

# ADVERSE HEALTH EVENTS AND VACCINE HESITANCY

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# Motivation

## **Adverse health events are associated with two main types of costs**

- **Direct:** Costs of medical treatment and illness
- **Indirect:** Lower demand for treatment against infectious diseases  $\Rightarrow$  higher disease burden

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## **Indirect costs depend on how broadly experiences are generalized**

- Experience of an adverse event from a drug may spill over to decisions
  1. on the same drug
  2. on other drugs
  3. on other medical treatments

# This Paper

**Research Question:** How do experiences with adverse health events affect vaccine hesitancy?

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**We study impact on COVID-19 vaccination from:**

- A particularly severe adverse event (narcolepsy from the swine flu vaccine)
  - ↪ Testbed for *how* experiences are used for (health) decisions
- Recurring and representative adverse events
  - ↪ Assess social costs of weakened immunization outcomes that arise from behavioral responses

# Preview of Findings

- **Severe adverse vaccine events have long-lasting effects on vaccination decisions**
  - ↑ perceived **common** risk of vaccines
- **...but generalization is narrow**
  - Strong responses **within same vaccine/brand**; small effects from other drugs on vaccination and from vaccine events on other medical decisions
- **Effects also among high-health-literacy individuals individuals and established vaccines**
  - Evidence of experiences crowding out statistics

# Literature

- **Experience-based decision making**

(Bordalo, Burro, et al., [2024](#); Bordalo, Gennaioli, and Shleifer, [2022](#); Graeber, Roth, and Zimmermann, [2024](#); Laudenbach, Malmendier, and Niessen-Ruenzi, [2019](#); Malmendier, [2021](#); Tversky, [1977](#))

⇒ Document how experiences are used for health decisions that affect others

- **Medical malpractice and healthcare demand**

(Alsan and Wanamaker, [2017](#); Archibong and Annan, [2023](#); Lowes and Montero, [2021](#); Martinez-Bravo and Stegmann, [2021](#))

⇒ Move from rare scandals to recurring adverse events relevant for health policy

# Agenda

- Background
- Conceptual Framework for Immunization Decisions
- Method
- Results – Evidence from
  - Swine flu-induced narcolepsy
  - Recurring and representative adverse events
  - Spillovers to well-established vaccines
- Discussion

# Background

## *The Narcolepsy Scandal*

- During the 2009–2010 Swine flu pandemic, Sweden underwent a mass vaccination program. More than 60% of the Swedish population vaccinated with **Pandemrix**
- Pandemrix turned out to be associated with **Narcolepsy**, an incurable disease associated with **excessive daytime sleepiness and sudden muscle weakness**
- Estimated that 150–200 ( $\approx 1/20,000$ ) individuals developed narcolepsy. Primarily young individuals affected [Details](#)
- 400 individuals claimed reimbursement for Pandemrix-induced narcolepsy

[Saliency in Media & Google Searches](#)

# Background

## *Pathogenetic mechanisms*

- Current scientific consensus that **Pandemrix triggered narcolepsy** (Edwards et al., 2019; Persson et al., 2014)
- Virtually nothing known about pathogenetic mechanisms of Pandemrix-induced narcolepsy nor narcolepsy in general
- No evidence of elevated risk of developing other severe diseases
- No evidence narcolepsy serves as contraindication for COVID-19 vaccine; no general recommendation against taking the vaccine

# Conceptual Framework

- Decision maker weights perceived benefits against perceived costs; vaccinate if:

$$\hat{\pi}^B B \geq \hat{\pi}^C C \quad (1)$$

- Primary focus on  $\hat{\pi}^C$ , the perceived **risk of adverse events from a medical drug**.

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- Primary focus on  $\hat{\pi}^C$ , the perceived **risk of adverse events from a medical drug**.
- $\hat{\pi}$  combines best available knowledge,  $\pi$ , and experience-based estimate,  $\hat{\pi}_E$ .

$$\hat{\pi} = (1 - \theta)\pi + \theta\hat{\pi}_E \quad (2)$$

- $\theta$  measures cost of acquiring information about true risk (Health illiteracy)

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- Let  $S(e, T) \equiv S(e)$  denote the **similarity** between experience  $e$  and experiencing adverse event from COVID-19 vaccine,  $T$
- Two key drivers of  $\hat{\pi}_E$ : recall  $r(e) \in [0, 1]$  and simulation  $\sigma(e) \in [0, 1]$ .
  - Probability of **recall** increasing in similarity but decreasing in the number, and similarity, of other experiences.

$$r(e) = \frac{S(e)}{\sum_{u \in E} S(u)} \quad (3)$$

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- Ability to **simulate**  $T$  also increasing in similarity

$$\sigma(e) \geq \sigma(u) \Leftrightarrow S(e) \geq S(u) \quad (4)$$

# Conceptual Framework

Recall-weighted average simulation of "adverse event from COVID-19 vaccine" given by

$$\hat{\pi}_E = \sum_{e \in E} r(e)\sigma(e) = \frac{\sum_{e \in E} \sigma(e)S(e)}{\sum_{u \in E} S(u)} \quad (5)$$

⇒ Trade-off between interference and simulation implies that only sufficiently similar experiences will boost  $\hat{\pi}_E$

# Four Predictions

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3. Suppose adding  $e$  and  $e'$  to  $E$  increases  $\hat{\pi}_E$ . Then,  $e$  **boosts  $\hat{\pi}_E$  more than  $e'$  if and only if  $S(e) > S(e')$** 
  - Adverse event from influenza vaccine will boost  $\hat{\pi}_E$  more than experiencing heart attack

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  - Adverse event from influenza vaccine will boost  $\hat{\pi}_E$  more than experiencing heart attack
4. **Other experiences interfere** with the ability of recalling  $e$ .
  - Individuals with more healthcare experiences (larger database  $E$ ) react less to adding experience  $e$

# Health Data

## **Adverse Events** (Medical Products Agency)

- Universe of reported suspected adverse events from spontaneous reporting system 2005–2022

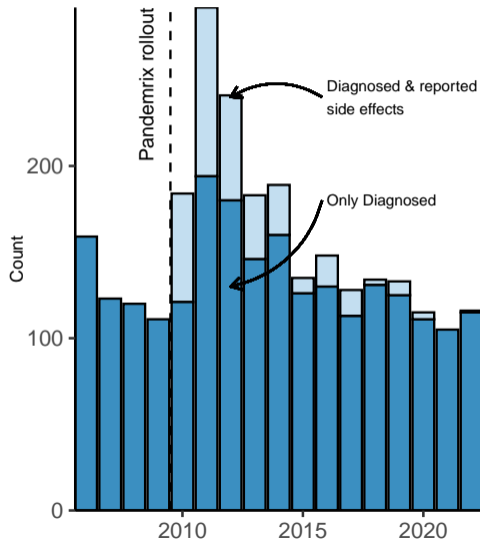
## **Diagnoses and Drugs** (National Board of Health and Welfare)

- All specialist care visits and all drug prescriptions 2005–2022

## **Vaccines** (Public Health Authority & Regional Healthcare Authorities)

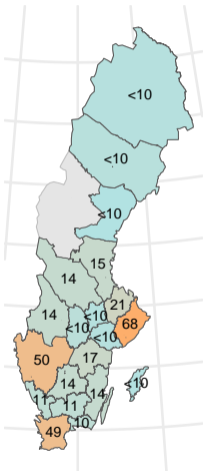
- COVID-19 vaccines: vaccine brands, timing
- Child vaccines: Measles vaccinations, etc. 2013–2024.
- 16% of **Pandemrix vaccinations** (10% of Swedish population)

# Rising Narcolepsy Cases After Pandemrix Vaccination Campaign



- Reported link between narcolepsy and Pandemrix in Summer 2010
- Increased incidence of narcolepsy following years
- Increase among non-reporters. Likely under-diagnosis before swine flu.

