



CDC post-authorization/post-licensure safety monitoring of COVID-19 vaccines

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Vaccine Safety Team

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Background

- U.S. government has a responsibility for public safety with respect to vaccines
 - Monitoring is independent from manufacturers and covers all vaccines
 - USG maintains the largest, most robust, and most sophisticated safety monitoring systems available and agencies collaborate on analyses

Background (cont.)

- CDC's Advisory Committee on Immunization Practices (ACIP) has established a COVID-19 Vaccine Safety Technical Sub-Group
 - Advise federal agencies on planning and preparation for post-authorization/post-licensure safety monitoring of COVID-19 vaccines
 - Independently review and evaluate safety data
- Post-authorization/post-licensure safety data on COVID-19 vaccines will be regularly presented at public ACIP meetings

CDC vaccine safety monitoring for COVID-19

- Vaccine Adverse Event Reporting System (VAERS)
- Vaccine Safety Datalink (VSD)
- Clinical Immunization Safety Assessment (CISA) Project
- “v-safe” text monitoring active surveillance
- Additional COVID-19 vaccine safety monitoring programs
- Safety monitoring in pregnancy

**Vaccine Adverse Event Reporting System (VAERS):
The U.S. early warning safety monitoring system**



VAERS

Vaccine Adverse Event Reporting System

Co-managed by
CDC and FDA

<http://vaers.hhs.gov>

VAERS Vaccine Adverse Event Reporting System
www.vaers.hhs.gov

- About VAERS
- Report an Adverse Event
- VAERS Data
- Resources
- Submit Follow-Up Information

Have you had a reaction following a vaccination?

1. Contact your healthcare provider.
2. [Report an Adverse Event](#) using the VAERS online form or the new downloadable PDF. *New!*

Important: If you are experiencing a medical emergency, seek immediate assistance from a healthcare provider or call 9-1-1. CDC and FDA do not provide individual medical treatment, advice, or diagnosis. If you need individual medical or health care advice, consult a qualified healthcare provider.

¿Ha tenido una reacción después de recibir una vacuna?

1. Contacte a su proveedor de salud.
2. [Reporte una reacción adversa](#) utilizando el formulario de VAERS en línea o la nueva versión PDF descargable. *Nuevo!*



What is VAERS?



REPORT AN ADVERSE EVENT

Report significant adverse events after vaccination.



SEARCH VAERS DATA

Download VAERS Data and search the CDC WONDER database.



REVIEW RESOURCES

Find materials, publications, learning tools, and other resources.



SUBMIT FOLLOW-UP INFORMATION

Upload additional information related to VAERS reports.

Vaccine Adverse Event Reporting System (VAERS)

Strengths

- National data
- Accepts reports from anyone
- Rapidly detects safety signals
- Can detect rare adverse events
- Data available to public

Limitations

- Reporting bias
- Inconsistent data quality and completeness
- Lack of unvaccinated comparison group
- Generally cannot assess causality

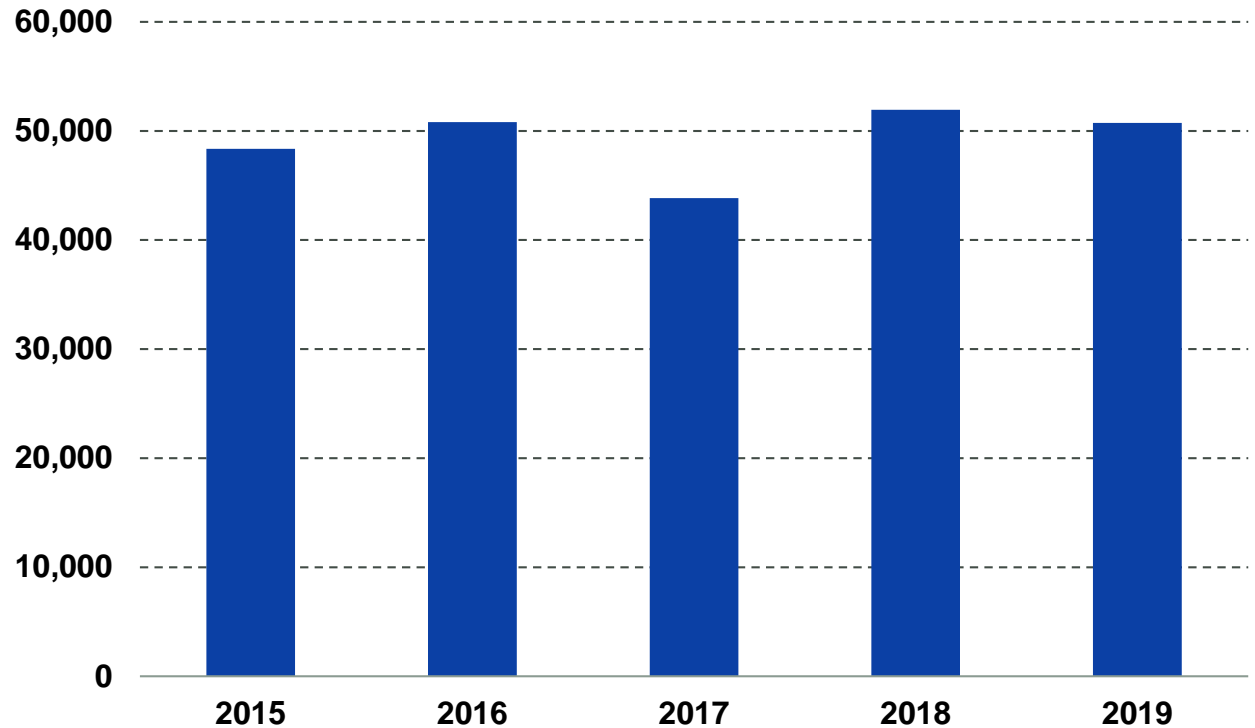
- VAERS accepts all reports from all reporters without making judgments on causality or clinical seriousness of the event
- As a hypothesis generating system, VAERS identifies potential vaccine safety concerns that can be studied in more robust data systems

