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SARS-CoV2 Breakthrough Infections in Elderly Third Booster and Vaccinated Population Considered Vaccine Immune During Omicron (B.1.1.529)Variant Surge in Israel.

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Abstract

The fourth booster vaccination was approved in Israel during Omicron (B.1.1.529) variant surge due to increasing SARS-CoV2 breakthrough infections among recently vaccinated, reasons for this resurgence is not clear.

In this Observational study, we analyzed verified SARS-CoV2 infections among over 60 years of age based on vaccination schedule (December 20, 2020-January 29, 2022); infections, severe illness and deaths based on vaccine immunity (between August 1, 2021-January 29, 2022) using Israel COVID-19 dashboard data.

There were a total of 214,394 SARS-CoV2 infections (December 20, 2020-Janaury 29, 2022; based vaccination schedule), 165,899 infections; 6,267 severe illnesses and 2,031 deaths (August 1, 2021-Janaury 29, 2022) analyzed based vaccine immunity among over 60 years old. Vaccination with two doses, maintained vaccine effectiveness (VE) of 93.2% (95% CI 90-95.5%) for 16 weeks until May 8, 2021 with 14.2% breakthrough infections. When there were no public health restrictions (June-July 2021) partially vaccinated has significantly lower infection rates (X^2 [2, N=721]=190.79,p<0.001) with VE of 80.4% (95% CI 69.1-98.3%), while infection rates among vaccinated with two doses and unvaccinated are not statistically significant and decline of VE to 6.4% (95% CI -9.9-19.3%) among vaccinated with two doses. After reinstatement of restrictions since July 29, 2021, the VE of vaccinated with two doses improved to 68.0% (95% CI 56.7-76.7%), the third booster showed significantly higher breakthrough infections (26.4%) and a shorter period of 12 weeks effectiveness until October 23, 2021 and by November 20, 2021 the infections rates of vaccinated with third booster are not statistically better than partially vaccinated (X^2 [1, N=54]=1,85, p=0.17). During the Omicron variant surge, the VE of third booster declined to 42.7% (95% CI 39.9-45.3%) and the infection rates were significantly higher than vaccinated with two doses (X^2[1,N=5898]=8.50, p=0.003) as of January 15, 2022 and subsequently showed improvement in VE to 51.7% (95% CI 50.2-53.2%) and significantly lower infection rates than vaccinated with two doses (X^2[1,N=12380]=98.28, p=<0.001) by January 29, 2022. The vaccinated without validity group (partially vaccinated; past 1-2 doses with expired Green Passes) showed significantly lower infection rates (X^2 [1, N=15727]=295.3, p<0.001) during December 5,2021-January 29, 2022 period compared to vaccinated with validity (95% of them received third booster dose, and have Green Pass access) group that showed significantly increased infection rates and substantially increased percentages of severe illness and deaths.

Vaccination with the third booster associated with brief protection and higher breakthrough infections compared to prior vaccination with two doses. The vaccinated population, who are considered immune according to the new vaccination policy, showed significantly increased infections, substantial increases in severe illness, and deaths during Omicron surge. However, those considered non-immune showed significantly decreased infections. There was a stronger association between public health restrictions and infections among the vaccinated groups. There is an urgent need to protect the elderly population by adopting uniform protective measures and surveillance protocols.

Introduction

The third booster vaccination against COVID-19 disease,caused by Severe Respiratory Distress Syndrome-2 (SARS-CoV2) virus was approved in Israel on July 30, 2021 due to waning of vaccine effectiveness during the beginning of the Delta variant (B.1.617.2) surge[1,2]. The Israeli authorities recommended the administration of the fourth booster dose to any one age 60 or older, the immunocompromised and healthcare workers on December 21, 2021[3]. The Israeli authorities also issued a directive for the booster dose to be administered for those eligible for vaccination as early as 3 months after the second dose due to sharp increase in the number of coronavirus infections particularly with the Omicron (B.1.1.529) variant[4].

Israel implemented a highly successful vaccination program by vaccinating majority of the eligible population very early, and also instituted public health restrictions through “Green Pass” with enforcement by fines effective February 21, 2021 based on the vaccination status as part of the reopening[5–8]. On May 5, 2021, Israeli authorities citing good expected protection from vaccination extended the validity of initially issued Green Pass certificates until December 31, 2021[9]. The “Green Pass” would allow, vaccinated (two doses) and recovered persons after the SARS-CoV2 infection to enter the Green Pass designated public facilities without restrictions[5–7]. With thenew cases at low rates, the Israeli government lifted all public health restriction that were in place effective June 1, 2021and the Green Passrestrictions were reinstated again effective July 29, 2021 during the Delta variant surge[6,10,11]. The Green Pass rules were changed effective October 1, 2021;where thepersons who are vaccinated per new vaccination policy will havecontinued Green Pass access,and expiresfor others who are not vaccinated per recommendations[5,6,12].

The Israeli Ministry of Health dashboard also shows an alarming high rate of infections with rapidly raising rate of severe illness and deaths among over 60 years old who are considered to be vaccinated with full immunity per current vaccination guidelines (vaccinated with validity) since the beginning of the Omicron variant surge in early December 2021[13].

In this observational study, we undertook a comprehensive analyses of breakthrough infections particularly among over the 60 years old population who received the third booster dose all of whom are considered vaccinated with immunity to understand the reasons for rapidly decline of vaccine protection requiring the fourth booster dose recommendations from the Israeli health officials within a short period after the majority of over 60 years old population vaccinated with the third booster dose[13].

Materials and Methods

In this Observational study, we analyzed the national wide surveillance database of the verified SARS-CoV2 infections among over 60 years old age that were reported in Israel during the December 20, 2020 to January 29, 2022 using the Ministry of Health COVID-19 dashboard data.