# Sample Definition: Treatment Group



## Treatment group

**385** individuals who

- i)* Reported narcolepsy as an adverse event from Pandemrix
- ii)* Were first diagnosed with narcolepsy **after** swine flu pandemic

# Sample Definition: Placebo Control



## Pre swine flu-narcolepsy

**847** individuals diagnosed with narcolepsy **before** the swine flu pandemic

## Sample Definition: Control



### **Pandemrix**

**1M** Individuals who received Pandemrix but did not develop narcolepsy

# Empirical Strategy

## **Two key Challenges**

- Bridging effect of reported vs. actual adverse events
- Separating the direct effect of adverse events on hesitancy from the mediated effect through having narcolepsy

# Empirical Strategy

*Bridging effects of reported vs. actual adverse events*

**Goal:** Estimate effect of **developing** AE ( $\Delta_{AE}$ ).

Can use observed difference between reporters and non-reporters

$$\Delta_R = E[Y(\cdot, 1) \mid \text{Reported} = 1, X] - E[Y(\cdot, 0) \mid \text{Reported} = 0, X]$$

as a proxy for

$$\Delta_{AE} = E[Y(1, \cdot) \mid \text{AE} = 1, X] - E[Y(0, \cdot) \mid \text{AE} = 0, X]$$

Under three assumptions:

1. **Random reporting among developers**
2. **Equivalence of reported & unreported (Source irrelevance)**
3. **Rarity of adverse events (Developers do not dilute control group)**

# Empirical Strategy

## *DiD estimator*

**Goal:** Isolating the direct effect of adverse events on hesitancy from mediation through narcolepsy.

**Total effect = Hesitancy effect + Narcolepsy effect**

$$\tau_{post} = \mathbb{E} [Y_{ith} | h = \text{Narc. post}, t = \text{Pandemrix}] - \mathbb{E} [Y_{ith} | h = \text{No narc.}, t = \text{Pandemrix}]$$

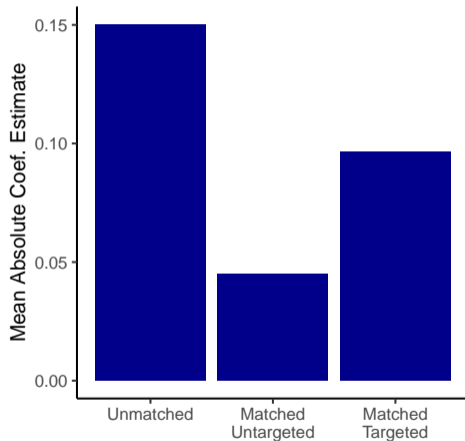
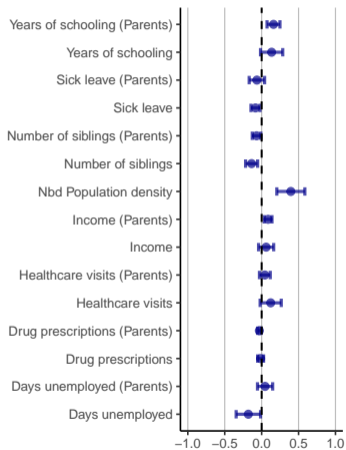
**Narcolepsy effect**

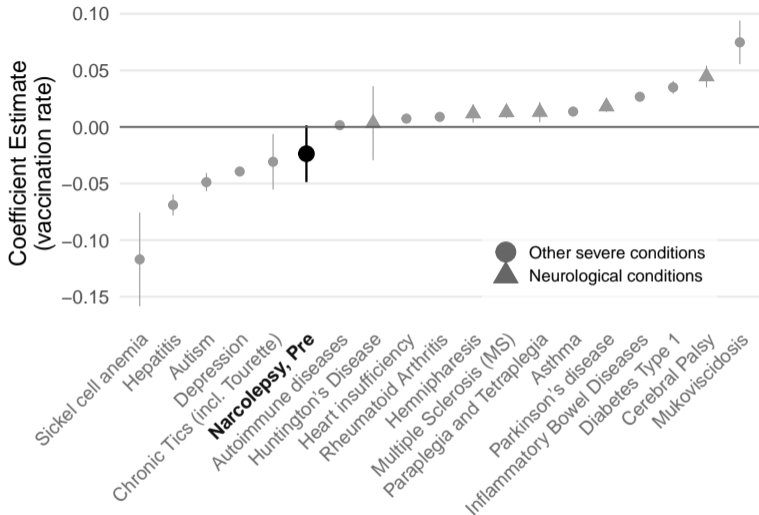
$$\tau_{pre} = \mathbb{E} [Y_{ith} | h = \text{Narc. pre}] - \mathbb{E} [Y_{ith} | h = \text{No narc.}]$$

**Hesitancy effect of exposure to Pandemrix-induced narcolepsy**

$$\tau_{dd} = \tau_{post} - \tau_{pre}$$

# Balance

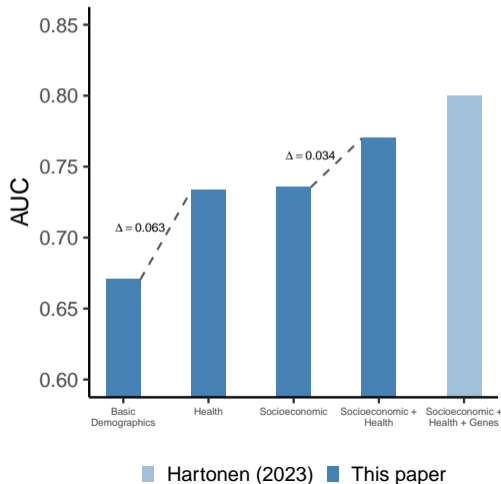




- No evidence individuals with narcolepsy "should" not take the COVID-19 vaccine

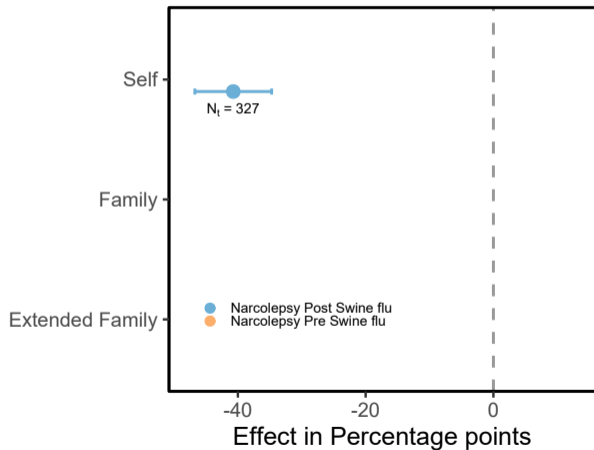
# Quantifying the Aggregate Role of Healthcare Experiences

*Predicting who takes the COVID-19 vaccine*



- Health and socioeconomic equally important (AUC = 0.73)
  - Near best available prediction (AUC = 0.8, Hartonen et al. 2023)
- ↪ Descriptive evidence that experiences matters

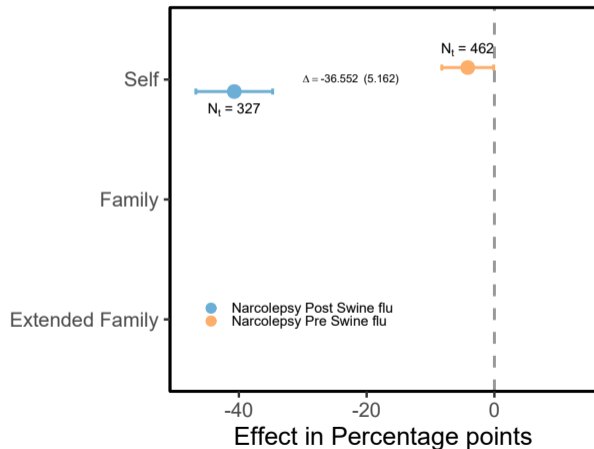
# Costs of Vaccination $\Rightarrow$ Worsened Immunization



**Outcome:** COVID-19 Vaccine Taken (1/0)

- Narcolepsy  $\Rightarrow$  40 pp lower take up of COVID-19 vaccine.