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/jurisdictions, healthy people, those with co-morbidities, etc.



VAERS total U.S. reports received by year



Approaches to analyzing VAERS data

- Traditional methods
 - Clinical review of individual reports
 - Aggregate report review (automated data), e.g., case counts, frequencies of adverse event coding terms, reporting rates, reporting trends over time
- Statistical data mining methods
 - Detects disproportional reporting of specific vaccine-adverse event combinations in VAERS database

VAERS timeliness

- VAERS traditionally has provided initial data on the safety profile of new vaccines when they are introduced for use in the population
- COVID-19 vaccine reports will be processed (i.e., reviewed, coded, incorporated into VAERS database) within 1-5 business days:
 - Death reports: 1 day
 - Reports classified as serious*: 3 days
 - Reports classified as non-serious: 5 days
- CDC and FDA receive updated datasets daily
- Data mining runs conducted every 1-2 weeks

*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

Experience from H1N1



Persons using assistive technology might not be able to fully access information in this file. For assistance, please send e-mail to: mmwrq@cdc.gov. Type 508 Accommodation and the title of the report in the subject line of e-mail.

Safety of Influenza A (H1N1) 2009 Monovalent Vaccines --- United States, October 1--November 24, 2009

The Food and Drug Administration (FDA) licensed the first 2009 influenza A (H1N1) monovalent vaccines ("H1N1 vaccines") on September 15, 2009 (1). The H1N1 vaccines are available as a live, attenuated monovalent vaccine (LAMV) for intranasal administration and as monovalent, inactivated, split-virus or subunit vaccines for injection (MIV). The licensure and manufacturing processes for the monovalent H1N1 vaccines were the same as those used for seasonal trivalent inactivated (TIV) or trivalent live, attenuated influenza vaccine (LAIIV); none of these vaccines contains an adjuvant (2). Vaccine safety monitoring is an important component of all vaccination programs. To assess the safety profile of H1N1 vaccines in the United States, CDC reviewed vaccine safety results for the H1N1 vaccines from 3,783 reports received through the U.S. Vaccine Adverse Event Reporting System (VAERS) and electronic data from 438,376 persons vaccinated in managed-care organizations in the Vaccine Safety Datalink (VSD), a large, population-based database with administrative and diagnostic data, in the first 2 months of reporting (as of November 24). VAERS data indicated 82 adverse event reports per 1 million H1N1 vaccine doses distributed, compared with 47 reports per 1 million seasonal influenza vaccine doses distributed. However, no substantial differences between H1N1 and seasonal influenza vaccines were noted in the proportion or types of serious adverse events reported. No increase in any adverse events under surveillance has been seen in VSD data. Many agencies are using multiple systems to monitor H1N1 vaccine safety (2). Health-care providers and the public are encouraged to report adverse health events that occur after vaccination.

