State of Israel
Ministry of Health
משרד הבריאות

THE HEBREW
UNIVERSITY
OF JERUSALEM

Comparing Booster to 2-Doses Using Quasi-Experimental Designs

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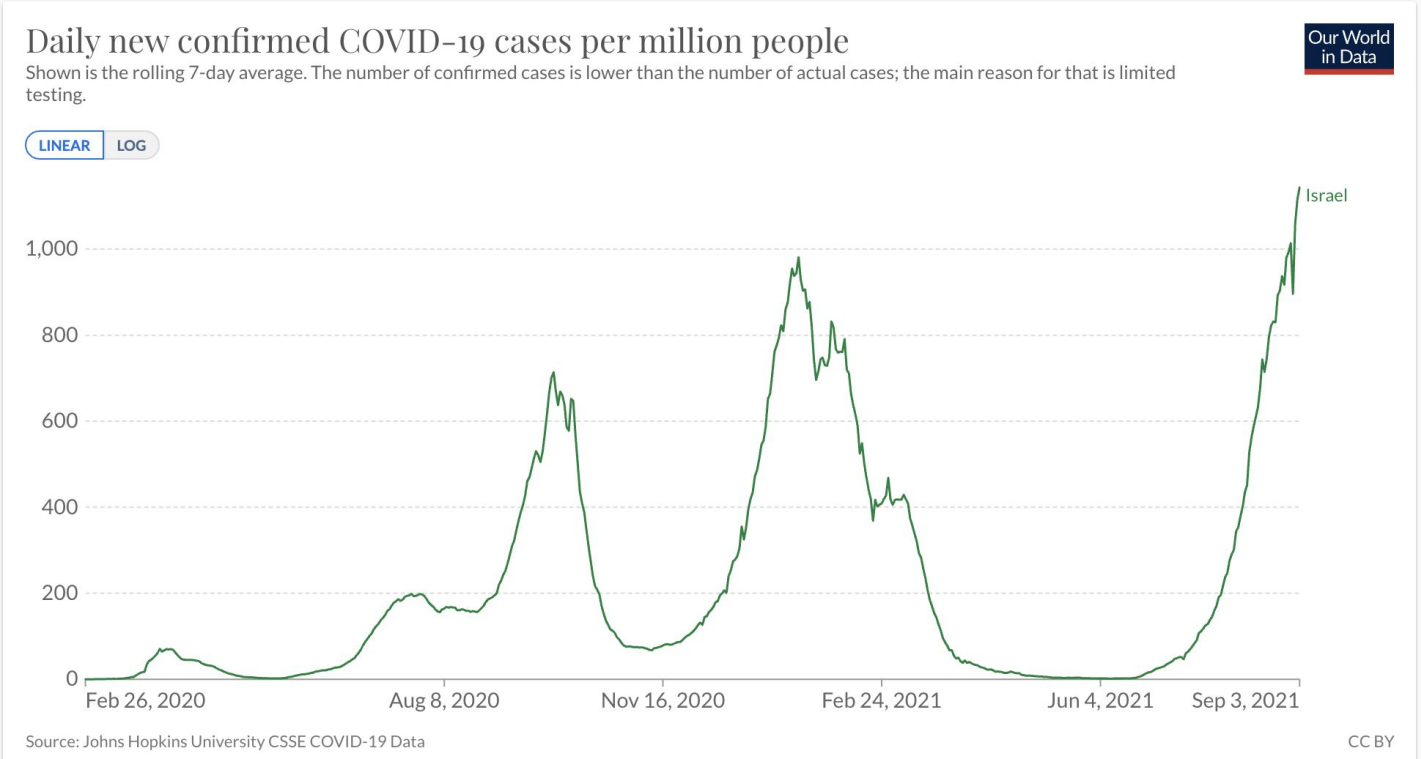
April 11th, 2024

Outline

1. **Analysing the booster dose: Challenges**
2. **Quasi-Experimental Designs**
3. **Comparing 2nd Dose to Booster**

The Delta Wave

During July 2021 Israel experienced its **highest levels of infection** up to that time in spite of **widespread (>60%) 2nd dose** vaccination



The booster dose

Based on

- evidence of vaccination waning immunity
- booster dose given to immunocompromised individuals
- the trajectory towards exceeding national hospitalization capacity

Israel decided to begin a **3rd dose vaccination campaign** on July 30th, 2021, starting with the elderly.

HEALTH AND SCIENCE

Fauci says he wouldn't be surprised if Covid vaccines require three shots for full regimen, instead of two

PUBLISHED THU, SEP 2 2021•3:50 PM EDT | UPDATED FRI, SEP 3 2021•8:41 PM EDT

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Research questions

- Do we need a booster dose?
- Should it be part of the protocol?
- Does a booster dose restore the protection that waned?
- Does a booster dose increase the protection?

