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

Waning immunity and booster protection data from Israel

Yair Goldberg - Technion

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

October. 4th, 2021

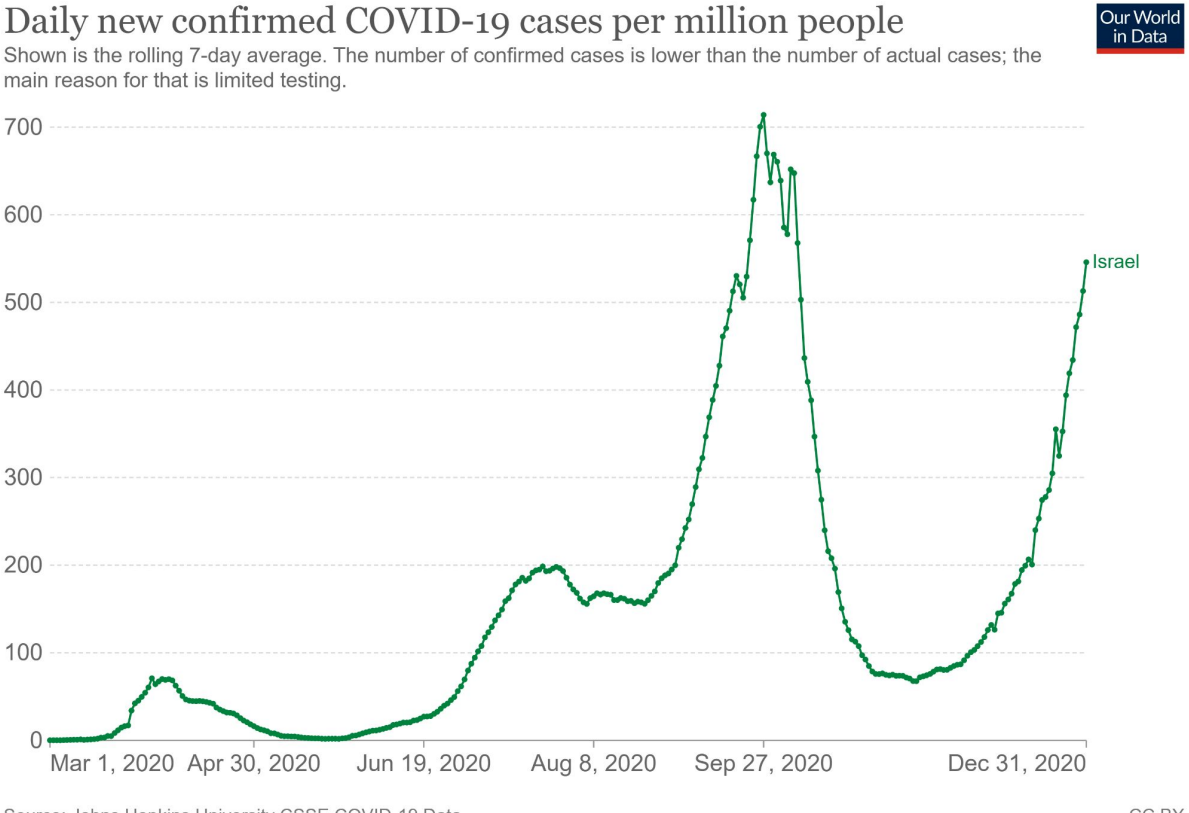
Outline

1. *Vaccine campaign - Dec 2020 - April 2021*
2. *The Delta outbreak in Israel - June 2021 - now*
3. *Waning immunity*
4. *The booster dose*

Outline

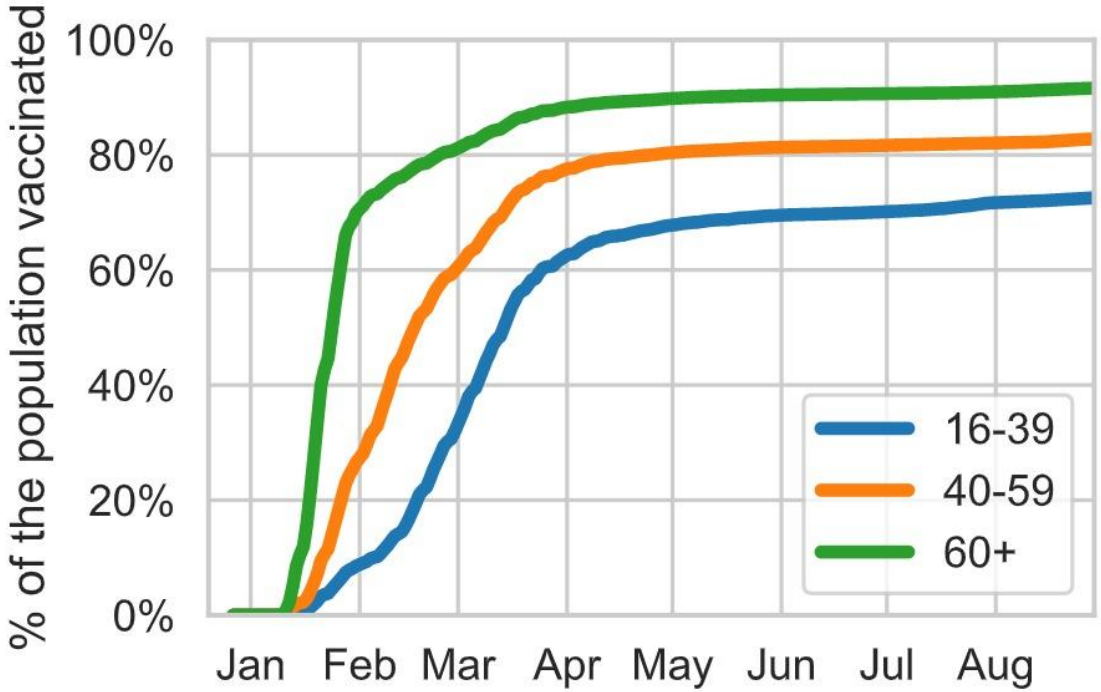
1. *Vaccine campaign - Dec 2020 - April 2021*
2. *The Delta outbreak in Israel - June 2021 - now*
3. *Waning immunity*
4. *The booster dose*

Israel began a vaccination campaign at the end of 2020 during a surge in cases



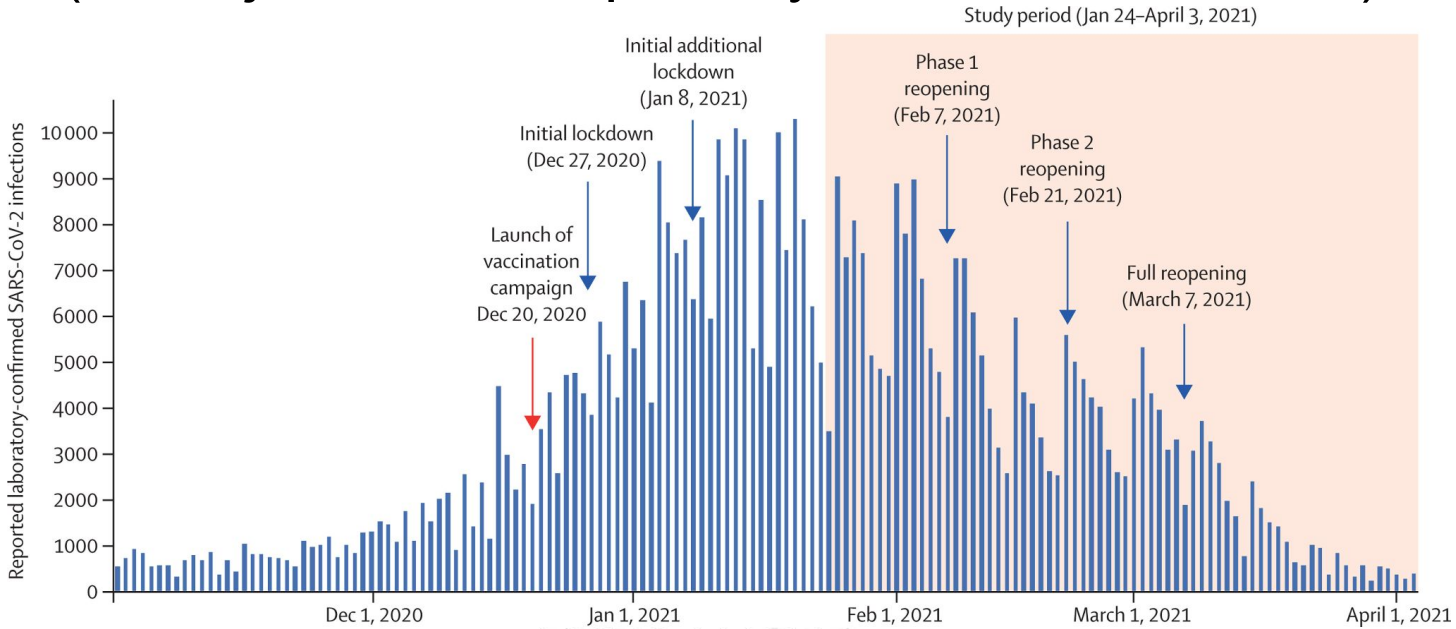
MINISTRY OF HEALTH

The vaccination campaign started early in Israel using the Pfizer BNT162b2 with 3 week regimen



MINISTRY OF HEALTH

Over 100-fold decrease in cases following vaccination campaign (in conjunction with partially effective lock-down)



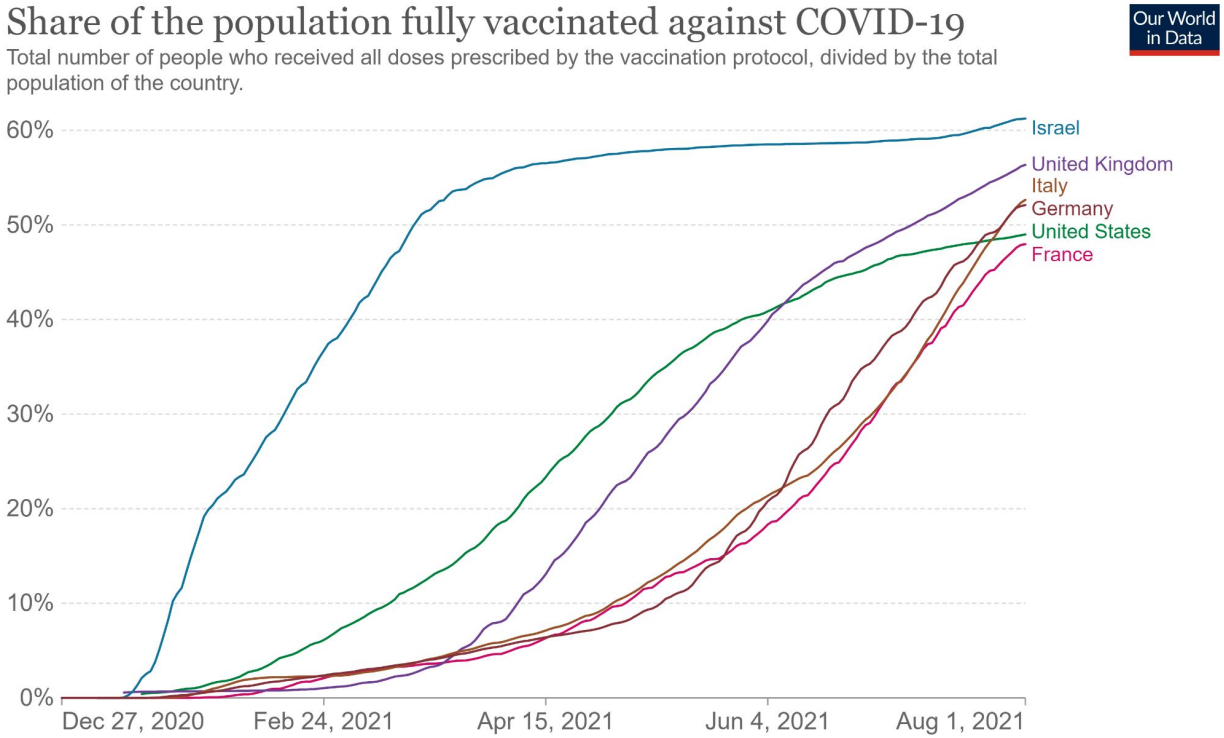
THE LANCET

Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data

Eric J Haas, Frederick J Angulo, John M McLaughlin, Emilia Anis, Shepherd R Singer, Farid Khan, Nati Brooks, Meir Smaja, Gabriel Mircus, Kaijie Pan, Jo Southern, David L Swerdlow, Luis Jodar, Yeheskel Levy, Sharon Alroy-Preis

