Regulatory Science: Innovations in Assessing Effectiveness, Safety and Benefit-Risk for Biologics

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Director

Office of Biostatistics and Epidemiology

CBER, FDA

Bass Meeting

November 3, 2015

Overview of Presentation

1. Organization of FDA, CBER and OBE

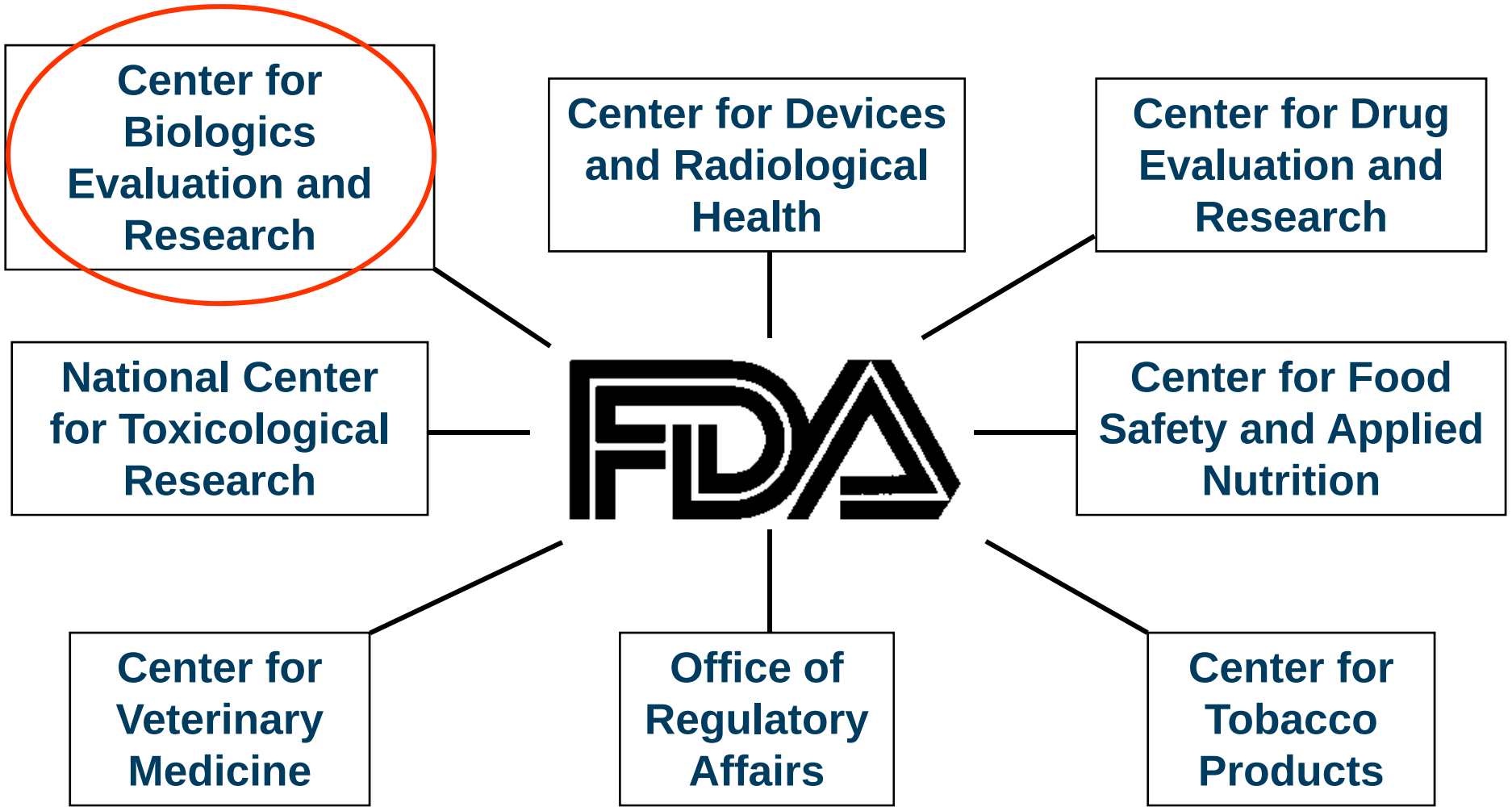
2. Big Data

3. Postmarket Surveillance and FDA Sentinel Initiative (Safety)
   - CBER Sentinel PRISM and BloodSCAN

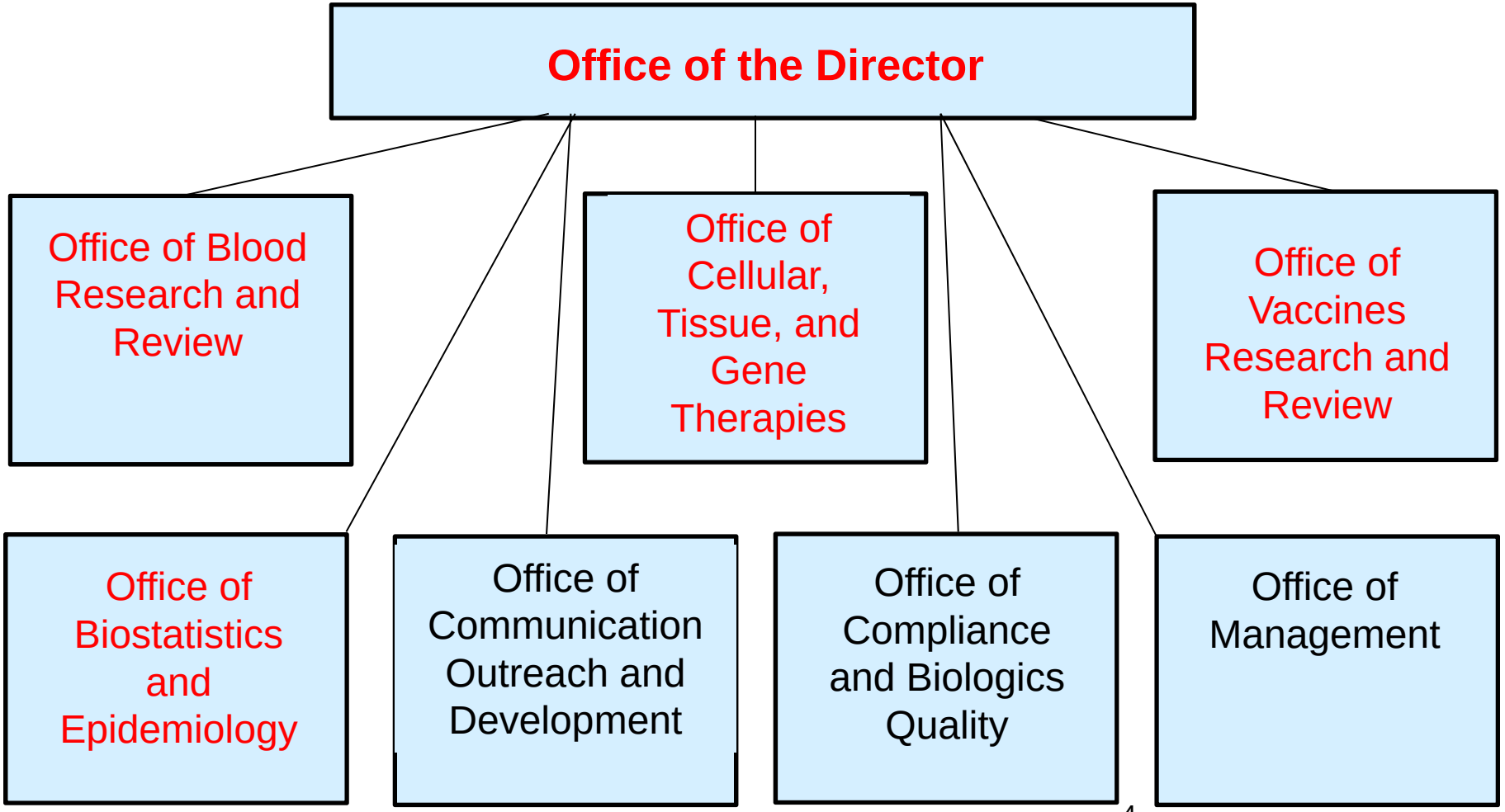
4. Evaluation of Biologic Product Effectiveness
   - CMS data and Flu vaccine

5. Quantitative Benefit-Risk Assessment
   - Evaluation of Blood and Blood Product Safety

1. FDA Organization



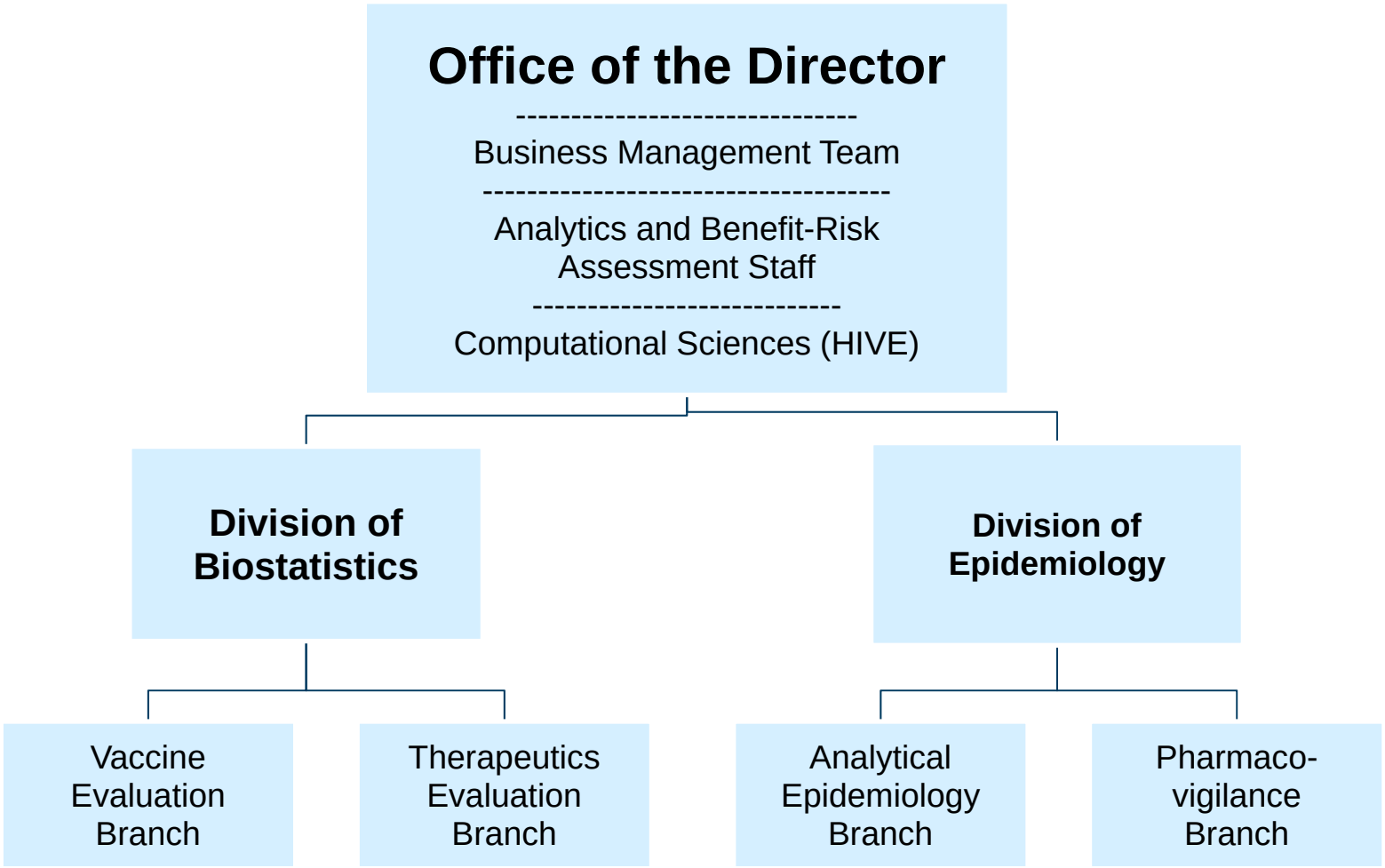
Center for Biologics Evaluation and Research



CBER Product Areas

- Vaccines
- Blood derivatives (Albumin, IVIGs, clotting factors)
- Blood (whole, plasma, RBCs, platelets)
- Allergenic extracts
- Human tissue products
- Human cellular products (stem cell transplants)
- Related devices
- *Future gene therapies*

OBE Organizational Structure



Pre-licensure Review
(some post-licensure)

Post- and Pre-licensure Review

Functions of the Office of Biostatistics & Epidemiology

Office of the Director, OBE (3 FTEs)

Computational Sciences (HIVE) (3 FTEs + 20 Fellows)

- Computational analyses and modeling
- Next generation sequencing, simulation, etc.

