Effectiveness of mRNA vaccines and waning of protection against SARS-CoV-2 infection and severe covid-19 during predominant circulation of the delta variant in Italy: retrospective cohort study

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ABSTRACT

OBJECTIVES

To estimate the effectiveness of mRNA vaccines against SARS-CoV-2 infection and severe covid-19 at different time after vaccination.

DESIGN

Retrospective cohort study.

SETTING

Italy, 27 December 2020 to 7 November 2021.

PARTICIPANTS

33 250 344 people aged ≥16 years who received a first dose of BNT162b2 (Pfizer-BioNTech) or mRNA-1273 (Moderna) vaccine and did not have a previous diagnosis of SARS-CoV-2 infection.

MAIN OUTCOME MEASURES

SARS-CoV-2 infection and severe covid-19 (admission to hospital or death). Data were divided by weekly time intervals after vaccination. Incidence rate ratios at different time intervals were estimated by multilevel negative binomial models with robust variance estimator. Sex, age group, brand of vaccine, priority risk category, and regional weekly incidence in the general population were included as covariates. Geographic region was included as a random effect. Adjusted vaccine effectiveness was calculated as (1−IRR)×100, where IRR=incidence rate ratio, with the time interval 0-14 days after the first dose of vaccine as the reference.

RESULTS

During the epidemic phase when the delta variant was the predominant strain of the SARS-CoV-2 virus, vaccine effectiveness against SARS-CoV-2 infection significantly decreased (P<0.001) from 82% (95% confidence interval 80% to 84%) at 3-4 weeks after the second dose of vaccine to 33% (27% to 39%) at 27-30 weeks after the second dose. In the same time intervals, vaccine effectiveness against severe covid-19 also decreased (P<0.001), although to a lesser extent, from 96% (95% to 97%) to 80% (76% to 83%). High risk people (vaccine effectiveness −6%, −28% to 12%), those aged ≥80 years (11%, −15% to 31%), and those aged 60-79 years (2%, −11% to 14%) did not seem to be protected against infection at 27-30 weeks after the second dose of vaccine.

CONCLUSIONS

The results support the vaccination campaigns targeting high risk people, those aged ≥60 years, and healthcare workers to receive a booster dose of vaccine six months after the primary vaccination cycle. The results also suggest that timing the booster dose earlier than six months after the primary vaccination cycle and extending the offer of the booster dose to the wider eligible population might be warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Campaigns for a booster dose of vaccine for covid-19, targeting high risk groups and elderly people, have started in several countries, but extending to the general eligible population and its timing are debated

No studies have evaluated vaccine effectiveness more than seven months after the primary vaccination cycle to assess the combined effect of possible waning of immunity provided by the vaccine and dominance of the delta variant of the SARS-CoV-2 virus

WHAT THIS STUDY ADDS

The effectiveness of mRNA vaccines against any SARS-CoV-2 infection and severe covid-19 decreased to 33% (95% confidence interval 27% to 39%) and 80% (76% to 83%), respectively, at 27-30 weeks after the second dose of vaccine

High risk people (residents in long term care facilities, people with comorbidities, and immunocompromised people) and those aged ≥60 years no longer seemed to have substantial protection against SARS-CoV-2 infection at 27-30 weeks after the primary vaccination, and the initial high vaccine effectiveness against severe covid-19 was greatly reduced in high risk people (43%, 3% to 67%) compared with other population groups (range 64-85%)

The findings support recommending a booster dose of vaccine no later than six months after the primary vaccination cycle with mRNA vaccines, giving priority to high risk groups and elderly people

Introduction

The covid-19 vaccination campaign in Italy started on 27 December 2020. The campaign targeted healthcare workers, people with an increased risk of severe disease (eg, elderly people or high risk populations), and essential non-healthcare workers (eg, school staff). The campaign was subsequently extended to the general population, with a priority scheme based on age. Up to

24 November 2021, 47 037 541 people (87.1% of the population aged >12 years) had received at least one dose of vaccine, and 45 538 845 (84.3%) had completed the primary vaccination cycle according to the schedule of the brands of the four authorised vaccines in Italy: Comirnaty BNT162b2, Pfizer-BioNTech; Spikevax mRNA-1273, Moderna; Vaxzevria ChAdOx1 nCoV-19, Oxford-AstraZeneca; and Janssen Ad26.COV2-S recombinant, Janssen-Cilag International NV. Eighty three per cent of those who received at least one vaccine dose were vaccinated with an mRNA vaccine: Comirnaty (Pfizer) 70.2%, Spikevax (Moderna) 12.8%.[1]

Randomised trials have shown high efficacy of mRNA vaccines against symptomatic covid-19.[2 3] The effectiveness of these vaccines in reducing morbidity and mortality from SARS-CoV-2 infection has been confirmed by observational data in real world scenarios.[4-10] Campaigns for the vaccine booster dose targeting high risk groups and elderly people have started in several countries. Based on published studies, clarity is needed on whether the predominant circulation of the delta variant of the SARS-CoV-2 virus has reduced vaccine effectiveness and whether this effect, combined with potential waning of immunity provided by the vaccine, supports the expansion of a booster dose to all population groups and the timing of the booster dose.[11-20] Studies focusing on vaccine effectiveness against any SARS-CoV-2 infection caused by the delta variant showed estimates ranging from 18% (95% confidence interval −13% to 40%) in the general population of Qatar to 85% (61% to 95%) in the general population of Quebec, Canada, approximately six months after completion of the primary vaccination cycle.[21] Among the arguments raised against the need for a booster dose is that although vaccine effectiveness against any SARS-CoV-2 infection seems to wane over time since vaccination, effectiveness against severe covid-19 remains high. Based on this argument, to reduce the circulation and lethality of the virus and the possible insurgency of new variants, using the available resources to improve complete primary vaccination coverage, including in lower income countries, has been suggested as a major benefit.[22-25]

To our knowledge, no studies conducted in real world scenarios have evaluated vaccine effectiveness more than seven months after completion of the primary vaccination cycle. Our aim, based on a longer follow-up time, was to estimate the effectiveness of mRNA vaccines in preventing SARS-CoV-2 infections (symptomatic or asymptomatic) and severe covid-19 (admission to hospital or death) at different times after vaccination, by epidemic phase, age group, and priority risk category.