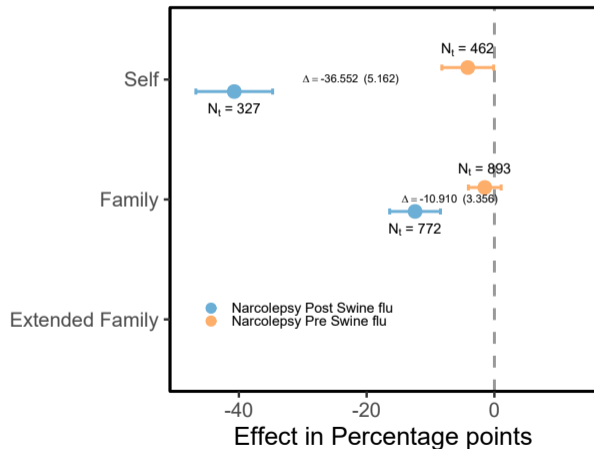
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- $\hookrightarrow$  36 pp lower bound of hesitancy effect

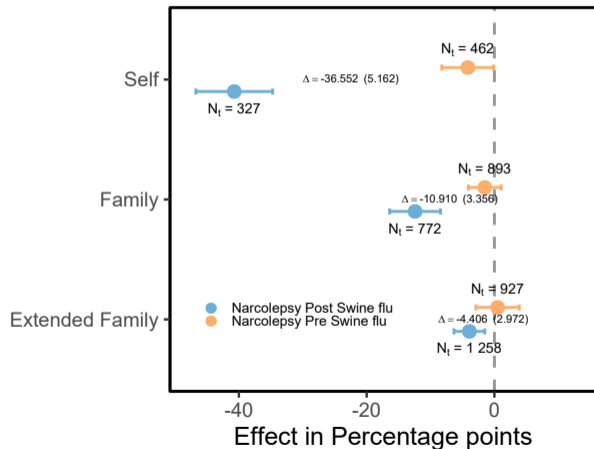
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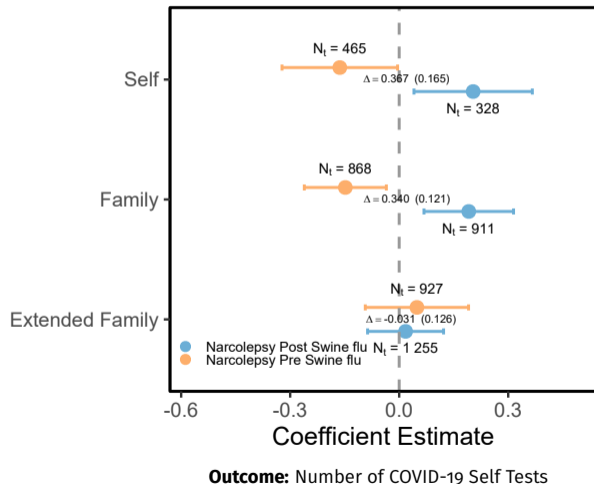


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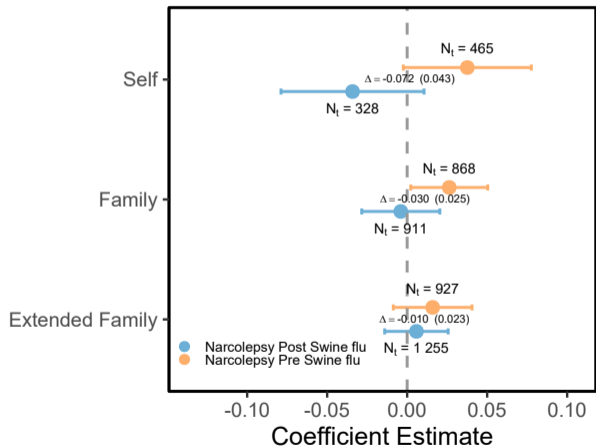
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- 4pp among extended family members

# Results are not Explained by Lower Perceived Benefits

- Treated individuals take **more** self tests



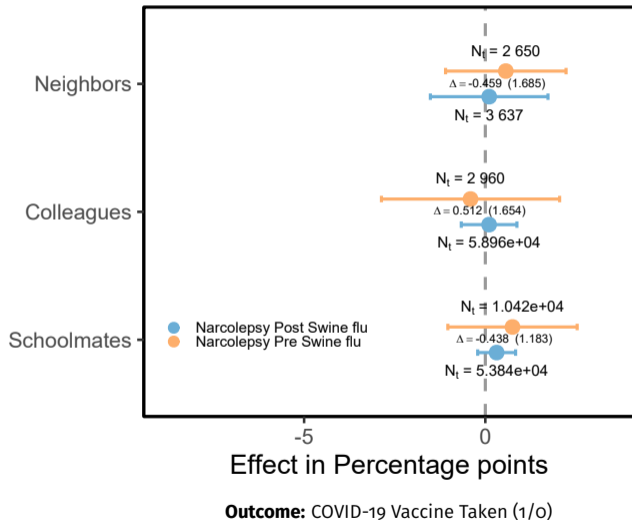
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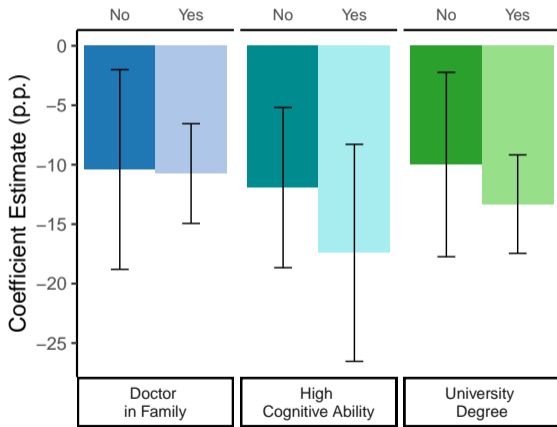
**Outcome:** Phone calls for Medical Advice

- Treated individuals take **more** self tests
  - No difference in COVID-19 related phone calls for medical advice
- ↪ Perceived benefits unlikely to have been altered

# No Spillovers to Broader Networks



# No Importance of Health Literacy



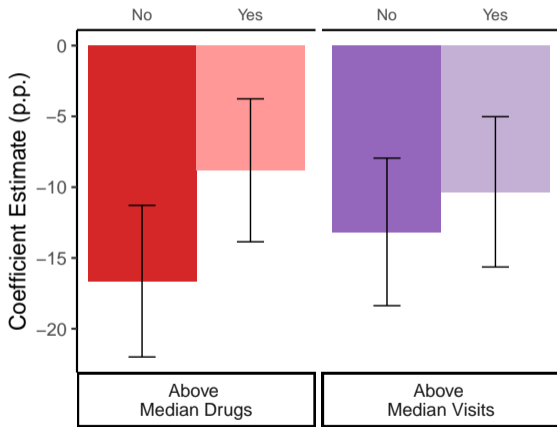
**Outcome:** COVID-19 Vaccine Taken (1/0) among family members

- **Two opposing forces:**

- high health literacy → better assessment of  $\pi$
- Negative experiences crowd out information

↪ No support of either;  
Individuals with high literacy  
also affected.

