Safety Throughout the Life Cycle of Vaccines

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Disclaimer

The findings and conclusions in this presentation have not been formally disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.
Division of Biostatistics
Organizational Chart

Division Director

Therapeutic Evaluation Branch
- Hematology Team
- Diagnostics and Screening Team
- Cell and Gene Therapy Team

Vaccine Evaluation Branch
- Viral and Bioassay Team
- Bacterial/Allergenic Team
Outline

• Vaccines 101
• Safety in Pre-Market
• Postmarket and SCCS
• Passive Surveillance and VAERS
• Active Surveillance
  - VSD, PRISM, Federal Partners
• Open methodological questions
• Conclusions
Vaccine 101
Vaccines are not drugs!

- Administered to healthy people
- Designed to prevent disease
- Importance of herd immunity

Need high buy-in
Maintaining confidence in vaccines is key
Vaccines are not drugs!!

- Like other biologics, vaccines are **licensed**
- FDA: premarket review
- Vaccines in post-market:
  - HHS: FDA, CDC, NVPO
  - Global: WHO, EMA, .....
- Pandemic and Seasonal flu Vaccines:
  - New variants keep coming
- Lot release review
Federal Plans to Monitor Immunization Safety for the Pandemic 2009 H1N1 Influenza Vaccination Program

Federal Immunization Safety Task Force

U.S. Department of Health and Human Services
Agency for Healthcare Research and Quality
Centers for Disease Control and Prevention
Food and Drug Administration
Health Resources and Services Administration
Indian Health Service
National Institutes of Health
Department of Defense
Department of Veterans Affairs


Advisory Committees in Red
Immunological Assay

- Required for all vaccines
- Carefully reviewed at FDA
- Immune response endpoint
  Correlate of protection (?)
  see papers by Gilbert et al
  Example: Antibody to HBV
- Surrogate endpoint (?)
  see papers by Gilbert or Prentice
Lot-to-Lot Consistency

• Three lots of vaccine
• Used in a 3 arm study
  ....often sub-study of bigger trial
• Three lots must be comparable
  ....similar to a bioequivalence criteria
• Immunological assay variability can be an issue
  ....Important for design
Vaccine Development

• Phase 1  Safety studies
• Phase 2  Different doses and schedules
  • Hundreds of patients
  • Characterize very common A.E.
• Phase 3  Pivotal studies for licensure
  • Plan for pharmacovigilance
• Unsafe vaccines don’t get to next phase!
• Sometimes additional safety registry
Efficacy Trials

• First of a kind vaccines:
  Endpoint based on case definition
• Usually has a placebo arm
• Cannot control disease exposure
• Large trials and super-superiority
• VE=Vaccine Efficacy=
  \[1 - \frac{\text{disease rate, V}}{\text{disease rate, C}}\]
• Flu  VE>40% (95% Lower Conf Bound)
Several trials: common

- Different age classes (e.g. flu)  
  Infants, kids, adults, elderly  
- Common concomitant vaccines  
- International trials  
  Higher background rates  
  Relevance to US? (e.g. strain types)  
- Safety data are captured in all
Immunogenicity trials

• 2\textsuperscript{nd} of a kind
• Disease prevalence is now lower
• Active control arm
• Non-inferiority of an immune response endpoint (NI Margin: talk with OVRR)
• Multiple serotypes: multiple endpoints trivalent flu, Prevnar 13
• Interpretation of safety data?
Plan for Pharmacovigilance: During BLA review (DE)

- International Conference on Harmonization (ICH) Guidance for industry: E2E Pharmacovigilance Planning format
- Early consideration of FDAAA 2007 options
- Postmarketing studies are informed by:
  - Experience with post marketing surveillance strengths and limitations
  - Experience with similar products
  - Safety issues identified by Clinical and Statistical reviewers during pre-licensure review
Vaccines are not drugs !!!

• Some rare but serious events: linked to vaccine use
  • Guillian Barre Syndrome
    (Swine Flu 1970s)
  • Intussusception (Rotavirus 1990s)
  • Severe allergic reactions (Vaccines & eggs)

• May trigger additional studies or spur serious post-market surveillance
Inference for safety in phase 3

- Most studies use 1:1 allocation
- Some expose more to new vaccine
- Flu guidance for established mfg: Rule out 1 in 300 adverse event
- Inference with very big N, very small p
  Most articles assume rate > .01 or 1%
Inference Methods Study:
Pre-specified adverse events