Reports to VAERS


Health-care providers and manufacturers are required to report to VAERS certain adverse events in vaccinees brought to their attention after vaccination with licensed U.S. vaccines;* however, health-care providers and members of the public also may report other adverse events voluntarily. VAERS enables early detection of potential new, rare, or unusual patterns of adverse events, which then can be investigated using other methods and systems to determine whether an actual association with vaccination exists (3). With the initiation of the federal H1N1 vaccination program, VAERS was enhanced by providing VAERS contact information on influenza vaccination record cards, advertising in medical journals, utilizing state vaccine safety coordinators, and increasing the number of staff members who code reports and obtain and review medical records; these changes were made to encourage VAERS reporting and to increase the capacity to analyze additional reports to rapidly identify any safety signals.

CDC and FDA staff members searched the VAERS database to identify all U.S. reports of adverse events after vaccination with H1N1 vaccines and 2009--10 seasonal influenza vaccines during July 1--November 24. The first doses of H1N1 LAMV became available to the public in the United States on October 5, and H1N1 MIV became available the following week. VAERS reports were coded as fatal or nonfatal serious adverse events (defined by federal regulation as those resulting in death, life-threatening illness, hospitalization, prolongation of hospitalization, persistent or significant disability, or congenital anomaly) or as nonserious,[†] and reporting rates per 1 million doses distributed as of November 20 were calculated.[§]

VAERS reports coded as serious adverse events are reviewed by medical officers and assigned to predetermined broad diagnostic categories. To verify the reported event, medical records are requested and reviewed for all serious adverse event reports and for any reports (both serious and nonserious) that describe patients with possible Guillain-Barré syndrome or anaphylaxis. Cause of death is determined as stated in medical or autopsy records. Reports to VAERS indicate only that health events occurred after vaccination; causality generally cannot be determined solely by reports to VAERS. Excluded were 62 reports with insufficient information.

Experience from H1N1

vaccine licensed in mid-Sep 2009
did not become available until mid- to late-Oct
analytic period this analysis thru Nov 24
MMRW published Dec 4
(<2 mo. after start of vaccination)

 [CDC Home](#) | [Search](#) | [Health Topics A-Z](#)

MMWR

Early Release
December 4, 2009 / 58(Early Release);1-6

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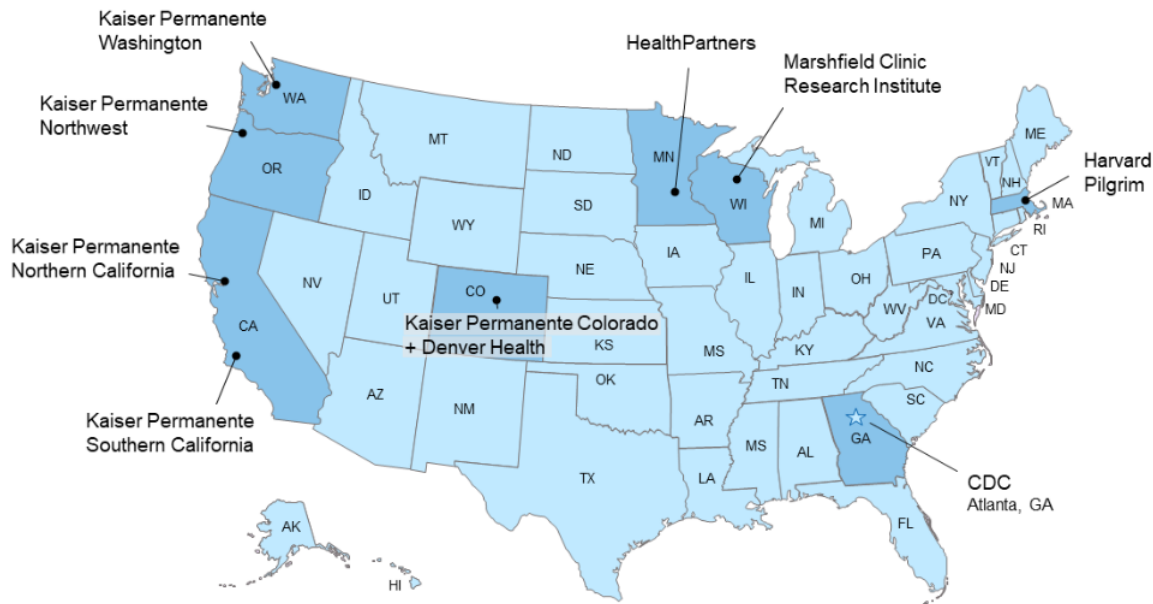
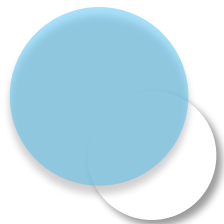
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**Vaccine Safety Datalink (VSD):
Active surveillance and research**



