990	79,365,000	921,445	11.610	11.679	-5,457	-5,457
1991	79,984,000	911,245	11.393	11.421	-2,290	-7,747
1992	80,570,000	885,443	10.990	11.194	-16,448	-24,195
1993	81,187,000	897,270	11.052	10.994	4,696	-19,499
1994	81,422,000	884,661	10.865	10.820	3,683	-15,816
1995	81,661,000	884,588	10.832	10.670	13,297	-2,519
1996	81,896,000	882,843	10.780	10.542	19,535	17,016
1997	82,061,000	860,389	10.485	10.434	4,150	21,166
1998	82,024,000	852,382	10.392	10.346	3,740	24,906
1999	82,101,000	846,330	10.308	10.277	2,611	27,517
2000	82,213,000	838,797	10.203	10.224	-1,758	25,759
2001	82,350,000	828,541	10.061	10.188	-10,430	15,329
2002	82,489,000	841,686	10.204	10.167	3,023	18,352
2003	82,541,000	853,946	10.346	10.161	15,278	33,629
2004	82,517,000	818,271	9.916	10.168	-20,772	12,858
2005	82,470,000	830,227	10.067	10.189	-10,040	2,817
2006	82,377,000	821,627	9.974	10.222	-20,426	-17,609
2007	82,267,000	827,155	10.055	10.267	-17,485	-35,093
2008	82,110,000	844,439	10.284	10.324	-3,228	-38,321
2009	81,901,000	854,544	10.434	10.391	3,519	-34,802
2010	81,751,000	858,768	10.505	10.469	2,952	-31,850
2011	80,233,100	852,328	10.623	10.556	5,381	-26,469
2012	80,399,000	869,582	10.816	10.653	13,100	-13,369
2013	80,767,000	893,825	11.067	10.759	24,890	11,521
2014	81,198,000	868,356	10.694	10.872	-14,468	-2,947
2015	82,175,700	925,200	11.259	10.994	21,742	18,795
2016	82,521,700	910,902	11.038	11.123	-7,004	11,791
2017	82,740,900	932,272	11.267	11.259	701	12,491
2018	83,019,200	954,874	11.502	11.401	8,397	20,889
2019	83,166,700	939,520	11.297	11.548	-20,889	0
2020	** 83,190,556	*** 985,996	11.852	11.700	12,667	12,667

* expected deaths under a secular cubic logistic trend model for 1990 to 2019
** preliminary as of 30/9/2020 [45]; *** preliminary as of 5/26/2021 [35]

reflects the daily data analysed, summarized by weeks for convenient tabular presentation. The optimum lag between positive rate and positive deaths was determined as the lag in days maximizing Spearman rank correlation of 7-day smoothed daily counts [25,36]. Inverse variance weighted (straight line) regression served to analyse the association between positive deaths and positive rates with an emphasis on temporal stability, variability, or clustering. Table 2 contains the total deaths in Germany from 1990 through 2020 [35,37], whereby the counts for 2020 and 2021 through 5/16/2021 are preliminary as of 5/26/2021. For analyses of raw or smoothed death counts and positive rates, rank correlation, weighted ordinary regression, weighted generalized linear regression (GLM), Poisson regression, and linear logistic regression were employed. Software used was MS-Excel-365 (2016), Wolfram MATHEMATICA 11.3, and mostly SAS/STAT software 9.4 (SAS Institute Inc: SAS/STAT User's Guide, Cary NC: SAS Institute Inc, 2014).

RESULTS

Optimum lag between positive tests and positive deaths

Spearman rank correlation has been employed previously for estimating an optimum time lag [36] between daily positive deaths and lagged positive rates in Germany [25]. An optimum delay of 15.7 (10.8, 19.8) days was found in data from February to November 2020. Applying the same method to the extended data from 2/24/2020 through 5/26/2021, the updated optimum delay was 16.9 (11.1, 23.1) days, with an optimum rank correlation of 0.927 (0.913, 0.939). See Figure 1 for details of the optimum lag estimation.

Trends of lagged positive rate and positive deaths

Utilizing the time lag of rounded 17 days for an optimum association between positive deaths and lagged positive rate in the RKI data, Figure 2 shows congruence of lagged positive rate and positive deaths up to 11/27/2020. From 11/28/20 this tight initial association increasingly dissolves. A formal change-point analysis [38, 39] based on the minimum deviance criterion (data and statistical parameters not shown) confirmed the significant structural change in November 2020: p-value < 0.0001.

Temporal clustering of positive individuals and positive tests

Figure 3 depicts the highly significantly temporally clustered association between positive deaths and 17 days lagged positive rate from a different viewpoint. In the combined periods 2/24 to 11/27/20 and 03/30 to 05/26/2021, daily positive deaths increased by 24.6 per 1% increase of the positive rate with R2 = 0.940. From 11/28 to 12/15/2020, 12/16 to 03/08/2021, and 03/09 to 03/29/2021, the further period-specific slopes were 156.5 R2 = 0.758, 66.4 R2= 0.958, and -139.7 R2 = 0.803, respectively. An overall interactive GLM, linear in the positive rate, yields R2 = 0.982. If quadratic and cubic terms and corresponding interactions are included, these are highly significant with p < 0.0001, and R2 slightly increases to 0.984. Using Poisson regression, linear in the positive rate, model fit is rather poor with scale 4.1, AIC 9846.2, deviance 7190.3 with 430 degrees of freedom, and thus overdispersion 16.7. The goodness of fit increases considerably when including quadratic and cubic positive rates: scale 2.0, AIC 44064, and deviance 1746.5 with 428 degrees of freedom, and thus overdispersion 4.1. The p-value for the interaction 'period*lagged positive rate' is less than 0.0001, for the four periods.

