BREAKOUT DISCUSSION

How Should Future Maternal Immunization Safety Data Be Generated?

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Need for Surveillance Systems

Expanding Programs

Maternal immunisation programs are scaling globally — requiring safety evaluation across highly diverse data environments.

Uneven Infrastructure

Some settings have integrated EHRs, longitudinal mother–infant linkage, access to vaccine registries/accurate exposure data, reliable gestational age estimates, robust outcome measures, and decades of experience conducting real world studies. Others do not.

Multi-Dimensional Challenge

The gap is not only scientific — it spans infrastructure, measurement, harmonisation, feasibility, and sustainability.

Real-World Evidence vs. Clinical Trials

Clinical Trials

Gold standard in evidence generation

- Highly controlled experiments with strict eligibility criteria
- Excellent for determining if a vaccine works safely in ideal conditions
- May not represent the general population seen in clinical practice
- Typically have limited sample sizes and follow-up periods
- Cannot address all safety questions before licensure

→

Real-World Evidence

RWE to address gaps remaining from clinical trials

- Studies real-world practice across a wide range of patients
- Insights into large, heterogeneous populations over long follow-up
- Complements trials with broader, post-licensure evidence
- Addresses safety questions not answered before licensure
- Captures vaccine performance across diverse health systems

CASE STUDY

Example: RSVpreF (Abrysvo®) & Preterm Birth

The Trial Signal

- Pfizer MATISSE Phase 3 trial (n=7,358)[1]
- Preterm birth: 5.7% (vaccine) vs 4.7% (placebo)
- Overall difference not statistically significant[1,2]
- Signal concentrated in upper middle-income countries (Argentina, South Africa)[2]
- FDA warning added; restricted to 32–36 weeks' gestation

What RWE Showed

- VAERS (2023–24): preterm birth 4.1% — within expected range[3]
- Weill Cornell study (n=2,973): 5.9% vs 6.7% unvaccinated — no significant difference[4]
- WHO GACVS (Nov 2024): benefits outweigh risks in 98% of simulations[5]
- Sequential surveillance and retrospective cohort studies from five health plans showed no increase in preterm birth against current or historical comparators[6,7]
- Large matched cohort study from France similarly showed no increase in preterm birth[8]

