

One year of SARS-CoV-2 pandemic: comparison of infection between health care workers and general population before and after vaccination

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KEYWORDS: SARS-CoV-2; COVID-19; RT-PCR; healthcare workers; epidemiology; vaccination

ABSTRACT

Background: *The Covid-19 pandemic in Italy has been characterized by three waves of infection during 2020. Vaccination of healthcare workers started in January 2021, earlier than that of other population groups. The main aim of this study is to compare the spread of the pandemic between HCW and the general population focusing on potential effects of the vaccination. Methods:* *The study consisted of a retrospective analysis of results of RT-PCR tests performed between 6 March 2020 and 4 April 2021 among HCWs from Bologna, Italy, and those of the general population of Emilia Romagna region. We calculated the crude proportion of positive RT-PCR tests over total tests and the crude prevalence of positive test in population; then, we conducted joinpoint analyses using the Joinpoint Regression Program of the National Cancer Institute. Results:* *The results of the joinpoint analysis show that both ϕ and ψ ratio indicators have a similar pattern, with a sharp increase during the early phase of the pandemic, and a strong decrease at the end of the first wave around week 15. In both indicators there are no significant changes in the trend after week 25. Pandemic spread among HCWs appeared earlier than in the general population, but it otherwise appeared to have comparable features. A decline in infection was apparent among HCWs after vaccination. Conclusions:* *Surveillance of HCWs would inform on the epidemic in the general population. The apparent effectiveness of the anti-SarsCoV2 vaccine will likely occur in the general population.*

INTRODUCTION

Coronavirus are RNA viruses of the family Coronaviridae (1, 2), which consist of alpha CoV, beta CoV, gamma CoV and delta CoV genera based on genomic structure(3).

Seven different coronaviruses from alpha and beta genera are known to infect and cause disease in humans. These include viruses that cause severe acute respiratory syndrome (SARS-CoV), the Mid-

dle East respiratory syndrome (MERS-CoV) (4), and SARS-CoV-2. All of them are relatively highly infective and lethal.

In December 2019, for the first time a large number of viral pneumonia was reported in Wuhan city, Hubei province, China (5). The virus was initially named the 2019 novel coronavirus (2019-nCoV), but then the International Committee of Taxonomy of Viruses named it SARS-CoV-2 (6).

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Due to globalization, intercultural exchanges and intercontinental travels, the SARS-CoV-2 spread rapidly around the world, and since the onset, the number of infected individuals and deaths has risen constantly; in fact, as of the end of April 2021, COVID-19 has already been responsible for 148 million infections and more than 3 million deaths globally (7).

Considering this, countries all around the world planned prevention strategies to reduce the transmission rate and consequently, the burden of COVID-19. Therefore, scientific research in the world has focused on development of vaccine against SARS-CoV-2 (8).

In Italy, Coronavirus spread started in February 2020, and the government reacted by adopting containment measurements, including a national lockdown between March and May 2020. Furthermore, pandemic spread has led to strong consequences on healthcare system (9).

Vaccination of Italian healthcare workers (HCWs) started at the end of December 2020, while that of other population groups started in March 2021.

We aimed at studying the patterns of the infection in HCWs compared to the general population, with focus on potential effects of the vaccination campaign.

METHODS

The study consisted of a retrospective analysis of results of RT-PCR tests performed among HCWs employed in a large university hospital, in a specialized orthopedic hospital or in other public hospitals in Bologna, Northern Italy, that were included in a surveillance program managed by the Occupational Health Unit of the university hospital.

These data were compared to those of the population of Emilia Romagna, the region in which Bologna is located; these data were obtained from the national Civil Protection Authority (10).

HCWs who either experienced a close contact with a confirmed case of Covid-19 (whether a coworker or a patient) or exhibited symptoms compatible with COVID-19 (either two major symptoms, including cough, sore throat, fever, myalgia, asthenia, anosmia, ageusia, and dyspnea, or one major and two minor symptoms, including rhinorrhea, chills, arthralgia, diarrhea, conjunctivitis, and vesicular

erythema) were tested for SARS-CoV-2 infection and were included in a surveillance program, that included telephone contacts for symptoms monitoring and, where required, the prescription of medications. A further group of asymptomatic HCWs were screened on a voluntary basis.

Nasopharyngeal/oropharyngeal swab samples were analyzed by RT-PCR according to the guidelines proposed by the World Health Organization (11). Samples were collected between 6 March 2020 and 4 April 2021.

We abstracted results for the same period on swabs provided by the Civil Protection Authority, based on aggregate data provided by the Regions coordinated by the Ministry of Health, with the support of the Civil Protection and the National Institute of Public Health, to collect timely information on the number of positive tests, deaths, hospital admissions and intensive care admissions in each Province of Italy. Because of lack COVID-19 tests during pandemic spreads, swabs were mainly performed on symptomatic persons and asymptomatic close contacts; furthermore, we have no data about age, sex and job title in the general population.

Since the data on RT-PCR tests in the regional population are available only in aggregate form, and it is not possible to link the results of multiple tests performed by the same individual, we performed the analysis on the data aggregated by week, under the assumption that it was unlikely that the same individual tested positive more than once within the same week. In other words, the number of positive tests during a week represents a good approximation of the number of subjects who tested positive during that week. We tested this assumption using the data on HCWs. We abstracted, for both HCWs and the general population; the number of positive tests, the number of tests performed, and the number of people at risk, the latter was considered constant over time for each week between March 9, 2020 and April 4, 2021.

We then calculated, for each week and for both HCWs and the general population, the crude proportion of positive RT-PCR tests over total tests (p), and the crude prevalence of positive test in the population (q). We then used 2 letters of the Greek alphabet to calculate the ratios of these indicators among HCWs and in the general population: φ

= $p(\text{HCW}) / p(\text{pop})$; $\psi = q(\text{HCW}) / q(\text{pop})$, and analyzed how they changed over time. To this aim we conducted joinpoint analyses using the Joinpoint Regression Program of the National Cancer Institute (Joinpoint Regression Program, Version 4.9.0.0. Statistical Research and Applications Branch, National Cancer Institute, March 2021) (12) to identify changes in trends over time, setting the maximum number of changes to 5.

Vaccination of HCWs started at the end of December 2020. Almost all vaccinated HCWs received a double dose of the Comirnaty vaccine (BioNTech/Pfizer), while only a very small percentage in the final phase of the vaccination campaign received the Moderna COVID-19 (mRNA-1273) vaccine or the Oxford / AstraZeneca COVID-19 vaccine.

