

CBER Surveillance Program:

Biologic Effectiveness and Safety (BEST) Initiative

Population-based Healthcare Data

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U.S. Food and Drug Administration (FDA)



Learning Objectives

Participants shall be able to:

- Explain the purpose and scope of the CBER Surveillance Program and BEST
- Distinguish the unique characteristics of CBER products and how they influence approaches to post-market surveillance
- Describe BEST capabilities that are available for use by CBER product review offices to assist product efficacy and safety monitoring

Overview

- **Real World Evidence and Real World Data**
- **CBER Surveillance Program Overview**
- **Infrastructure of BEST Initiative**
- **How to use RWD for regulatory work?**



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Real World Evidence and Real World Data: Definitions

Real world evidence means data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than *traditional clinical trials*



Real-World Data (RWD) are data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources.

Real-World Evidence (RWE) is the clinical evidence regarding the usage and potential benefits or risks of a medical product derived from analysis of RWD.



Scope of the RWE Program

Evaluates the potential use of RWE to support changes to labeling about drug product effectiveness, including:

- Adding or modifying an indication, such as a change in dose, dose regimen, or route of administration
- Adding a new population
- Adding comparative effectiveness or safety information



Postmarketing
Evaluation
(Phase IV)

Framework for Evaluating RWD/RWE for Use in Regulatory Decisions



Considerations

- Whether the **RWD** are fit for use
- Whether the **trial or study design** used to generate **RWE** can provide adequate **scientific evidence** to answer or help answer the regulatory question
- Whether the **study conduct** meets **FDA regulatory requirements**

Support for Regulatory Decisions



- Geographic incidence of babesiosis for blood donation guidance
- Adverse events related to transfusion of leukoreduced blood components for universal leukoreduction policy risk assessment model
- Rate of transfusion in high-risk populations for Zika risk assessment (pregnant women, immunocompromised, elderly)

Support for Regulatory Decisions



- Validating potential data source for FDA or sponsor's planned PMR or PMC activity
- Public communication/label revision
- Complements Adverse Event Surveillance
 - Conduct studies to refine/evaluate signals generated in the post-market period such as by VAERS

Poll Question #1



The scope of a RWE program is to evaluate the potential use of RWE to support changes to labeling about drug product effectiveness includes:

- A. Adding or modifying an indication, such as a change in dose, dose regimen, or route of administration
- B. Adding a new population
- C. Adding comparative effectiveness or safety information
- D. All of the above



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CBER Surveillance Program



FDA CBER Mission Focus

Ensure biologic-product safety and effectiveness through active surveillance

CBER Surveillance Program's Vision

To create and utilize an effective national post-market surveillance system for CBER-regulated products to provide data for evidence-based regulatory decisions

CBER-Regulated Products



Vaccines (preventative and therapeutic)



Blood (components and derived)



Human Tissues and Cellular Products



Gene Therapies



Xenotransplantation Products

CBER Active Surveillance Program Collaborative

Through multiple contracts and partnerships, CBER works with a diverse group of epidemiologists, data scientists and clinical experts to conduct active surveillance studies.



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Why the BEST Initiative?

Biologic products' special characteristics

- Require special components in an active surveillance system

Upgrading infrastructure

- Access to Electronic Health Record (EHR) data sources
- Reduce data lag
- Easier, faster, affordable access to medical charts
- On-demand analytic capabilities (no tools)
- Large-scale capacity

Unique Characteristics of Biologics



- 1. Vaccines are administered to healthy populations and children**
 - Low threshold for risk of adverse events (AEs)
- 2. Continuous monitoring of blood supply for safety**
 - Continuous monitoring of AEs following blood transfusion
- 3. Occurrence of emerging infectious diseases**
 - Continuous safety surveillance of vaccines and blood
 - Preparedness for pandemics



