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

Jennifer Clark Nelson, PhD
Director of Biostatistics
Group Health Research Institute

Affiliate Professor of Biostatistics
University of Washington

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“Making America’s Results Safe Again”

GroupHealth.

“Stronger (Results) Together”

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A biostatistician's role

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

SCIENCE

What's the research question of interest?

METHOD

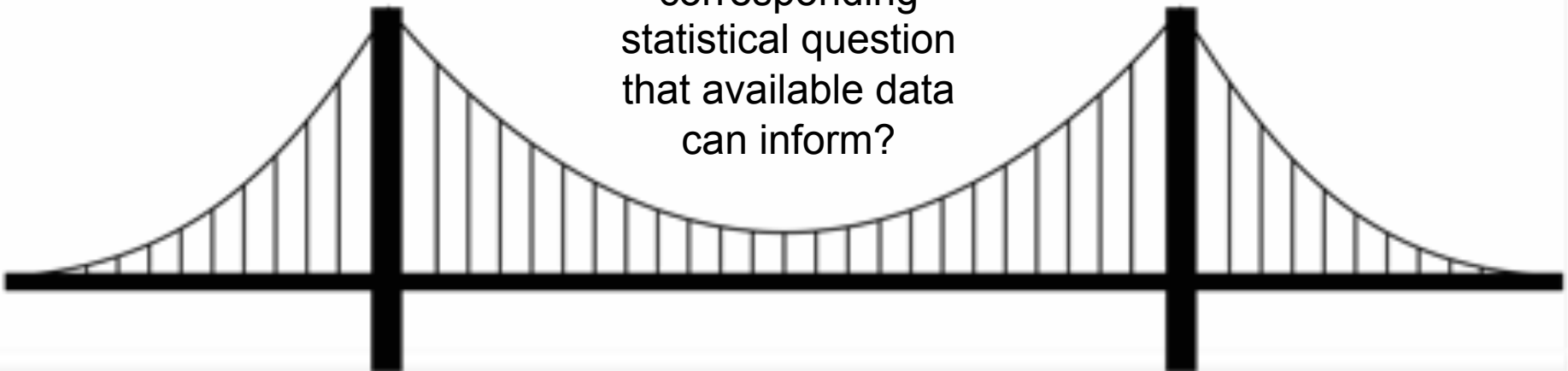
What's the corresponding statistical question that available data can inform?

DATA

What kind of data?

Of what quality?

How much is needed?



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Outline

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- Background examples
- What is Sentinel's 'research question'?
- A biostatistician's approach to addressing it
  - Building an example method
  - Broader lessons learned & implications for safety surveillance strategy

Example #1: Effectiveness of influenza vaccine in seniors

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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


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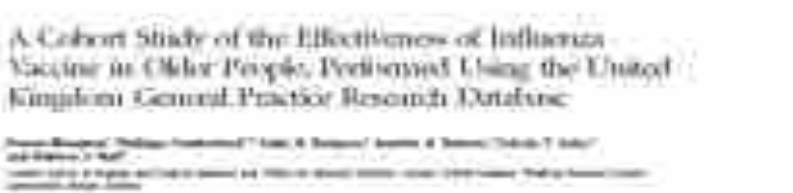
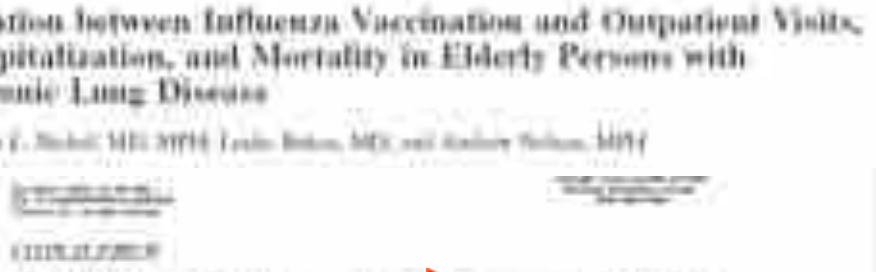
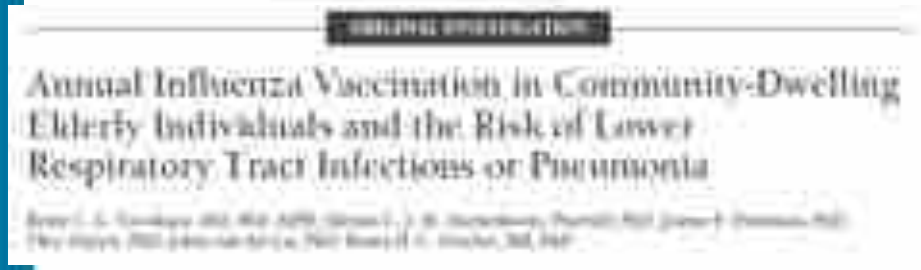