RESULTS

From March 9, 2020 to April 4, 2021, a total of 20,109 HCWs were included in the study, of whom 7,451 from the university hospital, 1,703 from a specialized orthopedic hospital and 10,955 from other public hospitals. Among them, a total of 96,122 RT-PCR tests were performed (average 4.8

tests/HCW), of which 5,187 were positive (5.4%), 90,627 were negative and 308 were not interpretable. A total of 2,968 HCW (14.8%) had at least one positive test (average 1.75 positive tests/positive HCW); among multiple positive tests in the same HCW, 165 (3.18% of all positive tests) were performed in the same week. Descriptive results of HCWs RT-PCR tests are shown in Table 1.

In the same period among the general population of Emilia Romagna ($N = 4,474,292$), a total of 4,958,917 RT-PCR tests were performed (average 1.1 test/subject), of which 341,735 were positive (6.9%), and 4,617,182 were negative. Detailed results by week are reported in Supplementary Table 1.

The trends of the proportion of positive RT-PCR tests over total tests (p) and of the prevalence of positive tests in the population (q) in both HCW and regional population are shown in Figures 1 and 2, respectively. The ratios between HCW and the regional populations (ϕ and ψ) are shown in Figures 3 and 4.

The results of the joinpoint analysis are shown in Supplementary Table 1. Both ϕ and ψ ratio indicators show a similar pattern, with a sharp increase during the early phase of the pandemic, and a strong

Table 1. Descriptive analysis of HCWs RT-PCR tests by gender, age and job title

	Negatives, No.	Not Interpretable, No.	Positives, N.	Total, n.
Total	90,627	308	5,187	96,122
Sex				
Men	26,018	75	1,549	27,642
Women	64,048	233	3,587	67,868
Not available	/	/	/	612
Age group				
<35	23,728	59	1,291	25,078
35-44	19,922	70	1,112	21,104
45-54	25,434	81	1,491	27,006
55+	20,990	98	1,243	22,331
Not available	/	/	/	603
Job title				
Administration	662	3	47	712
Physician	21,860	58	1,054	22,972
Nurse	40,903	118	2,367	43,388
Other HCW	27,202	129	1,719	29,050

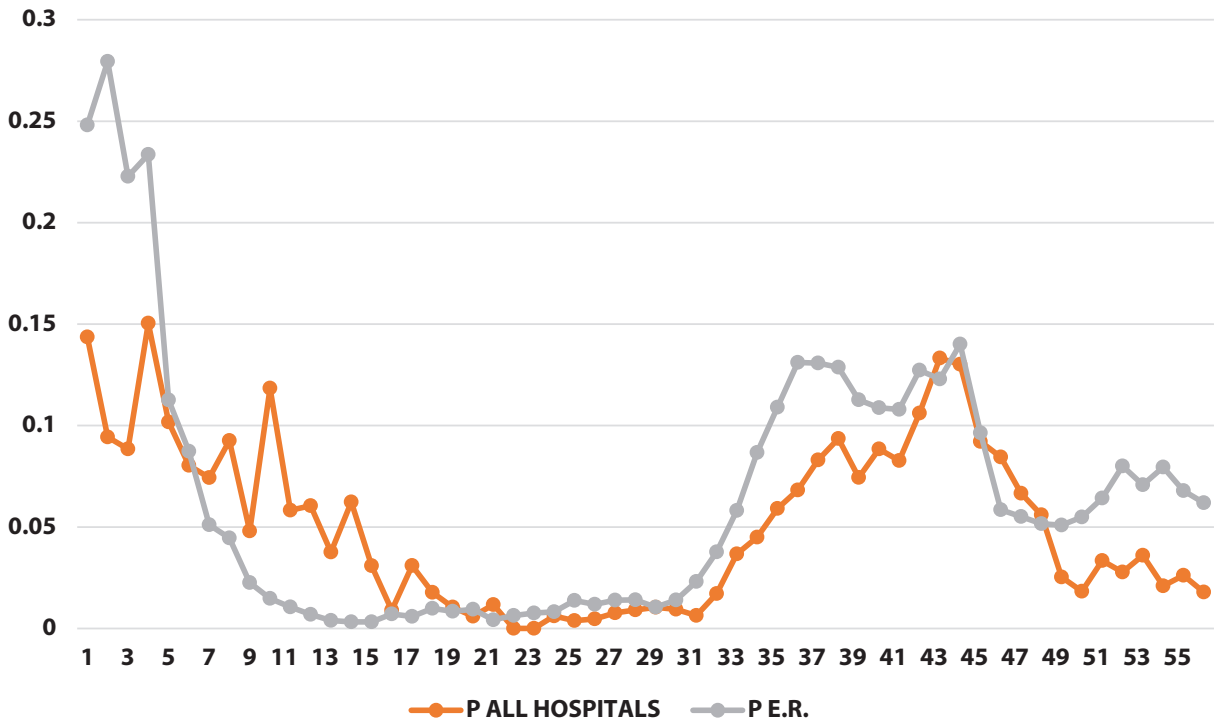


Figure 1. Proportion of positive swabs [p] (on the y-axis) as a function of weeks (on the x-axis)