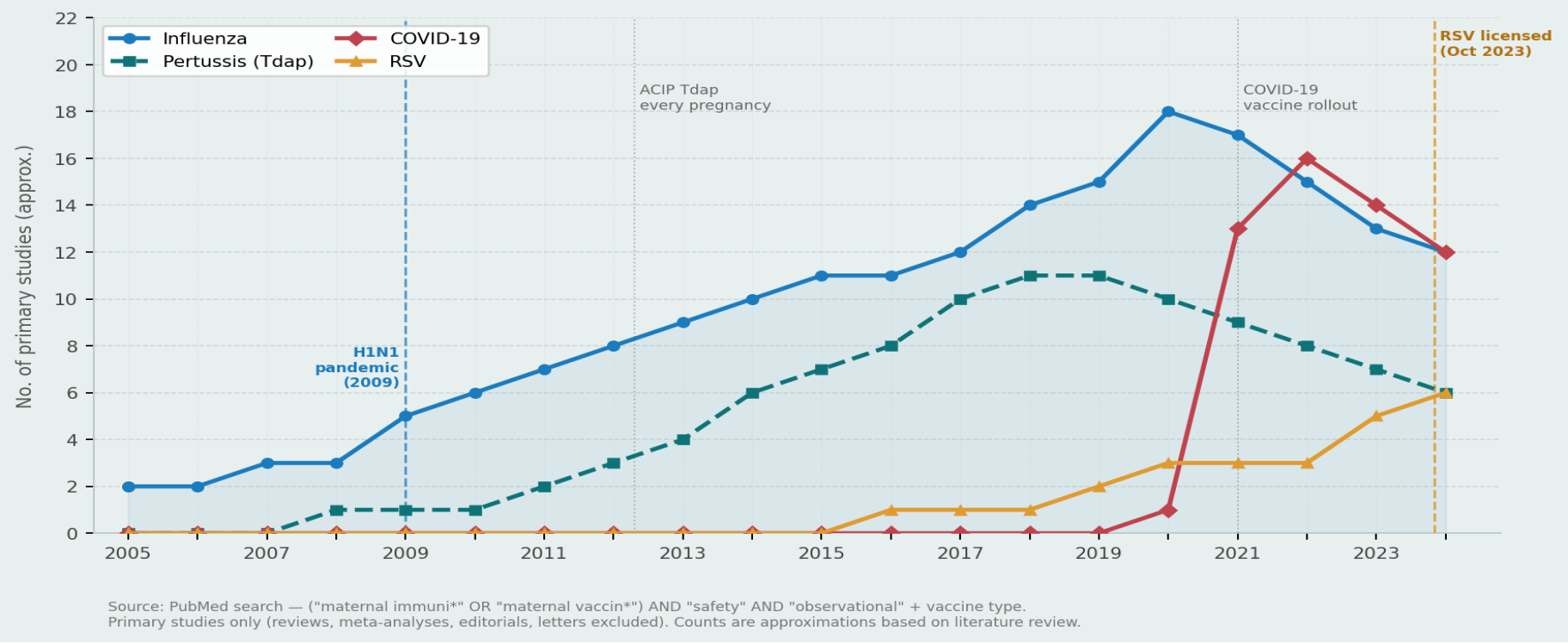
The Lesson

- Trial signal raised concern; RWE provided reassurance
- RCT populations may not reflect vaccinated populations in high-income settings
- Post-licensure surveillance is essential — not optional
- RWE and trials are complementary, not competing

[1] Kampmann et al. (2023). Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. NEJM.; [2] Madhi et al. (2025). Obstet Gynecol. doi: 10.1097/AOG.0000000000005817; [3] Moro et al. (2024). Safety of RSVpreF Vaccine in Pregnant Persons — Vaccine Safety Datalink, 2023–24. MMWR; [4] Son et al. (2024). RSV Vaccination in Pregnancy and Birth Outcomes. JAMA Network Open; [5] WHO GACVS (2024). Safety of maternal vaccination against RSV. WHO Weekly Epidemiological Record, March 2025; [6] Michnick et al. (2026). Sequential Safety Surveillance of RSVpreF Vaccination During Pregnancy Early in the Postapproval Period. JAMA Netw Open; [7] Michnick et al. (2026). Interim Safety of RSVpreF Vaccination During Pregnancy. JAMA doi:10.1001/jama.2025.23452; [8] Gabet et al. (2026). Obstet Gynecol. doi: 10.1097/AOG.0000000000006121.

Maternal Immunization Safety Research: We've Come a Long Way…

Primary observational studies only • PubMed search: ("maternal immuni*" OR "maternal vaccin*") AND "safety" AND "observational" + vaccine type • Excludes reviews, meta-analyses, editorials, letters



Influenza: ~190 studies (2005–2024) • Pertussis: ~120 studies (rise post-2012 ACIP recommendation) • COVID-19: ~57 studies (spike 2021–2022) • RSV: ~20 studies (emerging post-2023 licensure)

Data Sources for Maternal Immunization Safety Research

Healthcare records systems

Routine clinical data, captured during care

Electronic health records
Diagnoses, prescriptions, visits

Claims / insurance data
Billing, procedures, utilization

Hospital discharge records
Inpatient diagnoses, procedures

Registries

Structured population-level data collection

Immunization registries
Vaccine type, date, dose, provider

Pregnancy / birth registries
Gestational age, outcomes, birth defects

Disease-specific registries
Confirmed diagnoses, severity, outcomes

Surveillance systems

Active and passive safety monitoring

Passive surveillance
Spontaneous adverse event reports (e.g. VAERS)

Active surveillance
Systematic monitoring in defined populations (e.g. VSD)

