Vaccines and Related Biological Products Advisory Committee Meeting

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State of Israel
Ministry of Health
משרד הבריאות

WEIZMANN INSTITUTE OF SCIENCE

TECHNION
Israel Institute of Technology

The Gertner Institute

THE HEBREW UNIVERSITY OF JERUSALEM

Protection by 4th dose of BNT162b2 against Omicron in Israel

Israeli MOH, Weizmann Institute of Science,
Gertner Institute, Hebrew University & Technion

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Sharon Alroy-Preis & Ron Milo have no competing financial interests to disclose.

Israel MOH and Pfizer have a data sharing agreement. In relation to the booster effectiveness study presented here, only final results of the analysis were shared with Pfizer.

Based on rapid rise in Omicron cases, and early evidence for waning of 3rd dose protection against confirmed infections, Israel decided to begin a 4th vaccination campaign on Jan. 2nd, 2022.

Eligible individuals were those aged 60+ and medical staff whose 3rd dose was administered 4+ months ago.

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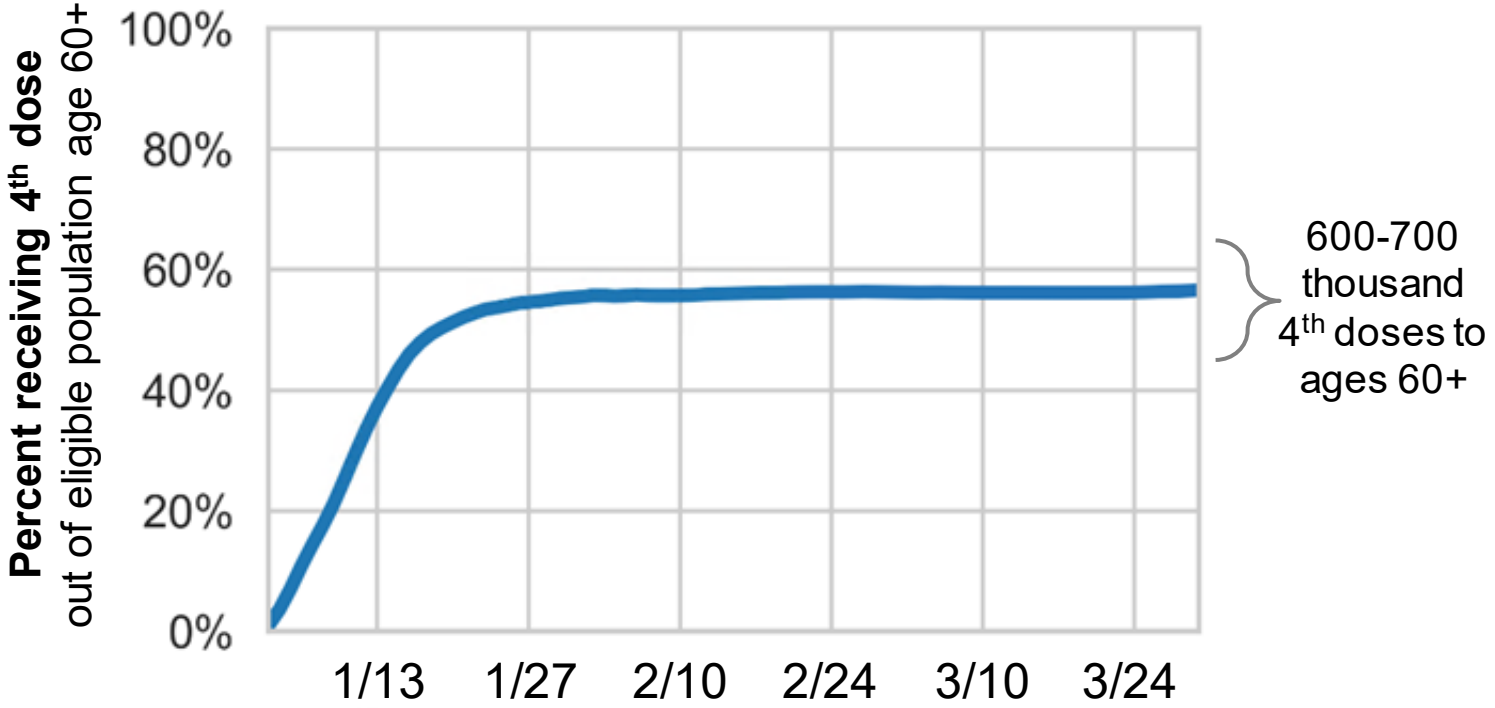
About half of Israel elderly population received a 4th dose