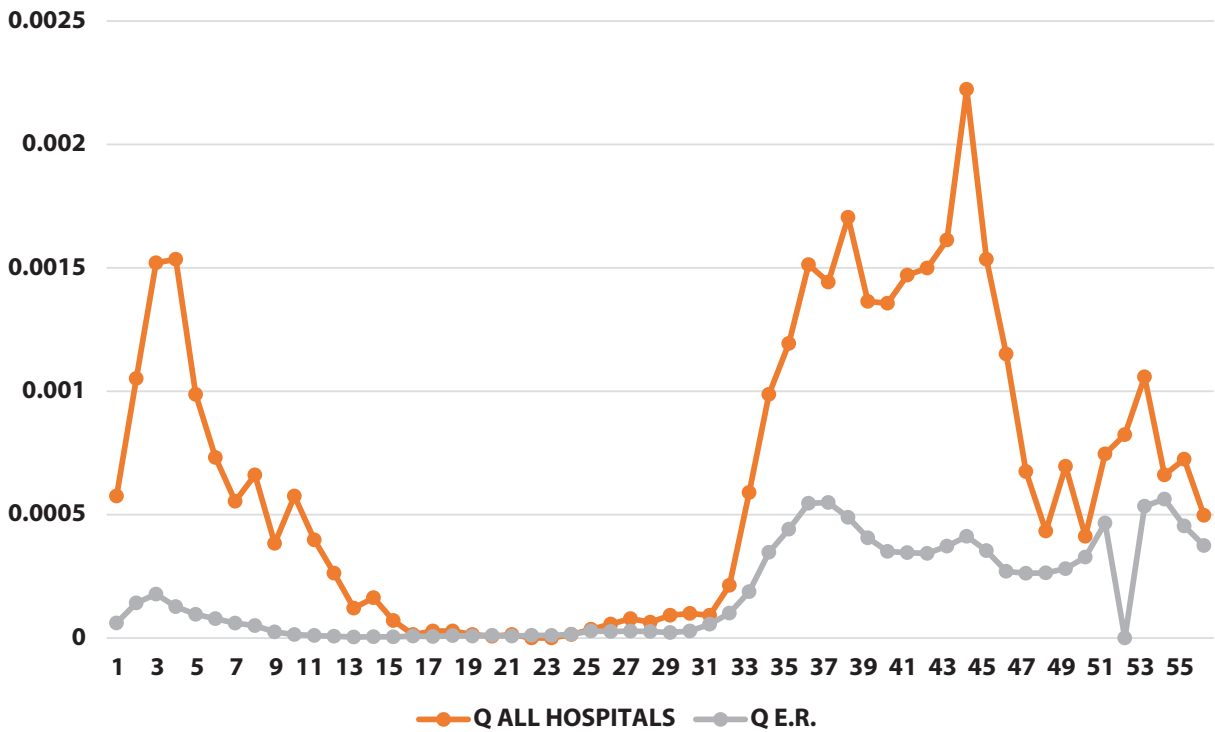


Figure 2. Positivity rate [q] (on the y-axis) as a function of weeks (on the x-axis)

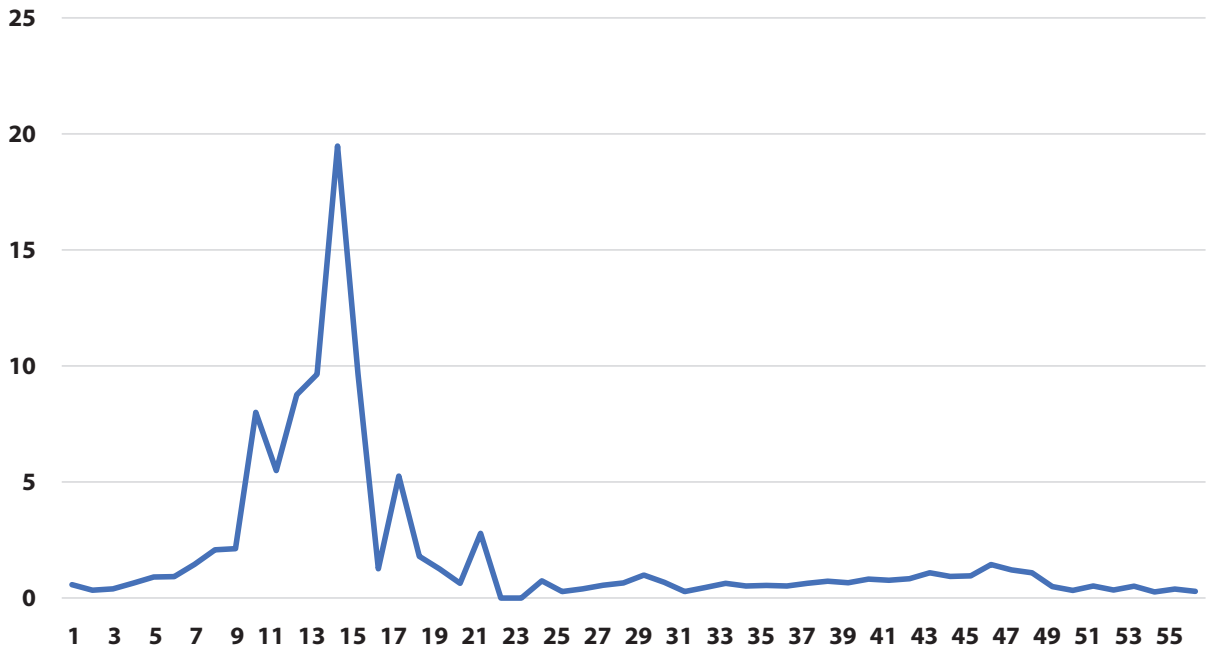


Figure 3. Ratio between proportion of positive swabs [ϕ] (on the y-axis) as a function of weeks (on the x-axis)

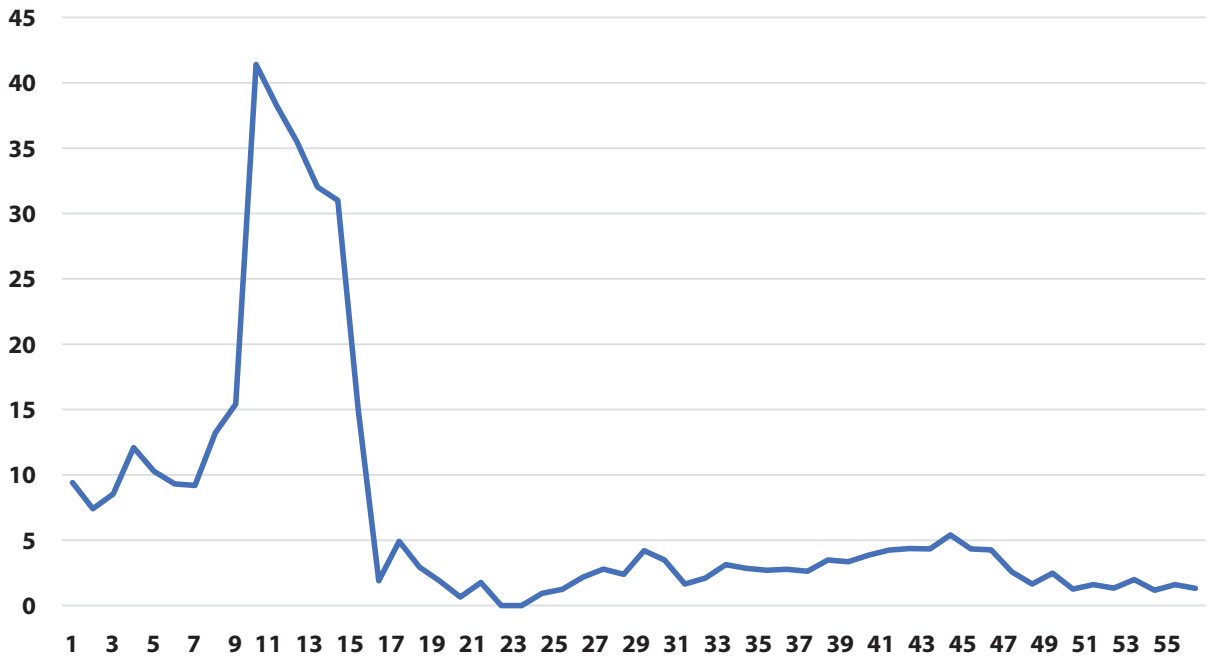


Figure 4. Ratio between positivity rate [ψ] (on the y-axis) as a function of weeks (on the x-axis)

decrease at the end of the first wave around week 15. In both indicators there are no significant changes in the trend after week 25.

