

Statistical Issues in Evaluating Safety of Vaccine Products – Perspective from an FDA Statistician

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Disclaimer

This presentation reflects the reviewer's thoughts, it does not necessarily represent official FDA policy or recommendation.

Outline

- Introduction
- Pre-licensure Issues
 - Phase 1
 - Phase 2
 - Phase 3
- Post-licensure Issues
- Examples
- Summary

Introduction

- Vaccines are for healthy individuals
- Licensed vaccine may ultimately be used in millions of humans
- Goal to ensure that a vaccine is **NOT** associated with any serious adverse events
- How to be sure that something is **NOT** true?
- Have a *reasonable degree* of assurance that a vaccine is safe before licensure
- **MORE CHALLENGING THAN EFFICACY!**

Pre-licensure Issues

Phase 1

- Usually open-label, uncontrolled
- Small number (20-30) of healthy adults
- Conservative stopping rules based on safety parameters
- Main goal is to describe initial safety profile for human use
- No statistical hypotheses

Pre-licensure Issues

Phase 2

- Randomized, double-blind, controlled
- Hundreds of subjects
- Dose selection to minimize AE rates
- Statistical issue: optimal dosage
- Hypotheses forming
- Estimate rates of:
 - common local reactions (e.g., pain)
 - systemic adverse reactions (e.g., fever)
 - laboratory abnormalities

Pre-licensure Issues

Phase 3

- Evaluation of less common AEs in a randomized setting prior to licensure
- Statistical issues related to safety:
 - Risk difference vs. risk ratio
 - Sample size
 - Missing data on a diary card
 - Multiple comparisons of systemic AEs
 - Rare and serious adverse events

Risk Difference or Risk Ratio

- Risk difference:
 - may be useful metric for public health policymakers
 - e.g., determine how many new hospital beds are needed
 - Tend to minimize the risk of uncommon AEs associated with vaccination
- Risk ratio more appropriate for assessing less common AEs for preventive vaccines

Sample Size

- “Rule of 3” for sample size calculation
- Size of safety database
 - enough for “level of comfort”
- If trial is large (e.g., VE trials):
 - Actively monitor a subset for common AEs
 - Follow all subjects for serious AEs (SAEs)
- If trial is small (e.g., immunogenicity trials):
 - A large supplemental safety trial is necessary

Missing Data on a Diary Card

- Commonly 7-day or 14-day diary cards
- No observation vs. observed nothing
- Imputation not useful
- Sensitivity analysis
 - Replace missing with highest and lowest rating on scale, then compare risks

Multiple Comparisons of Systemic AEs

- Typically each test at 0.05 alpha level
- Minimization of type 2 error (failure to identify true safety signal) more critical than type 1 error (detecting false signal)
- No statistical adjustment
- False association in overall final assessment of safety

Rare and Serious Adverse Events

- E.g., seizures, hospitalizations, death, etc.
- DSMB (Data & Safety Monitoring Board) plays important role
 - Role of statisticians on DSMB?
- Post-licensure monitoring

Post-licensure Issues

- Phase 4 monitoring

- VAERS

Phase 4 Monitoring

- Post-licensure monitoring important due to difficulty in assessing safety pre-licensure
- May be randomized but often observational
- Historical control or self control
- Case-control or case-series studies common

VAERS

- Vaccine Adverse Events Reporting System
- Maintained jointly by FDA and CDC
- Voluntary reporting instead of active monitoring

VAERS (*cont.*)

- Estimate risk by using # cases reported divided by the estimated total number of doses administered
- Limitations include:
 - Lack of an unvaccinated control group
 - Underreporting
 - Uncertainty of the number of doses administered
 - Time lags in both symptom onset and event reporting

Examples

- Menactra and Guillian-Barré Syndrome (GBS)
- Rotavirus vaccines and intussusception (IS)

Menactra & GBS

- Meningococcal conjugate vaccine licensed January 2005
- 11-55 years old
- As of June 2008:
 - 29 GBS cases confirmed aged 10-19
- Phase 4, Harvard Pilgrim study
<http://clinicaltrials.gov/ct2/show/NCT00575653>

Menactra and GBS (*cont.*)

- 6 weeks window after vaccination
- Background rate estimated using data from CDC Vaccine Safety Datalink database (VSD)
- Relative reporting rate: 0.94
- 95% CI: (0.60, 1.49)
- Limitations apply

Rotavirus Vaccines & IS (Rotashield)

- 1st US rotavirus vaccine
- Licensed in August 1998
- Intussusception (IS): “telescoping” of bowel leading to obstructions symptoms, could be fatal if not treated
- Pre-licensure:
 - 5 cases in 10,054 vaccinees
 - 1 case in 4633 placebo control
 - No statistically significant difference

Rotavirus Vaccines & IS (Rotashield)

- Post-licensure: 10 months, after 1.5 million doses administered
 - 15 cases of IS reported to VAERS
 - 13 cases after 1st dose, median age 3 month
- Manufacturer voluntarily withdrew vaccine from market in October 1999 and license revoked on November 15, 2002

Rotavirus Vaccines & IS (RotaTeq)

- Rotavirus Efficacy and Safety Trial (REST)
- Randomized, double-blind, placebo control
- Study based on IS as endpoint
- Predetermined success criteria
- Group sequential design
- DSMB monitored the safety boundaries

Rotavirus Vaccines & IS (RotaTeq)

- Licensed February 2006
- IS cases followed closely by FDA and CDC
- As of June 30, 2008:
 - Relative reporting rate: 0.44
 - 95% CI: (0.35, 0.54)
- VAERS limitations apply

Summary

- Pre-licensure can provide safety profile for local and systemic AEs
- Pre-licensure trials can never be large enough to detect all rare AEs
- Post-licensure surveillance needs improvement
- Need both pre- and post-licensure monitoring to obtain complete safety profile

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