Methods

Data sources and selection of the study population

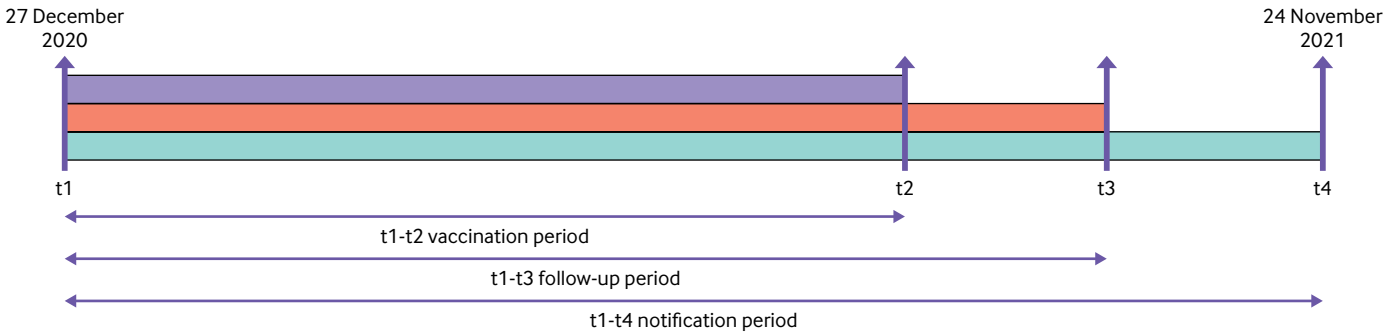
We used deterministic record linkage by individual tax code to combine data from the Italian National Vaccination Registry (held by the Ministry of Health) for people who had been vaccinated, with data on notified people who had tested positive for SARS-CoV-2 infection from the National covid-19 Integrated Surveillance System (coordinated by the Italian National Institute of Health).[1 26] Data were extracted on 24 November 2021 from both sources. We selected all 35 877 432 records of people aged ≥16 years who had received the first dose of an mRNA vaccine before 25 October 2021, thus accounting for at least 14 days of follow-up and 17 days of possible delay in notification of SARS-CoV-2 infection (fig 1 and supplementary fig 1). We did not consider people aged 12-15 years because this age group only had access to vaccination from June 2021, limiting the available follow-up time.

For the analysis of patients with severe covid-19 (that is, SARS-CoV-2 infection followed by admission to hospital or death within 28 days), we considered only people who received a vaccine before 27 September 2021, to allow another four weeks of observation for possible worsening of clinical symptoms (fig 1). Individuals diagnosed as having SARS-CoV-2 infection before receiving their first vaccine dose (n=2 626 441, 7.3%) and those with missing or inconsistent data (n=647, 0.002%) were excluded, and thus 33 250 344 people who had received at least one dose of vaccine were available for the analysis (supplementary fig 1).

Outcomes and time of infection and exposure

We studied the incidence of two endpoints: SARS-CoV-2 infection of any severity (symptomatic or asymptomatic) and severe covid-19 (infection with subsequent admission to hospital or death within 28 days). We considered all notified people who had tested positive for SARS-CoV-2 infection in Italy, confirmed in a laboratory by polymerase chain reaction (PCR 97.6%) or, from 15 January 2021, also by antigen test (2.4%). Patients who were reported to have been admitted to hospital or died within four weeks of infection for causes related to covid-19 were classified as severe disease. According to Italian guidelines, based on indications from the World Health Organization,[27] a death was considered related to covid-19 if it occurred in the presence of a clinical and instrumental picture suggestive of covid-19, in the absence of a clear cause of death different from covid-19 (eg, road accident), and in the absence of a complete clinical recovery from the disease. Time of infection was the date of onset of symptoms or the date of testing positive, if symptoms or their date of onset were not reported.

Our data did not include information on possible deaths that occurred for causes unrelated to covid-19. Therefore, based on life tables by region, age, and sex for the year 2020 published by the Italian Institute of Statistics,[28] assuming a uniform distribution of deaths over the year, we imputed the expected date of death of people who were vaccinated who did not have a diagnosis of infection to calculate the person days of exposure (see supplementary material for more details). Follow-up ended on the date of SARS-CoV-2 infection for those with an infection of any severity or severe covid-19 before the possible administration of a booster vaccine dose. Conversely, follow-up ended on the date of administration of a booster dose or on the



Event	Period		
	t1-t2 vaccination period	t1-t3 follow-up period	t1-t4 notification period
SARS-CoV-2 infection (symptomatic and asymptomatic)	27 December 2020 to 24 October 2021	27 December 2020 to 7 November 2021	27 December 2020 to 24 November 2021
Severe disease (admission to hospital and death)	27 December 2020 to 26 September 2021	27 December 2020 to 10 October 2021	

Fig 1 | Timeline of periods of selection and events in the study population

imputed date of death, or was otherwise censored on 7 November 2021 and 10 October 2021 for those who, on those dates, had not received a booster dose and were alive and who did not have a diagnosis of SARS-CoV-2 infection or severe covid-19, respectively.

Statistical analysis

Individual time of exposure was divided into weekly time intervals from the first and second doses of vaccine. We then used multilevel negative binomial regression models with robust variance estimator to estimate incidence rate ratios, with 95% confidence intervals, of SARS-CoV-2 infection and severe covid-19 after partial (>14 days after the first dose to ≤14 days after the second dose) and complete (>14 days after the second dose) vaccination compared with the time interval 0-14 days after the first dose (reference exposure, assumed as a proxy for people who were not vaccinated). Time of exposure was measured in days and included as offset in the models.

The potential confounders included in the models as fixed effects were: sex, age group (16-24 years, five year age groups from 25-29 to 80-84 years, and ≥85 years), brand of vaccine (Comirnaty (Pfizer) and Spikevax (Moderna)), vaccination priority group (none, healthcare workers, residents of long term care facilities, people with comorbidities, immunocompromised people, and essential non-healthcare workers (eg, school staff)), and regional weekly incidence in the general population, derived from the national covid-19 surveillance data. Geographical region of vaccination (defined according to the Eurostat nomenclature of territorial units for statistics, NUTS-2) was included in the models as random effect to account for clustering at the local level.[29] The same multivariable model was used to evaluate possible loss of immunity provided by the mRNA vaccine against SARS-CoV-2 infection and severe covid-19 over time after the second dose, with the time interval 0-14 days after the first dose and 3-4 weeks after the second dose of vaccine as the reference values (3-4 weeks being the time interval where the highest level of immune protection provided by mRNA vaccines was seen in our data).

We grouped the analyses by epidemic phase, distinguishing between the alpha phase, from 27 December 2020 to 13 June 2021, when circulation of the SARS-CoV-2 alpha variant (B.1.1.7) was dominant, and the delta phase, from 19 July 2021 until the censoring dates, when the delta variant (B.1.617.2) was dominant.[30] Vaccine effectiveness was calculated as (1−IRR)×100, where IRR=incidence rate ratio. We also conducted analyses grouped by sex, wider age groups (16-39, 40-59, 60-79, and ≥80 years), and by priority risk category, distinguishing between healthcare workers and the overall group of people at increased risk of severe covid-19, referred to here as high risk people (that is, residents of long term care facilities, people with comorbidities, and immunocompromised people).

Finally, we conducted a sensitivity analysis with the time interval 4-10 days from the first dose of vaccine as the reference exposure to estimate vaccine effectiveness, given that some protection might be evident 10 days after the first vaccination, and that a deferral bias could affect the incidence in the few days immediately after the first dose (eg, people with symptoms are likely to have postponed vaccination).[9] The analyses were performed with Stata/MP version 16.1 (StataCorp, Texas, USA).