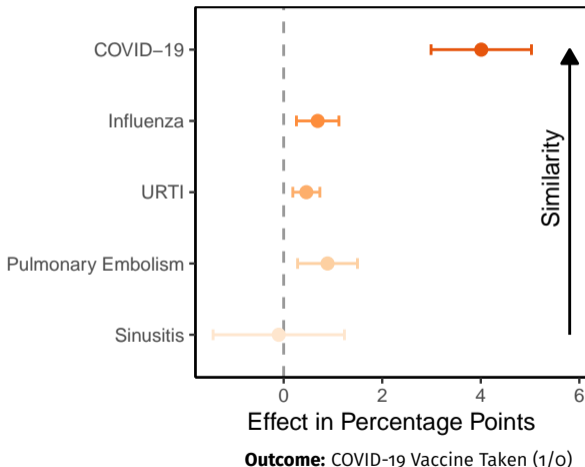
# Modest Importance of Database Size



**Outcome:** COVID-19 Vaccine Taken (1/0) among family members

- $\geq 6$  (Median), in five years before narc.  $\Rightarrow$  Smaller Effects
  - Visits ( $\geq 0.6$ /year) has no impact
- $\hookrightarrow$  Similar experiences with drugs cause interference

# Experiencing Benefits of Vaccination $\Rightarrow$ Improved Immunization



- Exposure to vaccine preventable diseases  $\Rightarrow$  **Higher** uptake of COVID-19 vaccine.
- Smaller effects for vaccine-preventable, seasonal diseases
- Little/No effects for non-vaccine-preventable diseases

# What we Learned so far

- Large effects for close family members (**Prediction 1**)
  - ↳ Increased perceived risk of rather than decreased benefits of vaccines
- No larger effects for less educated individuals (**Prediction 2**)
  - ↳ No differential cost of acquiring information
- Small/no effects for more distant network members
  - ↳ Exposure intensity matters(!)
- Symmetric effects of shock to benefits, effect size increasing in similarity between experience and simulated outcome (**Prediction 3**)
  - ↳ Effects largest for COVID-19 and Influenza
- Modest heterogeneity by previous experiences (**Prediction 4**)
  - ↳ Highlights importance of interference.

## Additional Results/Robustness

- No generalization to healthcare visits
  - Healthcare visits across time [Results](#)
- Some evidence of individuals reasoning as if learning about their predisposition
  - Partners [Results](#)
  - Narcolepsy long after 2010 [Results](#)
- Magnitude of costs  $C$  matters
  - Mild adverse events from swine flu vaccine [Results](#)
- No evidence of other behavioral stories
  - Heterogeneity by gender & age (Social Learning) [Results](#)

# General Adverse Events

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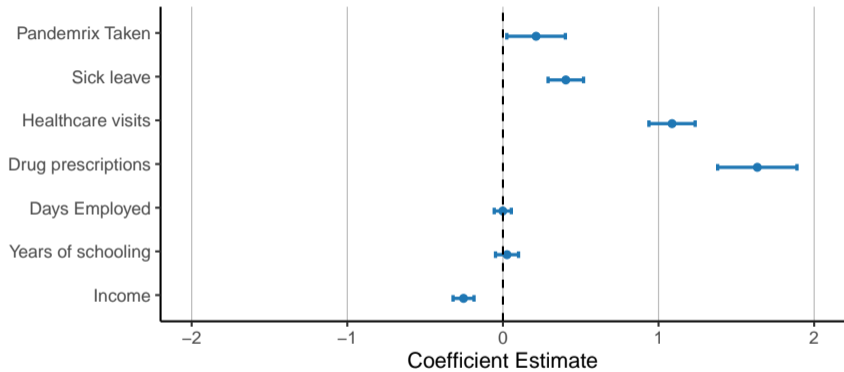
## Data

- Focus on adverse events that are **severe** and **reported by healthcare professionals**
- Broadly representative of commonly recurring adverse events.

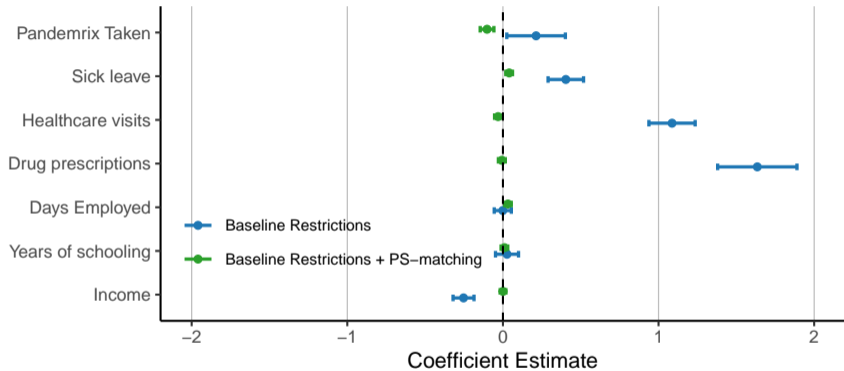
## Method

- Find comparable individuals based on **health history** and **socioeconomic characteristics**
- Match 1:1 on propensity scores within birth year  $\times$  drug year  $\times$  drug-cells

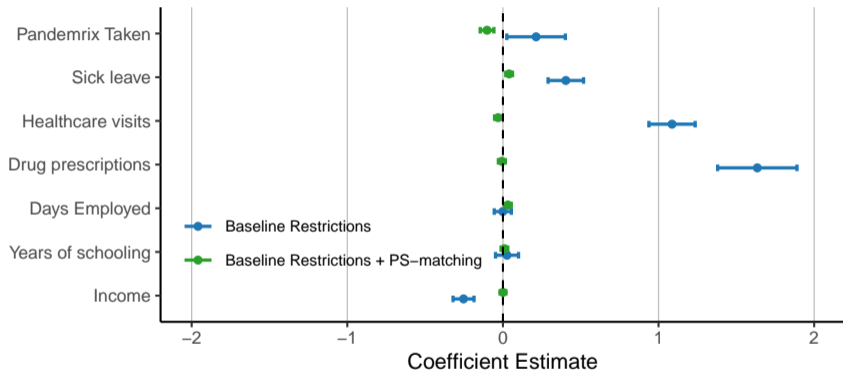
# Balance



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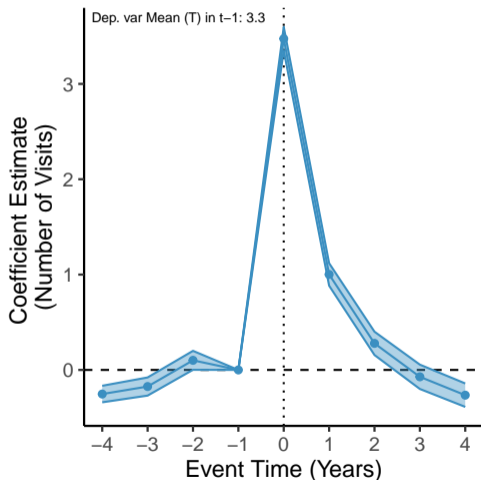


# Balance



- Individuals with severe adverse events differ in health but not in socioeconomic characteristics. (Opposite holds true for mild adverse events)

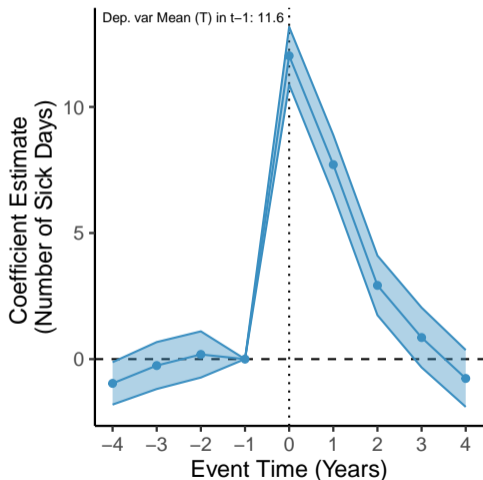
# Adverse Events Have Negative Effects on Health



