

Article

Primary SARS-CoV-2 Infections, Re-infections and Vaccine Effectiveness during the Omicron Transmission Period in Healthcare Workers of Trieste and Gorizia (Northeast Italy), 1 December 2021–31 May 2022

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Abstract: *Objective:* To evaluate the incidence of primary and recurrent COVID-19 infections in healthcare workers (HCWs) routinely screened for SARS-CoV-2 by nasopharyngeal swabs during the Omicron wave. *Design:* Dynamic Cohort study of HCWs ($N = 7723$) of the University Health Agency Giuliano Isontina (ASUGI), covering health services of the provinces of Trieste and Gorizia (Northeast Italy). Cox proportional hazard model was employed to estimate the risk of primary as well as recurrent SARS-CoV-2 infection from 1 December 2021 through 31 May 2022, adjusting for a number of confounding factors. *Results:* By 1 December 2021, 46.8% HCWs of ASUGI had received the booster, 37.2% were immunized only with two doses of COVID-19 vaccines, 6.0% only with one dose and 10.0% were unvaccinated. During 1 March 2020–31 May 2022, 3571 primary against 406 SARS-CoV-2 recurrent infections were counted among HCWs of ASUGI, 59.7% ($=2130/3571$) versus 95.1% ($=386/406$) of which occurring from 1 December 2021 through 31 May 2022, respectively. All HCWs infected by SARS-CoV-2 during 1 December 2021 through 31 May 2022 presented mild flu-like disease. Compared to staff working in administrative services, the risk of primary as well as recurrent SARS-CoV-2 infection increased in HCWs with patient-facing clinical tasks (especially nurses and other categories of HCWs) and in all clinical wards but COVID-19 units and community health services. Regardless of the number of swab tests performed during the study period, primary infections were less likely in HCWs immunized with one dose of COVID-19 vaccine. By contrast, the risk of SARS-CoV-2 re-infection was significantly lower in HCWs immunized with three doses ($aHR = 0.58$; 95% CI: 0.41; 0.80). During the study period, vaccine effectiveness ($VE = 1 - aHR$) of the booster dose declined to 42% against re-infections, vanishing against primary SARS-CoV-2 infections. *Conclusions:* Though generally mild, SARS-CoV-2 infections and re-infections surged during the Omicron transmission period. Compared to unvaccinated colleagues, the risk of primary SARS-CoV-2 infection was significantly lower in HCWs immunized just with one dose of COVID-19 vaccines. By Italian law, HCWs immunized only with one dose were either suspended or re-assigned to job tasks not entailing patient facing contact; hence, while sharing the same biological risk of unvaccinated colleagues, they arguably had a higher level of protection against COVID-19 infection. By contrast, SARS-CoV-2 re-infections were less likely in HCWs vaccinated with three doses, suggesting that hybrid humoral immunity by vaccination combined with natural infection provided a higher level of protection than vaccination only. In this stage of the pandemic, where SARS-CoV-2 is more infectious yet much less pathogenic, health protection measures in healthcare premises at higher biological risk seem the rational approach to control the transmission of the virus.

Keywords: primary SARS-CoV-2 infection; SARS-CoV-2 re-infection; COVID-19; healthcare workers; vaccine effectiveness



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1. Background

The Omicron variants, spread worldwide from December 2021, immediately determined a massive surge of SARS-CoV-2 infections in the general population, peaking in January 2022. These variants are characterized by higher infectivity yet low pathogenicity in individuals immunized by vaccination or natural SARS-CoV-2 infection. Although recovery from COVID-19 was supposed to generate immune response conferring protective immunity, as all RNA viruses, SARS-CoV-2 is in fact prone to mutate into distinct strains, with a genetic composition varying by geographical area [1].

During the Omicron transmission period, recurrent SARS-CoV-2 infections, defined as re-infections in the same individual with genetic viral strains different from the primary infection confirmed at PCR and partitioned each other by at least 90 days, also surged [2,3]. As with other human coronaviruses, re-infections with different SARS-CoV-2 variants are in fact possible regardless of pre-existing humoral immunity [4,5]. For instance, in a Malaysian study on 3,432,651 COVID-19 cases recorded from 1 April 2021 through 31 March 2022, 62,522 (1.8%) of which being at least one episode of recurrent infection, the incidence rate of re-infection during the predominant-Omicron periods increased dramatically, becoming 6.6 times higher (IRR = 4.55; 95% CI 4.51; 4.58) than previous waves (IRR = 0.69; 95% CI 0.67–0.71) [6].

The first case of recurrent COVID-19 was reported in a 25-year-old male from Washoe County (Nevada, USA), infected by SARS-CoV-2 on 18 April 2020 and re-infected by a genetically different variant on 5 June 2020, after two negative tests undertaken in May 2020 during follow-up, with the second infection symptomatically more severe than the first [7]. Seventeen cases of genetically confirmed COVID-19 re-infections were identified during 1 January 2020–12 October 2020, 20% of which presenting with more severe symptoms than the primary infection [8]. By contrast, although remarkably more frequent, recurrent infections during the Omicron transmission period were clinically milder [2]. Nevertheless, identifying the true incidence of COVID-19 re-infection is complicated without population-based studies.

HCWs are an optimal target to assess the impact of the Omicron variant because they are systematically screened for SARS-CoV-2 infections and are at the frontline due to their job tasks and thus exposed to high occupational biological risk. All HCWs at the University Health Agency Giuliano-Isontina (ASUGI), comprising the provinces of Trieste and Gorizia (Friuli-Venezia Giulia Region, Northeast Italy)—the majority immunized with the booster dose by 1 January 2022—were followed-up since the start of the pandemic to monitor and characterize any SARS-CoV-2 infection in nasopharyngeal swabs, estimating the risk of breakthrough infections and vaccine effectiveness (VE) [9–12]. While COVID-19 vaccination reportedly reduced the risk of severe disease as well as infection during the Gamma and Delta transmission periods [13], the uncontrolled spread of Omicron occurred mainly outside healthcare settings, due to its high transmissibility in the general population and higher standard of preventive measures applied in healthcare settings since the start of the pandemic [2].

2. Aims

The aim of the study was to ascertain the incidence of SARS-CoV-2 infection and re-infection during the Omicron transmission period in a population of HCWs with relatively high COVID-19 vaccine uptake yet regularly screened for SARS-CoV-2 infection, hence an ideal target to estimate VE over a period of 6 months, adjusting for a number of relevant confounders. To the best of our knowledge, no data on VE against Omicron are available till the end of May 2022.

3. Methods

3.1. Ethical Considerations

This study was approved by the Italian Medicine Agency (AIFA) and the Ethics Committee of Italian National Institute of Infectious Diseases (INMI) Lazzaro Spallanzani and

by regional ethics committee (CEUR) of Friuli-Venezia Giulia Region (Reg N.188/2022). In compliance with Italian legislation on privacy law, informed consent from study participants was waived since patients' data routinely collected for healthcare reasons were managed anonymously within the framework of an approved study protocol. The cohort contributed to the ORCHESTRA database, a European Union (EU) project funded by Horizon 2020. This study followed the Strengthening of Observational Studies in Epidemiology (STROBE) reporting guidelines.

