Post-Authorization Safety Monitoring

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Why Safety Monitoring Matters

- Ensure that benefits of vaccines outweigh the risks for individuals and populations
  - High standards as often for healthy people, prevention and large number of people exposed (attributable risk)
- Optimize the use of limited resources
- Improve and maintain public confidence in vaccines – high vaccine coverage

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Post hoc ergo propter hoc

after this, therefore because of this", is a logical fallacy …since that event *followed* this one, that event must have been *caused* by this one.

The fallacy lies in coming to a conclusion based *solely* on the order of events, rather than taking into account other factors that might rule out the connection.

http://dictionary.sensagent.com/post+hoc+ergo+propter+hoc/en-en/

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Adverse Events Following Immunization (AEFI) will occur

- Important to differentiate between coincidental events and events causally related to vaccination
  - 2,500 miscarriages and 3,000 heart attacks each day in US
- Important to rapidly identify and follow-up vaccine safety signals
- Robust scientific follow up takes time

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Pro's of Clinical Trials

- The Gold Standard - Double blind, randomized trials
  - Reduce Confounding
  - Reduce Bias
- Strict inclusion and exclusion criteria
  - Reduces risk to participants
  - Reduces Confounding
- Incremental phases to minimize risk and optimize information obtained

Limitations of Clinical Trials

- Inclusion/Exclusion criteria
  - Can not evaluate AEs in persons excluded from studies (medicated, concurrent medical conditions)
  - Can not evaluate delayed AEs
- Small sample size
  - Can not evaluate rare AEs
  - Can not evaluate AEs in sub-populations

Sample Sizes Needed to Detect Rare Adverse Events

Rates (%)	Sample Size *	No. Potentially Affected**
0.1 vs. 0.2	50,000	200,000
0.1 vs. 0.3	17,500	400,000
0.05 vs. 0.1	100,000	100,000
0.01 vs. 0.02	500,000	20,000
0.01 vs. 0.03	175,000	40,000

*Two-arm trial, power 80%, alpha (2 sided) = 5%
** Assumes 100% of adults vaccinated, risk after 1 dose

Source: adapted from Ellenberg 2001

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Post-Authorization Studies

- Expand safety profile to include:
  - Intermediate or rare AEs
  - Subpopulations
- Address emerging safety issues

Passive Surveillance

- Purpose: to detect signals of unanticipated events that may deserve further follow-up
- Primary Limitation: Usually can not determine if event is caused by vaccine or coincidental
  - Lack of good denominator and comparison (unvaccinated) group
  - Potential Bias (under-reporting, incomplete reporting, over-reporting, etc).

Vaccine Adverse Event Reporting System (VAERS)

- Co-administered by CDC and FDA
- Accepts reports from anyone
- Limitations
  - Under reporting
  - Incomplete data
- Designed for detecting signals or generating hypothesis
  - Can not assess causality

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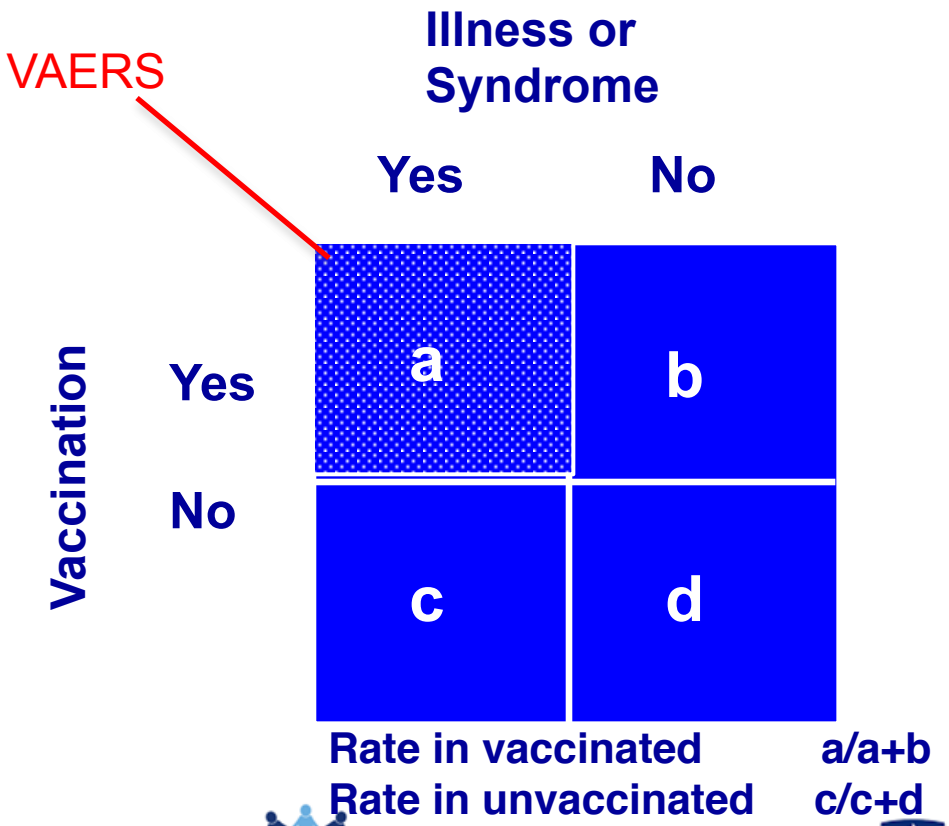
Establishing Causal Link: Adverse Event and Vaccine