Sentinel surveillance
Hospital/site-based signal detection networks

Research platforms & cohorts

Purpose-built infrastructure for population-level research

Prospective cohorts
Enrolled pregnant women, longitudinal follow-up

Research networks
Multi-site data sharing for pooled analyses

Trials and studies
RCTs, post-licensure studies, case-control designs

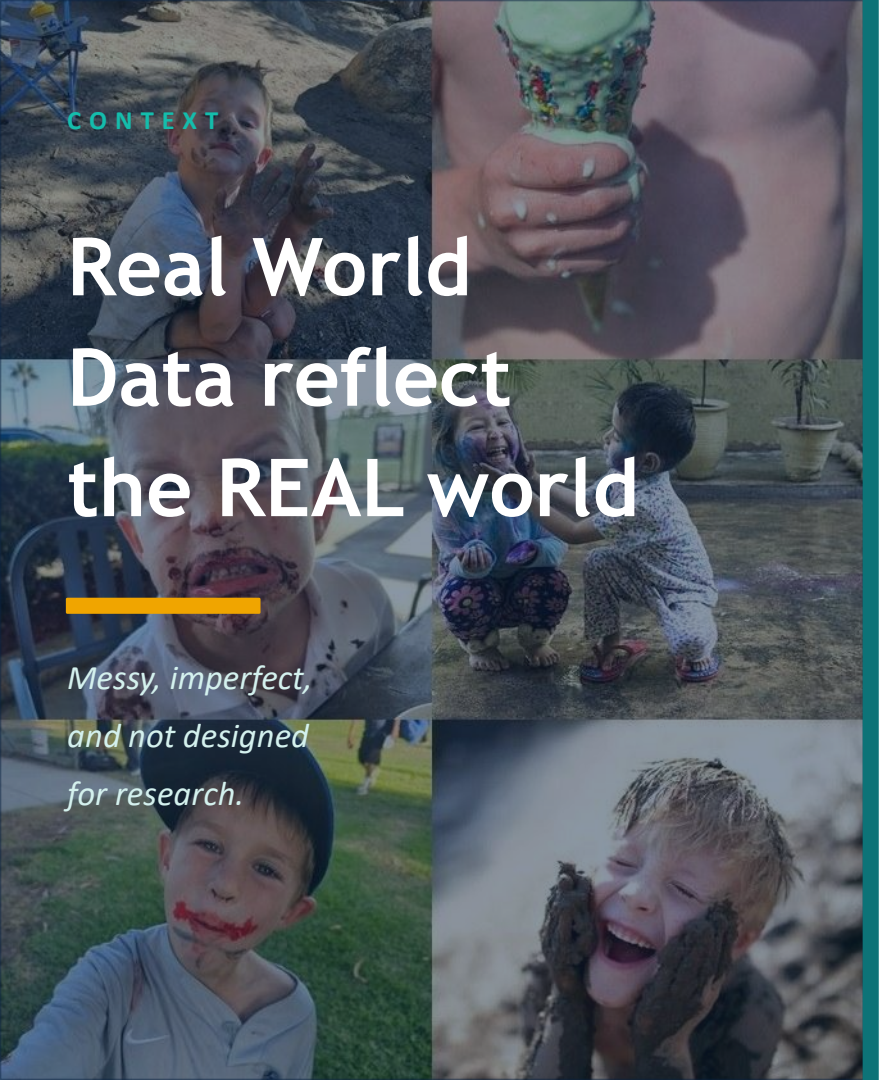
Linkage & harmonization

Cross-source integration enabling research-grade datasets

Record linkage
Mother–infant, cross-system linkage

Data harmonization
Common data models, cross-country standards

Global data networks
VSD, GVDN, GAIA, coordinated platforms



CONTEXT

Real World Data reflect the REAL world

Messy, imperfect, and not designed for research.

Collected for Operational Purposes

Generated through routine healthcare delivery, population surveillance, or other purposes other than research.

Not Standardized

Formats, coding systems, and data fields vary widely across sites and systems.

Requires Adaptation for Research

Meaningful analysis demands careful processing, validation, and contextualisation.