## Event-year impact

- **Specialized Healthcare Visits: +3**

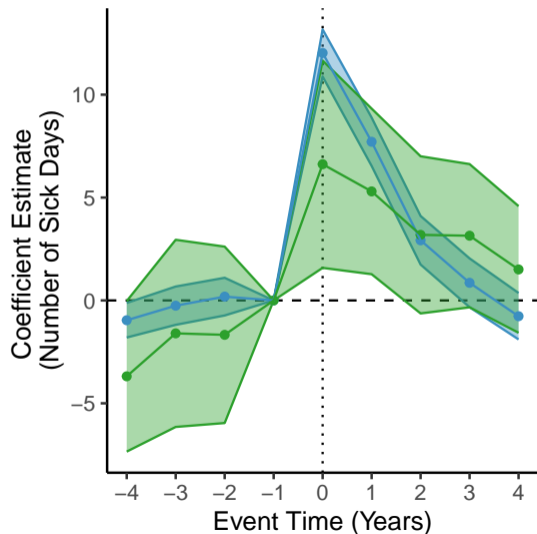
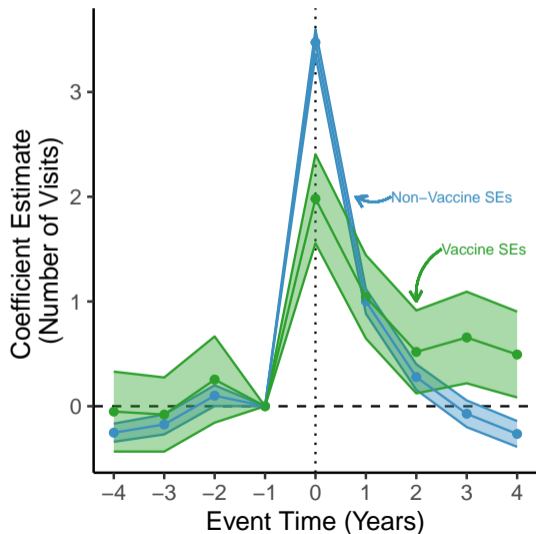
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## Event-year impact

- **Specialized Healthcare Visits: +3**
- **Sick days: +12**

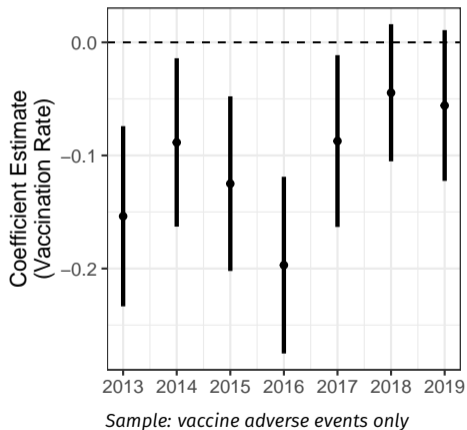
# Vaccine SEs and non-vaccine SEs are Equally Severe



# Results

	Non-vaccine Adverse Events			Vaccine Adverse Events		
	Vaccine Taken	Number of Doses	Days Elapsed	Vaccine Taken	Number of Doses	Days Elapsed
<b>Diseased Individuals</b>						
adverse event	-0.017 (0.003)	-0.051 (0.011)	-1.32 (0.62)	-0.11 (0.013)	-0.075 (0.043)	14.0 (2.99)
N. Treated	15 294	13 974	13 974	849	686	686
<b>Family Members</b>						
adverse event	-0.003 (0.003)	0.031 (0.010)	0.48 (0.42)	-0.059 (0.013)	-0.13 (0.039)	7.88 (1.91)
N. Treated	34 018	31 445	31 445	2 048	1 771	1 771

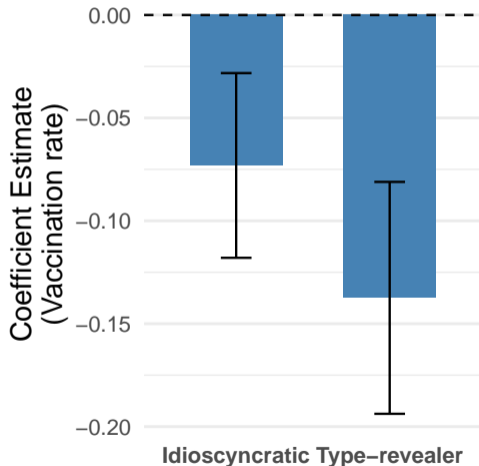
# Experiences are Sticky



## Key Findings

- Effect size does not fade for more distant adverse events
  - Results Robust to reweighting by age and drug
- ↪ Implies experiences have **persistent influence** on vaccination

# Learning About Predisposition



## Evidence for belief updating

- **Idiosyncratic adverse events:** weak signals  $\Rightarrow$  little updating
  - **Type-revealer adverse events:** stronger signals  $\Rightarrow$  sharper belief updating
- $\hookrightarrow$  Individuals act on signals that reveal predisposition

# Taking Stock—General Adverse Events

## Main Finding:

- Overall, adverse events **do not** reduce future vaccine take-up in a meaningful way.

## Additional Insights:

- Larger effects for vaccine adverse events compared to other drugs
  - ⇒ **Similarity** (not severity) matters.
- No smaller effect for experiences long time ago.
  - ⇒ Memories are **sticky**.
- Larger effects for adverse events that are "Type-revealing"
  - ⇒ Individuals **update beliefs rationally** in that they put more weight on experiences that matter for true risk.

## Deteriorated Trust: Evidence from Children's Vaccines

# Spillover to Children's Vaccines

- Consider effects on vaccines part of the child vaccination program from 2013 and onwards
  - These are **well-established** and severe adverse events are known to be **very rare**
- ⇒ Information about risk of adverse event is easily accessible. In turn, we interpret changes in immunization outcomes as evidence of decreased trust (shift in  $\theta$ )

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- Focus on:
    - **Diphtheria** Three doses given within first year.
    - **Pneumococcus** Three doses given within first year.
    - **Measles** First dose given after 18 months.
  - Define **Adherence=1** if individual follows vaccination schedule (Takes recommended number of doses)

# Parents' Adverse Events Spill Over to Children's Vaccines

*Design A: Pandemrix narcolepsy (parents) → children's vaccines*

	Measles	Diphtheria	Pneumococcus	Index
<b>Children</b>				
Narcolepsy post Pandemrix	-0.074 (0.046)	-0.043 (0.047)	-0.093 (0.053)	-0.070 (0.043)
Odds ratio	0.190 [0.053, 0.769]	0.337 [0.109, 1.246]	0.277 [0.114, 0.723]	
Num. Obs.	495	495	495	495

*Notes:* Confidence intervals computed using Fisher's exact test in square brackets. Coefficients reported as shares.

Design B: Adverse Vaccine Events (excl. Pandemrix/COVID-19) → Children's Vaccines

$$y_{pb} = \delta_b + \gamma_p + \beta T_{pb} + \epsilon_{pb}$$

- $T_{ipb} = 1$  if child born after parent reports severe adverse event
- $\delta_b$  denote birth order fixed effects;  $\gamma_p$  denote parent fixed effects

Measles	Diphtheria	Pneumococcus	Index
-0.102	-0.028	-0.100	-0.077
(0.050)	(0.068)	(0.063)	(0.057)

⇒ Within families, outcomes worsen for children born *after* a parental adverse event—consistent with Design A

# Facts vs Fallacy

## *MMR & Autism Controversy*

**RQ:** Do adverse events need to be real for hesitancy to arise?

### **Background**

- 1998: Wakefield study in *The Lancet* claimed MMR–autism link.
- Retracted in 2010; later evidence finds no causal association.

⇒ Effects suggest that suspected adverse events do not need scientific backing

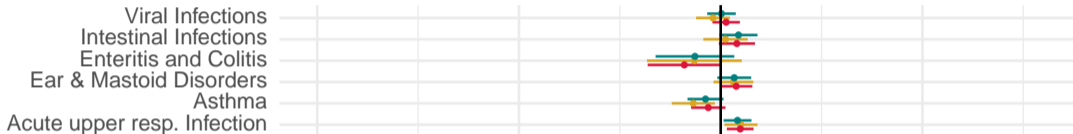
### **Method**

- Compare vaccination of children born *before vs. after* a sibling develops autism at young age

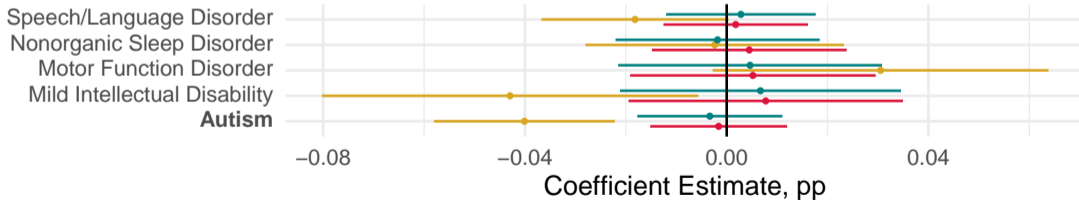
# Facts vs Fallacy

## Results

### Other Common Diseases Developed Before age 5



### Mental and Behavioural Disorders



# Conclusion

## Main findings

- Negative experiences with healthcare are **sticky** but **domain specific**
- Results for child vaccines suggest experiences crowd out statistics
- Negative experiences can trigger hesitancy **without scientific backing**