As shown on Figures1-2, we simultaneously undertaken comprehensive analysis of SARS-CoV2 infections (n=214,394) that were

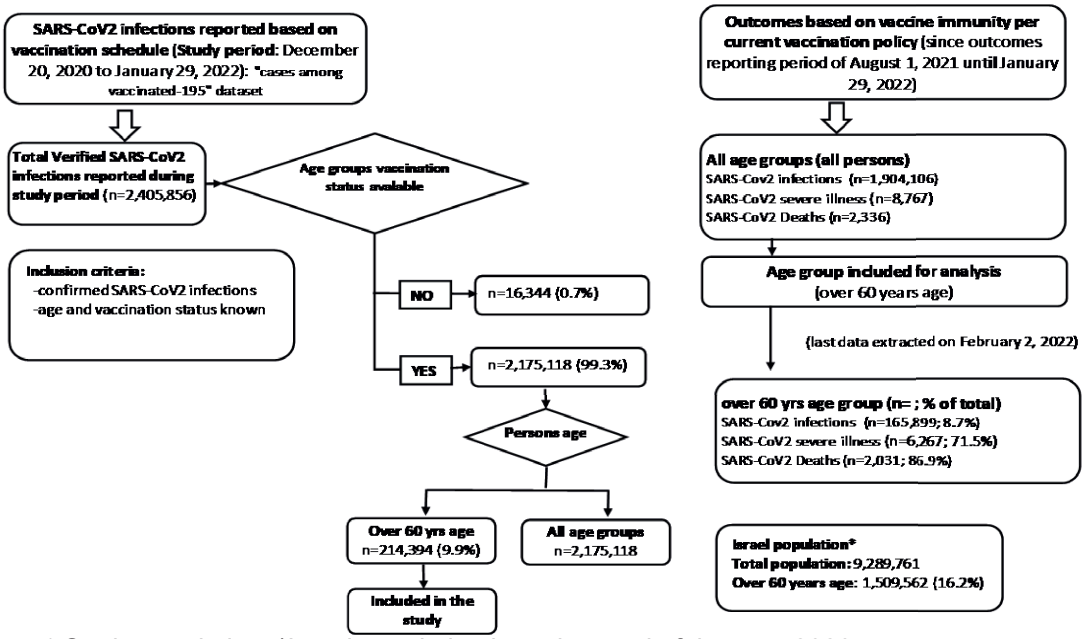

Figure1:Study population. *Israel population based on end of the year 2020 census.

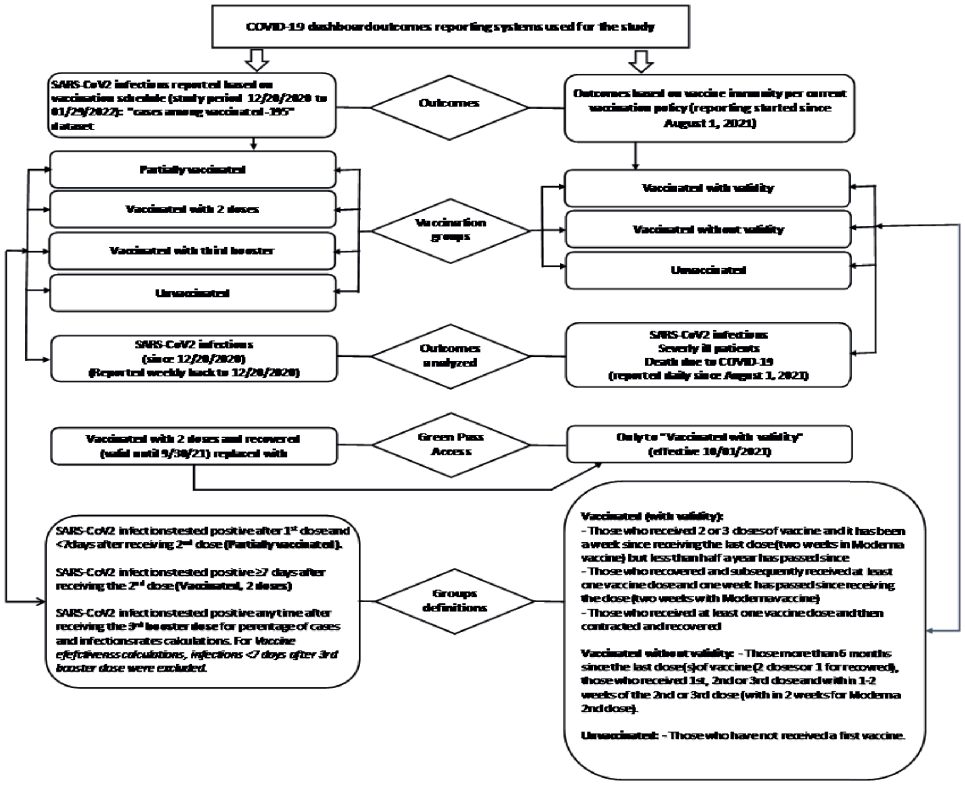

Figure2:Flow chart showing the databases used and the definition of outcomes analyzed in the study.

SARS-CoV2 Breakthrough infections in elderly third booster and vaccinated population considered vaccine immune in Israel.

reported in Israel based on regular vaccination schedule since December 20, 2020 and SARS-CoV2 infections (n=165,899), sever illness (n=6,267) and deaths (n=2,031) that were reported based on vaccine immunity status per new vaccination policy reporting of which started since August 1, 2021. We chose over 60 years age groups as Israel publicly reporting outcomes based on new vaccination policy-among over and under 60 years old age groups only and since the 0-18 years age groups have higher rates of unvaccinated and lower rates of third booster vaccination, we did not include under 60 years age group for the analysis[13].

The Israel Ministry of Health COVID-19 dashboard, "cases among vaccinated" datasetofweekly verified SARS-CoV2 infections among age groupsbased on vaccination status since December 20, 2020 was used for the analysis SARS-CoV2 infections.The SARS-CoV2 infections≥7 days post second dose considered vaccinated with 2 doses, the events post 1st dose until <7 days post 2nd dose is considered partially vaccinated and infections any time after receiving third booster considered infections after third booster dose.

During the Delta surge, there were numerous public policy decisions undertaken by Israel Ministry of Health, including the lifting of the Green Pass restrictions effective June 1, 2021; reinstatement of Green Pass restriction and the administration of 3rd booster by the end of July 2021, cancellation of Green Passes for those vaccinated without validity effective October 1, 2021, and the recommendations for the administration of 4th booster on December 21, 2021 in the setting of the Omicron variant surge.