3.2. Study Population

This study investigated incidence of SARS-CoV-2 infections and re-infections among HCWs of ASUGI ($N = 7723$), including 4 hospitals and community as well as public health services spread across the provinces of Trieste and Gorizia. The vast majority of HCWs of ASUGI were vaccinated with Comirnaty (Pfizer BioNTech), 47% receiving the booster dose by 1 December 2021 and 67% by 1 January 2022. Unvaccinated HCWs were suspended from work or re-assigned to job tasks not involving patient contact.

3.3. Data Collection

The dynamic cohort included HCWs employed by ASUGI (provinces of Trieste and Gorizia, North-eastern Italy) on a permanent contract. Data collected included demographic characteristics (sex, age, job task, education, worksite), number of doses of COVID-19 vaccines received, date of vaccination and date of any positive swab test results, either as primary (incident) or secondary (recurrent) SARS-CoV-2 infection from March 1, 2020 (start of the pandemic in Trieste and Gorizia) until 31 May 2022. Some HCWs were employed by ASUGI during the study period, some other retired before 31 May 2022.

From 15 April 2020, ASUGI implemented a monthly routine screening schedule for all HCWs using nasopharyngeal swabs and PCR (polymerase chain reaction) for virus detection. All HCWs underwent a monthly testing schedule for SARS-CoV-2. HCWs operating in high-risk clinical areas as COVID-19 units or accident and emergency (A&E), or those dealing with immunocompromised patients, were screened weekly for SARS-CoV-2. Additionally, HCWs were swab tested in case of symptoms consistent with COVID-19 or if they had been in close contact with a COVID-19 confirmed case [12].

3.4. Study Endpoints

The present study investigated the incidence of primary as well as recurrent SARS-CoV-2 infections from 1 December 2021 through 31 May 2022, a period dominated by the Omicron variant in Friuli-Venezia Giulia Region.

A recurrent COVID-19 infection was defined as an infection in the same individual with genetic viral strains different from the primary infection, confirmed at PCR and partitioned at least 90 days from primary infection [14].

As already explained above, the surveillance scheme adopted by ASUGI requires all HCWs to swab test for SARS-CoV-2 on a monthly basis, unless operating in clinical areas with higher biological risk, where screening testing schedule was weekly.

During the study period, HCWs infected by SARS-CoV-2 needed to remain in isolation for at least 7 days, and were allowed to return to work only after a negative RT-PCR test. Conversely, the isolation time for unvaccinated HCWs was at least 10 days by Italian law. In compliance with CDC guidelines, HCWs were exempted from screening tests against SARS-CoV-2 for 3 months since COVID-19 diagnosis, to avoid possible false positive results. Viral RNA may in fact persist for up to 90 days since positive test [15].

3.5. Statistical Analysis

Continuous variables were expressed as mean and standard deviation (SD). Categorical variables are expressed as number and percentages. Groups were compared using the *t*-test for normally distributed continuous variables and chi-square tests for categorical variables.

The incidence rates of primary as well as recurrent SARS-CoV-2 infections were estimated by number of person-days (p-d) during the study period (1 December 2021–31 May 2022), by number of doses of COVID-19 vaccines received 7+ days (14+ days in case of only one dose) before any infection.

A multivariable Cox proportional hazard regression model was fitted to investigate the incidence of primary and recurrent SARS-CoV-2 infections, selecting terms to be included in the final model by backward stepwise procedure from variables displayed in Table 1. HCWs were followed up over time from 1 December 2021 until SARS-CoV-2 primary or recurrent infection or (if never infected) until 31 May 2022, controlling for a number of potential confounders, including number of doses of COVID-19 vaccine received 7+ days (14+ days in case of only one dose) before infection. HCWs employed by ASUGI after 30 November 2021 were followed up since date of employment, whereas retirees during 1 December 2021–31 May 2022 were followed up until date of retirement. In both multiple Cox regression models, tests for interaction were carried out for age, job tasks, workplace, number of doses of COVID-19 vaccine, and number of swab tests performed during the study period.

Table 1. Distribution of variables. Number (N), percentage (%), mean \pm standard deviation (SD), median and interquartile range (IQR).

FACTOR	STRATA	NUMBER	Col %
Sex	Female	5308	68.7
	Male	2415	31.3
Age (years)	Mean \pm SD	46.6 \pm 12.0	
	Median (IQR)	48.6 (36.2; 56.7)	
	<41	2468	32.0
	41–50	1751	22.7
ASUGI Site	51–60	2453	31.8
	61+	1051	13.6
	Gorizia-Monfalcone	2589	33.5
Incident SARS-CoV-2 infections (Total = 3541)	Trieste	5134	66.5
	TOTAL (1 Mar 2020–31 May 2022)	3571	100
	I (1 Mar 2020–31 May 2020)	214	6.0
	II (1 Jun 2020–30 Sep 2020)	16	0.5
	III (1 Oct 2020–31 Dec 2020)	535	15.0
	IVa (1 Jan 2021–31 Mar 2021)	294	8.2
	IVb (1 Apr 2021–30 Sep 2021)	107	3.0
	V (1 Oct 2021–30 Nov 2021)	275	7.7
VI (1 Dec 2021–31 May 2022)	2130	59.7	
SARS-CoV-2 re-infections (Tot = 406)	TOTAL (1 Mar 2020–31 May 2022)	406	100
	I (1 Mar 2020–31 May 2020)	0	0
	II (1 Jun 2020–30 Sep 2020)	2	0.5
	III (1 Oct 2020–31 Dec 2020)	4	1.0
	IVa (1 Jan 2021–31 Mar 2021)	2	0.5
	IVb (1 Apr 2021–30 Sep 2021)	5	1.2
	V (1 Oct 2021–30 Nov 2021)	7	1.7
	VI (1 Dec 2021–31 May 2022)	386	95.1

Table 1. Cont.