MINISTRY OF HEALTH

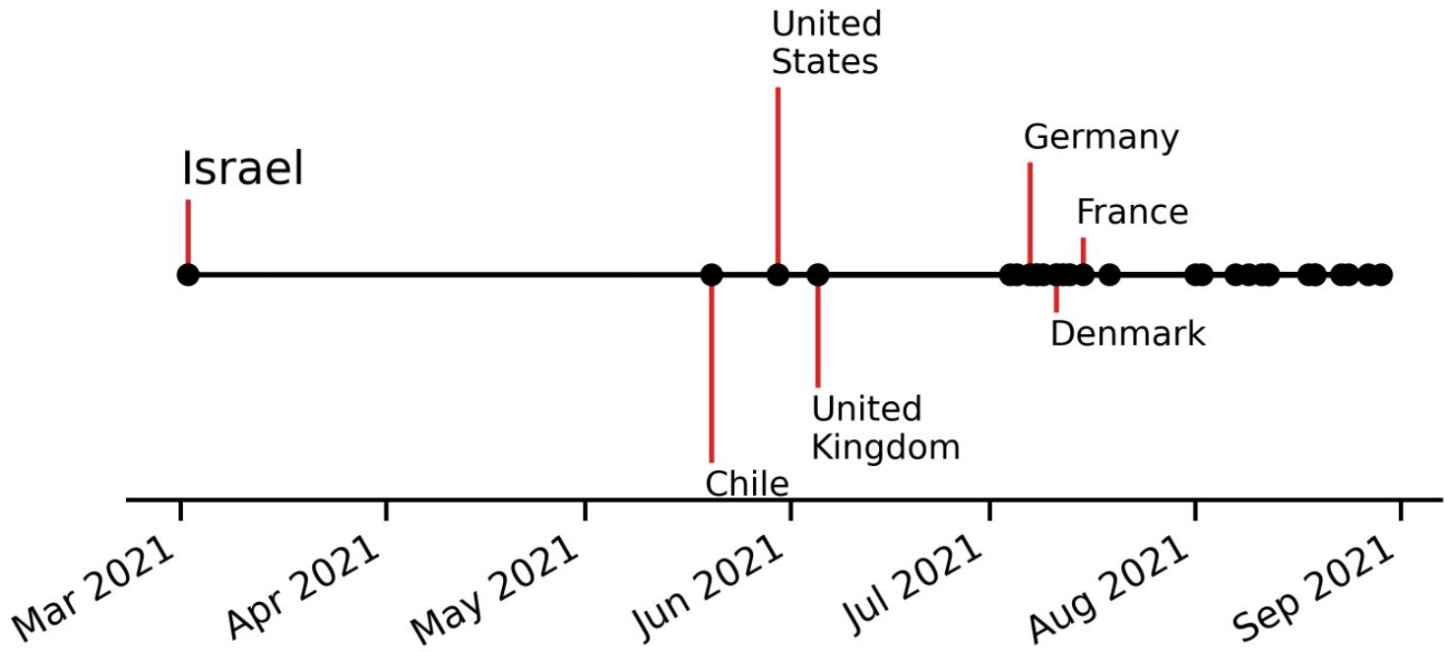
Israel reached high levels of population-wide immunity early on



Source: Official data collated by Our World in Data – Last updated 12 September 2021, 12:00 (London time)
Note: Alternative definitions of a full vaccination, e.g. having been infected with SARS-CoV-2 and having 1 dose of a 2-dose protocol, are ignored to maximize comparability between countries.
OurWorldInData.org/coronavirus • CC BY

MINISTRY OF HEALTH

Israel reached high levels of population-wide immunity
≈3 months before most countries



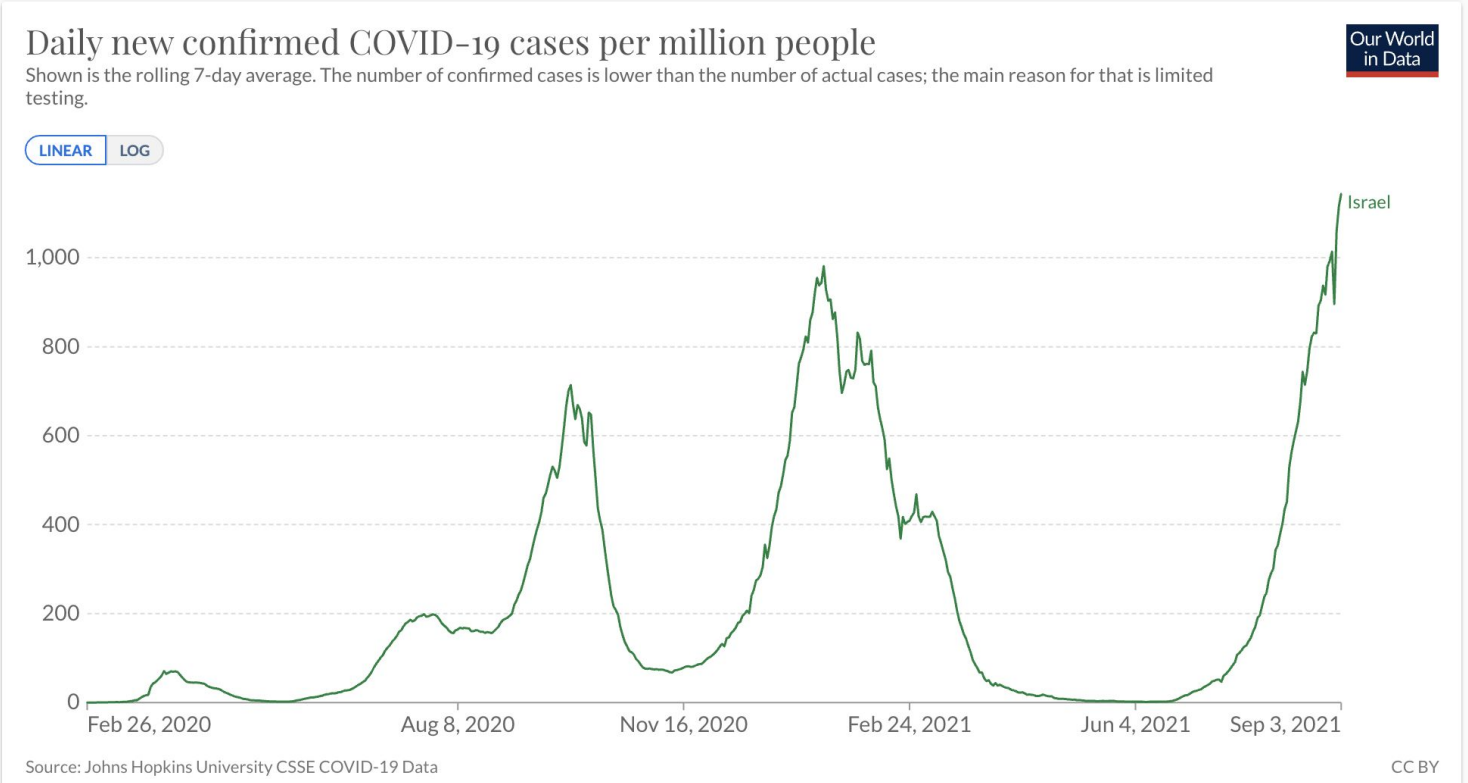
Israel has large testing capacity (16,000 daily tests per million) & comprehensive electronic COVID19 records for the entire population

MINISTRY OF HEALTH

Outline

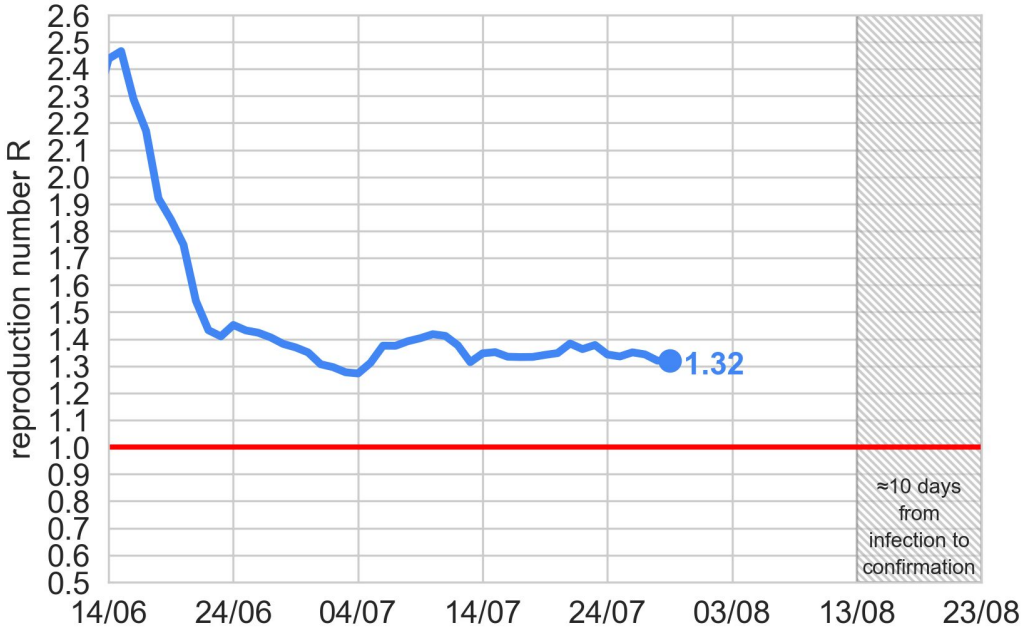
1. *Vaccine campaign - Dec 2020 - April 2021*
2. ***The Delta outbreak in Israel - June 2021 - now***
3. *Waning immunity*
4. *The booster dose*

Israel now experiences its **highest levels of infection** (delta variant) in spite of **widespread (>60%) 2nd dose** vaccination



MINISTRY OF HEALTH

The reproduction number was high in during June and July with doubly vaccinated cases rising rapidly

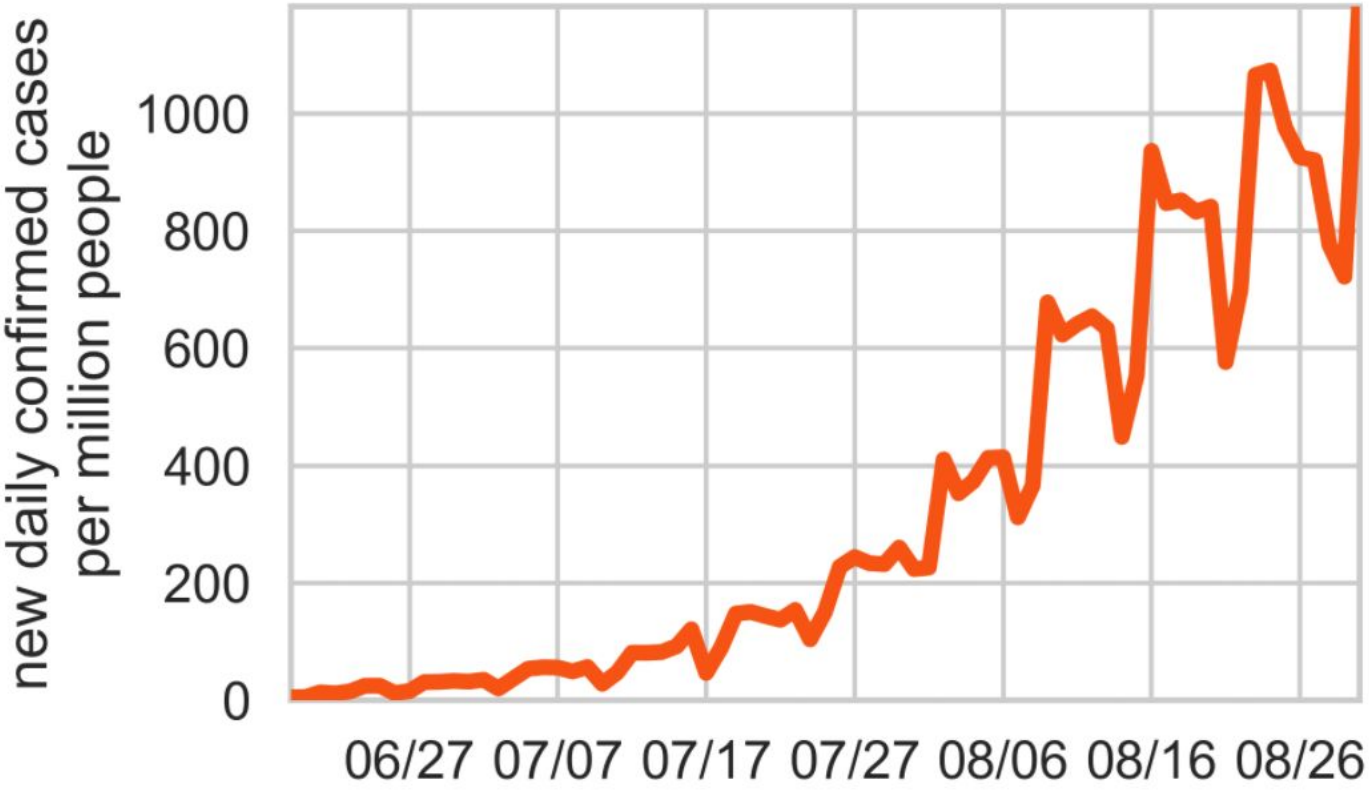


→ currently doubling every two weeks

MINISTRY OF HEALTH

Daily cases rose by more than 100-fold in 1.5 months

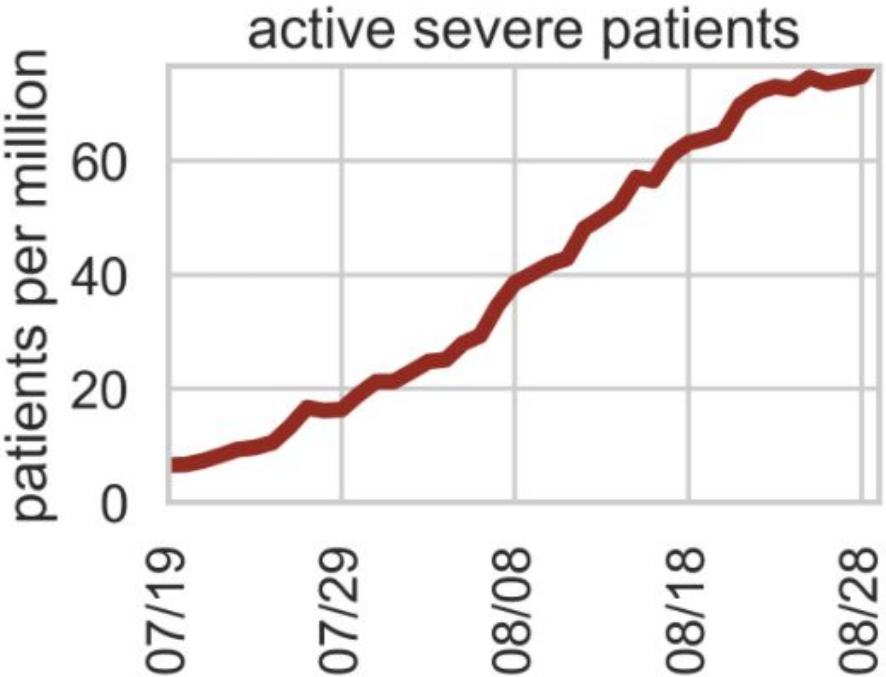
Based on PCR testing performed in Israel for both symptomatic and asymptomatic individuals