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Source: R T Chen

Perception of VAERS

"There have been estimates that fewer than 10 percent, even as low as 1 to 4 percent, of adverse events which occur after prescription drug or vaccine use are ever reported to government adverse event reporting systems….If only 1 to 4 percent of all adverse events associated with GARDASIL vaccination are being reported to VAERS, there could have been up to 38,000 health problems after GARDASIL vaccination in 2006 which were never reported"

Barbara Loe Fisher, National Vaccine Information Center (NVIC)
http://www.nvic.org/nvic-archives/pressrelease/hpvfeb212007.aspx

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Assessing Associations between Vaccines & Adverse Events: Active Surveillance

- Vaccine Safety Datalink (VSD)
- Post-licensure Rapid Immunization Safety Monitoring (PRISM) Network
- CBER Biologics Effectiveness and Safety (BEST
- Centers for Medicare & Medicaid Services (CMS)
- Department of Defense (DoD)
- Department of Veterans Affairs (VA)

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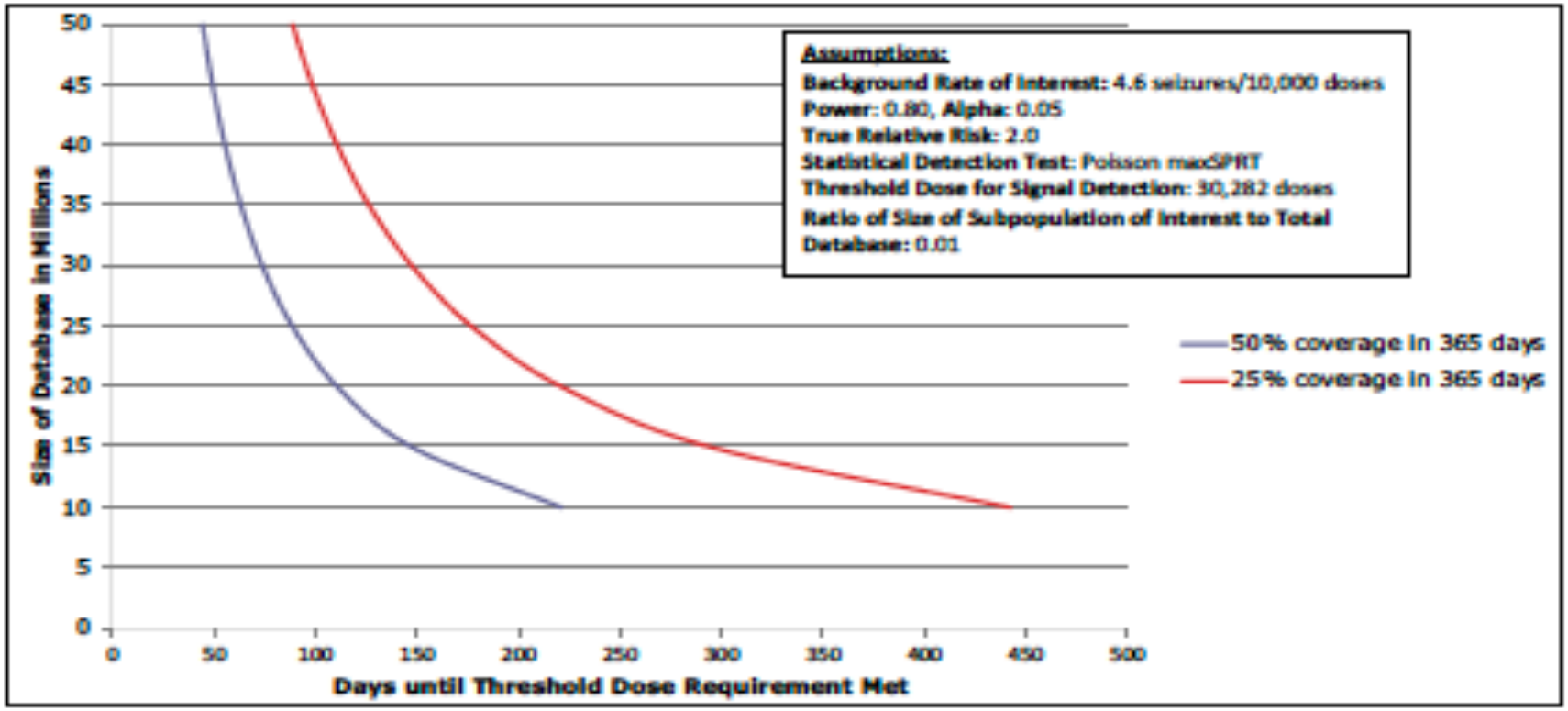
Size Matters: Effect Size of Database and Vaccine Coverage Rate on Time Until Signal Detection



