Connecting the data to the science: A biostatistician’s role in advancing safety knowledge

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“Making America’s Results Safe Again”
“Stronger (Results) Together”
A biostatistician’s role

• More than being a skeptic
• More than doing fancy math
• For me …

SCIENCE
What’s the research question of interest?

DATA
What kind of data?
Of what quality?
How much is needed?

METHOD
What’s the corresponding statistical question that available data can inform?
Outline

• Background examples
• What is Sentinel’s ‘research question’?
• A biostatistician’s approach to addressing it
  o Building an example method
  o Broader lessons learned & implications for safety surveillance strategy
Example #1: Effectiveness of influenza vaccine in seniors

How effective is it among those aged 65 years and older?

- Despite U.S. recommendations for annual vaccine, it’s highly debated
- Important to know the magnitude of the benefit (to judge need for alternate strategies, e.g., higher dose vaccine)
- Largest efficacy trial (Govaert et. al. JAMA 1994)
  - Found reduction in risk: RR=0.50 (0.35, 0.61) among 60+ years
  - Restricted to healthy persons
  - Lacked power among 70+ years: RR=0.77 (0.39-1.51)
- Evidence gap = ‘real-world’ effectiveness among those 65+ years (i.e., among those less healthy) or in oldest subgroups 70+ years
- Answers have come from observational health care database studies
Influenza Vaccination in Community-Dwelling Elderly

Impact on Mortality and Influenza-Associated Morbidity

Bettie C. G. Voordouw, MD, MPH; Paul D. van der Linden, PharmD, PhD; Simon Stroumian, PhD; Johan van der Leij, MD, PhD; Miriam C. J. M. Sturkenboom, PharmD, PhD; Bruno H. C. Stricker, MD, PhD

Benefits of Influenza Vaccination for Low-, Intermediate-, and High-Risk Senior Citizens

Kristin L. Nickel, MD, MPH; J. Wuorenmaa, RN, BSN; T. von Steinberg, MD
MANY studies show influenza vaccine prevents ~50% of all deaths.
These studies fail to explain why...

<table>
<thead>
<tr>
<th>Estimated risk reductions for vaccinated versus unvaccinated seniors are...</th>
<th>Not specific to season of the year</th>
<th>The largest apparent vaccine benefit has been found prior to influenza season, when no effect is expected.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inconsistent with ecologic data</td>
<td>Not specific to seasons with good match between the vaccine and circulating strains</td>
<td>Despite large increases in vaccination coverage, from 15-20% in 1980 to over 65% in 2001, the incidence of influenza is relatively unchanged.</td>
</tr>
<tr>
<td>Implausibly high</td>
<td>Not specific to events reasonably attributable to influenza infection</td>
<td>Vaccination could not prevent 50% of deaths even if vaccine were 100% effective since, at most, only 10% of all deaths during influenza season are due to influenza.</td>
</tr>
<tr>
<td>High estimates are observed in mismatch years when there may be little true effect.</td>
<td>In conflict with biologic evidence</td>
<td>Reductions for injury and trauma hospitalization are similar in magnitude to reductions for pneumonia hospitalization.</td>
</tr>
</tbody>
</table>
Relative risk of all-cause death before, during, & after influenza season

Null hypothesis - no effect of vaccine

Bias in adjusted RR

Relative Risk in vaccinated vs unvaccinated

Before influenza 

During influenza

After influenza

Jackson, LA. et al. Intl J Epi 2005
### Covariates defined by ICD9 codes

<table>
<thead>
<tr>
<th>Covariate</th>
<th>ICD9 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart disease</td>
<td>093, 112.81, 130.3, 391, 393-398, 402, 404, 410-429, 745, 746, 747.1, 747.49, 759.82, 785.2, and 785.3</td>
</tr>
<tr>
<td>Lung disease</td>
<td>011, 460, 462, 465, 466, 480-511, 512.8, 513-517, 518.3, 518.8, 519.9, and 714.81</td>
</tr>
<tr>
<td>Diabetes</td>
<td>250, 251</td>
</tr>
<tr>
<td>Renal disease</td>
<td>274.1, 408, 580-591, 593.71-593.73, and 593.9</td>
</tr>
<tr>
<td>Cancer</td>
<td>200-208, 140-198, and 199.1</td>
</tr>
<tr>
<td>Others…</td>
<td></td>
</tr>
</tbody>
</table>
Likely source of the problem