- Exact methods:
  Computationally burdensome in phase 3
  For safety: symmetric methods
  95% confidence interval
  Want appropriate one sided values
- Score methods are compromise (Newcombe)
- Wald and related methods are poor
- Farrington and Manning for NI not implemented
  the same across packages.
Risk difference (RD) or Relative Risk (RR)

- Very rare events, RR exaggerates risk
- RR when control has zero events?
- Deeks et al: RR more stable across studies
- RD provides excess risk estimate
  number of cases per 100,000
- Reporting both makes sense (SPERT, 2009)
- Control of alpha: rarely done if small number of pre-specified events.
RotaShield

• As of 1998, rotavirus was the most common cause of severe gastroenteritis in infants and children less than 5 y.o. in the U.S.
  – 500,000 physician visits, 50,000 hospitalizations, 20 deaths/year in the U.S.
  – 600,000 deaths/year worldwide
• The first rotavirus vaccine, RotaShield was licensed in August 1998
• RotaShield was voluntarily taken off the market in 1999
RotaShield and intussusception

• Very soon after licensure, reports of intussusception temporally associated with RotaShield began appearing in VAERS

• Intussusception is a potentially life-threatening bowel obstruction
  – Background incidence in infants ~ 0.0004 cases / year

• Following investigation, CDC determined that 1 – 2 additional cases of intussusception would be caused by RotaShield per 10,000 infant-years
The REST trial (1)

- Thus, intussusception was a major concern for future rotavirus vaccine candidates
- Development of the RotaTeq vaccine included the Rotavirus Efficacy and Safety Trial (REST)
- 69,625 subjects were vaccinated (n=34,837) or placebo (n=34,788)
- The primary efficacy endpoint was based on cases of disease
  - But this was only assessed in 5,673 (8%) of subjects
The REST trial (2)

• The sample size was driven by the safety endpoint of intussusception
  – Subjects actively monitored for potential intussusception at 7, 14 and 42 days post each dose, then every 6 weeks for 1 year
  – Primary safety win criterion was upper bound of the 95% CI for RR to be ≤ 10 without hitting safety stopping boundaries
  – Group sequential design
    • Initial analysis at n = 60,000
    • Subsequent analyses after each 10,000 subjects up to 100,000
• Study concluded with 6 cases in the vaccine arm, 5 in the placebo arm
Lessons learned from a huge safety trial

• A huge trial may only be possible with a relatively easy-to-ascertain primary safety endpoint

• Embedding efficacy and detailed safety subsets in the overall safety trial improves efficiency
  – Always a good idea to collect whatever efficacy and safety information is feasible

• With a background incidence of ~1/10,000, even 60,000 – 100,000 subjects will only permit ruling out an RR of 10.
  – Safety trials have to operate within realistic constraints
Vaccines vs Drugs in Postmarket
Key differences

• Fewer possible confounders with vaccines
• Drugs: indications and duration can vary
• Vaccines: limited exposures
• Larger premarket studies imply:
  Looking for very rare A.E.s in postmarket
Self controlled case series

- Tutorial in Stat in Med (see references)
- Developed methods for vaccine safety
- Each subject serves as own control
- Efficient signal detection
- Doesn’t formally address who is at risk
- OMOP methodology comparisons….this can outperform many other methods.
Self-Controls

Vaccination

Days

-56

-15

0

42

84

Comparison window (pre)

Risk window

Comparison window (post-post)
Vaccine Adverse Event Reporting (VAERS)
Passive Surveillance: VAERS

• Voluntary reports
• Patients, physicians, others
• Most fields are publicly available
• Case of no denominators… how many are exposed to product?
• CBER review: Division of Epidemiology
• Use Empirica Signal Detection Software
Passive Surveillance: AERS and VAERS

• STRENGTHS:
  – Open-ended for hypothesis generation
  – Potential detection of new or rare adverse events
  – Timeliness
  – Geographic diversity
  – Capability to monitor production lots

• LIMITATIONS:
  – Missing and inaccurate data
  – Under-reporting/Stimulated reporting
  – Absence of controls and denominators
  – Inability to assess causation
  – Low likelihood of detection for long latency events
CBER research initiative

- Text mining of narratives in VAERS
- 2 stage process:
  - using natural language processing to extract features from text
  - use supervised learning methods to develop classification rule.

Can evaluation of narratives improve yield rate of anaphylaxis?
Review by Medical Officers

- Manual search and review of case reports for H1N1 anaphylaxis (10/12/2009-06/30/2010).

