



Does Size Really Matter in Post-Licensure Vaccine Safety Monitoring?

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Importance of Post-Licensure Surveillance

- Vaccine safety standards high
- Clinical trials pre-licensure ensure vaccines used have favorable safety profile, however there are limitations
 - Power
 - Subpopulations
 - Delayed onset events
 - Use in general population once licensed
- Passive surveillance (VAERS) can detect signals but rigorous follow-up usually required



Large Linked Databases: The Vaccine Safety Datalink (VSD) Model

- Rapidly monitor newly introduced vaccines and investigate signals
- 10 Managed Care Organizations with @9.5 million persons (3% of US pop)
- Includes nearly all medical encounters
 - Inpatient, outpatient, hospitalization, pharmacy
- Decentralized distributed data model
- Cohort, nested case control, and Rapid Cycle Analysis (RCA)



Rapid Cycle Analysis (RCA)

- Real-time safety surveillance for newly introduced vaccines
- Outcomes pre-determined with specified time window
- Background (expected) rates determined
- Post-vaccination rates compared to expected rates regularly
- Statistical adjustment for multiple testing



RCA Strengths and Limitations

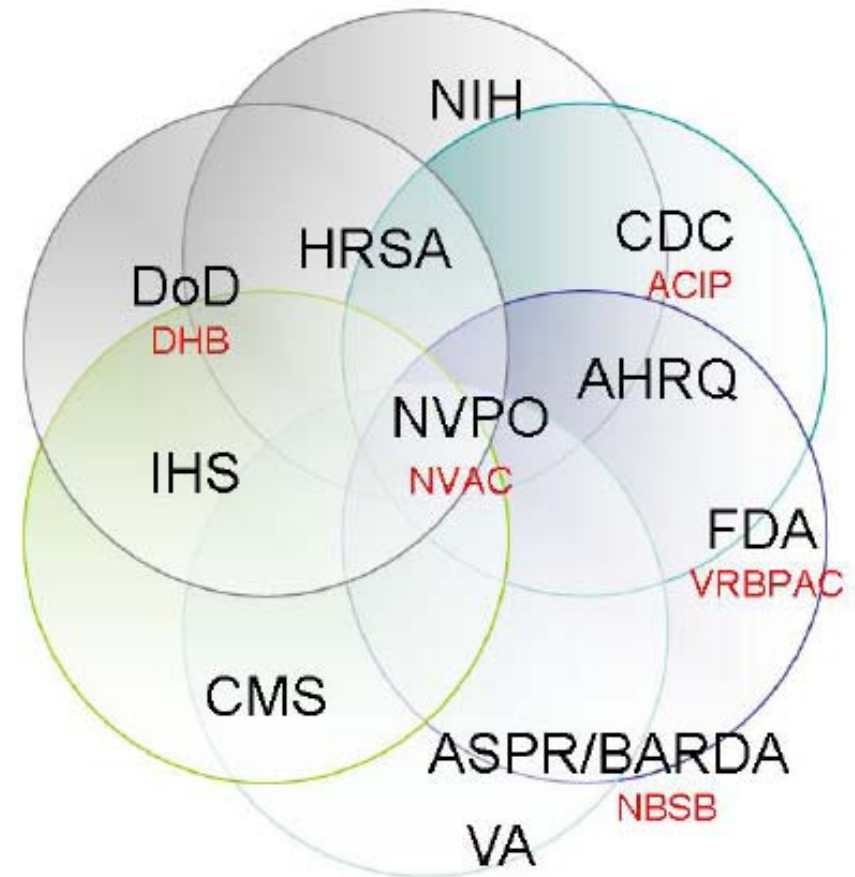
- Rapidly monitor safety of newly introduced vaccines on regular and ongoing basis
- Signals from RCA require further evaluation
 - 90% of signals turn out to be spurious
- ICD-9 codes vary in positive predictive value
- Chart review often necessary



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



<http://www.flu.gov/professional/federal/fed-plan-to-mon-h1n1-imm-safety.pdf>

Advisory Committees in Red



Monitoring H1N1 Vaccine Safety: Existing Large Linked Databases

Data Source	Agency/ Dept.	Pop. Covered
Vaccine Safety Datalink (VSD)	CDC	9 million (managed care population)
Veteran Patients & VA Employee and Volunteers	VA	1 million (veterans and feds)
Defense Medical Surveillance System	DoD/FDA/ CDC	2.6 million (military active duty)
National Claims History File & Enrollment Database	CMS/FDA	46 million (elderly and disabled)



Monitoring H1N1 Vaccine Safety: Enhancements to the Current System

Data Source	Agency/ Dept.	Pop. Covered
Post-licensure Rapid Immunization Safety Monitoring (PRISM)	NVPO/ FDA/CDC	14 million (persons in health plans in 8 states)
Indian Health Service Resource & Patient Management Database	IHS/FDA	1.4 million (Native Americans)



Each System has Unique Characteristics

- VSD large population with tremendous experience and expertise
- DoD, VA, and IHS include special populations
- CMS extremely large and mostly elderly
- PRISM includes general population, multiple outcomes, and large numbers of persons



FDA Sentinel Initiative

- FDA Act of 2007 requires post-marketing surveillance to include 100 million persons by 2012
- Distributed data network to include medical practices, hospitals, delivery systems, health plans, and insurers
- Mini-Sentinel to develop and test approaches and methods



Why Does Size Matter?