A Cohort Study of the Effectiveness of Influenza
Vaccine in Older People, Performed Using the United
Kingdom General Practice Research Database


Effectiveness of Influenza Vaccine
in the Community-Dwelling Elderly


Relation between Influenza Vaccination and Outpatient Visits,
Hospitalization, and Mortality in Elderly Persons with
Chronic Lung Disease


ORIGINAL INVESTIGATION
Annual Influenza Vaccination in Community-Dwelling
Elderly Individuals and the Risk of Lower
Respiratory Tract Infections or Pneumonia

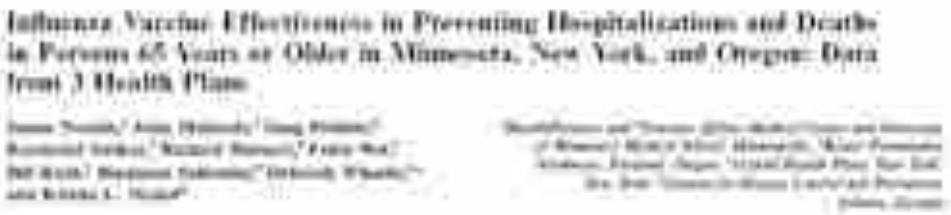

Additive protective effect of influenza and pneumococcal vaccines in
elderly persons


ORIGINAL INVESTIGATION
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 Simonian, PhD;
Johan van der Lei, MD, PhD; Miriam C. J. M. Sturkenboom, PharmD, PhD; Bruno H. C. Stricker, MD, PhD


Influenza Vaccination and Reduction
in Hospitalizations for Cardiac Disease
and Stroke among the Elderly