FACTOR	STRATA	NUMBER	Col %
Number of swab tests (1 December 2021– 31 May 2022)	0	602	7.8
	1–3	754	10.6
	4–6	1189	16.7
	7–10	1759	24.7
	11+	3419	48.0
	TOTAL	7723	100
Number of doses of COVID-19 Vaccine (by 31 May 2022)	0	608	7.9
	1	186	2.4
	2	868	11.2
	3	6047	78.3
	4	14	0.2
Vaccine type	Comirnaty (Pfizer/BioNTech)	7388	95.7
	Spikevax (Moderna)	306	4.0
	Vaxzevria (Oxford-Astra Zeneca; N = 21)		
	Janssen (Johnson & Johnson; N = 7)	29	0.4
	Nuvaxovid (Novavax; N = 1)		
	TOTAL	7723	100
Job task	Administrative	628	8.1
	Doctor	1567	20.3
	Nurses	2733	35.4
	Other HCWs	1642	21.3
	Technician	1153	14.9
	TOTAL	5843	100
Educational level (Missing: 1880)	Junior secondary	2733	46.8
	Secondary	380	6.5
	Bachelor's degree	1085	18.6
	Postgraduate diploma	1645	28.2
	TOTAL	7723	100
Workplace	Administrative services	935	12.1
	Community services	2339	30.3
	Radiology services (technician)	562	7.3
	Surgical ward	1167	15.1
	Medical and geriatric ward	1449	18.8
	COVID-19 area	245	3.2
	Accident and emergency (A&E)	757	9.8
	Non-clinical workers and other	269	3.5

Results were expressed as hazard ratio unadjusted (HR) and adjusted (aHR) with 95% confidence interval (95% CI).

Finally, vaccine effectiveness (VE = 1-aHR) against primary as well as recurrent SARS-CoV-2 infections was estimated by number of doses of COVID-19 vaccines received 7+ days (14+ days in case of only one dose) before infection.

Cases with missing values were excluded from the analysis. A two-sided $p < 0.05$ was considered significant.

Statistical analyses were performed using STATA 14.2 (StataCorp LLC, College Station, TX, USA).

4. Results

As can be seen from Table 1, the ASUGI cohort comprised 7723 HCWs: 5134 (66.5%) employed in the Province of Trieste health district and 2589 (33.5%) in Gorizia, with 68.7% being females. The mean age of ASUGI HCWs was 47 years, 46.8% (=2733/7723) had an educational level limited to junior secondary school, 18.6% (=1085/7723) had a bachelor's degree, and 28.2% (=1645/7723) had a postgraduate diploma; 35.4% (=2733/7723) of HCWs were employed as nurses, 20.3% (=1642/7723) as doctors, 14.9% (=1153/7723) as technicians, 21.3% (=1642/7723) as other types of HCWs, and 8.1% (=628/7723) as administrative clerks. HCWs were predominantly employed in community and primary care services (30.3%=2339/7723), 18.8% (=1449/7723) in medical/geriatric hospital wards, 15.1% (=1167/7723) in surgical wards, 9.8% (=757/7723) in A&E, 7.3% (=562/7723) in radiology services, 3.2% (=245/7723) in COVID-19 units, 12.1% (=93/7723) in administrative services, and 3.5% (=269/7723) as other non-clinical workers.

By 1 December 2021, 46.8% HCWs had received the booster, 37.2% were immunized with two doses, 6.0% with one dose and 10.0% were unvaccinated. By 31 May 2022, 9 HCWs had received four doses of COVID-19 vaccine, 78.4% three, 11.2% two, 2.3% one dose, and 8.1% were unvaccinated (Table 2 and Figure 1).

Table 2. COVID-19 vaccination coverage of health care workers of ASUGI, by number of doses and calendar month, 1 December 2021–31 May 2022. Number and row percentage (%).

DATE	Total HCWs	0 Doses	1 Dose	2 Doses	3 Doses	4 Doses
1 December 2021	7662	767 (10.0)	458 (6.0)	2850 (37.2)	3613 (46.8)	0
1 January 2022	7475	651 (8.6)	384 (5.1)	1500 (19.4)	5161 (66.8)	0
1 February 2022	7448	619 (8.30)	274 (3.7)	1156 (15.6)	5399 (72.5)	0
1 March 2022	7436	614 (8.3)	223 (3.0)	1068 (14.4)	5531 (74.4)	0
1 April 2022	7400	611 (8.3)	198 (2.7)	1031 (13.9)	5560 (75.1)	6
1 May 2022	7364	603 (8.2)	181 (2.5)	877 (11.5)	5703 (77.4)	9
31 May 2022	7345	595 (8.1)	171 (2.3)	822 (11.2)	6052 (78.4)	9

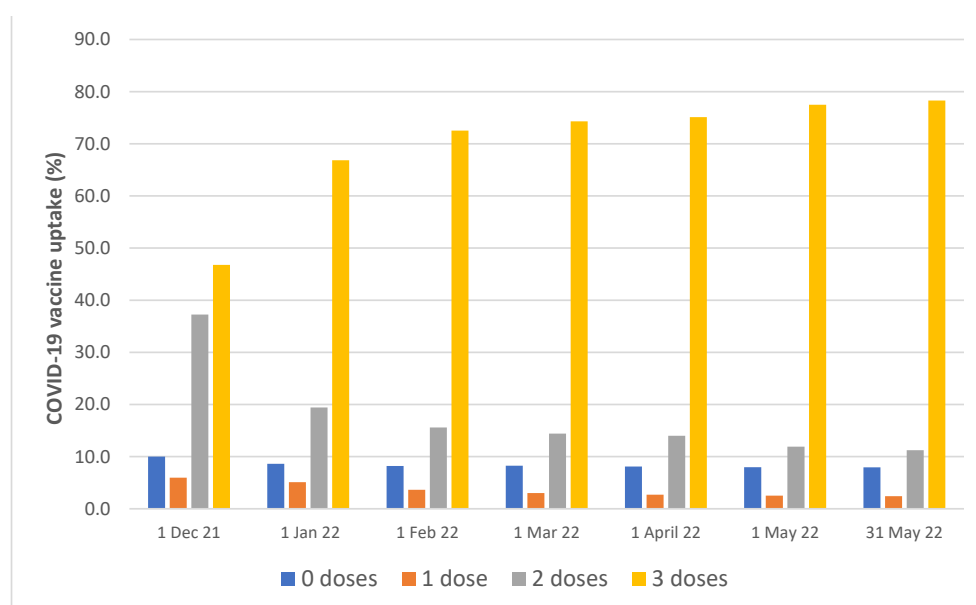


Figure 1. COVID-19 vaccine uptake (%) of HCWs of ASUGI, by number of vaccine doses and calendar month (1 December 2021–31 May 2022).

Almost the totality of HCWs (95.7% = 7388/7723) were vaccinated with Comirnaty (Pfizer/BioNTech) and 4.0% (=306/7723) with Spikevax (Moderna). The remaining

HCWs (0.4% = 29/7723) received either Vaxzevria (Oxford/Astrazeneca $N = 21$), Janssen (Johnson & Johnson $N = 7$), or Nuvaxoid (Novavax: $N = 1$). Moreover, 92.2% (=7121/7723) of HCWs undertook at least one swab test during 1 December 2021–31 May 2022 against 7.8% (=602/7723) never testing.

As can be appreciated from Figures 2 and 3, the majority of primary (59.6% = 2130/3571) and recurrent (95.1% = 386/406) SARS-CoV-2 infections, both peaking in January 2022, were acquired from 1 December 2021 onward.