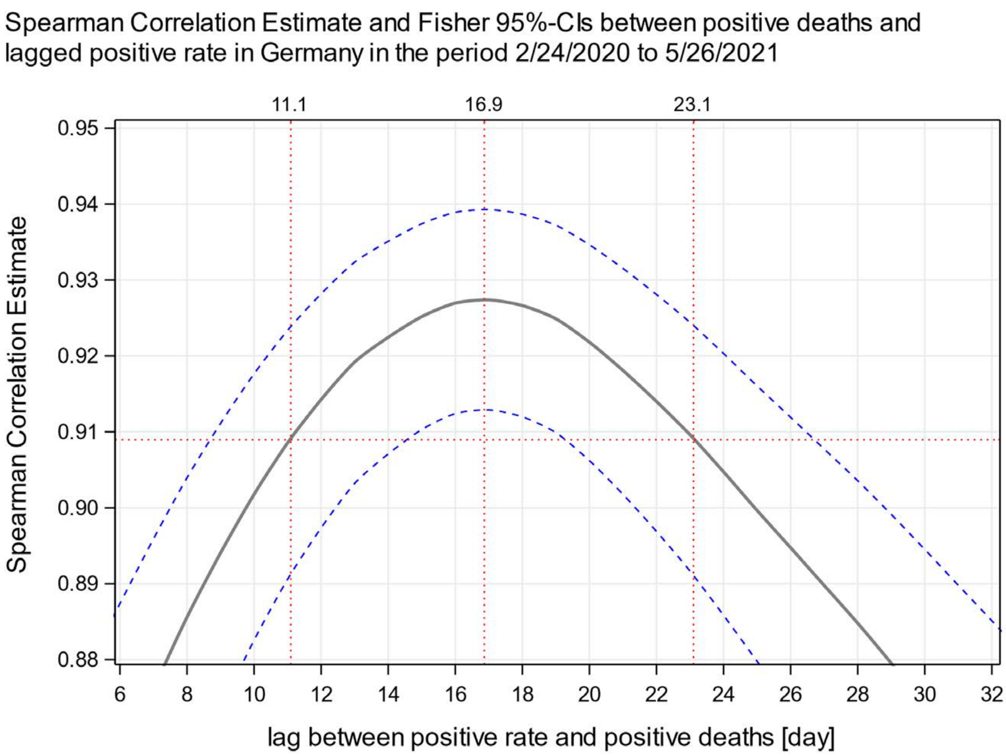

Figure 1. Spearman rank correlation (black solid curve) between positive deaths and lagged positive rate in the period 2/24/2020 to 5/26/2020; optimum time lag 16.9 days, 95%-CI (11.1, 23.1); the red dotted horizontal line runs 1.96∗*sqrt*(2) standard errors below the maximum Spearman correlation of 0.927 (0.913, 0.939) at 16.9 days; the intersections of the red dotted horizontal line with the Spearman correlation curve define an approximate 95%-CI for the optimum time lag.

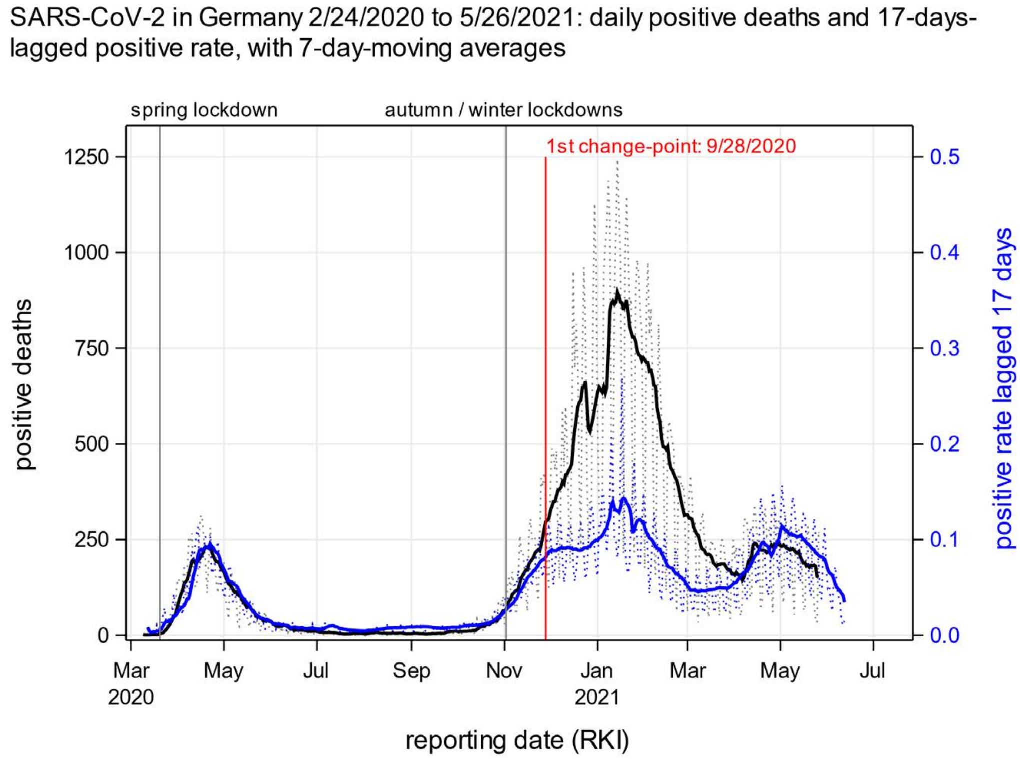

Figure 2. SARS-CoV-2 in Germany: daily positive deaths (black, dotted) and optimum 17 days-lagged positive rate (blue, dotted) with corresponding 7-day-moving averages (solid) 2/24/2020 to 5/26/2021; the red vertical line indicates a 1st change-point followed by several structural changes [39,44] of the association between positive rate and positive deaths, see Figure 3; the vertical black lines indicate the start of the major lockdowns in Germany.

