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Original article

Nationwide effectiveness of five SARS-CoV-2 vaccines in Hungary—the HUN-VE study

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ABSTRACT

Objectives: The Hungarian vaccination campaign was conducted with five different vaccines during the third wave of the coronavirus disease 2019 (COVID-19) pandemic in 2021. This observational study (HUN-VE: Hungarian Vaccine Effectiveness) estimated vaccine effectiveness against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and COVID-19-related mortality in 3.7 million vaccinated individuals.

Methods: Incidence rates of SARS-CoV-2 infection and COVID-19-related mortality were calculated using data from the National Public Health Centre surveillance database. Estimated vaccine effectiveness was calculated as 1 − incidence rate ratio ≥7 days after the second dose for each available vaccine versus an unvaccinated control group using mixed-effect negative binomial regression controlling for age, sex and calendar day.

Results: Between 22 January 2021 and 10 June 2021, 3 740 066 Hungarian individuals received two doses of the BNT162b2 (Pfizer-BioNTech), HB02 (Sinopharm), Gam-COVID-Vac (Sputnik-V), AZD1222 (Astra-Zeneca), or mRNA-1273 (Moderna) vaccines. Incidence rates of SARS-CoV-2 infection and COVID-19-related death were 1.73–9.3/100 000 person-days and 0.04–0.65/100 000 person-days in the fully vaccinated population, respectively. Estimated adjusted effectiveness varied between 68.7% (95% CI 67.2%–70.1%) and 88.7% (95% CI 86.6%–90.4%) against SARS-CoV-2 infection, and between 87.8% (95% CI 86.1%–89.4%) and 97.5% (95% CI 95.6%–98.6%) against COVID-19-related death, with 100% effectiveness in individuals aged 16–44 years for all vaccines.

Conclusions: Our observational study demonstrated the high or very high effectiveness of five different vaccines in the prevention SARS-CoV-2 infection and COVID-19-related death. **Zoltán Vokó, Clin Microbiol Infect 2022;28:398**

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic started on 31 December 2019 when the first cases of pneumonia of unknown aetiology were reported from the city of Wuhan, China [1]. The disease was declared a global pandemic by the World Health Organization on 11 March 2020 [2].

In Hungary, the first outbreak was limited in magnitude, however, the second wave resulted in considerable excess mortality by the end of 2020 compared with previous years [3] and the country was facing an even more intensive third wave in early 2021 with close to 30 000 SARS-CoV-2-related deaths. At the peak of the third wave in March and April 2021, five different COVID-19 vaccines were available and widely used in Hungary: two mRNA vaccines (BNT162b2—Pfizer-BioNTech and mRNA-1273—Moderna), two vector vaccines (AZD1222—AstraZeneca and Gam-COVID-Vac—-Sputnik-V), and one inactivated vaccine (HB02—Sinopharm).

Emerging real-world evidence suggests that the effectiveness of COVID-19 vaccines might be even better than expected based on the results of randomized, controlled trials [4–13]. A real-world study from Israel reported 96.5% adjusted effectiveness rates for mRNA vaccines against SARS-CoV-2 infection after the second dose [4]. Another study from the USA estimated that mRNA vaccine effectiveness (Pfizer-BioNTech and Moderna together) was 90% among fully immunized health-care workers for the prevention of infection [8]. Another study from the UK found a 65% lower chance of a new SARS-CoV-2 infection in people aged ≥16 years after a single dose of either the AstraZeneca or the Pfizer-BioNTech vaccine compared with the unvaccinated population [9]. In a recent study from Chile, conducted among more than 10 million fully vaccinated individuals, the inactivated SARS-CoV-2 vaccine SinoVac showed adjusted effectiveness rates of 65.9% for the prevention of SARS-CoV-2 infection and 86.3% for the prevention of COVID-19-related death ≥14 days after the second dose [12].

The wide range of vaccines available in Hungary allows for the assessment of vaccine effectiveness in a real-world setting in a Central European country and puts Hungary in the unique position of providing detailed information on multiple vaccine types from the same country. Therefore, the primary aim of our retrospective, population-based study (HUN-VE: Hungarian Vaccine Effectiveness) was to estimate the effectiveness of five available vaccines against SARS-CoV-2 infection and COVID-19-related death during a rapid peak of the pandemic in Hungary, which was dominated by the B.1.1.7 strain of the SARS-CoV-2 virus.