Patient and public involvement

Because the study was a register based retrospective cohort design, we did not involve participants or members of the public in the study design, interpretation of the results, or development of the dissemination strategy.

Results

Table 1 shows the characteristics of the 33 250 344 individuals included in the study, all of whom were vaccinated. Most were vaccinated with Comirnaty (Pfizer) (28 319 825, 85.2%). We found that the distribution of sociodemographic characteristics by brand of vaccine did not differ substantially between the two groups.

Effectiveness of mRNA vaccines against SARS-CoV-2 infection and severe covid-19 by epidemic phase

Overall, the effectiveness of complete vaccination (>14 days after the second dose of vaccine) against SARS-CoV-2 infection of any severity decreased from the alpha phase (79%, 95% confidence interval 77% to 81%) to the delta phase (69%, 67% to 71%) (table 2). The decrease was minimal in individuals aged <60 years but was much more marked in those aged ≥60 years, in healthcare workers, and in high risk individuals. Although the overall effectiveness of complete vaccination against severe covid-19 remained substantially stable, even slightly increasing from 89% (88% to 91%) to 91% (90% to 92%), we found a marked reduction in vaccine effectiveness in people aged ≥80 years and in high risk people.

Reduction of the protective effect of mRNA vaccines over time since vaccination

Overall, compared with the time interval ≤2 weeks after the first dose of vaccine, we found that during the delta phase, vaccine effectiveness against SARS-CoV-2 infection decreased from 82% (95% confidence interval 80% to 84%) at 3-4 weeks after the second dose of vaccine (that is, the time interval where the highest level of immune protection provided by mRNA vaccines was found in our data) to 33% (27% to 39%) at 27-30 weeks (that is, six months after the second vaccine dose when a booster dose of vaccine is generally recommended). Conversely, vaccine effectiveness remained substantially stable during the alpha phase, slightly increasing from 81% (79% to 83%) at 3-4 weeks after the second dose of vaccine to 90% (86% to 92%) at 19-21 weeks (fig 2). Vaccine effectiveness against severe covid-19 also decreased during the delta phase, although to a lesser extent, from 96% (95% to 97%) at 3-4 weeks after the second dose to 80% (76% to 83%) at 27-30 weeks, whereas vaccine effectiveness slightly increased during the alpha phase, from 88% (86% to 90%) at 3-4 weeks after the second dose to 95% (90% to 97%) at 15-18 weeks (fig 2).

The risk of SARS-CoV-2 infection of any severity during the delta phase was 3.7 times higher (95% confidence interval 3.3 to 4.2) at 27-30 weeks than at 3-4 weeks after the second dose of vaccine, whereas the risk of infection was reduced by about 40% at 19-21 weeks after the second dose during the alpha phase (incidence rate ratio 0.56, 0.43 to 0.72) (supplementary fig 2A-B). Compared with 3-4 weeks after the second dose of vaccine, we found that the risk of severe covid-19 during the delta phase was 5.5 times higher (3.9 to 7.9) at 27-30 weeks after the second dose, whereas during the alpha phase, the risk of severe covid-19 was reduced by almost 60% at 15-18 weeks after the second vaccine dose (incidence rate ratio 0.43, 0.24 to 0.80) (supplementary fig 2C-D).

During the delta phase, loss of protection against SARS-CoV-2 infection after the peak at 3-4 weeks after the second dose of vaccine was more pronounced in high risk people and those aged 60-79 years (supplementary fig 3). At 27-30 weeks after the second dose, vaccine effectiveness was estimated to be similar to no protection in high risk people (−6%, 95% confidence interval −28% to 12%), in people aged ≥80 years (11%, −15% to 31%), and in those aged 60-79 years (2%, −11% to 14%) (fig 3).

Loss of protection against severe covid-19 after the peak at 3-4 weeks after the second dose of vaccine during the delta phase was more pronounced in high risk people and in those aged 40-59 years (supplementary fig 4), although vaccine effectiveness at 27-30 weeks after the second dose still seemed relatively high in those aged 40-59 years (85%, 95% confidence interval 79% to 89%) (fig 4). In contrast, we found that vaccine effectiveness at 27-30 weeks after the second dose of vaccine was greatly reduced in high risk people (43%, 3% to 67%) compared with other population groups (vaccine effectiveness 64-85%) (fig 4).

During the delta phase, vaccine effectiveness against SARS-CoV-2 infection and severe covid-19 more than 30 weeks after the second dose and up to 42 weeks and 38 weeks, respectively, was 21% (95% confidence

Table 1 | Characteristics of individuals included in the study, vaccinated with the Pfizer or Moderna vaccine, Italy, 27 December 2020 to 24 October 2021. Data are number (%) of individuals

	Comirnaty (Pfizer) (n=28 319 825; 85.2%)	Spikevax (Moderna) (n=4 930 519; 14.8%)	Total mRNA vaccines (n=33 250 344)
Sex			
Women	14 581 304 (51.5)	2 433 309 (49.4)	17 014 613 (51.2)
Men	13 738 521(48.5)	2 497 210 (50.6)	16 235 731 (48.8)
Age group			
16-39 years	8 727 440 (30.8)	1 862 377 (37.8)	10 589 817 (31.8)
40-59 years	10 411 903 (36.8)	1 762 830 (35.8)	12 174 733 (36.6)
60-79 years	5 789 187 (20.4)	881 216 (17.9)	6 670 403 (20.1)
≥80 years	3 391 295 (12.0)	424 096 (8.6)	3 815 391 (11.5)
Geographical macroarea*			
North West	7 566 823 (26.7)	1 372 455 (27.8)	8 939 278 (26.9)
North East	5 515 153 (19.5)	937 221 (19.0)	6 452 374 (19.4)
Centre	5 676 106 (20.0)	979 483 (19.9)	6 655 589 (20.0)
South and Islands	9 561 743 (33.8)	1 641 360 (33.3)	11 203 103 (33.7)
Priority risk category			
Healthcare workers	1 406 055 (5.0)	47 475 (1.0)	1 453 530 (4.4)
LTCF residents	247 289 (0.9)	26 207 (0.5)	273 496 (0.8)
People with comorbidities†	3 484 198 (12.3)	562 174 (11.4)	4 046 372 (12.2)
Immunocompromised†	63 309 (0.2)	11 203 (0.2)	74 512 (0.2)
Other risk categories‡	2 426 948 (8.6)	435 869 (8.8)	2 862 817 (8.6)
None	20 692 026 (73.1)	3 847 591 (78.0)	24 539 617 (73.8)

LTCF=long term care facility.
*Eurostat nomenclature of territorial units for statistics (NUTS-1).[27]
†Conditions defining comorbidities, giving priority access to vaccination, and conditions defining immunocompromise, are listed in the supplementary material.
‡Including people with risk exposure not specified (n=1 074 329; 37.5%), people living with individuals at increased risk of severe covid-19 (n=806 070; 28.2%), school staff (n=313 013; 10.9%), and others (n=669 405; 23.4%).