We performed an analysis the percentage of SARS-CoV2 casesamong over 60 years age group based on the vaccination status during; the time period of the lifting of the Green Pass restrictions during the week starting May 30,2021 to July 31, 2021 and three time periods during third booster dose administration campaign and Omicron variant surge (August 1-October 2, 2021; October 3-December 4, 2021 and December 5, 2021-January 29, 2022). Theinfection rates per 100,000 populationfor every four week was compared among the vaccination groups and the vaccine effectiveness was also calculated for every four weeks among over 60 years age group to evaluate the effectiveness of vaccination among partially, fully vaccinated with two doses since January 2021 and the third booster dose recipients (SARS-CoV2 infections <7 days after third booster were excluded for vaccine effectiveness calculations).

*Comparative analysis of infections, severely ill patients and mortality based on the status of vaccine immunity as pernew vaccination policy and Green Pass entry criteria:*As shown on the Figure 2, after the approval of the third booster dose and reinstatement of Green pass restrictions during the Delta variant surge, the Israeli authorities alsoreporting outcomes and changed Green Pass eligibility criteria based on if the vaccination status of a person is according to newvaccination policy. A person is considered 1) *vaccinatedwith validity* (those who received 2 or 3 doses of vaccine and it has been a week since receiving the last dose [two weeks in Moderna vaccine] but less than half a year has passed since; those who recovered and subsequently received at least one vaccine dose and one week has passed since receiving the dose [two weeks with Moderna vaccine] and or those who received at least one vaccine dose and then contracted and recovered); 2) *vaccinated without validity* (those who have received 2 doses of vaccine or recovered with 1 doses and have not received an another dose within 6 months; those received 1-3 doses and within 1-2 weeks after second dose [2 weeks with Moderna] and <7days of 3rd booster); and 3) *Unvaccinated* - Those who have not received a first vaccine.The dashboard reports over and under 60 years age groups outcomes (SARS-CoV2 infections, severely illness and deaths from SARS-CoV2) based on the immunization statussince August 1, 2021.We analyzed data on over 60 years old SARS-CoV2 infections,

severe illness and deaths since from August 1, 2021-January 29, 2022. The weekly infection rates per 100,000 population among vaccination groups and vaccine effectiveness was also calculated weekly since August 1, 2021 until January 29, 2022. *Statistical analysis:*The study population for the infection rates and vaccine effectiveness was derived from thedatabase ("vaccinated-per-day") that list complete daily vaccinations for all age groups and aggregates of 1st, 2ndand 3rd booster dose for over 60 years age group for the study period was calculated[14]. Total population for each age group was obtained from Israel census 2020 that lists population of Israel for each year from 1 to100+ years and unvaccinated number was derived from the cumulative number of vaccinated(with one dose, 2 doses and third dose) dailyfor over 60 years age group during the study period[15].The weekly population of over 60 years vaccinated with validity, vaccinated without validity and unvaccinated also derived based on the definition criteria for each vaccination group. The incidence rate was calculated as numberof SARS-CoV2 infectionsper 100,000 persons days for each studied groups and the incidence rate ratio (IRR) was calculated among compared groups. The partially vaccinated, vaccinated with two doses, the third booster, vaccinated with validity group, vaccinated without validity groups compared with unvaccinated for the vaccine effectiveness calculations. Vaccine effectiveness was calculated as (1-IRR) x 100.The lower and the upper bounds for the confidence interval for vaccination effectiveness were calculated based on how each of the individual proportions varied. Also, in order to attain an overall confidence level of 95%, the confidence level for the individual proportions were raised to 97.5%. The Chi-Square Goodness of Fit Test was performed to determine whether the proportion of outcomes (infection rates, severe illness and or deaths per 100,000) were equal between vaccination groups for each period. Statistical analysis for Chi-Square test was performed using R software, version 4.1.2.

Results and Discussion

Study population

A total of 214,394 SARS-CoV2 infections amongover 60 years old population (n=1,509,562; 16.2% of Israeli Population) based on vaccination schedule and 165,899 SARS-COV-2 infections; 8,767severe illness and 2,336 SARS-CoV2 deaths reported based on vaccine immunity included in study (Figures 1-2).

Infections reported based on regular vaccination schedule

Among over 60 years age group, 214,394 SARS-CoV2 infections were analyzed(Table 1, Table S1a-b)during the study period (December 20, 2020-Janury 29, 2021). During December 20, 2020-May 29, 2021 period (n=40,689 SARS-CoV2 infections) prior to lifting of public health restrictions, 7.6% of infections (n=3,079) occurred in the vaccination with two doses and 37.5% (n=15,247) occurred in partially vaccinated. Vaccine effectiveness of two doses maintained as shown on Figure 3a (93.2% [95% CI 90.0-95.5%) and partially vaccinated (81.0% [95% CI 62.4%-93.9%) as of May 8, 2021. The infections rates significantly lower for vaccinated with two doses (X^2[1,N=33],=7.52, p=0.006) compared to partially vaccinated, and breakthrough infection rates of 14.2%for during the first 16 weeks since receiving the second dose in between January 17- May 8, 2021.