Materials and methods

This nationwide, retrospective, observational study examined the effectiveness of five different vaccines against SARS-CoV-2 infection and COVID-19-related deaths, using data from the National Public Health Centre between 22 January 2021 and 10 June 2021. The study population included Hungarian residents (i.e. the census population) aged 16 years and older. Besides age, the only inconsistencies in the data were exclusion criteria, e.g. a person receiving two different vaccines; no information on the type of the second vaccine dose; the vaccination date preceding the first potential date of vaccine application; less than 14 days passing between the two doses; the date of diagnosis preceding the date when the first case was reported; or the date of death preceding the vaccination date. Only a few dozen cases were excluded for reasons other than age outside the study age range. Cases of SARS-CoV-2 infection were reported on a daily basis using a centralized system via the National Public Health Centre. The report is based on (a) COVID-19-related symptoms identified by hospital physicians and general practitioners and (b) positive nucleic acid amplification test reported by microbiological laboratories. Cases identified by symptoms were confirmed by PCR or antigen test included in the European Commission rapid test list [14].

The prevalence of the COVID-19 variant B.1.1.7 was estimated based on swabs tested with variant-specific real-time PCR or viral genome sequencing. Outcomes of SARS-CoV-2 infection were established if one of the following criteria applied: (a) negative antigen rapid tests or PCR test and/or at least 10 days have passed since the positive SARS-CoV-2 test result, or (b) the patient died.

COVID-19-related mortality was defined as death during SARS-CoV-2 positivity, regardless of whether death was the direct consequence of COVID-19 infection or other underlying causes. The definition was based on World Health Organization recommendations and defined by the health-care government in the National Social Information System [15]. Patients with confirmed SARS-CoV-2 infection who died without previously declared recovery and another clear cause of death were classified as COVID-19-related deaths.

Individuals were classified as fully vaccinated if at least 7 days had passed since the administration of the second dose of any vaccine type. Sensitivity analyses were conducted ≥14 and ≥28 days after the administration of the second dose. The unvaccinated, control population included individuals who had not received any dose of any COVID-19 vaccine type. Individuals aged <16 years were excluded from the analysis, as well as those receiving single-dose Janssen vaccine because of short follow-up times.

Vaccine effectiveness (calculated as 1 − incidence rate ratio) was examined separately for each vaccine versus the control, unvaccinated population. Five different fully vaccinated groups were established based on vaccine types.

The first day of our study was 22 January 2021, because the second dose of the Pfizer-BioNTech vaccine, which was the first vaccine to be used in Hungary, was first administered on 15 January. On the first study day, the number of unvaccinated persons were the number of Hungarian residents aged 16 years and older. Individuals with SARS-CoV-2 infection and those receiving vaccines were removed from the unvaccinated group on a daily basis, and in case of vaccination they were added to the partially vaccinated group (from the day of the first dose till the second vaccination plus 6 days) and then, further, to the fully vaccinated group. Individuals with SARS-CoV-2 infection were moved to the respective case group. Person-days for each partially and fully vaccinated group were calculated by adding up the number of persons in each group for each day.

The main outcomes of the HUN-VE study were the incidence of SARS-CoV-2 infection and COVID-19-related death. Incidence rates (number of outcomes divided by person-days of observation) for both outcomes were calculated from T0 for each fully vaccinated group as well as their respective unvaccinated control groups. Data were stratified by age (16–24, 25–34, 35–44, 45–54, 55–64, 65–74, 75–84, ≥85 years). The confidence intervals of the crude rates were obtained from Poisson regression using STATA (version 16.1; StataCorp, College Station, TX, USA).

As there was evidence for over-dispersion in the data, mixed-effect negative binomial regression models were used to derive adjusted incidence rate ratios with 95% CIs for each outcome adjusted for age group, sex and calendar day (modelled as a random effect), which is better suited for over-dispersed count data than the traditional Poisson regression. As a sensitivity analysis, additional models were fitted with calendar week as fixed effect. The model is a random intercept model, which allows for different incidence rates in the reference category (i.e. unvaccinated) each day, but assumes fixed effect of the vaccines among partially and among fully vaccinated persons depending on their age and sex.

Separate models were fitted to estimate age-group-specific effects using interaction terms between age group and vaccination. Age strata without a case of death were omitted from the respective analyses, because otherwise the models did not converge.