Comparing

2nd dose cohort vs booster dose cohort

1. Are the two cohorts similar?
   “Treatment assignment” is not random
2. Individuals move between cohorts
3. **2nd dose** is already waned
4. Vaccine effectiveness was calculated against Alpha

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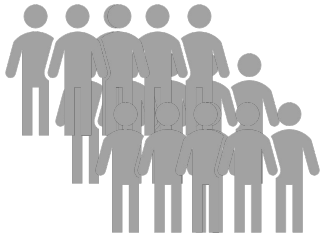
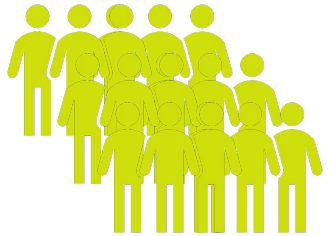
Clinical Trial

2-Doses



Number of incidences
per outcome

Booster



Random assignment - the cohort are similar except the treatment assignment

Population

Differences between cohorts

- socio-economic status
- age
- place of residence
- exposure

Detection differences

- tendency to test
- green passport

Matching

- Use a distance measure for matching each **treatment subject** to the closest **control subject**
- Check for balance between the obtained cohorts
- Perform the analysis on the obtained cohorts

Regression Discontinuity Design

- Getting treatment depends on a threshold
  e.g., vaccination eligibility age 16 and above
- Individuals that are close to either side of the threshold are not very different
- Analyze cohorts of individuals just below and just above thresholds

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MoH Data

- 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
  - 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)

Matching

Waned 2nd dose vs booster

- Match individuals with a **booster dose** with similar individuals who on the same day had only the **2nd dose**
  same age group, sex, place of residence, time of 2nd dose etc.
- Follow-up for both individuals ended
  - at the time of an infection,
  - at the end of the study,
  - or when the nonbooster individual received a booster dose
- Calculate the Kaplan-Meier curve
- Similar to Clalit study - Dagan et al (2021)

Matching

Waned 2nd dose vs booster

Outcome	Age	Poisson Regression [95% CI]	Matching [95% CI]
Confirmed infection	60+	12.3 [11.8, 12.8]	9.5 [7.8, 11.4]
	50-59	12.2 [11.4, 13]	9.4 [5.2, 13.0]
	40-49	9.7 [9.2, 10.3]	8.4 [6.2-10.6]
	30-39	9 [8.4, 9.7]	7.3 [5.7, 8.7]
	16-29	17.2 [15.4, 19.2]	13.3 [5.9, 18.8]
Severe illness	60+	17.9 [15.1, 21.2]	12.4 [4.3, 30.4]