VSD

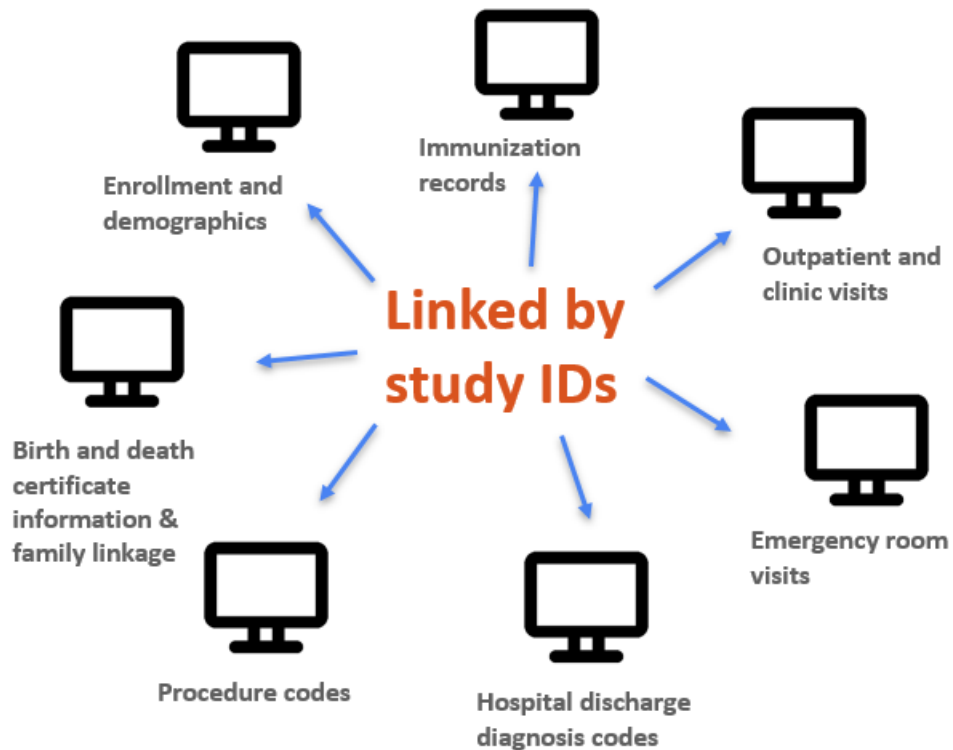
Vaccine
Safety
Datalink



9 participating integrated healthcare organizations

Data on over 12 million persons per year

VSD electronic files + chart review



+



VSD planned monitoring for COVID-19 vaccine safety

- Near real-time sequential monitoring (Rapid Cycle Analysis)
 - Weekly analyses on accumulating data with adjustment for sequential testing
 - Outcomes being monitored are pre-specified
- Tree-temporal scan data mining
 - Mines VSD database to detect associations between vaccination and outcomes
 - No limitation or restriction on outcomes (i.e., outcomes not pre-specified)
- Monitoring for vaccine-mediated enhanced disease (VMED)

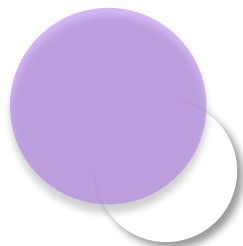
VSD timeliness

- VSD data are refreshed weekly
- ~2-week data lag from a patient encounter with the healthcare system until the data are in refreshed database (processing, coding, QA/QC)

Clinical Immunization Safety Assessment Project: Case reviews and clinical research