However, when we restricted the joinpoint analysis starting from week 26 (beginning of September 2020, i.e., excluding the first wave of the epidemic) we could observe a significant decrease for the ratio of prevalence of positive tests over total tests (indicator ϕ) starting from week 47 (end of January, slope=-0.29) and for the ratio of the prevalence of positive tests in the population (indicator ψ) starting from week 41 (end of December, slope=-0.23). (Table 2)

DISCUSSION

Between March 2020 and April 2021, each HCW from public hospitals in Bologna performed an average of 4.8 RT-PCR tests, with 5.4% overall positive results. As expected, the number of tests performed in the population of the region was lower (1.1 test/person), and the proportion of positive tests was higher (6.9%). While we were able to calculate that 14.8% of HCWs was tested positive at least once, we cannot provide a comparable number for the regional population.

Data on RT-PCR tests in the regional population are only available in aggregate form and it is not possible to link the results of multiple tests performed by the same individual; we therefore performed the analysis on aggregate data per week, under the assumption that it was unlikely that the same individual had tested positive more than once in the same week. Among multiple positive tests in the same HCW, 165 (3.18% of all positive tests)

were performed in the same week; it is likely that in the regional population this percentage is even lower, due to the lower proportion of people being tested compared to HCWs. (Supplementary Figure 1)

While the trends in the general population have been previously reported, both for Emilia-Romagna region and for Italy at large, few reports have been published on prevalence of infection in HCWs. [13]

In an Italian HCWs seroprevalence study during the first wave of last spring, no differences in seropositivity were observed by sex, while older HCWs had higher positivity than other groups, and nurses had higher positivity compared to physicians, but not other HCWs (14).

In an American study, results indicate that vaccination can have a substantial impact on mitigating COVID-19 outbreaks, even with limited protection against infection (15).

In another American study SARS-CoV-2 cases occurred in 1.4% of HCWs given at least a first dose and 0.3% of HCWs given both vaccine doses; the results indicate a positive impact of COVID-19 vaccines on SARS-CoV-2 case rates (16).

The main result of our analysis is that pandemic spread among HCWs appears earlier than in the general population, but it otherwise appears to have comparable features (curve slope). Furthermore, the decline in infection among HCWs after vaccination is shown, that can be considered an indirect measure of the effectiveness of the anti-SarsCoV2 vaccine, and will likely occur also in the general population. Joinpoint regression demonstrated a clear effect of vaccination with decrease of the variable ϕ starting from week 47 (end of January, slope=-0.29)

Table 2. Slopes in Joinpoint Regression (week 26-56)

	1	2	3	4	5	6
p (Hospitals)*	+33.05 (26-36)	+6.03 (36-44)	-15.62 (44-56)	/	/	/
p (E.R.)*	-5.53 (26-29)	+48.15 (29-35)	+0.48 (35-44)	-27.28 (44-47)	+7.45 (47-54)	-12.75 (54-56)
q (Hospitals)*	+54.10 (26-35)	+2.97 (35-45)	-36.42 (45-48)	+16.36 (48-53)	-19.17 (53-56)	/
q (E.R.)*	-10.05 (26-29)	+71.52 (29-35)	-5.05 (35-49)	+34.05 (49-52)	-10.37 (52-56)	/
Ratio p (ϕ)	+0.16 (26-29)	-0.19 (29-32)	+0.06 (32-47)	-0.29 (47-50)	-0.01 (50-56)	/
Ratio q (ψ)	+0.53 (26-29)	-0.63 (29-32)	+0.28 (32-41)	-0.23 (41-56)	/	/

*values transformed into logarithms; p - Proportion of positive swabs; q - Positivity rate

and of the variable ψ starting from week 41 (end of December, slope=-0.23) (Table 2). This analysis allows to demonstrate that the difference of the slopes before and after the change is significant.

There are several limitations to this study. First of all, for the data in the general population we relied on published data from government websites, and could not assess the validity of the datasets.

Secondly, we compared the data of HCW from the city of Bologna with those of the population of the whole region. The comparison might be inappropriate during the first wave of the epidemic, in which the distribution of infections was particularly high in areas of the regions outside Bologna. In addition, p and q indicators are influenced by rate of testing among HCWs and general population (accessibility of swab test was higher for HCWs). (Supplementary Figure 1)

The last issue is the lack of information on determinants of infection in the general population. Previous studies conducted among HCWs try to prove the effectiveness of the use of PPE, before the vaccination campaign; a multicentric study performed during spring 2020, showed no differences of infection risk in job titles, but a decline in risk with the use of surgical mask, with not additional protection by use filtering facepiece 2 or 3 (FFP2/FFP3) (13).

The main strength of our study lies in being able to have a large number of data: (i) population of HCWs is composed by 20,109 persons, while Emilia-Romagna residents are 4,474,292; (ii) the period of observation was long (56 weeks).

CONCLUSION

The main result of our analysis is that pandemic spread among HCWs appears earlier than in the general population, but it otherwise appears to have comparable features.

Furthermore, the decline in infection among HCWs after vaccination is demonstrated and it can be considered an indirect measure of the effectiveness of the anti-SarsCoV2 vaccine. Other studies are needed to define how long that effect will last.

DECLARATIONS: Ethics approval and consent to participate. All methods were carried out in accordance with relevant guidelines and regulations. The study was reviewed

and considered exempt by the Ethics Committee of the University of Bologna. Informed consent was not deemed necessary by the Ethics Committee of the University of Bologna.

