COVID-19 vaccine safety monitoring

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On behalf of:

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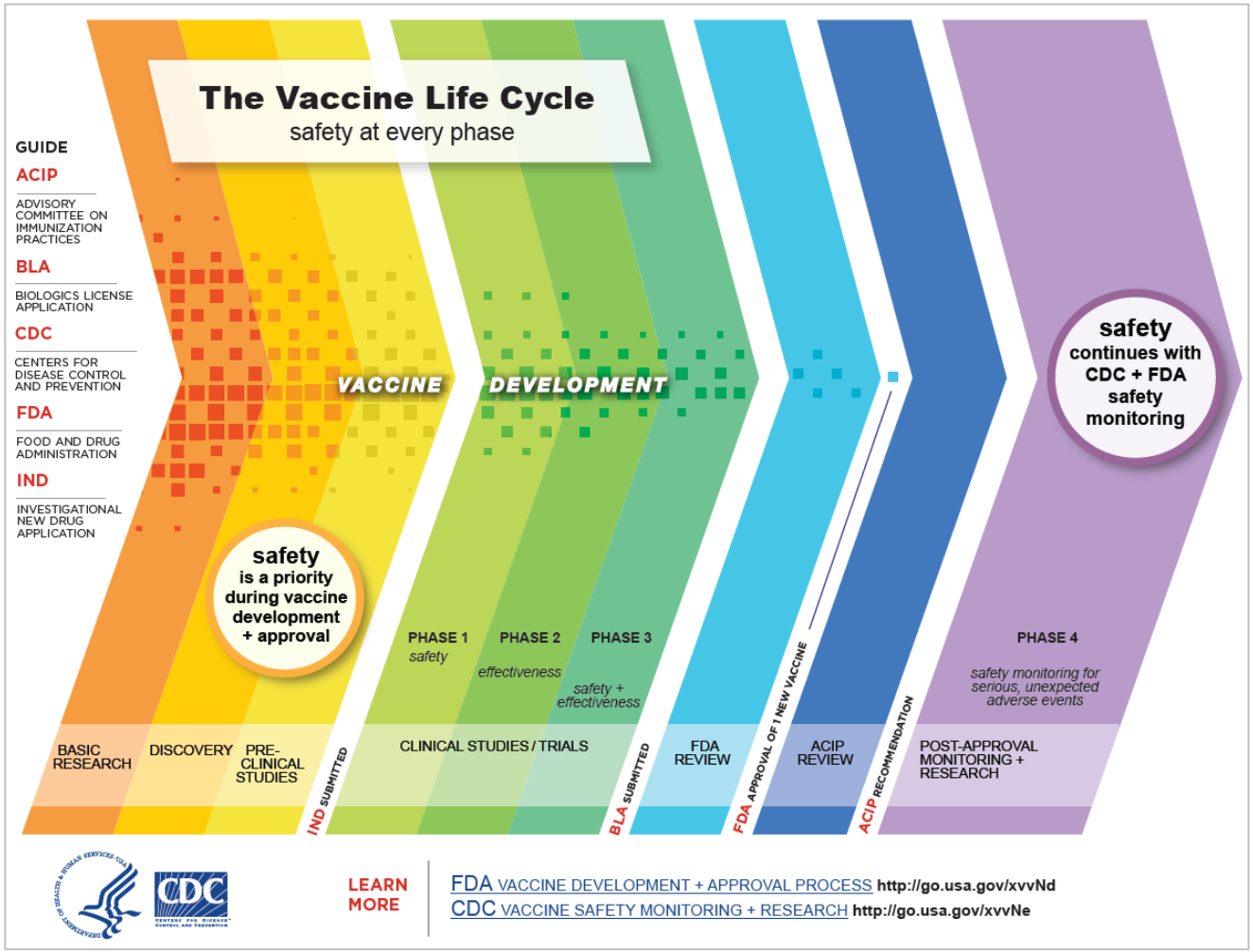
- Safety is a priority during all phases of vaccine development, approval, and use
- Post-licensure (post-authorization) safety monitoring is an established part of the vaccine life cycle
- Monitoring COVID-19 vaccine safety will be a coordinated effort by multiple federal agencies



https://www.cdc.gov/vaccinesafety/ensuringsafety/history/index.html#anchor_1593624850886

Rationale for post-licensure/post-authorization vaccine safety monitoring

- Safety standards for vaccines are high
- Pre-licensure trials are not optimal for:
  - Detecting rare adverse events (numbers enrolled too small)
  - Monitoring vaccine safety in a real-world environment
  - Assessing safety in special populations (e.g., pregnant women and people with certain pre-existing medical conditions often excluded)
  - Evaluating adverse events with delayed onset