CISA



**Clinical
Immunization
Safety
Assessment**

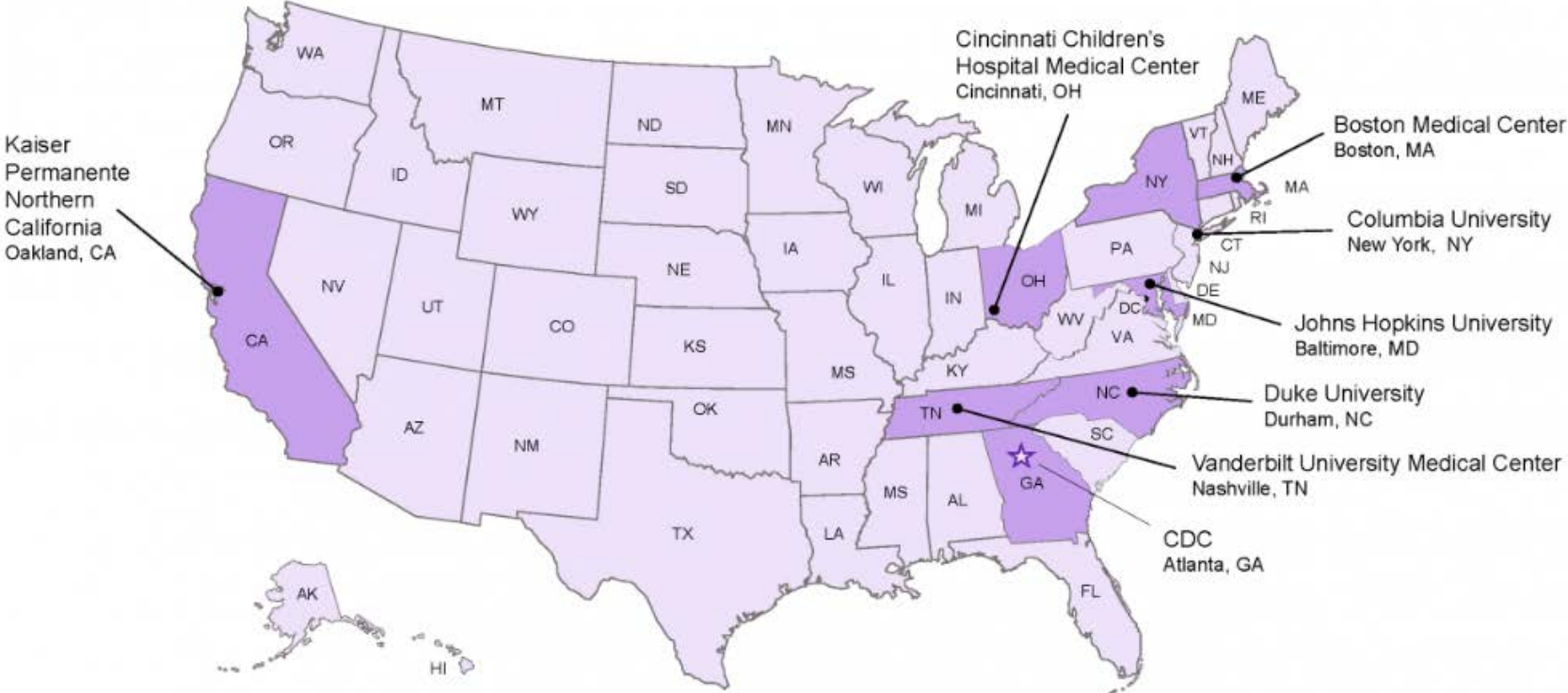
7 participating medical
research centers

vaccine safety experts

- assist U.S. healthcare providers with complex vaccine safety questions about their patients[†]
- conduct clinical research

[†]More information about clinical consults available at <http://www.cdc.gov/vaccinesafety/Activities/CISA.html>

CISA: Collaboration between CDC and 7 medical research centers

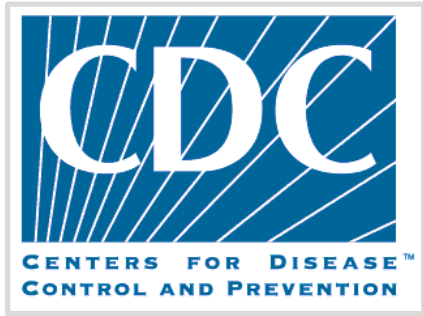


v-safe

v-safe text monitoring for COVID-19 vaccine safety

- v-safe is a new smart-phone based active surveillance program for COVID-19
 - Uses text messaging to initiate web-based survey monitoring
 - Conducts electronic health checks on vaccine recipients
 - Daily for first week post-vaccination
 - Weekly thereafter until 6 weeks post-vaccination
 - Includes active telephone follow-up through the VAERS program with people reporting a clinically important* event during any v-safe health check
 - Data will be available daily

*Refer to v-safe figure on next slide



1. Text message check-in or email from CDC (daily 1st week post-vaccination and weekly thereafter until 6 weeks post-vaccination)

Vaccine recipient completes web survey



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Vaccine recipient

2. Clinically important event(s) reported

- ✓ Missed work
- ✓ Unable to do normal daily activities
- ✓ Received medical care

v-safe
after vaccination
health checker



VAERS call center



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3. A VAERS customer service representative conducts active telephone follow-up on a clinically important event and completes a VAERS report if appropriate