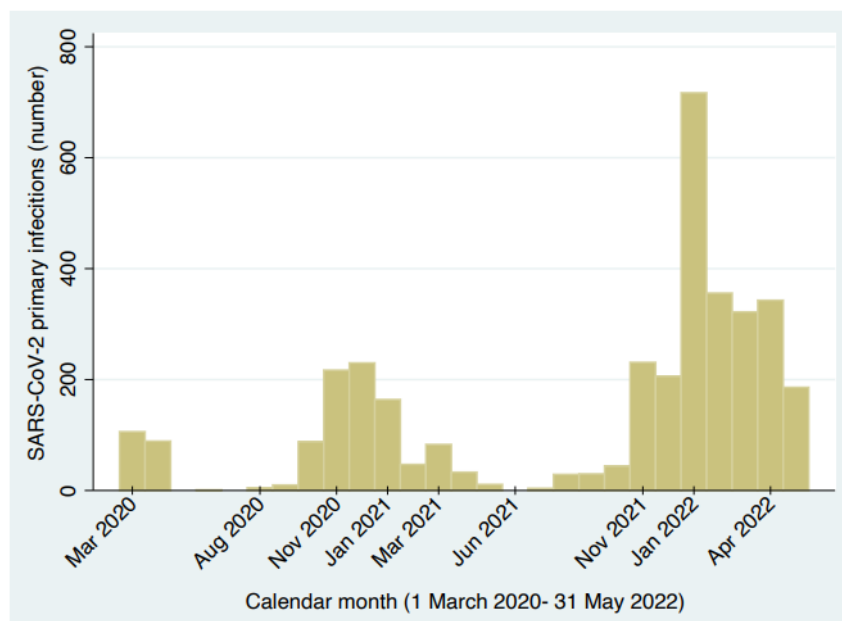


Figure 2. Number of primary SARS-CoV-2 infections ($N = 3571$) in health care workers in ASUGI, by calendar month, 1 March 2020–31 May 2022.

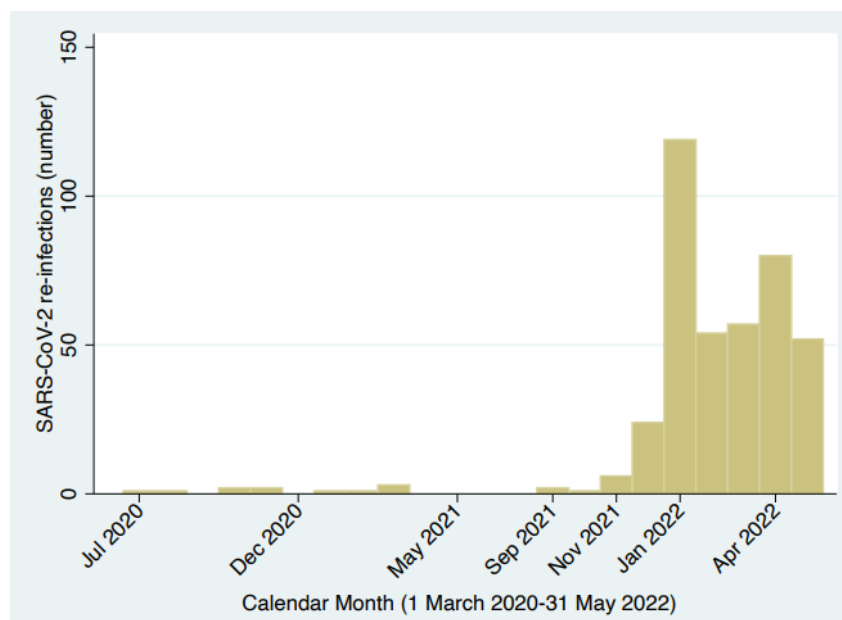


Figure 3. Number of SARS-CoV-2 re-infections (Total = 406) in health care workers (HCWs) of ASUGI, by calendar month, 1 March 2020–31 May 2022.

Table 3 displays the crude incidence rates of primary as well recurrent SARS-CoV-2 infections among HCWs of ASUGI between 1 December 2021 and 31 May 2022, by number of doses of COVID-19 vaccines received 7+ days (14+ days in case of only one dose) before

infection. As can be noted, the overall crude incidence rate of primary infections was 9.7×1000 person-days (p-d), broken down as follows (by number of vaccine doses):

- 14.2×1000 p-d among unvaccinated HCWs;
- 6.2×1000 p-d among HCWs immunized with only one dose;
- 12.5×1000 p-d in those vaccinated with 2 doses;
- 9.1×1000 p-d with 3 doses.

Table 3. Crude incidence rates of primary and recurrent SARS-CoV-2 infections during 1 December 2021–31 May 2022, by number of doses of COVID-19 vaccine received 7+ days (14+ days in case of only one dose) before infection. Number of cases, person-days (p-d) at risk and raw incidence ($\times 1000$ p-d).

Factors	Type of SARS-CoV-2 Infection (01/12/2021–31/05/2022)	Analysis Time			
		Cases	Person-Days (p-d) at Risk	Raw Incidence ($\times 1000$ p-d)	
Total SARS-CoV-2 infections	Primary	2130	219781	9.7×1000	
	Total	386	107,939	3.6×1000	
	Recurrent	Primary infection before 01/12/2021	354	39,761	8.9×1000
		Primary infection after 30/11/2021	32	68,178	0.5×1000
		Primary	187	13,183	14.2×1000
		Total	93	12,199	7.6×1000
0	Recurrent	Primary infection before 01/12/2021	73	5973	12.2×1000
		Primary infection after 30/11/2021	20	6226	3.2×1000
		Primary	39	6268	6.2×1000
		Total	29	6803	4.3×1000
1	Recurrent	Primary infection before 01/12/2021	29	2544	11.4×1000
		Primary infection after 30/11/2021	0	3993	0
		Primary	177	14,207	12.5×1000
		Total	106	19,694	5.4×1000
2	Recurrent	Primary infection before 01/12/2021	102	12,726	8.0×1000
		Primary infection after 30/11/2021	4	6968	0.6×1000
		Primary	1680	184,719	9.1×1000
		Total	141	68,558	2.1×1000
3	Recurrent	Primary infection before 01/12/2021	133	17,833	7.5×1000
		Primary infection after 30/11/2021	8	50,725	0.2×1000

The overall crude rate of re-infections was 3.6×1000 p-d. If the primary SARS-CoV-2 infection had occurred before 1 December 2021 the incidence rate of recurrent infection was 8.9×1000 p-d, broken down as follows, by number of COVID-19 vaccine doses received 7+ days (14+ days in case of only one dose) before re-infection:

- 12.2×1000 p-d among unvaccinated;
- 11.4×1000 p-d in HCWs immunized with one dose;
- 8.0×1000 p-d in HCWs immunized with two doses;
- 7.5×1000 p-d in HCWs immunized with three doses.