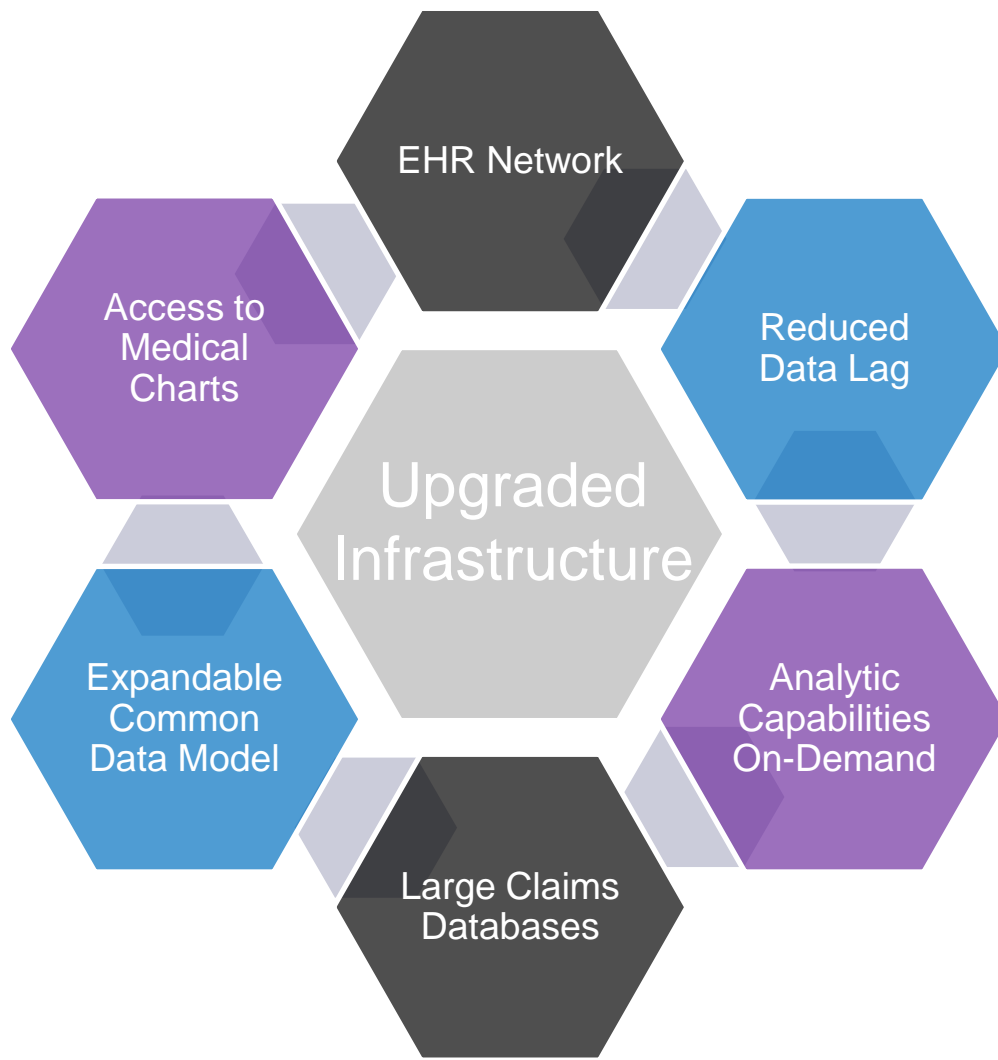
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BEST Initiative



A modern surveillance system that can perform diverse queries and studies.