Analytics and Benefit-Risk Assessment Staff (15 FTEs + 10 Fellows)

- Conducts quantitative benefit risk assessments & modeling
- Simulation modeling and quantitative analyses
- Epidemiology Team

Business Management Team (6 FTEs)

- Special support for administration, contracting, and research fellows

Division of Biostatistics (35 FTEs + 1 Fellow)

- Review of clinical study and bioassay data and statistical analyses
- Methods Development

Division of Epidemiology (31 FTEs)

- Review adverse event reports, pharmacovigilance plans, study protocols
- Conducts surveillance and epidemiological studies, Sentinel, CMS, etc.

OBE Mission

Regulatory Review

- EvaluateEffectiveness, Safety, Surveillance, Benefit-Risk Assessment data submitted to the Center in support of regulatory requirements.
- Represents the Center on statistical , epidemiological and benefit-risk assessment evaluations of medical products.
- Collaborates with other Centers to provide reviews and assessments of regulated biological products.
- Contributes to the development of regulatory policy.

Regulatory Science (supports Review)

- Research and Development
- Methods and Application
- Data Analyses
- Interdisciplinary – Biostatistics, Epidemiology, Clinical Studies, High Performance Computing, Modeling/Simulation, Benefit-Risk Assessment

2. Big Data – What is it?

- Large datasets: Medical databases, Clinical trial data, Next generation sequencing, and others
- Can be Real World Data, Observational Study data, Clinical experience, patient registries, etc.

Requires

- Collaboration – multidisciplinary effort incl. epidemiologists, biostatisticians, informaticians, computer programmers
- Advanced hardware to perform analyses
- Software tools to organize, analyze and visualize data (data mining, Natural language processing, artificial intelligence, etc.)

Big Data Challenges for evaluating Biologic Effectiveness and Safety

- Confounding and Bias
- Selection bias , sampling bias, representative population
- Missing data
- Inaccurate recording of exposure or outcome
- True positive, true case (meets case definition)
- Recall bias

3. Postmarket Surveillance and FDA Sentinel Initiative (Safety)

Postmarket Surveillance Prior to 2007

- Reliance on Passive Adverse Event Reporting –
- Product Adverse Event report submitted by Health care provider, patient or manufacturer to FDA

- FDA Adverse Event Reporting System (FAERS)
- Vaccine Adverse Event Reporting System (VAERS)
- Useful for Safety Signal Identification or hypothesis generation
- Many limitations: can't get rate info, bias in reporting, lag in reporting, etc.

Routine Pharmacovigilance

- All-inclusive surveillance for medical products conducted by both the US FDA and sponsors
  - Continuous safety monitoring with passive surveillance
  - Disproportionality analyses of spontaneous reports
  - Periodic reports (PSURs or PAERS)
  - Signal detection, issue evaluation, labeling updates
  - Medical literature review
- Contact with international public health and regulatory agencies

Passive Surveillance: Vaccine Adverse Event Reporting System

- Co-administered by FDA and CDC
- Reporting by paper or electronic versions of a standard form
- Contractor enters data and MedDRA codes
- Over 40,000 reports received annually
  - ~20% serious (9116 in FY 2012)
  - Serious AE reports are manually reviewed by medical officers
  - Nonserious reports assessed primarily through data mining

CBER Active Surveillance Development

- Large medical databases are population-based and can supply AE rate information
- 2003 CBER began using Center for Medicare & Medicaid Services (CMS) databases for Vaccine Safety and Blood Utilization and Safety studies
- CMS is a large insurance program covers >94% elderly (≥65yrs old) in US
- Administrative / billing data that has many limitations – reimbursement issues, recording/coding errors, covers mainly elderly, etc.

FDA Amendments Act of 2007

FDAAA required FDA to develop a postmarket risk identification and analysis system to link and analyze safety data from multiple sources, with at least

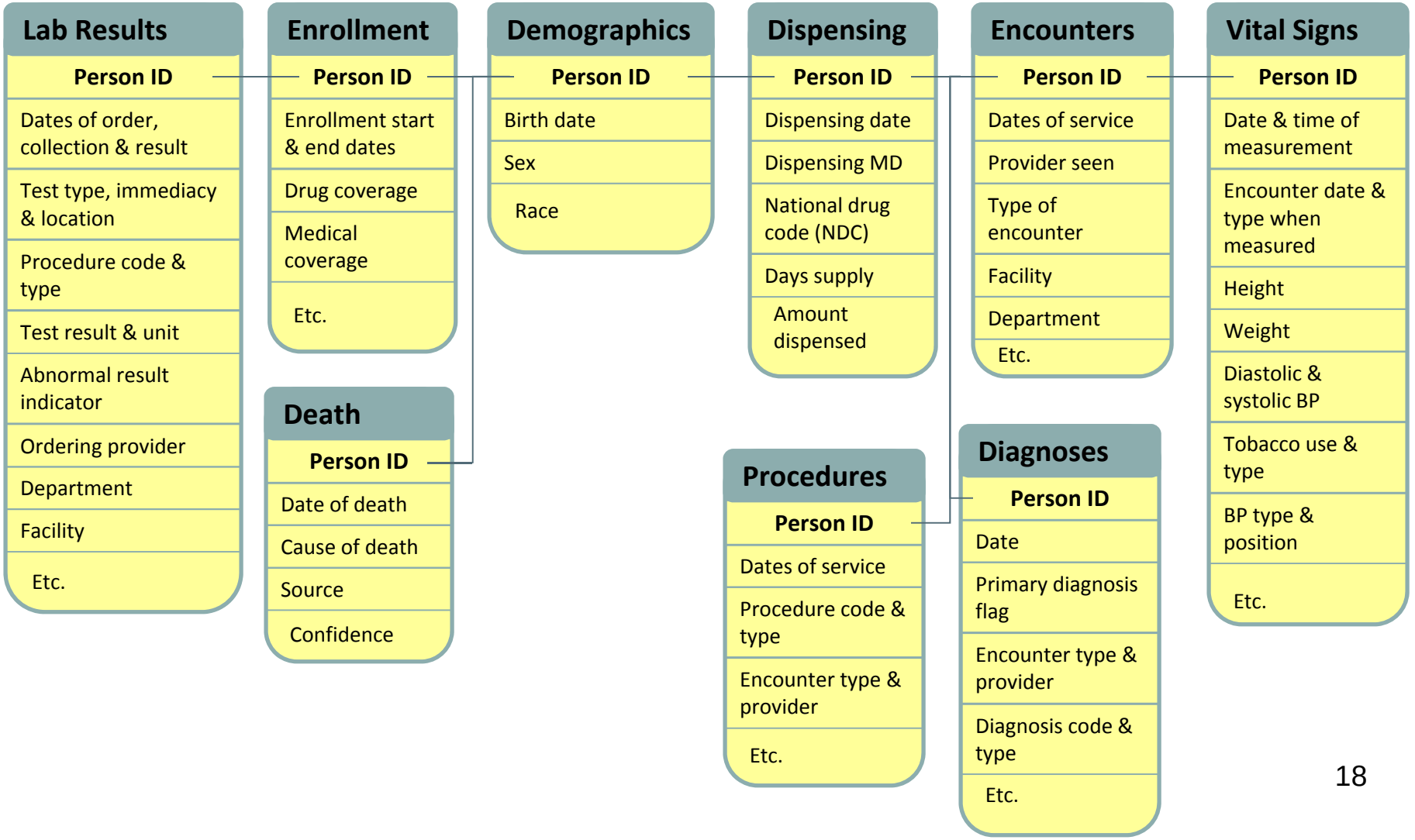
25 million patients by 2010 and

100 million patients by 2012.

FDA Sentinel Initiative

- A postmarket (population-based) risk identification and analysis system started as Mini-Sentinel in 2008
- Distributed data model – Data partners run Sentinel programs on their data
- FDA receives summary tables, information
- Data in Common Data Model – common data fields/variables across all partners
- Currently covers ~189 million person in US
- 20 data partners – includes insurers, and one inpatient partner (HCA)

Mini-Sentinel Common Data Model (CDM)