Katherine Yi, unpublished

SIGNAL ≠ ASSOCIATION ≠ CAUSALITY

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- The Need:
  - Vaccine adverse events occur rarely for each clinician
  - Medical “outliers” difficult to advance science on, like orphan disease (leukemia)
- The Solution:
  - Academic centers of excellence
  - Vaccine safety clinicians
  - Clinical subspecialty for referrals
  - Laboratory research capabilities

Source: R T Chen

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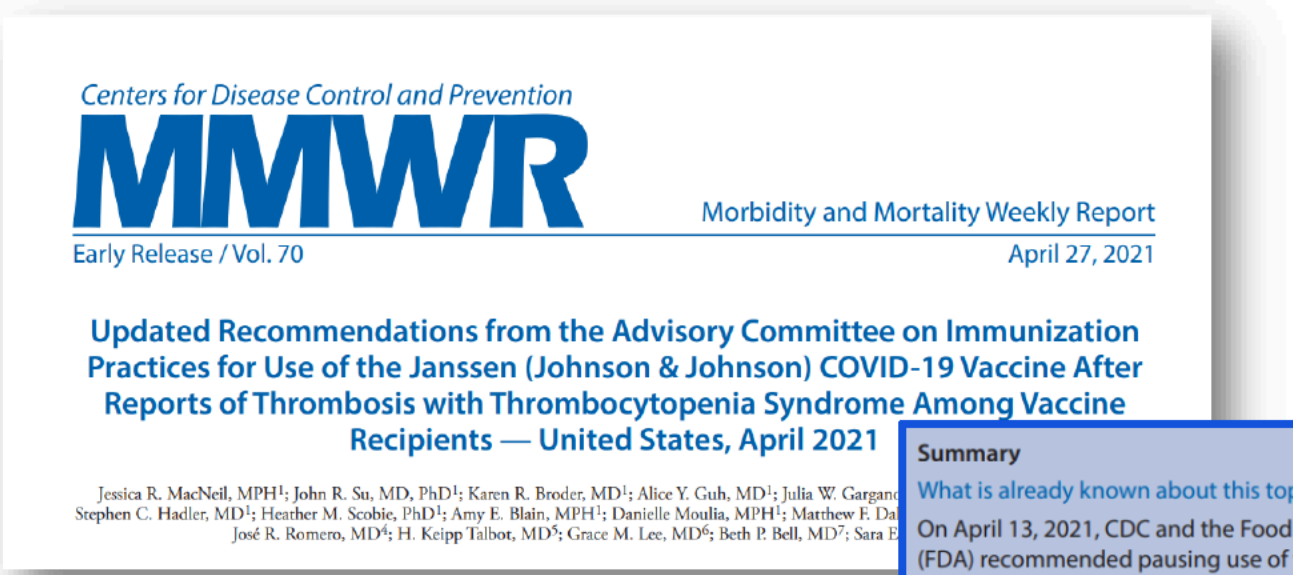