The study was approved by the Central Ethical Committee of Hungary (OGYÉI/40741-2/2021).

Results

Fig. 1 shows the daily number of SARS-CoV-2 infections, the number of persons covered by available vaccine supply by week and the introduction of different vaccines with the date of their respective second doses.

In total, 3 740 066 individuals received the second dose of the vaccine during the study period. The most frequently used vaccine type was the Pfizer-BioNTech vaccine (n = 1 497 011), followed by Sinopharm (n = 895 465), Sputnik-V (n = 820 560), AstraZeneca (n = 304 138) and Moderna (n = 222 892) (Table S1). Individuals aged 65 years or older were predominantly vaccinated using the Pfizer-BioNTech and Sinopharm vaccines (Figure S1).

In the study period, 371 212 SARS-CoV-2 infections occurred in the unvaccinated and 6 912 in the fully vaccinated study populations. In total, 13 533 COVID-19-related deaths were found, including 553 deaths in the fully vaccinated cohorts.

The incidence rates of SARS-CoV-2 infection varied between 1.73 and 9.3/100 000 person-days in the fully vaccinated population, and between 49.49 and 62.33/100 000 person-days in the unvaccinated control groups. The incidence rates of COVID-19-related deaths varied between 0.04 and 0.60/100 000 person-days in the vaccinated and between 1.56 and 1.89/100 000 person-days in the unvaccinated groups (Table 1). Available vaccine supply by week according to different vaccine types is detailed in Table S2.

After adjustment for age, sex and calendar day, the estimated effectiveness against SARS-CoV-2 infection was as follows: Pfizer-BioNTech: 83.3% (95% CI 82.6%–83.9%); Moderna: 88.7% (95% CI 86.6%–90.4%); Sputnik-V 85.7% (95% CI 84.3%–86.9%); AstraZeneca: 71.5% (95% CI 69.2%–73.6%); Sinopharm: 68.7% (95% CI 67.2%–70.1%) (Table 2). Overall estimated adjusted vaccine effectiveness against COVID-19-related death varied between 87.8% (95% CI 86.1%–89.5%) and 97.5% (95% CI 95.6%–98.6%) for different vaccine types; however, it was 100% in the 16–44 year age cohorts for all vaccines (Table 2).

Sensitivity analyses examining vaccine effectiveness ≥14 days and ≥28 days after the second dose yielded similar results to the main analysis (Tables S3, S4). As can be seen in Table S5, vaccine efficacy was much less in the partially vaccinated population, namely during the period from the day of first vaccination till the first 6 days after vaccination.

Fixed-effects models with calendar week as a covariate produced basically the same vaccine efficacy point estimates as the mixed-effect models and, as expected, wider confidence intervals (Table S6).

Discussion

Our nationwide observational study examined the effectiveness of five COVID-19 vaccines against SARS-CoV-2 infection and COVID-19-related death among 3.7 million individuals. All investigated vaccines showed overall high (>50%) or very high (>80%) effectiveness against SARS-CoV-2 infection and very high effectiveness against COVID-19-related mortality. The emergency approval of five different vaccines led to the prevention of more than 9 500 deaths.

Our study showed adjusted effectiveness rates of 83.3% and 84% for the Pfizer-BioNTech vaccine against SARS-CoV-2 infection ≥7 and ≥ 14 days after the second dose, respectively, which are