Campaign began on Jan. 2nd

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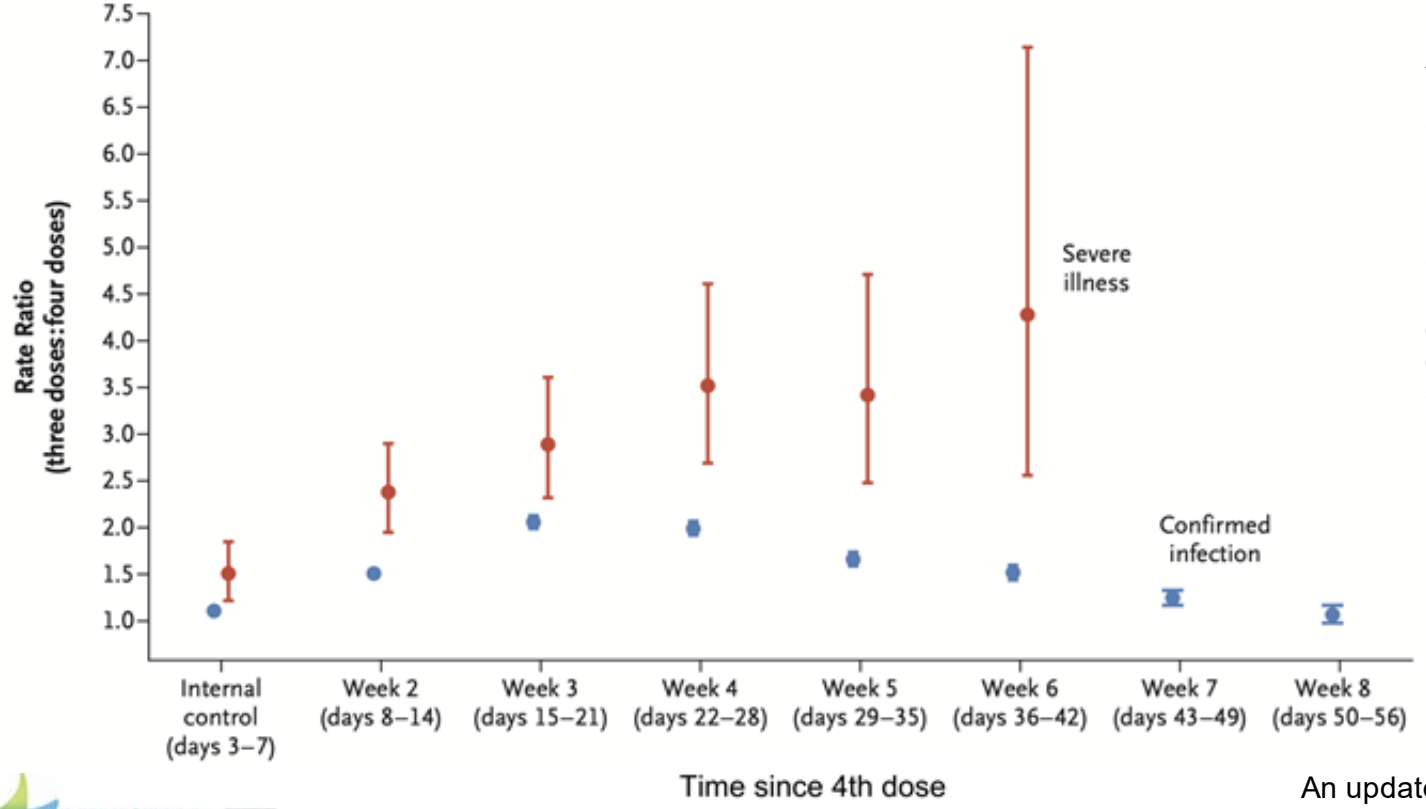
Study analyzes data of ≈1.2 million people eligible for 4th dose