## Policy

- Information nudges/education unlikely to restore trust as also highly educated individuals are affected by adverse events
- Indirect costs from reduced uptake most relevant when the benefit of vaccination is low (e.g., COVID-19 boosters)
- Testing and surveillance should consider novelty of risks. New drugs → stronger testing; old drugs → communicating risks

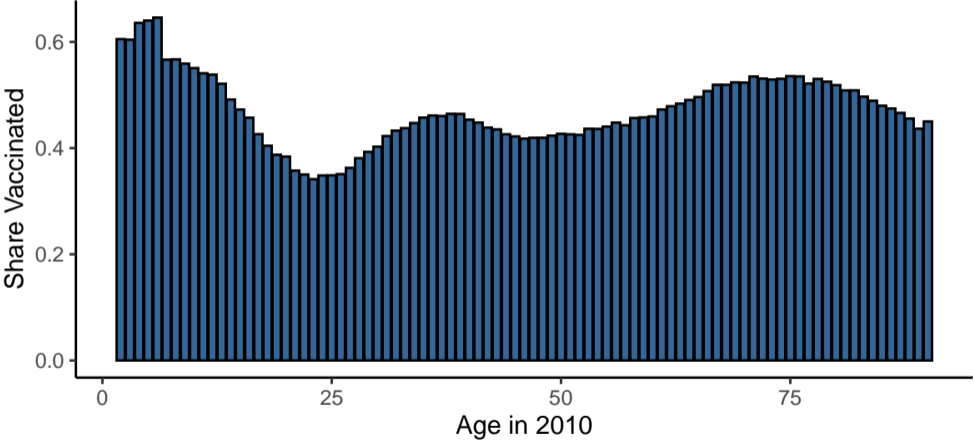
# Where go next? / Future Research

- Undoing effects of negative experiences
  - Information unlikely to work; Can reimbursement restore trust?
  - Optimal reimbursement when suspected adverse events can not be confirmed
  - Role of positive experiences in crowding out negative experiences? (Ashraf et al., 2024)
- Role of how information about risks is communicated
  - Role of salient narratives in media for misguiding beliefs **(In progress)**
  - Costs of overly simplified messages about risks

Thank you!

# Appendix

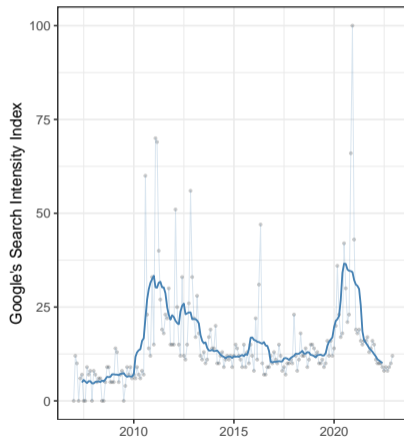
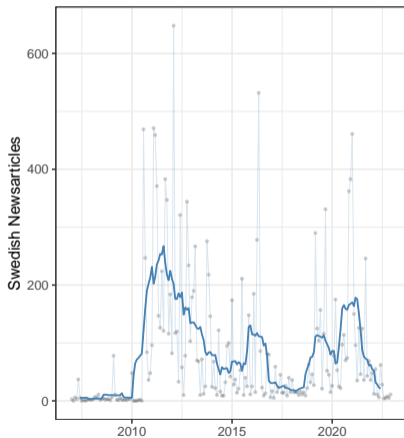
# Age Among Pandemrix Takers



Back

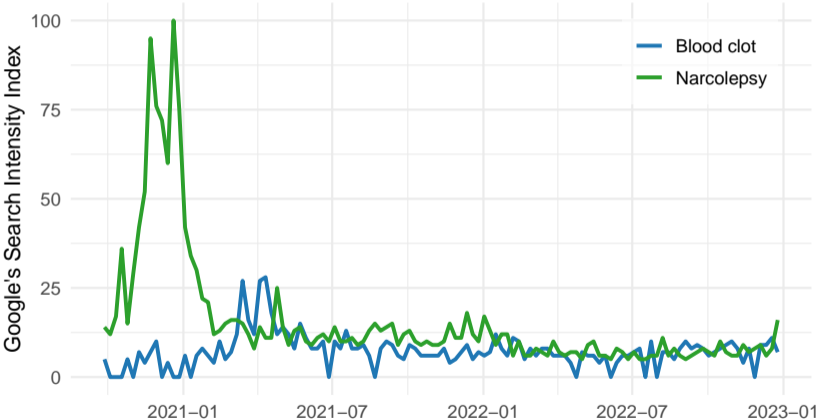
# Salience of Narcolepsy Scandal

## *Searches and News Articles*



# Saliency of Narcolepsy Scandal

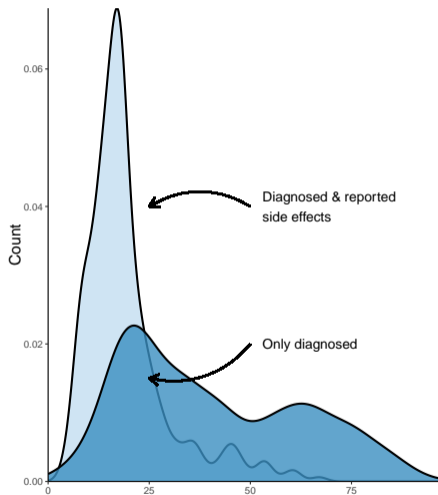
*Relative to Blood Clot*



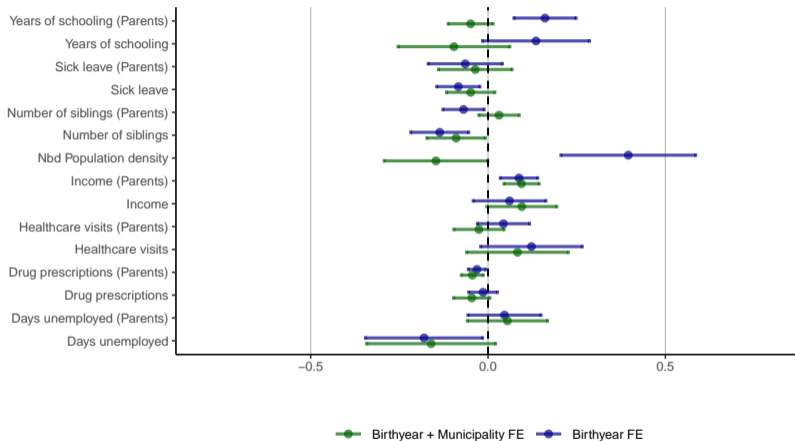
# Age at Onset of Narcolepsy

- In cross-section, Pandemrix narcolepsy cases are significantly younger.
- On average aged 15 when they developed narcolepsy and 26 during onset of COVID-19 pandemic.

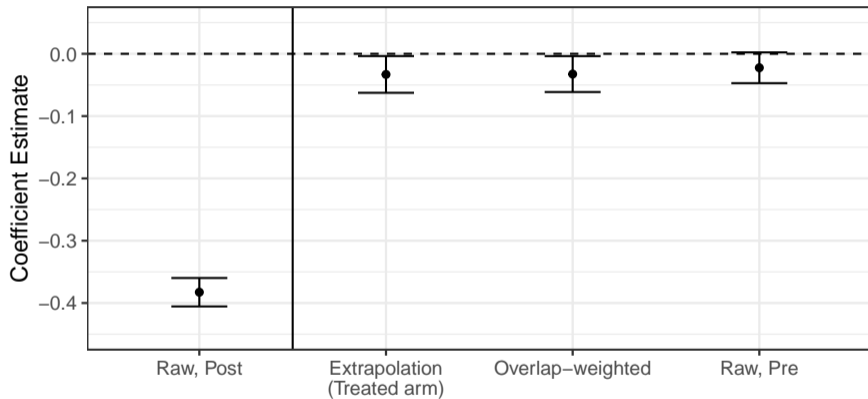
⇒ Allows us to study spillovers onto schoolmates, colleagues and family members.