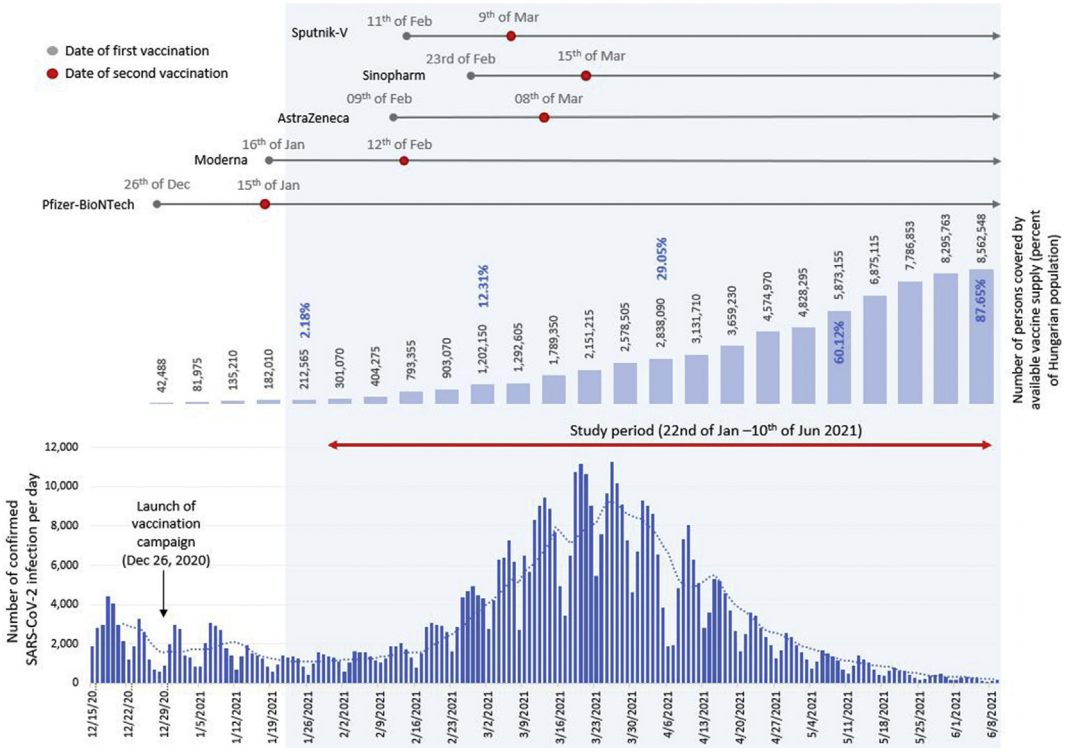

Fig. 1. Launch dates of different vaccine types, dates of their respective second doses, daily number of confirmed SARS-CoV-2 infections, and number of persons covered by available vaccine supply in Hungary between 15 December 2020 and 10 June 2021 by weeks. The dotted line shows the 7-day moving average.

Table 1
Person-days, number of events and incidence rates of SARS-CoV-2 infections and COVID-19-related deaths in the fully vaccinated population as well as in their respective unvaccinated control groups