During the May 30, 2021-July 31, 2021 coinciding with lifting of all public health restrictions, 91.6% (n=4,676) of total (n=5,107) SARS-CoV2 infection occurred among vaccinated with two doses, with decline of vaccine effectiveness to 6.4% (95% CI -9.9-19.3%). There were 0.7% (n=35) of infections in partially vaccinated, maintained 80.4% (95% CI 69.9-98.3%) vaccine effectiveness and their infection rates (Table S1b) were significantly lower (X^2[1,N=382]=163.61, p=<0.001) compared to vaccinated two doses. There was no statistically significant difference in infection ratesof vaccinated two doses and

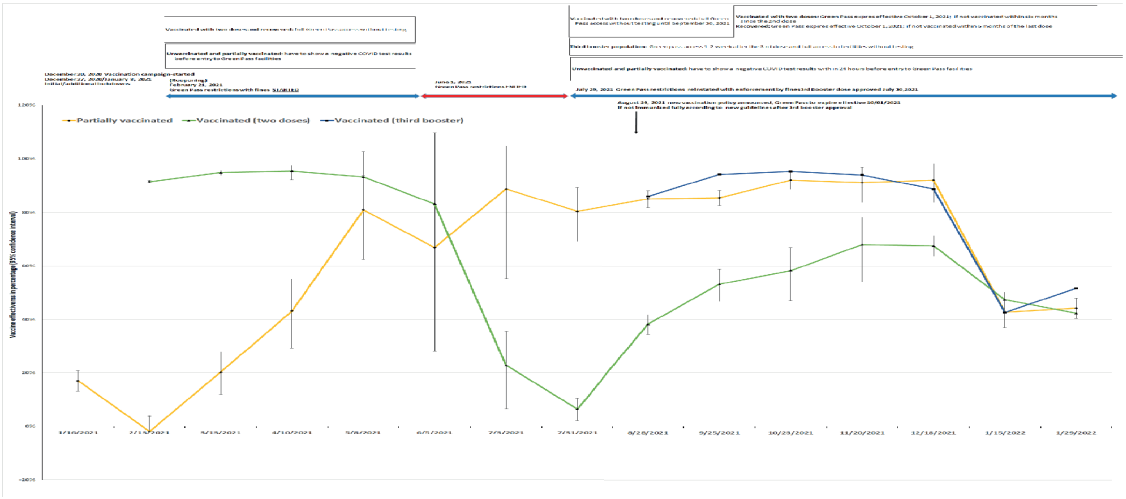

Figure 3a: Vaccine effectiveness among vaccinated groups in over 60 years old population. Complete data on SARS-CoV2 infections, incidence rates and vaccine effectiveness (95% CI) included in the Tables 1. During the time of lifting of restrictions in June-July 2021 period, vaccine effectiveness was lowest among vaccinated with two doses which is driven by increased breakthrough infections in that age group as shown on Table 1 and increased infection rates approached same as unvaccinated as shown on Figure S1a-c. Vaccinated with two doses regained vaccine effectiveness during the period of reinstatement of restrictions which is driven by lower infection rates among vaccinated and higher infection rates among unvaccinated as shown on Figure S1a-b. Partially vaccinated maintained protection during the lifting of the restrictions and during Delta variant surge until December 2021. During the 4 weeks period ending January 15, 2022 there is significant decline in vaccine effectiveness among the 3rd booster, vaccinated with 2 doses and partially vaccinated with infection rates equalized on Figures S1a-b among vaccinated groups by January 15, 2022 with unvaccinated still having higher infection rates. Higher infection rates of minority unvaccinated population as shown on Figures S1a can overestimate the vaccine effeteness calculations of majority other vaccinated groups (3rd booster, vaccinated with two doses and Partially vaccinated) as of January 15, 2022 if incidence rate ratio (IRR) is calculated comparing unvaccinated, despite highest percentage of breakthrough infections as noted in Table 1 and Table 2 among vaccinated group (s).

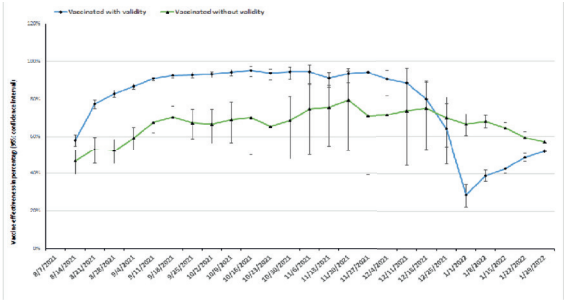

Figure 3b: WeeklyVaccine effectiveness among vaccinated groups based on vaccine immunity in over 60 years old population. Complete data on SARS-CoV2 infections, incidence rates and vaccine effectiveness (95% CI) included in the Tables 2.

unvaccinated (X^2[1,N=655],=0.80, p=0.36).

The public health restrictions and Green pass were reinstated effective July 29, 2021, during August 1-October 2, 2021 (n=26,746 SARS-CoV2 infections) and October 3-December 4, 2021 (n=2,627 SARS-CoV2 infections), the partially vaccinated maintained vaccine effectiveness of 95.1% (95% CI 81.8-88.1%) to 91.1% (95% CI 83.7-96.9%), vaccinated with two doses improved vaccine effectiveness to

Study period	Total SARS-CoV2 infections (Over 60 years age) (n=%)	SARS-CoV2 infections (n=% of each age groups) and vaccination status						
	Partially vaccinated*	Vaccinated (2 doses)‡	Vaccinated (3rd booster)ø	Unvaccinated				
December 20,2020-January 15, 2022	214,394 (100%)	19,425 (9.1%)	33,080 (15.4%)	119,489 (55.7%)	42,400 (19.8%)			
December 20,2020-May 29, 2021	40,689 (100%)	15,247 (37.5%)	3,079 (7.6%)	-	22,363 (55.0%)			
May 30, 2021-January 19, 2022	173,705 (100%)	4,178 (2.4%)	30,001 (17.4%)	119,489 (68.8%)	20,037 (11.5%)			
Distribution of SARS-CoV2 infection in the study population during May 30, 2021-January 29, 2022 (since the start of Delta variant and during Omicron variant surge)								
Study period	Total SARS-CoV2 infections (n=%)	SARS-CoV2 infections (n=% of each age groups) and vaccination status						
	Partially vaccinated*	Fully vaccinated (2 doses)‡	Vaccinated (3rd booster)ø	Unvaccinated				
May 30-July 31, 2021	5,107 (100%)	35 (0.7%)	4,676 (91.6%)	-	396 (7.8%)			
August 1-October 2, 2021	26,746 (100%)	419 (1.6%)	13,540 (50.6%)	7,018 (26.2%)	5769 (21.6%)			
October 3-December 4, 2021	2,627 (100%)	41 (1.6%)	697 (26.5%)	864 (32.9%)	1,025 (39.0%)			
December 5, 2021-January 29, 2022	139,225 (100%)	3,683 (2.6%)	11,088 (8.0%)	111,607 (80.2%)	12,847 (9.2%)			
SARS-CoV2 infections, incidence rate per 100,000 person days and vaccine effectiveness during the study period.								
Study period *	SARS-CoV2 Infections (over 60 years age)				Incidence rateper 100,000 person days			Vaccine effectiveness (%; 95% CI)	
	Partially vaccinated	Vaccinated (two does)	Vaccinated (third booster) €	Unvaccinated	All persons	Partially vaccinated	Vaccinat-ed (two does)	Vaccinated (third booster) €	Unvaccinated	Partially vaccinated	Vaccinated (two does)	Vaccinated (third booster)
1/16/2021	7522	0		11630	19152	41.2				17.0% (13.1% to 20.8%)		
2/13/2021	6120	1566		6527	14213	74.6	6.2		181.2	(-1.9% (17.9% to 3.6%)	91.5% (90.8% to 92.2%)	
3/13/2021	1365	1000		3181	5546	45.8	3.0		267.1 209.6	20.2% (11.9% to 27.9%)	94.8% (94.2% to 95.4%)	