Table 2 | Effectiveness of mRNA vaccines against SARS-CoV-2 infection and severe covid-19 by epidemic phase, Italy, 27 December 2020 to 7 November 2021

	Any SARS-CoV-2 infection*						Severe covid-19†					
	Alpha phase			Delta phase			Alpha phase			Delta phase		
	No of individuals	Incidence per 100 000 PD	VE‡ (%) (95% CI)	No of individuals	Incidence per 100 000 PD	VE‡ (%) (95% CI)	No of individuals	Incidence per 100 000 PD	VE‡ (%) (95% CI)	No of individuals	Incidence per 100 000 PD	VE‡ (%) (95% CI)
Total												
0-14 days after 1st dose	32 895	13.6	Reference	16 416	15.1	Reference	6251	2.6	Reference	677	0.7	Reference
15 days after 1st dose to 14 days after 2nd dose	21 574	7.5	49.0 (44.7 to 53.0)	34 773	7.7	50.2 (47.5 to 52.7)	3385	1.2	60.1 (56.4 to 63.6)	736	0.2	80.1 (74.6 to 84.4)
>14 days after 2nd dose	16 428	3.9	79.0 (76.8 to 80.9)	116 480	4.1	69.0 (66.7 to 71.2)	1228	0.3	89.4 (87.6 to 91.0)	5023	0.3	91.1 (89.7 to 92.2)
16-39 years												
0-14 days after 1st dose	4666	17.0	Reference	11 506	17.7	Reference	107	0.4	Reference	210	0.4	Reference
15 days after 1st dose to 14 days after 2nd dose	2114	7.9	61.3 (56.3 to 65.7)	21 919	9.3	50.3 (48.0 to 52.5)	33	0.1	72.8 (57.7 to 82.5)	179	0.1	79.0 (74.6 to 82.7)
>14 days after 2nd dose	3361	5.6	78.9 (75.6 to 81.7)	30 110	4.2	74.7 (72.6 to 76.6)	33	0.1	89.4 (72.9 to 95.9)	209	0.0	92.6 (89.4 to 94.8)
40-59 years												
0-14 days after 1st dose	9480	11.3	Reference	4171	11.9	Reference	540	0.6	Reference	301	1.1	Reference
15 days after 1st dose to 14 days after 2nd dose	4859	6.9	52.1 (47.3 to 56.5)	10 439	6.3	47.8 (44.2 to 51.2)	151	0.2	72.1 (67.0 to 76.3)	211	0.1	87.0 (82.3 to 90.5)
>14 days after 2nd dose	5880	5.7	77.9 (75.0 to 80.5)	44 860	4.3	66.0 (63.4 to 68.5)	112	0.1	88.4 (84.0 to 91.5)	510	0.1	96.3 (95.7 to 96.8)
60-79 years												
0-14 days after 1st dose	7815	9.9	Reference	663	8.5	Reference	1633	2.1	Reference	128	2.0	Reference
15 days after 1st dose to 14 days after 2nd dose	4850	4.5	47.6 (40.9 to 53.6)	1911	4.9	45.0 (38.0 to 51.2)	641	0.6	65.7 (58.6 to 71.6)	208	0.6	72.4 (64.6 to 78.5)
>14 days after 2nd dose	2346	2.5	82.2 (80.1 to 84.1)	24 844	3.7	56.4 (51.2 to 61.0)	178	0.2	91.2 (88.8 to 93.1)	1393	0.3	90.5 (88.7 to 92.1)
≥80 years												
0-14 days after 1st dose	10 934	21.2	Reference	76	7.5	Reference	3971	7.7	Reference	38	4.6	Reference
15 days after 1st dose to 14 days after 2nd dose	9751	11.8	38.2 (32.2 to 43.7)	504	5.1	36.8 (18.2 to 51.1)	2560	3.1	55.2 (50.5 to 59.4)	138	1.8	63.8 (50.5 to 73.5)
>14 days after 2nd dose	4841	2.9	79.8 (76.9 to 82.4)	16 666	4.3	35.0 (17.4 to 48.9)	905	0.5	89.9 (87.9 to 91.6)	2911	1.0	76.7 (69.2 to 82.3)
Healthcare workers												
0-14 days after 1st dose	8144	40.8	Reference	37	21.5	Reference	303	1.5	Reference	0	0	Reference
15 days after 1st dose to 14 days after 2nd dose	4161	13.5	64.2 (61.1 to 67.1)	160	8.0	62.0 (48.1 to 72.2)	90	0.3	80.4 (74.8 to 84.7)	5	0.3	NC
>14 days after 2nd dose	8211	6.2	82.9 (80.7 to 84.7)	13 526	8.9	54.0 (39.1 to 65.2)	120	0.1	93.5 (90.2 to 95.7)	229	0.2	NC
High risk people§												
0-14 days after 1st dose	8463	15.4	Reference	237	12.1	Reference	186.	3.4	Reference	32	1.9	Reference
15 days after 1st dose to 14 days after 2nd dose	5638	7.6	46.2 (41.9 to 50.2)	1444	6.3	45.0 (32.0 to 55.6)	917	1.2	62.0 (57.7 to 65.8)	140	0.7	66.7 (45.9 to 79.5)
>14 days after 2nd dose	2613	4.0	83.8 (81.9 to 85.5)	23 097	5.1	51.7 (41.6 to 60.1)	401	0.6	90.5 (88.3 to 92.2)	1627	0.5	79.6 (72.2 to 85.0)

PD=person days; NC=not calculable; VE=vaccine effectiveness.
*Including individuals with and without symptoms of SARS-CoV-2 infection.
†Individuals with covid-19 who were admitted to hospital or died within 28 days of testing positive.
‡Vaccine effectiveness adjusted by sex, age group, priority risk category, brand of mRNA vaccine, and regional weekly incidence in the general population. Region of vaccination was included in the models as a random effect.
§Including people with comorbidities, immunocompromised people, and residents of long term care facilities.