Vaccine	Age	SARS-CoV-2 infection						COVID-19-related mortality					
		Observation time (100 000 person-days)		Unvaccinated		Fully vaccinated		Observation time (100 000 person-days)		Unvaccinated		Fully vaccinated	
		Unvaccinated	Fully vaccinated	Number of cases	Incidence rate per 100 000 person-days	Number of cases	Incidence rate per 100 000 person-days	Unvaccinated	Fully vaccinated	Number of cases	Incidence rate per 100 000 person-days	Number of cases	Incidence rate per 100 000 person-days
Pfizer-BioNTech	16–24	1061.22	20.06	35 822	33.76	89	3.56	1132.24	20.12	18	0.02	0	0.00
	25–34	1349.30	46.94	65 687	48.68	253	4.75	1480.34	48.16	96	0.06	0	0.00
	35–44	1502.24	73.03	83 955	55.89	391	4.84	1677.69	76.08	327	0.19	0	0.00
	45–54	1271.52	96.35	85 813	67.49	610	5.84	1465.06	102.97	916	0.63	7	0.07
	55–64	1031.48	97.10	52 619	51.01	432	4.04	1156.81	105.70	2146	1.86	10	0.09
	65–74	762.46	128.23	29 286	38.41	335	2.34	829.58	137.08	3735	4.50	26	0.19
	75–84	385.37	135.78	13 386	34.74	666	4.54	430.57	151.99	3690	8.57	118	0.78
	85+	136.89	54.21	4644	33.93	485	8.17	154.43	55.69	2052	13.29	119	2.14
Total		7500.48	651.71	371 212	49.49	3261	4.83	8326.73	697.80	12 980	1.56	280	0.40
Moderna	16–24	811.82	1.94	33 244	40.95	3	1.55	874.01	1.94	17	0.02	0	0.00
	25–34	1020.50	3.75	60 310	59.10	1	0.27	1136.76	3.89	89	0.08	0	0.00
	35–44	1114.45	6.70	76 122	68.30	6	0.90	1270.15	7.11	304	0.24	0	0.00
	45–54	912.44	9.06	77 696	85.15	7	0.77	1084.07	10.10	839	0.77	0	0.00
	55–64	715.07	10.26	46 808	65.46	19	1.85	826.46	11.40	1911	2.31	2	0.18
	65–74	462.47	15.61	25 280	54.66	16	1.02	521.49	16.64	3215	6.17	5	0.30
	75–84	226.81	14.53	10 718	47.26	35	2.41	266.44	16.38	2979	11.18	4	0.24
	85+	91.11	10.69	3564	39.12	52	4.86	105.81	10.95	1602	15.14	13	1.19
Total		5354.67	72.54	333 742	62.33	139	1.92	6085.20	78.41	10 956	1.80	24	0.31
Sputnik-V	16–24	591.86	11.05	23 423	39.58	13	1.18	644.80	11.05	13	0.02	0	0.00
	25–34	731.96	23.18	41 105	56.16	29	1.25	832.25	24.24	78	0.09	0	0.00
	35–44	777.35	49.35	47 315	60.87	59	1.20	911.24	51.91	251	0.28	0	0.00
	45–54	609.21	64.93	48 697	79.93	95	1.46	757.07	71.00	656	0.87	0	0.00
	55–64	459.01	72.05	29 257	63.74	155	2.15	555.33	77.86	1481	2.67	3	0.04
	65–74	242.47	62.05	14 427	59.50	131	2.11	292.71	65.64	2318	7.92	5	0.08
	75–84	126.79	10.53	6091	48.04	25	2.38	160.76	11.90	2021	12.57	4	0.34
	85+	62.63	0.90	2284	36.47	1	1.11	74.62	0.93	1130	15.14	0	0.00
Total		3601.28	294.03	212 599	59.03	508	1.73	4228.80	314.53	7948	1.88	12	0.04
AstraZeneca	16–24	600.56	1.51	23 585	39.27	6	3.97	653.93	1.51	13	0.02	0	0.00
	25–34	743.30	2.91	41 487	55.81	16	5.50	844.33	3.07	78	0.09	0	0.00
	35–44	790.44	8.82	47 886	60.58	79	8.96	925.38	9.30	255	0.28	0	0.00
	45–54	620.69	29.43	49 229	79.31	310	10.53	769.67	32.13	667	0.87	5	0.16
	55–64	468.33	25.48	29 605	63.21	270	10.60	565.36	28.15	1507	2.67	5	0.18
	65–74	249.30	3.92	14 682	58.89	5	1.27	299.95	5.16	2364	7.88	0	0.00
	75–84	129.59	1.80	6213	47.94	3	1.66	163.81	3.29	2078	12.69	0	0.00
	85+	63.61	0.29	2338	36.76	1	3.41	75.70	0.35	1157	15.28	1	2.86
Total		3665.82	74.17	21 025	58.66	690	9.30	4298.13	82.96	8119	1.89	11	0.13
Sinopharm	16–24	539.91	5.44	18 950	35.10	5	0.92	590.16	5.44	10	0.02	0	0.00
	25–34	664.45	8.14	32 581	49.03	6	0.74	759.97	9.15	68	0.09	0	0.00
	35–44	699.55	10.57	36 219	51.78	24	2.27	826.87	12.09	230	0.28	0	0.00
	45–54	541.16	10.03	37 517	69.33	29	2.89	681.98	12.40	569	0.83	0	0.00
	55–64	404.88	57.42	22 350	55.20	456	7.94	496.80	61.95	1294	2.60	12	0.19
	65–74	205.25	167.36	10 668	51.98	1124	6.72	252.94	175.96	1994	7.88	82	0.47
	75–84	111.88	79.42	4700	42.01	593	7.47	144.35	88.53	1701	11.78	104	1.17
	85+	57.06	7.78	1873	32.82	77	9.90	68.36	8.05	984	14.40	28	3.48
Total		3224.13	346.17	164 858	51.13	2314	6.68	3821.43	373.57	6850	1.79	226	0.60

Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

somewhat lower than those reported in the phase III clinical trial and real-world analyses [4–6,16]. Differences in real-world vaccine effectiveness may be the result of differences in patient cohorts. In Hungary, Pfizer-BioNTech and Moderna vaccines were the preferred options for patients with chronic conditions such as type 2 diabetes or cardiovascular disease, which may limit vaccine effectiveness [17]. It is important to note that despite similarities in study methodology, neither our study nor the Israeli analysis [4] adjusted for potential confounders other than age, sex and calendar time, therefore, the results are not directly comparable because of potential residual confounding. In our study, effectiveness of the Pfizer-BioNTech vaccine against COVID-19-related death was found to be 90.6% and 90.3% $\geq$ 7 and $\geq$14 days after the second dose, respectively, in line with observations from the Israeli study [4].