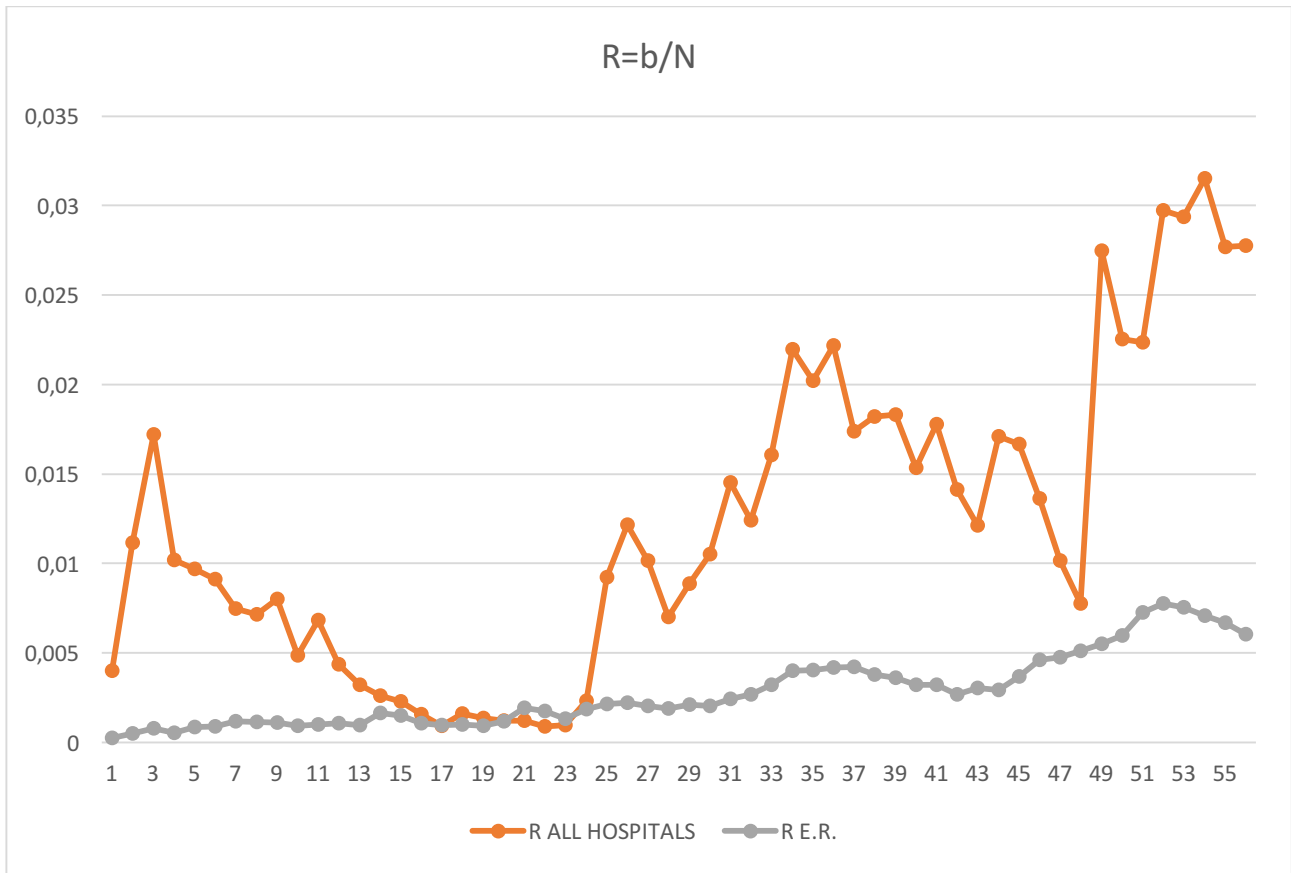
COMPETING INTEREST: None to declare.

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Supplementary figure 1. Rate of making swabs (r)