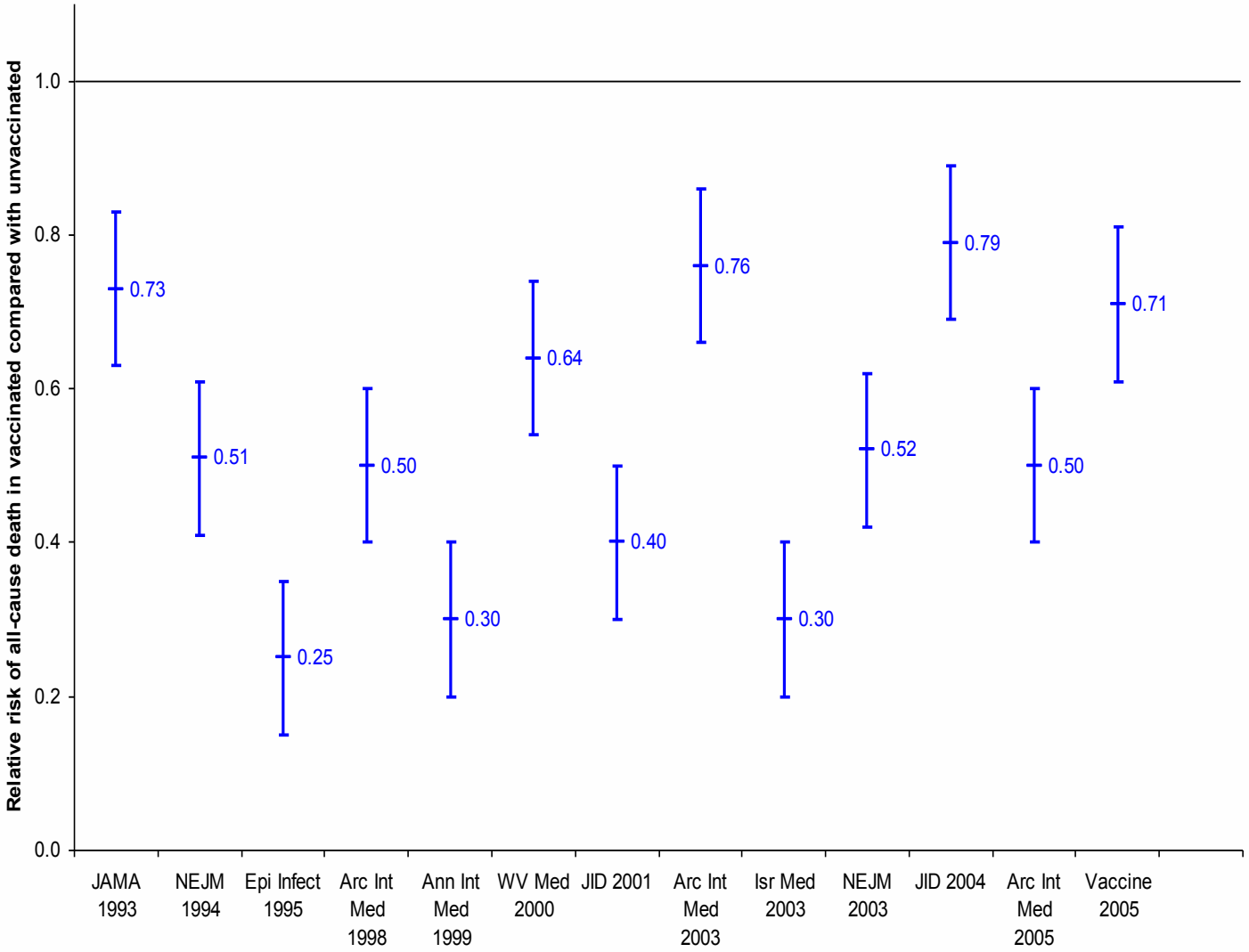

ORIGINAL INVESTIGATION
Benefits of Influenza Vaccination for Low-,
Intermediate-, and High-Risk Senior Citizens
Kristin L. Nichol, MD, MPH; J. Wuorenma, RN, BSN; T. von Sternberg, MD


Influenza Vaccination and Risk of Mortality
Among Adults Hospitalized With
Community-Acquired Pneumonia


Influenza Vaccine Effectiveness in Preventing Hospitalizations and Deaths
in Persons 65 Years or Older in Minnesota, New York, and Oregon: Data
from 3 Health Plans


Annual Revaccination Against Influenza
and Mortality Risk in Community-Dwelling
Elderly Persons