Our study was among the first to examine the individual effectiveness of the Moderna vaccine in a real-world setting among 222 892 persons, of whom 36% were $\geq$65 years old. Overall

Table 2
Estimated unadjusted and adjusted effectiveness of five different vaccine types against SARS-CoV-2 infection and COVID-19-related death in the fully vaccinated study population ≥7 days after the second dose in Hungary

Vaccinated person			Vaccine effectiveness							
			SARS-CoV-2 infection				COVID-19-related mortality			
Vaccine	Age	*n*	Unadjusted	95% CI[a]	Adjusted	95% CI[a]	Unadjusted	95% CI[a]	Adjusted	95% CI[a]
Pfizer-BioNTech	16–24	67 149	86.6%	(83.4%–89.2%)	82.3%	(78.1%–85.7%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	25–34	144 278	88.4%	(86.8%–89.8%)	83.2%	(80.8%–85.2%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	35–44	208 085	89.8%	(88.7%–90.8%)	84.2%	(82.4%–85.8%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	45–54	231 593	90.3%	(89.4%–91.0%)	85.6%	(84.3%–86.9%)	89.1%	(77.1%–94.8%)	84.2%	(66.8%–92.5%)
	55–64	232 871	91.5%	(90.6%–92.4%)	85.0%	(83.4%–86.5%)	94.9%	(90.5%–97.3%)	92.7%	(86.5%–96.1%)
	65–74	310 079	94.4%	(93.7%–95.1%)	85.3%	(83.5%–86.9%)	95.8%	(93.8%–97.1%)	94.3%	(91.6%–96.1%)
	75–84	230 046	88.9%	(87.8%–89.8%)	82.1%	(80.4%–83.6%)	90.9%	(89.1%–92.5%)	91.3%	(89.6%–92.8%)
	85+	72 910	78.0%	(75.5%–80.2%)	74.3%	(71.4%–76.8%)	83.9%	(80.7%–86.6%)	87.1%	(84.5%–89.3%)
Total		1 497 011	90.6%	(90.2%–90.9%)	83.3%	(82.6%–83.9%)	74.3%	(71.0%–77.1%)	90.6%	(89.4%–91.7%)
Moderna	16–24	10 312	96.2%	(88.3%–98.8%)	80.5%	(39.4%–93.7%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	25–34	20 658	99.5%	(96.8%–99.9%)	97.0%	(78.6%–99.6%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	35–44	34 890	98.7%	(97.1%–99.4%)	90.6%	(79.1%–95.8%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	45–54	40 781	99.1%	(98.1%–99.6%)	93.6%	(86.7%–97.0%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	55–64	35 726	97.2%	(95.6%–98.2%)	84.5%	(75.7%–90.1%)	92.4%	(69.6%–98.1%)	80.3%	(20.9%–95.1%)
	65–74	39 118	98.1%	(96.9%–98.9%)	93.2%	(88.8%–95.8%)	95.1%	(88.3%–98.0%)	91.1%	(78.7%–96.3%)
	75–84	27 111	94.9%	(92.9%–96.3%)	88.9%	(84.5%–92.0%)	97.8%	(94.2%–99.2%)	97.0%	(92.0%–98.9%)
	85+	14 296	87.6%	(83.7%–90.5%)	84.1%	(79.0%–87.9%)	92.2%	(86.5%–95.5%)	92.5%	(87.0%–95.6%)
Total		222 892	96.9%	(96.4%–97.4%)	88.7%	(86.6%–90.4%)	83.0%	(74.6%–88.6%)	93.6%	(90.5%–95.7%)