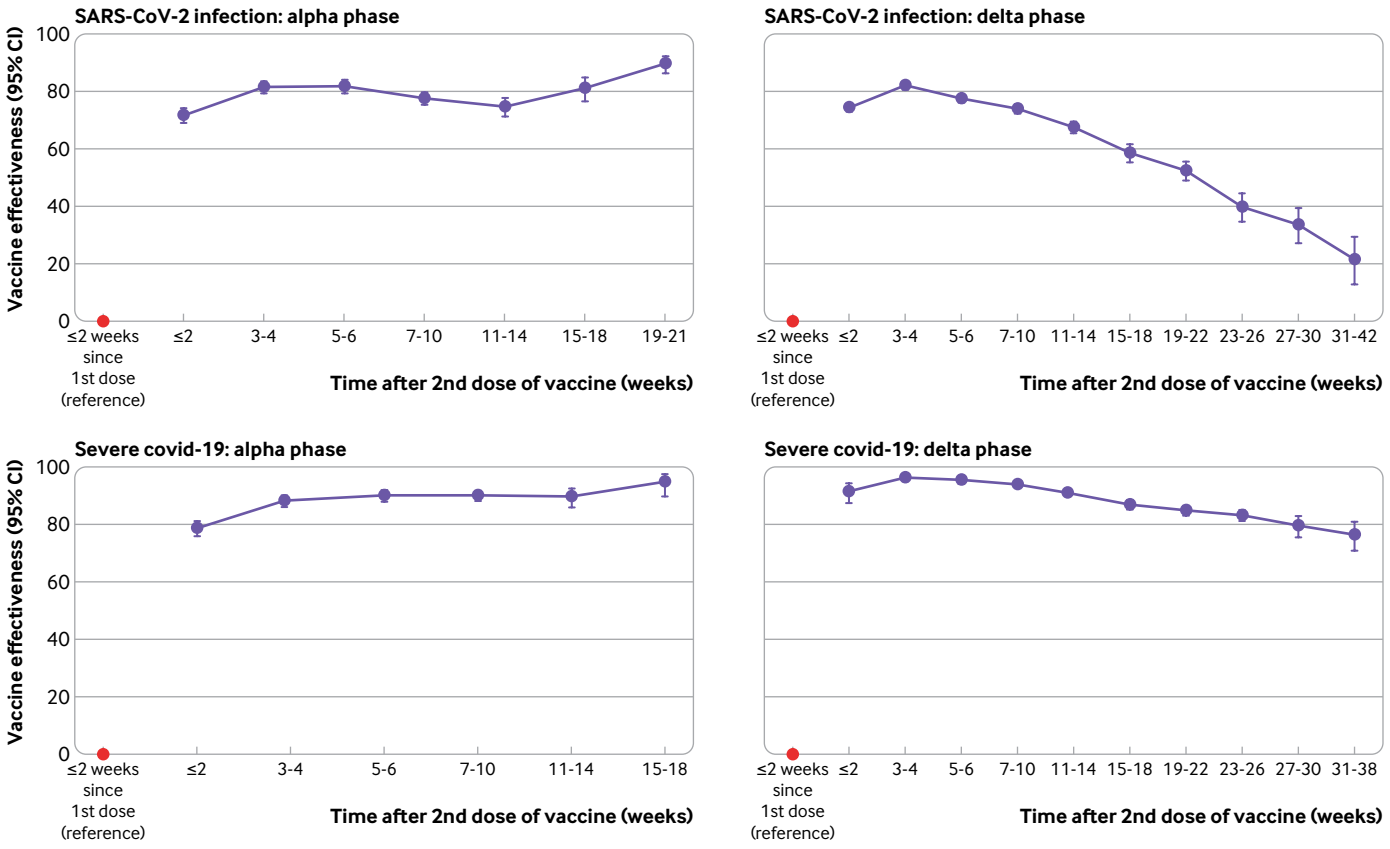


Fig 2 | Effectiveness of mRNA vaccines against SARS-CoV-2 infection and severe covid-19 at different time intervals after completion of the primary vaccination cycle, by epidemic phase, Italy, 27 December 2020 to 7 November 2021. Vaccine effectiveness calculated as (1−IRR)×100, where IRR=incidence rate ratio

interval 12% to 29%) and 76% (71% to 81%), showing a progressive decrease from the peak at 3-4 weeks after the second dose in all groups (fig 2, fig 3, and fig 4). The analysis grouped by sex did not show substantial differences between women and men (supplementary fig 5).

Discussion

Principal findings

In Italy, the overall effectiveness of complete vaccination with mRNA vaccines against any SARS-CoV-2 infection decreased from 79% (95% confidence interval 77% to 81%) during the alpha phase to 69% (67% to 71%) during the delta phase, whereas vaccine effectiveness against severe covid-19 remained relatively stable at around 90%. Comparing the two epidemic phases, however, we did not see a substantial reduction in vaccine effectiveness against SARS-CoV-2 infection in the population aged <60 years, although we found a reduction in vaccine effectiveness against severe disease in the high risk population, from 91% (88% to 92%) during the alpha phase to 80% (72% to 85%) during the delta phase, and in people aged ≥80 years, from 90% (88% to 92%) during the alpha phase to 77% (69% to 82%) during the delta phase.

During the delta phase, we found that at 27-30 weeks after the second dose of vaccine (that is, six months after the second dose when a booster dose of vaccine is generally recommended), vaccine effectiveness against SARS-CoV-2 infection and severe covid-19 was reduced to 33% (27% to 39%) and 80% (76% to 83%), respectively. The decrease in vaccine effectiveness against SARS-CoV-2 infection was more pronounced in high risk people (−6%, −28% to 12%) and in those aged ≥60 years (vaccine effectiveness 2-11%), who no longer seemed to be protected by the vaccine at 27-30 weeks after the second dose. Vaccine effectiveness against severe covid-19 at 27-30 weeks after the second dose was greatly reduced in high risk people (43%, 3% to 67%) compared with the other population groups (vaccine effectiveness 64-85%).

Comparison with other studies

Our findings are consistent with other studies. A retrospective cohort study in the US showed reduced overall effectiveness of the Comirnaty (Pfizer) vaccine against infection with the delta variant of the SARS-CoV-2 virus of 75% (95% confidence interval 71% to 78%), waning from 93% at one month after full vaccination to 53% after four months.[14] The same study also estimated that the overall effectiveness of the Comirnaty (Pfizer) vaccine against hospital admission after infection with the delta variant was 93% (84% to 96%), close to that seen for other variants (95%, 90% to 98%). A study conducted in Israel showed that immunity against the delta variant of the SARS-