Distributed data network

- No central repository
- Data are maintained and reside behind firewall of each data contributor

Data are standardized

- Transformed into a common data model (CDM)



Types of Real World Data Sources



Claims/Administrative Billing Data

- Collected for transactional recordkeeping, reimbursement
- Payment/billing
- ~250 million patients

Electronic Health Records Data

- Document routine clinical care
- Collected to document elements of clinical care and support physician decision-making
- ~100 million patients

*Patient interaction with the U.S. healthcare system generates data.
CBER Surveillance Program utilizes secondary data.*

Administrative Claims vs EHR



	Administrative Claims	Electronic Health Records
Capture of care	Encounters across the healthcare continuum	Snapshot of patient's clinical experience
Scope of patients	Insured patients only	Insured and uninsured patients
Timely access	Data lag (3-9 months)	Little to no data lag
Biologics information	Injection or Dispensing	Prescribing
Inpatient biologics data	No	Some
Follow-up and diagnoses recorded across the care continuum	Yes	Usually incomplete
Clinical data (laboratory results, vital signs, clinical reports, etc.)	No	Yes
Health behavior information (body mass index, alcohol, smoking, etc.)	No	Yes
Biologics filled out-of-plan, vaccines out-of-plan, free samples, and over-the-counter biologics	No	Yes/No

BEST Initiative Data Sources

Data Source*	Database Type	Number of Patients Covered (Millions)	Time Period Covered
CMS- Medicare	Claims	105	2005 - present
MarketScan Commercial and Medicare Supplemental	Claims	254	1999 - 2019
MarketScan Medicaid	Claims	48	1999 - 2019
Blue Health Intelligence	Claims	33.6	2012 - present
Optum - Adjudicated	Claims	66	1993 - present
Optum - Pre adjudicated	Claims	22	2017 - present
HealthCore	Claims	76	2006 - present
CVS Health	Claims	26	2014 - present
OneFlorida Clinical Research Consortium - Medicaid	Claims	6.7	2012 - present
OneFlorida Clinical Research Consortium - EHR	EHR	5.6	2012 – present
Optum EHR	EHR	102	2007 - 2020
MedStar Health Research Institute	EHR	6	2009 - present
PEDSnet	EHR	6.2	2009 - present
IBM CED	Linked EHR Claims	5.4	2000 - present
Optum Integrated Claims - EHR	Linked EHR Claims	25	2007 - 2020
OneFlorida Clinical Research Consortium – Linked EHR Claims	Linked EHR Claims	1.5	2012 - present

*Data lag varies for different databases, and it is approximately 3 months.

Poll Question #2



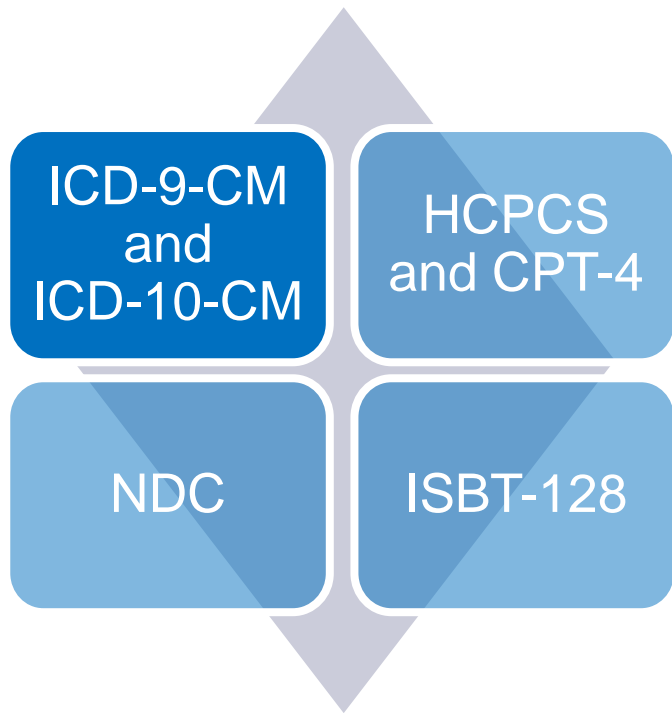
What are some unique characteristics of biologics important to biologic surveillance :

- A. The blood supply is static and does not need to be monitored continuously
- B. Unlike drugs, vaccines are administered to healthy populations and children, therefore there is low threshold for risk of adverse events (AEs).
- C. Both A and B
- D. None of the above