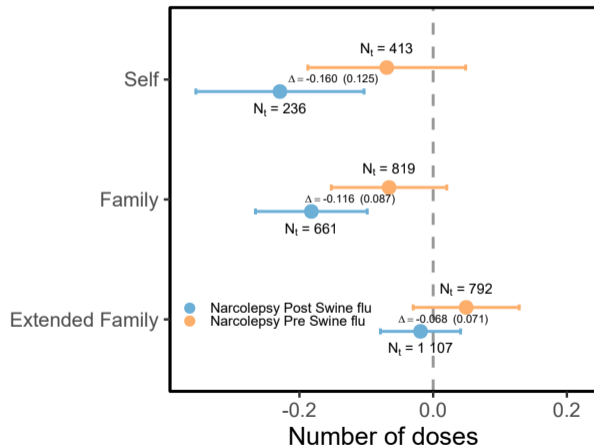
# Imbalance Partly Explained by Geography



# Reweighting/Extrapolating Placebo Control sample



# Costs of Vaccination $\Rightarrow$ Worsened Immunization

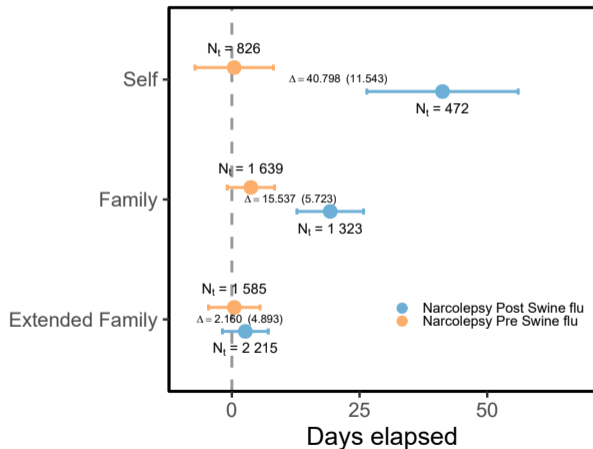


**Outcome:** Number of Doses (Conditional on at least one dose)

- Slightly fewer doses conditional on getting first dose
- $\hookrightarrow$  Effects small relative to extensive margin

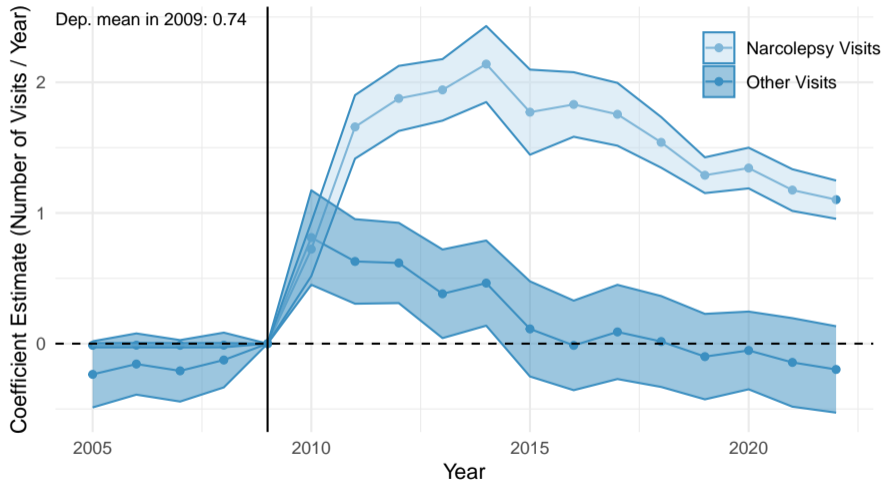
# Costs of Vaccination $\Rightarrow$ Worsened Immunization

- Exposure to narcolepsy  $\Rightarrow$  delay of first dose

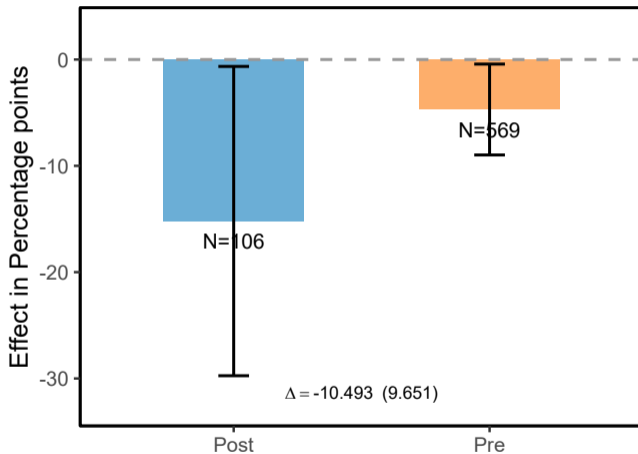


**Outcome:** Days between date available and first dose taken

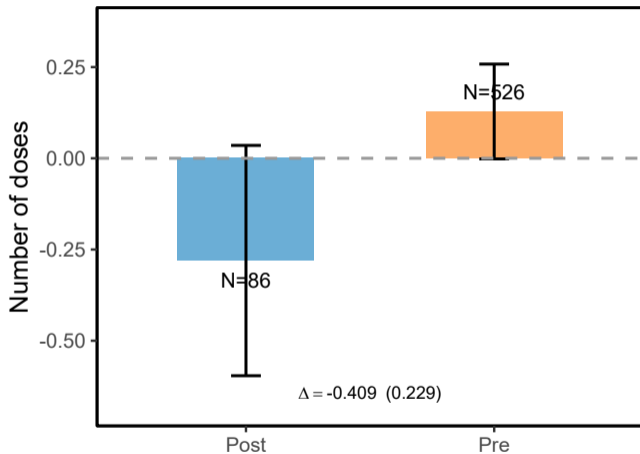
# Healthcare Visits among Narcolepsy Patients