WEEK	Nweek	AOSP				UNIBO				AOSP + UNIBO (N=52157)					AUSL (N=76685)					IOR (N=11921)										
		POS	NEG	N.D.	TOTAL	POS	NEG	N.D.	TOTAL	A AOSP	NEG	N.D.	B AOSP	P AOSP	Q AOSP	R AOSP	A AUSL	NEG	N.D.	B AUSL	P AUSL	Q AUSL	R AUSL	A IOR	NEG	N.D.	B IOR	P IOR	Q IOR	R IOR
9.3-15.3	1	20	181	0	201	16	46	0	62	36	227	0	263	0,137	0,0007	0,005	35	222	3	260	0,135	0,0005	0,003	10	31	0	41	0,244	0,0008	0,003
16.3-22.3	2	32	384	0	416	7	114	0	121	39	498	0	537	0,073	0,0007	0,01	81	722	0	803	0,101	0,0011	0,01	28	201	0	229	0,122	0,0023	0,019
23.3-29.3	3	46	673	6	725	7	145	4	156	53	818	10	881	0,06	0,001	0,017	122	1021	8	1151	0,106	0,0016	0,015	39	344	5	388	0,101	0,0033	0,033
30.3-5.4	4	60	477	0	537	11	71	0	82	71	548	0	619	0,115	0,0014	0,012	113	486	0	599	0,189	0,0015	0,008	32	186	0	218	0,147	0,0027	0,018
6.4-12.4	5	48	609	0	657	3	61	0	64	51	670	0	721	0,071	0,001	0,014	84	435	2	521	0,161	0,0011	0,007	4	120	0	124	0,032	0,0003	0,01
13.4-19.4	6	43	410	0	453	3	76	0	79	46	486	0	532	0,086	0,0009	0,01	42	535	0	577	0,073	0,0005	0,008	15	158	0	173	0,087	0,0013	0,015
20.4-26.4	7	27	397	0	424	4	55	0	59	31	452	0	483	0,064	0,0006	0,009	45	439	1	485	0,093	0,0006	0,006	2	80	0	82	0,024	0,0002	0,007
27.4-3.5	8	22	315	0	337	5	43	0	48	27	358	0	385	0,07	0,0005	0,007	62	451	0	513	0,121	0,0008	0,007	4	103	0	107	0,037	0,0003	0,009
4.5-10.5	9	11	380	0	391	0	64	0	64	11	444	0	455	0,024	0,0002	0,009	42	574	0	616	0,068	0,0005	0,008	1	53	0	54	0,019	8E-05	0,005
11.5-17.5	10	17	171	0	188	0	30	0	30	17	201	0	218	0,078	0,0003	0,004	61	335	0	396	0,154	0,0008	0,005	3	67	0	70	0,043	0,0003	0,006
18.5-24.5	11	13	160	0	173	0	22	0	22	13	182	0	195	0,067	0,0002	0,004	42	677	0	719	0,058	0,0005	0,009	1	46	0	47	0,021	8E-05	0,004
25.5-31.5	12	5	179	0	184	2	16	0	18	7	195	0	202	0,035	0,0001	0,004	29	338	0	367	0,079	0,0004	0,005	1	42	0	43	0,023	8E-05	0,004
1.6-7.6	13	3	83	0	86	0	28	0	28	3	111	0	114	0,026	6E-05	0,002	14	282	0	296	0,047	0,0002	0,004	0	42	0	42	0	0	0,004
8.6-14.6	14	2	59	0	61	2	21	0	23	4	80	0	84	0,048	8E-05	0,002	18	227	0	245	0,073	0,0002	0,003	1	39	0	40	0,025	8E-05	0,003
15.6-21.6	15	0	67	0	67	0	32	0	32	0	99	0	99	0	0	0,002	9	151	0	160	0,056	0,0001	0,002	1	64	0	65	0,015	8E-05	0,005
22.6-28.6	16	0	57	0	57	0	16	0	16	0	73	0	73	0	0	0,001	1	108	0	109	0,009	1E-05	0,001	1	40	0	41	0,024	8E-05	0,003
29.6-5.7	17	0	44	0	44	0	9	0	9	0	53	0	53	0	0	0,001	1	57	0	58	0,017	1E-05	8E-04	3	15	0	18	0,167	0,0003	0,002
6.7-12.7	18	0	46	0	46	0	20	0	20	0	86	0	86	0	0	0,001	3	116	0	119	0,025	4E-05	0,002	1	39	0	40	0,025	8E-05	0,003
13.7-19.7	19	0	60	0	60	0	17	0	17	0	77	0	77	0	0	0,001	1	98	0	99	0,01	1E-05	0,001	1	13	0	14	0,071	8E-05	0,001
20.7-26.7	20	0	29	0	29	0	5	0	5	0	34	0	34	0	0	7E-04	0	76	0	76	0	0	1E-03	1	57	0	58	0,017	8E-05	0,005
27.7-2.8	21	1	70	0	71	0	10	0	10	1	80	0	81	0,012	2E-05	0,002	1	77	0	78	0,013	1E-05	0,001	0	12	0	12	0	0	0,001
3.8-9.8	22	0	36	0	36	0	13	0	13	0	49	0	49	0	0	9E-04	0	64	0	64	0	0	8E-04	0	12	0	12	0	0	0,001
10.8-16.8	23	0	39	0	39	0	16	0	16	0	55	0	55	0	0	0,001	0	64	0	64	0	0	8E-04	0	15	0	15	0	0	0,001
17.8-23.8	24	2	116	0	118	0	43	0	43	2	159	0	161	0,012	4E-05	0,003	0	132	0	132	0	0	0,002	0	35	0	35	0	0	0,003
24.8-30.8	25	4	180	0	184	0	61	0	61	4	241	0	245	0,016	8E-05	0,005	1	939	0	940	0,001	1E-05	0,012	0	111	0	111	0	0	0,009
31.8-6.9	26	4	242	0	246	2	83	0	85	6	325	0	331	0,018	0,0001	0,006	2	1255	0	1257	0,002	3E-05	0,016	0	124	0	124	0	0	0,01
7.9-13.9	27	8	355	0	363	1	63	0	64	9	418	0	427	0,021	0,0002	0,008	2	869	0	871	0,002	3E-05	0,011	0	132	0	132	0	0	0,011
14.9-20.9	28	6	200	1	207	0	42	0	42	6	242	1	249	0,024	0,0001	0,005	3	620	1	624	0,005	4E-05	0,008	0	112	0	112	0	0	0,009
21.9-27.9	29	3	223	0	226	3	72	0	75	6	295	0	301	0,02	0,0001	0,006	7	788	0	795	0,009	9E-05	0,01	0	152	0	152	0	0	0,013
28.9-4.10	30	5	155	0	160	2	62	0	64	7	217	0	224	0,031	0,0001	0,004	7	1163	0	1170	0,006	9E-05	0,015	0	88	0	88	0	0	0,007
5.10-11.10	31	5	413	0	418	3	98	0	101	8	511	0	519	0,015	0,0002	0,01	5	1454	0	1459	0,003	7E-05	0,019	0	66	0	66	0	0	0,006
12.10-18.10	32	15	315	0	330	6	144	0	150	21	459	0	480	0,044	0,0004	0,009	8	1180	0	1188	0,007	0,0001	0,015	1	80	0	81	0,012	8E-05	0,007
19.10-25.10	33	25	478	0	503	7	156	0	163	32	634	0	666	0,048	0,0006	0,013	42	1375	0	1417	0,03	0,0005	0,018	0	170	0	179	0	0	0,015
26.10-1.11	34	44	827	1	872	12	153	1	166	56	980	2	1038	0,054	0,0011	0,02	70	1751	0	1821	0,038	0,0009	0,024	13	221	0	234	0,056	0,0011	0,02
2.11-8.11	35	45	688	1	734	13	123	0	136	58	811	1	870	0,067	0,0011	0,017	106	1637	1	1744	0,061	0,0014	0,023	4	226	0	230	0,017	0,0003	0,019
9.11-15.11	36	65	709	0	774	8	146	0	154	73	855	0	928	0,079	0,0014	0,018	122	1757	2	1881	0,065	0,0016	0,025	18	296	0	314	0,057	0,0015	0,026
16.11-22.11	37	69	528	0	597	11	119	1	131	80	647	1	728	0,11	0,0015	0,014	111	1423	0	1534	0,072	0,0014	0,02	12	172	0	184	0,065	0,001	0,015
23.11-29.11	38	65	457	2	524	15	114	0	129	80	571	2	653	0,123	0,0015	0,013	141	1559	2	1702	0,083	0,0018	0,022	19	191	0	210	0,09	0,0016	0,018
30.11-6.12	39	61	320	0	381	14	121	0	135	75	441	0	516	0,145	0,0014	0,01	106	1687	8	1801	0,059	0,0014	0,023	11	252	0	263	0,042	0,0009	0,022
7.12-13.12	40	66	293	1	360	12	108	0	120	78	401	1	480	0,163	0,0015	0,009	98	1342	16	1456	0,067	0,0013	0,019	15	208	0	223	0,067	0,0013	0,019
14.12-20.12	41	73	314	1	388	13	144	0	157	86	458	1	545	0,158	0,0016	0,01	112	1657	2	1771	0,063	0,0015	0,023	9	177	0	186	0,048	0,0008	0,016
21.12-27.12	42	91	281	0	372	10	122	0	132	101	403	0	504	0,2	0,0019	0,01	104	1287	5	1396	0,074	0,0014	0,018	6	83	0	89	0,067	0,0005	0,007
28.12-3.1	43	83	292	0	375	14	55	0	69	97	347	0	444	0,218	0,0019	0,009	124	1077	5	1206	0,103	0,0016	0,016	6	48	0	54	0,111	0,0005	0,005
4.1-10.1	44	87	344	1	432	13	85	0	98	100	429	1	530	0,189	0,0019	0,01	208	1632	2	1842	0,113	0,0027	0,024	5	28	0	33	0,152	0,0004	0,003
11.1-17.1	45	59	187	0	246	10	93	0	103	69	280	0	349	0,198	0,0013	0,007	146	1792	17	1955	0,075	0,0019	0,025	1	39	0	40	0,025	8E-05	0,003
18.1-24.1	46	39	259	0	298	11	82	0	93	50	341	0	391	0,128	0,001	0,007	108	1373	5	1486	0,073	0,0014	0,019	4	37	0	41	0,098	0,0003	0,003
25.1-31.1	47	34	206	1	241	7	59	0	66	41	265	1	307	0,134	0,0008	0,006	52	1039	5	1095	0,047	0,0007	0,014	3	22	0	25	0,12	0,0003	0,002
1.2-7.2	48	18	227	0	245	3	51	0	54	21	278	0	299	0,07	0,0004															

