Overview of systems for active post-marketing medical product surveillance in the USA

Jennifer Clark Nelson, PhD
Biostatistics Unit, Group Health Research Institute
Department of Biostatistics, University of Washington

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Outline

- **Background**
  - Gaps in existing safety evidence base
  - A role for big health care data?
    - Overview: data capture, components, and structure

- **Newly proposed active safety surveillance systems**
  - Vaccine Safety Datalink (CDC)
  - Sentinel Initiative (FDA)

- **Strengths and limitations**

- **Summary**
Lifecycle of a Medical Product

Discovery
(2-10 years)

Preclinical Testing
(lab and animal testing)

Phase I
(20-30 healthy volunteers used to check for safety and dosage)

Phase II
(100-300 patient volunteers used to check for efficacy and side effects)

Phase III
(1,000-3,000 patient volunteers used to monitor reactions to long-term drug use)

FDA Review & Approval

Postmarketing Testing

Year

0  2  4  6  8  10  12  14  16
Gaps in pre-licensure safety data

- **Randomized, controlled clinical experiments**
  - High quality data, designed to evaluate efficacy
  - Can study common, acute adverse events

- **Limitations**
  - Restricted samples → less generalizable
  - Short follow-up → not longer-term safety effects
  - Small samples → lack power for rare events

- **At approval, we don’t know about the risks of**...
  - Common adverse events outside the trial setting
  - Uncommon or later onset adverse events
Gaps in traditional post-licensure data

- **Passive spontaneous reporting systems**
  - National (VAERS, AERS), commercial databases
  - Voluntary AE reports by patients or physicians
  - Rapidly available, low quality (hypothesis generation)

- **Phase IV studies**
  - Prospective randomized trial or large prospective observational cohort study
  - More reliable (population-based) data
  - Hypothesis testing possible, often geared to efficacy
  - Study results not available rapidly
Withdrawal of Rotavirus Vaccine Recommendation

In July 1999, CDC recommended that health-care providers and parents postpone use of the rhesus rotavirus vaccine-tetravalent (RRV-TV) (RotaShield[Registered]*)*, Wyeth Laboratories, Inc., Marietta, Pennsylvania), for infants, at least until November 1999. This action was based on reports to the Vaccine Adverse Event Reporting System of intussusception (a type of bowel obstruction that occurs when the bowel folds in on itself) among 15 infants who received rotavirus vaccine. Also at that time, the manufacturer, in consultation with the Food and Drug Administration, voluntarily ceased further distribution of the vaccine.

On October 22, 1999, the Advisory Committee on Immunization Practices (ACIP), after a review of scientific data from several sources, concluded that intussusception occurs with significantly increased frequency in the first 1-2 weeks after vaccination with RRV-TV, particularly following the first dose. Therefore, ACIP no longer recommends vaccination of infants in the United States with RRV-TV and withdraws its recommendation that RRV-TV be administered at 2, 4, and 6 months of age. Children who received rotavirus vaccine before July and remain well are not now at increased risk for intussusception.

Rotavirus remains the cause of a substantial health burden for children in the United States. It accounts for 20-40 deaths annually, and greater than 50,000 hospitalizations from severe diarrhea and dehydration. Vaccination against rotavirus would be the optimal means to prevent such illnesses. RRV-TV was recommended because it was shown in prelicensure trials to be a safe and effective vaccine. In those trials, RRV-TV prevented rotavirus in at least 50% of cases of diarrhea and almost all of the hospitalizations. Postlicensure evaluation, however, has identified intussusception as an uncommon, serious adverse event associated with the vaccine.
2005: Prospective vaccine surveillance begins (VSD)
2006: IOM reports on *The Future of Drug Safety*
2007: FDA Amendments Act passed by Congress
  - Mandates a national, electronic surveillance system
  - To actively monitor drugs, devices, and biologics
  - To capture data on 100 million patient lives by 2012
2008: FDA launches ‘Sentinel Initiative’ response
2009: FDA funds Mini-Sentinel pilot
  - To establish data infrastructure and test methods
2011: Mini-Sentinel can ‘query’ >100 million people
2013: Routine prospective surveillance pilot begins
2014: Sentinel Initiative coordinating center awarded
Stages of post-market surveillance

- **Signal Generation**: To identify potential associations between *any* medical product & adverse event (often 100’s, 1000’s of pairs).
  