MANY studies show influenza vaccine prevents ~50% of all deaths

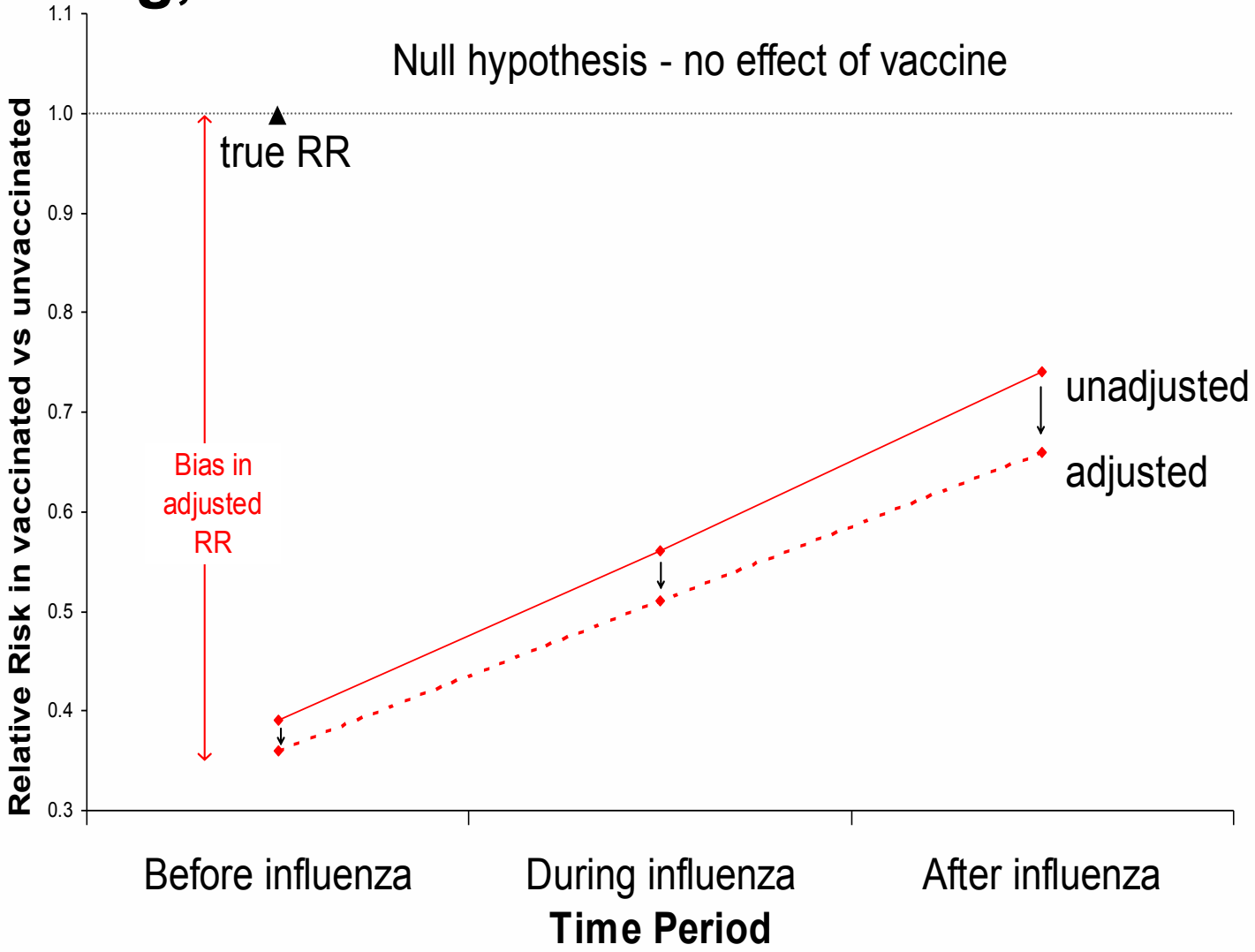


These studies fail to explain why…

Estimated risk reductions for vaccinated versus unvaccinated seniors are…	Not specific to season of the year	The largest apparent vaccine benefit has been found prior to influenza season, when no effect is expected.
	Inconsistent with ecologic data	Despite large increases in vaccination coverage, from 15-20% in 1980 to over 65% in 2001, the incidence of influenza is relatively unchanged.
	Implausibly high	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.
	Not specific to seasons with good match between the vaccine and circulating strains	High estimates are observed in mismatch years when there may be little true effect.
	Not specific to events reasonably attributable to influenza infection	Reductions for injury and trauma hospitalization are similar in magnitude to reductions for pneumonia hospitalization.
	In conflict with biologic evidence	Immune response to influenza vaccination declines with age, but estimated risk reductions do not.

Nelson JC et al. J Clin Epidemiol 2009

Relative risk of all-cause death before, during, & after influenza season



Jackson, LA. et al. Intl J Epi 2005

Covariates defined by ICD9 codes

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Covariate	ICD9 codes
Heart disease	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
Lung disease	011, 460, 462, 465, 466, 480-511, 512.8, 513-517, 518.3, 518.8, 519.9, and 714.81
Diabetes	250, 251
Renal disease	274.1, 408, 580-591, 593.71-593.73, and 593.9
Cancer	200-208, 140-198, and 199.1
Others…	

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

Characteristic	% "not diseased" cases (n=34)	% "not diseased" controls (n=203)
Diagnosis of dementia identified by chart review	32	3
Requires assistance for ambulation	56	12
Requires assistance for bathing	32	3
Influenza vaccination	29	78

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?