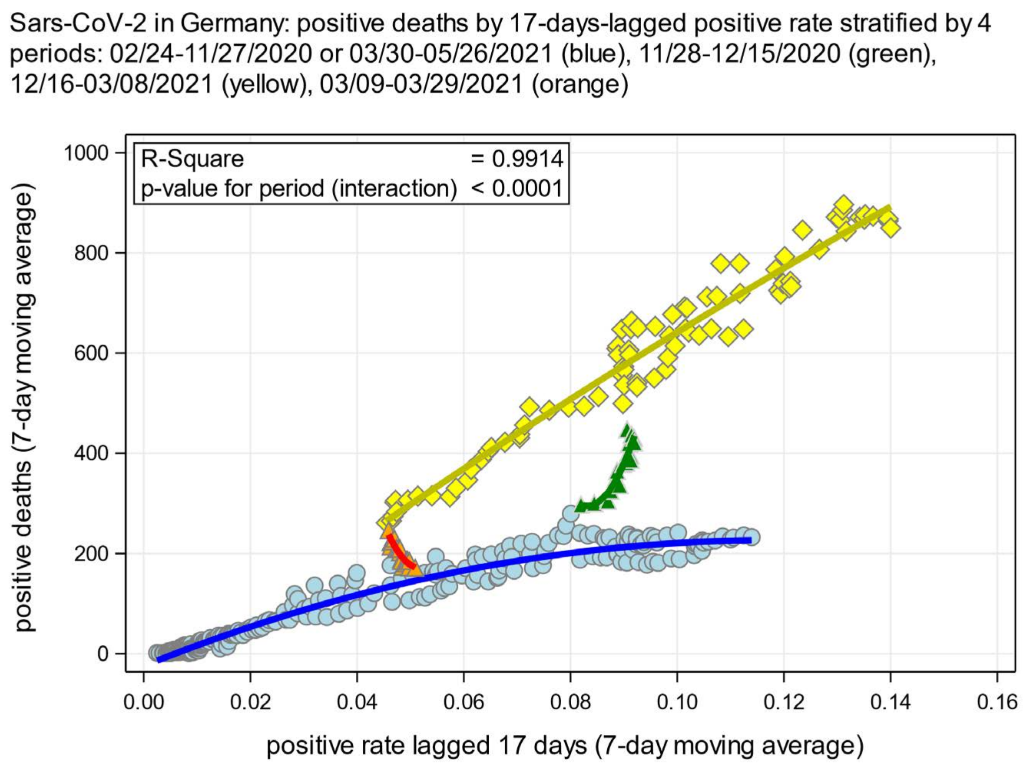

Figure 3. SARS-CoV-2 in Germany: daily positive deaths by 17 days lagged positive rate stratified by period; p-values for period and for all linear period∗positive rate interactions < 0.0001.

Expected versus observed total deaths in the year 2020

Table 2 compiles the official annual population and total death counts for Germany from 1990 to 2019, as well as corresponding preliminary counts for 2020 [35, 37]. A parsimonious optimum cubic polynomial logistic trend (R2=0.91) was fit to these data in the period 1990 to 2019. This yielded the expected counts per 1000 population in Table 2. The total deaths in 2020 are 1.3% more than predicted by the trend from 1990 through 2019. The excess of 1.3% translates to 12,667 (-20,886, 45,115) additional cases in 2020. The p-value for the excess in 2020 is 0.4543. Figure 4 depicts the cubic trend of total deaths per 1000 population in Germany from 1990 through 2020. Figure 4 includes 95%-confidence bands for annual mean values, and it highlights the insignificant excess mortality in 2020 compared to the overall variability of the secular total mortality trend from 1970 to 2019.

COVID-19-status of deaths during periods

In view of the total deaths and the positive deaths in Table 1 and considering the four distinct periods identified in Figure 3, we can assess the temporal development of the odds of negative tested or not at all tested deaths versus positive deaths. Table 3 presents these calculations by choosing period 1 as the reference period. It turns out that the odds ratio of not dying with or due to corona infection during the first period versus the remaining periods varies between 2 and 7. On average the odds ratio is 5.56. This could imply that the virus was up to 6 times more deadly during winter compared to the rest of the year. Or it could mean overcounting [40] of positive deaths due to unspecific signals, false positives (insufficient discrimination from influenza [5]), and disproportional more testing among the elderly and moribund compared with younger parts of the population. Table 3, last row, implies 49,475 excess or overcounted