Roles and responsibilities in vaccine safety monitoring (manufacturers vs. U.S. government)

Post-licensure (authorization) safety monitoring

- Manufacturers have Phase 4 responsibilities for their individual products
  - Based on standard regulatory obligations as specified by FDA
  - Can be guided by results from clinical trials
  - Conducted or managed by manufacturers' pharmacovigilance programs with regulatory oversight by FDA
  - May include post-marketing commitments, post-marketing requirements, and pregnancy registries
  - Also includes vaccine adverse event (AE) monitoring and reporting of AEs to the Vaccine Adverse Event Reporting System (VAERS)

Post-licensure (authorization) safety monitoring

- U.S. government has a responsibility for public safety
  - 1986 National Childhood Vaccine Injury Act – authorized VAERS
  - Monitoring is independent from manufacturers (i.e., no financial stake, less real and perceived conflict of interest, important for public confidence)
  - Monitoring covers all vaccines from all manufacturers in a comprehensive and integrated fashion
  - USG manages large data systems that are standing, long-term investments in public health surveillance (e.g., VAERS, VSD, CMS)
  - Surveillance data from VAERS are made publicly available and surveillance findings are presented at federal advisory committee meetings

Post-licensure (authorization) safety monitoring

- Manufacturers play a critical role in post-authorization safety monitoring

  however;

- We can't get all the answers from manufacturer monitoring
  - USG maintains and has constant access to the largest, most robust, and most sophisticated electronic monitoring systems available
    - The systems and the methods used by USG agencies are complementary
  - USG agencies can freely cooperate and collaborate
    - Share information, leverage expertise in other agencies, support each others' surveillance efforts
    - Can act in a coordinated and integrated way