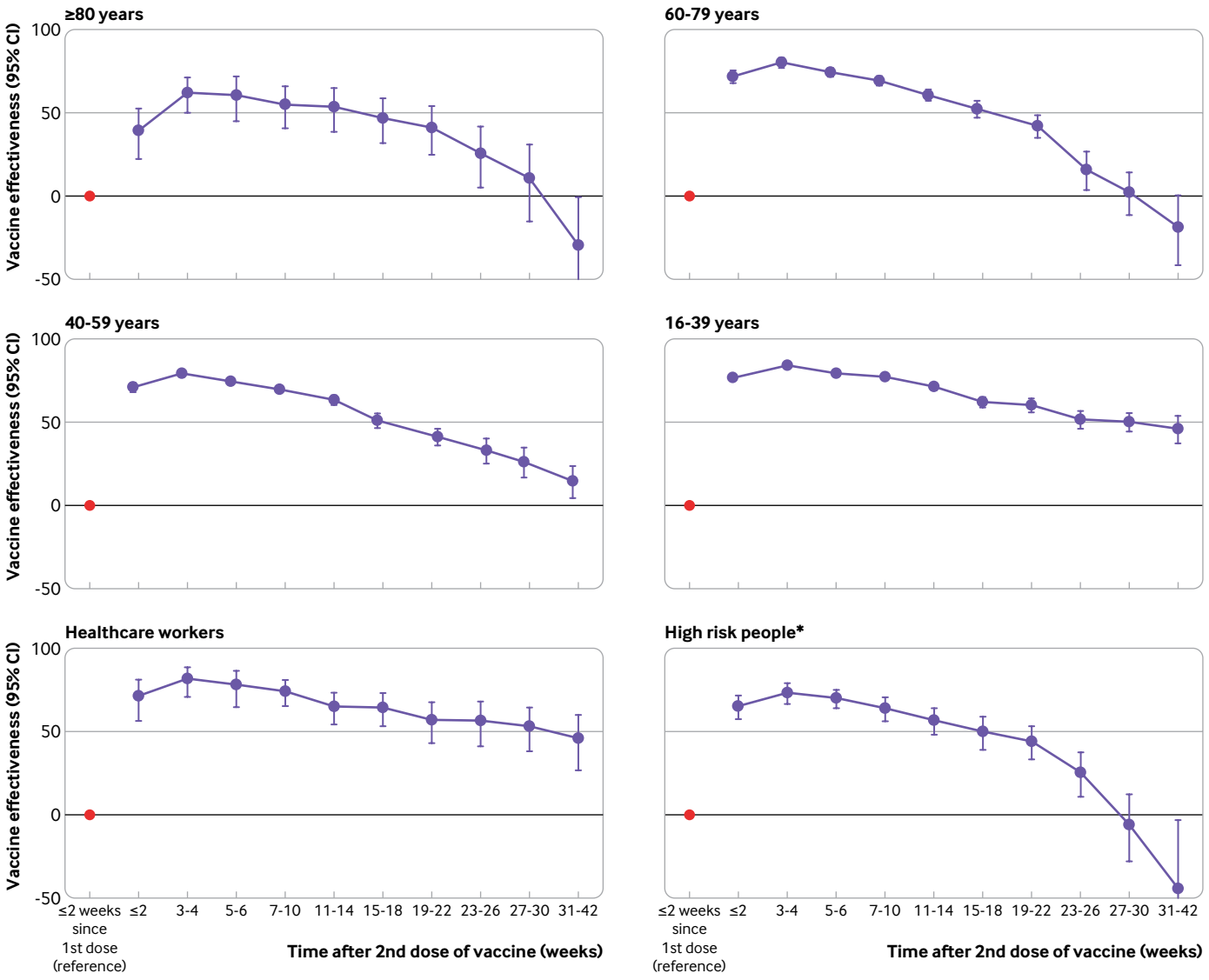


Fig 3 | Effectiveness of mRNA vaccines against SARS-CoV-2 infection during the delta phase by age group and priority risk category, Italy, 19 July to 7 November 2021. Vaccine effectiveness calculated as (1–IRR)×100, where IRR=incidence rate ratio. *Including people with comorbidities, immunocompromised people, and residents of long term care facilities

CoV-2 virus waned in all age groups a few months after receiving the second dose of vaccine.[19] Another study of the mRNA vaccines Comirnaty (Pfizer) and Spikevax (Moderna) estimated vaccine effectiveness at 74% (65% to 85%) against SARS-CoV-2 infection during an epidemic surge of the delta variant in Oregon, US.[17] Studies in Scotland and England showed that the effectiveness of complete vaccination with the Comirnaty (Pfizer) vaccine against SARS-CoV-2 infection and severe covid-19 caused by the delta variant was 79% (75% to 82%) and 96% (86% to 99%), respectively.[11 18]

Strengths and limitations of this study

From a public health perspective, frequent updates of estimates of vaccine effectiveness and the possible waning effect of vaccines over time are important to guide evidence based decisions on the possibility and timing of booster doses of vaccines, and to identify priority groups. Routinely collected data from surveillance and vaccination registries allows frequent updates, without the need for ad hoc studies involving greater resources and a longer time to conduct to provide useful results, which might be inappropriate in specific contexts. In Italy, for example, where access to work or other types of activities (eg, attending cinemas or indoor restaurants) is available only to people with a green pass, a test negative control design or a cohort study with individuals who were not vaccinated as the control group would probably give biased estimates because the green pass can be obtained after vaccination or after a negative test and is valid for 48 hours. This restriction implies that a high number of swabs are performed every day in Italy, mostly in people who are not vaccinated but who want to go to work or take part in other social activities, thus introducing selection bias in the control group. The design of our study avoided this bias because our study was based on data only from