SARS-CoV2 Breakthrough infections in elderly third booster and vaccinated population considered vaccine immune in Israel.

4/10/2021	224	365	851	1440	12.4	1.0	79.6	43.3% (29.3% to 55.2%)	95.4% (94.5% to 96.2%)			
5/8/2021	13	116	155	284	0.9	0.3	16.7	81.0% (62.4% to 93.9%)	93.2% (90.0% to 95.5%)			
6/5/2021	3	42	21	66	0.2	0.1	2.4	66.9% (-48.4% to 106.5%)	83.2% (55.7% to 92.6%)			
7/3/2021	2	388	41	431	0.1	1.0	4.9	88.8% (55.3% to 104.9%)	22.8% (-32.2% to 49.3%)			
7/31/2021	33	4278	353	4664	2.4	11.3	44.0	80.4% (69.1% to 98.3%)	6.4% ((-9.9% to 19.3%)			
8/28/2021	177	9583	2519	2422	16576	13.1	54.2	12.3	320.3	85.1% (81.8% to 88.1%)	38.3% (33.9% to 42.3%)	86.0% (84.6% to 87.2%)
9/25/2021	220	3525	2121	2908	8971	16.7	53.9	6.7	420.3	85.5% (82.6% to 88.2%)	53.2% (49.3% to 56.8%)	94.2% (93.7% to 94.7%)
10/23/2021	45	901	735	1074	2793	3.6	19.1	2.2	167.1	92.1% (88.9% to 95.1%)	58.3% (51.9% to 63.9%)	95.3% (94.5% to 95.9%)
11/20/2021	14	166	266	285	736	1.1	4.1	0.8	46.6	91.1% (83.7% to 96.9%)	68.0% (56.7% to 76.7%)	94.0% (92.1% to 95.4%)
12/18/2021	9	118	371	206	706	0.7	3.1	1.1	34.4	92.1% (83.7% to 98.3%)	67.6% (53.6% to 77.7%)	88.8% (85.1% to 91.4%)
1/15/2022	1252	3535	38623	4058	47662	108.7	99.9	109.0	693.9	42.8% (37.0% to 48.3%)	47.5% (43.5% to 51.2%)	42.7% (39.9% to 45.3%)
1/29/2022	2426	7497	72329	8688	91154	463.5	479.5	401.8	3037.8	44.3% (40.4% to 48.1%)	42.4% (39.4% to 45.2%)	51.7% (50.1% to 53.2%)

Table 1: Distribution of all confirmed SARS-CoV2 infections and vaccine effectiveness among vaccination groups during the study period.

*SARS-CoV2 infections tested positive after 1st dose and <7days after receiving 2nd dose (Partially vaccinated).

#SARS-CoV2 infections tested positive ≥7 days after receiving the 2nd dose (Vaccinated, 2 doses)

@SARS-CoV2 infections tested positive any time after receiving the 3rd booster dose

€SARS-CoV2 infections <7 days (n=2,525) of the third booster were excluded for vaccine effectiveness calculations.

Study period	Outcomes	All persons over 60 yrs age; n=(%)	Vaccinated (with validity)	Vaccinated without validity	Unvaccinated
August 7-October 2, 2021	**Infections**	24,721 (100%)	10,099 (40.9%)	8,854 (35.8%)	5,768 (23.3%)
	Severe illness	3,289 (100%)	808 (24.6%)	940 (28.6%)	1541 (46.9%)
	Deaths	1,205 (100%)	290 (24.1%)	367 (30.5%)	548 (45.5%)
	Odds of severe illness	13.3%	8.0%	10.6%	26.7%
	Case fatality rate	4.9%	2.9%	4.1%	9.5%
October 3-December 4, 2021	**Infections**	2,601 (100%)	972 (37.4%)	594 (22.8%)	1,035 (39.8%)
	Severe illness	535 (100%)	111 (20.7%)	73 (13.6%)	351 (65.6%)
	Deaths	301 (100%)	50 (16.6%)	47 (15.6%)	204 (67.8%)
	Odds of severe illness	20.6%	11.4%	12.3%	33.9%
	Case fatality rate	11.6%	5.1%	7.9%	19.7%
December 5, 2021-January 15, 2022	**Infections**	138,577 (100%)	118,004 (85.2%)	7,724 (5.6%)	12,849 (9.3%)
	Severe illness	2,443 (100%)	1,383 (56.6%)	287 (11.7%)	773 (31.6%)
	Deaths	525 (100%)	300 (57.1%)	48 (9.1%)	177 (33.7%)
	Odds of severe illness	1.8%	1.2%	3.7%	6.0%
	Case fatality rate	0.4%	0.3%	0.6%	1.4%

Vaccination status of over 60 years age group -based on new vaccination policy

SARS-CoV2 Breakthrough infections in elderly third booster and vaccinated population considered vaccine immune in Israel.

