Overview of the U.S. Vaccine Safety Surveillance Systems & Ongoing Scientific Activities to Monitor Maternal Vaccine Safety

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September 9, 2014

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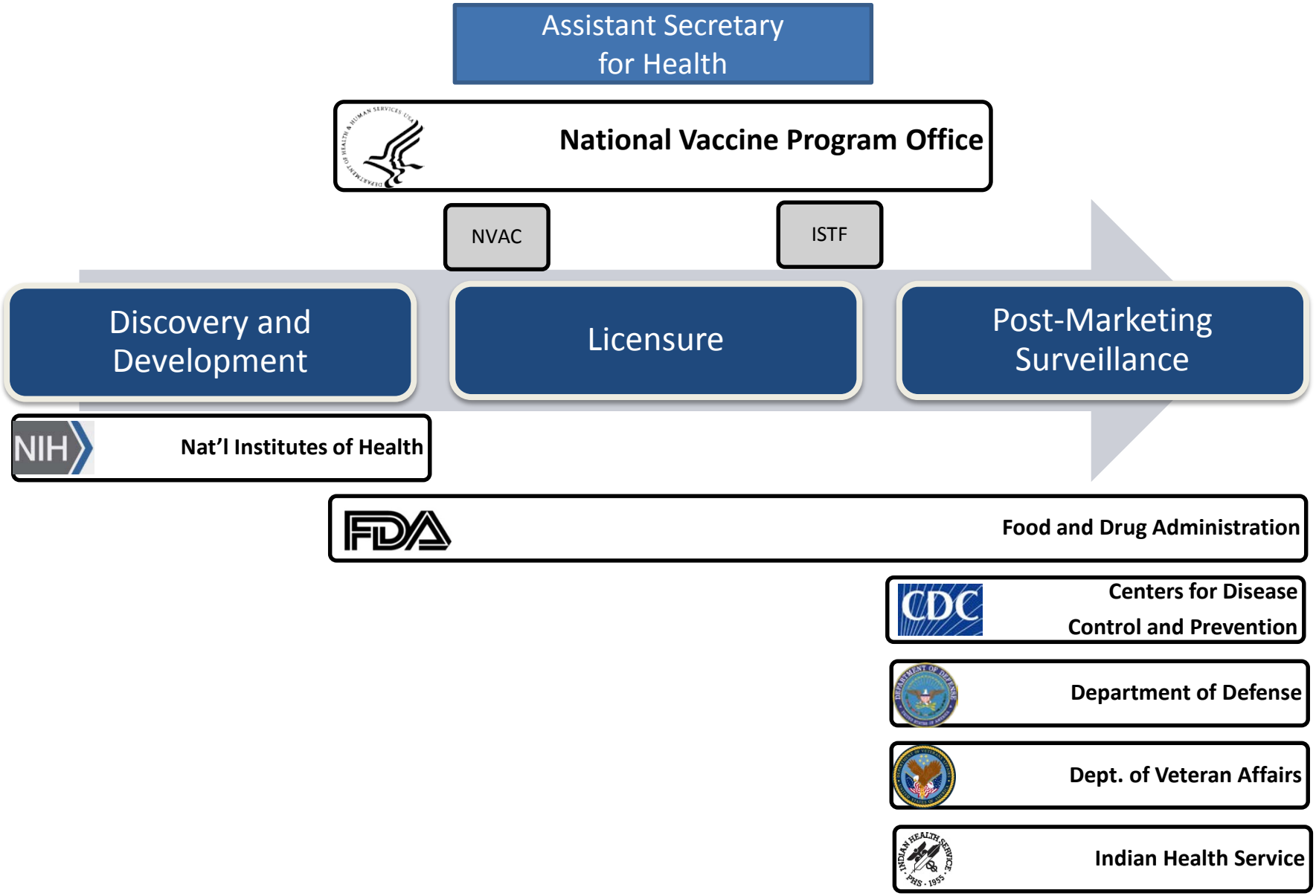
Overview: National Vaccine Safety System



Pre-Licensure Vaccine Safety Activities

Leading Institution	Vaccine Safety Scientific Activity
NIH	*Identification and development of vaccine candidates*
NIH	*Design of novel vaccine strategies*
NIH	*Investigate the variability in human immune responses*
NIH	*Improve vaccine immunomodulators, administration, and formulations*
FDA	*Vaccine development*
FDA	*Study of pathogenicity*