Data Challenges

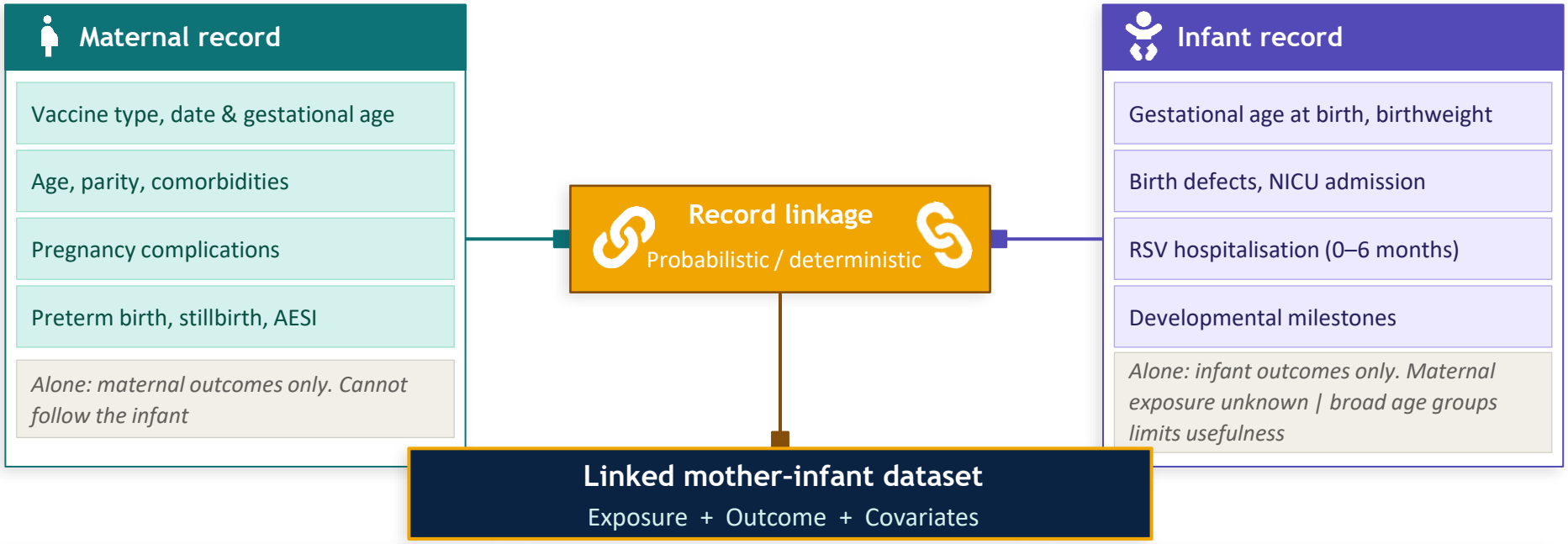
Foundational Data Challenges

- Gestational age assessment
- **Complete** vaccine exposure ascertainment
- **Mother–infant linkage**
- Standardized maternal & neonatal outcomes
- Follow-up across pregnancy and infancy
- Data quality and completeness
- Comprehensive data on confounders (e.g., socio-economic variables, medical comorbidities, health behaviors)
- Ability to follow infants longitudinally for outcomes later in life

Methodological Challenges

- Misclassification of exposure, timing & outcomes
- **Time-varying exposure during pregnancy**
- Confounding by indication & healthcare-seeking behavior
- Selection bias and incomplete follow-up
- **Cross-site / cross-country harmonisation**

Mother-Infant Record Linkage Is Essential



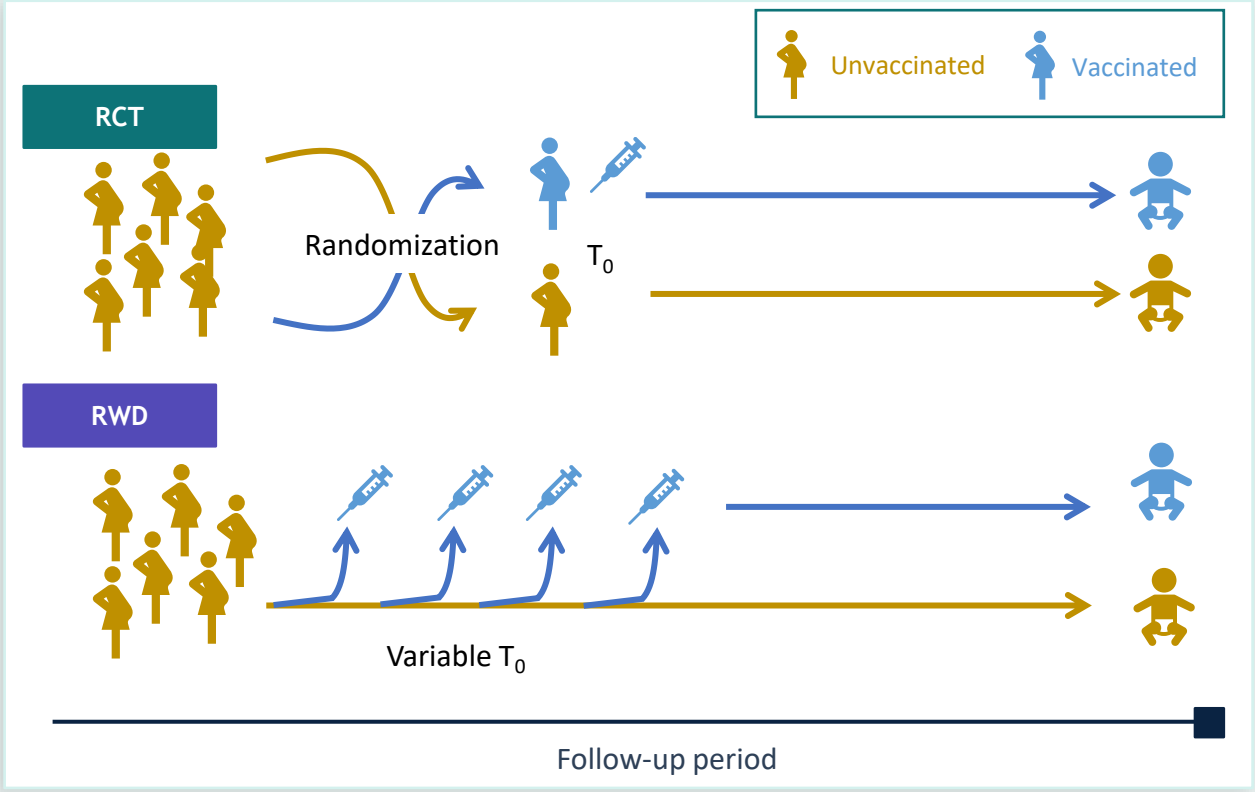
Research question: Did vaccination increase the risk of PTB or neonatal death?