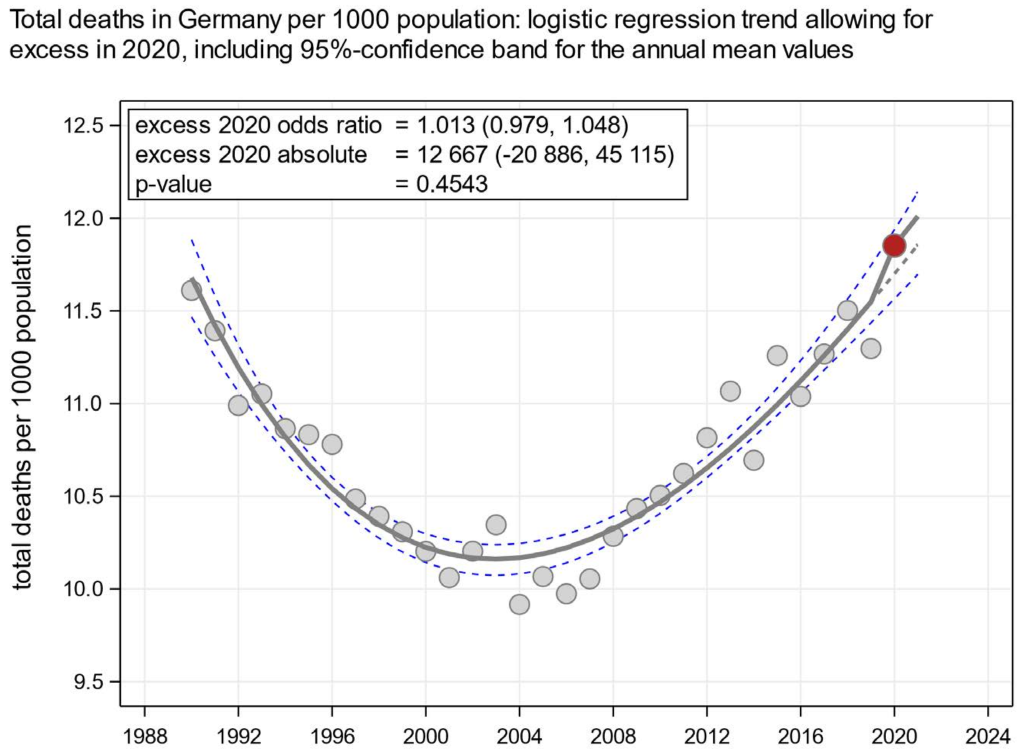

Figure 4. Total deaths in Germany 1990 to 2020 per 1000 population and 3rd degree polynomial logistic regression trend allowing for a deviation in 2020; the grey dashed line indicates the null-effect model; for the data see Table 2.

Table 3. Deaths by COVID-19-status in Germany during four periods of stable associations between positive deaths and 17-days-lagged positive rate according to Figure 3; approximate seven-day reporting delay of positive deaths; the 1st period is the reference period; COVID-19-status is significantly associated with period: contingency table Chi^2 p-value < 0.0001.

Period	total	No COVID-19	COVID-19	Odds	Odds ratio	log(OR)	SE	Wald-Chi^2	p-value
1	845,543	818,144	27,399	0.033	1.00	0.000	0.0087	0.00	1.0000
2	56,520	49,631	6,889	0.139	4.14	1.422	0.0142	9957.44	< 0.0001
3	272,948	223,489	49,459	0.221	6.61	1.888	0.0079	57130.98	< 0.0001
4	54,914	50,935	3,979	0.078	2.33	0.847	0.0176	2324.24	< 0.0001
2 to 4	384,382	324,055	60,327	0.186	5.56	1.715	0.0076	51280.58	< 0.0001

deaths in the second and third waves under the assumption that the virus or the pandemic was as deadly in the second and third waves as they were in the first.

DISCUSSION

The associations between the daily SARS-CoV-2 positive deaths, the 17 days lagged positive rate, and the daily total deaths during the first 458 days of the corona pandemic in Germany 2/24/20 through 5/26/2021 were updated and scrutinized with a focus on temporal stability or variability. A strong artificial four-phasic temporal clustering of the association between positive deaths and 17 days lagged positive rate was found. Two possible explanations for this clustering exist in principle: (1) unknown or unacknowledged natural determinants driving the pandemic, e.g., seasonality [5] and the spread of unnoticed more deadly virus variants from November 2020 onward, or (2) discontinuities and artefacts in not representative corona metrics, reporting regimes, and statistics. Beginning the series of autumn/winter lockdowns in Germany on 11/3/2020, testing of asymptomatic persons reportedly decreased. Nevertheless, testing was still mandatory for healthy people for traveling and other access reasons and the ensuing daily positive rates did not profoundly change, whereas the positive deaths sharply increased [25, 41], especially so in nursing homes despite the lockdowns [42]. Of special interest is the strict negative correlation between lagged positive rate and deaths in the 4th period in Figure 3. The slope is: -139.7 (-172.6, -106.9), p-value < 0.0001, R2 = 0.803. It is conjectured that this behaviour is not due to biologic and epidemiologic causes, but is rather an artefact of disproportionate testing frequencies of younger versus older patients, e.g., children versus the moribund parts of the population.

In view of Figure 2, Figure 3, Figure 5, and Table 3, the question arises: Was the virus or the pandemic more deadly during the second and third waves compared to the first, or reflects this discrepancy an overcounting of the COVID-19 deaths in the second and third waves, for whatever reason? Morfeld et al. [32] analysed total mortality in Germany, January to October 2020. They found no overall excess mortality expressed as total-SMR of 1.01 (0.99, 1.04). However, their approach was biased since they did not consider the secular upward trend in mortality from 2004, see Figure 4. They rather compared the mortality in 2020 with ' … an average (arithmetic and geometric) of the death counts in the reference years 2016 bis 2019' [32]. Figure 4 demonstrates no significant excess mortality in Germany in 2020, and Table 3 implies nearly 50,000 possibly overcounted deaths in the second and third waves under the assumption that the virus or the pandemic was as deadly in the second and third waves as they had been in the first. The large differences in the presumed COVID-19 deaths between the first and the subsequent waves described here call for clarification. Bassetti et al. emphasized the perils that lie in the subjective perception of information: '... we must recognize that our judgement could theoretically be at risk ... to be influenced by the numerator and the denominator we see in our everyday life [2]. In view of the findings