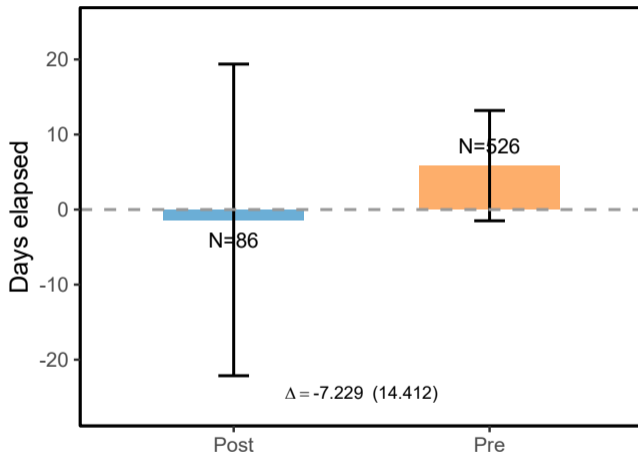
# Partners



# Partners

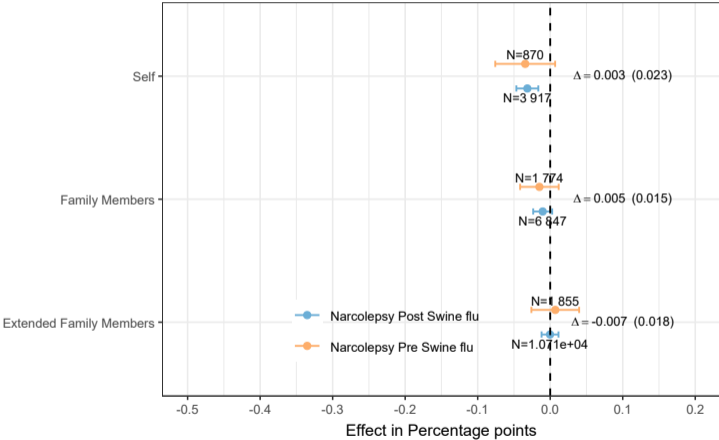


# Partners



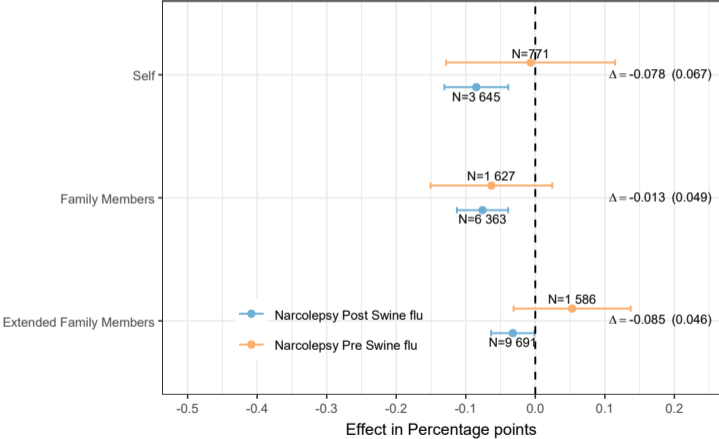
# Costs of Vaccination

## Covid Vaccine Taken



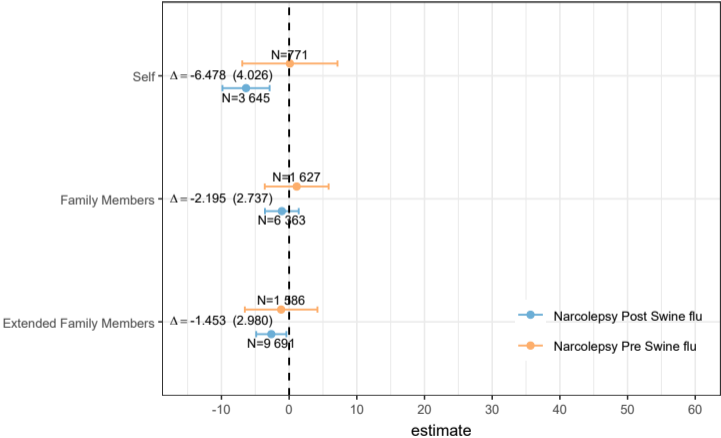
# Costs of Vaccination

*Number of doses (Conditional on at least one dose)*

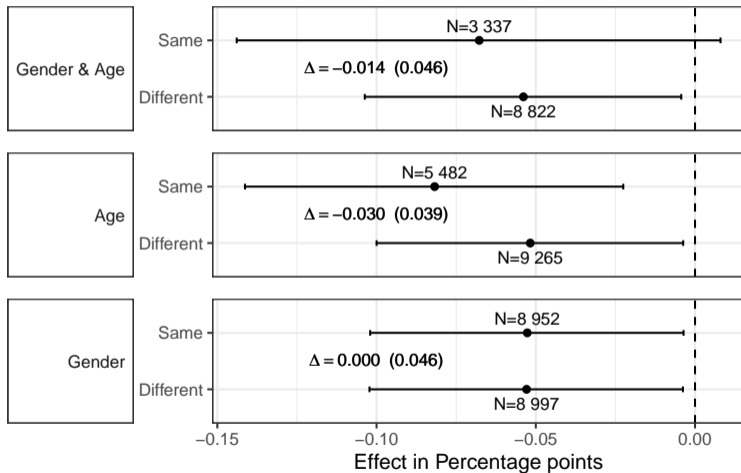


# Costs of Vaccination

*Days elapsed until first dose*



# Social Learning

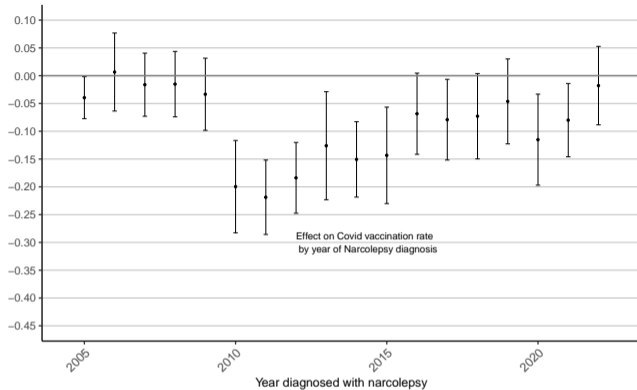


# Matching details

- 1:1 propensity score matching on own and parental or only parental characteristics depending on birth year and whether narcolepsy is Pandemrix-induced or not.

	<b>Birth year &lt; 1990</b>	<b>Birth year <math>\geq</math> 1990</b>
<b>Pre swine flu</b>	Parental characteristics	Parental characteristics
<b>Post swine flu</b>	Parental and own characteristics	Parental characteristics

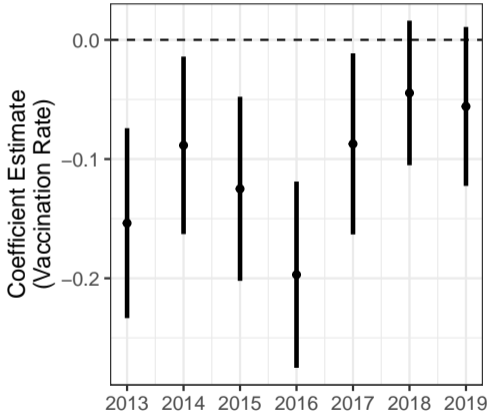
- LASSO to choose covariates among: Years of schooling, field of education, Days sick, Gender, Number of siblings, Income, Number of healthcare visits, Number of drug prescriptions, Days unemployed, population density, Country of origin, Diagnoses (ICD chapters), drugs (ATC level 1)



- Primarily individuals who likely developed narcolepsy from Pandemrix affected.

Back

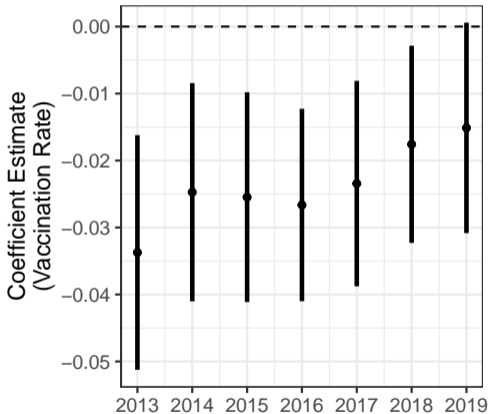
# Experiences are Sticky



## Key Findings

- Effect size does not fade for more recent adverse events
  - Results Robust to reweighting by age and drug
- ↪ Implies experiences have **persistent influence** on vaccination

# Experiences are Sticky



## Key Findings

- Effect size does not fade for more recent adverse events
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# Examples of Adverse Events

## *Idiosyncratic vs. Type-learner*

### Idiosyncratic

- **Psychostimulants** — Fluctuating mood symptoms
- **Aspirin** — Nasal disorders (epistaxis)
- **Levothyroxine** — Asthenic conditions

### Type-learner

- **Penicillins** — Allergic conditions NEC
- **Enalapril** — Angioedemas
- **Sirolimus** — Breathing abnormalities

# Descriptive statistics – Child vaccination program

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## Panel A: Share adhering

	diphtheria	Pneumococcus	Measles	Covid (Parents)
Abstention	1.3	2	4.1	10.6
Partial adherence	4.6	9		31.0
Full Adherence	94.1	89	95.9	42.8

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## Panel B: Correlation matrix

	diphtheria	Pneumococcus	Measles	Covid (Parents)
diphtheria	1.000			
Pneumococcus	0.739	1.000		
Measles	0.474	0.453	1.000	
Covid (Parents)	0.167	0.157	0.160	1.000

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