By contrast, the overall crude rates of re-infections if the primary SARS-CoV-2 infection had occurred after 30 November 2021 was 0.5×1000 p-d, broken down as follows, by number of COVID-19 vaccine doses received 7+ days (14+ days in case of only one dose) before re-infection:

- 3.2×1000 p-d among unvaccinated,
- 0×1000 p-d in HCWs vaccinated with one dose,
- 0.6×1000 p-d in HCWs immunized with two doses, and
- 0.2×1000 p-d in HCWs vaccinated with three doses.

Table 4 shows a univariable and multivariable Cox regression model for primary SARS-CoV-2 infections in HCWs of ASUGI during 1 December 2021–31 May 2022. As can be noted, there was a highly significant ($p < 0.001$) interaction between job task and age. In particular, compared to clerks younger than 41 years, the risk of incident SARS-CoV-2 infection was consistently and significantly higher for all clinical tasks, especially nurses < 50 years of age. Across all job tasks, an inverse risk pattern declining with age can be appreciated. Likewise, with the exception of COVID-19 units, community health services and other non-clinical areas, the risk of SARS-CoV-2 infection was significantly higher for all clinical units compared to administrative services.

Table 4. Cox proportional regression model for the risk of primary SARS-CoV-2 infection (1 December 2021–31 May 2022). Hazard ratio unadjusted (HR) and adjusted (aHR), with 95% confidence interval (95% CI). Multivariable model fitted onto 1994 complete observations. HCWs never tested for SARS-CoV-2 during 1 January–31 May 2022 ($N = 602$) were excluded from the analysis.

Factor	Strata	Cox Regression Analysis	
		Univariable HR (95% CI)	Multivariable aHR (95% CI)
Sex	Female	Reference	Reference
	Male	0.87 (0.80; 0.96)	0.93 (0.83; 1.04)
Age (years)	<41	Reference	
	41–50	1.27 (1.14; 1.42)	
	51–60	1.11 (1.00; 1.24)	
	61+	0.84 (0.72; 0.97)	
ASUGI site	Gorizia-Monfalcone	Reference	
	Trieste	0.92 (0.84; 1.00)	
Vaccine type	Comirnaty (Pfizer/BioNTech)	Reference	
	Spikevax (Moderna)	0.92 (0.73; 1.16)	
	Other *	0.68 (0.30; 1.51)	
N. Doses of COVID-19 vaccines	0	Reference	
	1	0.41 (0.29; 0.58)	
	2	0.85 (0.69; 1.04)	
	3	0.58 (0.50; 0.67)	

Table 4. Cont.

Factor	Strata	Cox Regression Analysis				
		Univariable HR (95% CI)		Multivariable aHR (95% CI)		
N. Swab tests (1 Dec 2021– 31 May 2022)	1–3	Reference	COVID-19 vaccine doses	0	Reference	
				1	4.15 ^{−10} (1.57 ^{−10} ; 1.09 ^{−9})	
				2	0.59 (0.23; 1.49)	
				3	0.47 (0.21; 1.08)	
	4–6	1.27 (1.03; 1.56)	COVID-19 vaccine doses	0	0.87 (0.37; 2.04)	
				1	0.36 (0.11; 1.16)	
				2	0.74 (0.32; 1.73)	
	7–10	1.40 (1.16; 1.69)	COVID-19 vaccine doses	0	1.16 (0.51; 2.64)	
				1	0.30 (0.09; 0.96)	
				2	0.85 (0.38; 1.93)	
	10+	0.96 (0.80; 1.15)	COVID-19 vaccine doses	0	0.88 (0.40; 1.95)	
				1	0.34 (0.14; 0.84)	
				2	0.65 (0.29; 1.47)	
	Job task	Administrative clerks	Reference	Years of age	<41	Reference
					41–50	2.55 (1.45; 4.49)
					51–60	2.28 (1.41; 3.67)
61+					1.07 (0.61; 1.89)	
Doctor		1.16 (0.97; 1.38)	Years of age	<41	1.29 (0.84; 1.99)	
				41–50	2.46 (1.62; 3.73)	
				51–60	2.31 (1.45; 3.68)	
				61+	1.70 (1.02; 2.84)	
Nurses		1.39 (1.18; 1.64)	Years of age	<41	3.12 (2.11; 4.61)	
				41–50	3.01 (2.00; 4.52)	
				51–60	2.21 (1.46; 3.37)	
				61+	2.08 (1.22; 3.53)	
Other HCWs		1.39 (1.16; 1.65)	Years of age	<41	2.70 (1.74; 4.20)	
				41–50	2.84 (1.87; 4.33)	
				51–60	2.30 (1.51; 3.49)	
				61+	2.52 (1.55; 4.10)	
Health technicians		1.20 (0.99; 1.44)	Years of age	<41	2.38 (1.59; 3.56)	
				41–50	2.78 (1.80; 4.30)	
				51–60	1.97 (1.26; 3.09)	
				61+	1.66 (0.96; 2.87)	
Workplace	Administrative services	Reference		Reference		
	Community health services	1.42 (1.22; 1.65)		1.18 (0.98; 1.43)		
	Radiology services (technicians)	1.48 (1.21; 1.82)		1.58 (1.26; 1.97)		
	Surgical wards	1.34 (1.13; 1.59)		1.43 (1.17; 1.76)		
	Medical and geriatric wards	1.28 (1.09; 1.50)		1.34 (1.11; 1.63)		
	COVID-19 areas	1.04 (0.78; 1.40)		1.07 (0.78; 1.47)		
	Accident and emergency (A&E)	1.25 (1.04; 1.50)		1.28 (1.03; 1.59)		
	Non-clinical and other	1.32 (1.01; 1.71)		1.12 (0.79; 1.59)		
Years of employment (linear term)	1.01 (1.01; 1.01)		1.01 (1.01; 1.02)			
Educational level	Junior secondary	Reference				
	Secondary	0.77 (0.62; 0.95)				
	Bachelor's degree	1.01 (0.88; 1.15)				
	Postgraduate diploma	0.85 (0.75; 0.95)				

* Vaxzevria (Oxford/Astrazeneca; N = 21), Janssen (Johnson & Johnson; N = 7), or Nuvaxoid (Novavax; N = 1).

As can be seen from Table 4, there was also a significant interaction ($p = 0.010$) between number of doses of COVID-19 and number of swab tests performed during the study period. Apart from HCWs swab tested 4–6 times, the risk of primary SARS-CoV-2 infection was significantly and consistently lower in HCWs vaccinated only with one dose, compared to unvaccinated colleagues, whereas VE of three as well as two doses vanished.