  ![Diagram of the process]

  - **A**: All flu reports N=6034
  - **B**: Manual search N=237
  - **C**: Confirmed N=100

- Important to automate:
  - the whole process, but step 2 requires MO (<=>pdf files) review.
  - at least step 1 and provide MOs with the low number of reports for further review in step 2.
Training set: Classification Results

<table>
<thead>
<tr>
<th>Text Miner</th>
<th>MOs’ review</th>
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<th></th>
</tr>
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<tbody>
<tr>
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<td>Pos</td>
<td>Neg</td>
<td>Totals</td>
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<td>Pos</td>
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<td>535</td>
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<tr>
<td>Neg</td>
<td>54</td>
<td>5445</td>
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<tr>
<td>Totals</td>
<td>237</td>
<td>5797</td>
<td>6034</td>
<td></td>
</tr>
</tbody>
</table>

Sensitivity: 77.2%  PPV: 34.2%
Specificity: 94.0%  NPV: 99.0%
Independent validation

Independent validation of algorithm, truth determined by manual review (N=689):

PPV=30%   NPV=99%

PPV hurt by low prevalence, but NPV suggests text miner can be used to enrich the dataset.
Vaccine Safety DataLink
CDC and FDA
CDC Vaccine Safety Datalink (1991)

- Eight geographically diverse health maintenance organizations that participate in a large linked database representing approximately 3% of U.S. population
- Surveillance and “Hypothesis testing” studies can be conducted
  - Vaccination (exposure)
  - Outpatient, emergency department, hospital and laboratory coding data (health outcomes)
  - Demographic variables (confounders)
  - Accessible medical chart review
VSD Rapid Cycle Analysis

• Method motivated by Wald SPRT:
  Wald: Simple vs Simple Hypotheses
• Near continuous monitoring (weekly)
• Extension to composite alternative
• Two variants:
  Poisson: #events vs expected counts
  Binomial: event rates exposed vs not exp
Max SPRT
Kulldorff et al (2011)

• Likelihood ratio statistic
• (Poisson or binomial)

• Length of surveillance fixed (e.g. 2 yrs)
• Time is expected counts not calendar time
• Rapid detection important
Mini-Sentinel is Part of FDA’s Sentinel Initiative

**Sentinel Initiative**
Public-private partnership

**Mini-Sentinel**
- Collaboration of data partners, academia, non-profit organizations
- Covers all FDA regulated medical products

**Federal Partners Collaboration**
- Department of Defense (DoD)
- Department of Veterans Affairs (VA)
- Centers for Medicaid & Medicare Services (CMS)

**Postlicensure Rapid Immunization Safety Monitoring program (PRISM)**

**Blood Safety Continuous Active Surveillance Network (Blood-SCAN)**

**OMOP***

**Brookings Institution**

*Observational Medical Outcomes Partnership*
PRISM Basics

• Mini-Sentinel program dedicated to vaccine safety
• Claims based system with data from 4 national health plans
  – Aetna, HealthCore (Wellpoint), Humana, Optum (United Healthcare)
  – Data linked to 8 vaccine registries in USA
• Access to medical records and pharmacy data

Analytic Modular Programs

• Represents next step in standardization
  – From quick query to standardized analytic programs

• Designed to address 2 problems
  – Facilitates simultaneous monitoring of numerous FDA approved medical products
  – Reduces start-up time and resources of customized analyses

• Semi-automated product safety assessments
  – Predefined algorithms to identify exposures, outcomes, comparators
  – Standardized confounding control
  – Analytic choices chosen to cover most scenarios
Prespecified event: 3 Methods Initially Selected

1. **Self-controlled design**
   - Useful for single or short-term exposures or when no independent comparator group is available
   - When between-person confounding is large but within-person confounding is modest

2. **Exposure match cohort**
   - Uses propensity or disease risk scores in fixed or variable ratio
   - Provides flexible choices of effect measures, multiple endpoints and broad range of alerting rules

3. **Full cohort design with regression**
   - Permits a high degree of analytic flexibility (e.g., the ability to simultaneously evaluate interactions, multiple comparison groups, and subgroups)
PRISM Methods: Improving Causal Inference

• Improve on design-based confounding control
  – Traditionally use matching (age, site, sex), stratification
  – Limited by number of confounders or high dimensionality
  – Loss of efficiency (cannot use entire cohort)
  – Method like Lunceford and Davidian (2004)
    Group sequential element for surveillance
See ms by Cook et al (Mini-sentinel site)
Data Mining Development

• Test whether it is possible to detect adverse events without pre-specifying them a priori
• Develop statistical approach to simultaneously evaluate hundreds of different adverse events
  – Advantage: detect unexpected adverse events
  – Disadvantages: not possible to adjust for all possible confounders, as they vary by disease outcomes
    Finding optimum risk window for all events is hard
    Hierarchy of events imperfect.