TUTTE LE AZIENDE (N=140763)										POPOLAZIONE GENERALE E.R. (N=31320044)															
A ALL HOSPITALS	NEG	N.D.	B ALL HOSPL	HOSPIT	S.E	LL HOSPIT	S.E.	L HOSPIT	S.E.	A E.R.	B E.R.	P E.R.	S.E.	Q E.R.	S.E.	R E.R.	S.E.		RATE P	S.E.	RATE Q	S.E.			
81	480	3	564	0,144	0,002	0,0006	0,0002	0,004	4E-04	1913	7710	0,2481	0,000204	6,11E-05	3,70E-06	0,000246	7,41399E-05		0,578867478	0,002481515	9,42E+00	0,000169			
148	1421	0	1569	0,094	0,002	0,0011	0,0002	0,011	7E-04	4462	15968	0,2794	0,000212	0,000142	5,63E-06	0,00051	1,06736E-05		0,337607721	0,002072038	7,40E+00	0,000229			
214	2183	23	2420	0,088	0,002	0,0015	0,0003	0,017	9E-04	5564	24969	0,2228	0,000197	0,000178	6,31E-06	0,000797	1,33412E-05		0,396901939	0,002011803	8,54E+00	0,000275			
216	1220	0	1436	0,15	0,003	0,0015	0,0003	0,01	7E-04	3970	16995	0,2336	0,0002	0,000127	5,33E-06	0,000543	1,10134E-05		0,643911932	0,002528833	1,21E+01	0,000276			
139	1225	2	1366	0,102	0,002	0,001	0,0002	0,01	7E-04	3009	26718	0,1126	0,000149	9,61E-05	4,63E-06	0,000853	1,38015E-05		0,903702972	0,002137214	1,03E+01	0,000222			
103	1179	0	1282	0,08	0,002	0,0007	0,0002	0,009	7E-04	2462	28212	0,0873	0,000133	7,86E-05	4,19E-06	0,000901	1,41842E-05		0,920311727	0,001921508	9,31E+00	0,000191			
78	971	1	1050	0,074	0,002	0,0006	0,0002	0,007	6E-04	1890	37012	0,0511	0,000104	6,03E-05	3,67E-06	0,001182	1,62439E-05		1,453732178	0,001852179	9,19E+00	0,000166			
93	912	0	1005	0,093	0,002	0,0007	0,0002	0,007	6E-04	1566	35147	0,0446	9,76E-05	5,00E-05	3,34E-06	0,001122	1,58267E-05		2,074827655	0,002045843	1,32E+01	0,000181			
54	1071	0	1125	0,048	0,002	0,0004	0,0001	0,008	6E-04	780	34562	0,0226	7,03E-05	2,49E-05	2,36E-06	0,001104	1,56994E-05		2,123893805	0,00150909	1,54E+01	0,000138			
81	603	0	684	0,118	0,002	0,0006	0,0002	0,005	5E-04	436	29469	0,0148	5,71E-05	1,39E-05	1,76E-06	0,000941	1,44953E-05		8,001422475	0,002279219	4,14E+01	0,000169			
56	905	0	961	0,058	0,002	0,0004	0,0001	0,007	6E-04	326	30770	0,0106	4,84E-05	1,04E-05	1,52E-06	0,000982	1,48074E-05		5,497418177	0,00165267	3,83E+01	0,000141			
37	575	0	612	0,06	0,002	0,0003	0,0001	0,004	5E-04	232	33606	0,0069	3,91E-05	7,41E-06	1,29E-06	0,001073	1,54776E-05		8,76195889	0,001681148	3,55E+01	0,000114			
17	435	0	452	0,038	0,001	0,0001	8E-05	0,003	4E-04	118	30470	0,0039	2,95E-05	3,77E-06	9,18E-07	0,000973	1,47395E-05		9,643748582	0,001341962	3,20E+01	7,75E-05			
23	346	0	369	0,062	0,002	0,0002	9E-05	0,003	4E-04	165	51087	0,0032	2,67E-05	5,27E-06	1,09E-06	0,001631	1,9077E-05		19,47831978	0,001705036	3,10E+01	9,01E-05			
10	314	0	324	0,031	0,001	7E-05	6E-05	0,002	3E-04	148	46815	0,0032	2,67E-05	4,73E-06	1,03E-06	0,001495	1,82656E-05		9,645061728	0,001219912	1,50E+01	5,94E-05			
2	221	0	223	0,009	7E-04	1E-05	3E-05	0,002	3E-04	235	32876	0,0071	3,97E-05	7,50E-06	1,29E-06	0,00105	1,5311E-05		1,263184488	0,000666015	1,89E+00	2,66E-05			
4	125	0	129	0,031	0,001	3E-05	4E-05	9E-04	2E-04	181	30485	0,0059	3,62E-05	5,78E-06	1,14E-06	0,000973	1,47395E-05		5,255551176	0,001222899	4,92E+00	3,76E-05			
4	221	0	225	0,018	9E-04	3E-05	4E-05	0,002	3E-04	303	30648	0,0099	4,68E-05	9,67E-06	1,47E-06	0,000979	1,47848E-05		1,795735129	0,00093303	2,94E+00	3,76E-05			
2	188	0	190	0,011	7E-04	1E-05	3E-05	0,001	3E-04	238	28421	0,0084	4,31E-05	7,60E-06	1,30E-06	0,000907	1,42313E-05		1,253132832	0,000720982	1,87E+00	2,66E-05			
1	167	0	168	0,006	5E-04	7E-06	2E-05	0,001	2E-04	344	36701	0,0094	4,56E-05	1,10E-05	1,57E-06	0,001172	1,61751E-05		0,633232016	0,000544357	6,46E-01	1,89E-05			
2	169	0	171	0,012	8E-04	1E-05	3E-05	0,001	2E-04	252	60259	0,0042	3,06E-05	8,05E-06	1,34E-06	0,001924	2,07168E-05		2,784739627	0,000758787	1,77E+00	2,66E-05			
0	125	0	125	0	0	0	0	9E-04	2E-04	347	54449	0,0064	3,77E-05	1,11E-05	1,58E-06	0,001738	1,96918E-05		0	3,76993E-05	0,00E+00	1,58E-06			
0	134	0	134	0	0	0	0	1E-03	2E-04	315	41246	0,0076	4,11E-05	1,01E-05	1,50E-06	0,001317	1,71453E-05		0	4,10571E-05	0,00E+00	1,5E-06			
2	326	0	328	0,006	5E-04	1E-05	3E-05	0,002	3E-04	479	58143	0,0082	4,26E-05	1,53E-05	1,85E-06	0,001856	2,03481E-05		0,743604997	0,000550631	9,29E-01	2,66E-05			
5	1291	0	1296	0,004	4E-04	4E-05	4E-05	0,009	7E-04	890	66519	0,0138	5,52E-05	2,84E-05	2,52E-06	0,002124	2,17647E-05		0,279567007	0,000440633	1,25E+00	4,21E-05			