  **Example**: Data mining of passive adverse event reports

- **Signal Refinement**: To *rapidly* evaluate the magnitude of suspected associations between several target product-event pairs.
  
  Active surveillance is intended to fill this gap.

- **Signal Evaluation**: To establish or refute causality between a particular product and adverse event of interest.
  
  **Example**: Phase IV trial or rigorous epidemiological cohort study
A role for **big health care data?**
(...and what does that even mean?)

Administrative health care data are collected by public and private organizations for the purposes of registration, transaction and record keeping, usually during the delivery of health care services (i.e., they are not collected for research purposes)
Record Generation Process

Patients has symptoms, acute illness etc.

Encounter with health professional

Examination, history, diagnostics

Diagnosis

Interventions including drug prescribing

Pharmacy encounter

Potential Sources of Bias

Indigent patients without coverage and patients with insufficient insurance are less likely to seek professional care.

Incomplete documentation of clinical status; Misdiagnosis; False ranking of ‘primary diagnosis’.

Miscoding of drug, strength, dose; Non-recording of free samples and over-the-counter drugs.

Incomplete record keeping.

Miscoding of primary and secondary diagnoses; Miscoding of procedures; Failure to file claims.

Transaction error; Lag-time until adjudication and final filing; Loss to follow-up if patient has left the system.

Incomplete / false record linkage

* Electronic Medical Record

Adopted from:
Schneeweiss S, et al.
Example uses of administrative healthcare databases

- Observational research studies (e.g., epidemiology, comparative effectiveness, health services)
- **Public health safety surveillance**
- Policy analyses/evaluations
- Economic evaluations (cost-effectiveness)
- Clinical studies
- Risk adjustment
- Health Effectiveness Data and Information Set (HEDIS) requirements
### US private databases, examples

- MarketScan
- Pharmetrics
- United Health
- Healthcore
- Premier inpatient
- GE Healthcare
- HMO Research Network
US public databases, examples

- Healthcare Cost and Utilization Project (HCUP)
- Medicare and Medicare Part D
- SEER-Medicare Linked Databases
- Vaccine Safety Datalink (VSD) (for CDC)
- Veterans Administrative Databases
- Mini-Sentinel Distributed Database (for FDA)
- Patient-Centered Clinical Data Research Network
- NIH Collaboratory (pragmatic clinical trial demonstration projects)
Basic contents of databases

- Diagnoses (ICD-9 or ICD-10, dates)
- Procedures (CPT/HCPCS, dates)
- Pharmacy dispensings (drug name, dates)
- Demographics (age, sex, enrollment)
- Costs or charges of services
- Care setting (e.g., outpatient, ER, inpatient)
- Type of provider (e.g., primary, specialty)
- Supplemental data (EMR data: labs, vitals, indications; disease registries, death data, census data, other patient/provider info)
Data Capture Summary

- Created for administrative (and clinical) purposes
  - Health care system encounters (outpatient, inpatient, procedures, pharmacy) create electronic claims to the payer for reimbursement
  - Paper or electronic medical record captures standard medical and clinical data gathered in one provider’s office.
- Data are linked across various sources (e.g., clinical records, billing data, lab results, insurance claims, electronic health records, and vitals)
- An integrated picture of health & healthcare emerges
- Data elements defined by a common data model can be linked across data partners for multi-site research
Vaccine Safety Datalink (VSD)

- Established in 1990
- A collaborative project among CDC & 10 managed care organizations (MCOs)
- Priorities
  - To evaluate the safety of newly licensed vaccines or new recommendations for existing vaccines
  - To develop & evaluate new methods for safety
- Pre-2004: traditional retrospective studies (~12 month lag)
- Post-2004: near-real time evaluations (weekly updates)
Captures medical care and vaccination data
- Large population: >9.6 million (>3% of U.S. population)
- Population-based: members from 10 (now 6) health plans
VSD Annual Data Files

- ER Visits
- Hospital discharge diagnosis codes
- Enrollment and demographics
- Procedure Codes
- Linked by Study IDs
- Birth and death certificate information & Family Linkage
- Outpatient and Clinic visits
- Immunizations Records
The VSD Distributed Data Model (DDM)