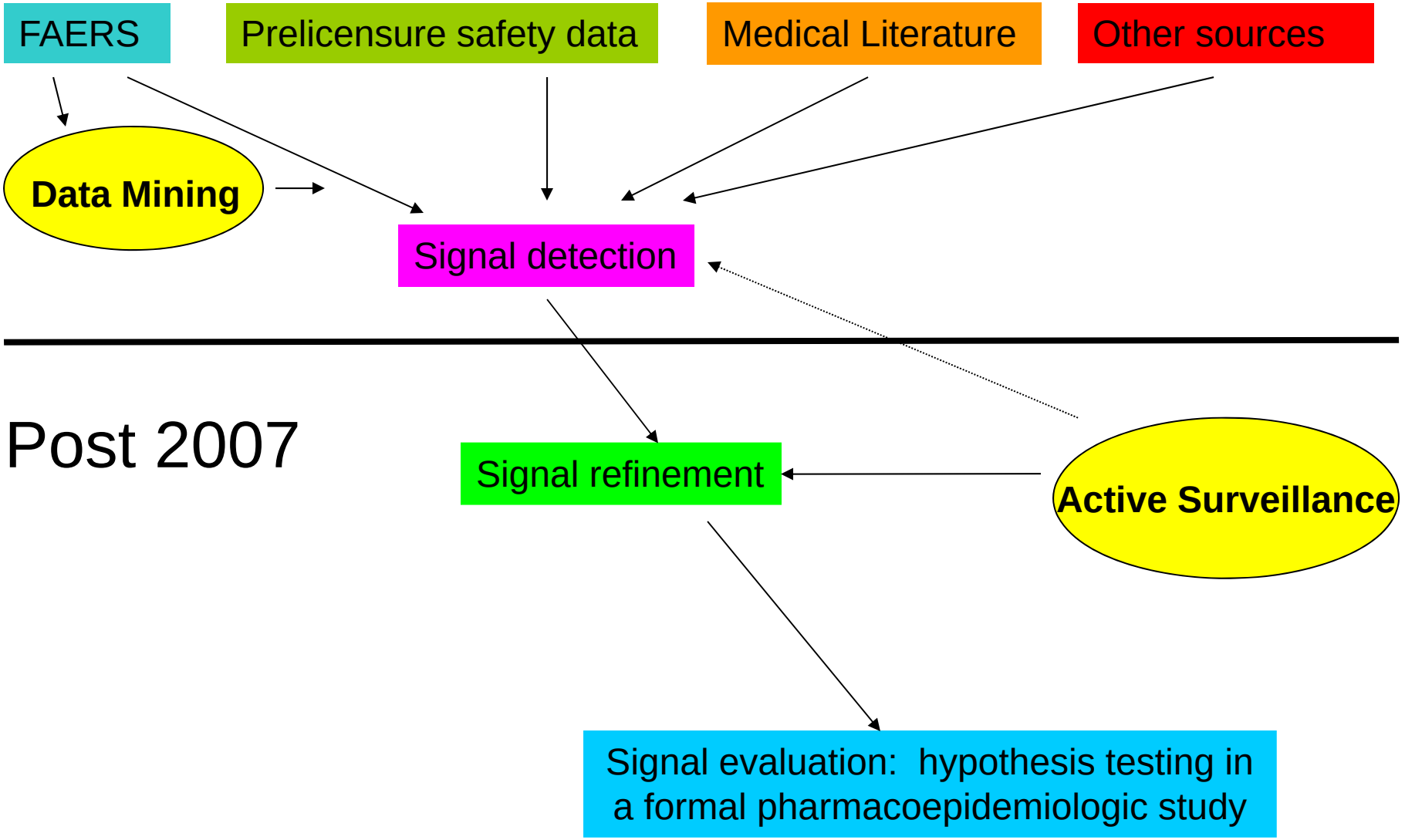
Mini-Sentinel Partner Organizations

Lead – HPHC Institute

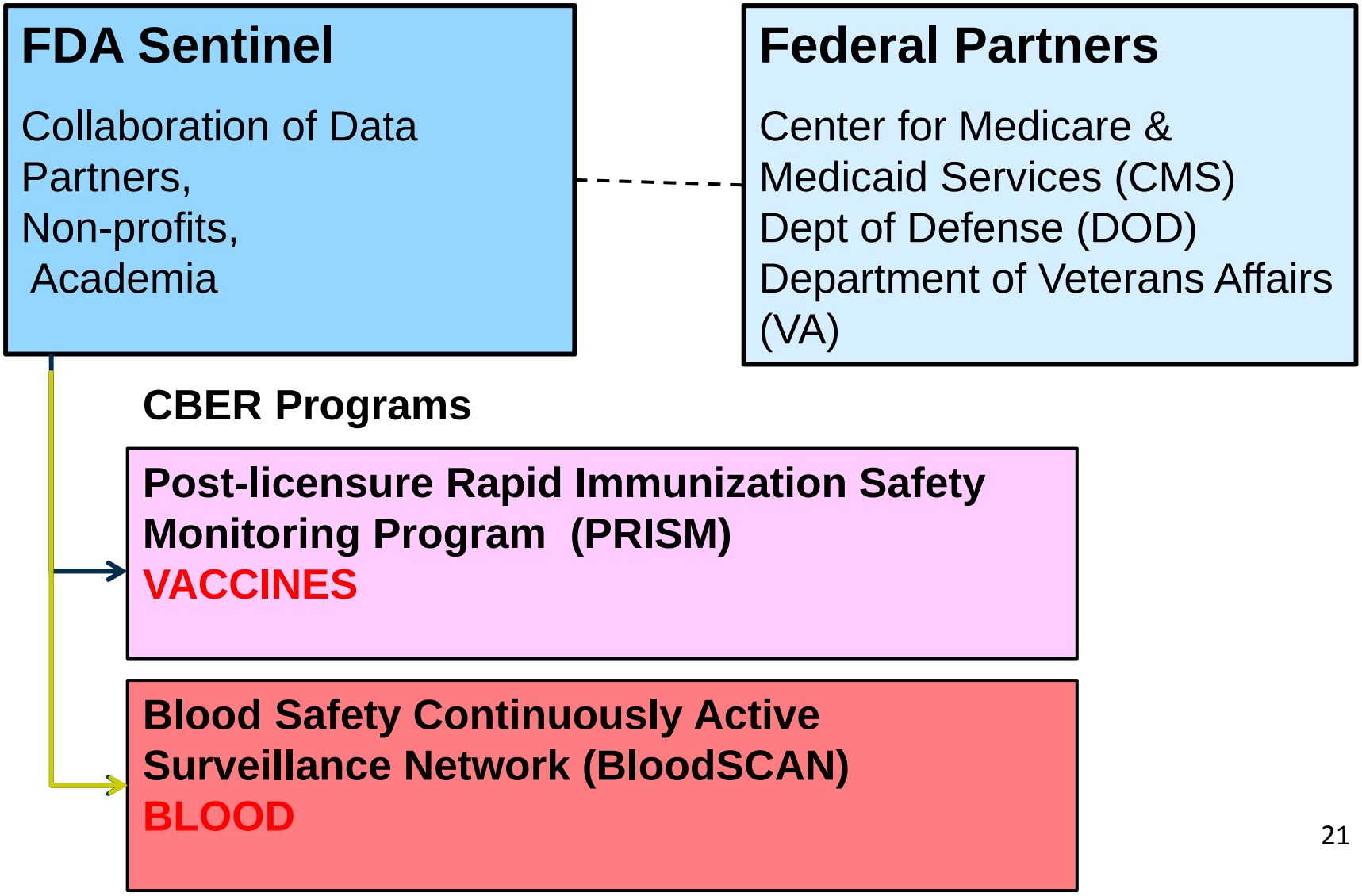
Data and scientific partners

Scientific partners

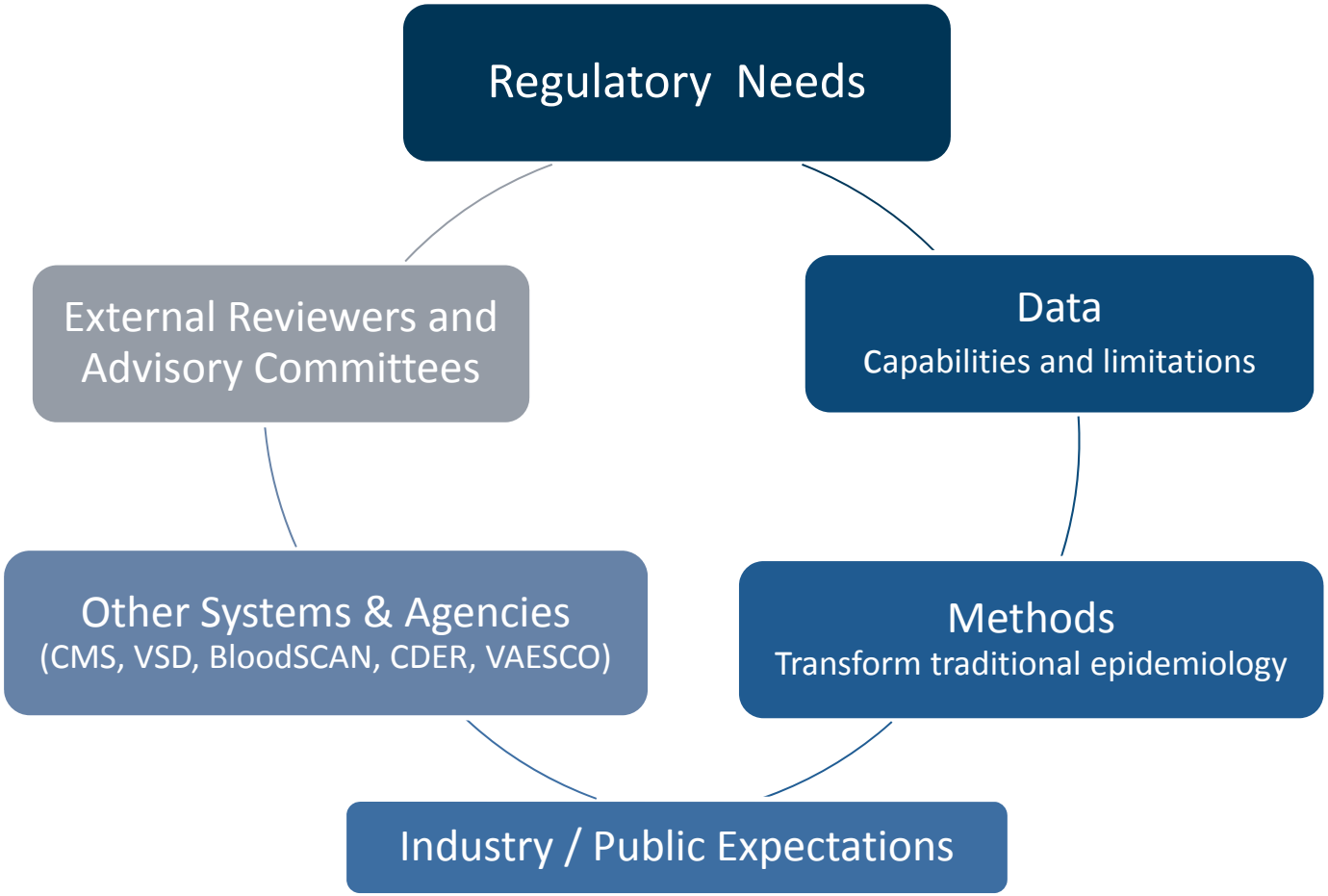
Institute for Health


FAERS
Prelicensure safety data
Medical Literature
Other sources
Data Mining
Signal detection
Post 2007
Signal refinement
Active Surveillance
Signal evaluation: hypothesis testing in a formal pharmacoepidemiologic study

FDA Sentinel Initiative and CBER



PRISM Inputs / Influences



Sentinel Distributed Querying Approach

Three ways to query MS data*:

1. **Pre-tabulated summary tables**
2. **Reusable, modular SAS programs (MP)**
   - Level 1 MP: Cohort Identification and Descriptive Analysis Tools
   - Level 2 MP: + Analytic Adjustment Tools (e.g., Propensity score matching, regression analysis)
   - Level 3 MP (PROMPT): + Sequential Analysis and Signaling Tools
3. **Protocol-Based Assessments (custom SAS programs)**

Reports of all queries posted at www.minisentinel.org once results are deemed final by the FDA.