8	1704	0	1712	0,005	5E-04	6E-05	5E-05	0,012	8E-04	823	69142	0,0119	5,13E-05	2,63E-05	2,42E-06	0,002208	2,219E-05		0,392680437	0,000483653	2,16E+00	5,32E-05			
11	1419	0	1430	0,008	6E-04	8E-05	6E-05	0,01	7E-04	876	63189	0,0139	5,53E-05	2,80E-05	2,50E-06	0,002018	2,12158E-05		0,553403431	0,000618588	2,79E+00	6,24E-05			
9	974	2	985	0,009	7E-04	6E-05	6E-05	0,007	6E-04	836	59479	0,0141	5,57E-05	2,67E-05	2,44E-06	0,001899	2,0582E-05		0,648018145	0,000673299	2,39E+00	5,64E-05			
13	1235	0	1248	0,01	7E-04	9E-05	7E-05	0,009	7E-04	688	65414	0,0105	4,82E-05	2,20E-05	2,22E-06	0,002089	2,1585E-05		0,992063492	0,000717591	4,20E+00	6,78E-05			
14	1468	0	1482	0,009	7E-04	1E-04	7E-05	0,011	7E-04	894	64010	0,014	5,55E-05	2,85E-05	2,52E-06	0,002044	2,13518E-05		0,674763833	0,000684413	3,49E+00	7,04E-05			
13	2031	0	2044	0,006	6E-04	9E-05	7E-05	0,015	8E-04	1759	76156	0,0231	7,1E-05	5,62E-05	3,54E-06	0,002432	2,32858E-05		0,275328064	0,000565077	1,64E+00	6,79E-05			
30	1719	0	1749	0,017	9E-04	0,0002	0,0001	0,012	8E-04	3178	84307	0,0377	9E-05	0,000101	4,75E-06	0,002692	2,44957E-05		0,454977683	0,000920033	2,11E+00	0,000103			
83	2179	0	2262	0,037	0,001	0,0006	0,0002	0,016	9E-04	5875	101153	0,0581	0,000111	0,000188	6,48E-06	0,00323	2,68248E-05		0,631552356	0,00133041	3,14E+00	0,000171			
139	2952	2	3093	0,045	0,001	0,001	0,0002	0,022	0,001	10863	125279	0,0867	0,000133	0,000347	8,80E-06	0,004	2,98399E-05		0,518341263	0,001467001	2,85E+00	0,000222			
168	2674	2	2844	0,059	0,002	0,0012	0,0002	0,02	1E-03	13811	126747	0,109	0,000147	0,000441	9,93E-06	0,004047	3,0014E-05		0,541942477	0,001669058	2,71E+00	0,000244			
213	2908	2	3123	0,068	0,002	0,0015	0,0003	0,022	0,001	17112	130516	0,1311	0,00016	0,000546	1,10E-05	0,004167	3,04539E-05		0,520241421	0,00178489	2,77E+00	0,000274			
203	2242	1	2446	0,083	0,002	0,0014	0,0003	0,017	9E-04	17209	131603	0,1308	0,000159	0,000549	1,11E-05	0,004202	3,0581E-05		0,634500314	0,001951929	2,63E+00	0,000268			
240	2321	4	2565	0,094	0,002	0,0017	0,0003	0,018	9E-04	15303	118901	0,1287	0,000158	0,000489	1,05E-05	0,003796	2,9072E-05		0,727018271	0,002059781	3,49E+00	0,000291			
192	2380	8	2580	0,074	0,002	0,0014	0,0003	0,018	9E-04	12729	112974	0,1127	0,000149	0,000406	9,52E-06	0,003607	2,83417E-05		0,660324797	0,0018568	3,36E+00	0,00026			
191	1951	17	2159	0,088	0,002	0,0014	0,0003	0,015	9E-04	10994	101051	0,1088	0,000147	0,000351	8,86E-06	0,003226	2,68082E-05		0,813114732	0,002007944	3,87E+00	0,00026			
207	2292	3	2502	0,083	0,002	0,0015	0,0003	0,018	9E-04	10838	100425	0,1079	0,000147	0,000346	8,79E-06	0,003206	2,67253E-05		0,76676379	0,001948177	4,25E+00	0,00027			
211	1773	5	1989	0,106	0,002	0,0015	0,0003	0,014	8E-04	10734	84351	0,1273	0,000158	0,000343	8,75E-06	0,002693	2,45002E-05		0,833334321	0,002177296	4,37E+00	0,000273			
227	1472	5	1704	0,133	0,002	0,0016	0,0003	0,012	8E-04	11661	94882	0,1229	0,000155	0,000372	9,12E-06	0,003029	2,59794E-05		1,083937856	0,002401306	4,34E+00	0,000283			
313	2089	3	2405	0,13	0,002	0,0022	0,0003	0,017	9E-04	12904	92105	0,1401	0,000164	0,000412	9,59E-06	0,002941	2,56003E-05		0,928947396	0,002378366	5,40E+00	0,000332			
216	2111	17	2344	0,092	0,002	0,0015	0,0003	0,017	9E-04	11096	115066	0,0964	0,00014	0,000354	8,89E-06	0,003674	2,86028E-05		0,955914633	0,002044437	4,33E+00	0,000276			
162	1751	5	1918	0,084	0,002	0,0012	0,0002	0,014	8E-04	8454	144437	0,0585	0,000111	0,00027	7,77E-06	0,004612	3,20316E-05		1,443811663	0,001964129	4,26E+00	0,000239			
95	1326	6	1427	0,067	0,002	0,0007	0,0002	0,01	7E-04	8209	148909	0,0551	0,000108	0,000262	7,65E-06	0,004754	3,25187E-05		1,2082256	0,001761209	2,58E+00	0,000183			
61	1018	11	1090	0,056	0,002	0,0004	0,0001	0,008	6E-04	8275															

Supplementary Table 2. Slopes in Joinpoint Regression (week 1-56)

	1	2	3	4	5	6
P (Hospitals)*	-4.12 (1-10)	-17.12 (10-26)	33.11 (26-36)	+6.02 (36-44)	-15.61 (44-56)	/
P (E.R.)*	-6.71 (1-4)	-35.51 (4-13)	+8.12 (13-29)	+38.32 (29-36)	-4.37 (36-56)	/
Q (Hospitals)*	+69.76 (1-3)	-20.31 (3-24)	+50.16 (24-35)	+4.35 (35-44)	-24.43 (44-48)	+3.23 (48-56)
Q (E.R.)*	+20.37 (1-16)	+12.55 (16-30)	+72.75 (30-35)	-5.07 (35-49)	+34.11 (49-52)	-10.38 (52-56)
Ratio P (ϕ)	+1.00 (1-14)	-2.83 (14-18)	+1.95 (18-21)	-1.96 (21-24)	+0.66 (24-27)	-0.01 (27-56)
Ratio Q (ψ)	+2.93 (1-13)	-11.28 (13-16)	-0.12 (16-22)	-0.81 (22-25)	+1.33 (25-28)	-0.06 (28-56)

*values transformed into logarithms