Bar On, et al. (2022). https://www.nejm.org/doi/full/10.1056/NEJMoa2115926

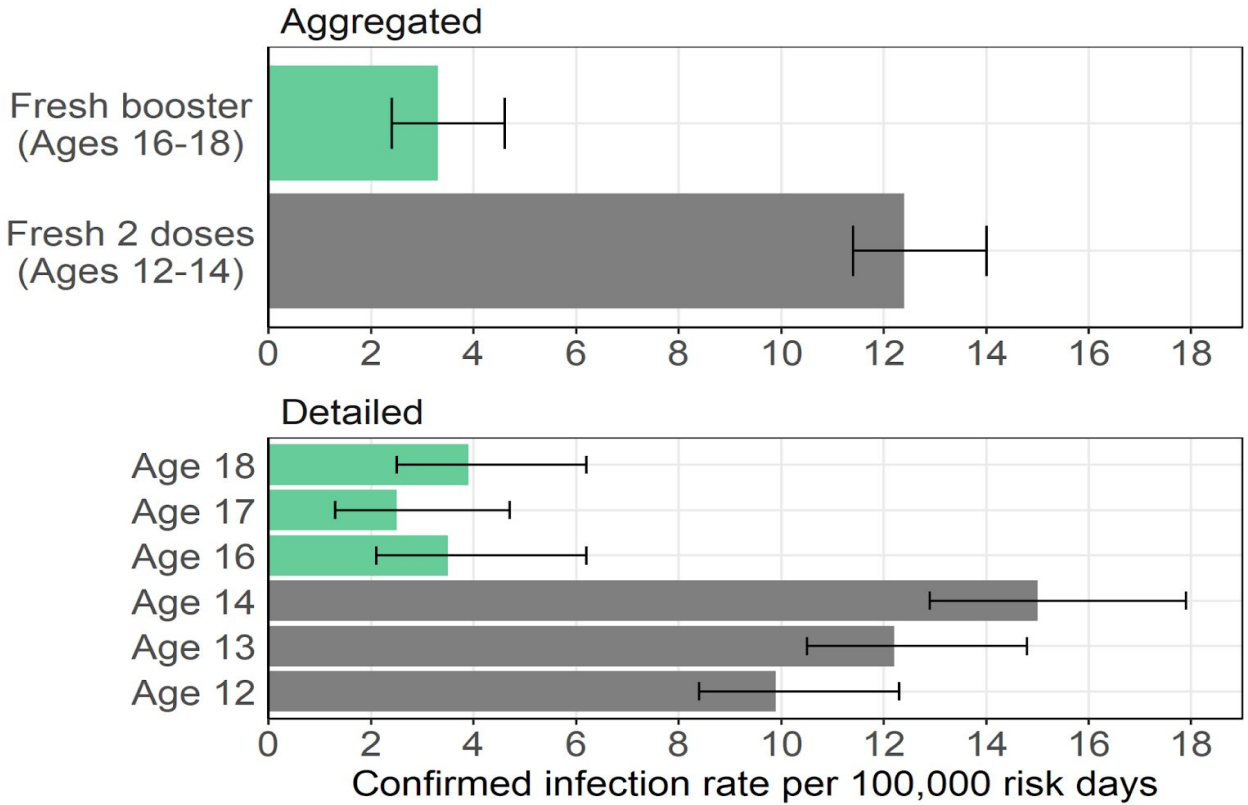
Regression discontinuity design

Fresh 2nd dose vs booster

- Comparing a **fresh booster dose** to a **fresh 2nd dose** is difficult
- Most individuals were already doubly-vaccinated by August 2021
- Those who got a 2nd dose during July - August 2021 had different characteristics
- No natural control (**fresh 2nd dose**) group
- Vaccination campaign for ages 12-15 started on June 2021