A system that eliminates need for individual level, standardly-defined data (outcome, exposure, covariates) to be transferred across sites:

- Data Partners maintain physical control of their data
- Data Partners understand their data best (valid use requires their input)
- Avoids many concerns about inappropriate use of confidential data
- No need to create/secure/manage a complex, central data warehouse
- Facilitates simultaneous, multi-site processing of (SAS) programs submitted by CDC/VSD data analysts
- Allows routinely conducted and timely research because of
  - Weekly data updating
  - Rapid turn-around of submitted programs/requests
Real-Time Vaccine Safety Surveillance for the Early Detection of Adverse Events

Tracy A. Lieu, MD, MPH,*† Martin Kulldorff, PhD,* Robert L. Davis, MD, MPH,‡
Edwin M. Lewis, MPH,§ Eric Weintraub, MPH,‡ Katherine Yih, PhD, MPH,* Ruihua Yin, MS,*
Jeffrey S. Brown, PhD,* and Richard Platt, MD, MSc,* for the Vaccine Safety Datalink Rapid Cycle Analysis Team

Background: Rare but serious adverse events associated with vaccines or drugs are often nearly impossible to detect in prelicensure studies and require monitoring after introduction of the agent in large populations. Sequential testing procedures are needed to detect vaccine or drug safety problems as soon as possible after introduction.

Objective: To develop and evaluate a new real-time surveillance system that uses dynamic data files and sequential analysis for early detection of adverse events after the introduction of new vaccines.

Research Design: The Centers for Disease Control and Prevention (CDC)-sponsored Vaccine Safety Datalink Project developed a real-time surveillance system and initiated its use in an ongoing study of a new meningococcal vaccine for adolescents. Dynamic data files from 8 health plans were updated and aggregated for analysis every week. The analysis used maximized sequential probability ratio testing (maxSPRT), a new signal detection method that supports continuous or time-period analysis of data as they are collected.

Conclusions: Real-time surveillance combining dynamic data files, aggregation of data, and sequential analysis methods offers a useful and highly adaptable approach to early detection of adverse events after the introduction of new vaccines.

Key Words: vaccine safety, active surveillance, sequential analysis, meningococcal vaccine, drug safety

(Med Care 2007;45: S89–S95)

Concerns about the safety of vaccines and drugs introduced in recent years have highlighted the need to enhance systems for early detection of potential adverse events. Uncommon but serious adverse events have led to the withdrawal of both biologic and pharmacologic agents from the market. Examples include the discontinuation of rotavirus vaccine after reports of intussusception (a rare, but serious, gastrointestinal event).
Update: Recommendations from the Advisory Committee on Immunization Practices (ACIP) Regarding Administration of Combination MMRV Vaccine

On February 27, 2008, new information was presented to the Advisory Committee on Immunization Practices (ACIP) regarding the risk for febrile seizures among children aged 12--23 months after administration of the combination measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad®, Merck & Co., Inc., Whitehouse Station, New Jersey). This report summarizes current knowledge regarding the risk for febrile seizures after MMRV vaccination and presents updated ACIP recommendations that were issued after presentation of the new information. These updated recommendations remove ACIP’s previous preference for administering combination MMRV vaccine over separate injections of equivalent component vaccines (i.e., measles, mumps, and rubella [MMR] vaccine and varicella vaccine).

The combination tetravalent MMRV vaccine was licensed by the Food and Drug Administration (FDA) on September 6, 2005, for use in children aged 12 months--12 years (1). MMRV vaccine can be used in place of trivalent MMR vaccine and monovalent varicella vaccine to implement the recommended 2-dose vaccine policies for prevention of measles, mumps, rubella, and varicella (1, 2). The first vaccine dose is recommended at age 12--15 months and the second at age 4--6 years.

In MMRV vaccine prelicensure studies, an increased rate of fever was observed 5--12 and 0--42 days after the first vaccine dose, compared with administration of MMR vaccine and varicella vaccine at the same visit (3, 4). Because of the known association between fever and febrile seizures (5), CDC and Merck initiated postlicensure studies to better understand the risk for febrile seizures that might be associated with MMRV vaccination.