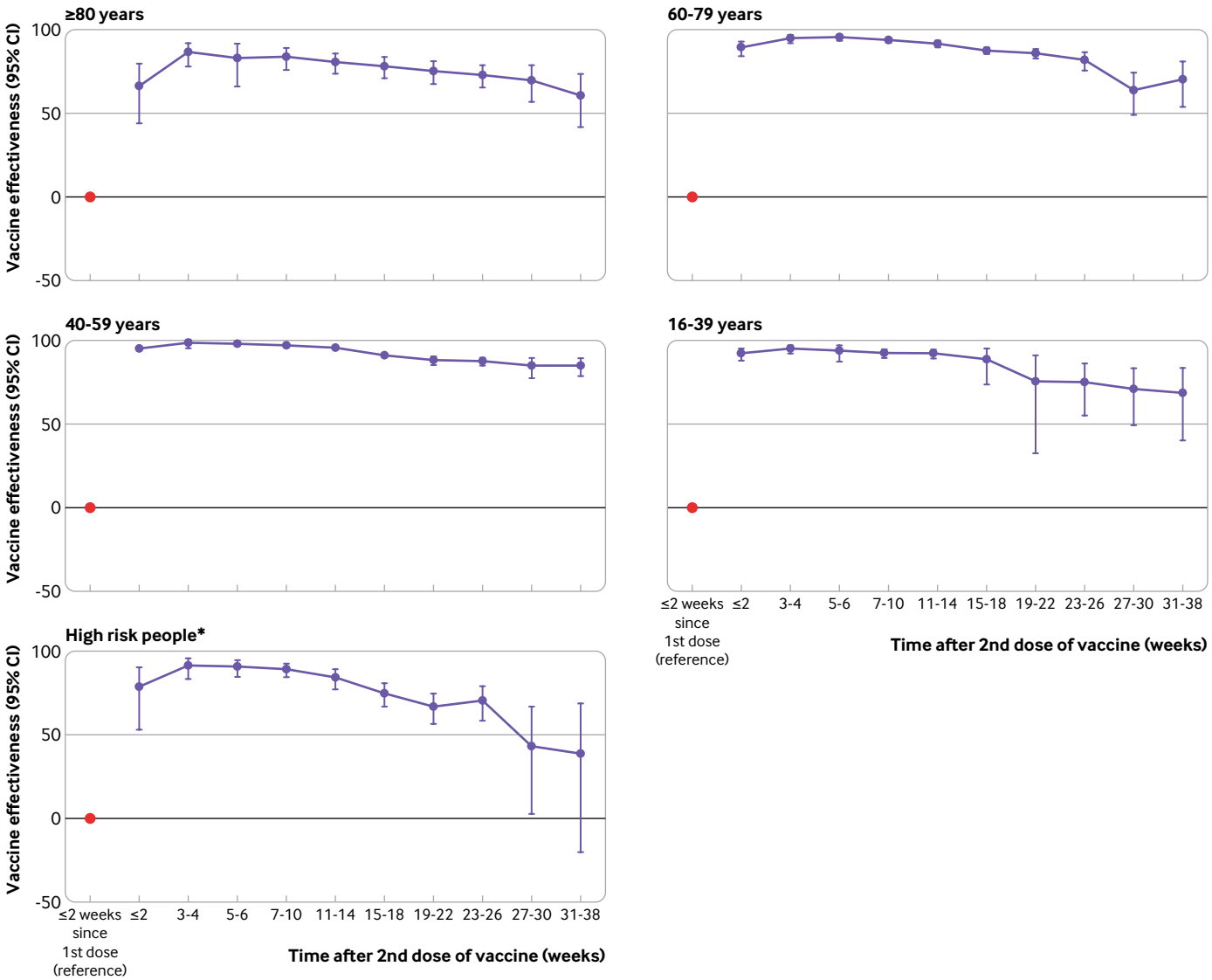


Fig 4 | Effectiveness of mRNA vaccines against severe covid-19 during the delta phase by age group and priority risk category, Italy, 19 July to 10 October 2021. Vaccine effectiveness calculated as (1−IRR)×100, where IRR=incidence rate ratio. *Including people with comorbidities, immunocompromised people, and residents of long term care facilities

people who were vaccinated, with the time interval 0-14 days after the first dose of vaccine used as the reference to estimate vaccine effectiveness (considered to be the period when there was no protection from the vaccine). This design was used in other studies on vaccine effectiveness in covid-19.[10 31 32]

Our study had several limitations. The available data did not allow us to distinguish between the effect of an overall waning of vaccine effectiveness because of a general reduction in immunity from the vaccine over time and the effect of a reduced immune response to infections specifically caused by the delta variant of the SARS-CoV-2 virus. Also, we could not control for individual behavioural factors that could have modified the risk of infection independently. Specifically, a progressive relaxation of legal restrictions favouring physical distancing took place in Italy in the summer of 2021 as the delta variant of the SARS-CoV-2 virus became dominant in the country. This relaxation could have increased the risk of infection in people who were fully vaccinated who might have felt more protected by vaccination compared with those who had received only one dose of vaccine. This increased risk could therefore have led to an underestimation of vaccine effectiveness and overestimation of the protection lost during the delta phase.

Healthcare workers more exposed to the risk of infection (eg, staff working in the emergency department) were generally vaccinated earlier and tested more frequently, and received a diagnosis of SARS-CoV-2 infection more promptly than other healthcare workers (eg, administrative staff). Consequently, although our results did not show a higher waning of vaccine effectiveness among healthcare workers than other population groups, loss of protection might have been overestimated.

We used the first two weeks after the first dose of vaccine as a proxy for the period with no protection

from the vaccine. The immune response to a vaccine is gradual, however, and people who received their first vaccine dose within this two week period might have had some degree of protection. Also, deferral bias could have affected the incidence of SARS-CoV-2 infection in the days immediately after the first dose of vaccine (that is, people with symptoms are likely to postpone vaccination). Hence by using the first two weeks after the first dose of vaccine as the reference could have underestimated vaccine effectiveness in our study.[9] However, results from a sensitivity analysis, with 4-10 days after the first vaccine dose as the reference, although showing slightly higher estimates of vaccine effectiveness, were similar to our main results (table 2), and the same trend in vaccine effectiveness over time was seen (figure 1, figure 2, figure 3, and supplementary material).

The characteristics of people who were vaccinated changed over time (that is, people at increased risk of infection and severe outcomes received their vaccine earlier than others) and, although we adjusted for priority risk category, we could have overestimated waning of protection from the vaccine, especially at later times after the second dose of vaccine. On the other hand, more susceptible individuals could have been infected earlier and hence excluded from the risk group used to estimate incidence at later time intervals, thus leading to overestimation of vaccine effectiveness and underestimation of its waning over time.

In some instances, estimates of vaccine effectiveness at the latest time intervals after the second dose of vaccine showed wide 95% confidence intervals (eg, for severe covid-19 in high risk people). Future analyses allowing robust estimates of vaccine effectiveness more than seven months after the primary vaccination cycle would be useful to better evaluate the effect of refusing or delaying a booster dose of vaccine in this vulnerable group.

Finally, although we accounted for competitive risk of death from causes other than covid-19, specific to region, age, and sex, residual bias is still possible in our estimates because of the differential mortality in some population subgroups. For example, people who are immunocompromised, those with comorbidities, and residents of long term care facilities are probably at higher risk of death from other causes compared with the general population of the same region, age, and sex, thus leading to underestimation of the waning effect in this population subgroup.

Conclusions

Our results, based on more than seven months of follow-up after the second dose of an mRNA vaccine, support the ongoing vaccination campaigns targeting high risk groups, people aged ≥60 years, and healthcare workers to receive a booster dose of vaccine six months after the primary vaccination cycle. Our results also suggest that timing the booster dose earlier than six months after the primary vaccination cycle and extending the offer of the booster dose to the wider eligible population might be warranted.

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Contributors: MF, MP, CM, SSA, AF, FDA, FR, AM-U, FMI, and PPe designed the study. MS, MDM, MT, CS, MM, RDC, SBa, and AB retrieved and prepared the data. MF, MP, MS, SSA, CS, VP, MM, and PPe carried out the analysis. MF, MP, CM, SSA, AF, FDA, FR, AM-U, AS, ATP, PPo, SBr, GR, FMI, and PPe wrote the manuscript. All authors critically revised and approved the final version of the manuscript. FMI and PPe are the guarantors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Ethical approval: Dissemination of covid-19 surveillance data was authorised by the Italian Presidency of the Council of Ministers on 27 February 2020 (ordinance No 640).

Data sharing: Because of data sharing legal restrictions, the dataset, including individual records, cannot be made publicly available. All point estimates with 95% confidence intervals plotted in the figures have been included in the web appendix together with additional data (supplementary materials). Further data will be shared on reasonable request to the corresponding author (MF).

FMI and PPe affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The results of the study might be published in a press release and on social media channels.

Provenance and peer review: Not commissioned; externally peer reviewed.