COVID-19 vaccine safety monitoring: systems and populations

VAERS

Vaccine Adverse Event Reporting System

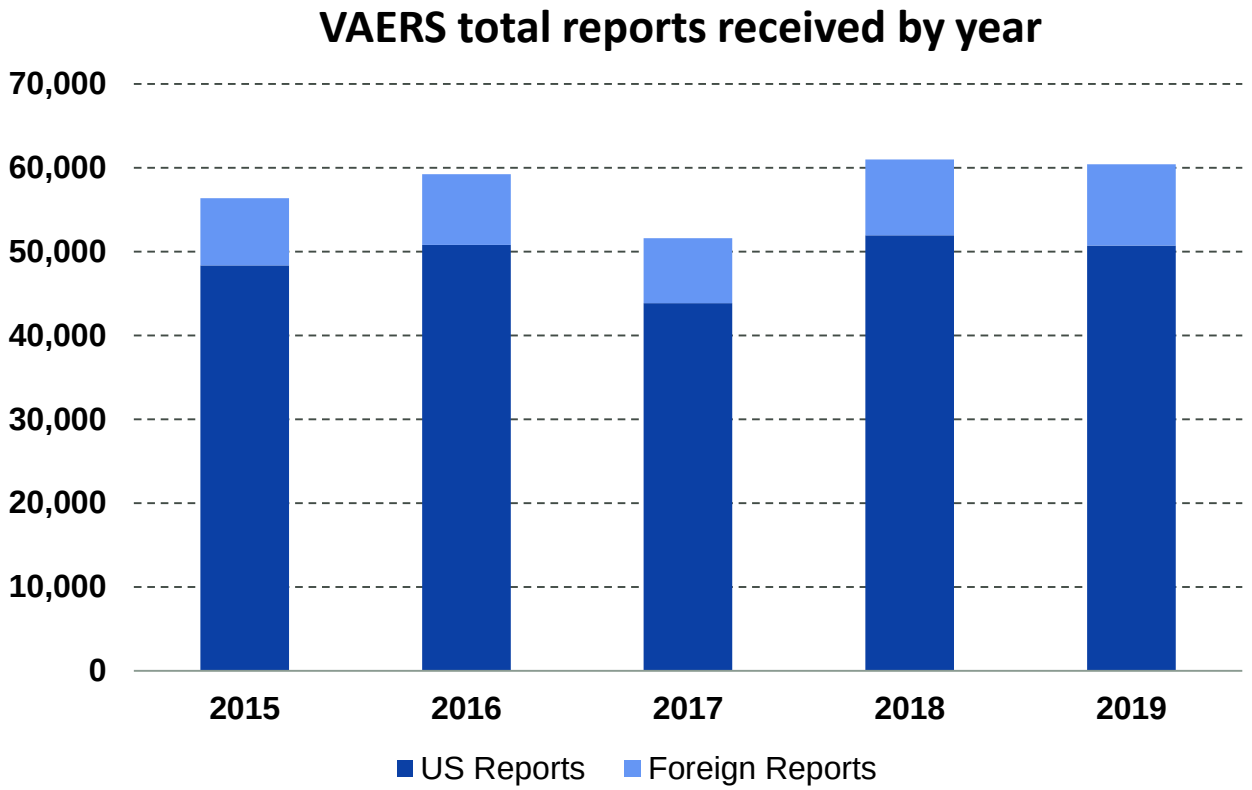
Co-managed by CDC and FDA

http://vaers.hhs.gov

Covered populations for COVID-19: Entire U.S. population

- VAERS has all 320 million U.S. residents as a covered population for safety monitoring
- i.e., all ages, races, states, healthy people, those with co-morbidities, etc.

CDC + FDA VAERS



Covered populations for COVID-19: older adults

- Active surveillance
  - FDA's Centers for Medicare & Medicaid Services (CMS) data monitoring (Medicare FFS and Medicare Advantage)
    - 55-60 million persons 65+ years old, 92% of the U.S. older adults
  - CDC's Vaccine Safety Datalink (VSD) (8 integrated health systems)
    - 1.8 million persons 65+ years old
  - Veterans Affairs (VA) data warehouse and electronic health record
    - ~1.56 million persons 65+ years old vaccinated annually for influenza in recent years

Covered populations for COVID-19: adults & children

- Active surveillance (cont.)
  - CDC's VSD active surveillance (8 integrated health systems)
    - 8 million persons 19-64 years old
    - 2.3 million persons <18 years old

Covered populations for COVID-19: adults & children

- FDA's Biologics Effectiveness and Safety (BEST) System
  - >100 million persons - using Claims (billing) data
  - >20 million persons - using Electronic Health Records (EHR)
  - 6.2 million children – using PEDSnet Clinical Research Consortium
  - 5 million persons - using Claims-EHR linked data
- FDA Sentinel - Post-Licensure Rapid Immunization Safety Monitoring (PRISM) Program
  - Harvard Pilgrim Healthcare Institute – Operations Center
  - 4 large insurers – HealthCore, Humana, Optum, Healthagen
  - Claims data with access to medical charts
  - Covers >100 million persons

Covered populations for COVID-19: adults & children

- DoD VAERS monitoring in collaboration with CDC through a VAERS data sharing agreement
  - 1.4 million active duty and 860,000 reserves (majority <30 years old); dependents and beneficiaries if seen in DoD healthcare facilities
- DoD active surveillance
  - DoD Immunization Healthcare Div plans to collaborate with the Armed Forces Health Surveillance Div to monitor vaccine safety in the DoD EHR systems
    - Defense Medical Surveillance System (DMSS) and DoD Personnel and Readiness COVID-19 Registry

Covered populations for COVID-19: adults & children

- Indian Health Service (IHS) VAERS monitoring in collaboration with CDC through a VAERS data sharing agreement (MOU in progress)
  - Mainly American Indian and Alaska Native patients seen in IHS and Tribal healthcare facilities
  - Analysis will be conducted by National Pharmacy & Therapeutics Committee and IHS Division of Epidemiology

Case review and inquiry response

Case reviews and inquiry response

- CDC's Clinical Immunization Safety Assessment (CISA) Project
  - Assists U.S. healthcare providers with complex vaccine safety questions about their patients by conducting in-depth clinical case reviews
  - Plan to establish a call service for clinician assistance
- CDC's Immunization Safety Office inquiry response program
  - Responds to vaccine safety inquiries and questions from the public, including patients, parents, healthcare providers, public health partners, and others
- DoD's Regional Vaccine Safety Hubs (RVSHs) for case evaluation and Vaccine Adverse Event Clinical System (VAECS)
  - Evaluates and track cases of adverse events following immunization in DoD and DoD-affiliated populations

Enhanced monitoring programs to meet the challenge of COVID-19

COVID-19 vaccine safety monitoring in early recipients

- Challenge
  - During the early phase of a national COVID-19 vaccination program, initial doses may be distributed to specific groups such as healthcare personnel and other essential workers
  - In this scenario, activities to enhance normal public health monitoring systems will be necessary
- Potential solutions
  - Active surveillance in early recipients through smartphone- and email-based web surveys, with directed reporting to VAERS (enhanced passive surveillance)
  - Vaccination capture and enhanced passive surveillance through other data sources from healthcare facilities

Healthcare workers, essential workers, etc.

Medically important adverse event reports to VAERS

VAERS

Local and systemic reactogenicity and follow-up to 6 weeks via text/web messaging

CDC Centers for Disease Control and Prevention

FDA

Safety check-up text messages or email from CDC

(e.g., Since your vaccination, have you had a fever or felt feverish?...)