- Differences between vaccinated and unvaccinated
  - Preferential use by healthier seniors
  - Selective under-use by frail seniors
- ICD-9 code methods don’t adjust for differences
  - Misclassify chronic disease (e.g., dementia)
  - Do not measure disease severity or functional status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>% “not diseased” cases (n=34)</th>
<th>% “not diseased” controls (n=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of dementia identified by chart review</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Requires assistance for ambulation</td>
<td>56</td>
<td>12</td>
</tr>
<tr>
<td>Requires assistance for bathing</td>
<td>32</td>
<td>3</td>
</tr>
<tr>
<td>Influenza vaccination</td>
<td>29</td>
<td>78</td>
</tr>
</tbody>
</table>

Jackson, LA. et al. Intl J Epi 2005
Example #2: Safety of combined measles-mumps-rubella-varicella (MMRV) vaccine

- In 2005, FDA licensed MMRV vaccine for children 12-23mos & 4-6 yrs
  - To decrease # of injections compared to MMR + V separately
- Prior studies, including pre-licensure data showed
  - Equivalence of immunogenicity (MMRV versus MMR + V)
  - MMRV (vs MMR + V) increases fever & rash w/in 5-12 days after dose 1 (RCT data, 12-23 month-olds)
  - MMR vaccine is associated with febrile seizures w/in 1-2 weeks → 1 additional febrile seizure per 3,000-4,000 doses
- Evidence gap = risk of rare AEs (e.g., seizure) for MMRV recipients

Should MMRV replace separate injections of MMR + V?

• Led by Kaiser Permanente Northern California (N Klein)
• Sequentially monitored targeted AE’s during MMRV uptake (12-23mos)
  o Pre-specified a few AE’s of interest (e.g., seizures w/in 0-42 days)
  o Used historical MMR comparators (some also received V)
  o Each week, captured vaccine & AE data and conducted Poisson-based maximized sequential probability ratio tests (RR=1 vs RR>1)
• After 43,353 MMRV doses: seizure signal detected; 7-10 day clustering
• Follow-up ‘end-of-surveillance’ analysis confirmed the result
  o Compared MMRV vs concurrent recipients of MMR + V
  o Validated presumptively-defined seizures with chart review
  o RR=~2 (1 additional seizure per 2,000 MMRV doses vs MMR + V)
• Interim data from independent study supported result (Jacobsen et. al.)
  o Merck-sponsored EHR database study in Kaiser Southern CA
Policy implications: Advisory Committee on Immunization Practices (ACIP)

• At licensure in Sept 2005
  o ACIP recommended a preference for MMRV over MMR + V
• February 2008: based on VSD surveillance & Merck interim data
  o ACIP changed the preference language ("no preference")
  o Recommended work group to conduct in-depth evaluation
• June 2009: based on 2 unpublished post-licensure studies, pre-licensure data, MMR+V literature, epidemiology/medical/psychosocial importance of seizure, program implementation, provider and parental attitudes regarding multiple injections and MMRV seizure risk
  o Dose 1: ACIP recommended MMR + V unless parent prefers MMRV after explanation of the benefits and risks of both options
  o Dose 2: ACIP expressed preference for MMRV
Adapting Group Sequential Methods to Observational Postlicensure Vaccine Safety Surveillance: Results of a Pentavalent Combination DTaP-IPV-Hib Vaccine Safety Study


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Initially submitted September 7, 2011; accepted for publication March 28, 2012.

To address gaps in traditional postlicensure vaccine safety surveillance and to promote rapid signal identification, new prospective monitoring systems using large health-care database cohorts have been developed. We newly adapted clinical trial group sequential methods to this observational setting in an ongoing safety study of a combination diphtheria and tetanus toxoids and acellular pertussis adsorbed (DTaP), inactivated poliovirus (IPV), and Haemophilus influenzae type b (Hib) conjugate vaccine (DTaP-IPV-Hib) among children within the Vaccine Safety Datalink population. For each prespecified outcome, we conducted 11 sequential Poisson-based likelihood ratio tests during September 2009–January 2011 to compare DTaP-IPV-Hib vaccines with historical recipients of other DTaP-containing vaccines. No increased risk was detected among 149,332 DTaP-IPV-Hib vaccinees versus historical comparators for any outcome, including medically attended fever, seizure, meningitis, encephalitis, nonanaphylactic serious allergic reaction, anaphylaxis, Guillain-Barré syndrome, or invasive Hib disease. In end-of-study prespecified subgroup analyses, risk of medically attended fever was increased among non-Hispanic Black children and increased among Hispanic children, both relative to the overall rate of medically attended fever.
Key ingredients for success

