Collaboration + big data: The need for partnerships to influence policy and practice

Grace M. Lee, MD MPH
Director, Center for Healthcare Research in Pediatrics
Co-Director, Population Health Sciences and Health Services Research Center
Associate Medical Director, Infection Prevention and Control
Symposium Objectives

1) **To bring together** scientists from diverse disciplines to discuss health research and methods that involve large health care data.

3) To discuss methodological challenges encountered in research, **share ideas for addressing them**, and brainstorm future directions.
Examples of Successful Partnerships in Vaccine Safety
Lifecycle Approach to Vaccine Safety

Pre-Market

Phase I, II, III trials

Uncertainty about benefits and risks

FDA licensure; CDC/ACIP recommendations

Post-Market

Transportability

Scientific and Ethical Issues in Studying the Safety of Approved Drugs, IOM 2012
VSD and PRISM

Vaccine Safety Datalink

• Established in 1990, funded by CDC
• 8 U.S. health plans
• ~9 million children and adults
• Rapid access to electronic health records, including immunization records

Post-licensure Rapid Immunization Safety Monitoring system

• Established in 2009, now part of FDA-funded Sentinel
• 4 national health insurers
• ~170 million children and adults
• Links health plan, state immunization registry and birth registry data
Vaccine Safety Datalink Partners

- Group Health Cooperative
- Northwest Kaiser Permanente
- No. CA Kaiser Permanente
- So. CA Kaiser Permanente
- Kaiser Permanente Colorado
- Health Partners
- Marshfield Clinic
- Harvard
- CDC
Sentinel (PRISM) Partners

HPHC Institute

Data and scientific partners

Scientific partners

Institute for Health
VSD and PRISM: Person-Level Files at Multiple Sites

For 8 VSD sites & 4 PRISM data partners
Updates person-level files on vaccine exposure and outcomes (e.g. weekly, monthly)

Submits programs to each site to provide aggregate counts of vaccines and health outcomes without person-level identifiers

Conduct analyses

Communicate
Framework & Tools (VSD & PRISM)

Purpose & Engagement

Signal Identification
Signal Refinement
Signal Evaluation

Tools

Data Mining
Standardized Tools & Queries
Protocol-based assessment

Temporal Scan
Group Sequential
SCRi design
CTC design

TreeScan
maxSPRT
CC design
Collaboration to Generate Evidence for Decision-Making in 2 Systems

• Rotavirus Vaccine and Intussusception (PRISM)
  • Rare outcome
  • Conflicting findings
  • Power needed
• Inactivated Influenza Vaccine and Febrile Seizures (VSD)
  • Common outcome
  • New finding
  • Timeliness needed
• Getting the right data to the right people at the right time and in the right format
Rotavirus Vaccine & Intussusception – Conflicting Evidence

• 1999-RotaShield withdrawn <1 year post-licensure for excess risk of IS (10-20 cases per 100,000)
• RotaTeq (2006) and Rotarix (2008) licensed for use after Phase III trials with >70,000 and >60,000 infants - no increased risk of IS found
• Post-licensure studies had conflicting findings*

• PRISM asked to evaluate risk for IS in a large population of infants

*Carlin, CID 2013; Velazquez, PIDJ 2012; Patel, NEJM 2011; Shui et al., JAMA 2012
Rotavirus and IS Protocol

- Partnership with 3 national insurers, academia and FDA
  - Epidemiologists, Biostatisticians, Clinicians, Regulatory Decision-makers, Project Managers, Programmer Analysts, Medical Record Review Teams
- 560,000 infants given ~1.4 million doses
- Self Controlled Risk Interval design used, adjusting for time-varying risk of IS
- Medical record review to validate exposures and outcomes

*https://www.sentinelssystem.org/vaccines-blood-biologics/assessments/191; Yih et al., NEJM 2014
RotaTeq Dose 1 was associated with an increased risk of IS in U.S.