	Date (all)	% Vaccinated with validity (proportion of 3rd booster)			% Vaccinated without validity	% un-vacci-nated
	7/31/2021	23.4%	0.0%		69.8%	6.8%
	8/14/2021	44.0%	63.0%		49.5%	6.6%
	8/28/2021	77.0%	85.5%		16.8%	6.2%
	9/4/2021	80.9%	88.2%		13.1%	6.1%
	10/2/2021	81.8%	94.9%		12.5%	5.7%
	10/23/2021	84.5%	96.2%		10.1%	5.4%
	11/6/2021	84.8%	96.6%		9.9%	5.3%
	12/4/2021	85.2%	97.0%		9.6%	5.2%
	12/25/2021	85.7%	97.1%		9.3%	5.1%
	1/15/2022	87.0%	96.8%		8.1%	5.0%
	1/29/2022	87.9%	96.9%		7.2%	4.9%

SARS-CoV2 infections, Incidence rate per 100,000 person days and vaccine effectiveness based on new vaccination policy.

Date (week ending)	SARS-CoV2 infections (over 60 years age)				Incidence rate per 100,000 person days		Vaccine effectiveness (%; 95% CI)	
	Vaccinated without validity	Vaccinated (validity)	Unvaccinated	All persons	Vaccinated without validity	Vaccinated (validity)	Unvaccinated	Vaccinated without validity	Vaccinated (validity)
8/7/2021	1725	1029	331	3085	22.3	48.1	46.5	52.0% (42.3% to 59.5%)	(-3.5%) (-26.2% to 14.3%)
8/14/2021	2153	1494	535	4182	41.2	32.2	76.9	46.5% (37.9% to 53.5%)	58.2% (51.1% to 64.1%)
8/21/2021	1522	1827	772	4121	53.8	25.9	114.4	53.0% (45.9% to 59.0%)	77.4% (74.1% to 85.1%)
8/28/2021	1012	1659	784	3455	57.0	20.4	119.6	52.3% (44.6% to 59.0%)	82.9% (80.5% to 85.1%)

9/4/2021	677	1358	768	2803	49.0	15.9	120.1	59.2% (51.8% to 65.5%)	86.8% (84.7% to 88.5%)
9/11/2021	458	860	699	2017	35.7	9.9	110.6	67.7% (61.0% to 73.3%)	91.0% (89.4% to 92.3%)
9/18/2021	509	799	779	2087	36.7	9.3	124.8	70.6% (64.8% to 75.4%)	92.5% (91.2% to 93.6%)
9/25/2021	478	648	661	1787	34.8	7.6	107.2	67.5% (60.8% to 73.1%)	93.0% (91.6% to 94.1%)
10/2/2021	320	425	439	1184	24.3	4.9	72.8	66.7% (58.0% to 73.6%)	93.2% (91.6% to 94.6%)
10/9/2021	196	262	304	762	16.1	3.0	52.1	69.1% (58.9% to 77.0%)	94.3% (92.5% to 95.6%)
10/16/2021	122	161	214	497	11.1	1.8	37.2	70.2% (57.7% to 79.4%)	95.1% (93.2% to 96.5%)
10/23/2021	76	115	117	308	7.1	1.3	20.6	65.5% (45.4% to 78.8%)	93.7% (90.5% to 95.9%)
10/30/2021	52	78	88	218	4.9	0.9	15.7	68.7% (46.2% to 82.6%)	94.4% (90.8% to 96.6%)
11/6/2021	37	70	78	185	3.5	0.8	14.0	74.7% (53.7% to 87.3%)	94.4% (90.5% to 96.7%)
11/13/2021	27	83	59	169	2.6	0.9	10.6	75.6% (50.7% to 89.2%)	91.3% (84.7% to 94.9%)
11/20/2021	25	69	65	159	2.4	0.8	11.8	79.5% (58.8% to 91.1%)	93.5% (88.5% to 96.3%)
11/27/2021	33	58	61	152	3.2	0.6	11.1	71.1% (43.7% to 86.3%)	94.2% (89.5% to 96.8%)
12/4/2021	26	76	49	151	2.6	0.8	9.0	71.5% (39.7% to 87.9%)	90.6% (82.6% to 94.7%)
12/11/2021	26	101	53	180	2.6	1.1	9.7	73.4% (44.8% to 88.6%)	88.5% (79.7% to 93.2%)
12/18/2021	23	169	50	242	2.3	1.9	9.2	74.9% (46.2% to 89.9%)	79.7% (65.2% to 87.3%)
12/25/2021	49	538	89	676	5.0	5.9	16.5	69.7% (47.5% to 83.3%)	64.0% (48.3% to 73.7%)

SARS-CoV2 Breakthrough infections in elderly third booster and vaccinated population considered vaccine immune in Israel.

1/1/2022	105	2112	175	2392	10.9	23.3	32.7	66.5% (50.9% to 77.6%)	28.8% (10.1% to 42.0%)
1/8/2022	469	8797	841	10107	50.8	96.5	158.4	68.0% (61.7% to 73.3%)	39.1% (32.4% to 44.8%)
1/15/2022	1715	29659	2955	34329	200.9	322.7	564.2	64.4% (60.9% to 67.6%)	42.8% (39.6% to 45.7%)
1/22/2022	2638	39679	4362	46679	340.6	428.0	836.0	59.3% (56.0% to 62.3%)	48.8% (46.5% to 51.0%)
1/29/2022	2699	36949	4324	43972	356.2	397.8	829.3	57.0% (53.7% to 60.2%)	52.0% (49.8% to 54.1%)

Table 2: Distribution of SARS-CoV2 infections, SARS-CoV2 infections with severe illness, SARS-CoV2 deathsand vaccine effectivenessduring study period based on immunization status according to new vaccination policy from August 1, 2021 to January 29, 2022.