MINISTRY OF HEALTH

Severe active cases increased >10-fold in a month

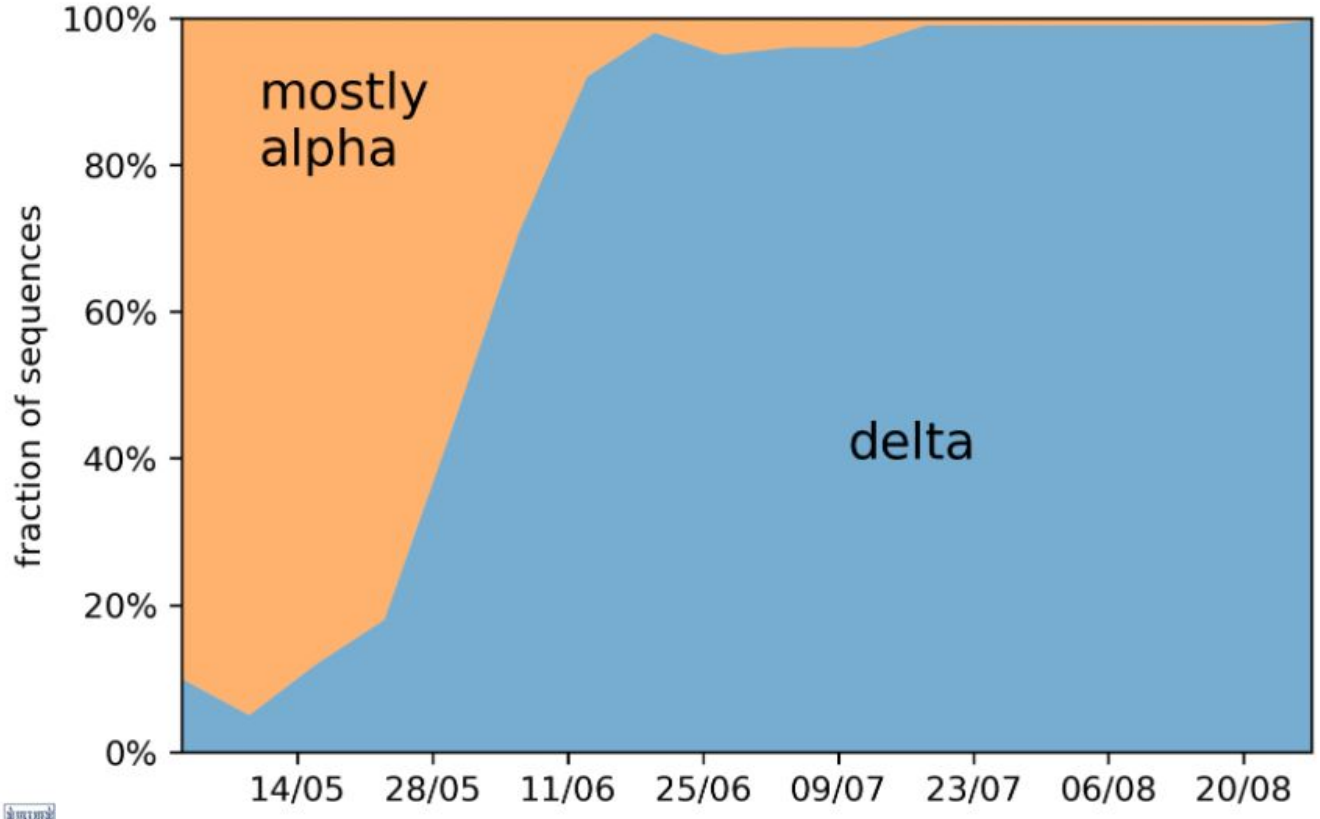
Severe disease: resting respiratory rate >30 breaths per minute, or oxygen saturation <94%, or PaO2/FiO2 <300



During July-early August:
60% vaccinated with 2 doses
40% unvaccinated

MINISTRY OF HEALTH

During June alpha was overtaken by the delta variant in Israel



MINISTRY OF HEALTH

Outline

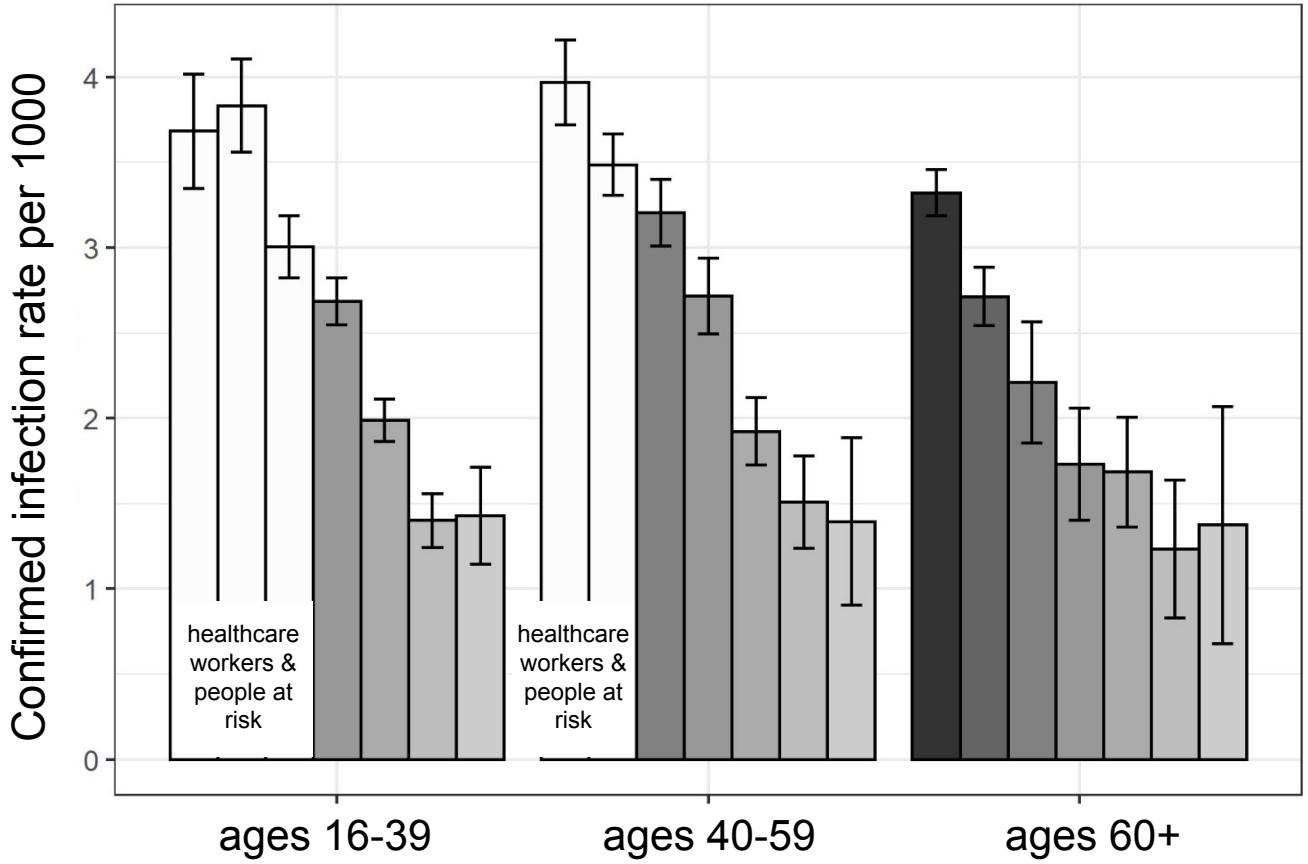
1. *Vaccine campaign - Dec 2020 - April 2021*
2. *The Delta outbreak in Israel - June 2021 - now*
3. ***Waning immunity***
4. *The booster dose*

MoH Data

- Israel has a centralized electronic medical records system
- Israeli Ministry of Health collects data routinely from all HMOs and hospitals
- The data is linked using the person's identity number
- All residents belong to an HMO
- By combining data from the Israeli Ministry of Health and the Israel Central Bureau of Statistics we obtained for each resident (over age 16)
  - Municipality of residence
  - Age
  - All PCR tests (dates and results)
  - Infection date (first and second if applicable) and severity
  - Vaccination date (first, second, and third if applicable)

Waning immunity was observed across age groups

Rate of confirmed **SARS-CoV-2 infections** stratified by vaccination period and age group
Per 1000 persons, during July 11, 2021 and July 31, 2021



Goldberg et al.,
https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1

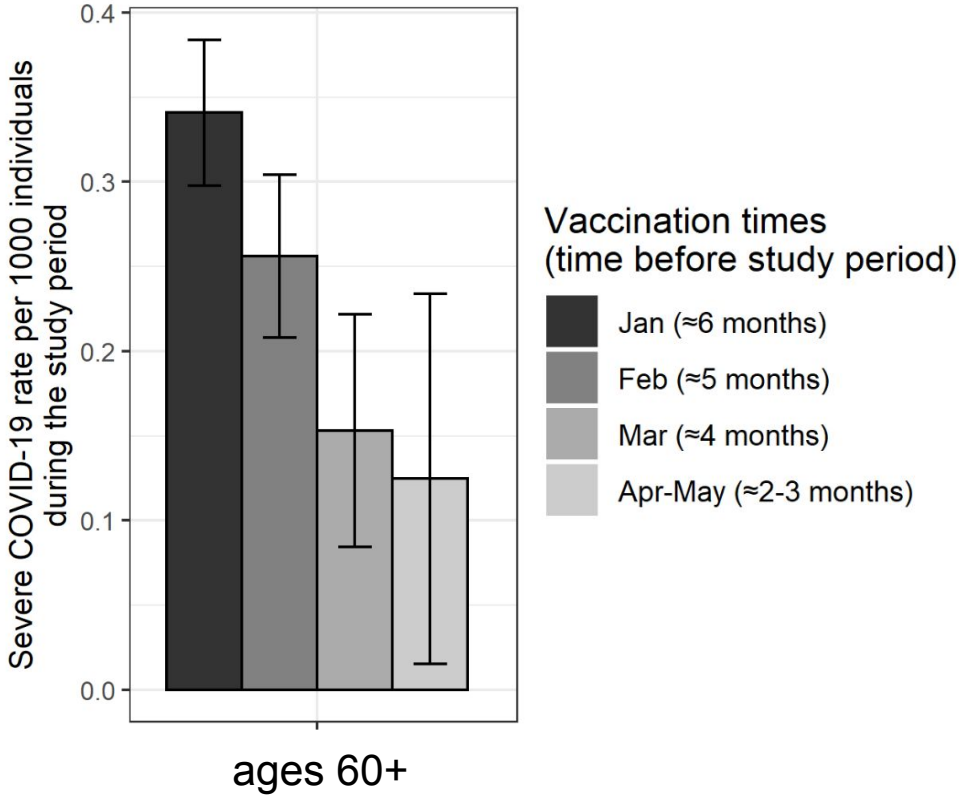
Vaccination times
(time before study period)

- Jan, 16-31 (≈6 months)
- Feb, 1-15 (≈5.5 months)
- Feb, 16-28 (≈5 months)
- Mar, 1-15 (≈4.5 months)
- Mar, 16-31 (≈4 months)
- Apr (≈3 months)
- May (≈2 months)

MINISTRY OF HEALTH

Waning immunity also observed for severe disease in 60+ group

Per 1000 persons, during July 11, 2021 and July 31, 2021

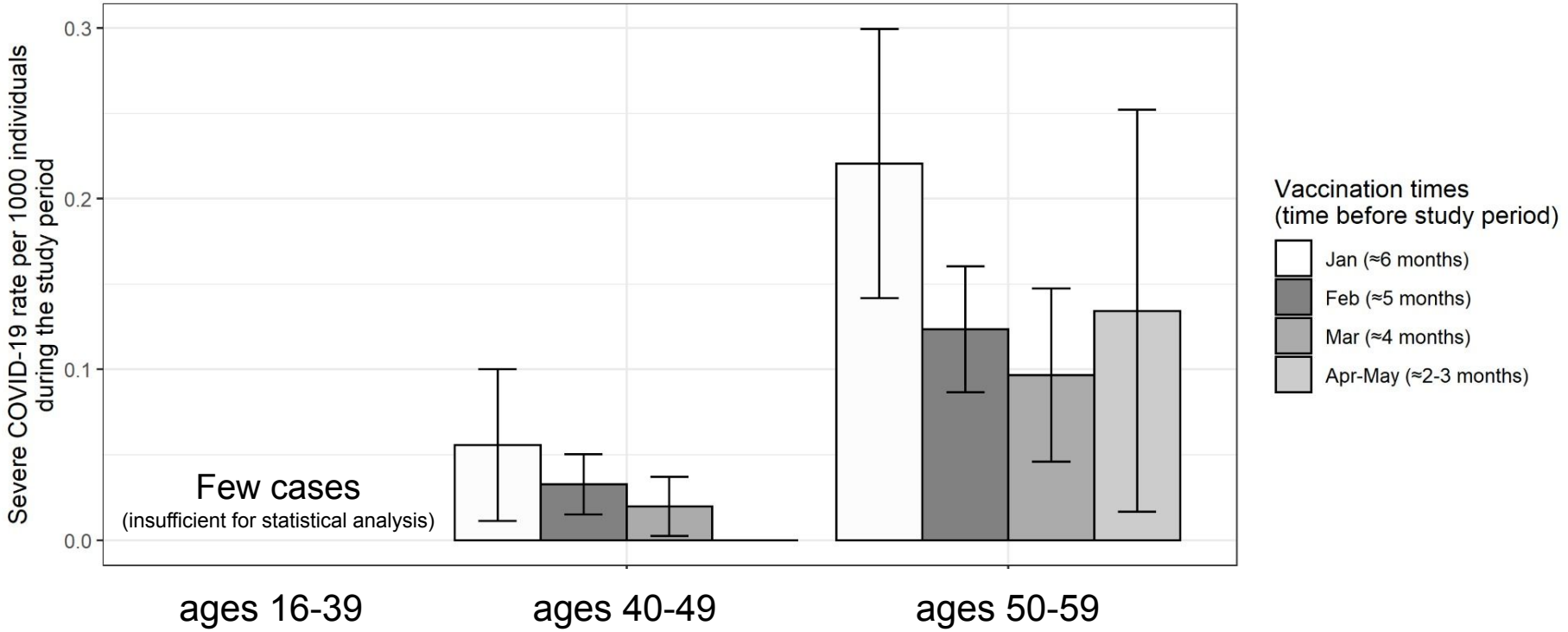


Goldberg et al.,
https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1

MINISTRY OF HEALTH

Waning immunity against severe disease may occur also in younger age groups

Rates of severe COVID-19 stratified by vaccination period and age group per 1000 persons, July 11 – Aug 15, 2021