Research question: Did time of vaccination affect the risk of PTB or neonatal death?

Research question: Did vaccination protect the infant from disease?

Without linkage: none of these research questions can be answered

Key Methodological Challenges: Immortal Time Bias



Why This Matters

Confounding

Vaccinated women in RWD differ systematically from unvaccinated women

Variable T_0

In RWD, vaccination occurs at different gestational ages — creating misaligned start times (T_0)

Immortal time

The period before vaccination is "immortal" — women cannot have the outcome before receiving the vaccine

Required fix

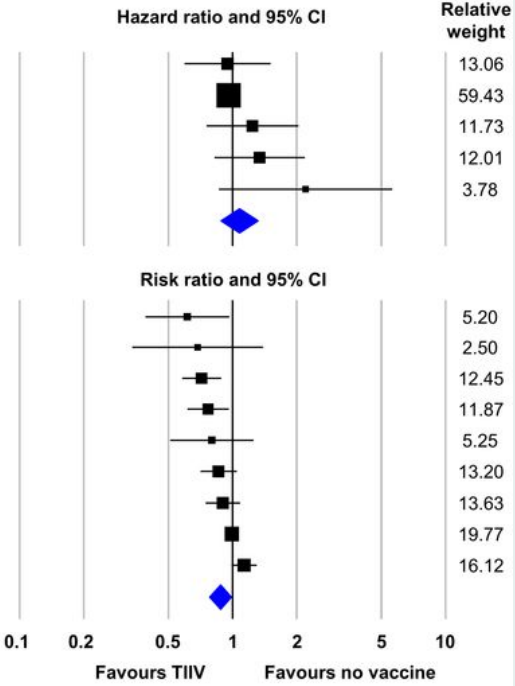
Must be accounted for in both study design and analytical approach (e.g., target trials)

Poor Control for Immortal Time Bias Changes Our Conclusions for PTB

✓ Accounts for ITB → HR 1.08 (0.89–1.30)

✗ No ITB control → RR 0.86 (0.76–0.97)