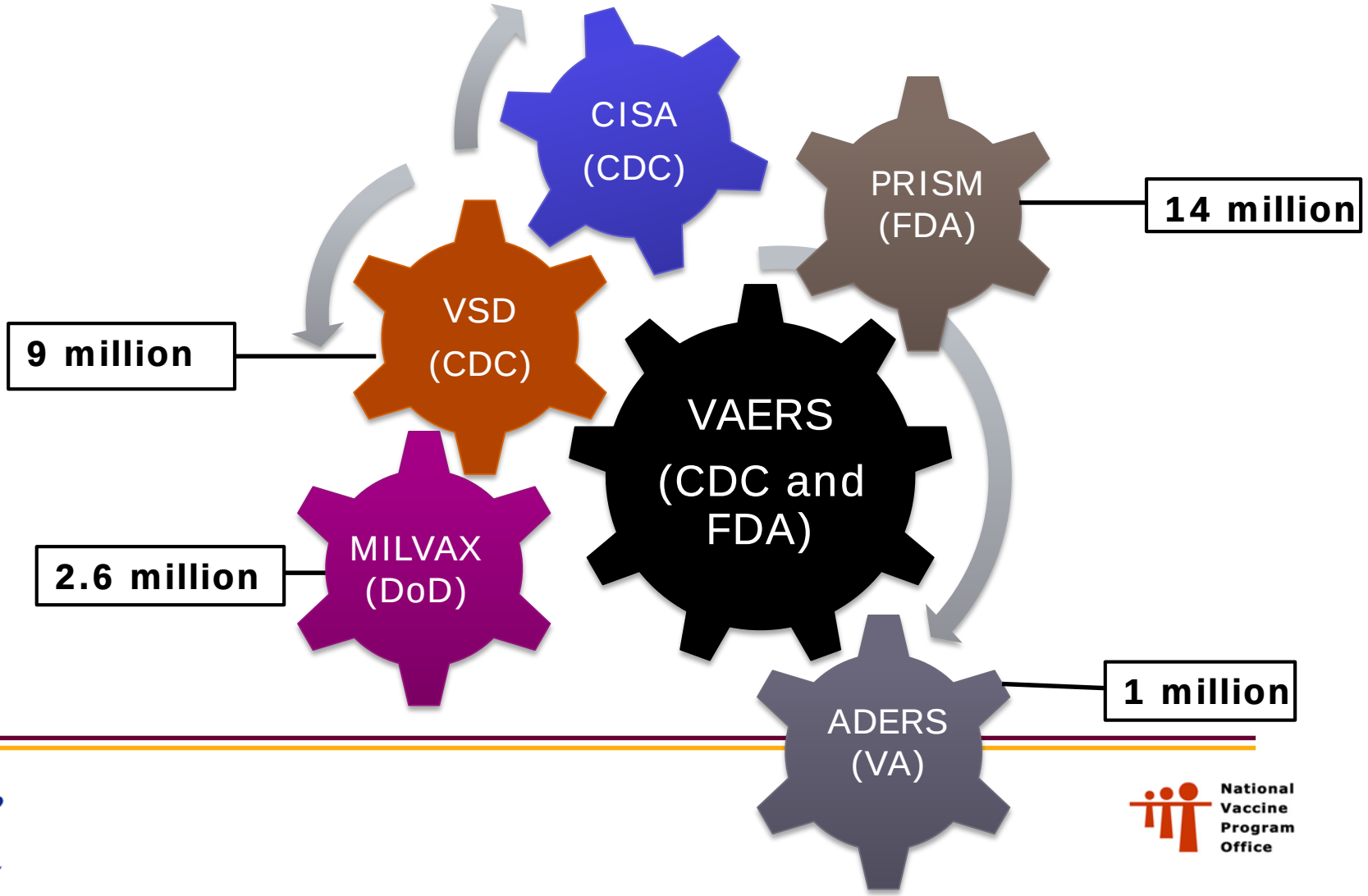
Why We Monitor Vaccine Safety After Licensure

- High safety standards expected for vaccines
  - Vaccines generally healthy (vs. ill for drugs)
  - Dual role of vaccinations
    - Individual protection
    - Societal protection (some vaccinations universally recommended or mandated)
- Pre-licensure trials are often too small to detect rare events and special populations may not be adequately represented

Post-licensure Vaccine Safety Monitoring Activities

- Rapidly identify new or rare adverse events of clinical importance
- Monitor changes in patterns for known adverse events
- Assess safety in special populations (e.g., pregnant women)
- Determine patient risk factors for particular adverse events
- Assess safety of vaccine lots (FDA)

Vaccination Safety Systems Working Together to Monitor & Test Maternal Immunization Safety



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Vaccine Adverse Event Reporting System (VAERS)

- National spontaneous reporting system for adverse events after US-licensed vaccines
  - In recent years, received around 30,000 U.S. reports annually
  - Accepts reports from healthcare providers, manufacturers and the public
  - Signs/symptoms of adverse event coded and entered into database
- Jointly administered by CDC and FDA
- Authorized by National Childhood Vaccine Injury Act of 1986