53.2(95% CI 49.3-56.8%) to 67.0% (95% CI 53.6-77.7%) range. During the same period the thirdbooster has vaccine effectiveness of 86.0% (95% CI 84.4% to 87.2%) and 94.0% (95% CI 92.1% to 95.4%). However, the comparison of infection rates (Table S1b) shows that the infection rates of third booster significantly better than partially vaccinated (X^2[1,N=165]=9.21, p=0.002) until October 23, 2021 for 12 weeks with 26.4% breakthrough infections; and then not statistically different than the partially vaccinated (X^2[1,N=54]=1.85, p=0.17) for the four weeks period ending November 20, 2021. During December 5, 2021-Janaury 15, 2022 (n=48,071 SARS-CoV2 infections), 81.3% (n=39,064) occurred among third booster;7.5% (n=3,591) among vaccinated with two doses, vaccine effectiveness of the third booster declined to 42.7% (95% CI 39.9 to 45.3%), vaccinated with two doses to 47.5% (95% CI 43.5 to 51.2%) and partially vaccinated to 42.8% (37.0 to 48.3%) as of January 15, 2021. Analysis of the infection rates during the four weeks period ending January 15, 2021 showed significantly increased infection rates among third booster (X^2[1,N=5898]=8.50, p=0.003) compared with vaccinated with two doses, and significantly highest infection rates of unvaccinated compared with all vaccinated groups (Table S1b). The vaccine effectiveness of the third booster improved to 51.7% (95% CI 50.1% to 53.2%) in the two weeks period preceding the January 29, 2022 associated with significantly lower infections rates (X^2[1,N=12380]=98.28, p<0.001) compared to vaccinated with two doses.

Outcomes based on new vaccination policy

After approval of the third booster Israel also started reporting outcomes based on new vaccination policy, since August 1, 2021 (Figure 1, Table 2);165,899 SARS-CoV2 infections; 6,267 severe illness and2,031 deaths were analyzed for period ending January 29, 2022. Those who were vaccinated per recommendations (vaccinated with validity), have Green

Pass access and for those with incomplete vaccination (vaccinated without validity), the existing Green Passes expires effective October 1, 2021. The vaccinated with validity group reported increasing SARS-CoV2 infections during this period (37,4% [n=972] for period ending December 4, 2021 and increased to 85.2% (n=118,004) during December 5, 2021-Janury 29, 2021. The vaccinated without validity group had 35.8% (n=18,854) SARS-COV2 infections until October 2, 2021 and the infections decreased to 5.6% (n=7,724) during December 5, 2021-Janaury 29, 2022 period. Analysis of infection rates (Tables S2a-e) demonstrates the vaccinated with validity group has significantly lower infection rates for periods ending October 2, 2021 (X^2[1,N=3704]=432.1, p<0.001) and December 4, 2021 (X^2[1,N=451]=197.3, p<0.001) compared to vaccinated without validity. The vaccinated validity group significantly higher infections during December 5, 2021-January 29, 2022 period (X^2[1,N=15727]=295.3, p<0.001) compared to vaccinated without validity group which showed lower infection rates. The vaccine effectiveness also declined sharply since December 18, 2021 for vaccinated with validity group to the lowest levels of 28.8% (95% CI 10.1 to 42.0%) for the week ending January 1, 2022 before making some improvement to 52.0 % (49.8 to 54.1%) as of January 29, 2022 (Figure 3b and Table 2).

During the December 5, 2021 to January 22, 2022 coinciding with Omicron variant surge (Table 2), analysis of all the outcomes showed the overall case fatality rate decreased to 0.4% (from 4.9% -11.6%) and odd of severe illness decreased to 1.8% (from 13.3% - 20.6%) during prior periods since August 1, 2021 and these improved outcomes seen across the vaccinated and unvaccinated groups. The significant increased breakthrough infections (85.2%) among vaccinated with validity group associated with a substantially increased percent of severe illness to 56.6% (from 24.5%-20.7%) and deaths to 57.1% (from 24.1-16.6%) during the prior two periods since August 1, 2021. An analysis of severe illness and deaths per 100,000 population of the respective group showed significantly higher rates of severe illness and deaths among unvaccinated with a slight but significantly lower deaths rates among vaccinated with validity group compared to vaccinated without validity group (X^2[1,N=57]=3.95, p=.047) for the December 5, 2021 to January 29, 2022 period (Table S2e).

Details of changes to the Green Pass program since it became effective on February 21, 2021, facilities that are covered under the Green Passdescribed in detail in the supplemental appendix and relevant information in the manuscript[5–7,9–12,16,17]. Detailed description weekly infection rates, analysis of the changing pattern of SARS-CoV2 infections, odd of severe illness and case fatality rates among vaccinated groups based on vaccine immunity included the supplemental appendix (Tables S1-S2, Figures S1-4).

Discussion

Since the third booster vaccination was approved on July 30, 2021 in Israel;82.8% of the over 60 years old werevaccinated with third boosterbyDecember 4, 2021. After the fourth booster dose was approved; 25.7% (60-69 yrs), 45.3% (70-79 yrs), 47.3% and 45% 80-89 years and 90+ years old age groups were vaccinated with the fourth booster as of January 30, 2022[13]. Our study shows that of the total (n=168,598) SARS-CoV2 infections that occurred since August 1, 2021 among over 60 years age group, 82.5% of infections (n=139,225) occurred during Omicron surge (December 5, 2021 to January 29, 2021) of which 80.2% of breakthrough infections occurred in vaccinated with third booster and 9.2% of infections in 5.0% of this age group unvaccinated population. There were significantly decreased infection rates with a decreasing breakthrough infection rate (8.0%) among

vaccinated with two doses without booster during the same period with waning of vaccine effectiveness of third booster dose for 4 weeks period ending January 15, 2022 to 42.7% (95% CI 39.4% to 45.3%). We also noted improvement of infection rates and vaccine effectives among the third booster population during January 16-Janury 29, 2022 period probably due to the effectiveness of the fourth booster dose this population received as was reported by the Israel Ministry of Health[18] and additionally decreased infection rates may also be due toextra precautions taken with the knowledge of the waning of vaccine protection requiring the additional booster dose[3,4]. The waning of vaccine effectiveness with two doses that we noted in our study is similar to previous studies[1,19].

We found that the third booster was not as protective as the previous vaccination with 2 doses. In our study, based on the infection rates and vaccine effectiveness calculations, vaccinated with two doses, maintained protection for the first 16 weeks since receiving the second dose (14.2% breakthrough infections) until May 8, 2021 and whereas the vaccinated with third booster, maintained effectiveness for first 12 weeks with 26.4% breakthrough infections.