- Temporal cluster on Days 3-7
- Attributable risk ranged from 0.2-3.2 excess cases/100,000 doses for first dose vaccinees
- "FDA has approved required revisions to the Prescribing Information and Patient Information for RotaTeq as a result of the new safety data from this Mini-Sentinel PRISM study."

https://www.sentinelstystem.org/communications/fda-safety-communications/295;
http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ucm356758.htm
Febrile Seizures in Australia—New finding

- Increased risk of FS in children <5 years following trivalent inactivated influenza vaccine (TIV) in the Summer of 2010
  - Rate of FS 9x higher than expected (~900 per 100,000 doses) in 1 vaccine manufacturer
  - No elevated risk seen for other TIV products
- Use of CSL vaccine was suspended for young children in both Australia and the U.S.
- VSD asked to conduct near real-time surveillance for FS during the 2010-11 season
Signal Identification – Tools available

• Primary approach: Self controlled risk interval design (SCRI)

• Alternative approach: Current vaccinated vs. historical vaccinated

Greene et al., AJE 2010; Greene et al., PDS 2011; Lee et al., Am J Prev Med 2011; Greene et al., AJE 2012
Sequential Analysis—Tools available

- Use sequential statistical methods to account for repeated testing done weekly
- Maximized sequential probability ratio test (maxSPRT) uses the log likelihood ratio (LLR)
  - Null hypothesis rejected if the LLR reaches a “critical value”
  - SCRI design → Binomial maxSPRT
  - Current vs. historical design → Poisson maxSPRT

Kulldorff et al., Sequential Analysis 2011; Li et al., Stat Med 2010; Lieu et al., Med Care 2007
Current vs. Historical, 6-59 mo

Tse et al., Vaccine 2012
Self-Controlled Risk Interval, 6-59 mo

Tse et al., Vaccine 2012
Signal Refinement & Evaluation

SCRI Design, Medical Record Review & Adjusted for Additional Confounders
Concomitant influenza and PCV13 vaccines were associated with an increased risk of febrile seizures. Risk of febrile seizures was higher in 2010-11.

Attributable risk varied by age, peaking at 45 per 100,000 doses at 16 months of age.

VIS and Label change.
Presented data to CDC, ACIP, AAP SOID and WHO (GACVS)

**BEFORE**
- Assumed decisions would depend on the quality of the data and our choice of study design and analytic approaches
- Focused on making sure these findings were robust (i.e. giving decision makers the best possible information available)

**AFTER**
- They believed our findings, but...
- Strong and varying opinions on what to recommend
  - Timing of communication regarding a “signal”?
  - Modifications to the immunization schedule to minimize risk of adverse events?
What You Need to Know

Influenza Vaccine

Inactivated

What You Need to Know

5 What are the risks from inactivated influenza vaccine?

Moderate problems:
Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time appear to be at increased risk for seizures caused by fever. Ask your doctor for more information.

Tell your doctor if a child who is getting flu vaccine has ever had a seizure.
Decision-Making in Context

• If you give two smart, reasonable people (or organizations) the same information about benefits and risks, they can make different choices. Why?
  • Thresholds for decision-making may be different
    • Implicit values may be driving decisions
  • Uncertainty affects how each of us makes decisions
    • Mental models may drive our response to uncertainty
    • Need for transparency raises the stakes

• Reconsidering recommendations to incorporate new information demonstrates a robust and ongoing DM process, not a failure
Stages of Collaboration

- Collaboration
- Cooperation
- Coordination
- Resource sharing & Networking

Dan Sanker, 2012
Understanding Perspective*

• Mindset of clinicians and policy makers
  • Anticipate the impact of alternative findings
  • Address barriers to acceptance

• Drivers of decision making

• B-R assessment
• Outcome Importance
• Uncertainty
• Resource Use
• Health Equity
• Acceptability
• Feasibility
Improvement Mindset

http://www.ihi.org/resources/PublishingImages/ModelforImprovement.jpg
http://nchica.org/wp-content/uploads/2015/02/Friedman.pdf (Charles Friedman)
Build Culture into the System