MINISTRY OF HEALTH

Data - only fully vaccinated persons

Data collected during July 11, 2021, and July 31, 2021

Variable (%)	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May	total
n	**1,073,766**	**971,218**	**746,944**	**818,975**	**748,932**	**324,996**	**100,414**	**4,785,245**
Infections (rate per 100,000)	**3,425 (319)**	**2,978 (306)**	**2,170 (290)**	**2,049 (250)**	**1,378 (184)**	**438 (135)**	**141 (140)**	**12,579**
Severe (rate per 100,000)	**215 (20)**	**95 (9.8)**	**12 (1.6)**	**16 (2.0)**	**5 (0.7)**	**5 (1.5)**	**0 (0.0)**	**336**
Age: 16-39	125,587 (11.7%)	195,580 (20.1%)	352,247 (47.2%)	549,089 (67.0%)	496,455 (66.3%)	217,622 (67.0%)	67,281 (67.0%)	
Age: 40-59	242,866 (22.6%)	417,618 (43.0%)	327,766 (43.9%)	208,072 (25.4%)	190,200 (25.4%)	78,249 (24.1%)	22,240 (22.1%)	
Age: 60+	705,313 (65.7%)	358,020 (36.9%)	66,931 (9.0%)	61,814 (7.5%)	62,277 (8.3%)	29,125 (9.0%)	10,893 (10.8%)	

Statistical Model

On any given day, the risk of individual

in **cohort i (e.g., vaccination period)**

with **risk profile** x

to get an outcome (e.g., hospitalization) **is** $h_i(x)$

The protection of **cohort i** with respect to **cohort Jan 16-31** is $\dfrac{h_{\text{Jan 16-31}}(x)}{h_i(x)}$

Assumptions

1. Piecewise-constant hazards: $h_i(x) = \exp\{\alpha_i + \beta^T x\}$;

   JanB, FebA, FebB, MarA, MarB, April, May

2. Constant hazard within cohort, given the risk profile
3. The effect of age may depend on the cohort

MINISTRY OF HEALTH

Fresh Vaccine Protects More

Protection (rate ratio) against Documented SARS-CoV-2 and severe COVID-19

Poisson regression adjusted for epi-week, past PCR tests, demographic group, and gender.

OUTCOME = Positive SARS-CoV-2 PCR test

Age	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May
16-39	**1**	**0.9** [0.8, 1]	**1.2** [1, 1.3]	**1.3** [1.1, 1.4]	**1.5** [1.4, 1.7]	**2** [1.7, 2.3]	**2** [1.6, 2.5]
40-59	**1**	**1.1** [1, 1.1]	**1.1** [1, 1.2]	**1.2** [1.1, 1.4]	**1.6** [1.4, 1.8]	**1.9** [1.6, 2.4]	**2.3** [1.6, 3.3]
60+	**1**	**1.1** [1.1, 1.2]	**1.3** [1.1, 1.5]	**1.6** [1.3, 2]	**1.6** [1.3, 2]	**2.1** [1.5, 2.9]	**2.1** [1.2, 3.4]

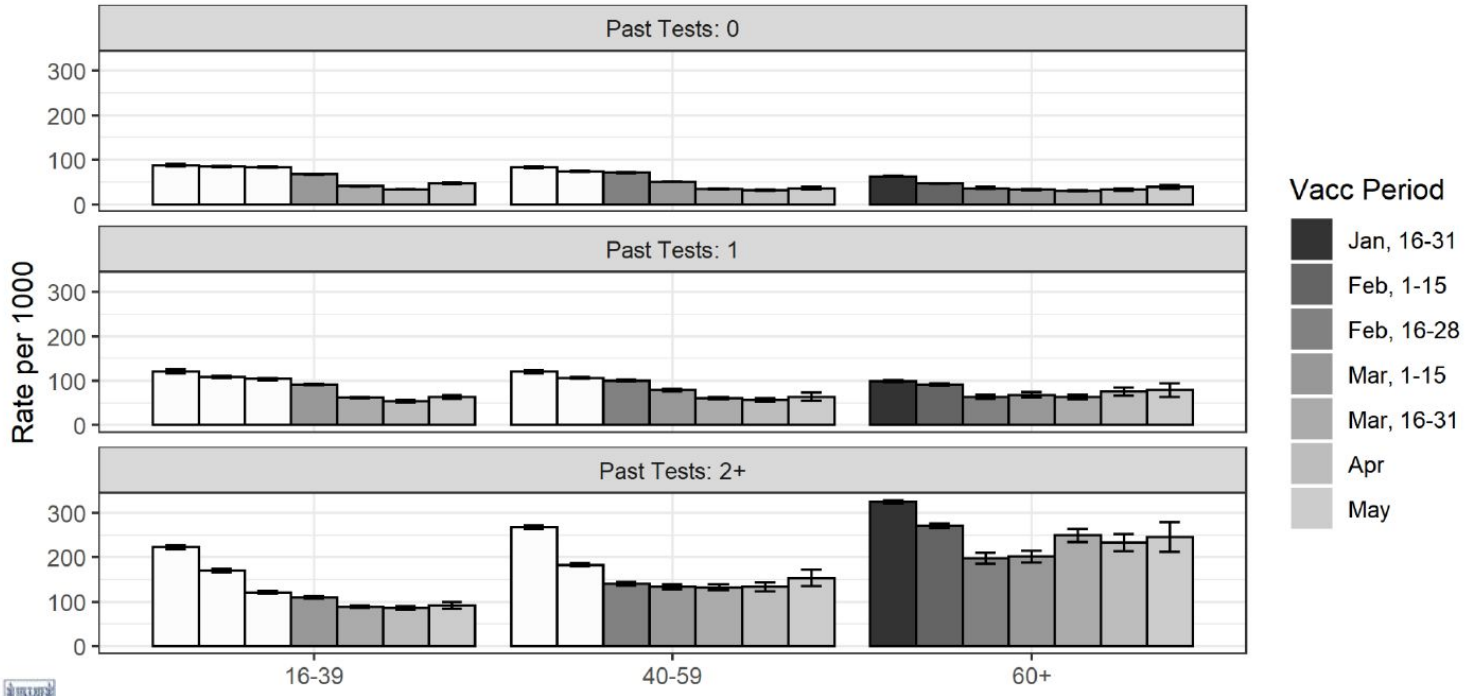
OUTCOME = Severe COVID-19

Age	Jan	Feb	Mar
40-59	**1**	**2.2** [0.8, 6.1]	**2.8** [0.7,1 1]
60+	**1**	**1.2** [0.9, 1.5]	**1.7** [1.0, 2.7]

MINISTRY OF HEALTH

Detection bias? Current PCR test rate stratified by past PCR tests

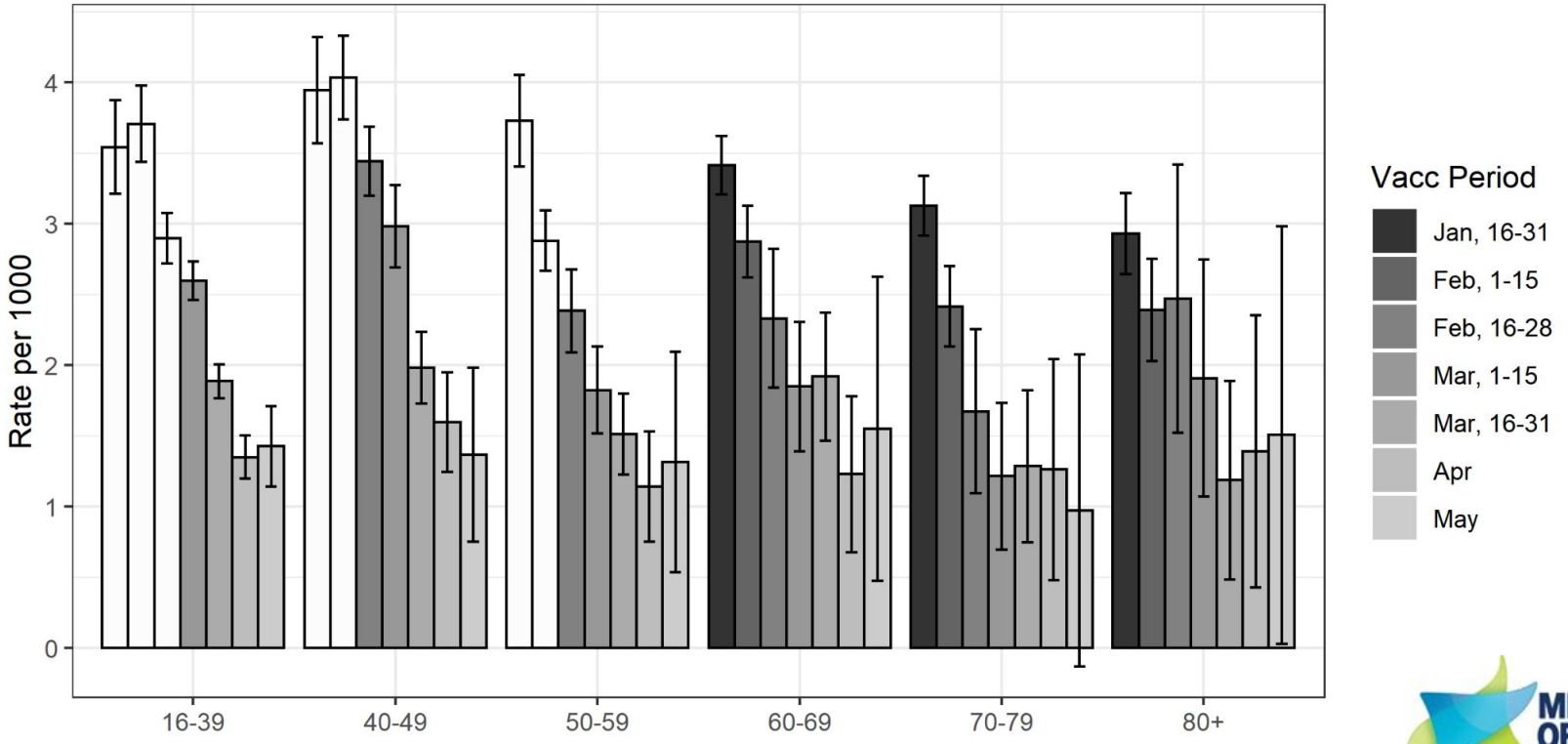
Number of PCR tests performed from July 11, 2021 to July 31,2021, grouped by vaccination period and age group, and stratified by past PCR tests



MINISTRY OF HEALTH

Waning immunity - detailed age groups

Rate of documented **SARS-CoV-2 infection** (per 1000 persons) during July 11, 2021, and July 31, 2021, stratified by vaccination period and age group
(#infections in 11/7-31/7／# fully vaccinated in period)✕1000



MINISTRY OF HEALTH

A substantial reduction in vaccine efficacy with vaccine age

*Comparison with unvaccinated population is problematic, as the unvaccinated population is small and differs in its characteristics from the vaccinated population

OUTCOME = Positive SARS-CoV-2 PCR test

Age	Jan 16-31	Feb 1-15	Feb 16-28	Mar 1-15	Mar 16-31	Apr	May
16-39	**50%** [45, 55]	**47%** [42, 52]	**58%** [55, 62]	**62%** [59, 64]	**68%** [65, 70]	**74%** [71, 77]	**73%** [67, 78]
40-59	**58%** [54, 62]	**61%** [58, 65]	**63%** [59, 66]	**67%** [63, 70]	**74%** [70, 77]	**78%** [73, 82]	**80%** [71, 86]
60+	**57%** [52, 62]	**63%** [57, 67]	**65%** [57, 71]	**73%** [66, 78]	**72%** [64, 77]	**73%** [63, 81]	**75%** [58, 85]

OUTCOME = Severe COVID-19

Age	Jan	Feb	Mar
40-59	**94%** [87, 97]	**98%** [95, 99]	**98%** [94, 99]
60+	**86%** [82, 90]	**88%** [84, 91]	**91%** [85, 95]

MINISTRY OF HEALTH

Even a seemingly modest 12 percentage point decline in effectiveness could translate to a 5-fold increase in severe cases among the vaccinated