- Timeliness for RCA & other study designs
- Power for rare events and subpopulations
- Value of having different populations under surveillance to confirm or refute findings



Timeliness for RCA & other study designs

- Dependent on number of vaccinated persons in database(s)
 - Number of persons under surveillance
 - Vaccine Coverage



Figure 1. Effect of Vaccine Coverage Rate on Time until Signal Detection

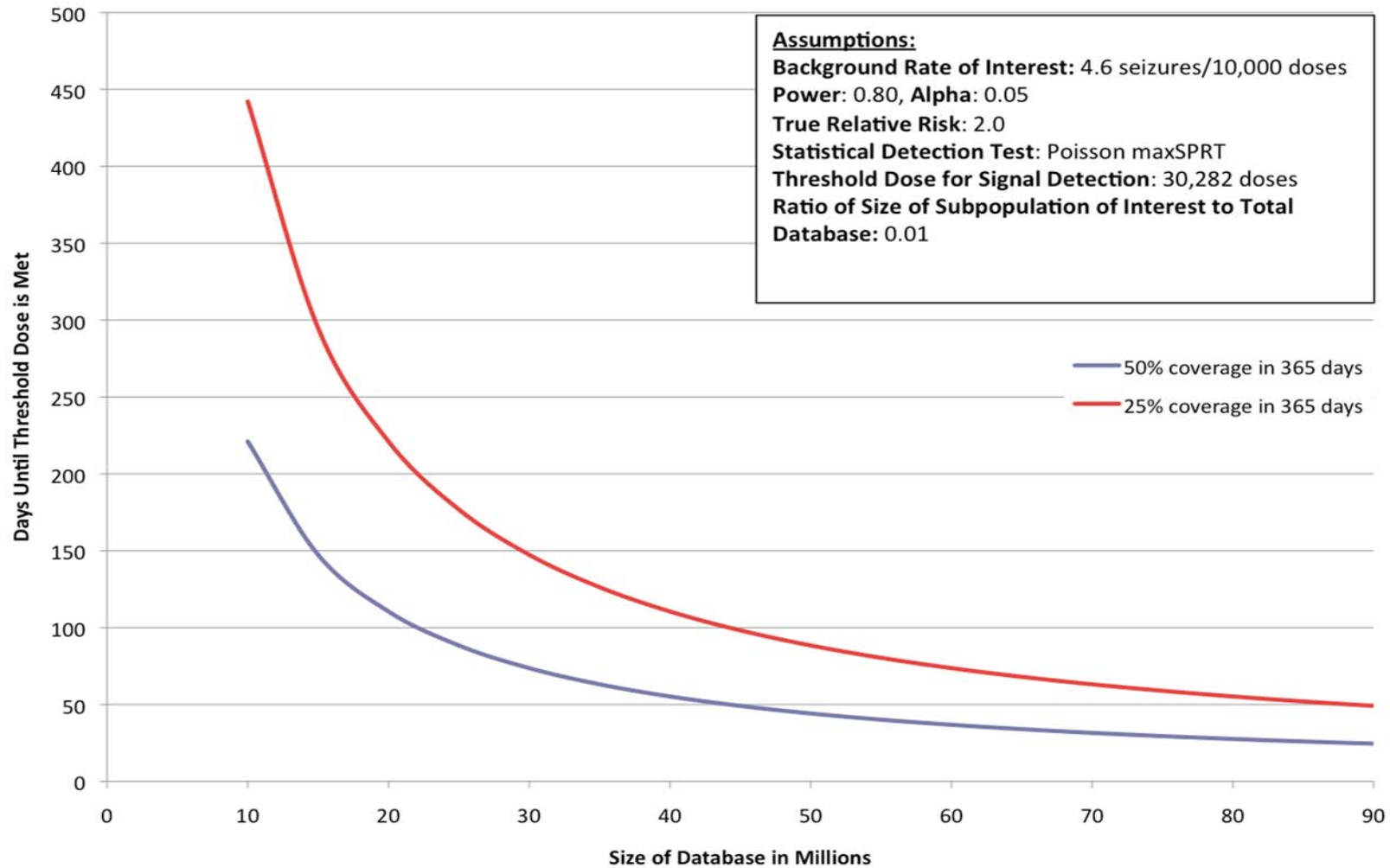
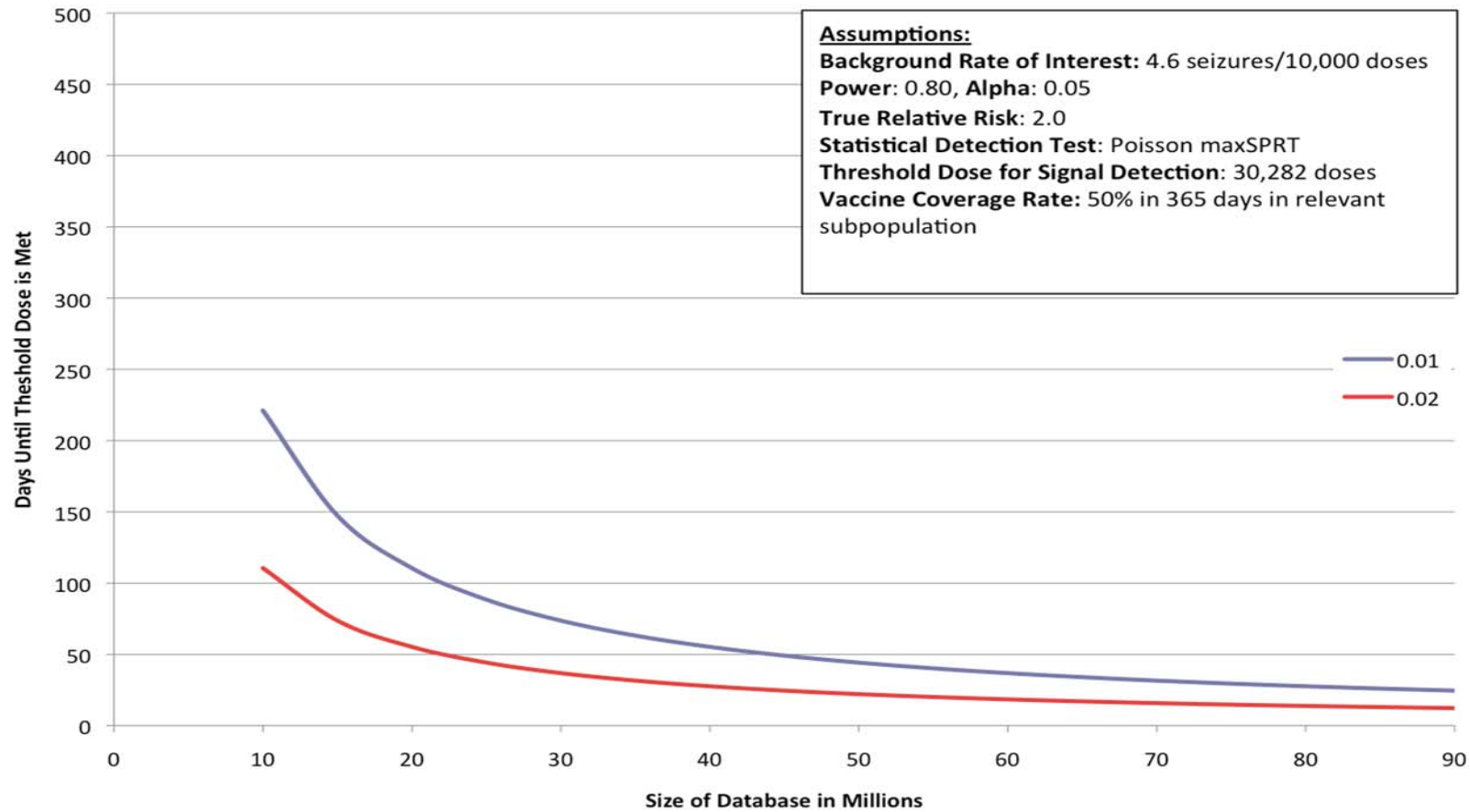


Figure 2. Effect of Ratio of Subpopulation Size to Total Database Size on Time until Signal Detection