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Early Release / Vol. 70 April 27, 2021

Updated Recommendations from the Advisory Committee on Immunization Practices for Use of the Janssen (Johnson & Johnson) COVID-19 Vaccine After Reports of Thrombosis with Thrombocytopenia Syndrome Among Vaccine Recipients — United States, April 2021

Jessica R. MacNeil, MPH[1]; John R. Su, MD, PhD[1]; Karen R. Broder, MD[1]; Alice Y. Guh, MD[1]; Julia W. Gargano
Stephen C. Hadler, MD[1]; Heather M. Scobie, PhD[1]; Amy E. Blain, MPH[1]; Danielle Moulia, MPH[1]; Matthew F. Da
José R. Romero, MD[4]; H. Keipp Talbot, MD[5]; Grace M. Lee, MD[6]; Beth P. Bell, MD[7]; Sara E

Summary

What is already known about this topic?

On April 13, 2021, CDC and the Food and Drug Administration (FDA) recommended pausing use of the Janssen COVID-19 vaccine after reports of thrombosis with thrombocytopenia syndrome (TTS) among vaccine recipients.

What is added by this report?

On April 23, the Advisory Committee on Immunization Practices concluded that the benefits of resuming Janssen COVID-19 vaccination among persons aged ≥18 years outweighed the risks and reaffirmed its interim recommendation under FDA's Emergency Use Authorization, which includes a new warning for rare clotting events among women aged 18–49 years.

What are the implications for public health practice?

Resuming use of the Janssen COVID-19 vaccine will ensure flexibility, choice, and improved access. Education about TTS risk with Janssen COVID-19 vaccine is critical.

https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7017e4-H.pdf

Tom Shimabukuro
ACIP, 5/12/2021

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Case finding for TTS following COVID-19 vaccines*

- Healthcare providers directly contact CDC about potential TTS cases
- FDA physicians screen incoming VAERS reports daily to identify potential TTS cases (i.e., screening of pre-processed reports)
- CDC searches the VAERS database of processed reports daily for possible TTS cases
- Medical records requested for all potential TTS case reports to confirm thrombosis with laboratory evidence of thrombocytopenia, using working case definition
- CDC and FDA medical officers review TTS case reports and available medical records; CISA experts including hematologists consulted

* Analytic period March 2–May 7, 2021

Characteristics of U.S. TTS cases after Janssen COVID-19 vaccination, N=28 (Tier 1=25, Tier 2=3, as of May 7, 2021)

- Median age: 40 years (range 18–59 years)
- Median time from vaccination to symptom onset: 9 days (range 3–15 days)
- All received the Janssen COVID-19 Vaccine before the pause on April 13, 2021
- Female (n=22), male (n=6)
- 19 of the 28 TTS cases has a cerebral venous sinus thrombosis (CVST)
- Pregnant or postpartum* (n=0)
- Past SARS-CoV-2 infection (n=5); 3 by history, 2 by nucleocapsid serology testing only
- Risk factors for thrombosis†
  - Systemic estrogen‡ (n=3)
  - Obesity (n=12)
  - Hypertension (n= 7)
  - Hypothyroidism (n=3)
  - Diabetes (n=3)
  - Current cigarette smoking (n=2)
  - Malignancy (n=1)
  - Fertility treatment (n=1)
  - Coagulation disorders (n=0)

* Within 12 weeks of delivery; † Reference source: https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis;
‡ 2 patients were taking combined oral contraceptives (COCs), 1 patient was on hormone therapy (HT) estradiol patch

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U.S. reporting rates of TTS after Janssen COVID-19 vaccination (as of May 7, 2021)

- 8.73 million total Janssen COVID-19 Vaccine doses administered*

	Females			Males		
Age group	TTS cases	Doses admin	Reporting rate† (per million)	TTS cases	Doses admin	Reporting rate† (per million)
18-29 yrs old	**3**	641,510	4.7	**2**	714,458	2.8
30-39 yrs old	**8**	642,745	12.4	**1**	728,699	1.4
40-49 yrs old	**7**	743,256	9.4	**1**	775,390	1.3
50-64 yrs old	**4**	1,463,416	2.7	**2**	1,505,505	1.3
65+ yrs old	**0**	814,947	0	**0**	697,925	0