Additional COVID-19 vaccine safety monitoring programs

Other planned vaccine safety monitoring activities

- Safety monitoring in Genesis HealthCare data
 - 350 long-term care facility sites in 25 states
 - Data include daily electronic medical record system updates of tests, diagnostic information, symptoms, vital signs, physician orders and medication administration
- Facilitated VAERS reporting for healthcare workers and long-term care facility residents in CDC's National Healthcare Safety Network

Pregnancy

COVID-19 vaccine safety monitoring in pregnancy

- Planned activities
 - Identifying and reviewing all VAERS reports involving COVID-19 vaccination and pregnancy and adverse pregnancy outcomes
 - Vaccine safety datalink (VSD) studies to evaluate COVID-19 vaccine safety in pregnancy, fetal death, and infant outcomes
 - Monitoring of vaccinated pregnant women and women who become pregnant after vaccination in v-safe

Summary

Summary

- CDC monitoring systems are capable of effectively monitoring COVID-19 vaccine safety both under EUA and post-licensure
- Analytic methods for VAERS and VSD have been validated through years of development and refinement
- Data refresh and updates are timely, allowing for analyses in near real-time
- Additional vaccine safety monitoring programs will contribute, especially early in the COVID-19 vaccination program

Extra vaccine safety slides

Preliminary list of VAERS AEs of special interest

- COVID-19 disease
- Death
- Vaccination during pregnancy and adverse pregnancy outcomes
- Guillain-Barré syndrome (GBS)
- Other clinically serious neurologic AEs (group AE)
 - Acute disseminated encephalomyelitis (ADEM)
 - Transverse myelitis (TM)
 - Multiple sclerosis (MS)
 - Optic neuritis (ON)
 - Chronic inflammatory demyelinating polyneuropathy (CIDP)
 - Encephalitis
 - Myelitis
 - Encephalomyelitis
 - Meningoencephalitis
 - Meningitis
 - Encephalopathy
 - Ataxia
- Seizures / convulsions
- Stroke
- Narcolepsy / cataplexy
- Autoimmune disease
- Anaphylaxis
- Non-anaphylactic allergic reactions
- Acute myocardial infarction
- Myocarditis / pericarditis
- Thrombocytopenia
- Disseminated intravascular coagulation (DIC)
- Venous thromboembolism (VTE)
- Arthritis and arthralgia (not osteoarthritis or traumatic arthritis)
- Kawasaki disease
- Multisystem Inflammatory Syndrome (MIS-C, MIS-A)

Preliminary list of VSD pre-specified outcomes for RCA

- Acute disseminated encephalomyelitis (ADEM)
- Acute myocardial infarction (AMI)
- Anaphylaxis
- Acute respiratory distress syndrome (ARDS)
- Arthritis and arthralgia / joint pain
- Convulsions / seizures
- Disseminated intravascular coagulation (DIC)
- Encephalitis / myelitis / encephalomyelitis / meningoencephalitis / meningitis / encephalopathy (not ADEM or TM)
- Guillain-Barré syndrome (GBS)
- Immune thrombocytopenia (ITP)
- Kawasaki disease (KD)
- Multisystem Inflammatory Syndrome in Children (MIS-C)
- Myocarditis / pericarditis
- Narcolepsy / cataplexy
- Stroke
- Transverse myelitis (TM)
- Venous thromboembolism (VTE)



CDC plans for vaccine effectiveness (VE) evaluation during EUA use and post-licensure

Stephanie Schrag, D Phil
Vaccine Taskforce, COVID-19 Response
Centers for Disease Control and Prevention

FDA VRBPAC Meeting
October 22, 2020



What Phase 3 trials may (and may not) clarify regarding vaccine efficacy

- Primary endpoints: symptomatic COVID-19
 - One trial will use moderate-to-severe COVID-19
- Secondary endpoints:
 - Severe COVID-19
 - Efficacy in key groups (elderly, disproportionately affected groups)
 - SARS-CoV-2 infection
 - Attempted by serology, but widely spaced blood draws
 - An early EUA may limit efficacy information available
- Pregnant women and children not included in initial trials



Need for post-authorization or licensure VE estimates

- More important than usual if an EUA is issued before full trial completion
 - Limited efficacy information for secondary endpoints
 - Limited insight into duration of protection
- Also needed for the usual reasons
 - Real world protection may differ from efficacy under trial conditions
 - Most COVID-19 vaccine products require 2 dose regimens and varying cold chain conditions: challenging to implement