The Vaccine Safety Datalink (VSD),* which routinely monitors vaccine safety by near real-time surveillance using computerized patient data, detected a signal of increased risk for seizures of any etiology among children aged 12--23 months after administration of MMR vaccine compared with administration of MMR vaccine (many children also received varicella vaccine). When children who received MMRV vaccine were
VSD’s general approach to surveillance

- Identify primary exposure and comparator populations
  - Historical comparators (compute expected counts)
  - Concurrent comparators (e.g., new user design)
  - Within-person comparisons (self-controlled designs)

- Pre-specify adverse event (AE) outcomes of interest
  - 5-10 AEs (AERs, pre-licensure, use outside US)

- Identify potential confounders
  - Age, gender, site, comorbidities, concomitant medications

- Routine dataset construction and sequential analysis
  - Update de-identified data regularly (e.g. weekly, monthly,…)
  - Repeatedly test hypotheses of interest over time
  - Signaling threshold controls overall false positive error rate
“To inform and facilitate development of a fully operational active surveillance system (Sentinel) that monitors the safety of all FDA-regulated products…” including vaccines, drugs, & devices

- Create distributed data network and data model
  - 17 Data Partners (VSD sites + many more)
  - As of December 2011: captured data on 126M lives
- Evaluate prospective safety surveillance methods

www.mini-sentinel.org
Mini-Sentinel’s Common Data Model*

- Built on VSD and HMORN models
- Populations with well-defined person-time for which medically-attended events are known
- Data is captured on 126 million people
  - 345 million person-yrs of observation time (2000-11)
  - 44 million currently enrolled, accumulating new data
  - 27 million with over 3 years of data
- 3 billion pharmaceutical dispensings
- 2.4 billion unique medical encounters
- 13 million people with $\geq 1$ laboratory test result

*As of December 2011
Mini-Sentinel Distributed Analysis

1- User creates and submits query (a computer program)
2- Data partners retrieve query
3- Data partners review and run query against their local data
4- Data partners review results
5- Data partners return results via secure network
6 Results are aggregated
Strengths of Healthcare Data

- Valuable source of data for quick, less costly studies
- Most contain large samples and are population based
- Can study “real world” effectiveness, safety, and use
- Most contain continuous (vs interval) assessments of exposure and outcome
- Some have near complete outpatient prescription data and outpatient/inpatient diagnoses & procedures
- Not subject to recall bias or non-response
- Technology has advanced capabilities and ease of accessing and working with the data
Limitations of Healthcare Data

- Data not collected for research (requires encounter)
- Generalizability to other populations (uninsured)
- Missing outcome (disease severity, onset, death), exposure (OTC meds), or confounders (SES, diet)
- Misclassification (rule diagnoses, disease onset date)
- Turnover rate in most MCOs is 20-30% a year
- Often cannot contact study subjects for further data
- Few have or allow access to medical charts
- Data influenced by formularies, practice patterns, etc.
- Changes in data collection or software (ICD-10)
- Inability to track the same individual coming in and out of the system
Summary

- Gaps in existing safety evidence base have motivated improvements and expansion of ‘big data’ infrastructures to support research
- Enormous growth in the use of large health care databases (& not just in US)
  - Rapid safety surveillance: VSD, Mini-Sentinel
  - Patient-centered research: PCORnet
  - Pragmatic clinical trials: NIH Collaboratory
- Data contents and quality differ among databases (know your data & their limits!)
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Mini-Sentinel Investigators, including FDA
Rich Platt, Jeff Brown, Grace Lee, Darren Toh, Azadeh Shoabi

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Rotashield vaccine & intussusception

- **Rotashield vaccine and rotavirus**
  - Licensed in 1998, 1st effective vaccine to prevent rotavirus
  - Most common cause of diarrhea among children
  - 55K hosp/year in US; 600K deaths/year worldwide

- **Pre-licensure intussusception (rare bowel obstruction) data**
  - 27 pre-licensure trials of rotavirus vaccines
  - 5 cases/10K vaccinees (0.05%) vs 1/4633 for placebo (0.02%)
  - Not statistically difference, but noted on package insert