* Source of doses administered: https://covid.cdc.gov/covid-data-tracker/#vaccinations; † Reporting rate = TTS cases per 1 million Janssen COVID-19 vaccine doses administered

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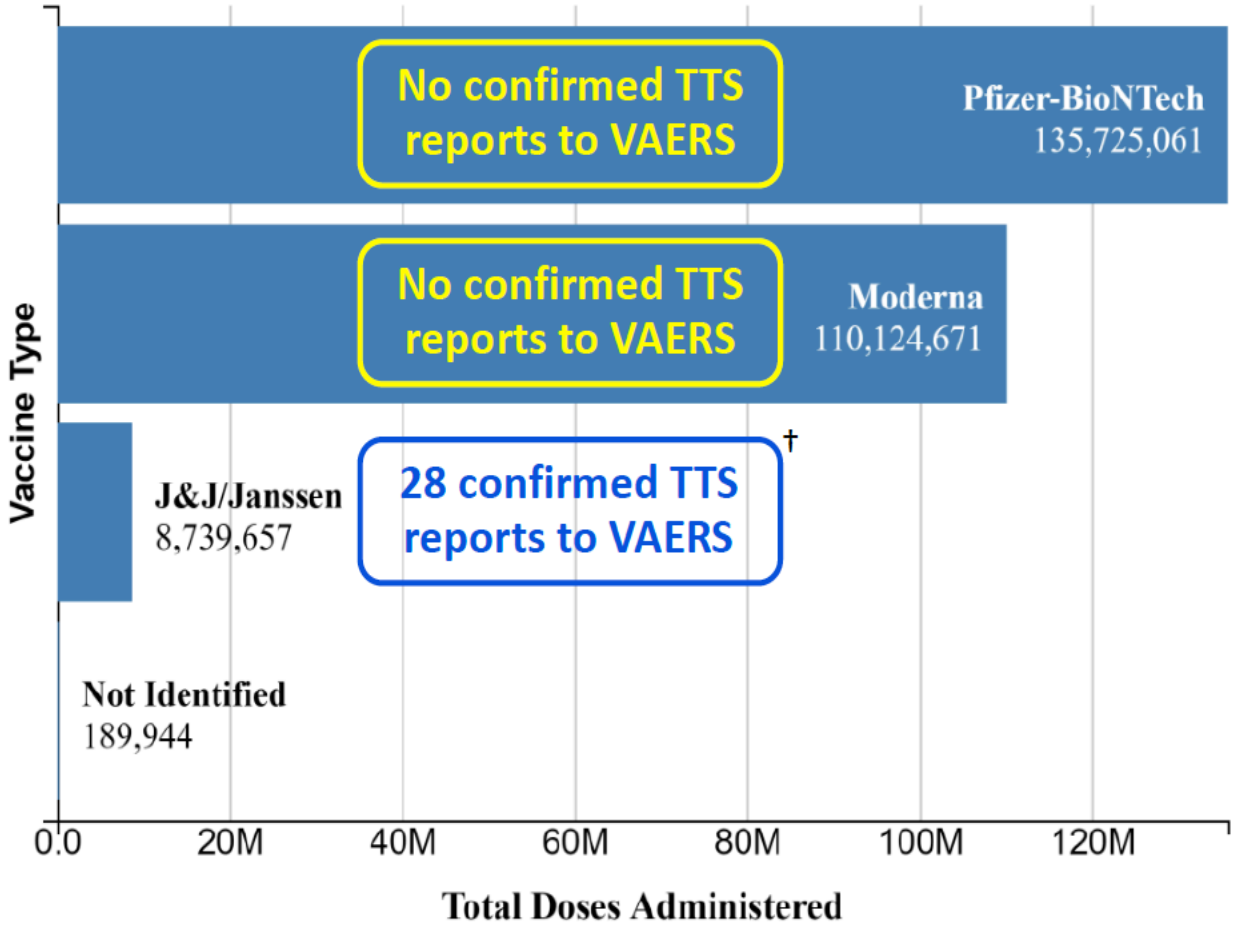
U.S. COVID-19 vaccine administration by product type and TTS reports to VAERS

(as of May 7, 2021)*



* Data source: https://covid.cdc.gov/covid-data-tracker/#vaccinations

† One CVST with thrombocytopenia case was observed in Janssen COVID-19 vaccine pre-authorization clinical trials in a 25-year-old male; this case is not included in the VAERS post-authorization confirmed case count