- 1.2M people age 60+ met study qualifications (>4 months since 3rd dose): 0.6M received 4th dose, 0.6M received 3rd but not 4th dose.

- During the analysis period, Jan 10th-Mar 2nd 2022, there were ≈160K confirmed infections and ≈1,700 severe hospitalizations.

Protection as a function of time since 4th dose

Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression



Analysis period for confirmed infection: all infections confirmed between Jan-10 to Mar-2, 2022.

Severe illness: all infections confirmed during Jan-10 to Feb-18, 2022 that deteriorated to severe illness during 14 days after confirmation.

*Severe disease (NIH definition): resting respiratory rate >30 breaths per minute, or O2 saturation <94%, or PaO2/FiO2 <300

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An update to : https://www.medrxiv.org/content/10.1101/2022.02.01.22270232v1

Protection as a function of time since 4th dose

Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression

Table 3. Results of the Quasi-Poisson Regression Analysis of Severe Covid-19.*

Group (Days from Vaccination)	No. of Severe Cases (Person-Days at Risk)	Adjusted Rate Ratio (95% CI)		Adjusted Rate Difference (95% CI)	
		Comparison with Three-Dose Group	Comparison with Internal Control Group	Comparison with Three-Dose Group	Comparison with Internal Control Group
				cases/100,000 person-days at risk	
Three-dose group	1210 (24,857,976)	Reference	—	Reference	—
Internal control group (3–7)	114 (2,673,746)	1.5 (1.2 to 1.9)	Reference	1.8 (0.9 to 2.6)	Reference
Four-dose groups					
Week 2 (8–14)	125 (4,073,168)	2.4 (2.0 to 2.9)	1.6 (1.2 to 2.1)	3.2 (2.7 to 3.7)	1.3 (0.6 to 2.2)
Week 3 (15–21)	99 (3,868,314)	2.9 (2.3 to 3.6)	1.9 (1.4 to 2.6)	3.6 (3.1 to 4.2)	1.7 (1.0 to 2.7)
Week 4 (22–28)	66 (3,639,393)	3.5 (2.7 to 4.6)	2.3 (1.7 to 3.3)	3.9 (3.4 to 4.5)	2.1 (1.4 to 3.0)
Week 5 (29–35)	47 (3,277,662)	3.4 (2.5 to 4.7)	2.3 (1.6 to 3.3)	3.9 (3.3 to 4.5)	2.0 (1.2 to 3.0)
Week 6 (36–42)	18 (2,133,014)	4.3 (2.6 to 7.1)	2.8 (1.6 to 4.9)	4.2 (3.4 to 4.9)	2.4 (1.3 to 3.4)