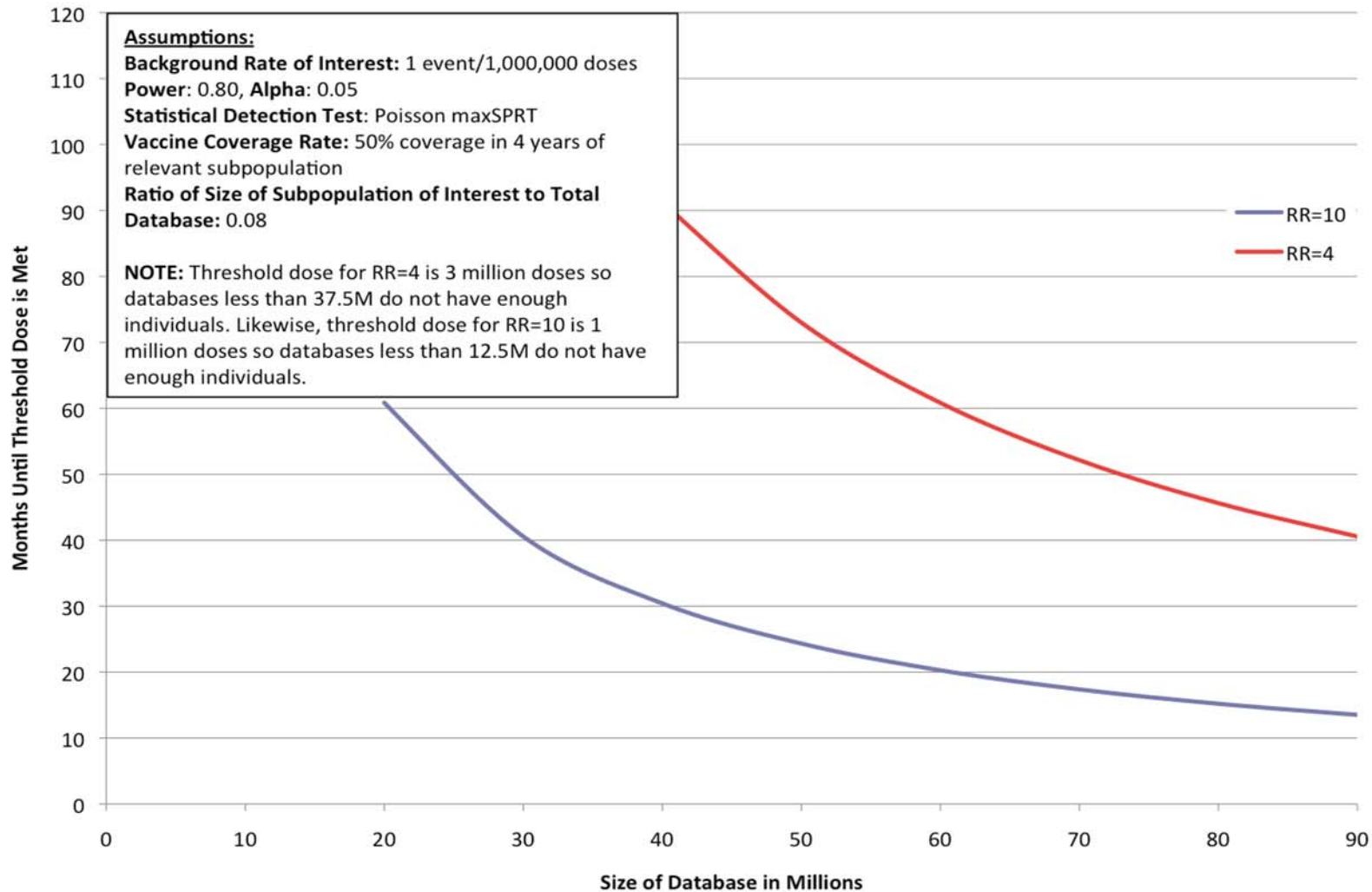


Timeliness for RCA & other study designs

- Dependent on number of vaccinated persons in database(s)
 - Number of persons under surveillance
 - Vaccine Coverage
- Magnitude of risk



Figure 3. Effect of Relative Risk on Time until Signal Detection



Larger is Better, but is there a Point of Diminishing Return?

- Need to consider vaccine benefits as well as safety
 - What level of risk needs to be ruled out?
 - Vaccine benefit may impact this
- Relative vs. Absolute Risk
 - 10 fold relative risk for GBS (42 days post-vaccination) is 10-20 excess cases of GBS per million vaccinees
- Risk/Benefit calculation may change over time (OPV vs. IPV)
- Cost of adding more sites
- Ability, timeliness and cost to conduct chart review



What is the Ideal Size?

Balancing Costs and Benefits

- No magic answer
 - Size impacts timeliness and power to look at rare events and subpopulations & low levels of risk
 - Different systems have different attributes
 - Post-licensure safety systems benefit from harmonized strategy taking advantage of availability of multiple databases
 - Optimize populations covered
 - Analytic abilities
 - Value of surge capacity (H1N1)
 - Capacity outside the US
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Acknowledgements

Judith C. Maro

Saad B. Omer

Martin Kulldorff

Grace Lee

W. Katherine Yih

Robert Davis