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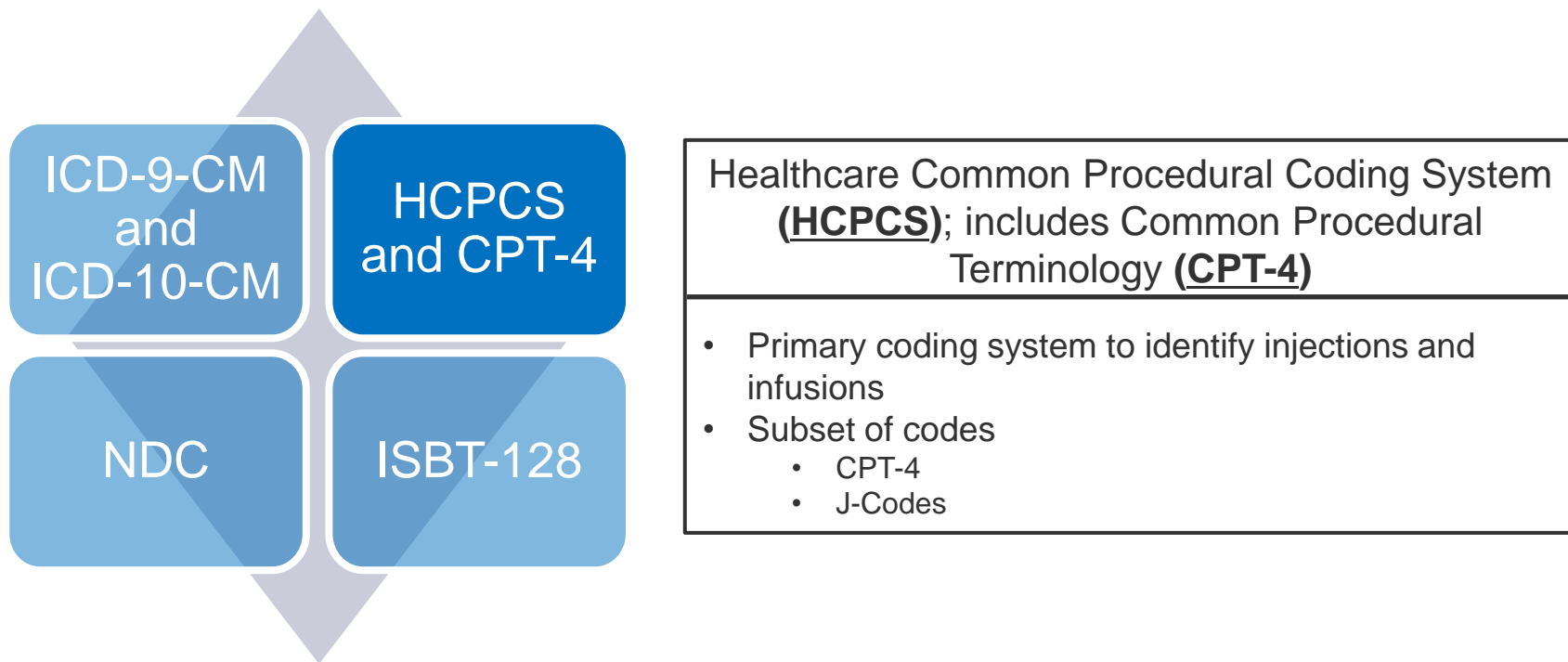
How are clinical events captured in data?



International Classification of Diseases (**ICD-9-CM, ICD-10-CM**)

- Standardized healthcare classification
- Diagnostic codes
 - Medical diagnosis
 - Symptoms
 - Injury
 - Disease
- Procedure codes
 - Surgical
 - Diagnostic
 - Therapeutic

How are clinical events captured in data?