Table 5 shows a univariable and multivariable Cox regression model for SARS-CoV-2 re-infections during 1 December 2021–31 May 2022 in HCWs of ASUGI. As with primary infections, there was a highly significant interaction term between age and job task ($p < 0.001$). As can be noted, compared to clerks, the risk of re-infection was significantly higher for all clinical tasks, especially nurses and other categories of HCWs. However, as compared to primary infections, the declining risk with age disappeared. Furthermore, the risk of re-infections was significantly higher in medical/geriatric wards (aHR = 2.09; 95% CI: 1.37; 3.21), A&E (aHR = 2.00; 95% CI: 1.26; 3.17) and non-clinical/other categories (aHR = 3.06; 95% CI: 1.30; 7.18). Finally, recurrent SARS-CoV-2 infections were less likely in HCWs immunized with three doses of COVID-19 vaccines (aHR = 0.58; 95% CI: 0.42; 0.81). Though non-significant, protection from the booster was consistently higher than two doses of COVID-19 vaccines, regardless the number of swab tests performed. However, VE of the booster declined to 42% against re-infections, vanishing for primary SARS-CoV-2 infections.

Figures 4 and 5 show A Kaplan-Meier curve for primary (Figure 4) and recurrent (Figure 5) SARS-CoV-2 infections respectively, in HCW of Trieste during 1 December 2021–31 May 2022 by number of COVID-19 vaccinations received 7+ days (14+ in case of only 1 dose received) before infection.

Table 5. Cox proportional regression model for the risk of SARS-CoV-2 re-infections (1 December 2021–31 May 2022). Hazard ratio unadjusted (HR) and adjusted (aHR), with 95% confidence interval (95% CI). Multiple model fitted onto 731 complete case (analysis) observations. HCWs never tested for SARS-CoV-2 during 1 January–31 May 2022 ($N = 602$) were excluded from the analysis.

Factor	Strata	Cox Regression Analysis	
		Univariable HR (95% CI)	Multivariable aHR (95% CI)
Sex	Female	Reference	Reference
	Male	0.71 (0.57; 0.89)	0.75 (0.59; 0.96)
Age (years)	<41	Reference	
	41–50	1.97 (1.54; 2.52)	
	51–60	2.21 (1.72; 2.84)	
	61+	0.64 (0.39; 1.06)	
ASUGI Site	Gorizia-Monfalcone	Reference	
	Trieste	1.00 (0.79; 1.24)	
Vaccine type	Comirnaty (Pfizer/BioNTech)	Reference	
	Spikevax (Moderna)	1.07 (0.68; 1.70)	
	Other *	135.78 (16.34; 1127.95)	
Doses of COVID-19 vaccines	0	Reference	Reference
	1	0.66 (0.43; 1.00)	0.95 (0.59; 1.54)
	2	0.85 (0.65; 1.12)	1.04 (0.76; 1.43)
	3	0.34 (0.26; 0.44)	0.58 (0.42; 0.81)
Swab tests (1 December 2021– 31 May 2022)	1–3	Reference	Reference
	4–6	3.49 (1.50; 8.09)	2.20 (0.67; 7.29)
	7–10	5.02 (2.21; 11.40)	2.27 (0.69; 7.41)
	11+	4.46 (1.98; 10.06)	1.49 (0.46; 4.86)

Table 5. Cont.

Factor	Strata	Cox Regression Analysis			
		Univariable HR (95% CI)	Multivariable aHR (95% CI)		
JOB TASK	Administrative clerks	Reference	Years of age	<41	Reference
				41–50	4.11 (1.29; 13.09)
				51–60	2.29 (0.69; 7.65)
				61+	4.27 (1.05; 17.41)
	Doctor	1.79 (1.08; 2.97)	Years of age	<41	1.84 (0.72; 4.71)
				41–50	3.20 (1.20; 8.52)
				51–60	4.32 (1.50; 12.39)
				61+	1.73 (0.39; 7.58)
	Nurses	3.80 (2.43; 5.95)	Years of age	<41	7.47 (3.26; 17.10)
				41–50	5.33 (2.22; 12.79)
				51–60	2.73 (1.09; 6.84)
				61+	13.51 (3.20; 57.04)
	Other HCWs	3.51 (2.21; 5.56)	Years of age	<41	4.57 (1.87; 11.15)
				41–50	4.70 (1.97; 11.22)
				51–60	5.01 (2.07; 12.17)
				61+	1.12 (0.22; 5.57)
	Health technician	1.72 (1.05; 2.82)	Years of age	<41	2.32 (0.99; 5.44)
				41–50	3.89 (1.47; 10.26)
				51–60	2.28 (0.76; 6.84)
				61+	3.50 (0.91; 13.54)
WORKPLACE	Administrative services	Reference		Reference	
	Community health services	2.68 (1.88; 3.83)		1.48 (0.96; 2.29)	
	Radiology services (technicians)	1.89 (1.11; 3.20)		1.95 (1.04; 3.65)	
	Surgical wards	1.80 (1.19; 2.71)		1.40 (0.87; 2.27)	
	Medical and geriatric wards	2.28 (1.59; 3.26)		2.09 (1.37; 3.21)	
	COVID-19 areas	1.52 (0.85; 2.73)		1.71 (0.90; 3.25)	
	Accident and emergency (A&E)	2.65 (1.80; 3.89)		2.00 (1.26; 3.17)	
	Non-clinical and other	3.59 (1.75; 7.35)		3.06 (1.30; 7.18)	
	Years of employment (linear term)	1.06 (1.05; 1.07)		1.05 (1.03; 1.07)	
Educational level	Junior secondary	Reference			
	Secondary	0.46 (0.28; 0.75)			
	Bachelor	0.88 (0.67; 1.16)			
	Post-graduate diploma	0.49 (0.36; 0.68)			

* Vaxzevria (Oxford / Astrazeneca; N = 21), Janssen (Johnson & Johnson; N = 7), or Nuvaxoid (Novavax; N = 1).

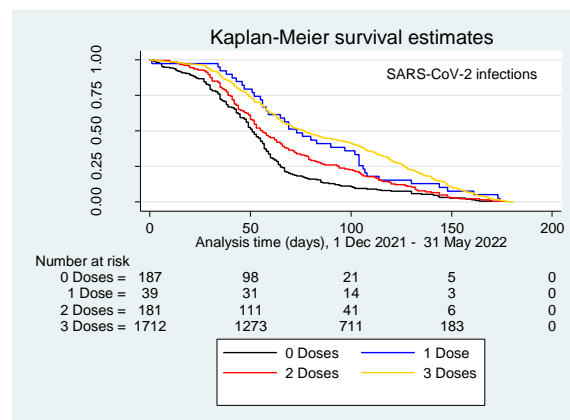


Figure 4. (Kaplan-Meier survival curve). SARS-CoV-2 primary infections (N = 2130) occurred in healthcare workers (HCWs) of ASUGI from 1 December 2021–31 May 2022, by number of doses of COVID-19 vaccines received 7+ days (14+ days in case of only one dose) before infection. Number of HCWs at risk by number of doses of COVID-19 vaccine received.