- Effectiveness in April for people vaccinated in Jan-March was high (e.g. 97%)
- Effectiveness in July for people vaccinated in January was reduced (e.g. 85%)

97% VE ⟶ 3% relative risk

85% VE ⟶ 15% relative risk

5-fold increase in relative risk

MINISTRY OF HEALTH

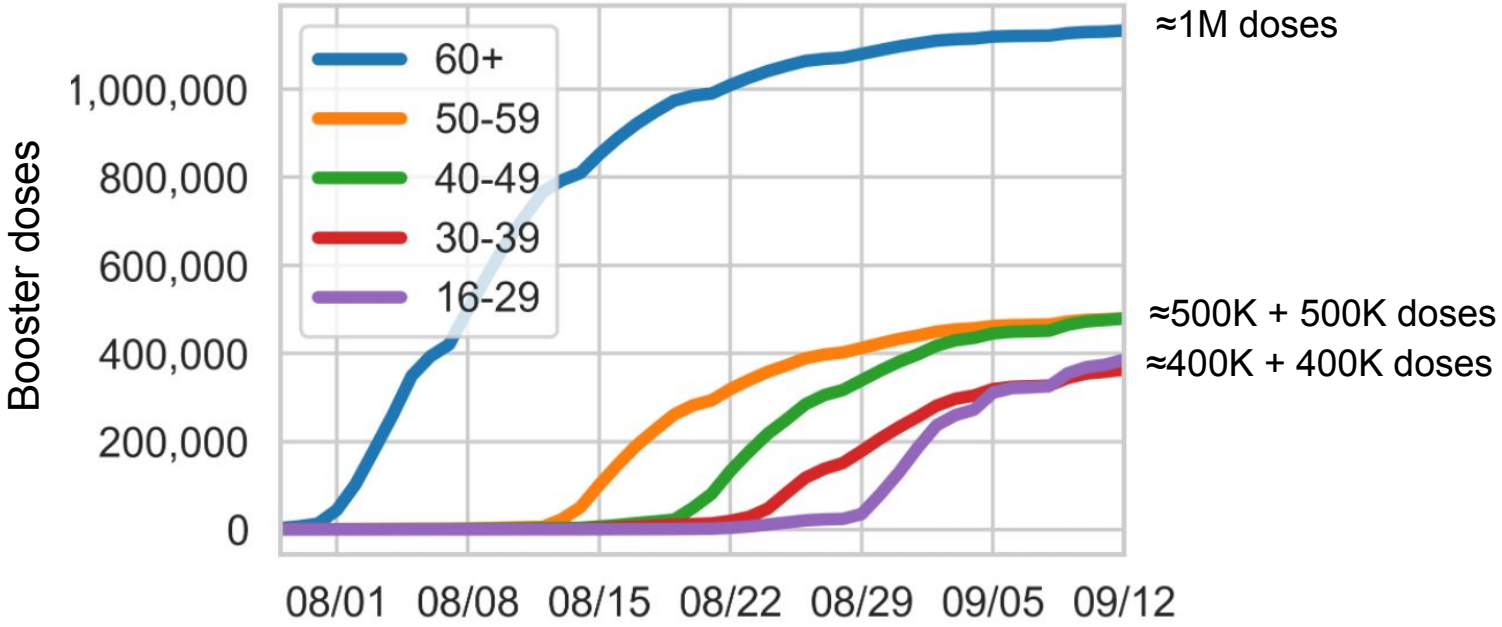
Based on evidence for waning in Israel, and the trajectory towards exceeding national hospitalization capacity given the rapid rise in severe cases, Israel decided to begin a 3rd vaccination campaign on July 30th, starting with the elderly.

MINISTRY OF HEALTH

Outline

1. *Vaccine campaign - Dec 2020 - April 2021*
2. *The Delta outbreak in Israel - June 2021 - now*
3. *Waning immunity*
4. ***The booster dose***

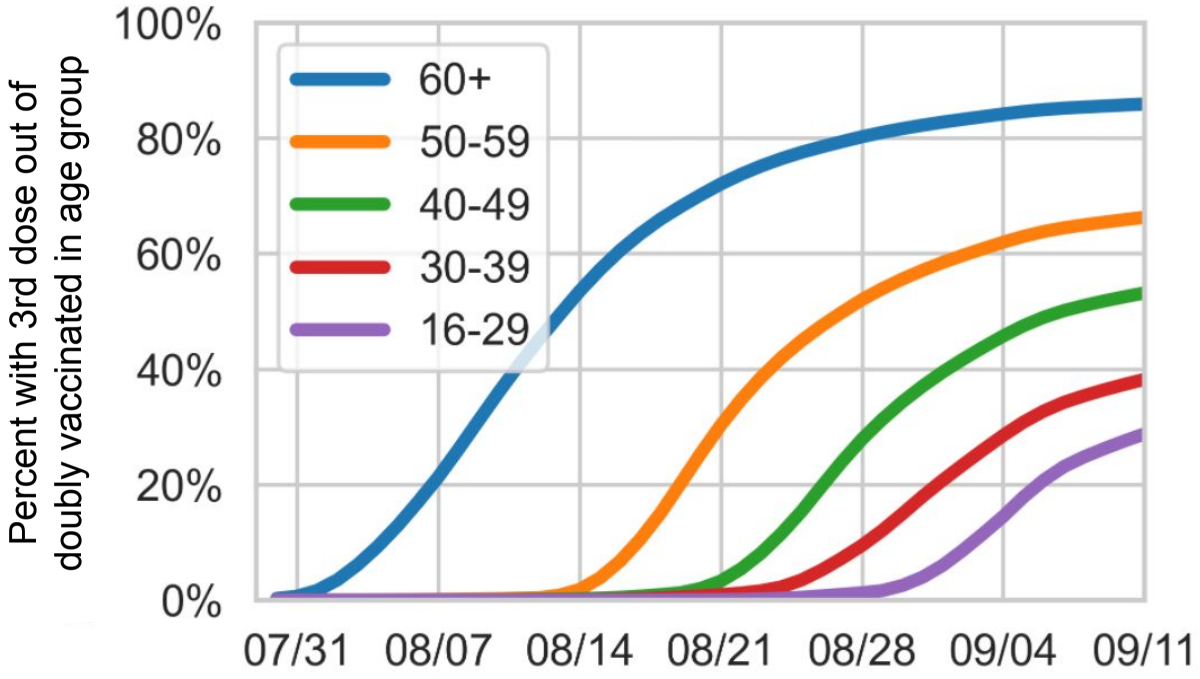
Booster campaign began in Israel on July 30th



>2.8 million booster doses to date

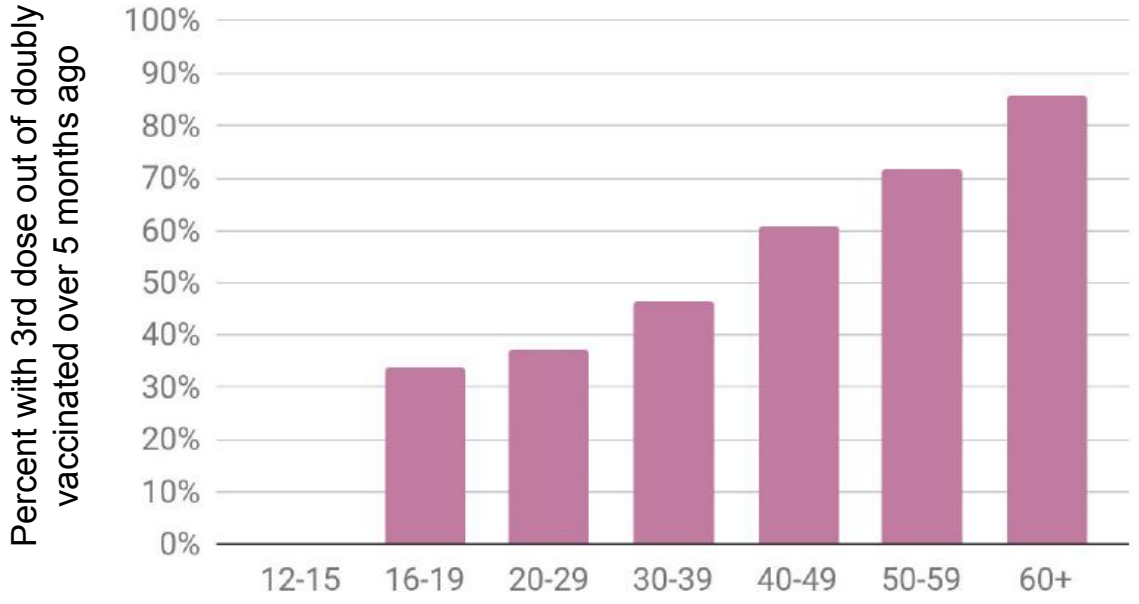
MINISTRY OF HEALTH

Large majority of elderly population received a 3rd dose



MINISTRY OF HEALTH

Overall half of the eligible population received a 3rd dose
(eligibility begins 5 months after the second dose)

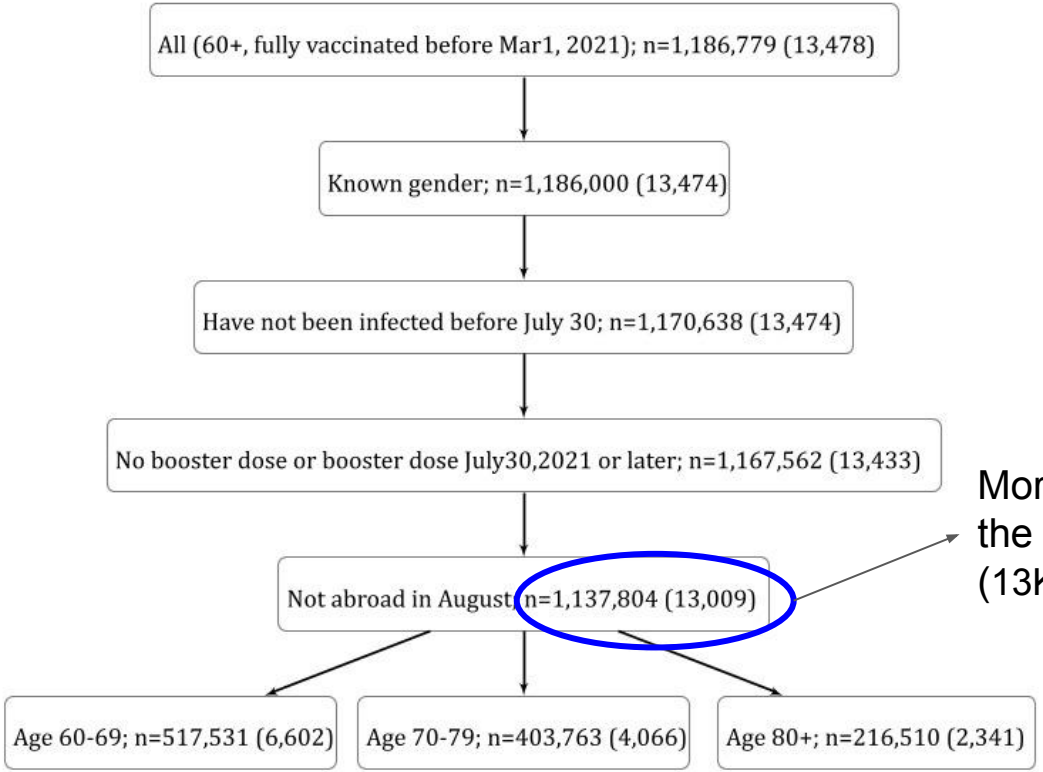


Updated: Sep. 13, 2021

MINISTRY OF HEALTH

Booster analysis covers most of the 60+ population

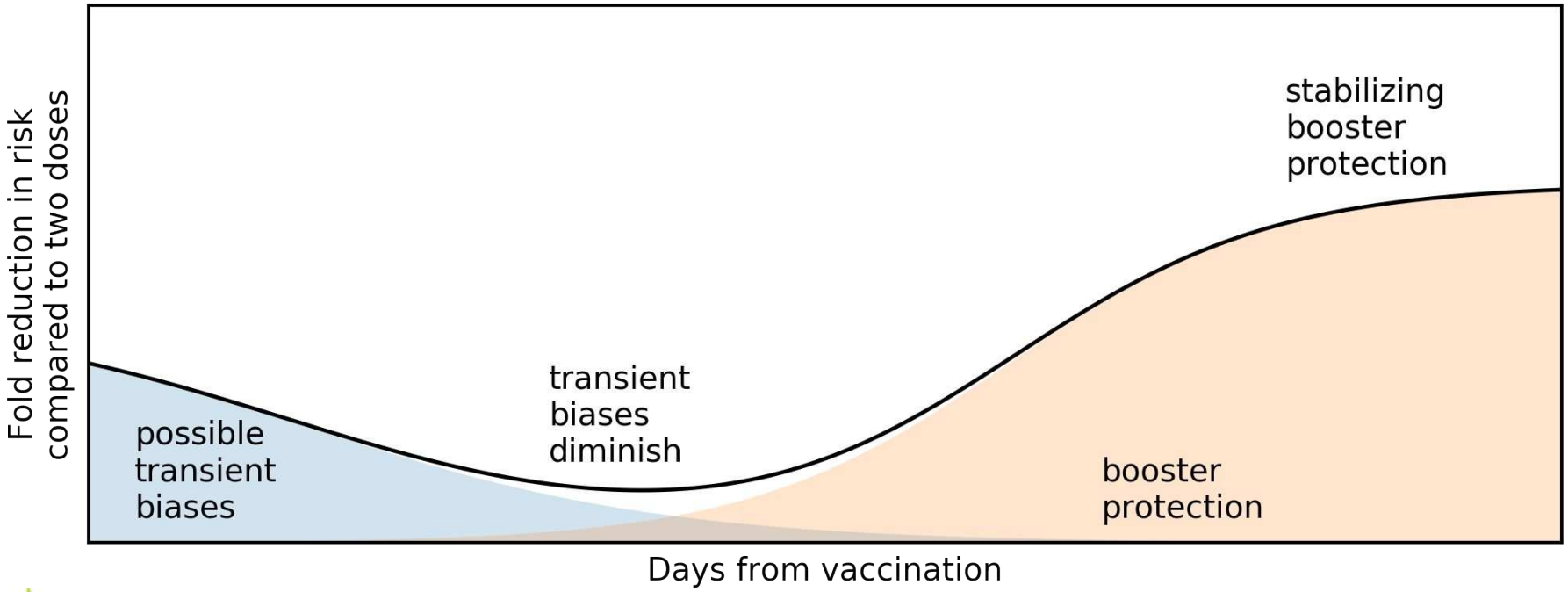
Data on 60+ who were fully vaccinated before March 2021
Analysis period from August 10 to August 31



More than 1.1M people in the analysis
(13K confirmed infections).