Vaccine Adverse Event Reporting System (VAERS) (co-managed CDC and FDA)[1]

Strengths

- National data; accepts reports from anyone
- Rapid signal detection; rare adverse events
- Collects information about vaccine, characteristics of vaccine
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Generally cannot assess if vaccine caused an adverse event
- Lack of unvaccinated comparison group
- Pregnancy inconsistently reported

1. VAERS website: http://vaers.hhs.gov

2. Some reports have no adverse event

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Vaccine Safety Datalink (VSD)

- Established in 1990
- A collaborative project between CDC and 9 integrated healthcare organizations
- Allows for planned vaccine safety studies as well as timely investigations arising from
  - Hypotheses from medical literature and pre-licensure clinical trials
  - Reports to VAERS
  - Changes in immunization schedules, or the introduction of new vaccines

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Vaccine Safety Datalink (VSD)

- *Data on over 9 million persons per year (~3% of US pop)*
- *Links vaccination data to health outcome (outpatient, emergency dept., inpatient) and demographic data*

Strengths

- All medical encounters are available
- Vaccine registry data
- Can calculate rates
- Can review medical records
- Tested algorithm to identify pregnancies
- Annual birth cohort = 100k

Limitations

- Sample size may be inadequate for very rare events
- Vaccines administered outside of medical home may not be captured
- Potential for lack of socioeconomic diversity
- Data lags

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Clinical Immunization Safety Assessment (CISA) Project

- Collaboration between CDC and 7 medical research centers
- Established by CDC to:
  - Serve as a vaccine safety resource for consultation on clinical vaccine safety issues
  - Develop strategies to assess individuals who may be at increased risk for adverse events following immunization (AEFI)
  - Conduct studies to identify risk factors and preventive strategies for AEFI, particularly in special populations

Clinical Immunization Safety Assessment (CISA) Project: Research

Strengths

- Can implement prospective, multi-site clinical studies (hundreds of subjects)
- Expertise in vaccine safety and many clinical areas
- Access to special populations receiving vaccines
- Detailed clinical/data on patients
- Can collect biological specimens
- Ability to recruit controls

Limitations

- Sample size limited to study rare adverse events
- Potential challenges to recruit and retain subjects
- May not have access to vaccine records for vaccines given outside site
- Potential for lack of geographic or race/ethnicity diversity
- Clinical studies may be labor and resource-intensive

Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

- Established in 2009
- Uses data from National Health Insurance Plans and Immunizations Registries
- Links data between databases, performs epidemiological studies and establishes new statistical methods of analysis
  - Monitors the largest U.S. population cohort
  - Links states by using immunization registries
  - Synergistic with existing federal systems

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Adverse Drug Event Reporting System (ADERS)

- VA's, Web based
  - National Program – Initiated March 2007
  - Provider and patient reported AE's
  - Medications and Vaccines
  - Over 400,000 reports
  - Linkage between VA ADERS and VAERS
  - Passive Surveillance: Weekly update identifying number, type, and sites of AE's