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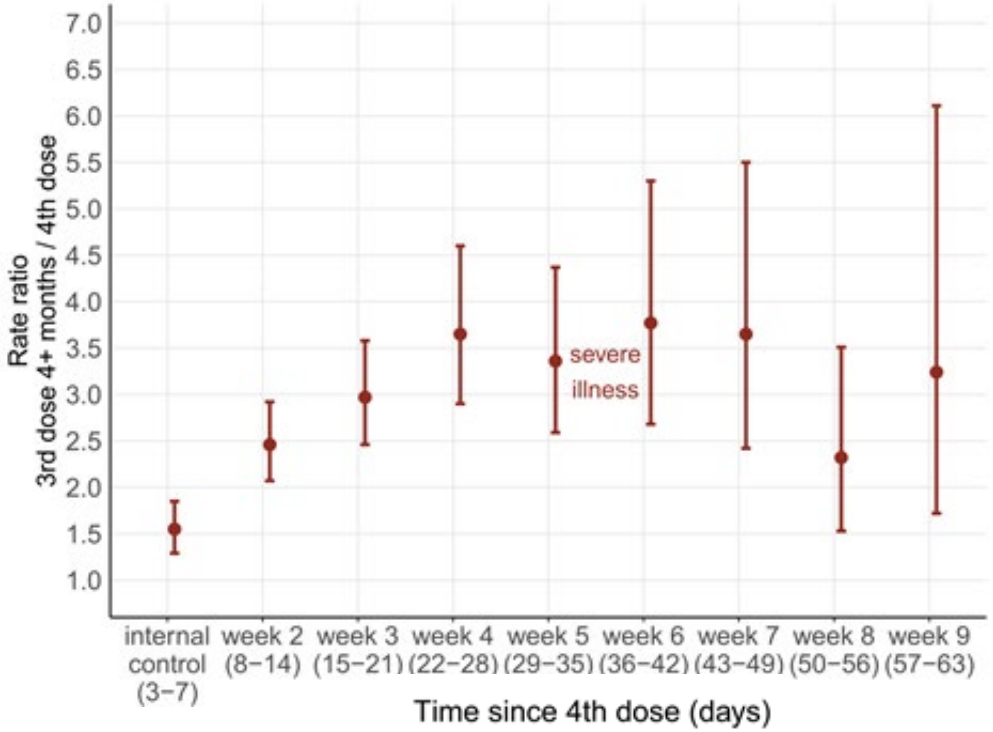
*Severe disease (NIH definition):
resting respiratory rate >30 breaths per minute, or O2 saturation <94%, or PaO2/FiO2 <300

Extra follow up period since peer review -
Protection as a function of time since 4th dose
Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression



Analysis period: all infections confirmed during Jan-10 to Mar-12, 2022, that deteriorated to severe illness during 14 days after confirmation.

*Severe disease (NIH definition): resting respiratory rate >30 breaths per minute, or O2 saturation <94%, or PaO2/FiO2 <300

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4th dose protection against mortality in 60+ age group

(Adjusted for age, gender, sector, and calendar day using quasi-Poisson regression)

Marginal VE against mortality:
76% [71%, 81%] (versus 3rd dose)
55% [35%, 69%] (versus 4th dose internal control group)

Mortality analysis period: all infections confirmed during Jan-10 to Mar-5, 2022 that resulted in mortality during 21 days after confirmation.

Mortality 3rd dose only (person-days at risk)	Mortality 4th dose day 12+ (person-days at risk)	Mortality internal control group (person-days at risk)	Adj. rate ratio for 4th dose day 12+ relative to 3rd dose [95% CI]	Adj. Rate ratio for 4th dose day 12+ relative to Internal control [95% CI]
453 (32,601,391)	95 (22,078,800)	35 (2,721,309)	**4.2** [3.4, 5.2]	**2.2** [1.6, 3.2]

Absolute rate difference per 100,000 risk-days: 1.3 (versus 3rd dose) and 0.5 (versus internal control group)