- **Post-licensure data**
  - 15 reports of intussusception to VAERS
  - Rotashield withdrawn in July 1999 (9 months after licensure)
  - Risk after 1st dose: 20-30 times that expected
### A. PATIENT INFORMATION

<table>
<thead>
<tr>
<th>1. Patient Identifier</th>
<th>2. Age at Time of Event, or Date of Birth:</th>
<th>3. Sex</th>
<th>4. Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In confidence</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>Female</td>
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<tr>
<td></td>
<td></td>
<td>Male</td>
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<tr>
<td></td>
<td></td>
<td>________ lb or ________ kg</td>
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</tr>
</tbody>
</table>

### B. ADVERSE EVENT, PRODUCT PROBLEM OR ERROR

Check all that apply:

1. [ ] Adverse Event  [ ] Product Problem (e.g., defects/malfunctions)
   2. [ ] Product Use Error  [ ] Problem with Different Manufacturer of Same Medicine

2. Outcomes Attributed to Adverse Event
   (Check all that apply)
   [ ] Death: (mm/dd/yyyy)  [ ] Disability or Permanent Damage
   [ ] Life-threatening  [ ] Congenital Anomaly/Birth Defect
   [ ] Hospitalization - initial or prolonged  [ ] Other Serious (Important Medical Events)
   [ ] Required Intervention to Prevent Permanent Impairment/Damage (Devices)

3. Date of Event (mm/dd/yyyy)  4. Date of this Report (mm/dd/yyyy)

5. Describe Event, Problem or Product Use Error

### D. SUSPECT PRODUCT(S)

1. Name, Strength, Manufacturer (from product label)
   #1
   #2

2. Dose or Amount  Frequency  Route
   #1
   #2

3. Dates of Use (if unknown, give duration) from/to (or best estimate)
   #1
   #2

4. Event Abated After Use Stopped or Dose Reduced?
   #1  Yes  No  Doesn't Apply
   #2  Yes  No  Doesn't Apply

5. Diagnosis or Reason for Use (Indication)
   #1
   #2

6. Lot #  7. Expiration Date
   #1
   #2

### E. SUSPECT MEDICAL DEVICE

1. Brand Name

2. Common Device Name

3. Manufacturer Name, City and State

4. Model #  Lot #  5. Operator of Device
   Catalog #  Expiration Date (mm/dd/yyyy)
   Serial #  Other #

6. If Implanted, Give Date (mm/dd/yyyy)
7. If Implanted, Give Date (mm/dd/yyyy)

8. Is this a Single-use Device that was Reprocessed and Reused on a Patient?
   [ ] Yes  [ ] No

9. If Yes to Item No. 8, Enter Name and Address of Reprocessor

6. Relevant Tests/Laboratory Data, Including Dates
The bottom line

- Existing gaps in safety evidence are problematic
- Some unsafe products are on the market too long
  - Rotashield: removed after 9 months due to VAERS
  - Vioxx: removed after 5 years due to Phase IV trial
- No single existing system is simultaneously
  - Large, generalizable (gap for pre-licensure RCTs)
  - Proactive, prospective, and population-based
    (gap for passive reports)
  - Available rapidly enough (gap for Phase IV studies)
Supplemental data elements

- Laboratory results
- Electronic medical records
  - Vital signs (e.g., BP, weight, height)
  - Procedure results (e.g., EF for heart failure, radiology images)
  - Indication for prescription
  - Flow sheets (PHQ-9, Medicare wellness survey)
- Disease registries (e.g., cancer, diabetes)
- Mortality and cause of death
- Census data
- Provider characteristics (e.g., gender, years practice)
- Patient characteristics (e.g., race, education, smoking status, family history, health behaviors)
Medication data

- Drug name, strength, date dispensed, quantity, form, route, days supply, provider, out pocket cost, NDC, therapeutic class, for each medication dispensed or claim submitted
  - Supplemental data may include directions for use, indication, intended duration, completion of therapy (e.g., chemotherapy)

- Record for each dispensing
VSD Population

- Collects medical care and vaccination data on more than 9.6 million members annually (3.1% of the US population)