MINISTRY OF HEALTH

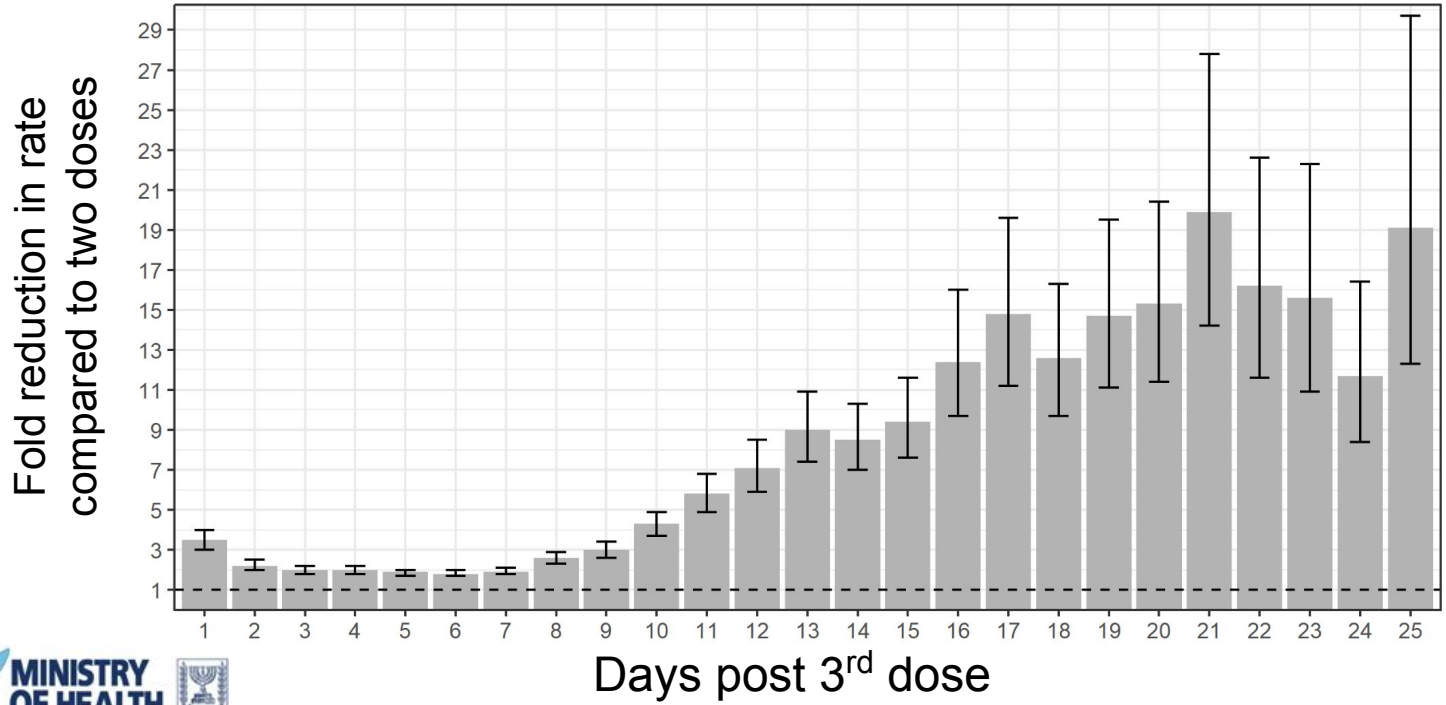
Reduction in risk due to booster is expected to be observed after ≈2 week delay



MINISTRY OF HEALTH

Booster protection against confirmed **infection** as a function of time post vaccination **ages 60+**

Poisson regression adjusted for age, gender, demographic group, 2nd dose period and calendar day.
Based on data from August 10 to August 31

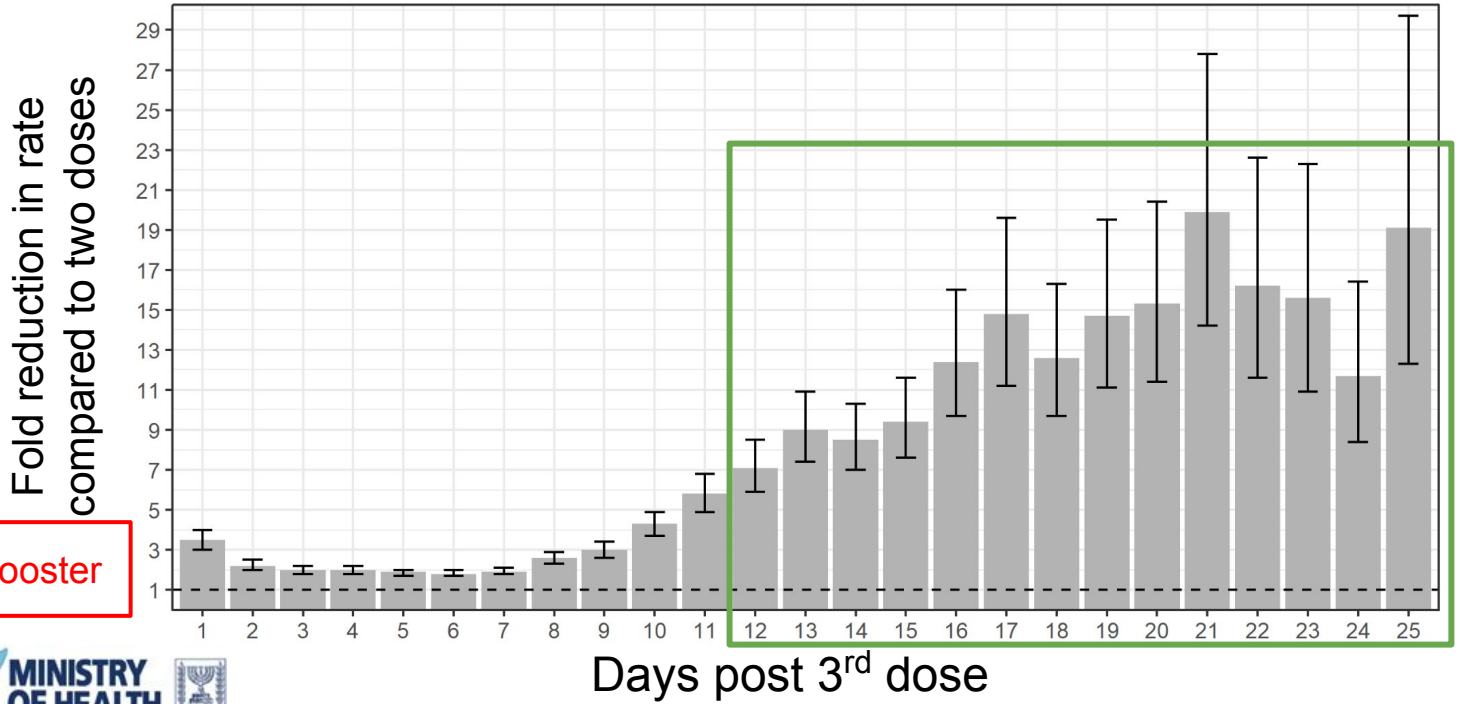


MINISTRY OF HEALTH

Bar-on et al., https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

Booster protection against confirmed **infection** as a function of time post vaccination **ages 60+**

Poisson regression adjusted for age, gender, demographic group, 2nd dose period and calendar day.
Based on data from August 10 to August 31

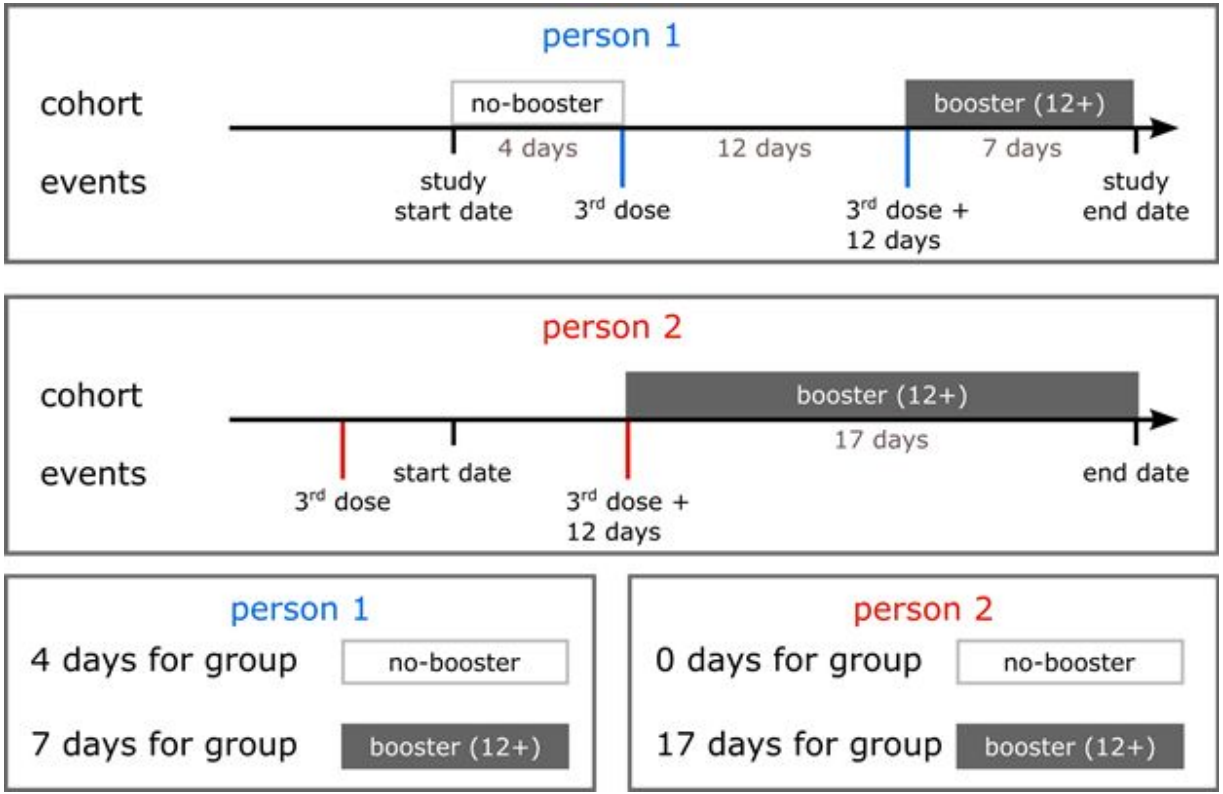


no booster

MINISTRY OF HEALTH

Bar-on et al., https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

Comparison between Booster/No-Booster Dynamic Cohorts



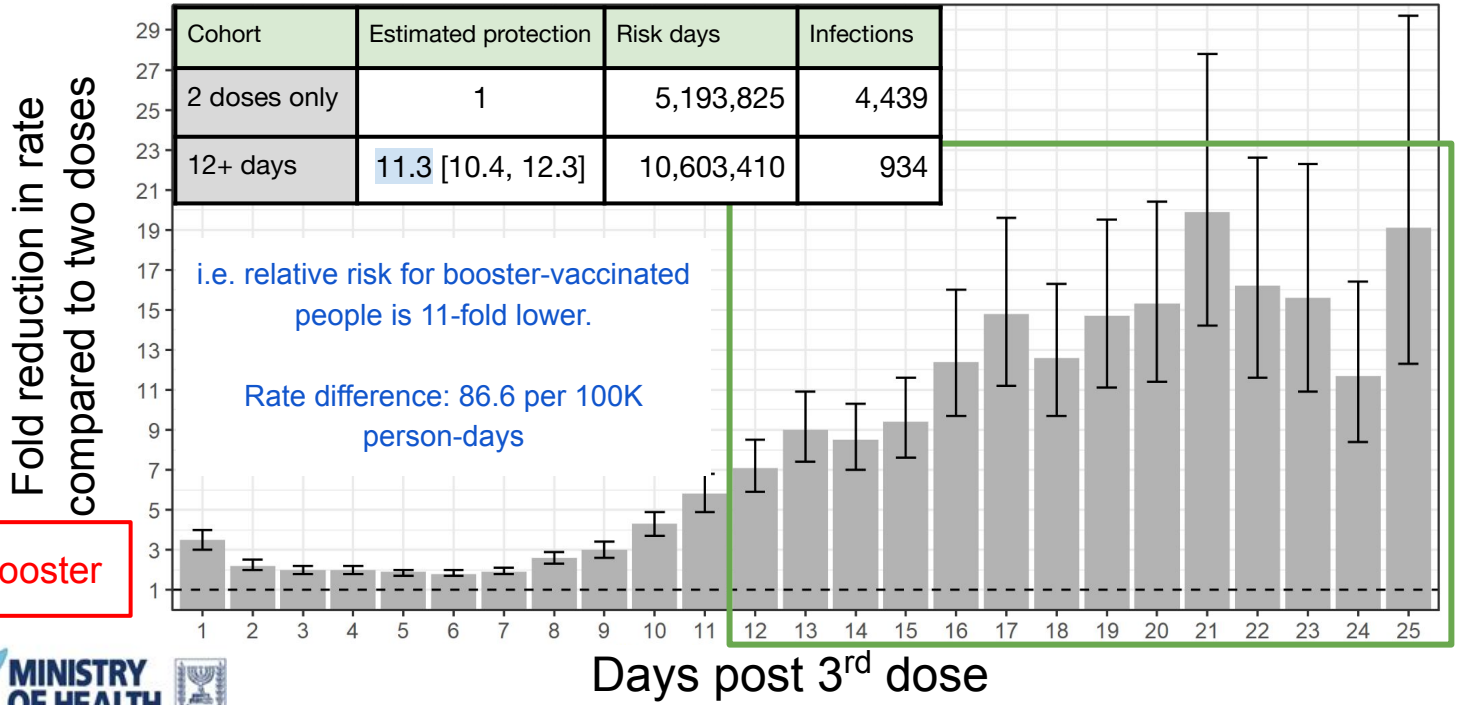
Bar-on et al., https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