VE policy priorities: Results of internal and external input

Priority	Product-specific VE question
Immediate First 2-4 months	<ul style="list-style-type: none">• Does a vaccine protect against symptomatic disease as expected?
Subsequent	<ul style="list-style-type: none">• VE against key outcomes<ul style="list-style-type: none">• Severe disease• Non-severe disease• SARS-CoV-2 infection (and potentially transmission)• VE in key sub-populations<ul style="list-style-type: none">• Elderly (including those in LTCF)• People with key underlying conditions (obesity, diabetes)• Disproportionately affected populations (Black, LatinX, Native American)• Regimen-related questions<ul style="list-style-type: none">• VE of a single dose; VE of mixed dose (more than 1 product) schedules
Later stage	<ul style="list-style-type: none">• Duration of protection• Comparative VE: Is one product better than another?• Viral evolution: Do genome changes threaten VE?



Strategies for CDC assessments of VE

- Facilitate rapid launch
 - Leverage existing platforms
 - For early phase vaccination (limited doses), focus on a population likely to be eligible
- Harmonize and coordinate across platforms and US government
 - Align as feasible case definitions, data elements, methods
 - Improve comparability of results
- Combine similar platforms
 - Improve geographic representation/capture of COVID-19 hotspots
 - Increase statistical power
 - Generate more timely and robust VE estimates
- Diversity of methods
 - Cohort
 - Case-control (test negative design; conventional)
 - Screening method/ecologic analyses
 - All observational methods have limitations



Challenges for observational COVID-19 VE studies

- Vaccination may correlate with risk of disease
 - People who get vaccinated may adopt other preventive behaviors
 - People who get vaccinated may take risks because they feel protected
- COVID-19 epidemiology is dynamic
- Likely ≥ 1 product in use simultaneously
 - Complicates estimation of product-specific VE



Currently planned COVID-19 VE studies: Adults > 18 years

VE priority	Prospective data collection	Electronic health record (EHR) and claims database analyses (coordination across USG)
Immediate priority: Does vaccine work as expected?	Test negative design (TND) case-control among healthcare workers	
Subsequent priorities Severe disease	TND; conventional case-control using facility controls	EHR datasets (CDC, VA, FDA): Retrospective cohort*
Non-severe disease	TND plus conventional (facility controls)	EHR cohorts (CDC, VA, FDA)
Infection (transmission)	<ul style="list-style-type: none"> • Prospective longitudinal cohorts <ul style="list-style-type: none"> • Health care & frontline workers • General community and/or household VE cohort (In planning) 	
Elderly (including a subset analysis of those in LTCF)	TND or conventional case-control among 65+ years (COVID-NET linked to CMS)	CMS cohort (FDA, CMS) EHR cohorts (CDC, VA, FDA)
Those with key underlying conditions	*Captured in above studies	CMS (FDA,CMS); EHR cohorts (CDC, VA, FDA)
Disproportionately affected racial/ethnic groups	TND in Navajo population; * Also captured in above studies	CMS (FDA, CMS); EHR cohorts (CDC, VA, FDA); Exploring IHS EHR (IHS)

* May sometimes also lend to TND, screening method



Additional analyses in earlier planning phase

- Screening method for snapshots of product-specific VE
 - Leverages disease surveillance platforms and state immunization registries
- Ecologic analyses of associations between disease incidence or seroprevalence (to the extent this can be interpreted) and vaccine coverage
- Comparisons of expected vaccine impact (based on mathematical models) with observed impact
- Studies in pregnant women, children
- Characterization of viral genomes to identify drift over time that may threaten vaccine protection
 - Leverages SPHERES project, <https://www.cdc.gov/coronavirus/2019-ncov/covid-data/spheres.html>



Conclusions

- Multiple questions of importance to vaccine policy will remain after EUA or licensure
- CDC portfolio leverages multiple platforms, data sources, and methods
- Portfolio will continue to evolve as more information from Phase 3 trials becomes available