After the 4th booster dose approval on December 21, 2021 and Israel also recommended booster dose to be administered for those eligible for vaccination as early as 3 months in the setting of Omicron surge[3,4]. These recommendationscorrelatewith the findings in our study regarding the shorted duration (12 weeks) of protection with the third booster.

In our study we also observed similar trend amongover 60 years old age “vaccinated with validity” population(considered to be currently vaccine immune) with 81.8% vaccination rates (94.9% of then are third booster recipients) as of October 2, 2021, also witnessed 40.9% breakthrough infections during August 1-October 2, 2021 period. There was a significant increase in infection rates (and percentage ofbreakthrough infections to 85.2%) during December 5, 2021 to January 29, 2021 period, coincidingtheOmicron variant surge in this group. This significant increase in breakthrough infections were associated with substantially increasedseverely illnesssubstantially increased percentage of deaths during the December 5, 2021 to January 29, 2021 period. During the same period, we observed significantly decreased infection rates among “vaccinated without validity” (considered to have no reliable vaccine immunity per vaccination policy) and a trend toward decreased percentages of severely illness anddeaths. The overall case fatality rate (CFR) during the Omicron surge in our study period (December 5, 2021-Janaury 29, 2022) declined to 0.4% (from 11.6% during October 3-December 4, 2021) with similar decline case fatality rate seen among vaccinated with validity group to 0.3% (from 5.1%), 0.6% in vaccinated without validity group (from 7.9%) and 1.4% in unvaccinated (from 19.7%) with vaccinated with validity group still showing trend towards significant decreased CFR than vaccinated without validity group and unvaccinated having the highest CFR. The disparities among deaths rates in these groups has to be interpreted with caution as the randomized controlled trials COVID-19 vaccines did not show demonstrable mortality benefit and were not adequately powered to demonstrate mortality benefit[20–24]. The Arab Israeli and orthodox Jewish population have higher infection rates, severe illness and significantly higher mortality prior to the start of vaccination program in Israel, and the adaptation of the vaccination including the third booster among Arab and orthodox Jewish Israeli population is significantly lower than the general population[25–29]. Accordingly, Arab and orthodox Jewish Israeli population is exapted to have higher baseline infection rates, severe illness and mortality which must be adjusted among the groups for all vaccine effectiveness calculations including the effectiveness for the

severe illness and deaths.

The improvement in the outcomes noted among vaccinated without validity group in our study even during the Omicron variant surge is probably due to extra precautions this population is taking after news of the scientific literature showing the third booster population are doing better than them and they also lost Green Pass access effective October 1, 2021 that would decrease their chances of exposure[6,30–33]. These changes in pattern of increasing infections among "vaccinated with validity" (majority of them are third booster population) group and the data on third booster dose population could be explained by the Green Pass restrictions that were changedEffective October 1, 2021 that would only allow vaccinated with validity group (all third booster dose and vaccinated with 2 doses within six months from last dose) to gatherings without restrictions that would have allowed condition for the spread of infections. The vaccinated with validitygroup may not be taking adequate precautions with scientific community reporting good effectiveness of the treatment they received[30–32]. The green pass restriction which are still in effect as of January 29, 2022, persons with expired Green passes as of September 30, 2021, partially vaccinated and the unvaccinated have to show the proof of a negative COVID-19 test results to enter the facilities. The partially vaccinated maintained protection during the lifting of restrictions and the Delta variant surge suggesting the behavioral component of taking all protective measures as they know that they were not fully protected yet until they receive the second dose.Similarly, changes in the infection rates during the period of lifting of all restriction (June 1-July 30, 2021) during whichvaccinated with two doses had the highest numbers of breakthrough infections with infection rates similar to unvaccinated (declined vaccine effectiveness), and this population showed improved vaccine effectives and lesser infection rates compared to unvaccinatedwhen the Green Pass restrictionsreinstatedalso an indication of the behavioral component of population making decisions based on public health experts' recommendations.

The potential confounding behavioral factors contributing to higher incidence of infections was also noted in RCT (mRNA-1273e group vs mRNA-1273p group), in vaccinated healthcare workforce during the Delta variant surge and community transmission in vaccinated population as reported by US CDC[19,34,35].

The strength of our study is that we performed a comprehensive analysis of nationwide real-world data of SARS-CoV2 infections in Israel since vaccination program began with comparison of infection rates, comparisons of percentages of infections and four weekly vaccine effectiveness among the compared vaccination groups. We also showed that in addition to vaccine effectiveness, by analyzing the complete data with multiple parameters we can detect changes in infection patterns in population early on so that corrective actions can be undertaken to protect against the spread of infections.

One limitation of our study is that it is an observational study of publicly reported data, however the findings of our study are similar to earlier publications on vaccine effectiveness including 3rd booster dose as published with the same data[30,31,36]. The other limitations of our study are the generalizability of the findings is limited to the population studied in Israel. However, our study findings have validity as reflected by actions of the Israeli authorities to recommend the third and fourth booster dose and revised recommendations on fourth booster dose in the setting of Omicron surge[2–4,37]. In our study, we observed a stronger correlation between the public health policy restrictions and infection rates among vaccinated groups, but unable to establish cause and effect which can only be addressed through randomized controlled trials.

Conclusions

Our results show that vaccination with the third booster dose among the over 60 years old population associated with higher breakthrough infections and shorter (12 weeks) duration ofprotection compared to prior vaccination with two doses. There were significantlyincreased percentage of breakthrough infections noted in vaccinated with validity population (majority of whom are vaccinated with the third booster) since the beginning and during Omicron variant surge and these are associated with substantial increases in severe illness and deathsamong this population who are considered to have full immunity per vaccination policy. There was also a stronger association between the behavior and the public policy restrictions driving breakthrough infections among the vaccinated populations during the Delta and Omicron variant surges. Our study findings suggests that there is an urgent need to protect the majority vaccinated elderly population from breakthrough infections with uniform and coherent protective measuresalong with surveillance protocols.

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