ITB?	Study	Country	Only during flu season?	Gestational age at birth, lower limit	ROB	Effect estimate	Lower limit	Upper limit	Events / Total: Vaccinated	Events / Total: Unvaccinated	Relative weight
Yes	Mohammed et al., 2020	Australia	No	> 20 weeks	7	0.94	0.59	1.49	40 / 599	97 / 2944	13.06
	Zerbo et al., 2017	USA	No	≥ 24 weeks	9	0.98	0.93	1.03	4183 / 64748	6740 / 81119	59.43
	Chambers et al., 2016	USA/Canada	No	NR, live births only	7	1.23	0.75	2.02	72 / 1092	21 / 379	11.73
	Ahrens et al., 2014	USA	No	≥ 25 weeks	6	1.37	0.84	2.23	24 / 310	83 / 1285	12.01
	Chambers et al., 2013	USA/Canada	No	NR, live births only	7	2.25	0.88	5.75	NR / < 841	NR / < 191	3.78
						1.08	0.89	1.30	4319+ / 66749+	6941+ / 85727+	
						Heterogeneity: I^2 = 28.178					
No	Omer et al., 2011	USA	Yes	NR, live births only	8	0.60	0.38	0.94	NR / NR	NR / NR	5.20
	Munoz et al., 2005	USA	No	≥ 21 weeks	7	0.67	0.33	1.36	12 / 218	54 / 674	2.50
	Olsen et al., 2016	Laos	Yes	NR, live births only	6	0.70	0.57	0.86	136 / 1819	242 / 1890	12.45
	Legge et al., 2014	Canada	No	≥ 20 weeks	8	0.75	0.60	0.94	92 / 1856	617 / 9437	11.87
	Adedinsewo et al., 2013	USA	Yes	NR, live births only	9	0.78	0.50	1.22	NR / NR	NR / NR	5.25
	Dodds et al., 2012	Canada	No	> 20 weeks	7	0.84	0.69	1.02	124 / 1925	584 / 7722	13.20
	Arriola et al., 2017	Nicaragua	Yes	≥ 28 weeks	7	0.88	0.73	1.06	NR / 1789	NR / 1479	13.63
	Nordin et al., 2014	USA	No	≥ 22 weeks	8	0.97	0.93	1.02	3390 / 57554	3478 / 57554	19.77
	McHugh et al., 2017	Australia	Yes	NR, live births only	7	1.14	0.99	1.31	436 / 2397	754 / 4718	16.12
						0.86	0.76	0.97	4190+ / 67558+	5729+ / 83474+	
						Heterogeneity: I^2 = 71.145					



[1] Wolfe et al. (2023). Safety of influenza vaccination during pregnancy: a systematic review. BMJ Open. 13:e066182. doi:10.1136/bmjopen-2022-066182

Harmonisation in Practice: One Question, Five Different Answers

Research question: "Did vaccination increase the risk of preterm birth?"

Data element	Country #1 Birth registry	Country #2 EHR	Country #3 Longitudinal cohort	Country #4 Birth registry	Country #5 Pregnancy registry
GA source	1st trimester US + LMP algorithm	EHR-derived; LMP or early US	Field-measured fundal height; LMP recalled	LMP from maternity card; US if available	Recalled LMP only; no routine US
GA stored as	**EDD date in record**	**Weeks gestation (integer)**	**Trimester category (1 / 2 / 3)**	**Date of vaccination only**	**Often missing or estimated post-hoc**
Precision	±3–5 days (US-confirmed)	±1 week	±2–3 weeks	Requires GA calculation from two separate records	±3–6 weeks
Can we answer?	**✓ Yes**	**✓ Yes**	**~ Partially**	**~ With workaround**	**✗ Not reliably**

The pooling problem: Country #1 contributes exact GA in days. Country #2 contributes integer weeks. Country #3 contributes a trimester category. Country #4 requires a workaround calculation. Country #5 cannot contribute reliably. Pooled analysis therefore rests on incompatible inputs.

This is a single variable, across five sites, for one research question. Real studies require harmonisation of dozens of variables simultaneously.

BREAKOUT DISCUSSIONS

Discussion Prompts

Submit your group recommendations here

How can we improve the collection and use of real-world data for maternal vaccine safety studies?

Discuss current gaps in the availability and/or use of data to support real world maternal immunization safety studies globally

Group ❶: GA is measured differently in different settings. How can we more completely and accurately estimate GA (or prematurity) globally in real-world data?

Group ❷: Maternal vaccination data is often fragmented and often not connected with infant data. How can we improve exposure measurement and linkages globally?

Group ❸: Non-randomized studies are prone to uncontrolled confounding. Are we capturing data on key confounders and how can we improve control of confounding in real world studies?

Group ❹: Analysis of real-world data on maternal vaccination is tricky. How can we standardize analytic methods across settings and studies?

Link to join: https://app.sli.do/event/h1SyCbAAJrnLHGuR829Sak