• Asked a tractable scientific question
  o Well-defined, homogenous population (healthy infants)
  o Correctly classified outcomes and outcome timing (PPV 95%+)
    – Acute (time-varying exposure/confounding NOT issues)
    – Severe (requires health care utilization, so NOT missing)
  o Simple, well-documented vaccine exposure (Mulloolly, AJE 1999)

• Sites knew their data (and each other) very well
  o Same 3-10 databases used to study vaccine safety since 1990
    – Well established trust and data sharing infrastructure
  o Practicing clinicians who ‘generate’ the data (& their idiosyncrasies)
  o Routine ‘general purpose’ quality checking (Madziwa 2016)
  o Periodic in-depth, targeted, ‘question-driven’ quality assessments

• Applied pre-defined principled methods
  o Question-driven, simple, scalable, transparent, and reproducible
Vision for Sentinel

“...a national electronic system that will transform FDA’s ability to track the safety of drugs, biologics, and medical devices once they reach the market.”

“...aims to develop and implement a proactive system that will complement existing systems that the Agency has in place to track reports of adverse events.”

“...enables FDA to actively query diverse automated healthcare data holders—like EHR systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.”

http://www.fda.gov/Safety/FDAsSentinelInitiative
Should MMRV replace separate injections of MMR + V?

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- Sequentially monitored targeted AE’s during MMRV uptake (12-23mos)
  - Pre-specified a few AE’s of interest (e.g., seizures w/in 0-42 days)
  - Used historical MMR comparators (some also received V)
  - Each week, captured vaccine & AE data and conducted Poisson-based maximized sequential probability ratio tests (RR=1 vs RR>1)
- After 43,353 MMRV doses: seizure (within 7-10 days) signal detected
- Follow-up ‘end-of-surveillance’ analysis with more data confirmed this
  - Compared MMRV vs concurrent recipients of MMR + V
  - Validated presumptively-defined seizures with chart review
  - Estimated $RR=\sim2$ from both surveillance and follow-up data
- Interim data from independent study supported result (Jacobsen et. al.)
  - Merck-sponsored EHR database study in Kaiser Southern CA
Risk of Febrile Seizure 7-10 days after MMRV Compared with MMR + V  
(83,107 MMRV and 376,354 MMR + V doses: 2000-08)

<table>
<thead>
<tr>
<th>Analyses Incorporates Chart-Confirmation Rate?</th>
<th>Relative Risk*</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1.98</td>
<td>1.43-2.73</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Yes</td>
<td>2.04</td>
<td>1.44-2.90</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Risk Difference  
4.3/10,000 doses (95% CI 2.6-5.6)

For every ~2,300 MMRV doses given instead of MMR + V, 1 additional febrile seizure will occur 7-10 days after vaccination.

*Poisson Regression adjusted for age, VSD site and each year and each respiratory season.
Building a new method

- Focuses on decision-relevant safety target of inference
  - Risk difference (RD) for a binary event and concurrent controls
- Is proactive and quick
  - Group sequential monitoring to allow early and routine estimation and testing as new users/data are observed
    - Unifying family of sequential boundaries (Kittelson et al. 1999)
  - Incorporates confounders w/propensity score (PS) weights
  - Employs exact (permutation) testing to account for rare events
- Acknowledges national, multi-site nature of the data
  - Site-stratified to address heterogeneity
    - Site-specific PS model & PS-weighted linear (RD) regression
    - Accounts for differences in variability of PS by site
- Allows secure data analysis
  - Meta-analytic approach requiring summary data only
How does it do all this?