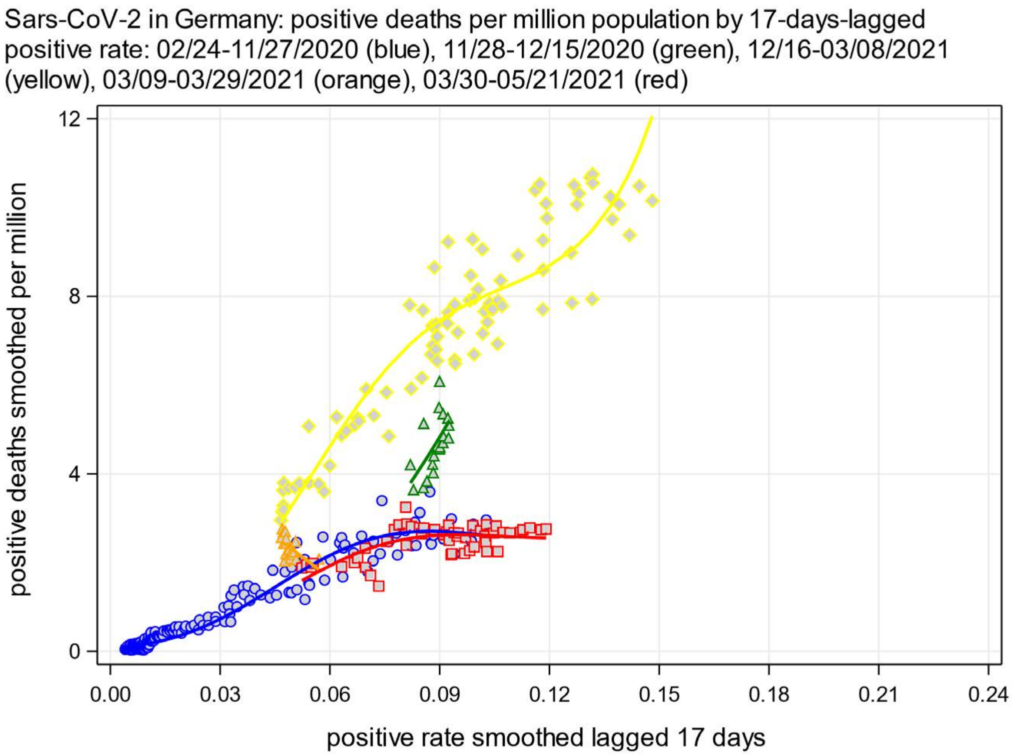

Figure 5. SARS-CoV-2 in Germany OWID data [30]: daily positive deaths smoothed by 17 days lagged positive rate stratified by period.

of this paper, we may complement the warnings by Basseti et al. with the insight that our scientific perception may also be misled by seemingly hard official figures in case the underlying scientific and administrative testing and pandemic control concepts are not sound, not stable, or not representative.

Whether vaccination in Germany starting on 12/27/2020 had already a visible effect on the pandemic until May 2021 is a difficult issue because Germany until May 2021 has vaccinated only about 10% of its population with two doses. German Medical Association President Klaus Reinhardt claimed in May 2021: whereas the vaccination coverage was "still far too low to give the all-clear", it was "nevertheless showing effect" [43]. However, it remains to be scrutinized whether this assumed vaccination effect can be separated properly from the natural seasonal variability of the pandemic. The strong decreases in positive rate and positive deaths visible in Figure 2 from January to May 2021 can thus most likely not be explained by the relatively rare vaccination in that period.

Whereas it is beyond the scope of the present paper, it is nevertheless interesting to look in every detail at the associations between lagged positive rate and positive deaths from an international perspective. Figures 5 to 7 provisionally display the corresponding OWID data [30] for Germany, United States, and India, stratified by five periods. In contrast to Germany, the United States and India show rather dissimilar associations between positive rates and positive deaths in the first and final periods. Therefore, the 1st and 5th periods were not combined in Figures 5 to 7 in contrast to in Figure 4. It shows that in all three countries there is distinct temporal clustering in principle. But the fine structure of the clustering is differing. This is likely due to unknown and unspecified determinants of the data like demographical population characteristics, reporting regimes, country-specific seasonal factors, and so on. Therefore, temporal clustering of lagged cases and deaths can be expected globally.

Major limitations of this study lie in (1) unknown precise dates of infections and deaths, (2) unknown positive rates among the deaths, as well as (3) unknown testing strategies, i.e., unknown representativeness of positive rates and positive deaths. As the weekly deaths in Germany during 2020 range from 16,168 in calendar week 28 to 25,499 in calendar week 52 the collective of the daily total deaths can be considered a relatively stable surrogate reference for the daily positive deaths. This justifies the consideration of the positive deaths without denominator or offset. The unavoidable overdispersion inherent to this approach is accounted for by ordinary regression automatically, as well as by deviance-scaled Poisson or logistic regression. The daily positive rate applies to all of Germany and can thus be taken at its face value.