Sentinel Distributed Querying Approach

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1. **Pre-tabulated summary tables**
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Majority of CBER Sentinel resources for product safety studies used for protocol-based studies

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   - Level 3 MP (PROMPT): + Sequential Analysis and Signaling Tools

3. **Protocol-Based Assessments (custom SAS programs)**

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CBER Sentinel Studies and Regulatory Process

Two Types of Studies

1. Biologic Product Safety Studies (Regulatory)

- Rotavirus Vaccines and Intussusception
- Influenza Vaccine Safety – febrile seizures, birth outcomes
- Transfusion-related Acute Lung Injury (TRALI)

2. Infrastructure and Methods Development

- Vaccine safety during pregnancy (esp Influenza)
- Pandemic preparation
- Development new data sources (e.g., inpatient)

Overview of CBER Sentinel Studies

	Surveillance Assessment	Protocol Posting Date	Final Report Posting Date
1	**Rotavirus vaccines and intussusception**	Posted 10/24/2011	Posted 6/14/2013
2	**Gardasil vaccine and venous thromboembolism**	Posted 3/30/2012	Spring 2015
3	**Influenza vaccines and febrile seizures**	Posted 1/25/2013	Posted 5/15/2014
4	**Influenza vaccines and birth outcomes**	Posted 2/25/2013	Fall 2016
5	**Influenza vaccine safety sequential analysis**	Posted 8/2/2013	Spring 2015
6	**Influenza vaccines and pregnancy outcomes**	Posted 9/18/2013	Spring 2016
7	**Thromboembolic events after immunoglobulin administration**	Posted 9/20/2013	Winter 2017
8	**Prevnar 13 vaccine and Kawasaki Disease**	Fall 2015	TBA
9	**TRALI after platelets, plasma, and red blood cells**	Winter 2016	TBA
10	**Gardasil vaccine (HPV4) TreeScan pilot (methods development)**	Winter 2015	TBA
11	**Influenza vaccine and febrile seizures in 4 influenza seasons**	Spring 2015	TBA
12	**Gardasil 9 general safety study**	Fall 2015	TBA
13	**Gardasil 9 and pregnancy outcomes**	TBA	TBA

http://mini-sentinel.org/assessments/medical_events/details.aspx?ID=188

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CBER Sentinel Studies and Regulatory Process

Sentinel PRISM Study (posted 6/14/2013): Rotavirus Vaccines and Intussusception (IS)

- During 2004-2011: 1.2 million RotaTeq vaccinations (507,000 first doses) and 103,000 Rotarix vaccinations (53,000 first doses) evaluated in infants 5 - 36 weeks of age
- Increased risk of IS in 21 day period after first dose RotaTeq, most cases occurred in first 7 days
- No increased risk found after second or third doses.

- FDA believes that benefits of RotaTeq and Rotarix vaccination continue to outweigh the risks, including the risk of intussusception

Vaccines, Blood & Biologics

Safety & Availability (Biologics)

Biologics Product Shortages Q&A

Recalls (Biologics)

CBER-Regulated Products: Shortages and Discontinuations

Report a Problem to the Center for Biologics Evaluation & Research

Biologic Product Security

Pandemics

Blood Safety & Availability

Tissue Safety & Availability

Vaccine Safety & Availability

HIV Home Test Kits

Resources for You

- 2013 Safety and Availability

FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Safety Communication — June 13, 2013

FDA Releases Final Study Results of a Mini-Sentinel Postlicensure Observational Study of Rotavirus Vaccines and Intussusception

FDA Approves Required Revised Labeling for RotaTeq Based on the Study Results

Purpose: To inform the public and healthcare providers that FDA is releasing final study results from a Mini-Sentinel postlicensure observational study of intussusception (a form of bowel obstruction) after vaccination with RotaTeq (Merck and Co., Inc.) and Rotarix (GlaxoSmithKline Biologicals).

Revised Labeling - Rotavirus Vaccines and Intussusception

FDA has approved required revisions to the Prescribing Information and Patient Information for RotaTeq as a result of the new safety data from this Mini-Sentinel PRISM study. New information was added to the Highlights, the existing intussusception subsection of the Warnings and Precautions section, and the Post-Marketing Experience section of the Full Prescribing Information, as well as to the Patient Information. The Mini-Sentinel PRISM study is the largest study of intussusception after rotavirus vaccines to date and identified an increased risk of intussusception in the 21 day time period after the first dose of RotaTeq, with most cases occurring in the first 7 days after vaccination. No increased risk was found after the second or third doses. These findings translate into 1 to 1.5 additional cases of intussusception per 100,000 first doses of RotaTeq.

The data from the Mini-Sentinel PRISM study regarding the risk of intussusception following the use of Rotarix were inconclusive. Based on this study, no changes were made to the Prescribing Information or to the Patient Information for Rotarix. However, based on data

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CBER Sentinel Studies and Regulatory Process

Sentinel PRISM Study (posted 5/15/2014): Influenza Vaccine and Febrile Seizures

- 2010-2011 Flu season increase in febrile seizure reports in Vaccine Adverse Event Reporting System (VAERS) for Fluzone (a Trivalent Influenza Vaccine or TIV)
- PRISM study of TIVs for 1.9 million children ≤5 yrs old during 2010-2011 season
- 842,325 met eligibility criteria –

  68 confirmed cases febrile seizure – within 20 days of vaccination
- Study showed no statistically significant association between TIVs and increased risk of febrile seizures

Vaccines, Blood & Biologics

Safety & Availability (Biologics)
- Biologics Product Shortages Q&A
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- Vaccine Safety & Availability
- HIV Home Test Kits

Resources for You

- 2014 Safety and Availability Communications

Update: FDA Postlicensure Rapid Immunization Safety Monitoring (PRISM) study demonstrates no statistically significant association between Trivalent Inactivated Influenza Vaccine and Febrile Seizures in Children during the 2010-2011 influenza season

May 15, 2014

This information supersedes the FDA Communication issued on January 20, 2011

During the 2010-2011 influenza season, the U.S. Food and Drug Administration (FDA) and the Centers

“This assessment […used…] FDA’s Mini-Sentinel pilot...”

manufactured by Sanofi Pasteur, Inc.) were received into the Vaccine Adverse Event Reporting System (VAERS).

Although VAERS can provide early indications of possible safety concerns, epidemiologic studies are necessary to determine whether adverse events are occurring more often than expected in people who receive a vaccine. To further investigate febrile seizures after vaccination with Fluzone as well as other TIVs administered to children less than 5 years of age during the 2010-2011 influenza season, FDA initiated a study using its Mini-Sentinel Postlicensure Rapid Immunization Safety Monitoring (PRISM) program, the largest vaccine safety surveillance program in the United States.[1] The study identified 1.9 million children aged 6 through 59 months who were enrolled in one of three health plans from July 1, 2010 to June 30, 2011. From this total, 842,325 met eligibility criteria ensuring that sufficient pre-vaccination and follow-up information would be available to investigators, with 68 confirmed cases of febrile seizures identified within 20 days after receipt of TIV. The study showed no statistically significant association between TIVs and increased risk of febrile seizures. Fluzone is the most widely used TIV in the U.S. in the age group that was included in the study. Based on these findings, FDA is

CBER Sentinel Studies and Regulatory Process

Impacts

Labeling change

- Required revised labeling for rotavirus vaccines based on Mini-Sentinel findings of an increased risk of intussusception after vaccination.

CBER Safety Communications

- **June 13, 2013:** FDA approves required revised labeling for rotavirus vaccines based on new safety data showing an increased risk of intussusception after vaccination.

- **May 15, 2014**: Mini-Sentinel PRISM study shows no statistically significant association between trivalent inactivated influenza vaccine and febrile seizures.

Summary

- Sentinel integrated into routine postmarket safety regulatory processes
  - Impacts pre- and post-market phases
  - Developing tools for signal detection, refinement and evaluation
- Majority of CBER projects have two-fold impact:
  - Addresses immediate regulatory question
  - Builds infrastructure or advances methods for future studies
- Working to apply Sentinel to all classes of CBER- regulated products
  - Vaccines
  - Blood components and plasma protein therapies
  - Human cells, tissues, and cellular and gene therapies

4. Evaluation of Biologic Product Effectiveness

–CMS data and Flu vaccine

Biologic Product Effectiveness

- Developmental area
- Licensure requires ‘adequate and well-controlled clinical studies’
- Can BIG DATA / observational data be used to support licensure of a product ???
- Can provide confirmation when clinical study data were minimal or accelerated approval, etc.
- Can it provide information for labeling???

Comparative effectiveness of High- vs. Standard-dose influenza vaccines among US residents aged ≥65 years, 2012-13 *

- Hector S. Izurieta[1], Nicole Thadani[2], David Shay[3,] Yun Lu[1], Riley Franks[2], Ivo Foppa[3,] Thomas MaCurdy[2], Douglas Pratt[1], A Maurer[2,] Richard Forshee[1], Chris Worrall[4], Jonathan Gibbs[2], Han Hong[2], Jeffrey Kelman[4]

- Food and Drug Administration (FDA), Rockville, MD, U.S.A.
- ACUMEN, Burlingame, CA, U.S.A.
- Centers for Disease Control and Prevention, Atlanta, GA, U.S.A.
- Centers for Medicare & Medicaid Services (CMS), Washington, DC, U.S.A.

** Reference: Izurieta, H.S. et al, Lancet Infect Dis 2015*

Background (1)

- An estimated 200,000 people hospitalized annually in US from seasonal flu complications
- Estimates of number of annual deaths vary by year but range from 3,000 to 49,000 per year
- Elderly at higher risk for influenza complications
- Elderly vaccinees produce lower hemagglutination inhibition (HI) titers
- Improving influenza vaccine effectiveness important for elderly (aged ≥65 years)

Background (2)

- In 2009, FDA licensed a High-dose (HD) trivalent influenza vaccine (TIV) containing 4 times more hemagglutinin antigen than standard-dose TIV for use among elderly

- Licensed under accelerated approval
  - Product for serious or life-threatening disease or condition
  - Surrogate endpoint reasonably likely to predict clinical benefit

- Accelerated approval of the HD vaccine based on HI titers

Background (3)

- *Sponsor conducted a required confirmatory study (n> 30,000) showing clinical benefit of HD vaccine
- 2011-2012 and 2012-2013 flu seasons
- Relative efficacy HD vs Standard against all vaccine strain type/subtypes =

  24.2% (95%CI, 9.7-36.5)

*DiazGranados,et al. NEJM 371;635-645. Aug14,2014

Background (4)

QUESTION FOR FDA STUDY:

Is HD vaccine more effective than standard-dose for preventing influenza-related hospital visits/admissions?

Relevance to FDA Regulatory Mission

Postmarket observational studies

- Enabled FDA to study difficult to evaluate influenza-related outcomes:
  - hospital visits
  - hospitalizations
- Provides additional clinical information on rare complications of influenza or other diseases
- Approach may be more broadly applicable

Methods

- Use of 'Big Data' – Center for Medicare & Medicaid Services (CMS) data for 2012–13 influenza season
- Retrospective cohort study, included beneficiaries ≥ 65 years who received high-dose or standard-dose inactivated influenza vaccines
- From community pharmacies that offered both vaccines within any two-week interval
- Relative vaccine effectiveness estimated by comparing outcome rates in beneficiaries during periods of high influenza circulation.