Additional potential data sources

- State Immunization Information Systems (i.e., vaccine registries) to capture ‘denominator’ data for adverse event rates
- Telehealth encounters in CDC’s Vaccine Safety Datalink (VSD)
- Healthcare provider and general public concerns
  - Tracking clinical case review requests submitted to CDC’s CISA and public inquiries submitted to CDC’s Immunization Safety Office
- FDA plans to develop new electronic data sources through EHR partners

Signal detection and signal assessment

Vaccine safety signal*

- The Council for International Organizations of Medical Sciences (CIOMS) proposed a signal as:
  - "Information…from one or multiple sources …, **which suggests a new potentially causal association, or a new aspect of a known association**, between an intervention and an event or set of related events, either adverse or beneficial, that is judged to be of sufficient likelihood to justify verificatory action."*
- In practice, efforts focus on detecting signals for "adverse" events

*Practical Aspects of Signal Detection in Pharmacovigilance: Report of CIOMS Working Group VIII. Geneva 2010.

Approaches to analyzing VAERS data (spontaneous reporting)

- Traditional methods
  - Clinical review of individual reports
    - Verify diagnosis and onset interval, characterize clinical and laboratory features, identify other potential risk factors
  - Aggregate report review (automated data), e.g., cases counts, frequencies of adverse event coding terms, reporting trends over time, reporting rates
- Statistical data mining methods
  - Detect disproportional reporting of specific vaccine-adverse event combinations in VAERS database
    - Empirical Bayesian and proportional reporting ratio analyses generate statistical signals when pre-specified thresholds are reached

VAERS timeliness for signal detection and assessment

- CDC and FDA receive updated VAERS datasets daily
- Processing actions for VAERS reports include:
  - MedDRA coding of symptoms
  - Redaction of personally identifiable information
  - Quality assurance
  - Preparation for posting on the secure VPN (for investigator access)
- Processing times for COVID-19 vaccines
  - Death reports: 1 day
  - Reports classified as serious*: 3 days
  - Reports classified as non-serious: 5 days

*Based on the Code of Federal Regulations if one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly or birth defect

Approaches to monitoring in EHR, administrative, and claims data

- Near real-time sequential monitoring (e.g., Rapid Cycle Analysis [RCA] in VSD)
  - Data are refreshed weekly in high volume situations
  - Pre-specified outcomes are monitored (i.e., identified in advance)
  - A surveillance activity, not the same as an epidemiologic study
  - Designed to detect statistical signals (values above specified statistical thresholds)
  - When a statistical signal occurs, assessment requires a series of evaluations using traditional epidemiologic methods
  - Chart-confirmation of diagnoses to confirm or exclude cases as true incident cases is a key part of statistical signal assessment

Closing

Importance of timeliness

- Real-time/near real-time safety monitoring will be critical during the early stages of the COVID-19 vaccination program
  - To characterize the safety profile of COVID-19 vaccines in a real-world environment
  - To rapidly assess COVID-19 vaccine safety in risk-based priority groups, such as older adults and individuals with certain pre-existing health conditions
- During a broad-based vaccination program, large amounts of COVID-19 vaccine are anticipated to be administered during a short period of time
  - Important to have established, high functioning systems and validated methods in place to rapidly detect and assess potential safety signals so public health action can be taken if necessary

Process

ACIP COVID-19 Vaccines WG

CDC: Kathleen Dooling, Sara Oliver

- Advise on planning for the use of COVID-19 vaccines and advise on all components of program implementation during a large-scale COVID-19 immunization program
- Review post-authorization/approval vaccine safety surveillance data

ACIP COVID-19 Vaccine Safety Tech. SG

CDC: Tom Shimabukuro

- Advise on the safety of COVID-19 vaccine candidates in development and safety monitoring of vaccines authorized/approved for use
- Review post-authorization/approval vaccine safety surveillance data

Closing thoughts

- Multiple U.S. Government agencies will use complementary systems and methods to monitor COVID-19 vaccines
- Current monitoring systems have the capacity to effectively monitor COVID-19 vaccine safety both under EUA and post-licensure
- Analytic methods have been validated through years of development and refinement
- Data refresh and updates are timely, and analyses occur in near real-time
- New data sources will contribute to COVID-19 vaccine safety monitoring, especially early in the vaccination program

Topics for future presentations to ACIP

- COVID-19 vaccine safety monitoring plans and methods
- Vaccine safety outcomes and adverse events of special interest
- Process for reviewing and presenting safety data as it becomes available

Questions?