Minor limitations are the provisional total deaths for 2020 by DESTATIS and the preliminary nature of the volatile RKI-data, which change from day to day because of continuous updates. However, in most cases, these changes are at most in the one-digit percent range. Another limitation is the unknown number

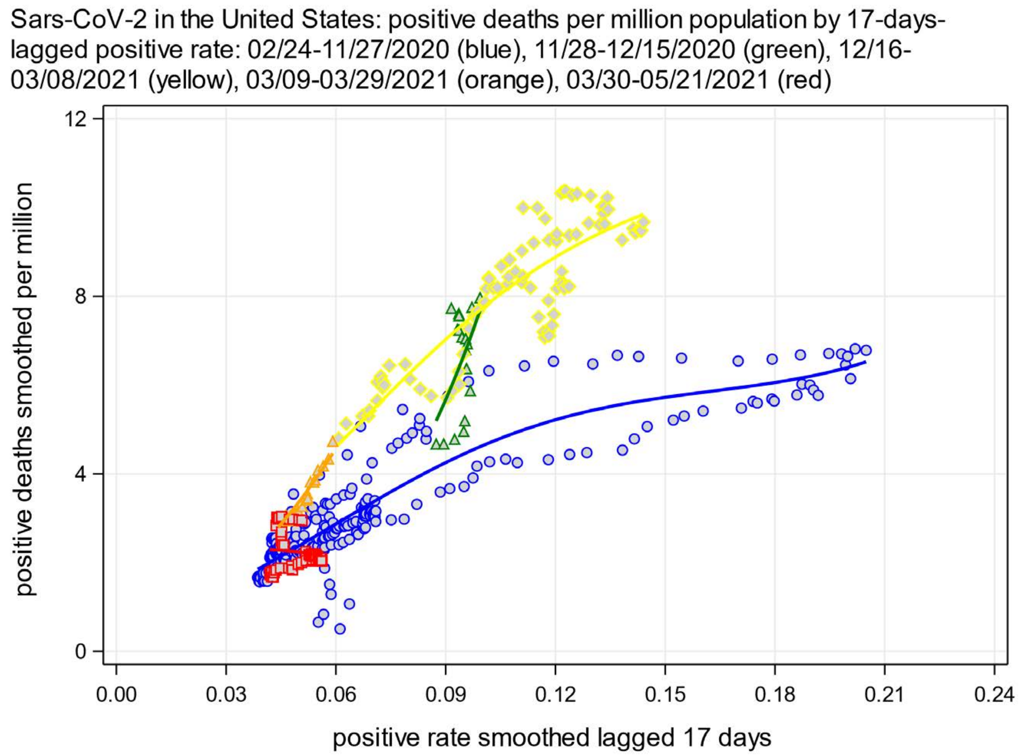

Figure 6. SARS-CoV-2 in the United States, OWID data [30]: daily positive deaths smoothed by 17 days lagged positive rate stratified by period.

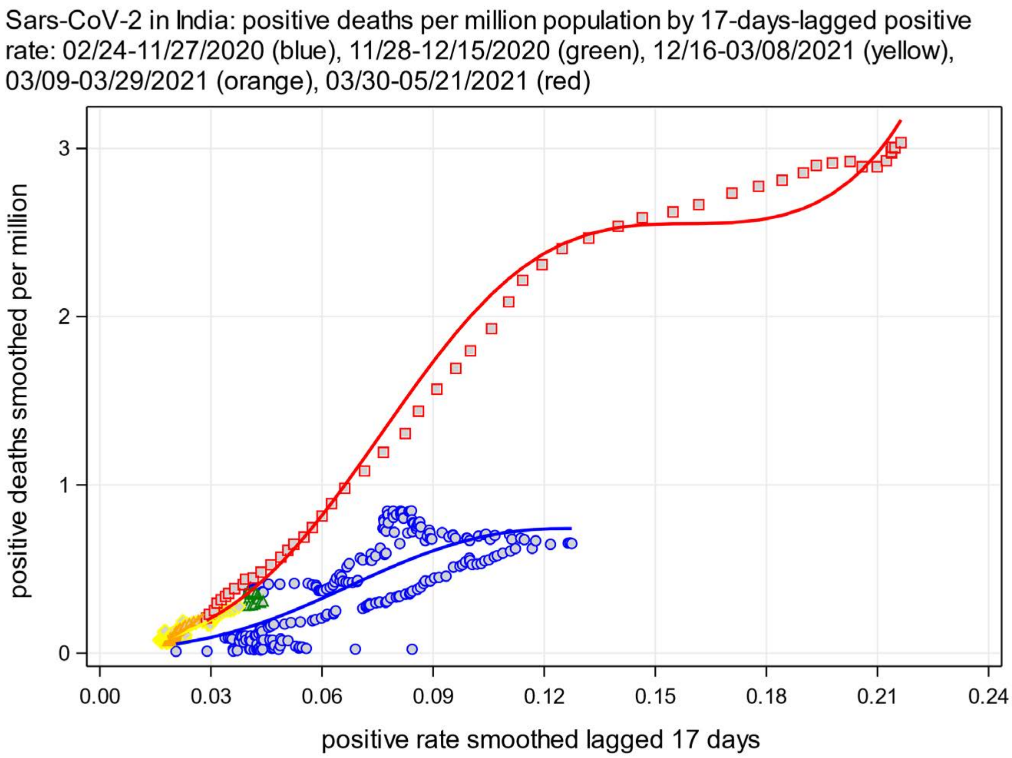

Figure 7. SARS-CoV-2 in India OWID data [30]: daily positive deaths smoothed by 17 days lagged positive rate stratified by period.

of tests performed per day. Unfortunately, only positive cases are reported. Reporting is not mandatory for negative cases, which is a considerable scientific drawback. As a substitute, the RKI reports the number of performed tests per week, which can be interpolated to tests per day. The problem is that these weekly test counts contain multiple tests for individual persons. However, it may be assumed that the number of tests reported is a reasonable proportional surrogate for the individual tests performed [25].