Sputnik-V	16–24	55 632	97.0%	(94.9%–98.3%)	75.5%	(57.7%–85.8%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	25–34	94 808	97.8%	(96.8%–98.5%)	82.7%	(75.1%–88.0%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	35–44	167 038	98.0%	(97.5%–98.5%)	84.7%	(80.1%–88.1%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	45–54	194 601	98.2%	(97.8%–98.5%)	85.7%	(82.4%–88.3%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	55–64	166 499	96.6%	(96.0%–97.1%)	84.8%	(82.1%–87.0%)	98.6%	(95.5%–99.5%)	96.7%	(89.8%–98.9%)
	65–74	120 096	96.5%	(95.8%–97.0%)	87.8%	(85.4%–89.8%)	99.0%	(97.7%–99.6%)	98.2%	(95.7%–99.3%)
	75–84	20 056	95.1%	(92.7%–96.7%)	85.9%	(79.1%–90.5%)	97.3%	(92.9%–99.0%)	95.4%	(87.8%–98.3%)
	85+	1830	97.0%	(78.4%–99.6%)	90.9%	(35.7%–98.7%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
Total		820 560	97.1%	(96.8%–97.3%)	85.7%	(84.3%–86.9%)	98.0%	(96.4%–98.8%)	97.5%	(95.6%–98.6%)
AstraZeneca	16–24	8995	89.9%	(77.5%–95.5%)	68.5%	(29.9%–85.9%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	25–34	15 313	90.2%	(83.9%–94.0%)	77.2%	(62.8%–86.1%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	35–44	32 886	85.2%	(81.6%–88.1%)	68.6%	(60.8%–74.9%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	45–54	88 266	86.7%	(85.1%–88.1%)	73.5%	(70.3%–76.5%)	81.9%	(56.5%–92.5%)	74.3%	(38.0%–89.3%)
	55–64	79 206	83.2%	(81.1%–85.1%)	68.3%	(64.1%–72.0%)	93.3%	(83.9%–97.2%)	90.8%	(77.8%–96.2%)
	65–74	51 838	97.8%	(94.8%–99.1%)	72.2%	(33.2%–88.5%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	75–84	23 722	96.5%	(89.2%–98.9%)	64.8%	(−9.2%–88.7%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	85+	3912	90.7%	(34.1%–98.7%)	38.7%	(0%**–91.4%)	81.3%	(−134%–91.4%)	38.3%	(−340%–91.4%)
Total		304 138	84.1%	(82.9%–85.3%)	71.5%	(69.2%–73.6%)	92.9%	(87.3%–96.1%)	88.3%	(78.7%–93.5%)
Sinopharm	16–24	65 720	97.4%	(93.7%–98.9%)	67.3%	(21.3%–86.4%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	25–34	91 946	98.5%	(96.7%–99.3%)	84.6%	(65.8%–93.1%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	35–44	104 018	95.6%	(93.5%–97.1%)	69.0%	(53.7%–79.3%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	45–54	80 960	95.8%	(94.0%–97.1%)	78.6%	(69.2%–85.2%)	100.0%	(NA–100.0%)	100.0%*	(NA–NA)
	55–64	126 028	85.6%	(84.2%–86.9%)	66.1%	(62.6%–69.3%)	92.5%	(86.8%–95.8%)	87.9%	(78.5%–93.1%)
	65–74	281 725	87.1%	(86.3%–87.8%)	71.1%	(69.0%–73.1%)	94.1%	(92.6%–95.2%)	91.1%	(88.9%–92.9%)
	75–84	130 323	82.2%	(80.6%–83.7%)	66.4%	(63.1%–69.4%)	90.0%	(87.8%–91.8%)	86.7%	(83.7%–89.1%)
	85+	14 745	69.8%	(62.1%–76.0%)	43.1%	(28.3%–54.9%)	75.7%	(64.7%–83.3%)	67.3%	(52.3%–77.6%)
Total		895 465	86.9%	(86.4%–87.5%)	68.7%	(67.2%–70.1%)	66.1%	(61.3%–70.3%)	87.8%	(86.1%–89.4%)