Results

- Between Aug 1, 2012 and Jan 31, 2013, we studied
  - 929 730 recipients of high-dose vaccine and
  - 1 615 545 recipients of standard-dose vaccine
- The high-dose vaccine was 22% (95% CI 15–29) more effective than the standard-dose vaccine for prevention of probable influenza infections and
- 22% (95% CI 16–27%) more effective for prevention of influenza hospital admissions (0.86 outcomes per 10 000 person-weeks in the high dose cohort *vs* 1.10 outcomes in the standard-dose cohort)

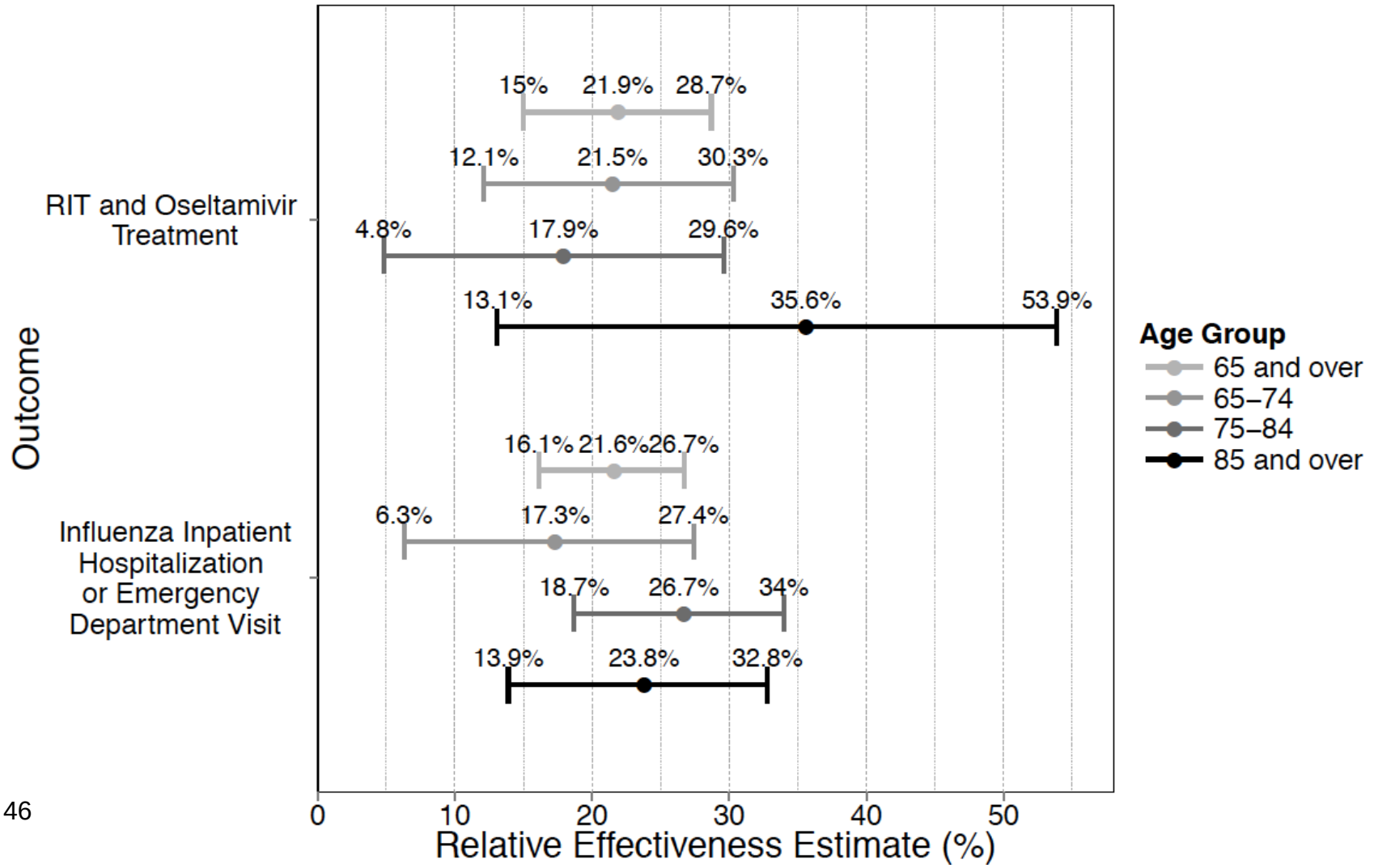
Cohort Breakdown

- Participants enrolled in each cohort were well balanced with respect to potential confounders

Balanced on characteristics:

- Sex
- Race
- Dual enrolled
- Age: 65 -74yrs, 75-84yrs, ≥ 85 yrs
- Region

Outpatient and Inpatient Outcome Rates By Age Group



Summary

- In US beneficiaries ≥65 years high-dose inactivated influenza vaccine -significantly more effective than standard-dose vaccine in preventing influenza-related medical encounters

- FDA's finding of higher effectiveness with the high-dose vaccine (22%) is consistent with sponsor findings (24.2%)

- **FDA larger population study shows**:

  Significant reduction in influenza-related hospital admissions in high-dose compared to standard-dose recipients, an outcome not shown in the randomized study conducted by the sponsor, despite its large size (N>30,000)

Summary

- Innovative analytic approaches can successfully inform decision-making
- Effectiveness studies showed HD influenza vaccine more effective than standard vaccine in elderly and
- Approach using postmarket observational data can be more broadly applied to other vaccines and biologics
- Innovative statistical approaches to trial design can improve chances of success for vaccines and other biologics

5. Quantitative Benefit-Risk Assessment
Evaluation of Blood and Blood Product Safety

B-R Assessment

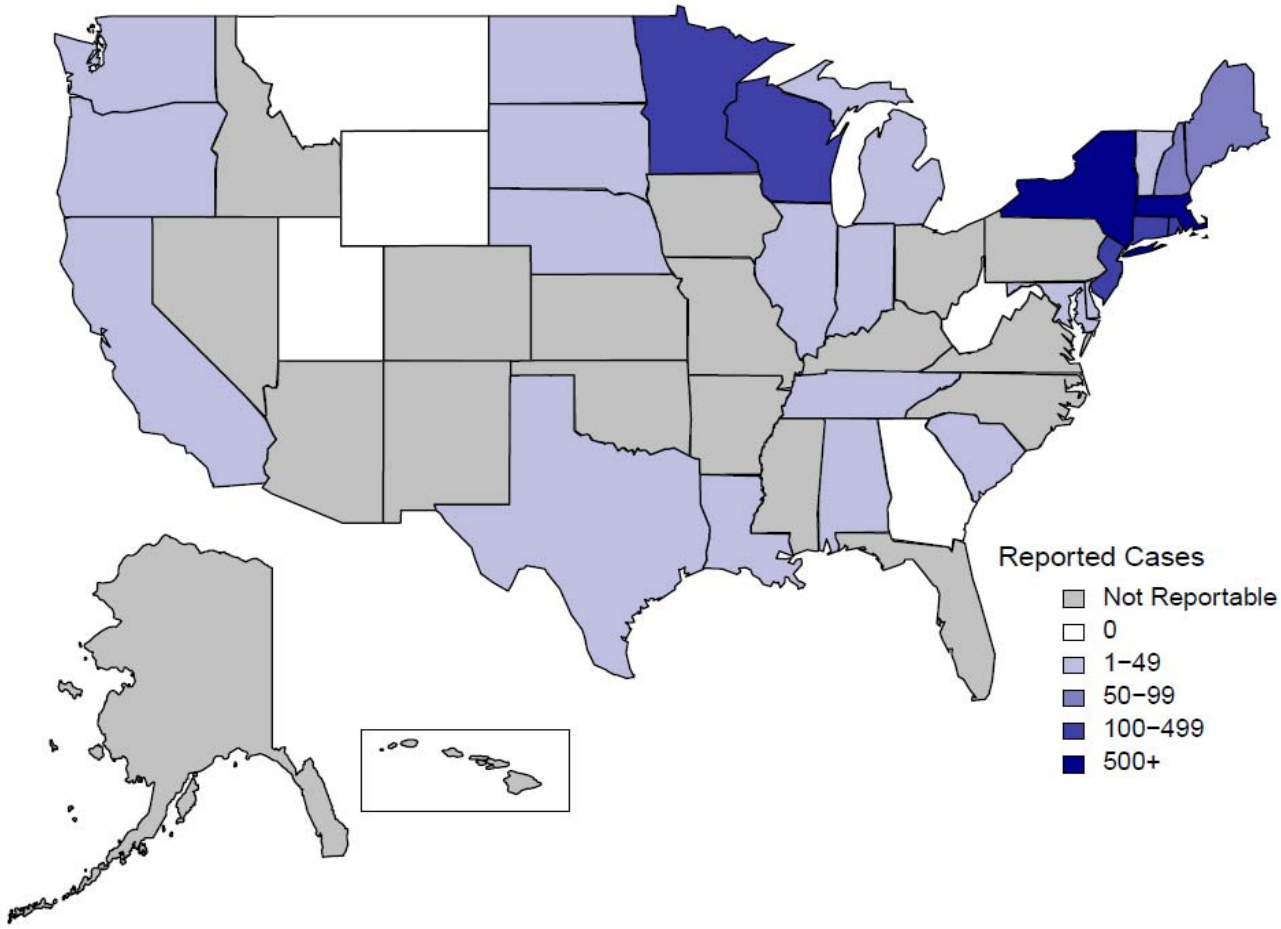
- Quantitative Benefit-Risk Assessment used to inform blood donation policies

- Used at May 13 FDA BPAC Meeting OBE presented a Quantitative Risk Assessment to evaluate benefits and risks of various blood donor testing strategies for babesiosis

Big Data used Benefit-Risk Assessment for Babesiosis and Blood Donation in the U.S.

- Babesiosis transmitted by tick vector and caused by protozoan *Babesia microti*
- Pathogen is bloodborne and can be transfusion-transmitted
- Vast majority of US cases reported in Northeastern, mid-Atlantic and upper Midwestern states
- Babesiosis is most frequent transfusion-transmitted infection in US – there is not a validated, licensed test

Figure 4: State-Level Distribution of Babesiosis Cases, as Reported to CDC, 2011-2013