CONCLUSION

The presented findings demonstrate that COVID-19 death count variability may not only be high between locations [1] but may also be extremely variable within locations across periods. Ad-hoc highly aggregated ecologic SARS-CoV-2 metrics and statistics are too crude and thus inappropriate for meaningful pandemic description and control due to unknown determinants and non-representative data generation. Seasonality and other diseases are among the important, however neglected, competing risk factors of infection and mortality. Total deaths in 2020 fall well within expected limits of random variation derived from the significant mortality upward trend in Germany from 2004 to 2019. Ignoring this upward trend is unreasonable and scientifically unsound. Therefore, the characterization of the pandemic should be based on transparent and representative population-specific testing strategies of cases and deaths. In other countries, similar but not identical time clustering was observed. Analysis of the complex relationships between cases and deaths around the world is beyond the scope of this paper but is planned for future publications.

DECLARATIONS

Ethical Approval and Consent to participate

Not applicable. Ethics approval and consent to participate are not required and not necessary, since only publicly available data and previously published information is being used.

Consent for publication

Not applicable. Only anonymous data is being used.

Availability of supporting data

The employed data has exclusively been published previously and/or it is contained in the Tables and in the Figures included in this paper.

Competing interests

The author declares that he has no conflicts of interest.

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Authors' contributions

Not applicable.

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REFERENCES

1. Ioannidis JPA. Global perspective of COVID-19 epidemiology for a full-cycle pandemic. Eur J Clin Invest. 2020; 50: e13423.

2. Bassetti M, Giacobbe DR. The COVID-19 insidious trick: Subjective perception of numbers. Eur J Clin Invest. 2021; 51: e13465.

3. Saleh FA, Sleem A. COVID-19: Test, Test and Test. Med Sci (Basel). 2020; 9: 1.

4. Baker KF, Hanrath AT, van der Loeff IS, Tee SA, Capstick R, Marchitelli G, et al. COVID-19 Management in a UK NHS Foundation Trust with a High Consequence Infectious Diseases Centre: A Retrospective Analysis. Med Sci (Basel). 2021; 9: 6.

5. Petti S, Cowling BJ. Ecologic association between influenza and COVID-19 mortality rates in European countries. Epidemiol Infect. 2020; 148: e209.

6. Konrad R, Eberle U, Dangel A, Treis B, Berger A, Bengs K, et al. Rapid establishment of laboratory diagnostics for the novel coronavirus SARS-CoV-2 in Bavaria, Germany, February 2020. Euro Surveill. 2020; 25: 2000173.

7. Surkova E, Nikolayevskyy V, Drobniewski F. False-positive COVID-19 results: hidden problems and costs. Lancet Respir Med. 2020; 8: 1167-1168.

8. Borger P, Rajesh Kumar M, Michael Y, Craig C, Kevin M, Klaus S, et al. Addendum - Corman Drosten Review Report by an International Consortium of Scientists in Life Sciences (ICSLS). Available at: https://zenodo.org/record/4433503#.YLJTMPkzY2w

9. Döhla M, Boesecke C, Schulte B, Diegmann C, Sib E, Richter E, et al. Rapid point-of-care testing for SARS-CoV-2 in a community screening setting shows low sensitivity. Public Health. 2020; 182: 170-172.

10. Jaafar R, Aherfi S, Wurtz N, Grimaldier C, Hoang VT, Colson P, et al. Correlation Between 3790 Quantitative Polymerase Chain Reaction–Positives Samples and Positive Cell Cultures, Including 1941 Severe Acute Respiratory Syndrome Coronavirus 2 Isolates. Clin Infect Dis. 2020. ciaa1491.

11. Backhaus A. Common Pitfalls in the Interpretation of COVID-19 Data and Statistics. Inter Econ. 2020; 55: 162-166.

12. Kennedy AP, Yam SCP. On the authenticity of COVID-19 case figures. PLoS One. 2020; 15: e0243123.

13. Gomathi S, Kohli R, Soni M, Dhiman G, Nair R. Pattern analysis: predicting COVID-19 pandemic in India using AutoML. World Journal of Engineering, 2020. ahead-of-print(ahead-of-print).

14. Dhiman G, Chang V, Singh KK, Shankar A. ADOPT: automatic deep learning and optimization-based approach for detection of novel coronavirus COVID-19 disease using X-ray images. J Biomol Struct Dyn. 2021; 1-13.

15. Gaurav D. The Effects of Coronavirus (COVID-19) on the Psychological Health of Indian Poultry Farmers. Coronaviruses. 2021; 2: 131-132.

16. Sodhi GK, Kaur S, Gaba GS, Kansal L, Sharma A, Dhiman G. COVID-19: Role of Robotics, Artificial Intelligence, and Machine learning during pandemic. Curr Med Imaging. 2021.

17. Poongodi M, Hamdi M, Malviya M, Sharma A, Dhiman G, Vimal S. Correction to: Diagnosis and combating COVID-19 using wearable Oura smart ring with deep learning methods. Pers Ubiquitous Comput 2021; 1.

18. Singh PD, Kaur R, Singh KD, Dhiman G. A Novel Ensemble-based Classifier for Detecting the COVID-19 Disease for Infected Patients. Inf Syst Front. 2021: 1-17.

19. Dhiman G, Kumar VV, Kaur A, Sharma A. DON: Deep Learning and Optimization-Based Framework for Detection of Novel Coronavirus Disease Using X-ray Images. Interdiscip Sci. 2021; 13: 260-272.

20. Gaurav D. Psychological Impact of Coronavirus (COVID-19) Disease on Cancer Patients. Coronaviruses. 2020; 1: 1-3.

21. Puschel K, Sperhake JP. Corona deaths in Hamburg, Germany. Int J Legal Med. 2020; 134: 1267-1269.

22. Istituto Superiore di Sanità. Report sulle caratteristiche dei pazienti deceduti positivi all'infezione da SARS-CoV-2 in Italia Aggiornamento del 27 gennaio 2021. 2020 [cited 2021 February 25]. Available from: https://www.epicentro.iss.it/coronavirus/sars-cov-2-decessi-italia.