- As of 12/31/2010:
  - 2,238,537 children (<18) enrolled
    - 3.0% of US population
  - 7,357,734 adults (≥18) enrolled
    - 3.1% of US population
  - Average yearly birth cohort ~ 96,000
VSD Centralized Data Model

Northwest Kaiser

Northern California Kaiser

Kaiser Colorado

Marshfield

Group Health

Health Partners

Southern California Kaiser

Harvard Pilgrim

Medical Record

Medical Record

Medical Record

Medical Record

Medical Record

Medical Record
The VSD Distributed Data Model

CDC

“Direct”

Hub

“Indirect”

SAS Programs, Logs, Output, & Analytical Datasets
HMO Research Network

- Consortium of 16 health plans and their affiliated research centers
- **Mission**: To facilitate and promote the unique research capabilities of member organizations
  - Fostering collaborative studies
  - Sharing methodologies & best practices
  - Disseminating & translating research findings
- Combined population = ~15 million individuals
- Geographically & socio-culturally diverse
Interconnected Data Resources at GHRI and other HMORN partners
Virtual Data Warehouse (VDW)

VDW is populated by automated data from the following sources:

- Tumor registry
- Enrollment
- Demographics
- Pharmacy
- Utilization – includes diagnoses & procedures
- Some vitals such as BMI & blood pressure
- Geocoding
- Laboratory
- Chemotherapy
- Radiology
- Pathology
Example of longitudinal data within HMORN

GHC Data Availability

Source
- Tumor
- Census
- Multiple Cause of Death
- Death
- Provider Specialty
- Vitals
- Outpatient Pharmacy
- Lab
- Procedures
- Diagnoses
- Utilization
- Enrollment
- Demographics

Year
- 1950
- 1960
- 1970
- 1980
- 1990
- 2000
- 2010
<table>
<thead>
<tr>
<th>Method</th>
<th>Used in</th>
<th>Statistic</th>
<th>Boundary</th>
<th>Confounding</th>
<th>Advantages</th>
<th>Limitations</th>
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<tbody>
<tr>
<td>GS-LD</td>
<td>RCTs</td>
<td>Any standardized normal</td>
<td>Error Spending, using normal approx (even spending, flat/Pocock-like)</td>
<td>Any (Matching, Stratification, Regression)</td>
<td>Easy to apply; flexible confounding control</td>
<td>Assumptions ok? (normal approx, independent data increments)</td>
</tr>
<tr>
<td>Lan &amp; Demets 1983</td>
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<tr>
<td>GS-LRT</td>
<td>RCTs, VSD Lai 1991 (GLRs), Kullstrum 2011 (MaxSPRT)</td>
<td>LRT</td>
<td>Unifying (or error spending) boundary, permutation derived (flat/Pocock-like)</td>
<td>Matching with fixed (1:M) ratio</td>
<td>Easy to apply; appealing interpretation</td>
<td>Information loss (restricted sample) too strict → lose cases; too loose → poor control</td>
</tr>
<tr>
<td>CSSP</td>
<td>Drug safety Li 2009 &amp; 2011</td>
<td>Number of AEs among exposed</td>
<td>Error spending, conditions on total # of AEs within strata (even spending)</td>
<td>Stratification (including on calendar time)</td>
<td>Works well for rare AEs</td>
<td>May not hold Type I error if strata small or testing highly frequent</td>
</tr>
<tr>
<td>GS-EE</td>
<td>VSD Cook 2012</td>
<td>Score statistic</td>
<td>Unifying (or error spending) boundary, permutation derived (flat/Pocock-like)</td>
<td>Regression</td>
<td>Flexible confounding control; few assumptions</td>
<td>Requires ‘enough’ AEs to estimate parameters; computer intensive</td>
</tr>
</tbody>
</table>
Outcome over time amongst MMRV recipients

<table>
<thead>
<tr>
<th>Table A.2: Outcome Counts and Risk % by Look and Covariate Strata Among MMRV</th>
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<tbody>
<tr>
<td>Look 1</td>
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<tr>
<td>--------</td>
</tr>
<tr>
<td>Total, Outcome(%)</td>
</tr>
<tr>
<td>Age, Outcome(%)</td>
</tr>
<tr>
<td>11m-12m</td>
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<tr>
<td>13m-14m</td>
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<tr>
<td>15m-16m</td>
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<td>17m-19m</td>
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<td>16</td>
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</table>