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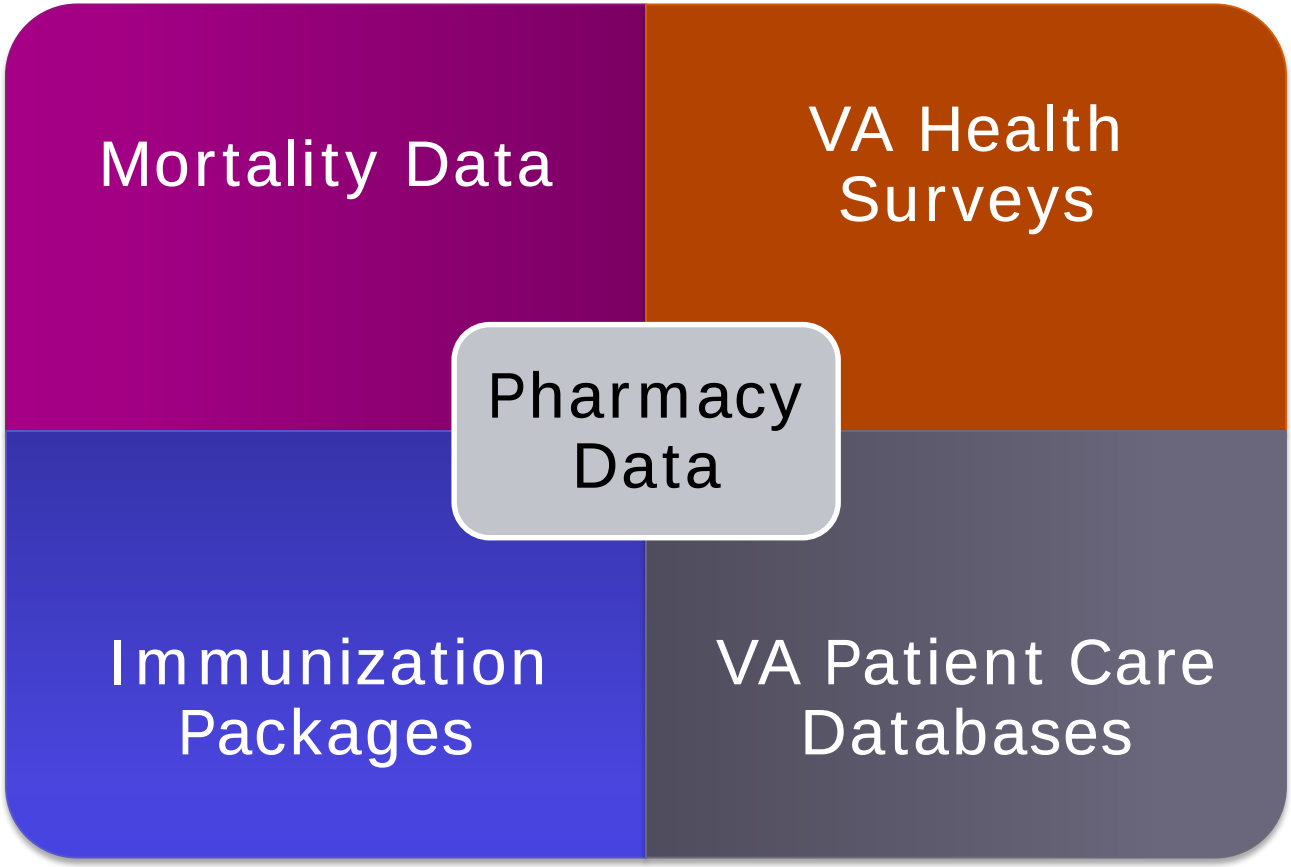
VA ADERS links Medication and Vaccine Data



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Ongoing Scientific Activities to Monitor Maternal Safety

Leading Agency / System	Scientific Activities
CDC	*Assessing the Feasibility of Monitoring Influenza Vaccine Safety in Pregnant Women Using Text Messaging*
CDC	*Immune response to influenza vaccination and effect on reproductive hormones*
CDC	***Clinical Study of Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Vaccine (Tdap) Safety in Pregnant Women***
DoD	*Support the Vaccines and Medications in Pregnancy Surveillance System (VAMPSS), which is a system to identify as early as possible the circumstances in which a drug or immunization administered during pregnancy may cause harm. (flu and Tdap)*
VA	*End of Season Analysis for Flu and Outcomes of Interest*
FDA	*Two population-based studies of pregnancy safety. Further research will identify pregnancy outcomes and analyze rare birth defects.*

CDC-NVPO Study: Clinical Study of Tdap Safety in Pregnant Women

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Study Goals

- Compare the rates of local and systemic reactions following Tdap in pregnant women with non-pregnant women
- Assess rates of preterm and small for gestational age (SGA) births in women who received Tdap during pregnancy
- Explore differences in local and systemic reactions in pregnant women who are receiving their 1st Tdap versus those who have received Tdap in the past

Additional Study Goals

- Assess additional obstetrical and infant outcomes
  - Maternal or fetal death
  - Placental abruption
  - Postpartum hemorrhage
  - Pregnancy related hypertension
  - Gestational diabetes
- Evaluate health outcomes and growth parameters in infants born to women who received Tdap (first 6 months of life)
- Registered in www.clinicaltrials.gov (NCT02209623)

Maternal Immunization Safety Surveillance Challenges

- Enrolling susceptible populations in clinical trials
- Case-control studies on vaccines currently recommended for pregnant women (Flu and Tdap)
- Large cohorts that will enable studying rare adverse events (birth defects)
- Defining the endpoint of a vaccine safety clinical trial: creating consensus across trials nationally and globally
- Liability concerns when administering vaccines recommended for pregnant women only and/or intended to protect the baby
- Linking health records of pregnant women and infants to enable long-term follow up of infant
- Safety and regulatory requirements to obtain a indication specific for pregnancy

Maternal Immunizations: Paving the Road for New Vaccine Research and Development

- WHO and Brighton Collaboration: efforts with harmonizing definitions to assess safety of immunization during pregnancy
  - Dr. Flor Muñoz (Baylor College of Medicine)

- Overview of DMID's consultative conferences on enrolling pregnant women in clinical trials of antimicrobials vaccines
  - Dr. Mirjana Nesin (NIH/NIAID/DMID)

- Regulatory issues of maternal immunization
  - Dr. Marion Gruber (FDA)

- Maternal immunization challenges and opportunities: perspective of vaccine developers and manufacturers
  - Ms. Phyllis Arthur (BIO)