23. Centers for Disease Control [Internet]. Understanding Death Data Quality: Cause of Death from Death Certificates. 2021. [cited 2021 May 12]. Available from: https://www.cdc.gov/nchs/data/nvss/coronavirus/cause-of-death-data-quality.pdf.

24. Robert Koch Institut [Internet]. Epidemiological profile on SARS-CoV-2 and COVID-19. 2021 [cited 2021 Mar 12]. Available from: https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/Steckbrief.html;jsessionid=9E18A09DFAB8F6563093DCF5B5DFFD5C.internet112?nn=13490888#doc13776792bodyText7.

25. Scherb H. SARS-CoV-2 in Germany: Association between deaths and positive rate. Eur J Clin Invest. 2021; 51: e13500.

26. Iacobucci G. Covid-19: Validity of key studies in doubt after leading journals issue expressions of concern. BMJ. 2020; 369: m2224.

27. Jewell NP, Lewnard JA, Jewell BL. Caution Warranted: Using the Institute for Health Metrics and Evaluation Model for Predicting the Course of the COVID-19 Pandemic. Ann Intern Med. 2020; 173: 226-227.

28. Eker S. Validity and usefulness of COVID-19 models. Humanit Soc Sci Commun. 2020; 7: 54.

29. Scheiner S, Ukaj N, Hellmich C. Mathematical modeling of COVID-19 fatality trends: Death kinetics law versus infection-to-death delay rule. Chaos Solitons Fractals. 2020; 136: 109891.

30. Our World in Data [Internet]. Research and data to make progress against the world's largest problems. 2021 [cited 2021 May 22]. Available from: https://ourworldindata.org/.

31. Morfeld P, Erren TC. [Deaths in nine regions of Italy in February/March 2020: "Mortality Excess Loupe" for SARS-CoV-2/COVID-19-Epidemiology in Germany]. Gesundheitswesen. 2020; 82: 400-406.

32. Morfeld P, Timmermann B, Groß VJ, Lewis P, Erren TC. [COVID-19: How did mortality change? - Mortality of women and men in Germany and its federal states until October 2020]. Dtsch Med Wochenschr. 2021; 146: 129-131.

33. Giattino C, Ritchie H, Roser M, Ortiz-Ospina E, Hasell J. Statistics and Research: Excess mortality during the Coronavirus pandemic (COVID-19). 2020 [cited 2021 May 13]. Available from: https://ourworldindata.org/excess-mortality-covid.

34. Robert Koch Institute [Internet]. COVID-19-Dashboard. 2021 [cited 2021 May 13]. Available from: https://experience.arcgis.com/experience/478220a4c454480e823b17327b2bf1d4/page/page_1

35. DESTATIS, Sonderauswertung zu Sterbefallzahlen der Jahre 2020/2021. 2021 [cited 2021 May 11]. Available from: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Sterbefaelle-Lebenserwartung/sterbefallzahlen.html.

36. Schechtman E, Shelef A. Correlation and the time interval over which the variables are measured - A non-parametric approach. PLoS One. 2018; 13: e0206929.

37. DESTATIS, Statistik der Sterbefälle, Statistisches Bundesamt Deutschland. 2021 [cited 2021 May 13]. Available from: https://www.regionalstatistik.de/genesis/online?operation=statistic&levelindex=0&levelid=1614272551425&code=12613#abreadcrumb.

38. Turner SL, Karahalios A, Forbes AB, Taljaard M, Grimshaw JM, Cheng AC, et al., Design characteristics and statistical methods used in interrupted time series studies evaluating public health interventions: protocol for a review. BMJ Open. 2019; 9: e024096.

39. Carlstein E, Müller HG, Siegmund D. Change-Point Problems (Lecture Notes - Monograph Series: Volume 23) Lecture Notes - Monograph Series : Vol. 23. 1994, Bethesda: Institute of Mathematical Statistics.

40. Ioannidis JPA, Axfors C, Contopoulos-Ioannidis DG. Population-level COVID-19 mortality risk for non-elderly individuals overall and for non-elderly individuals without underlying diseases in pandemic epicenters. Environ Res. 2020; 188: 109890.

41. Melnick ER, Ioannidis JPA. Should governments continue lockdown to slow the spread of covid-19? BMJ. 2020; 369: m1924.

42. Eberle L, Feldenkirchen M, Hassenkamp M, Knobbe M, Medick V, Rosenbach M, et al. Spiegel international. Germany Is Faring Poorly in the Second Wave of the Coronavirus. 2020 [cited 2021 May12]. Available from: https://www.spiegel.de/international/germany/germany-is-faring-poorly-in-the-second-wave-of-the-coronavirus-a-afc634db-9220-496b-8aca-fd19f2e0962f.

43. Welle D. Germany's COVID vaccine campaign 'showing effect'. 2021 [cited 2021 May 25]. Available from: https://www.dw.com/en/germanys-covid-vaccine-campaign-showing-effect/a-57426369.

44. Turner SL, Karahalios M, Forbes AB, Taljaard M, Grimshaw JM, Cheng AC, et al. Design characteristics and statistical methods used in interrupted time series studies evaluating public health interventions: a review. J Clin Epidemiol. 2020; 122: 1-11.

45. Statistisches Bundesamt (Destatis) Bevölkerungsstand am 30. September 2020. [Cited 2021 Jan 7]. Available from: https://www.destatis.de/DE/Themen/Gesellschaft-Umwelt/Bevoelkerung/Bevoelkerungsstand/Tabellen/zensus-geschlecht-staatsangehoerigkeit-2020.html.

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