*Abbreviations: Outcome(%) = Number(Risk %) of outcome within look and covariate stratum.
Outcome over time amongst MMRV recipients (cont)

| Table A.2: (Continued) Demographics by Outcome across Analysis Times among MMRV |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | Look 7 (0.089)  | Look 8 (0.093)  |
| Total, Outcome(%)              | 36              | 45              |
| Age, Outcome(%)                |                 |                 |
| 11m-12m                         | 15 (0.076)      | 20 (0.084)      |
| 13m-14m                         | 8 (0.091)       | 9 (0.084)       |
| 15m-16m                         | 5 (0.068)       | 7 (0.085)       |
| 17m-19m                         | 6 (0.194)       | 6 (0.163)       |
| 20m-23m                         | 2 (0.139)       | 3 (0.169)       |
| Sex, Outcome(%)                |                 |                 |
| Male                            | 16 (0.078)      | 21 (0.086)      |
| Female                          | 20 (0.101)      | 24 (0.101)      |
| Site, Outcome(%)               |                 |                 |
| 2                               | 2 (0.092)       | 2 (0.088)       |
| 4                               | 0 (0.000)       | 0 (0.000)       |
| 15                              | 30 (0.092)      | 35 (0.089)      |
| 16                              | 4 (0.075)       | 8 (0.128)       |

*Abbreviations: Outcome(%) = Number (Risk %) of outcome within look and covariate stratum.
### Table A.4: Demographics across Analysis Times among MMRV

<table>
<thead>
<tr>
<th></th>
<th>Look 1</th>
<th>Look 2</th>
<th>Look 3</th>
<th>Look 4</th>
<th>Look 5</th>
<th>Look 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total, N(Row%)</strong></td>
<td>2796 (5.8)</td>
<td>6970 (14.5)</td>
<td>11577 (24.0)</td>
<td>17376 (36.0)</td>
<td>24195 (50.2)</td>
<td>32123 (66.6)</td>
</tr>
<tr>
<td><strong>Age, N(Col%)</strong></td>
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<td>3424 (49.1)</td>
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## MMRV Demographics across Analysis Times (cont)

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<td>3687 (7.6)</td>
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<td>20m-23m</td>
<td>1437 (3.6)</td>
<td>1771 (3.7)</td>
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<td><strong>Sex, N(Col%)</strong></td>
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<tr>
<td>Male</td>
<td>20541 (50.9)</td>
<td>24548 (50.9)</td>
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<tr>
<td>Female</td>
<td>19785 (49.1)</td>
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<td><strong>Site, N(Col%)</strong></td>
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<td>2</td>
<td>2178 (5.4)</td>
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<td>394 (1.0)</td>
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<td>5311 (13.2)</td>
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</table>
Figure A.1: Uptake of MMR+V and MMRV over Time for Site 2
Uptake by Site

Figure A.2: Uptake of MMR+V and MMRV over Time for Site 4
Figure A.3: Uptake of MMR+V and MMRV over Time for Site 15
Figure A.4: Uptake of MMR+V and MMRV over Time for Site 16
Propensity Scores

- Propensity Score Definition
  - $P(\text{Exposed}|\text{Confounders}) = P(X|Z)$

- Why are they relevant to safety surveillance?
  - Allows for the adjustment of a large number of confounders even in the rare event setting given:
    - good proportion of exposed and unexposed
    - De-identifies data since numerous confounders combinations can give the same propensity score value

- How can they be used?
Confounding Control Using Propensity Scores

**Design-based Approaches**
- **Exposure Matching**
  - Match each exposed person to a set of controls with similar propensity scores
- **Stratification**
  - Stratify the population with propensity score strata

**Analysis-based Approaches**
- **Regression**
  - Adjust directly for propensity scores
- **Inverse Probability of Treatment Weighting**
  - Re-weights population based on propensity scores to average out the effect of confounding
What is IPTW?