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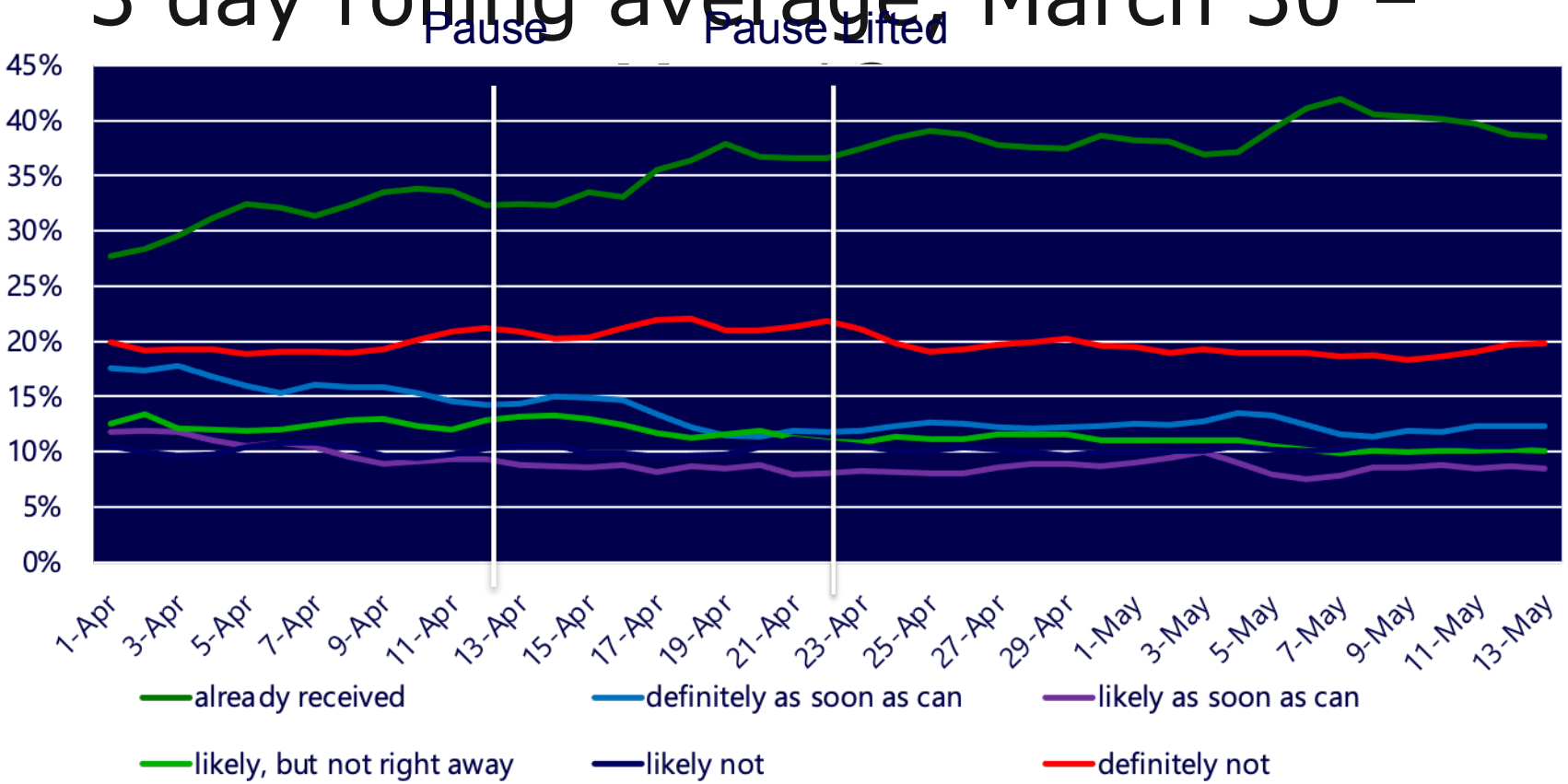
Intention to get vaccinated (*N* = 89,083)
3 day rolling average, March 30 –



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Where are we at?

- TTS following J&J vaccine very similar to those reported following AstraZeneca COVID-19 vaccine
- Need to better understand
  - Population(s) at risk
  - Level of risk attributable to vaccine
  - Biological mechanism
- Potential implication far bigger for LMICs

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