Regression discontinuity design

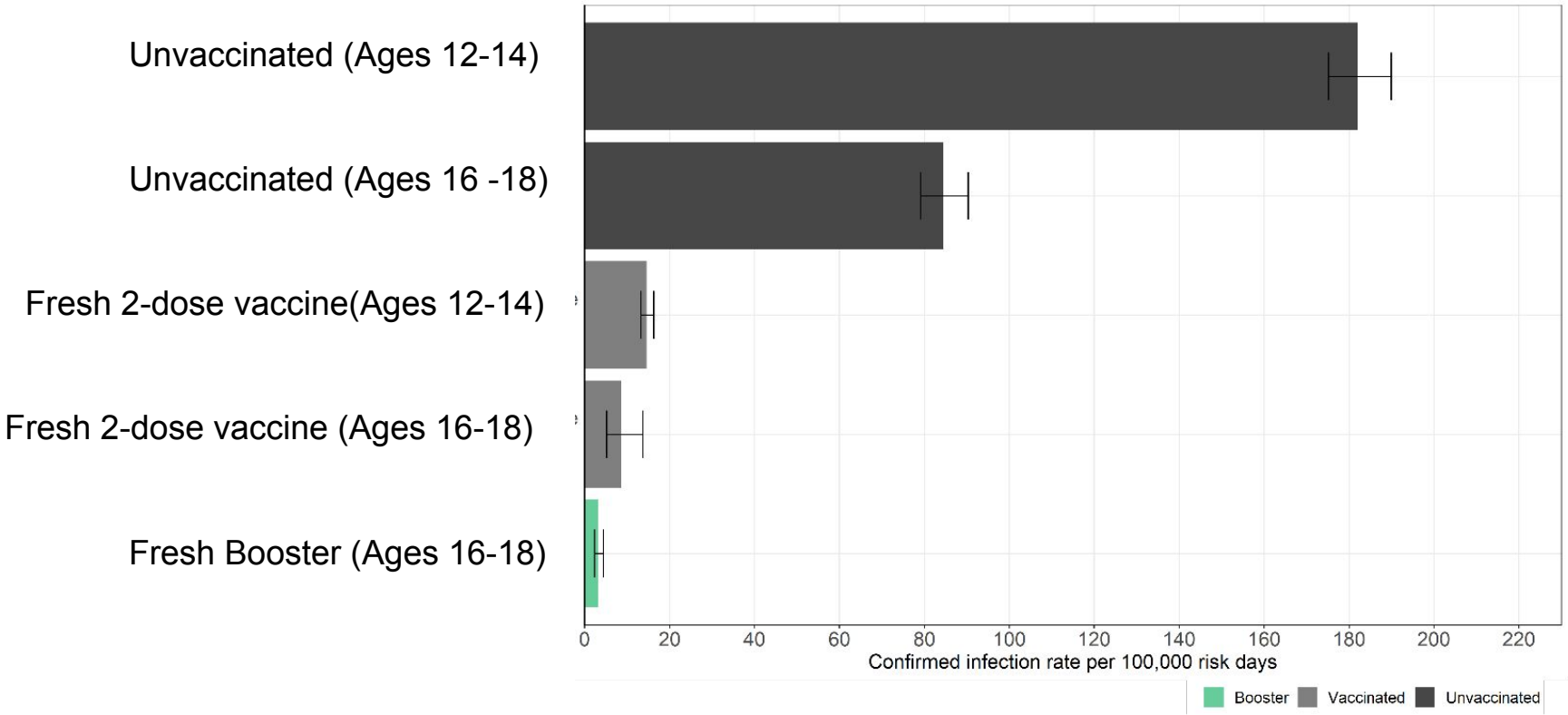
Fresh 2nd dose vs booster



Amir, et al. (2022). https://www.nature.com/articles/s41467-022-29578-w

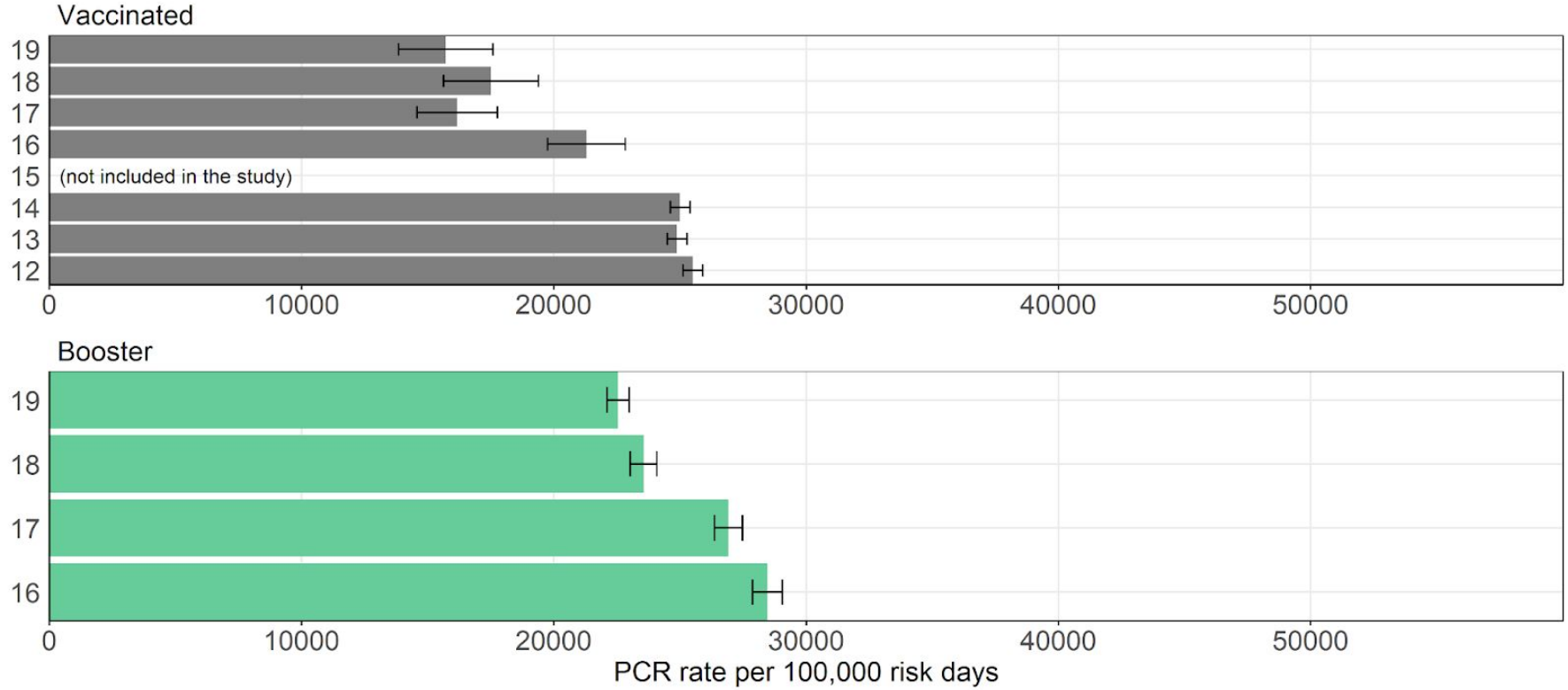
Regression discontinuity design

Sensitivity analysis - compare to other groups



Regression discontinuity design

Sensitivity analysis - PCR tests



Summary

- Quasi-experimental designs are a powerful statistical tool. We discussed
  - Matching
  - Regression discontinuity design
- Two case studies
  - Booster vs 2nd dose (using matching)
  - Booster vs fresh 2nd dose (using regression discontinuity design)

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