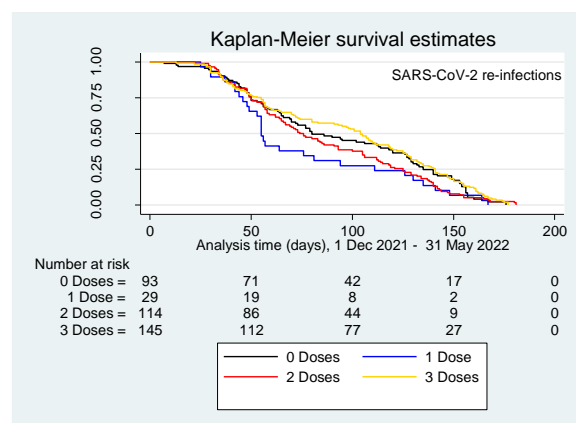


Figure 5. (Kaplan-Meier survival curve). SARS-CoV-2 re-infections ($N = 386$) in healthcare workers of ASUGI between 1 December 2021–31 May 2022, by number of doses of COVID-19 vaccines received 7+ days (14+ days in case of only one dose) before re-infection. Number of HCWs at risk by number of doses of COVID-19 vaccine received.

5. Discussion

5.1. Main Findings

In this cohort of HCWs primary and recurrent SARS-CoV-2 infections peaked in January 2022.

Compared to clerks employed in administrative services, the risk of primary as well as recurrent infections during the study period was significantly higher in all clinical tasks, particularly in nurses and other categories of HCWs, with a decreasing tendency against age for primary infections, across each job category.

Likewise, HCWs operating in all clinical units but COVID-19 areas and community health services were consistently more likely to acquire a primary or recurrent SARS-CoV-2 infection.

Regardless of the number of swab tests performed during the study period, the risk of primary infection was consistently lower in HCWs immunized just with one dose of COVID-19 vaccine. By contrast, the risk of SARS-CoV-2 re-infections was significantly lower in HCWs vaccinated with three doses.

Whilst being 42% against re-infections, VE of the booster vanished for primary SARS-CoV-2 infections.

5.2. Interpretation of Findings

From December 2021 onwards, the Omicron variant started to spread aggressively worldwide also among the vaccinated healthcare force, rapidly becoming dominant by January 2022 and increasing the risk of re-infections [2,16]. This variant, featured by a spike protein highly diverging from previous viral strains, raised immediate concerns for intrinsic high risk of vaccine breakthrough SARS-CoV-2 infection due to evasion of neutralizing antibody responses [17]. Although confirmed COVID-19 cases were featured by flu-like symptoms lasting 1–2 days and no hospitalization was recorded in the present study, other investigations reported also increased risk of symptomatic disease associated with Omicron as compared to previous variants [18].

The crude incidence rate of primary SARS-CoV-2 infection among unvaccinated HCWs of ASUGI during the Omicron transmission period (14.2×1000 p-d) was much higher than that reported for November 2020 (0.9357×1000 p-d) and December 2020 (0.9397×1000 p-d) in HCWs in Trieste before the implementation of the COVID-19 vaccination campaign [12]. Furthermore, in the present study we found a crude incidence rate of primary SARS-CoV-2 infection of 9.1×1000 p-d among HCWs immunized with three doses, a figure considerably higher than that reported for HCWs of Trieste during March–May 2021 (<0.05 cases $\times 1000$ person-years) [12], when VE was estimated to be 95%, in line with other reports [19]. However, in a small study on 85 nursing home residents and

48 HCWs from Cleveland (USA), the vast majority of both groups developed detectable Omicron-specific neutralizing activity following the booster dose with Comirnaty [20]. Although it is still unclear whether protection from COVID-19 increases with level of antibodies, the latter study endorsed the booster dose to increase the neutralizing activity and curb immunity waning over time [20].

While HCWs of ASUGI vaccinated only with one dose were less likely to acquire a primary SARS-CoV-2 infection from December 2021 onward (regardless the number of swab tests), the risk of re-infection was significantly lower in those immunized with three doses. A possible explanation of this finding should consider three interplaying factors: the level of humoral immunity by vaccination (increasing with the number of vaccine doses received), immunity acquired by natural infection and the occupational biological risk. The risk of infection with Omicron is known to increase in HCWs handling patients [2,21], and nurses and other categories of HCWs with jobs tasks entailing patient facing contact confirmed to be at higher risk of primary as well as recurrent SARS-CoV-2 infection in the present study. Moreover, for all job tasks the risk of primary infection tended to decline with age, since younger HCWs were generally assigned to job tasks with higher biological risk. Likewise, HCWs immunized just one dose were both exposed to a lower biological risk, since by Italian law most of them were either suspended from work or re-assigned to job tasks not entailing patient contact, unless previously infected by SARS-CoV-2. This might explain why HCWs vaccinated just with one dose were less likely to incur a primary SARS-CoV-2 infection than those immunized with two or three doses, confirming that the occupational biological risk and health protection measures had greater effect than humoral immunity on the transmissibility of SARS-CoV-2. In a previous study on HCWs in Trieste during the initial stages of the Omicron wave (until 7 February 2022) the vast majority of SARS-CoV-2 infections were in fact of non-occupational origin [2]. In addition to being exposed to a lower occupational biological risk (as a result of work suspension or re-assignment), it can also be reasonably argued that HCWs vaccinated with just one dose may have paid more attention to risk reduction measures outside the workplace.

By contrast, the lower risk of SARS-CoV-2 re-infection in those immunized with three doses endorsed the importance of natural immunity combined with vaccination to re-strengthen the protection against COVID-19, as already reported [22].

While humoral immunity likely had a role in preventing the severe form of COVID-19, its role against infection seems poor now, most likely due to high tendency of mutation of SARS-CoV-2. In this stage of the pandemic, where SARS-CoV-2 is more infectious yet less pathogenic, risk reduction measures in healthcare premises at higher biological risk seem the rational approach to control the transmission of the virus. Furthermore, integrative strategies for infection prevention and control, focusing on the main ports of entry of SARS-CoV-2 in the human body may also be pursued [23–27].

5.3. Generalizability

In a previous study on 7241 HCWs of ASUGI Trieste during 1 October 2020–7 February 2022, 1652 SARS-CoV-2 infections were counted, with a sharp increase in the number of SARS-CoV-2 infections ($N = 670$) observed from January 2022 on, as compared to the period 1 October–31 December 2020 ($N = 367$), the three months preceding the implementation of the national vaccination campaign against COVID-19 [2].

Likewise, in another study at San Matteo Hospital in Pavia (Northern Italy), the incidence of SARS-CoV-2 infection among HCWs was 146×1000 in pre-vaccination (15 October 2020–15 November 2020) versus 67×1000 in post-vaccination era (1 December 2021–15 January 2022). However, while VE was 83% during January–May 2021 (Alpha transmission period), SARS-Cov-2 infections started to surge in November 2021 in Pavia, peaking in December 2021 ($N = 182$), where 89% of cases were attributable to Omicron, most HCWs had received three vaccine doses and most SARS-CoV-2 infections occurred in HCWs immunized with three doses [28].

