# COVID-19 Vaccine Safety

Grace M. Lee, MD MPH
Chair, ACIP COVID-19 Vaccine Safety Technical Subgroup
Associate CMO, Stanford Children's Health
Professor of Pediatrics, Stanford University School of Medicine

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

Stanford MEDICINE

Stanford Children's Health

# 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 the role of ACIP is to deliberate about benefit-risk balance and recommendations for use
- ACIP is *routinely* updated on post-market safety and effectiveness data for vaccines, and modifies recommendations as needed
- For COVID-19 vaccines, a separate safety group was assembled in June 2020 to support the COVID-19 Vaccine Workgroup and the full ACIP on the safety of COVID-19 vaccines in development and post-authorization or post-licensure

# 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

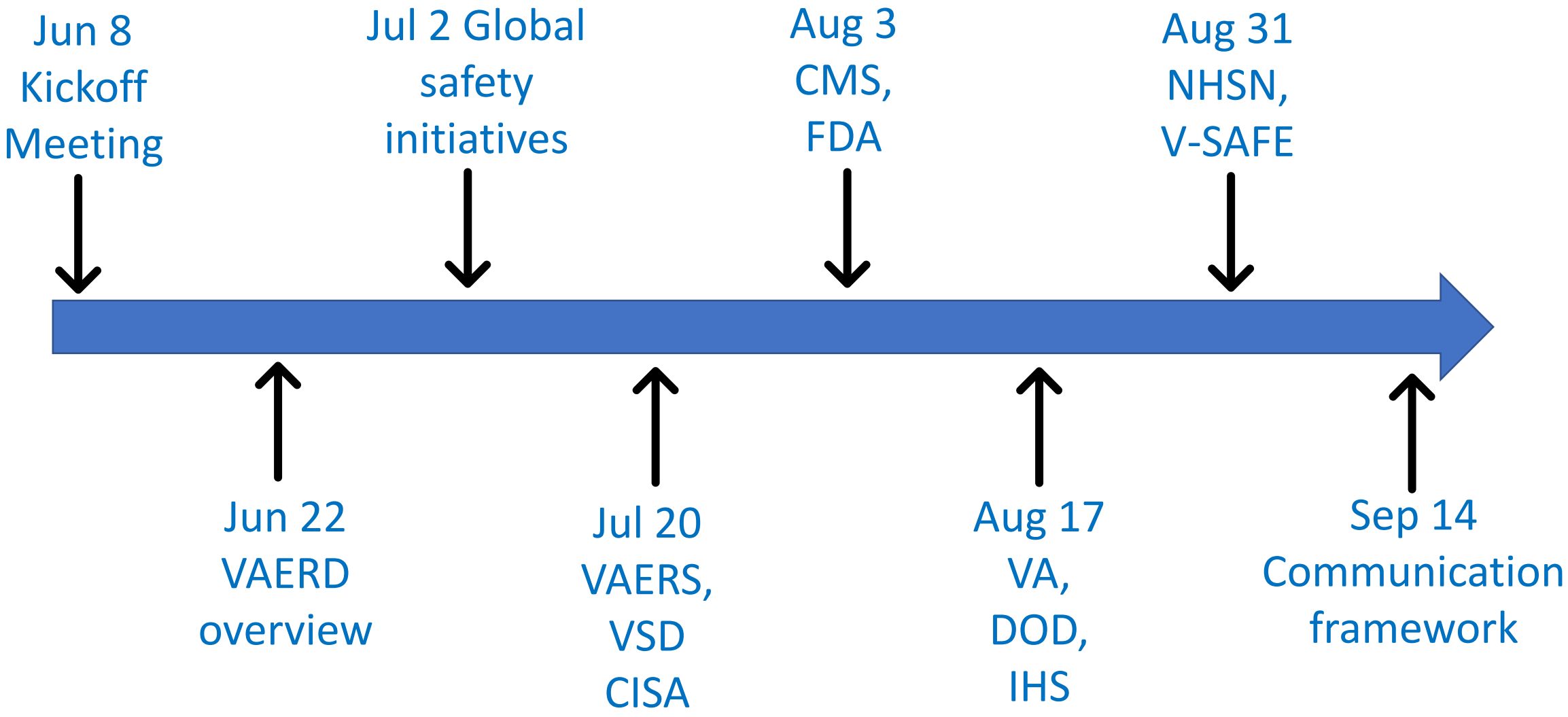
*-As of May 2020*

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



# 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 duration of follow-up needed to assess safety (i.e. benefit-risk balance) depends 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 can support 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*

*Salmon et al., Pediatrics, 2011

# Near real-time safety surveillance systems – designed for sensitivity

Statistical signals should be expected in a robust monitoring program

**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

Timely and thorough investigations of statistical signals are needed to distinguish *true* associations

Yih et al., Public Health Rep, 2010; Yih et al., Pediatrics 2011

# 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

*Safety Platform for Emergency vACcines (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 among members of the 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 collectively handle those signals that will define our country's ability to respond to COVID.*