1. Construct site-specific PS using logistic regression: \( \hat{\psi}_{si} = P(x \mid Z) \)

2. Calculate a site-specific adjusted IPTW risk difference and variance: \( \Delta_S \) & variance \( V(\Delta_S) \), incorporating estimation of the PS (Lunceford & Davidian 2004)

\[
\Delta_S = \left( \sum_{i=1}^{N_s} \frac{X_{si}}{\hat{e}_{si}} \right)^{-1} \sum_{i=1}^{N_s} \frac{X_{si} Y_{si}}{\hat{e}_{si}} - \left( \sum_{i=1}^{N_s} \frac{1 - X_{si}}{1 - \hat{e}_{si}} \right)^{-1} \sum_{i=1}^{N_s} \frac{(1 - X_{si}) Y_{si}}{(1 - \hat{e}_{si})} = \hat{\mu}_s^E - \hat{\mu}_s^U
\]

3. Sites send these to a central location with total sample size

Site 1
\( \Delta_1, V(\Delta_1) \)

Site 2
\( \Delta_2, V(\Delta_2) \)

\[ \ldots \]

Site 9
\( \Delta_9, V(\Delta_9) \)

Site 10
\( \Delta_{10}, V(\Delta_{10}) \)

\[ \Delta = \frac{\sum_{S=1}^{10} N_S \Delta_S}{\sum_{S=1}^{10} N_S} \]

Compare \( \Delta \) to its distribution (obtained via permutation) under \( H_0 \)

Repeat for each analysis time: 1, 2, \( \ldots \) T (Kittleson et al. 1999)
Comparison of methods for MMRV vaccine safety (VSD & Sentinel data)

- Original VSD active surveillance using historical controls
  - Signaled after 43,353 MMRV doses
  - Adjusted RR=~2 using Poisson MaxSPRT (continuous testing method)

- VSD follow-up analysis using concurrent controls + chart review
  - Adjusted RR of 1.98 (& adjusted RD of 4.3 per 10K vaccinated)
  - 83,107 MMRV and 376,354 MMR+V with chart reviewed outcomes

- Sequential RD estimation using concurrent controls, 4 Sentinel sites
  - Signaled after 17,321 MMRV doses
  - Adjusted RR of 2.86 and RD of 5.2 (metric upon which signal based)

- Sequential logistic regression, concurrent controls, 4 Sentinel sites:
  - Used aggregated (grouped) data by categorical exposure & confounders
  - Signaled after 48,233 MMRV doses
  - Adjusted OR of 2.37 (metric upon which signal was based) & RD of 5.3
Recap

- Focuses on **decision-relevant safety target** of inference
  - Signals based on interpretable risk difference (RD)
  - Is also statistically appealing
    - More stable than ratio measures when events are rare
    - More powerful and faster detection than ratio measures
- Is **proactive and quick**
  - Uses sequential monitoring for early and routine assessments
  - Can incorporates (many) confounders using PS weighting
  - Borrows RCT methods but relaxes usual large sample assumptions
- Acknowledges **national, multi-site** nature of the data
  - Uses site-stratification to address (likely) heterogeneity
- Allows **secure** data analysis
  - Meta-analytic approach requiring summary data only
Successful use of health care data is a balancing act

**Strengths**

- Less costly studies
- Large samples
- “Real world”
- Near complete outpatient prescription data
- Near complete outpatient and inpatient diagnoses and procedures
- No recall bias or non-response
- With infrastructure investment, ease of data access

**Limitations**

- Requires health encounter (selection)
- Generalizable? (insured only)
- Data influenced by formularies, practice patterns, software (ICD-10)
- Missing data (disease severity, onset, OTC meds, SES, diet)
- Misclassification (rule out diagnoses, disease onset date)
- Long-term follow-up? (turnover rate ~20-30% a year, hard to track in people and out of systems)
- Getting more data can be challenging (cannot contact study subjects, access to medical charts?)

Content courtesy of Denise Boudreau, PhD; Group Health Research Institute
Conclusions

• The role of health care data in addressing regulatory questions is complicated, uncertain, rapidly evolving, and depends on the question.

• Success will require us to…
  o **Zero in on tractable questions** (develop smart ways to identify them)
  o **Deeply understand the data** (how they arise & their limitations)
    – Involve (fewer) data partners with richest, highest quality data
    – Have well established trust and data sharing infrastructure
    – Integrate expertise from practicing clinicians who ‘generate’ the data with sound epi design & statistical analyses
    – Get supplemental data from other sources when needed
  o **Use pre-defined principled methods**
    – Question-driven, simple, transparent, and replicable
  o Make appropriate interpretation based on level of evidence provided

• Biostatisticians have a central role to play
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References


• Madziwa L on behalf of the Vaccine Safety Datalink Data Management Working Group. ICD-10: Early insights. Group Health Research Institute Data Analytics Fair, September 28, 2016, Seattle WA.


WONDERFUL THINGS THESE BRIDGES.