MINISTRY OF HEALTH

Relative risk for booster vaccinated is ≈11-fold lower against confirmed infection for ages 60+

Poisson regression adjusted for age, gender, demographic group, 2nd dose period and calendar day.
Based on data from August 10 to August 31

Cohort	Estimated protection	Risk days	Infections
2 doses only	1	5,193,825	4,439
12+ days	11.3 [10.4, 12.3]	10,603,410	934

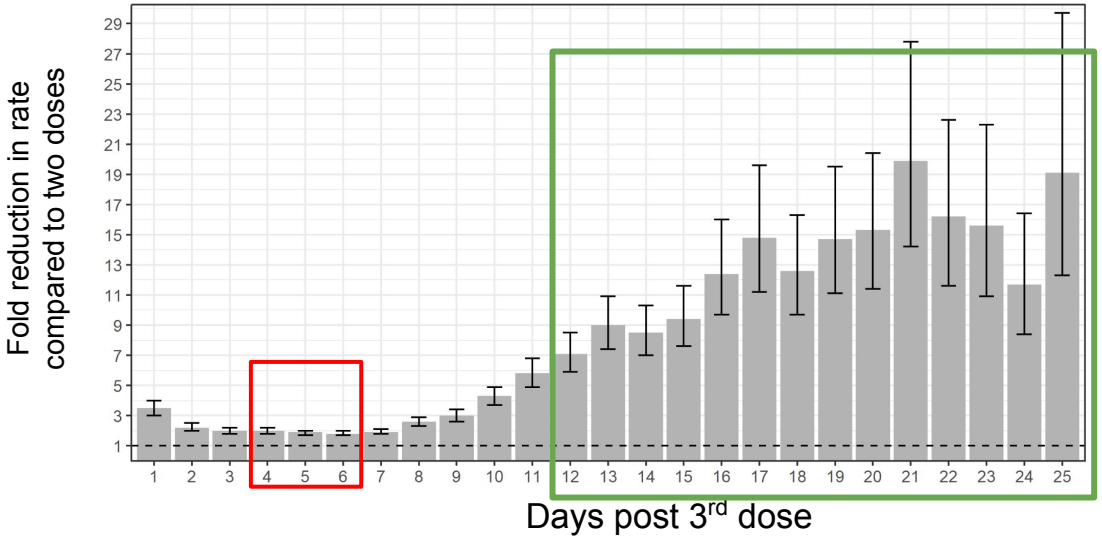


Bar-on et al., https://www.nejm.org/doi/full/10.1056/NEJMoa2114255

MINISTRY OF HEALTH

Results were tested by various methods and show high protection

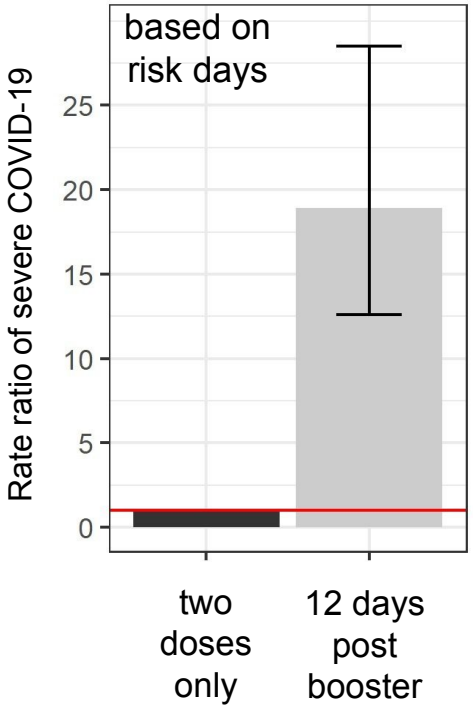
- **Using matching** of booster-vaccinated people with corresponding 2-dose vaccinated individuals (similar to Dagan et al.) → we got **11.6-fold** reduction
- **Comparing 12+ days to 4-6 days** post vaccination (when booster has little effect on confirmed infections) → we got **5.4-fold** reduction



MINISTRY OF HEALTH

Booster provides >10-fold reduction in relative risk of severe disease in 60+ age group

(**Poisson regression** controlling for age, gender, demographic group, 2nd dose period, and calendar day)



absolute rate difference
of 7.5 severe cases
per 100K person-days

MINISTRY OF HEALTH

Vaccine effectiveness (VE) **against delta** after **booster dose** returns to VE levels similar to **recent 2nd dose against alpha**

- If VE after waning is 50% for infection and increases 10-fold it becomes 95%
- If VE after waning is 80% for severe and increases 10-fold it becomes >97%

→ similar to reported values in first few months after 2nd dose
(e.g. Dagan et al., Polack et al.)

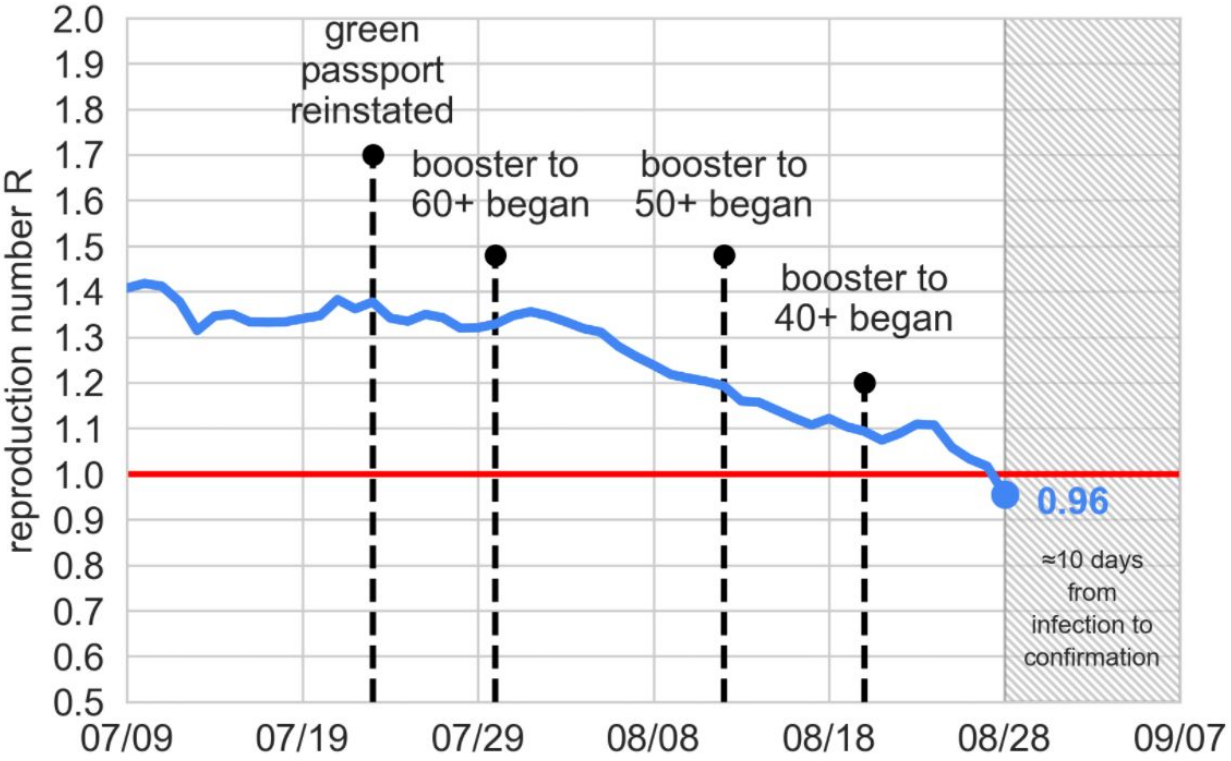
MINISTRY OF HEALTH

The reproduction number was high in the two months prior to decision on booster dose, with fully vaccinated cases rising rapidly

→ doubling every 10 days

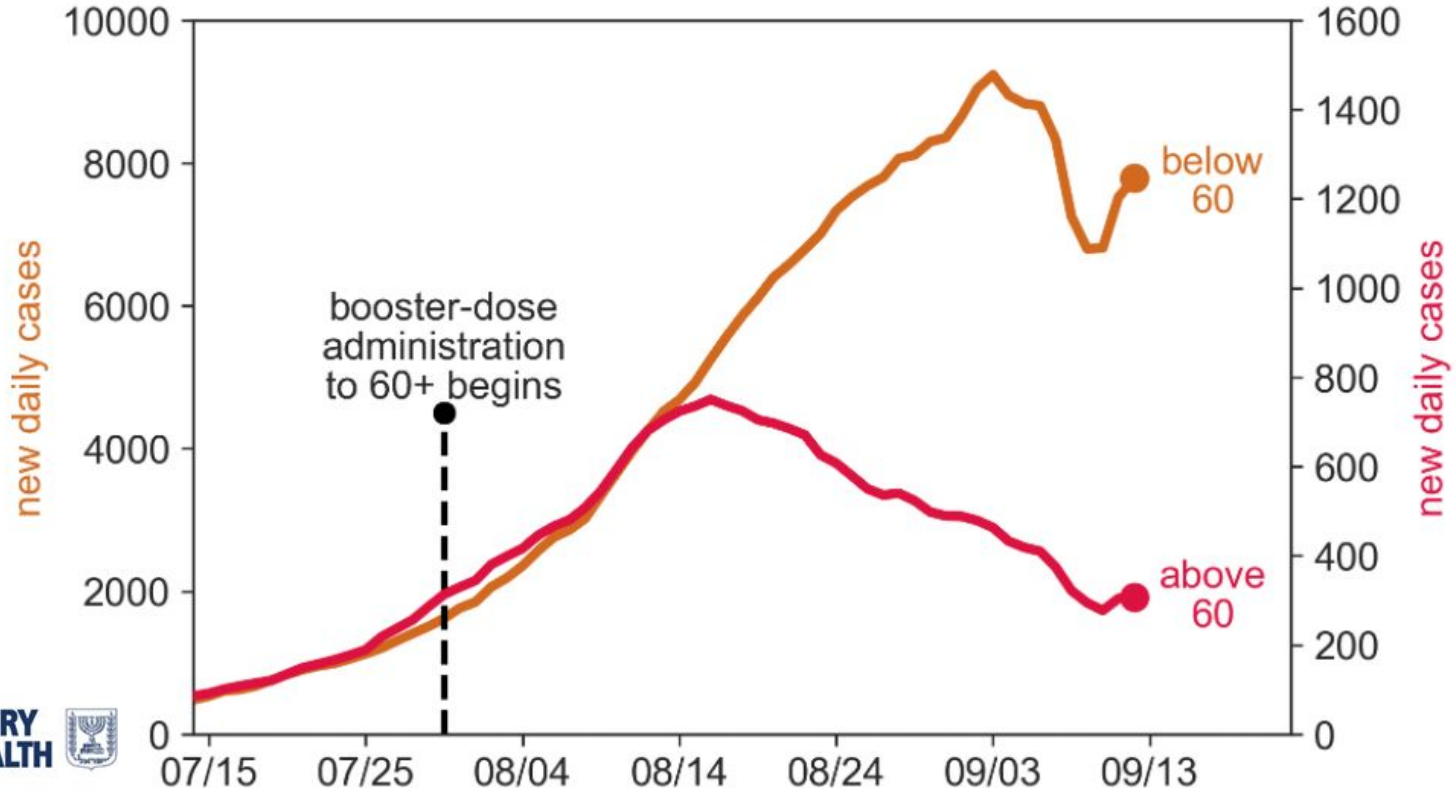
MINISTRY OF HEALTH

The reproduction number started decreasing in sync with the expected timing of the booster effect