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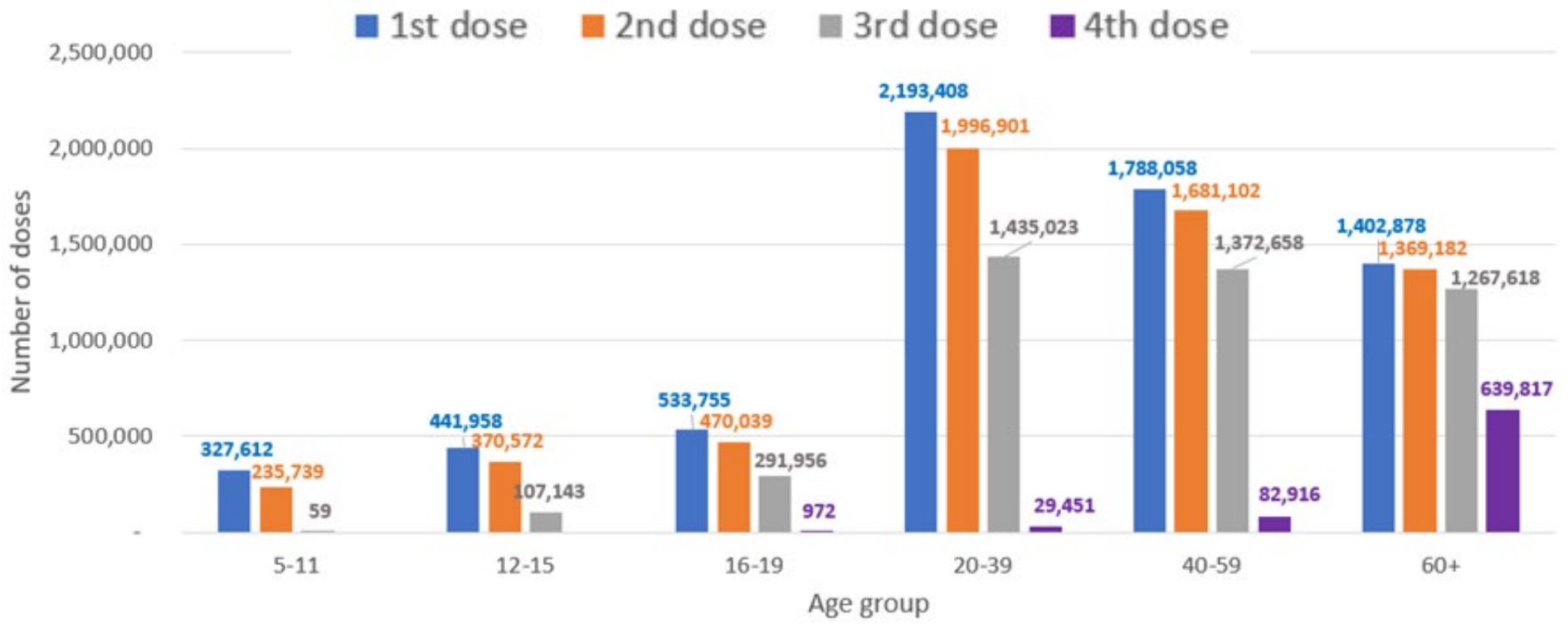
COVID-19 vaccine safety – ISRAEL
4th (2nd booster) dose

data updated March 29th, 2022

Division of Epidemiology
Public Health Services
Israel Ministry of Health

Distribution of Vaccinees by Age Group



Updated March 29th 2022

Second Booster (4th Dose) - Indications

- Age 60 years and older
- Individuals ≥ 18 years old with comorbidities and risk factors for developing severe COVID-19 and their caretakers
- Facility residents and their caretakers ≥ 18 years old
- Caretakers of elderly ≥ 18 years old
- Health care workers or other workers with significant exposure to COVID-19 in their workplace ≥ 18 years old

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- Rates of adverse events per million doses within 30 days
- Updated up to March. 29th, 2022
- Limitation: Reporting based on passive surveillance (active surveillance for myocarditis), and therefore subject to underreporting

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Adverse events reported following 4th dose
(753,156 2nd booster doses administered)

Mild reports	Serious reports
442	12

Serious Adverse event (SAE) definition*

Any adverse event that:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Results in congenital anomaly
- Other important medical events which required intervention

*https://www.fda.gov/safety/reporting-serious-problems-fda/what-serious-adverse-event

Hospitalization and death reports following vaccination are examined by an independent clinical work group using available clinical data

Number of reports by category

Adverse event category	number of reports
Systemic reactions	352
Local reactions	71
Neurologic reactions	14
Allergic reactions and Anaphylaxis	2
Other adverse events for surveillance	3*
Serious adverse events	12