Blood Derived Products

Example: Factor VIII

Plasma-derived

J7186

Alphanate®

J7187

Humate-P®

J7190

Koate®-DVI

Monoclate-P®

Hemofil M

Recombinant (long-acting)

J7199

Afstyla®

J7205

Eloctate®

J7207

Adynovate®

Recombinant (standard)

J7182

Novoeight®

J7285

Xyntha®

Kovaltry®

Kogenate® FS

Helixate® FS

Recombinate

Advate®

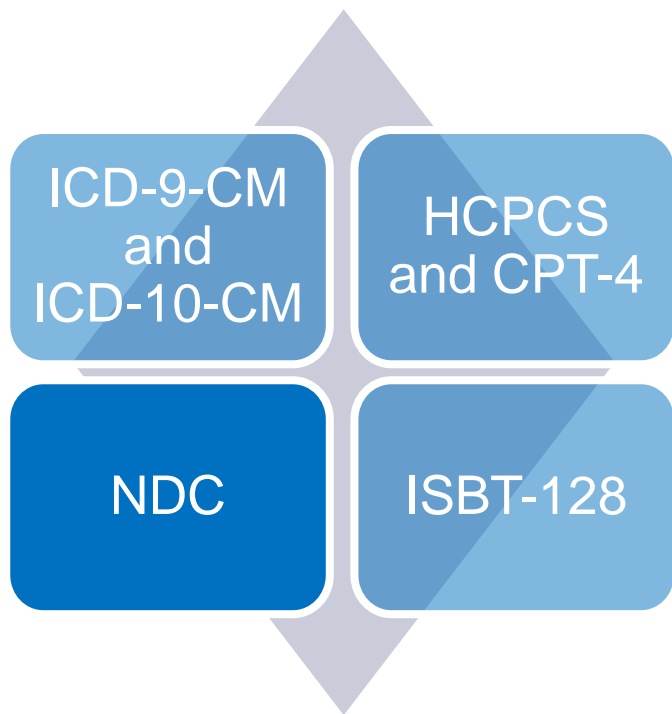
J7209

Nuwiq®

Other codes

- General HCPCS code – “unclassified biologics” (J3590)
- CPT-4 codes for intravenous infusion (99365, 96374, 96376)

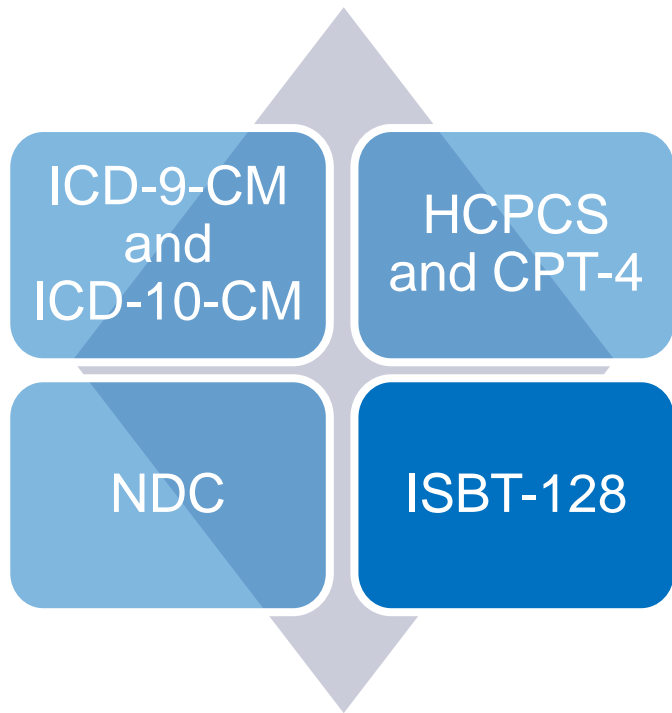
How are clinical events captured in data?



National Drug Codes (**NDCs**)

- Unique 10-digit, 3-segment numeric identifier assigned to each drug or biologic
- Very granular
 - Including dose
- For biologics, NDC codes are not always used for billing

How are clinical events captured in data?