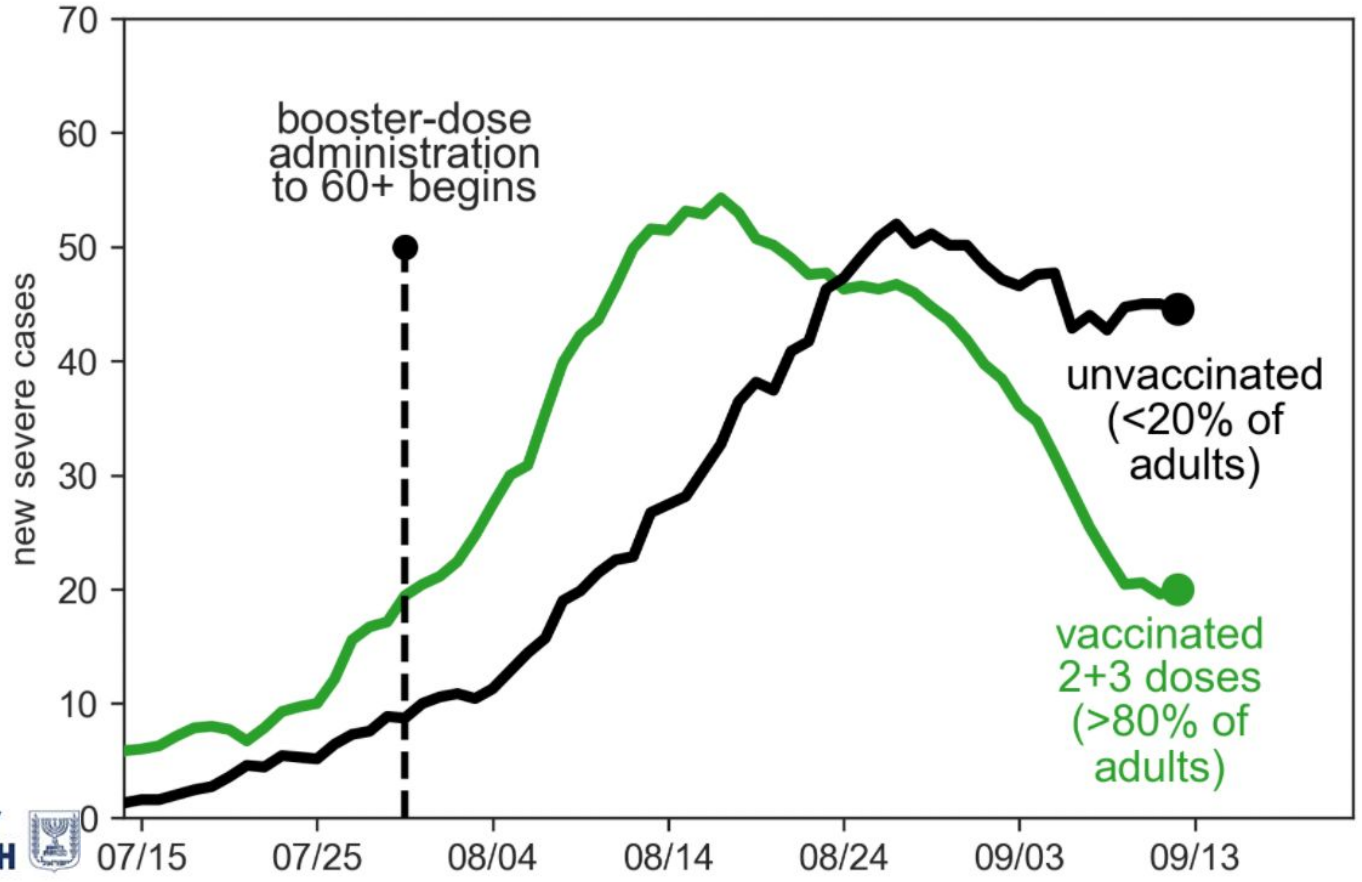
MINISTRY OF HEALTH

Large fraction of the older population received a third dose, leading to a substantial decrease in confirmed infections among people over 60y



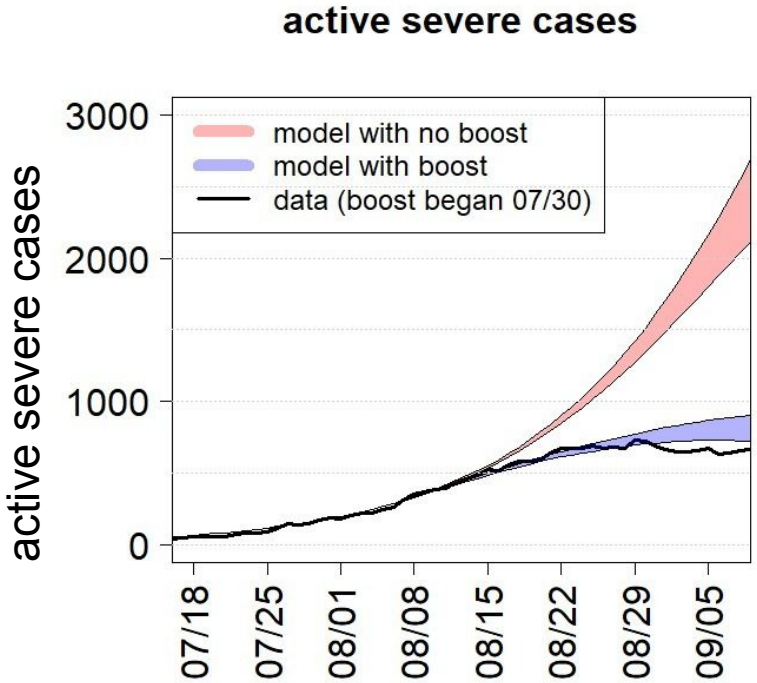
MINISTRY OF HEALTH

Following the third dose, severe cases sharply decreased



MINISTRY OF HEALTH

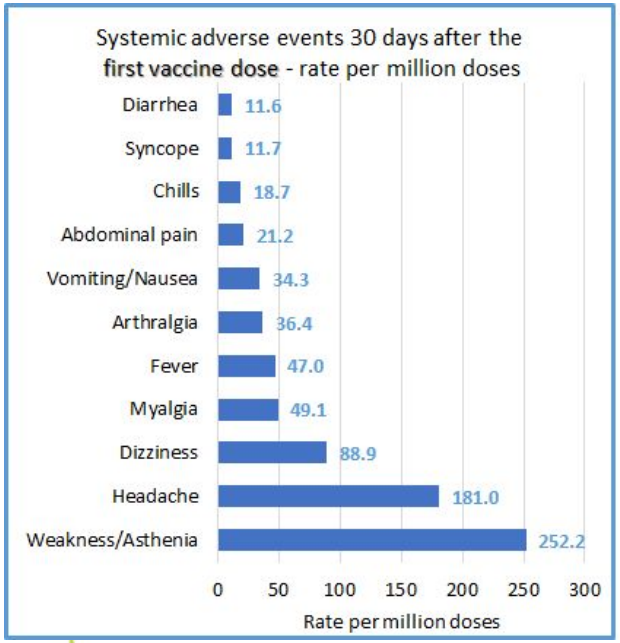
Our model's projections are that without the booster, or if the booster was administered a few weeks later, hospitalization could have significantly exceeded the national capacity



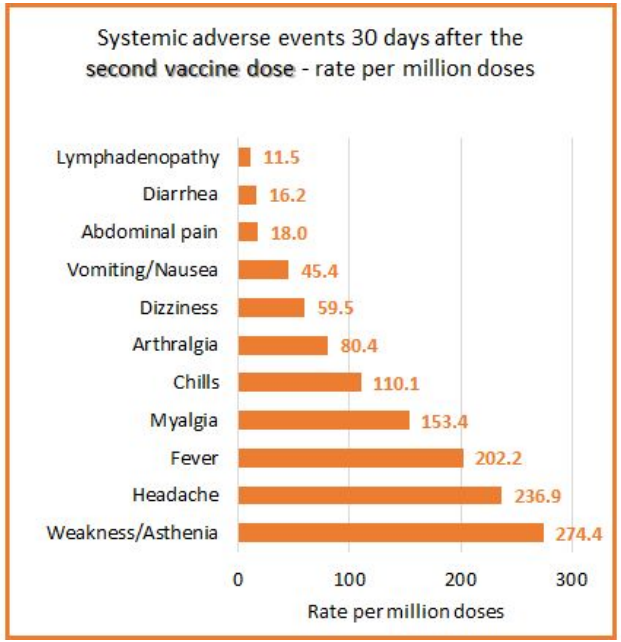
MINISTRY OF HEALTH

Rate of systemic adverse events by dose
(under-reporting expected in all cases)

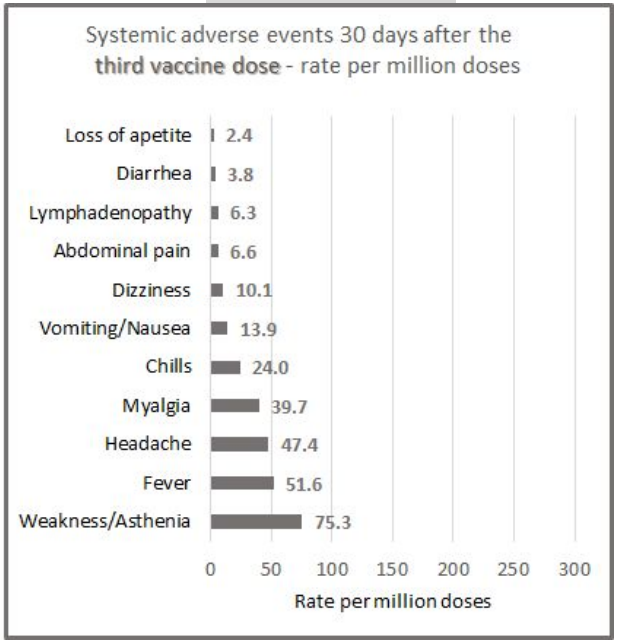
1st dose



2nd dose



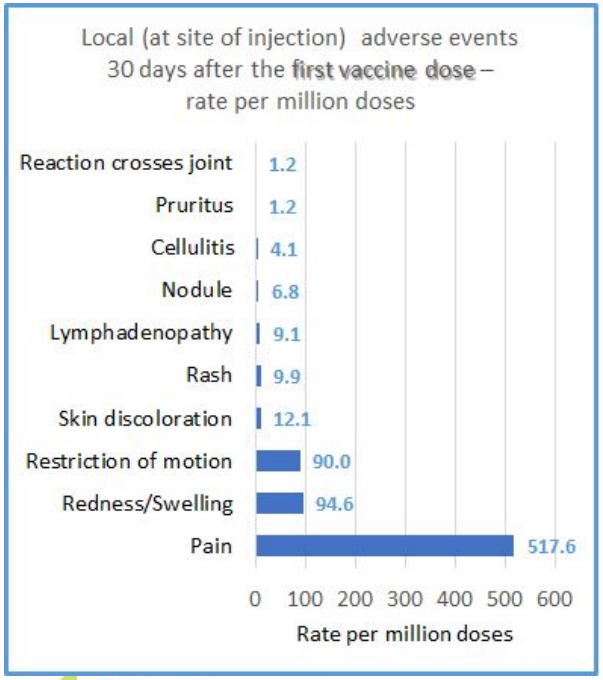
3rd dose



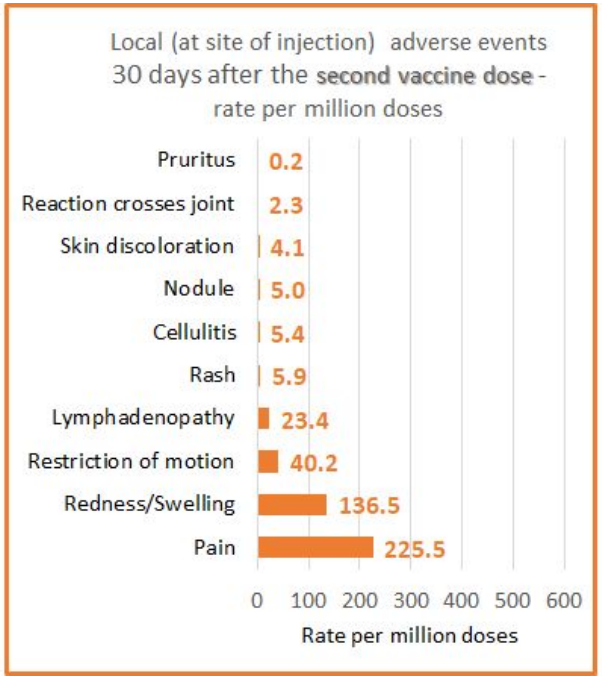
MINISTRY OF HEALTH

Rate of local adverse events by dose
(under-reporting expected in all cases)

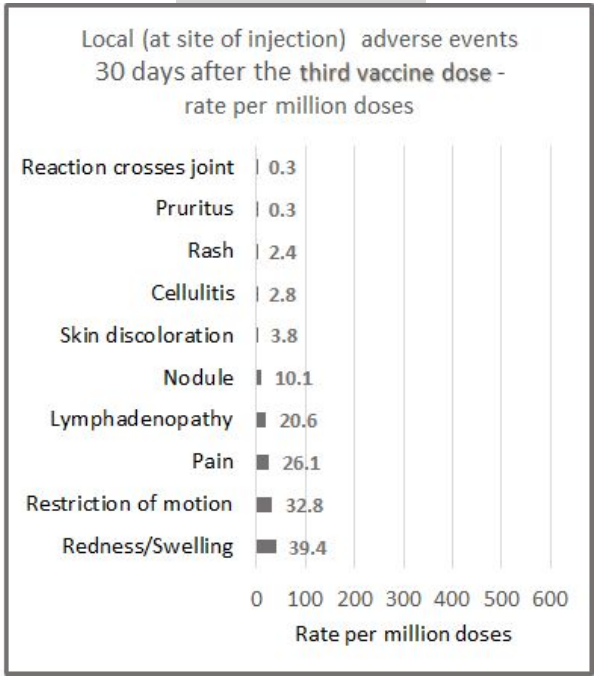
1st dose



2nd dose



3rd dose



MINISTRY OF HEALTH

Summary: Booster dose in Israel was effective and so far had safety profile similar to the other doses

- Waning immunity of the BNT162b2 vaccine after 6 months
- Booster dose shows ≈10 fold improved protection against confirmed infection and severe COVID19
- Administration of booster dose helped Israel dampen severe cases in the 4th wave

MINISTRY OF HEALTH