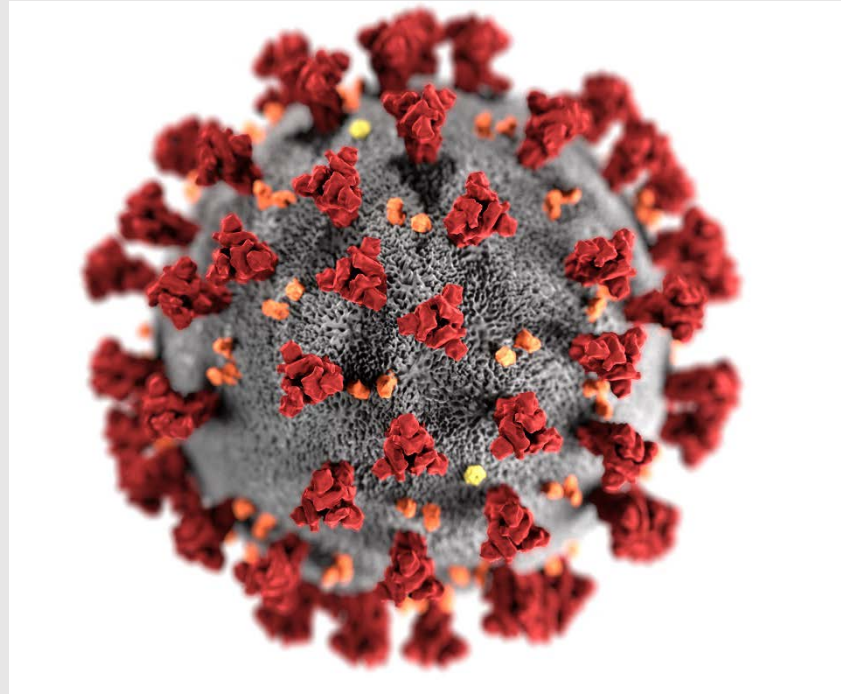
Platform acknowledgements (evolving list)

- Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET)
- Emerging Infections Program (EIP) Network
- U.S. Flu Vaccine Effectiveness (VE)
- Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN)
- Influenza Vaccine Effectiveness in the Critically Ill (IVY)
- Surveillance Platform for Enteric and Respiratory Infectious Organisms at the VA (SUPERNOVA)
- RSV Surveillance in Native Americans (RSV SuNA)
- New Vaccine Surveillance Network (NVSN)
- Pediatric Intensive Care Influenza
- Vaccine Effectiveness Study (PICFLU-VE)/ Overcoming COVID-19
- Marshfield Community Cohort
- Johns Hopkins Pediatric Cohort
- FluTES-C
- Household Influenza Vaccine Evaluation (HIVE) Study
- Coronavirus Household Evaluation and Respiratory Testing (C-HEaRT) Cohort Study
- Research on the Epidemiology of SARS-CoV-2 in Emergency Response and Healthcare Personnel (RECOVER)
- COVID Evaluation of Risk for Emergency Departments (COVERED) Project
- Vysnova
- Arizona-Reinfection
- Communities Organized to Prevent Arboviruses – COPA Coronavirus Disease 2019 (COCOVID)
- The Epidemiology of SARS-CoV-2 in Pregnancy and Infancy (ESPI) Network : Electronic Cohort
- The Epidemiology of SARS-CoV-2 in Pregnancy and Infancy (ESPI) Network : Community Cohort
- National Healthcare Safety Network (NHSN)
- Prevention EpiCenters
- FLU+COVID-19 VISION (EHR integration platform)
- SPHERES Open Genomics Consortium



Questions?

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov



The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Currently planned COVID-19 VE studies : Details

	Prospective data collection	Electronic cohort analyses (coordination across USG)
Immediate priority: Does vaccine work as expected?	TND among healthcare workers 3+ platforms with total 38 sites	
Subsequent priorities Severe disease	TND plus facility controls among adults 2-3 inpatient platforms: 17-23 hospitals *Designed to enrich for key race/ethnicity groups	EHR cohorts for adults (CDC, VA, FDA) VISION+: ≥8 health systems (~3.5M enrolled; CDC) VSD: 7 health systems (>10M enrolled; CDC) VA National database (~6 million enrolled; VA) BEST platform (FDA)
Non-severe disease	TND plus facility controls among adults 1 outpatient platform with 5-7 sites	EHR cohorts for adults (CDC, VA, FDA)
Infection (transmission)	Health care personnel / frontline worker prospective cohort ~5,000 adult participants New adult community VE cohort Weekly resp sample and PCR (Under exploration) Household VE transmission study (under exploration)	
Elderly (including those in LTCF)	Conventional case-control among 65+ years COVID-NET surveillance linked to CMS; controls selected from CMS population	CMS cohort for 65+ years and for LTCF residents (FDA) EHR cohorts for adults (CDC, VA, FDA)
Those with key underlying conditions	*Severe disease and elderly prospective studies designed to have sufficient power	CMS (FDA); EHR cohorts for adults (CDC, VA, FDA)
Disproportionately affected racial/ethnic groups	TND in Navajo population; *Severe disease and elderly prospective studies designed to have sufficient power	CMS (FDA); EHR cohorts for adults (CDC, VA, FDA) Exploring leveraging IHS EHR (IHS)