Pilot phase: can we detect known signals?
Mining: 3 Methods Being Evaluated

- Project led by Martin Kulldorff
  - DuMouchel’s Gamma Poisson Shrinker
  - Tree-based scan statistic with population based controls
  - Tree-based scan statistic with self-controls

- Basics of Tree Scan algorithm
  - Use a hierarchical tree
  - Evaluate cuts on the tree (assess observed vs. expected at each leaf)
  - Control for multiple testing

Example of a Small Tree

- Myocardial Infarction
- Cardiac Arrhythmia
- Cardiomyopathy
- Acute Renal Failure
- Kidney Infection

Cut
Tree-based SCAN Statistic

1. Scan the tree by considering all possible cuts on any branch
2. For each cut, calculate the likelihood
3. Denote the cut with the maximum likelihood as the most likely cut (cluster)
4. Generate 9999 Monte Carlo replications under $H_0$.
5. Compare the most likely cut from the real data set with the most likely cuts from the random data sets
6. If the rank of the most likely cut from the real data set is $R$, then the p-value for that cut is $R/(9999+1)$. 
Tree-based SCAN Statistic

1. Scan the tree by considering all possible cuts on any branch

   Helps answer, “Has FDA observed any new safety issues?” without pre-specifying a particular outcome likely cut (cluster)

2. For each cut, calculate the likelihood
3. Denote the cut with the maximum likelihood as the most likely cut (cluster)

4. Generate 9999 Monte Carlo replications under $H_0$.
5. Compare the most likely cut from the real data set with the most likely cuts from the random data sets
6. If the rank of the most likely cut from the real data set is $R$, then the p-value for that cut is $R/(9999+1)$. 
Implementation in distributed environment

• Methods assessed
  – Empirical Bayes Gamma Poisson Shrinker (DuMouchel)
  – Tree-based scan statistic (Kulldorff)

Open challenges:
  Multiplicity of risk windows or age classes
  Constellations of events
  Concomitant vaccines or drugs
Post-marketing Vaccine Safety Research: Federal Partners

• **Claims datasets**
  – Near-real time monitoring
  – Centers for Medicare and Medicaid (CMS)
    • Population >35 million

• **Comprehensive datasets**
  – Electronic data for near-real time monitoring
  – Access to medical records for diagnosis verification and hypothesis confirmation
  – > 1,000,000 beneficiaries in each dataset
    • Indian Health Service
    • Department of Defense
    • Veterans Administration
A fictional vaccine.....
<table>
<thead>
<tr>
<th>Important Identified Risks</th>
<th>Health Outcome</th>
<th>Action Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Anaphylaxis</td>
<td></td>
<td>• Quick queries to follow up any safety signals from passive surveillance</td>
</tr>
<tr>
<td>2. Syncope causing injury</td>
<td></td>
<td>• Routine pharmacovigilance</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Important Potential Risks</th>
<th>Health Outcome</th>
<th>Action Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Febrile seizures</td>
<td></td>
<td>• Prospective sequential surveillance with self controlled analysis</td>
</tr>
<tr>
<td>• Immune thrombocytopenic purpura</td>
<td></td>
<td>• Current vs. historical surveillance for rare events</td>
</tr>
<tr>
<td>• Myocarditis</td>
<td></td>
<td>• PMC observational study 50,000 subjects</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Routine pharmacovigilance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Important Missing Information</th>
<th>Health Outcome</th>
<th>Action Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Safety in pregnant women, older adults (&gt;64 years)</td>
<td></td>
<td>• Retrospective pregnancy safety study at 3 years postlicensure</td>
</tr>
<tr>
<td>2. Unanticipated adverse events</td>
<td></td>
<td>• Data mining</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Routine pharmacovigilance</td>
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FDA-CMS Project SafeVax: Rapid Assessment of Vaccine Safety

- Developed a novel approach to near real-time safety surveillance adjusting for delay in claims in collaboration with CMS

- 2009–2010 season: monitored safety of seasonal and H1N1 pandemic influenza vaccines
  - Approximately 45 million CMS beneficiaries and more than 3 million H1N1 pandemic vaccinations monitored

- Monitoring of GBS after seasonal influenza vaccine now routine

- More and better data for safety: other adverse events, improved access to medical records, possible exploration of Medicaid data
FDA Next Steps

- Better integrated safety summaries. Reviewing role critical.
- Data mining in premarket RCTs
  Pediatric vaccines...
- Gaining more hands-on experience with active surveillance datasets.
- Active engagement of DB/DE in best use of Passive Surveillance Data.
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