Number of 4th dose vaccinees		
AstraZenica	Moderna	Pfizer
81	602	752,473

*All adverse events reported following 4th dose were of vaccine manufactured by Pfizer

* case 1 - Atrial fibrillation 3 days following vaccination – medical history includes cardiac disease (age group 75-79)
case 2 – Susp. Myocarditis (Troponin+ chest pain), hospitalization not needed, referred to MRI (age group 50-54)
case 3 – Increased liver enzymes found in routine screening, hospitalization not needed (age group 65-69)

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Updated March 29th 2022

Serious adverse events reported following 4th dose

Medical history	Diagnosis	Days from vaccination	Age group
HTN, diabetes, chronic renal failure	Pericarditis	2 days	75-79
Dyslipidemia	Pericarditis	28 days	60-64
Chronic bronchitis, hypercholesterolemia, obesity, smoker	Pericarditis	17 days	70-74
HTN, diabetes, dyslipidemia	Pericarditis	1 day	70-74
HTN, diabetes, chronic renal failure	Renal failure exacerbation	8 days	70-74
Complex nursing patient - IHD, HTN, COPD, dementia, diabetes	Death	1 day	80-84

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Updated March 29th 2022

Serious adverse events reported following 4th dose

Medical history	Diagnosis	Days from vaccination	Age group
CHF, cardiomyopathy, atrial fibrillation, HTN, dyslipidemia	Pneumonia	10 days	80-84
HTN, hypercholesterolemia, obesity, diabetes with target organ damage, IHD, asthma	CVA	3 days	80-84
Active corona virus at admission, COPD	Myocarditis	28 days	70-74
No known relevant medical history	Myocardial infarction	27 days	60-64
HTN, dyslipidemia	Acute kidney failure	21 days	65-69
Epilepsy, HTN, diabetes, hyperparathyroidism	Seizure	2 days	65-69

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Updated March 29th 2022

Myocarditis & perimyocarditis cases and number of vaccinees (Pfizer) by age group and sex

Active surveillance. All cases reported in Israel Dec. 2020 - Mar. 29th, 2022[1]

Gender	Age Group	1st dose (0-21 days after the vaccine)			2nd dose (0-30 days after the vaccine)			3rd dose (0-30 days after the vaccine)			4th dose (0-30 days after the vaccine)		
		Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees
Female	5-11	158,185	0		113,218	0	0	23	0		0	0	
	12-15	212,762	0		177,909	1	177,909	50,449	0		0	0	
	16-19	257,503	0		231,241	2	115,621	145,530	2	72,765	421	0	
	20-24	269,472	1	269,472	248,780	5	49,756	183,186	0		1,603	0	
	25-29	252,008	0		234,265	2	117,133	167,328	0		2,510	0	
	30+	2,147,109	2	1,073,555	2,058,476	8	257,310	1,726,149	4	431,537	382,639	*2	191,320
Male	5-11	169,127	0		121,915	0	0	36	0		0	0	
	12-15	222,096	1	222,096	186,317	11	16,938	55,379	5	11,076	0	0	
	16-19	264,132	3	88,044	234,090	34	6,885	145,600	13	11,200	539	0	
	20-24	282,772	6	47,129	260,290	27	9,640	185,795	7	26,542	1,980	0	
	25-29	263,681	3	87,894	245,906	21	11,710	175,219	2	87,610	2,823	0	
	30+	2,006,779	6	334,463	1,929,859	28	68,924	1,622,533	17	95,443	359,066	0	
Total		**6,347,441**	**22**		**5,929,048**	**139**		**4,457,204**	**50**		**751,581**	**2**	

[1] Not including cases that have been ruled out by special committee

* Case 1 - Susp. Myocarditis – no hospitalization, to be confirmed by MRI in community. Case 2 – Active COVID-19 at admission

Two cases (Females) one of susp myocarditis reported 4 days following 4th dose, one case 28 days following 4th dose (active COVID-19 at admission)

Note: Sex unknown for 53,927 vaccine recipients, Age unknown for 329 vaccine recipients

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