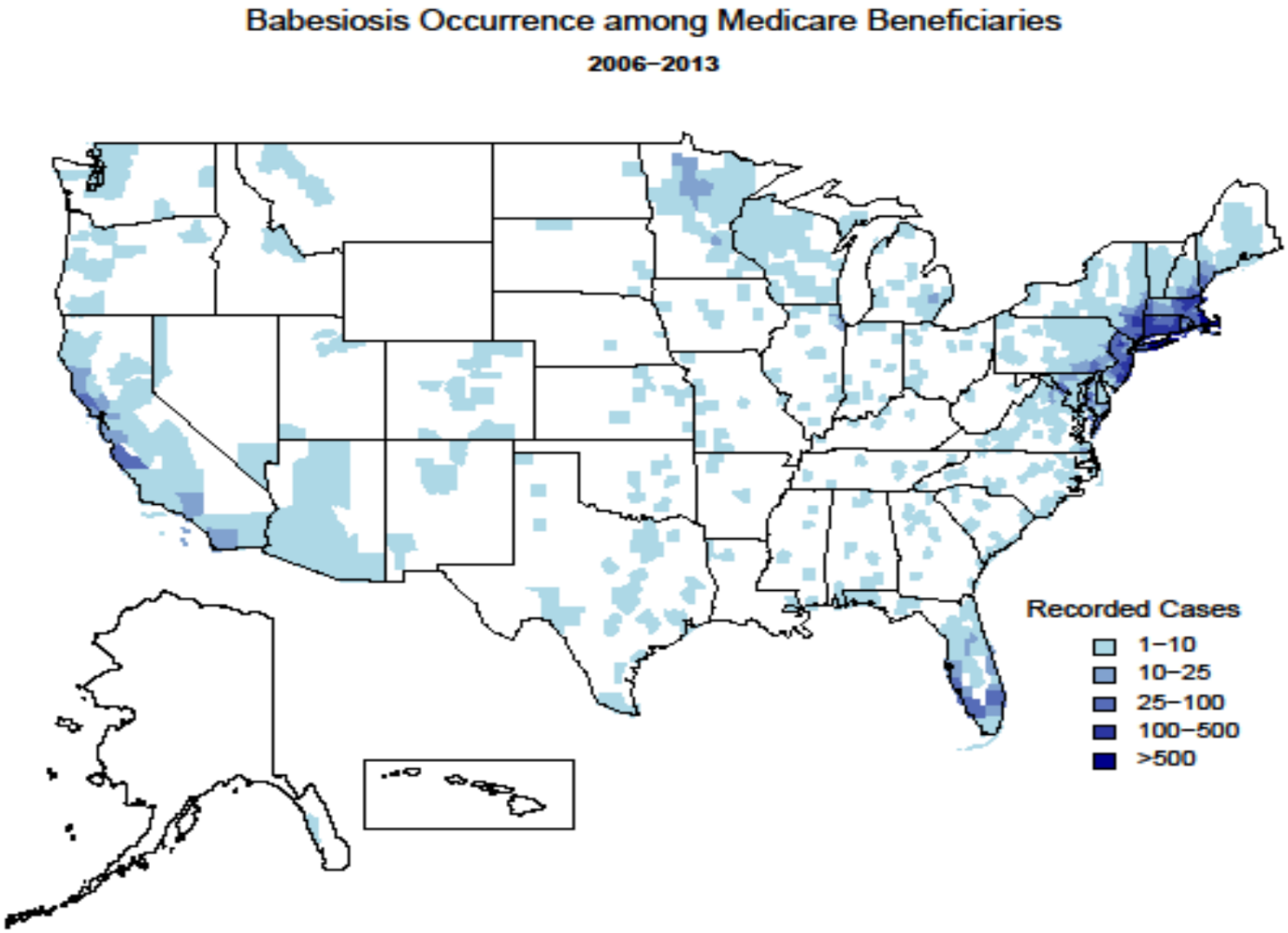
- **Sources:** Centers for Disease Control and Prevention.

•In *MMWR Summary of Notifiable Diseases 2011*. Centers for Disease Control & Prevention, 60(53): 28. July 5, 2013.

•In *MMWR Summary of Notifiable Diseases 2012.* Centers for Disease Control & Prevention, 61(53): 28. September 19, 2014.

•In *MMWR Final 2013 Reports of Nationally Notifiable Infectious Diseases*. Centers for Disease Control & Prevention, 63(32): 702-715. August 15, 2014.

Figure 1: Babesiosis Occurrence among the U.S. Elderly Medicare Beneficiaries During 2006-2013 by County of Residence (Babesiosis Heat Map)



These counts represent the number of Medicare beneficiaries with babesiosis in each county based upon the first recorded diagnosis

Methods

- CMS administrative data for calendar years 2006-2013 was used to ascertain:
  - Incident babesiosis cases based on the first recording of babesiosis diagnosis code during the study period, with no recorded babesiosis in the preceding 365 days;
  - Babesiosis occurrence rates per 100,000 Medicare beneficiaries overall and by calendar year, diagnosis month, and state of residence;
- CDC data for 2011-2013 was used to assess babesiosis occurrence rates per 100,000 residents by reporting state, utilizing U.S. Census data;
- Ranking of states was compared based on babesiosis rates using CDC and CMS data;

CMS Data Results

- During the 8-year period (2006-2013), CMS data investigation identified:
  - 10,301 unique beneficiaries with recorded babesiosis diagnosis;
  - National babesiosis rate of 5 per 100,000 beneficiaries;
  - State-specific rates up to 10 times higher than national rate;
  - Significantly increasing babesiosis occurrence in the U.S. during 2006-2013, with the highest rate in 2013;
  - Highest babesiosis rates in June, July, and August (trends similar to CDC results):
    - 79% of all cases were diagnosed from April through October;

Discussion

- Overall, babesiosis results on rankings of states and on occurrence trends over time and by diagnosis months were similar for CMS and CDC data;
- However, babesiosis occurrence rates identified using CDC case reporting data in the general population were substantially lower as compared to babesiosis occurrence identified by CMS data in the U.S. elderly, which could be due to:
  - Under-reporting or lack of reporting to CDC; and
  - Higher likelihood of underdiagnosing babesiosis in the general population vs. elderly since babesiosis is more likely to be asymptomatic in younger individuals as compared to older persons;
- Babesiosis occurrence rates among the Medicare beneficiaries based on CMS data provide the best available population-based estimate of babesiosis occurrence in the U.S. Blood donors/General Population and as such was further
- CMS data used to assess number of TTB units prevented and false positive units diverted, overall and by state, for different blood donor screening strategies.

Limitations

- Analyses were also based on the administrative databases, and consequently, there is:
  - Difficulty in identifying incident vs. prevalent cases as diagnosis codes do not necessarily represent incident events and tests are not well recorded;
  - Possible misdiagnosis or misrecording of babesiosis diagnosis;
  - Lack of clinical detail for diagnosis code verification and for TTB cases identification;
  - Lack of clinical information to ascertain *Babesia* species;
  - Test results are generally not available in claims data;
  - State-level results are based on beneficiary's state of residence, which may not be the state in which the individual was initially infected;
  - In the future, medical record review is needed to assess positive predictive value of the ICD-9-CM diagnosis code for babesiosis.

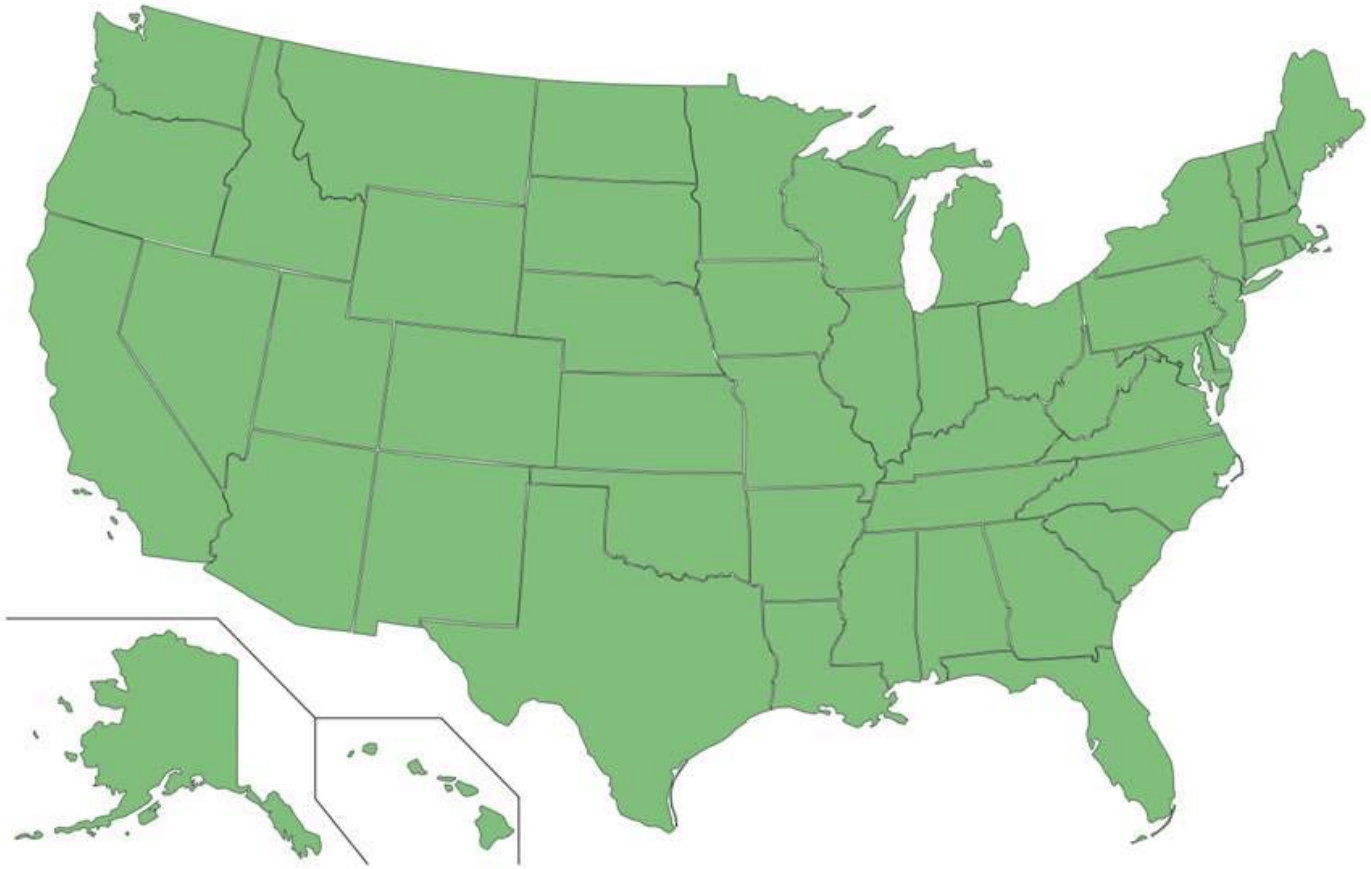
Testing for Babesiosis in blood donations

Serological Testing

- Tests for antibody which persists many weeks and months after recovery
- Proposed for all states (gives prevalence)

Nucleic Acid Testing (NAT)