In the present study VE of the booster declined to 42% for re-infections, vanishing against primary SARS-CoV-2 infections. Though non-significant, protection of the booster was consistently higher than two doses of COVID-19 vaccines, regardless the number of swab tests performed. Likewise, VE of three versus two doses of m-RNA vaccines against COVID-19 was estimated to be 33.2% in another study covering December 2021–January 2022 and hence a much shorter timeframe during the early stages of the Omicron wave [29].

In a study based upon telephone interviews conducted on 11,474 HCWs from New Delhi (India) during 1 December 2021–February 2022, among 83% immunized with two doses of COVID-19 vaccines (88% Covaxin vs. 11% Covishield), the incidence of primary SARS-CoV-2 infection was 34.8% (95% CI: 33.5%; 36.2%) and VE equaled 52.5% (95% CI: 3.9%–75.1%) among HCWs tested within 14–60 days of the second dose, declining thereafter [19]. While in the present study almost the entirety of HCWs were vaccinated with m-RNA vaccines (Comirnaty or Spikevax), in the latter Indian study the predominant COVID-19 vaccine administered to HCWs was Covaxin, an inactive virus.

5.4. Recurrent Infections

We counted 386 SARS-CoV-2 re-infections during 1 December 2021–31 May 2022, 354 of which with a primary infection occurred before 1 December 2021. The overall crude incidence rate of SARS-CoV-2 re-infection was 7.6×1000 p-d among unvaccinated HCWs, 4.3×1000 p-d in those receiving one dose, 5.4×1000 p-d in HCWs immunized with two doses, and 2.1×1000 p-d with three doses. Moreover, the rates re-infection were considerably lower if the primary SARS-CoV-2 infection was acquired from 1 December 2021 onward, endorsing the importance of humoral immunity by previous exposure to Omicron.

Out of 1388 COVID-19 cases notified between 1 March 2020–28 February 2022 among 2700 HCWs of a tertiary center in Mexico City (89.1% completing a primary vaccination cycle), 788 occurred during 1 December 2021–28 February 2022. Furthermore, 73 (5.6%) re-infections were notified, 71 (97.3%) involving individuals who had completed a primary COVID-19 vaccination schedule (two doses) [30]. The overall rate of re-infection in the latter Mexican study, 0.019×1000 p-d before December 2021, increased to 0.231 per 1000 thereafter (during the Omicron wave) [30].

In an Israeli study on 149,032 patients from the general population recovering from SARS-CoV-2 infection during the Delta wave (1 March 2021–26 November 2021), 83,356 (56%) of whom receiving subsequent vaccination during the study period, re-infections occurred in 354 vaccinated (0.0246 cases $\times 1000$ p-d) versus 2168 among 65,676 unvaccinated individuals (0.1021 cases $\times 1000$ p-d) [22], with no evidence of a difference in VE of one against two doses [31].

In the above Indian study on 11,474 HCWs from New Delhi during the Omicron wave, the incidence rate of re-infection was 4.56 (95% CI: 4.29; 4.85) $\times 1000$ p-d [32], an estimate much higher than that ($7.26 = 95\%$ CI: 6.09–8.66 $\times 100$ person-years) reported by another retrospective cohort study conducted between 3 March 2020 and 18 June 2021 (during the Delta wave) on 4978 SARS-CoV-2 infections in 15,244 HCWs from the same city [32]. In the latter Indian study, fully vaccinated HCWs had lower risk of re-infection (HR = 0.14; 95% CI: 0.08–0.23), symptomatic re-infection (HR = 0.13; 95% CI: 0.07; 0.24), and asymptomatic re-infection (HR = 0.16; 95% CI: 0.05; 0.53) compared to unvaccinated HCWs [32]. However, VE of the booster against Omicron declined and immunity seemed limited only to high exposure groups (such as HCWs) according to the above mentioned study on 62,522 (1.8%) episodes of re-infection out of 3432,651 SARS-CoV-2 cases diagnosed in Malaysia between 1 April 2021 and 31 March 2022, questioning the real benefit of a second booster for low exposure categories [6].

5.5. Strengths and Weaknesses

This study examined a relatively large cohort of HCWs ($N = 7723$) subject to stringent occupational surveillance against SARS-CoV-2 during a long observation time (6 months) dominated by the Omicron variant.

However, our study also has some limitations. In particular, we did not have information on established individual risk factors for COVID-19 morbidity and mortality, especially co-morbidities, which in addition to ethnicity and ABO groups, may arguably explain differences in incidence rate of Omicron infection by geographical area.

Moreover, we did not consider the impact of serologic antibody levels on the risk of SARS-CoV-2 infections.

6. Conclusions

SARS-CoV-2 infections and re-infections surged during 1 December 2021–31 May 2022 in HCWs of ASUGI, although presenting with mild flu-like symptoms.

By 1 December 2021, 46.8% HCWs of ASUGI had received the booster, 37.2% were immunized only with two doses of COVID-19 vaccines, 6.0% only with one dose and 10.0% were unvaccinated. Compared to unvaccinated colleagues, the risk of primary SARS-CoV-2 infections was significantly lower in HCWs immunized just with one dose. Protection against primary SARS-CoV-2 infection vanished in HCWs vaccinated with 2 or 3 doses. By Italian law, HCWs immunized only with one dose were either suspended or re-assigned to job tasks not entailing patient contact, hence, while sharing the same biological risk of unvaccinated colleagues, they arguably had a higher level of protection against SARS-CoV-2 infection. In fact, the risk of infection and re-infection was higher for clinical job tasks (nurses and other categories of HCWs) entailing patient facing contact and for clinical units compared to administrative services.

By contrast, SARS-CoV-2 re-infections were less likely in HCWs vaccinated with three doses. In particular, VE was 42% against re-infections, suggesting that hybrid humoral immunity by vaccination combined with natural infection provided higher protection than vaccination only.

While immunity had a role in preventing the severe form of COVID-19, its role against SARS-CoV-2 infection seems poor now, probably due to the high tendency of mutation of the virus. In this stage of the pandemic, where SARS-CoV-2 is more infectious yet less pathogenic, health protection measures in healthcare premises at higher biological risk seem the rational approach to contain the transmission of the virus.

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Institutional Review Board Statement: The study was conducted in accordance with the guidelines of the Declaration of Helsinki, and approved by the Italian Medicine Agency (AIFA) and the Ethics Committee of Italian National Institute of Infectious Diseases (INMI) Lazzaro Spallanzani and by the regional ethics committee (CEUR) of Friuli-Venezia Giulia Region (Reg N.188/2022).

Informed Consent Statement: Patient consent was waived since according to Italian privacy law (Legislative Decree 101/2018, D.Lgs 101/2018) patients' data routinely collected by the Italian National Health Service (NHS) can be used for scientific purposes within the frame of approved studies/protocols, provided sensitive information is anonymized.

Data Availability Statement: Data generated and analyzed during the current study are not publicly available, since they were purposively collected by the authors for the present study, but are available from the corresponding author on reasonable request.

Conflicts of Interest: The authors declare no conflict of interest.

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