1 Italian Government, Presidency of the Council of Ministers. Data repository. https://www.governo.it/it/dipartimenti/commissario-straordinario-lemergenza-covid-19/15974

2 Thomas SJ, Moreira EDJr, Kitchin N, et al, C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA covid-19 vaccine through 6 Months. *N Engl J Med* 2021;385:1761-73. doi:10.1056/NEJMoa2110345
3 El Sahly HM, Baden LR, Essink B, et al, COVE Study Group. Efficacy of the mRNA-1273 SARS-CoV-2 vaccine at completion of blinded phase. *N Engl J Med* 2021;385:1774-85. doi:10.1056/NEJMoa2113017
4 Dagan N, Barda N, Kepten E, et al. BNT162b2 mRNA covid-19 vaccine in a nationwide mass vaccination setting. *N Engl J Med* 2021;384:1412-23. doi:10.1056/NEJMoa2101765
5 Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *Lancet* 2021;397:1819-29. doi:10.1016/S0140-6736(21)00947-8
6 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: test negative case-control study. *BMJ* 2021;373:n1088. doi:10.1136/bmj.n1088
7 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet* 2021;397:1646-57. doi:10.1016/S0140-6736(21)00677-2
8 Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of covid-19 with the BNT162b2 and mRNA-1273 vaccines. *N Engl J Med* 2021;385:320-9. doi:10.1056/NEJMoa2107058
9 Hall VJ, Foulkes S, Saei A, et al, SIREN Study Group. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. *Lancet* 2021;397:1725-35. doi:10.1016/S0140-6736(21)00790-X
10 Mateo-Urdiales A, Spila Alegiani S, Fabiani M, et al, Italian Integrated Surveillance of COVID-19 study group, on behalf of the Italian COVID-19 vaccines registry. Risk of SARS-CoV-2 infection and subsequent hospital admission and death at different time intervals since first dose of COVID-19 vaccine administration, Italy, 27 December 2020 to mid-April 2021. *Euro Surveill* 2021;26:2100507. doi:10.2807/1560-7917.ES.2021.26.25.2100507
11 Sheikh A, McMenamin J, Taylor B, Robertson C, Public Health Scotland and the EAVE II Collaborators. SARS-CoV-2 Delta VOC in Scotland: demographics, risk of hospital admission, and vaccine effectiveness. *Lancet* 2021;397:2461-2. doi:10.1016/S0140-6736(21)01358-1
12 Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of covid-19 vaccines against the B.1.617.2 (delta) variant. *N Engl J Med* 2021;385:585-94. doi:10.1056/NEJMoa2108891
13 Pegu A, O'Connell SE, Schmidt SD, et al, mRNA-1273 Study Group§. Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants. *Science* 2021;373:1372-7. doi:10.1126/science.abj4176
14 Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. *Lancet* 2021;398:1407-16. doi:10.1016/S0140-6736(21)02183-8
15 Pouwels KB, Pritchard E, Matthews PC, et al. Effect of delta variant on viral burden and vaccine effectiveness against new SARS-CoV-2 infections in the UK. *Nat Med* 2021;27:2127-35. doi:10.1038/s41591-021-01548-7
16 Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 cases and hospitalizations among adults, by vaccination status - New York, May 3-July 25, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1306-11. doi:10.15585/mmwr.mm7037a7
17 Barlow RS, Jian K, Larson L. Effectiveness of COVID-19 vaccines against SARS-CoV-2 infection during a delta variant epidemic surge in Multnomah County, Oregon, July 2021. *MedRxiv* 2021: 2021.08.30.21262446https://www.medrxiv.org/content/10.1101/2021.08.30.21262446v1.full.pdf
18 Stowe J, Andrews N, Gower C, et al. Effectiveness of COVID-19 vaccines against hospital admission with the delta (B.1.617.2) variant. *khub* 2021. https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view/479607266
19 Goldberg Y, Mandel M, Bar-On YM, et al. Waning immunity after the BNT162b2 vaccine in Israel. *N Engl J Med* 2021;385:e85. doi:10.1056/NEJMoa2114228
20 Israel A, Merzon E, Schäffer AA, et al. Elapsed time since BNT162b2 vaccine and risk of SARS-CoV-2 infection: test negative design study. *BMJ* 2021;375:e067873. doi:10.1136/bmj-2021-067873
21 Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression.*SSRN* 2021. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3961378. doi:10.2139/ssrn.3961378
22 Krause PR, Fleming TR, Peto R, et al. Considerations in boosting COVID-19 vaccine immune responses. *Lancet* 2021;398:1377-80. doi:10.1016/S0140-6736(21)02046-8
23 Rubin R. COVID-19 vaccine makers plan for annual boosters, but it's not clear they'll be needed. *JAMA* 2021;326:2247-9. doi:10.1001/jama.2021.21291
24 Burki T. Booster shots for COVID-19-the debate continues. *Lancet Infect Dis* 2021;21:1359-60. doi:10.1016/S1473-3099(21)00574-0
25 Scott J, Richterman A, Cevik M. Covid-19 vaccination: evidence of waning immunity is overstated. *BMJ* 2021;374:n2320. doi:10.1136/bmj.n2320
26 Riccardo F, Ajelli M, Andrianou XD, et al, COVID-19 working group. Epidemiological characteristics of COVID-19 cases and estimates of the reproductive numbers 1 month into the epidemic, Italy, 28 January to 31 March 2020. *Euro Surveill* 2020;25:2000790. doi:10.2807/1560-7917.ES.2020.25.49.2000790
27 World Health Organization (WHO). International guidelines for certification and classification (coding) of COVID-19 as cause of death. https://www.who.int/classifications/icd/Guidelines_Cause_of_Death_COVID-19.pdf
28 Istituto Nazionale di Statistica (Istat). I.Stat Tavole di mortalità. http://dati.istat.it/Index.aspx?DataSetCode=DCIS_MORTALITA1
29 Eurostat. NUTS – Nomenclature of territorial units for statistics. 2021. https://ec.europa.eu/eurostat/web/nuts/nuts-maps.
30 Higher Institute of Health. Prevalenza e distribuzione delle varianti di SARS-CoV-2 di interesse per la sanità pubblica in Italia. 2021. https://www.iss.it/documents/20126/0/Bollettino+varianti+n.+9_17+settembre+2021.pdf/484b7aa2-2c0c-b109-4c31-087ed5c7b5af?t=1631890444760
31 Chodick G, Tene L, Patalon T, et al. Assessment of effectiveness of 1 dose of BNT162b2 vaccine for SARS-CoV-2 infection 13 to 24 days after immunization. *JAMA Netw Open* 2021;4:e2115985. doi:10.1001/jamanetworkopen.2021.15985
32 Chodick G, Tene L, Rotem RS, et al. The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data. *Clin Infect Dis* 2021;ciab438. doi:10.1093/cid/ciab438

Web appendix: Supplementary materials