Vaccine Safety Datalink: Near-real time safety surveillance (2006-2008)

- Led by Kaiser Permanente Northern California (N Klein)
- 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 signal detected; 7-10 day clustering
- Follow-up 'end-of-surveillance' analysis confirmed the result
  - Compared MMRV vs concurrent recipients of MMR + V
  - Validated presumptively-defined seizures with chart review
  - RR=~2 (1 additional seizure per 2,000 MMRV doses vs MMR + V)
- Interim data from independent study supported result (Jacobsen et. al.)
  - Merck-sponsored EHR database study in Kaiser Southern CA

Policy implications: Advisory Committee on Immunization Practices (ACIP)

- **At licensure in Sept 2005**
  - ACIP recommended a preference for MMRV over MMR + V
- **February 2008**: based on VSD surveillance & Merck interim data
  - ACIP changed the preference language ("no preference")
  - 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
  - Dose 1: ACIP recommended MMR + V unless parent prefers MMRV after explanation of the benefits and risks of both options
  - Dose 2: ACIP expressed preference for MMRV

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Practice of Epidemiology

Adapting Group Sequential Methods to Observational Postlicensure Vaccine Safety Surveillance: Results of a Pentavalent Combination DTaP-IPV-Hib Vaccine Safety Study

Jennifer C. Nelson*, Onchee Yu, Clara P. Dominguez-Islas, Andrea J. Cook, Do Peterson, Sharon K. Greene, W. Katherine Yih, Matthew F. Daley, Steven J. Jacobsen, Nicola P. Klein, Eric S. Weintraub, Karen R. Broder, and Lisa A. Jackson

* Correspondence to Dr. Jennifer C. Nelson, Biostatistics Unit, Group Health Research Institute, 1730 Minor Avenue, Suite 1600, Seattle, WA 98101 (e-mail: nelson.j@ghc.org).

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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 original 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 2008–January 2011 to compare DTaP-IPV-Hib vaccinees with historical recipients of other DTaP-containing vaccines. No increased risk was detected among 149,337 DTaP-IPV-Hib vaccinees versus historical comparators for any outcome, including medically attended fever, seizure, meningitis/encephalitis/myelitis, nonanaphylactic serious allergic reaction, anaphylaxis, Guillain-Barré syndrome, or invasive Hib disease. In ended-study prespecified subgroup analyses, risk of medically attended fever was

Key ingredients for success

- Asked a tractable scientific question
  - Well-defined, homogenous population (healthy infants)
  - Correctly classified outcomes and outcome timing (PPV 95%+)
    - Acute (time-varying exposure/confounding NOT issues)
    - Severe (requires health care utilization, so NOT missing)
  - Simple, well-documented vaccine exposure (Mulloolly, *AJE* 1999)
- Sites knew their data (and each other) very well
  - Same 3-10 databases used to study vaccine safety since 1990
    - Well established trust and data sharing infrastructure
  - Practicing clinicians who 'generate' the data (& their idiosyncrasies)
  - Routine 'general purpose' quality checking (Madziwa 2016)
  - Periodic in-depth, targeted, 'question-driven' quality assessments
    - Mullooly (1999, 2004, 2008), Shui (2009), Thyagarajan (2013)
- Applied pre-defined principled methods
  - 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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- Led by Kaiser Permanente Northern California (N Klein)
- 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=~2** 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)

Analyses Incorporates Chart-Confirmation Rate?	Relative Risk*	95% Confidence Interval	P Value
No	1.98	1.43-2.73	<0.0001
Yes	2.04	1.44-2.90	<0.0001

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 $\hat{e}_{si} = P(x \mid Z)$
2. Calculate a site-specific adjusted IPTW risk difference Δ_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 $\Delta_2, V(\Delta_2)$

...