Culture is important for sustainability:
• Develop a shared vision
  • Patients, public health, population health
• Establish values, standards and norms
  • Language is important
    • “When you speak to local authority representatives... it’s like talking to an alien.” (Public Health Academic)
• Create opportunities for connection & communication

Taylor-Robinson et al., PLoS ONE, 2012; Ganz et al., Crit Care Med 2016
Precision Medicine

Big Data & Analytics

Surveillance

Pragmatic Trials

Policy & Practice
VSD RCA Collaborators - Partial List (>125 VSD staff)

**Centers For Disease Control, VSD team**
- Frank DeStefano, MD
- Mike McNeil, MD
- Claudia Vellozzi, MD MPH
- Eric Weintraub, MPH
- Natalie McCarthy, MPH
- Julianne Gee, MPH
- Karen Broder, MD
- Tom Shimabukuro, MD

**Harvard Pilgrim Health Care**
- Richard Platt, MD, MSc
- Tracy Lieu, MD MPH
- Alison Tse, ScD
- Sharon Greene, PhD, MPH
- Katherine Yih, PhD, MPH
- Melisa Rett, MPH
- Martin Kulldorff, PhD
- Lingling Li, PhD
- Ruihua Yin, MS
- Robert Jin
- Rich Fox, MSW

**Health Partners Research Foundation,**
- James D. Nordin, MD MPH
- Elyse Kharbanda, MD
- Leslie Kuckler, MPH
- Beth Molitor, MBA

**Kaiser Permanente of Colorado**
- Matt Daley, MD
- David McClure, PhD
- Jason Glanz, MS, PhD
- Simon Hambidge, MD, PhD
- JoAnn Shoup

**Marshfield Clinic Research Foundation,**
- Edward Belonga, MD
- Stephanie Irving, MHS
- James Donahue, DVM, PhD

**Group Health Cooperative**
- Lisa Jackson, MD, MPH
- Jennifer Nelson, PhD
- Patti Benson, MPH

**Kaiser Permanente of No. California**
- Roger Baxter, MD
- Nicky Klein, MD, PhD
- Bruce Fireman, MPH
- Ned Lewis, MPH
- Paula Ray, MPH

**Northwest Kaiser Permanente**
- Allison Naleway, PhD
- John Mullooly, PhD
- Stephanie Irving, PhD
- Lois Drew

**So. California Kaiser Permanente**
- Hung Fu Tseng, PhD, MPH
- Steven Jacobson, MD, PhD
- Mike Marcy, MD
- Craig Cheetham, PharmD
- Lina Sy, MPH
- Lei Qian, PhD
- Marlene Gonzales, MPH
- Amy Liu, PhD
PRISM Collaborators

- HPHCI PRISM Team
  - Meghan Baker
  - Alison Tse Kawai
  - Katherine Yih
  - Sharon Greene
  - Martin Kulldorff
  - Lingling Li
  - Carolyn Balsbaugh
  - Diana Santiago
  - Sandra Feibelmann
  - David Cole
  - Lauren Zichetella
  - Robert Rosofsky

- HPHCI PRISM Team
  - Ruihua Yin
  - Robert Jin
  - Claudia Morena
  - Megan Reidy
  - Ashleigh Goff
  - Tricia Kennedy

- FDA/CBER
  - Steve Anderson
  - Azadeh Shoaibi
  - Michael Nguyen
  - David Martin
  - Robert Ball

- HPHCI MS Team
  - Rich Platt
  - Jeff Brown
  - Darren Toh
  - Nicolas Beaulieu
  - Roberta Constantine
  - Susan Forrow
  - Kim Lane
  - Jim Marshall
  - Lisa Trebino
  - Melisa Rett

- And many, many other MS Collaborators