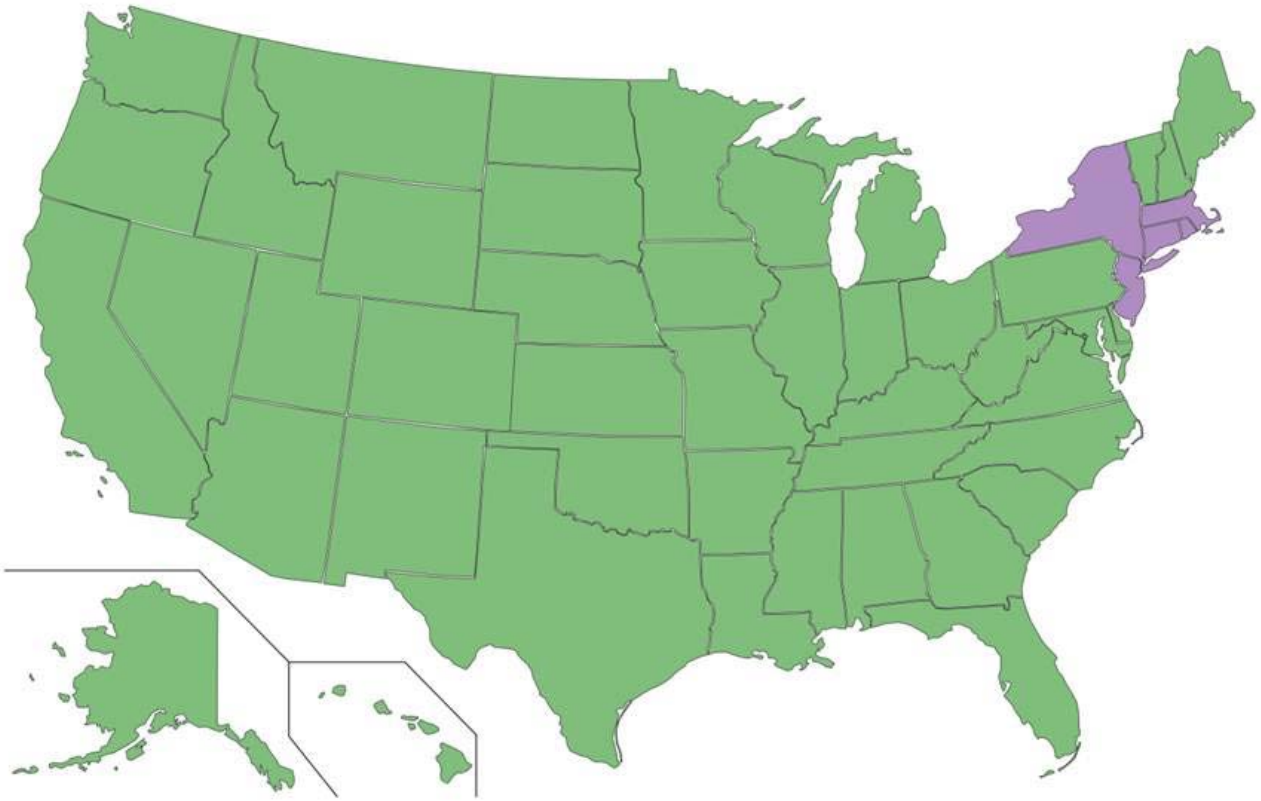
- Test that detects live parasites in blood during active infection but not after recovery
- Measures incident or new infections
- Proposed for 5 states, 9 states or 15 states with highest occurrence



S: 50 + DC

No Testing Serology only Serology + NAT

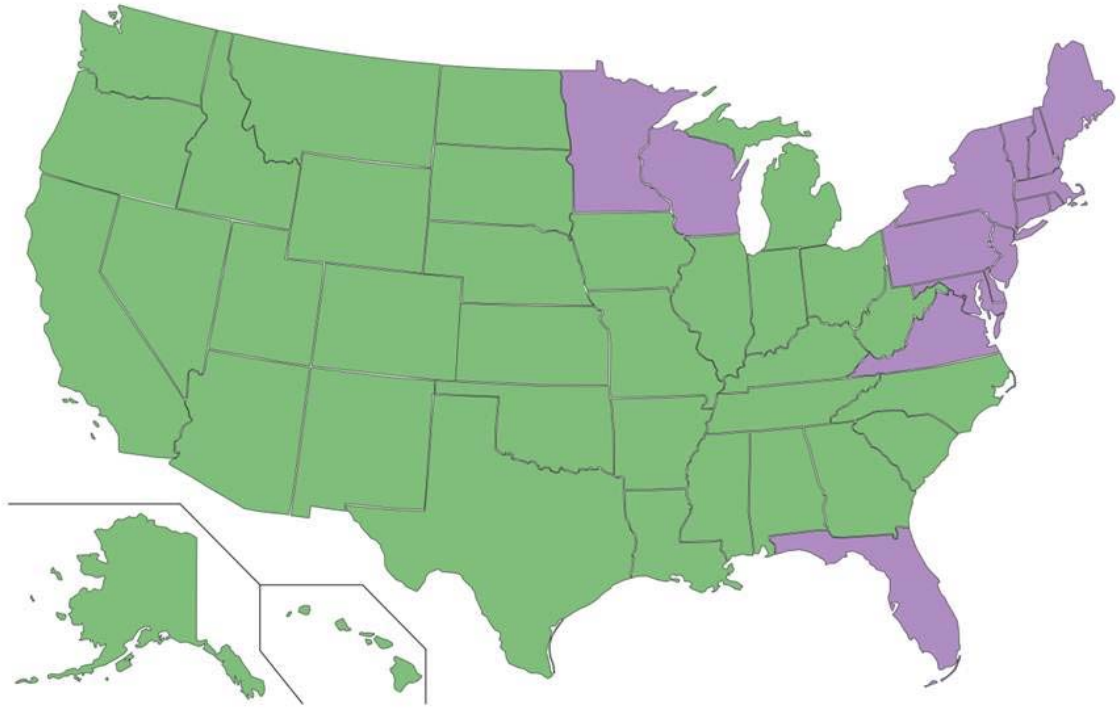
Scenario: Serology in 50 States Plus DC



CT
MA
RI
NY
NJ

S: 50 + DC,
N: 5

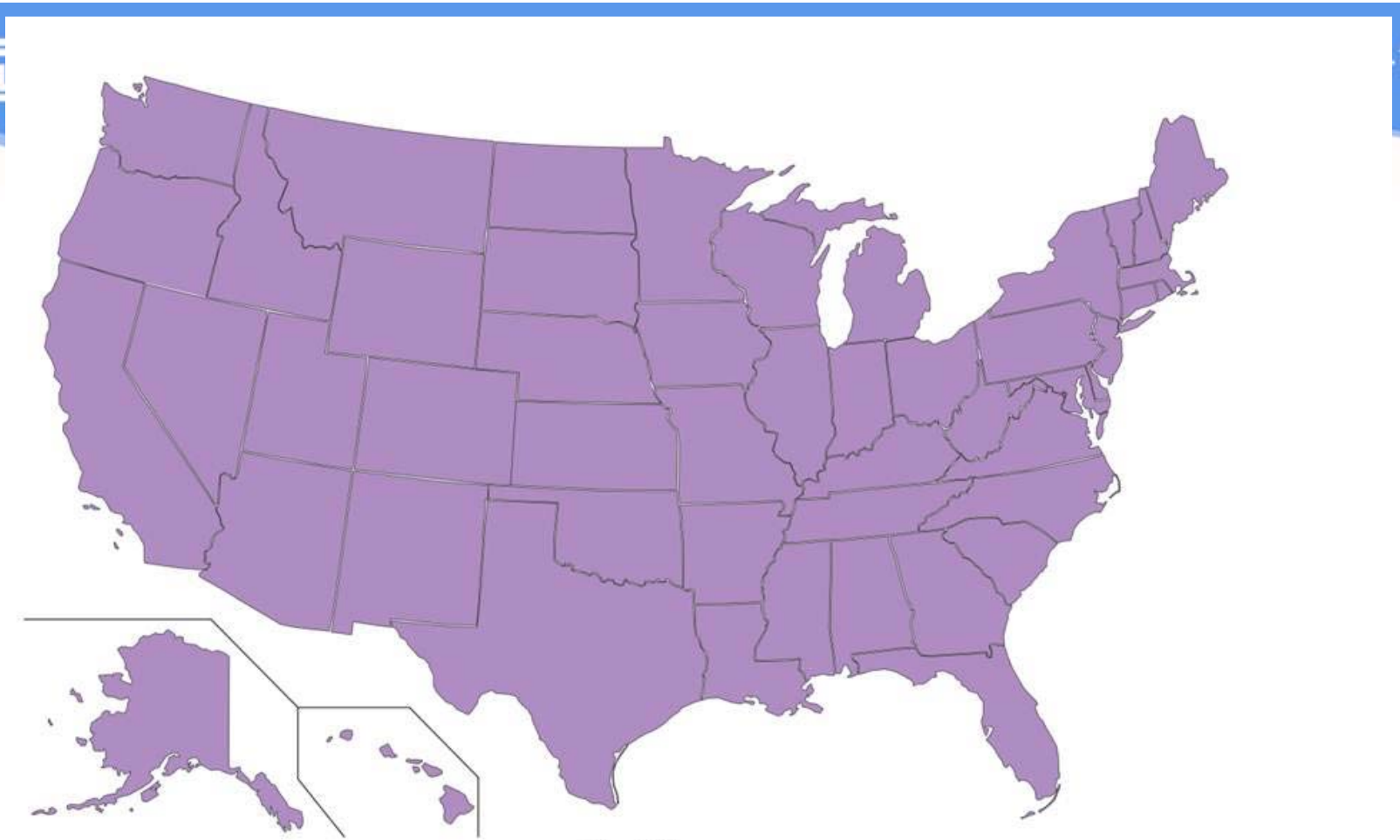
Scenario: Serology in 50 States Plus DC, Serology Plus NAT in 5 States



CT	NH	MD
MA	ME	DC
RI	MN	VA
NY	WI	VT
NJ		PA
		DE
		FL

S: 50 + DC,
N: 15 + DC

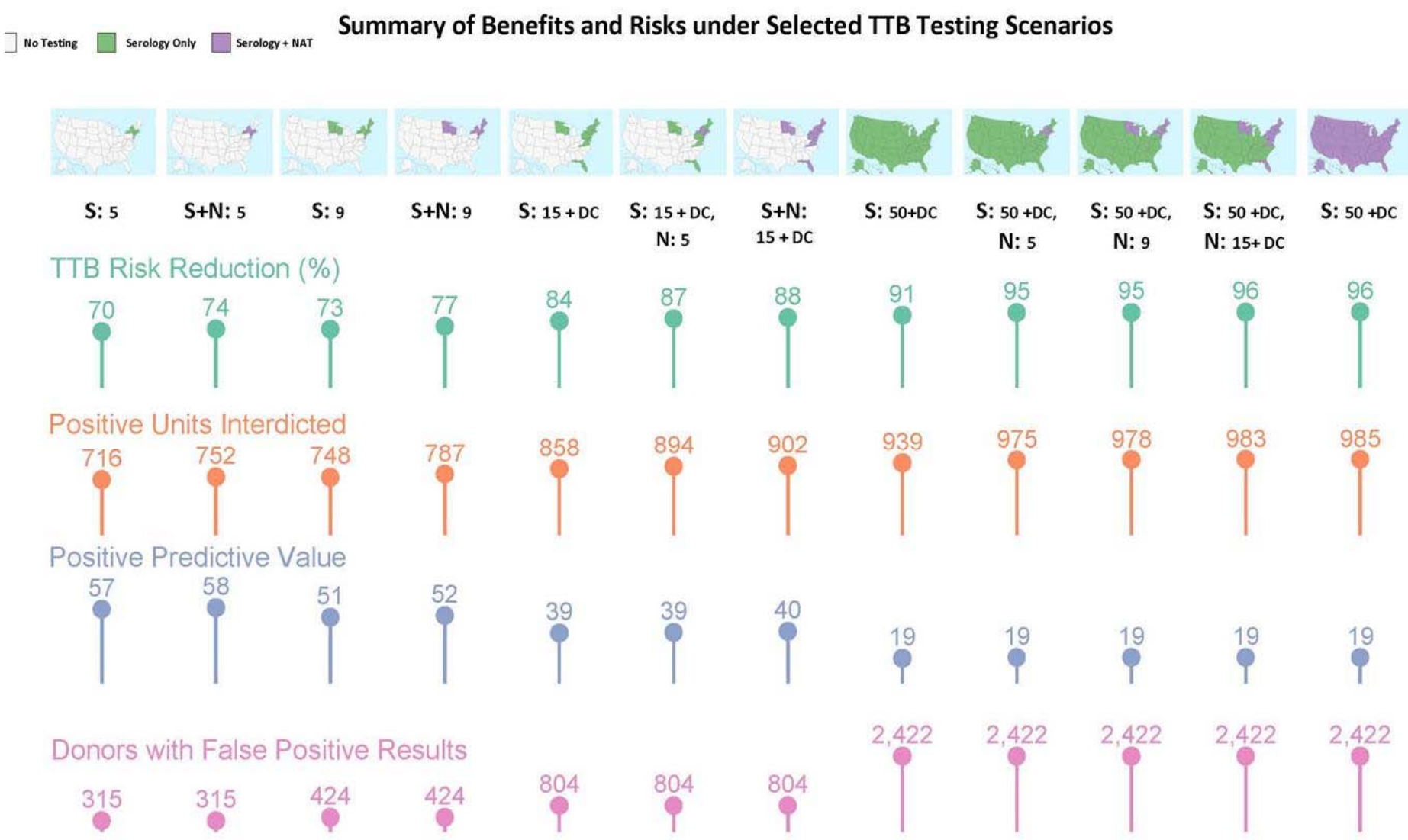
Serology in 50 States + DC, Serology Plus NAT in 15 States + DC