- **What is an inverse probability of treatment weight?**

  For those exposed
  - \[ \text{Weight} = \frac{1}{P(\text{Exposed} | \text{Confounders})} = \frac{1}{P(X|Z)} \]

  For those unexposed
  - \[ \text{Weight} = \frac{1}{P(\text{Unexposed} | \text{Confounders})} = \frac{1}{1 - P(X|Z)} \]

  Use these weights to estimate marginal RR, OR, Risk Difference
IPTW in Distributed Data Settings: Currently Available

- **IPTW**
  - Use site-specific propensity scores to create IPTW weights
  - Estimates: marginal OR, RR or Risk Difference
  - Issues:
    - Large Weights: Observations become too informative and variance inflates (Standardize weights, Trimming or Restriction)
    - Incorporate site-specific propensity score models: use bootstrapping or permutation to handle differential variability of propensity score across site, but not very computationally feasible.
    - Can we do this better?
What is a pragmatic trial??

- **Just an effectiveness Study??** (Patsopoulos, N.A. 2011)
  - Research Question:
    - Does an intervention actually work in a real life setting??
  - Generalizes to a larger population (no/limited inclusion or exclusion criteria)
  - No plans to improve or alter compliance for the experimental or the comparative treatment

- **Studies designed to provide information that can be directly adopted by healthcare providers (PCORI)**
  - Simpler than traditional RCTs
  - Conducted in routine clinical care settings
  - Relatively large

- **More cost-effective then standard RCTs**
  - Use EHR to collect outcomes and/or distribute intervention
  - More feasible/cheaper study designs (e.g. Cluster randomized)
Pragmatic Trials Initiatives

- **PCORI**
  - PCORnet
    - Large network of distributed healthcare data to conduct both pragmatic trials and observational studies
    - Spring 2014 Funding Announcement: Pragmatic Clinical Studies and Large Simple Trials to Evaluate Patient-Centered Outcomes

- **NIH Collaboratory**
  - “Rethinking Clinical Trials”
  - Health Care Systems Research Collaboratory
  - First round funded 7 Pragmatic Trials with 5 going to UH3 stage so far
  - Second round being announced soon.
Use of EHR Data in Pragmatic Trials for…

- **Study Population, Design, and Recruitment**
  - Use EHR to define eligible study population
  - Design/Randomization: Obtain information on clinic population to stratify cluster randomization on important variables (size, baseline outcomes, age of population, …)
  - Recruit participants through EHR systems

- **Implementing the intervention**

- **Data Collection**
  - Baseline Data
  - Confounders (patient, physician, or clinic level)
  - Primary and Secondary Outcomes (patient reported outcomes?)
Outcome Ascertainment using EHR data

- Common Outcome Assumptions/Issues
  - Health Outcomes: If someone is enrolled in the healthcare plan if there is no outcome coded then they don’t have it
    - Healthcare utilization varies for different participants is this assumption valid
    - Likely ok for serious health outcomes
  - Patient Reported or other Process Outcomes: Only obtain measures on those who attend a health care visit (e.g. Depression measures, blood pressure, weight)
    - Bias due to having a measure or not
    - Bias when the measure occurred
    - Bias how many measures occurred over a follow-up window
Pragmatic Trials are a cross between RCTs and Full observational studies

Do not assume randomization fixes all issues even individually randomized designs

Consider potential bias from outcome ascertainment, design choices (e.g. cluster), consent, ...

Apply statistical methods similar to full observational studies

More considerations in conducting sensitivity analyses to assess assumptions
Pragmatic Trials are becoming increasingly common

Using EHR data has advantages, but causes statistical complications

Large networks have formed or are being formed to conduct even larger multi-site pragmatic clinical trials

- Distributed Data systems are likely to be used to protect patient privacy
- Statistical methods that can be applied in distributed data networks will need to be developed to conduct such studies correctly.
**Permutation Approach for Rare Events**

- Under Ho: Adjusted Risk Difference = 0
- Outcome|Confounders independent of exposure
- Permutation Approach:
  - Fix outcomes and confounders and permute exposures within site
  - On permuted datasets calculate $\Delta_s^{(p)}$, $V(\Delta_s^{(p)})$
- Computational Advantages
  - For permuted datasets $P(X|Z) = P(X)$
  - Don’t need to refit propensity models on permuted data, but just assume propensities are fixed and calculate correct variance
- For analyses sites would also send these permuted summary data to a central location