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

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

CENTRAL

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

Compare Δ to its distribution (obtained via permutation) under H_o

Repeat for each analysis time: 1, 2, …T (Kittleson et al. 1999)

Comparison of methods for MMRV vaccine safety (VSD & Sentinel data)

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- 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

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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…
  - Zero in on tractable questions (develop smart ways to identify them)
  - 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
  - Use pre-defined principled methods
    - Question-driven, simple, transparent, and replicable
  - Make appropriate interpretation based on level of evidence provided
- Biostatisticians have a central role to play

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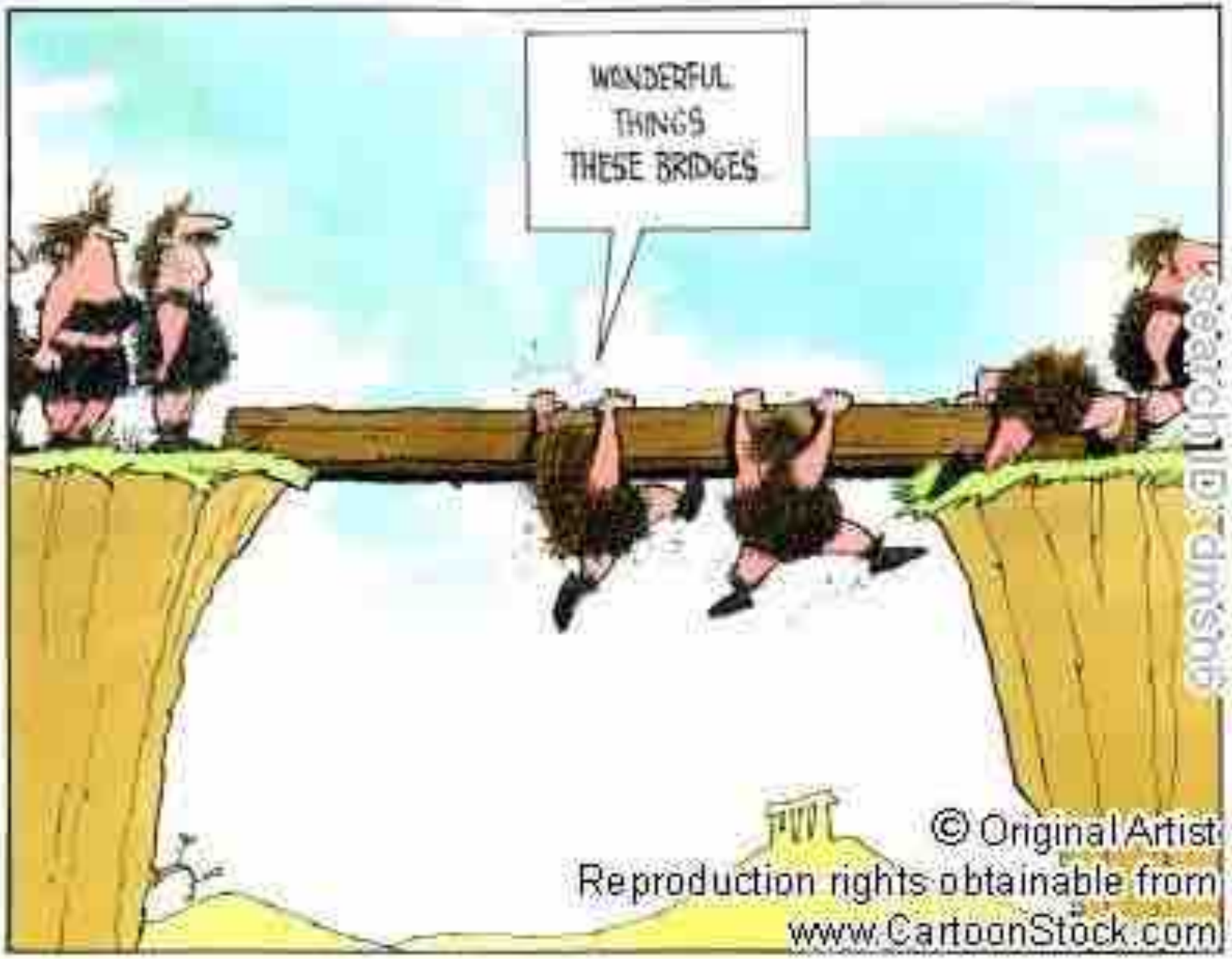
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