Abbreviations: COVID-19, coronavirus disease 2019; NA: value is not available as the stratum was not included in the model; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.
[a] The model including interaction with age did not converge with the inclusion of age groups with zero death, therefore, these were not included in these models.

effectiveness was 88.7% against SARS-CoV-2 infection and 93.6% against COVID-19-related death ≥7 days after the second dose. The results confirm the very high effectiveness of the Moderna mRNA vaccine in clinical trials and real-world setting [18,19].

In an interim analysis of a phase III trial conducted across three continents, the viral vector vaccine ChAdOx1 nCoV-19 (AstraZeneca) showed significant, 70.4%, effectiveness against SARS-CoV-2 infection after two doses [20]. Available real-world studies have reported 65%–86% effectiveness of the vaccine against SARS-CoV-2 infection after a single dose [9,20]. Most of our study population was younger than 65 years (73.9%), vaccine effectiveness was 68.27%–77.22% against SARS-CoV-2 infection in this cohort. Effectiveness against COVID-19-related death varied between 74.5% and 100% with rates close to 100% in most age cohorts, confirming the high effectiveness of the AstraZeneca vaccine.

In line with phase III trial results, our study demonstrated 85.7% effectiveness for the Sputnik-V vector vaccine against SARS-CoV-2 infection 7 days after the second dose [21]. Effectiveness against COVID-19-related death varied between 95.4% and 100% in different age cohorts, showing very high and persistent effectiveness both in older and younger age cohorts. To our knowledge, our study is the first to provide real-world effectiveness data on the Sputnik-V vaccine in a large population of 820 560 vaccinated Hungarian individuals, confirming phase III trial results.

Our study complements available evidence [12,13] by showing high effectiveness of the inactivated Sinopharm vaccine against SARS-CoV-2 infection and very high effectiveness against COVID-19-related death ≥7 days after the second dose in most age cohorts except for individuals aged 85 years or older. The effectiveness of Sinopharm in preventing COVID-19-related death varied according to age between 67.5% and 100% ≥ 7 days after the second dose, with an adjusted overall effectiveness of 87.8%. The magnitude of effect was similar to that of SinoVac, another type of inactivated SARS-CoV-2 vaccine, the effectiveness analysis of which was recently published from Chile [12].

The strengths of our study include its nationwide nature, the effectiveness analysis of five different SARS-CoV-2 vaccines during a powerful pandemic wave, the robust number of more than 3.7 million vaccinated individuals, and the almost 5-month study period.

It is important to note that our results have important limitations, some inherent in surveillance-based vaccine effectiveness studies. First, the study period was different for each vaccine, so the analysis implicitly assumes that the effect of each covariate, including vaccination is constant during the follow up. Second, despite adjustments for age, sex and calendar day, further important covariates such as co-morbidities, medications or socio-economic status were not included. For chronic diseases, for example, the validity issue is the extent to which the likelihood of receiving each vaccine differs for a given day, age and sex depending on whether or not a person has a chronic disease, and the extent to which the risk of infection and death and the likelihood of detection differ. Given that some vaccines were specifically indicated for use in elderly and chronically ill patients, the bias due to chronic disease (which may occur in addition to the age effect) may have been a fundamental cause of underestimation of the effectiveness of some vaccines in middle-aged people. However, among the elderly there was no differential indication for people with and without chronic disease. Third, cases could also be diagnosed based on clinical symptoms, which might have resulted in differential misclassification, somewhat overestimating vaccine efficacy because a physician could have been less likely to diagnose COVID-19 knowing a person was vaccinated. Differences in the likelihood of seeking SARS-CoV-2 testing, uptake of vaccines, site of vaccination, prognosis of COVID-19 and chance of detection may also have resulted in residual confounding. Importantly, vaccine effectiveness was demonstrated when the SARS-CoV-2 variant B.1.1.7 was the dominant strain in Hungary, therefore, the results do not represent the effectiveness of vaccines investigated against the delta variant (B.1.617.2) or against new, upcoming variants.

Besides, we also need to emphasize that clinical trials assessing vaccine effectiveness were mostly conducted against the original Wuhan strain, which may explain some differences between our results and clinical trials because several studies showed reduced neutralization activity and effectiveness against the B.1.1.7 variant compared with a non-B.1.1.7 variant [22–25].

In conclusion, in a large population of more than 3.7 million vaccinated individuals, all five investigated vaccine types were highly or very highly effective in the prevention of SARS-CoV-2 infection and COVID-19-related death during an intensive wave of the COVID-19 pandemic in Hungary. The results are largely consistent with phase III trial data and the limited number of available real-world studies.

Transparency declaration

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Author contributions

ZV, GS, RH and AG contributed to conceptualization, methodology, formal analysis, validation, data curation and writing‘—review & editing; ZK and IW contributed to conceptualization, methodology, investigation, visualization and writing—original draft; OS, EF-B and BP contributed to conceptualization, methodology, validation and writing—review & editing; AM, LK, MK and CM contributed to conceptualization, methodology, investigation and supervision; ZB contributed to writing—original draft; and GAM contributed to validation and project administration.

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Appendix A. Supplementary data

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