International Standard for Blood and Transplant (**ISBT**)-128

- Global standard for the terminology, identification, coding and labeling of medical products of human origin
 - Including blood, cell, tissue, milk, and organ products
- Very granular
 - Including storage and manufacturing processing
- Barcodes

Start with a Regulatory Question

How to use RWD for informing regulatory decisions?

Patient population

Interv

Com

- Characteristics:
 - Age (days, weeks, months, years)
 - Gender
 - Race/Ethnicity
- Health Status:
 - Healthy population
 - Diabetes, HIV, pregnancy, etc.



Patient population

Intervention

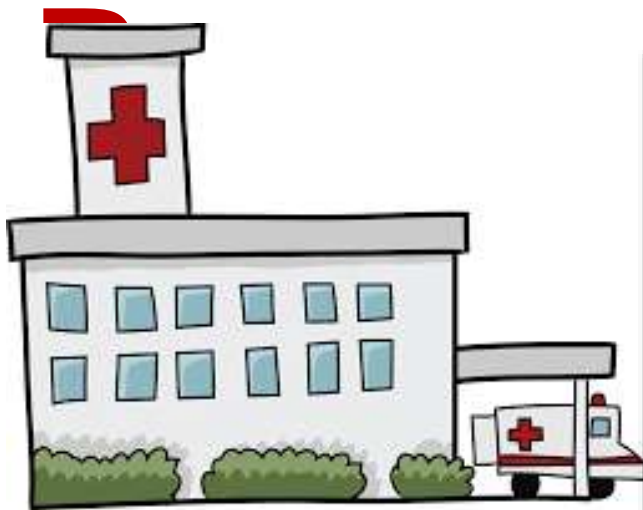
Comparison

Outcome

Time

- Exposure to:
 - Biologic (vaccine, blood products, tissue, etc.)
 - Procedure (i.e., transfusion)
- Control or comparator
- Brands and lot numbers
 - Absence of exposure
- Setting
 - Inpatient
 - Outpatient
 - Emergency Room (ER)





Outcome Time

- Adverse event
 - Acute
 - Chronic
- Setting of diagnosis
 - Inpatient
 - Outpatient
 - ER
- Temporality
- ICD-9/ICD-10 transition period

Patient

Intervention

Comparator

Outcome

Time

- Unit of analysis
 - Years, months, days, or hours
- Short-term vs long-term outcome
 - Limited follow-up data on each patient
- Data lag



REGULATORY QUESTION

Is there a difference in the odds of febrile seizures for children, 12-23 months of age, receiving first dose of MMRV vaccine, MMR and varicella vaccine, MMR vaccine without varicella vaccine, and varicella vaccine without MMR vaccine?

Patient population

Interv

Com

Characteristics

- Children
 - Age: 12-23 months
 - No history of seizures



Ime

Patient population

Intervention

Comparison

Outcome

Time

Vaccination:

- MMRV (no history of MMR or V vaccines in prior lookback)
- Compared to:
 - MMR plus V on the same day
 - MMR alone, no V
 - V alone, no MMR





pulation

on

Incidence of febrile seizures

- Medical setting (inpatient, outpatient, emergency room)
- ICD-9-CM, ICD-10-CM

Outcome

Time

Patient population

Interv

Time Period:

- Years (2000-2017)

Comp

Risk Window:

- 0-28 days after vaccination

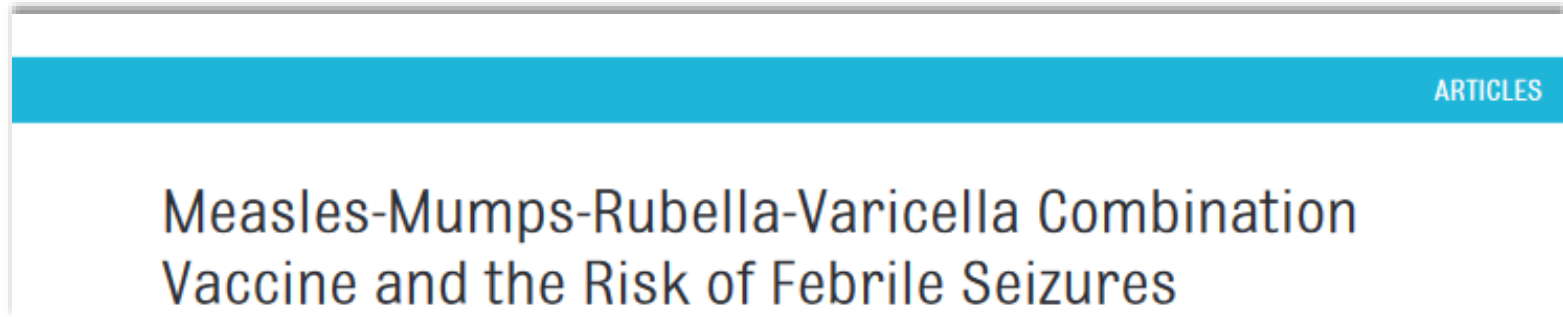
Outcome

Time



Vaccine Study (Test Case)

- To test the new system, reproduced components of a published study



Klein NP et al. Pediatrics. 2010 Jul;126(1):e1-8.

- **Study Objective:** To assess the risk of febrile seizures in children receiving first dose of Measles, Mumps, Rubella, & Varicella (MMRV) compared to that of MMR and Varicella administered separately on the same day

MMRV vs. MMR+V & Febrile Seizures in Children

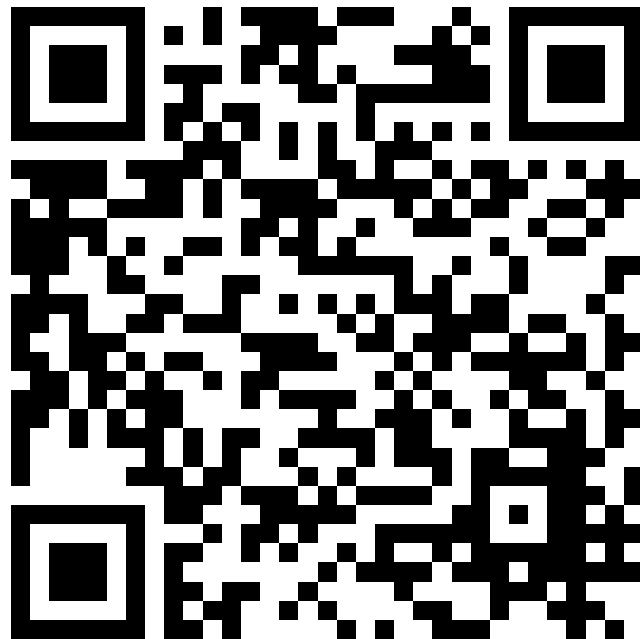
	Vaccine Safety Datalink (VSD) Study*	BEST: LRxDx Claims Database
Study Period	Jan. 2000-Oct. 2008	Jan. 2010-Oct. 2017
Age	12-23 months	1-2 years
Number of MMRV Patients (n)	83,107	920,948
Number of MMR+V Patients (n)	376,354	874,900
Risk Windows		
Week 1-2	7-10 days	7-10 days
	RR: 2.0 (95% CI=1.4-2.9)	OR: 1.86 (95% CI=1.38-2.04)
Week 1-6	0-42 days	0-28 days
	RR: 1.5 (95% CI=1.1-1.9)	OR: 1.26 (95% CI=1.22-1.42)

*Klein NP et al., Pediatrics, 2010; CI: Confidence Interval

MMRV vs. MMR+V & Febrile Seizures in Children

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www.bestinitiative.org

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Thank You