

COVID-19 Vaccine Safety

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Safety is not the absence of risk.... it is an acceptable balance of benefits and risks.

2 Independent Advisory Committees Review Safety

Vaccines and Related Biological Products Advisory Committee (VRBPAC)

- To provide advice to the Commissioner of FDA
- To evaluate data concerning **safety**, effectiveness and appropriate use of vaccines...for which the FDA has *regulatory* responsibility.

Advisory Committee on Immunization Practices

- To provide advice and guidance to the Director of the CDC
- To provide recommendations on *use* of vaccines in the U.S. civilian population based on disease epidemiology, **vaccine safety**, vaccine efficacy and effectiveness, quality of evidence reviewed, economic analyses, and implementation issues.

ACIP - Vaccine Safety

- Vaccine safety data is *routinely* considered by ACIP workgroups and full ACIP deliberations about benefit-risk balance and recommendations for use
- ACIP is *routinely* updated on post-market safety and effectiveness data for vaccines, and modifies recommendations, if needed.
- For COVID-19 vaccines, a separate safety group was assembled in Jun 2020 to support the COVID-19 Vaccine Workgroup and the full ACIP on the safety of COVID-19 vaccines in development and post-approval.

COVID-19 Vaccine Safety Technical (VaST) Subgroup

- ACIP members
 - Grace Lee
 - Beth Bell
 - Keipp Talbot
- Consultants
 - Ed Belongia
 - Matthew Daley
 - Kathy Edwards
 - Martin Kulldorff
 - Laura Riley Stanley Perlman
 - Vish Viswanath
- CDC Lead
 - Tom Shimabukuro
- Ex Officio Members
 - CDC
 - FDA
 - DoD
 - VA
 - IHS
 - HRSA
 - HHS
 - NIH
 - BARDA

VaST - Terms of Reference

-As of May 2020

Serve as the central hub for technical subject matter experts to:

- 1) Review and interpret pre-authorization /pre-licensure SARS-CoV-2 vaccine candidate safety data
- 2) Review and interpret post-authorization/post-licensure SARS-CoV-2 vaccine safety data
- 3) Provide advice and guidance on presenting post-authorization/post-licensure SARS-CoV-2 vaccine safety data to the COVID-19 Vaccines Work Group, the full ACIP, and the general public

COVID-19 Vaccine Safety Planning

VaST Meetings

Jun 8
Kickoff
Meeting

Jul 2 Global
safety
initiatives

Aug 3
CMS,
FDA

Aug 31
NHSN,
V-SAFE

Jun 22
VAERD
overview

Jul 20
VAERS,
VSD
CISA

Aug 17
VA,
DOD,
IHS

Sep 14
Communication
framework

Key Statements

1. Should safety monitoring for **Phase III clinical trials** be harmonized (e.g. definitions for AESIs, duration of follow-up)?

YES, critical for timely evaluation

- Can *combine* data, if appropriate; maximizes sample size for any given adverse event of special interest (AESI)
- Can *compare* safety across different vaccine platforms and trials, if appropriate; enables dynamic assessment of benefit-risk balance
- Harmonizing with international standards (e.g. Brighton) is preferred

Similar to FDA guidance on COVID-19 vaccine efficacy,
FDA guidance needed on vaccine safety standards

COVID-19 Clinical Trials and Vaccine Safety

- COVID-19 clinical trials in progress or planned include 30,000-50,000 participants per trial
 - Trials are designed for efficacy, but can also be designed for safety, if sufficient follow-up is allowed (e.g. rotavirus vaccine trials*)
- Minimum amount of follow-up needed to assess safety (i.e. benefit-risk balance) will depend on the types of adverse events and associated risk intervals

*Heyse et al., Clin Trials 2008;

Key Statements

2. Should safety monitoring for **post-authorization or post-licensure safety surveillance systems** be harmonized?

YES, critical for timely evaluation

- Common protocols, outcome definitions, risk windows, and approaches to severity grading needed for rapid evaluation of statistical signals
- However, different systems have different capabilities; may need to align, rather than harmonize

Capability for timely evaluation of statistical signals is crucial for vaccine confidence

Coordination across post-market safety surveillance systems is recommended*

Near real-time safety surveillance systems – designed for sensitivity

Syndromic Surveillance in 4 states

- 62 alerts corresponding to 17 distinct signals
- 2 true clusters of illness detected

Vaccine Safety Datalink experience

- 5 vaccines monitored for 5-7 AESIs each
- 10 *statistical* signals occurred
 - 9 were spurious
 - 1 was a true signal that led to a revised ACIP rec for MMRV vaccine

Statistical signals are expected in a robust monitoring program; timely and thorough signal investigation is needed to distinguish true associations

Adverse Events of Special Interest (AESI)

General AESI

Platform-specific AESI

- mRNA
- Viral vector
- Adjuvanted
- Etc.

Population-specific AESI

- Children
- Pregnant women
- Elderly
- Multiple co-morbidities

*SPEAC classification of AESI

VaST Transition Plans

-As of Sept 2020

Pre-authorization or Pre-licensure

- **Discuss prioritized AESI**, including standardized definitions (e.g. Brighton), risk intervals, severity grading
- **Discuss common protocols** for enhanced passive surveillance and active surveillance
- **Discuss approaches to signal refinement and signal evaluation**
- **Review and refine membership** of data review group

Post-authorization or Post-licensure

- Prospectively **review, evaluate and interpret** post-authorization or post-approval vaccine safety data from
 - Ongoing clinical trials
 - Passive, enhanced passive and active surveillance systems
- **Advise on signal refinement and signal evaluation**
- **Advise on data presentation** to ACIP and public

6 conditions for success

- 1) Ability to capture vaccine exposure in vaccine safety surveillance systems
- 2) Ability to define background rates in general population and among those with COVID-19 disease
- 3) Minimize conflicts of interest of data review group
- 4) Shared review and shared learning across all vaccine safety surveillance systems
- 5) Ability for data review group to discuss findings independently
- 6) Well-developed communication plan on safety issues

We have designed our systems to detect safety signals; it's how we handle those signals that will define our country's ability to respond to COVID.