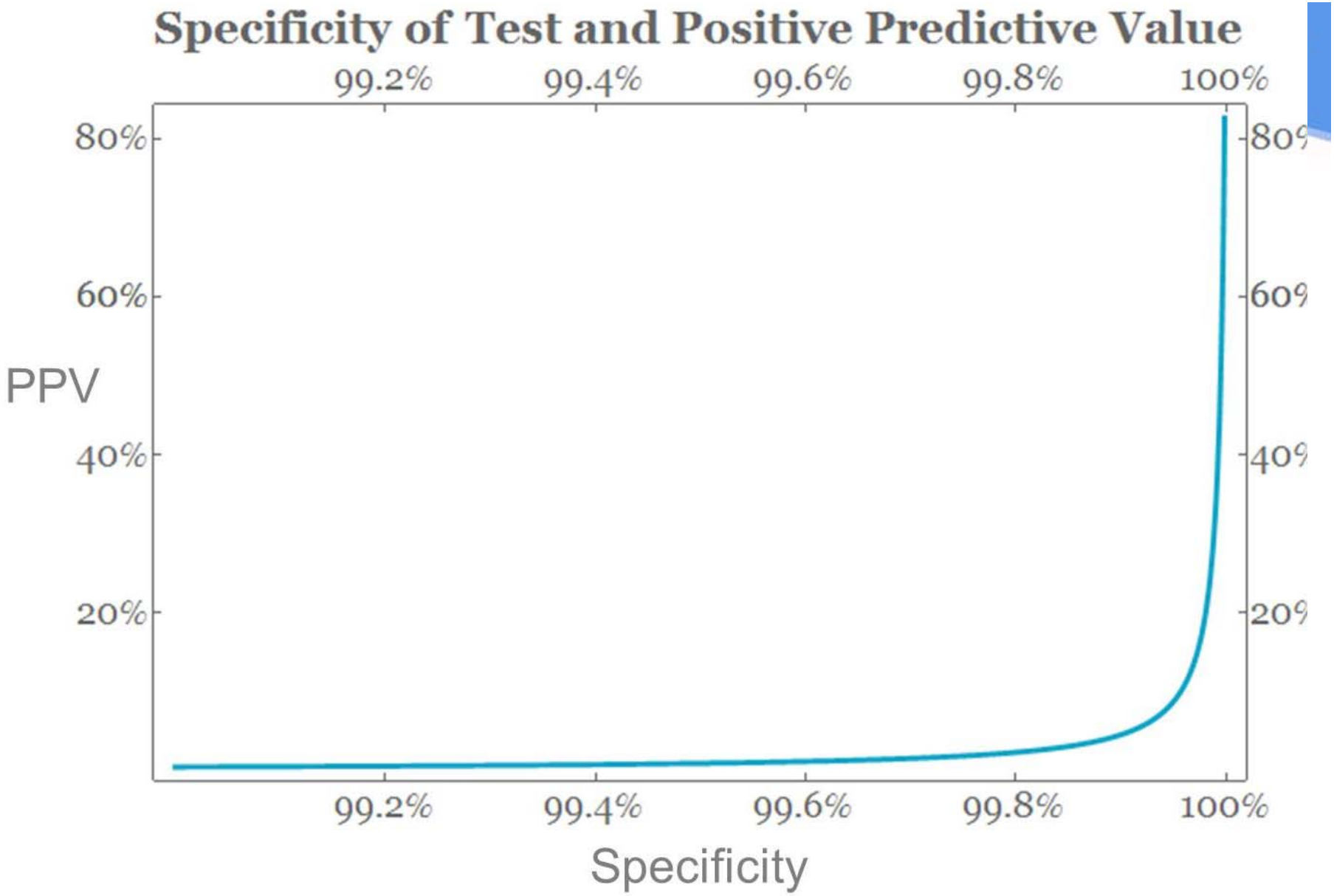
S+N: 50 + DC

No Testing | Serology only | Serology + NAT

Serology Plus NAT in 50 States Plus DC



Summary of Benefits and Risks Under Selected TTB Testing Scenarios



Importance of High Specificity

Sensitivity Analyses

- The results of the model change if the sensitivity and specificity of the test change or if the time to detection by NAT or seroconversion change
- Differences in these parameters do not affect the relative TTB risk contribution of each state
- The results are also affected by the estimates of babesiosis rate and blood donation rates
- Changes in these parameters will have less impact on percent risk reduction and PPV

Concluding Points

- The specificity of both NAT and serology needs to be very high
- Nationwide NAT would reduce risk by about 4.7 percentage points over nationwide serology
- There are several possible testing scenarios with similar benefit-risk profiles

Summary

- **Quantitative Risk Assessments inform decision-making about deferrals and other interventions when uncertainty is high**

- **Active Surveillance using large medical databases representing tens of millions of patients can provide improved estimates of rare adverse events**

- **Active surveillance can better identify at risk populations to target interventions**

- **Overall goal to ensure safe and effective products!**

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Table 1 Highlights: Overall Babesiosis Cases and Rates (per 100,000 Beneficiaries) for the Top 15 States, 2006-2013

Table 1a: Sorted by Babesiosis Rate

State*	All Years, 2006-2013
Connecticut †	1,307 (45.7)
Massachusetts †	2,161 (45.1)
Rhode Island †	247 (41.9)
New York	3,193 (26.8)
New Jersey †	980 (13.9)
Maryland †	312 (7.3)
New Hampshire †	85 (6.9)
Maine †	76 (5.6)
District of Columbia	15 (4.3)
Virginia †	245 (4.2)
Minnesota †	104 (3.8)
Vermont	24 (3.8)
Pennsylvania †	262 (3.1)
Delaware	25 (2.9)
Wisconsin †	111 (2.7)
Florida †	393 (2.7)

Table 1b: Sorted by Babesiosis Cases

State	All Years, 2006-2013
New York	3,193 (26.8)
Massachusetts †	2,161 (45.1)
Connecticut †	1,307 (45.7)
New Jersey †	980 (13.9)
Florida †	393 (2.7)
Maryland †	312 (7.3)
California †	279 (1.7)
Pennsylvania †	262 (3.1)
Rhode Island †	247 (41.9)
Virginia †	245 (4.2)
Wisconsin †	111 (2.7)
Minnesota †	104 (3.8)
New Hampshire †	85 (6.9)
Maine †	76 (5.6)
Texas †	65 (0.5)

* Includes District of Columbia. States are shown in descending order of babesiosis rate during the 8-year period.

† The trend in Babesiosis rates from 2006-2013 is statistically significant according to the Cochran-Armitage test for trend, using a significance level of $p<0.05$.

Table 1 Summary:

- Highest overall babesiosis occurrence rates (per 100,000) in five Northeastern states: Connecticut (46), Massachusetts (45), Rhode Island (42), New York (27), and New Jersey (14);
- These top five *Babesia*-endemic states accounted for 76.6% of all cases identified in the U.S. elderly;
- The nine endemic states (top five states plus Minnesota, Wisconsin, New Hampshire, and Maine) accounted for 80.2% of all cases in the elderly;
- Other states also had babesiosis recorded including, but not limited to, Maryland (7), Virginia (4), Pennsylvania (3), Florida (3), and California (2);
- Top 15 states from Connecticut through Florida, by descending babesiosis rate, accounted for 92.6% of all babesiosis cases in the elderly.

Table 2 Highlights: Overall Babesiosis Cases and Rates (per 100,000 residents) for Top 15 States, CDC 2011-2013 Data

Table 2a: Sorted by Babesiosis Rate

State	2011-2013			
	Total Number of Cases	Average Annual Cases	Resident Population (in Thousands)	**Babesiosis Rate (per 100,000 Residents)** [1]
Rhode Island	271	90.3	1,053	8.6
Connecticut	486	162.0	3,569	4.5
Massachusetts	894	298.0	6,628	4.5
New York	1,206	402.0	16,741	2.4
New Jersey	429	143.0	8,812	1.6
Maine	55	18.3	1,324	1.4
New Hampshire	54	18.0	1,321	1.4
Wisconsin	227	75.7	5,701	1.3
Minnesota	177	59.0	5,339	1.1
Vermont	9	3.0	625	0.5
Delaware	3	1.0	905	0.1
North Dakota	2	0.7	680	<0.1
Maryland	16	5.3	5,821	<0.1
South Dakota	1	0.3	826	<0.1
Nebraska	1	0.7	1,836	<0.1

Table 2b: Sorted by Babesiosis Cases

State	2011-2013			
	Total Number of Cases	Average Annual Cases	Resident Population (in Thousands)	Babesiosis Rate (per 100,000 Residents) [1]
New York	1,206	402.0	16,741	2.4
Massachusetts	894	298.0	6,628	4.5
Connecticut	486	162.0	3,569	4.5
New Jersey	429	143.0	8,812	1.6
Rhode Island	271	90.3	1,053	8.6
Wisconsin	227	75.7	5,701	1.3
Minnesota	177	59.0	5,339	1.1
Maine	55	18.3	1,324	1.4
New Hampshire	54	18.0	1,321	1.4
Maryland	16	5.3	5,821	<0.1
California	11	3.7	37,650	<0.1
Vermont	9	3.0	625	0.5
Delaware	3	1.0	905	0.11
North Dakota	2	1	680	<0.1
Nebraska	2	0.7	1,836	<0.1

Table 2 Summary:

- Highest overall babesiosis occurrence rates (per 100,000) in five Northeastern states: Rhode Island (8.6), Connecticut (4.5), Massachusetts (4.5), New York (2.4), and New Jersey (1.6);

- These top five *Babesia*-endemic states accounted for 85.2% of all cases (N=3,855) reported to CDC during 2011-2013;

- The top nine endemic states (top five states plus Minnesota, Wisconsin, New Hampshire, and Maine) accounted for 98.5% of all cases reported to CDC;

- Top 15 states from Rhode Island through Nebraska, by descending babesiosis rate, accounted for 99.4% of all babesiosis cases reported to CDC;