Vaccines and Related Biological Products Advisory Committee Meeting

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An Update of FDA Monitoring COVID-19 Vaccine Safety and Effectiveness

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VRBPAC Meeting
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COVID-19 Vaccines Monitoring

- As of February 16th, 2021, >55 million doses administered

- Large United States government agency effort to monitor safety and effectiveness of COVID-19 vaccines in post-authorization setting
  - FDA, CDC, VA, CMS, DOD, IHS, NIH

US Vaccine Surveillance Programs: Post-Licensure

1. **Passive Surveillance of Vaccines**
   a) Vaccine Adverse Event Reporting System (VAERS)
      - Management shared by CDC and FDA

2. **Active Surveillance Monitoring Program Updates**
   a) FDA-CMS Rapid Cycle Analysis
   b) Background Rate Analyses
   c) Surveillance Study Protocols
   d) Next Steps

FDA- CMS
(Center for Medicare & Medicaid Services)

Rapid Cycle Analysis
(Near-Real Time Surveillance)

Rapid-cycle analyses (RCA) or “Near real-time surveillance”

- Monitoring up to 20 or more pre-specified safety outcomes of interest :
  - FDA using CMS and BEST data
  - CDC using VSD
  - VA using their EHR data

Rapid-cycle analyses (RCA) or “Near real-time surveillance”

- Elements of the RCA :
  - Identify 15 possible Adverse Events of Special Interest (AESI)
  - Sufficient vaccine counts in CMS database
  - Background rate information for AESIs
  - Conduct RCA using CMS data

FDA Rapid Cycle Analysis of COVID-19 Vaccines : Working list of 15 possible adverse events of special interest (AESI)

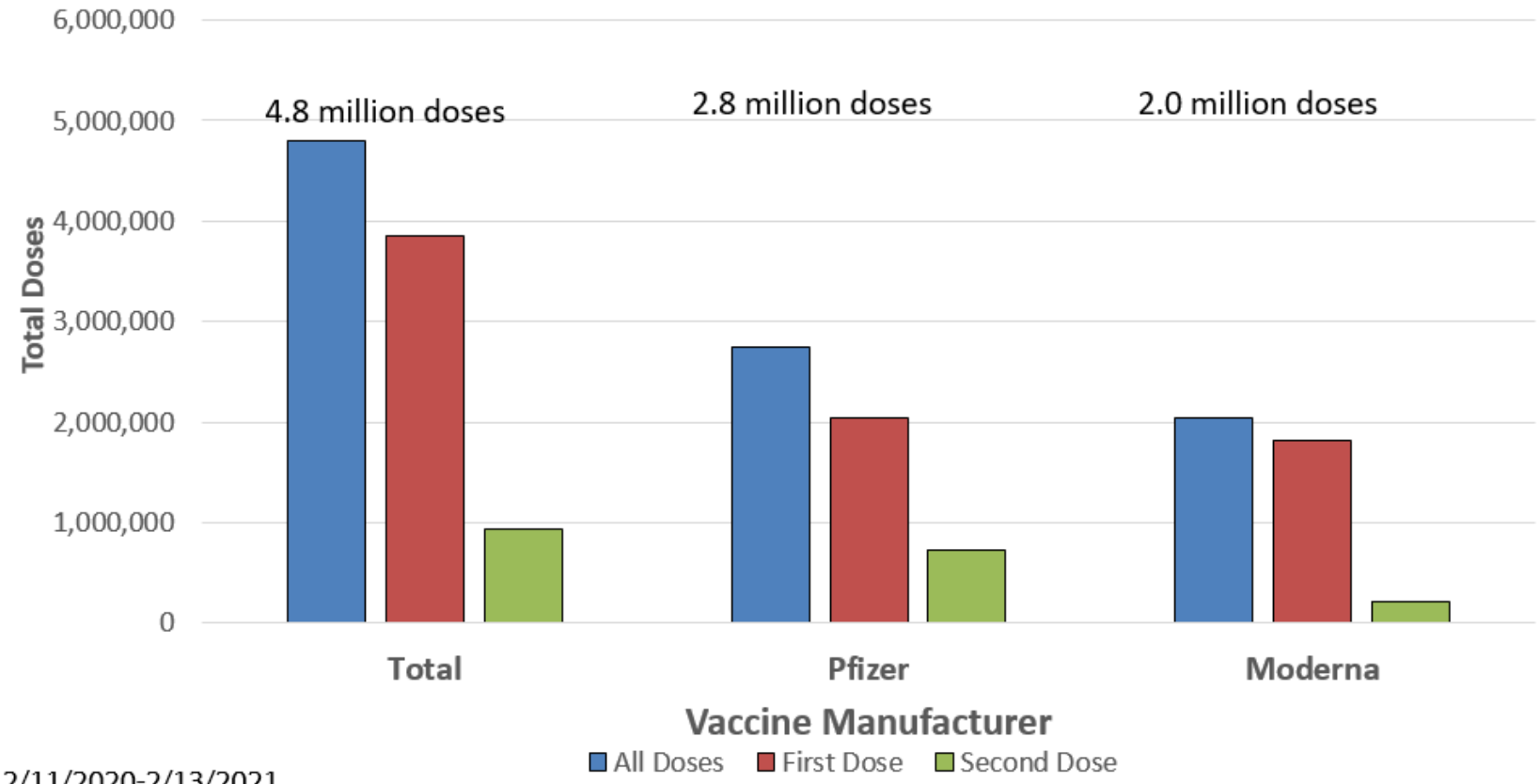
*AEs studied in other vaccines but not associated with COVID-19 vaccines in pre-authorization studies

- **Guillain-Barré syndrome**
- **Bell's Palsy**
- **Encephalomyelitis**
- **Transverse myelitis**
- **Narcolepsy**
- **Appendicitis**
- **Hemorrhagic stroke**
- **Non-hemorrhagic stroke**
- **Acute myocardial infarction**
- **Myocarditis/pericarditis**
- **Immune thrombocytopenia (ITP)**
- **Disseminated intravascular coagulation (DIC)**
- **Deep Vein Thrombosis (DVT)**
- **Pulmonary Embolism (PE)**
- **Multisystem Inflammatory Syndrome**

2b. CMS (Center for Medicare & Medicaid Services)

- **Federal Partners**
  - Ongoing FDA-CMS partnership on vaccine safety since 2002
  - Data cover nearly all of the 55 million elderly US beneficiaries ≥65yrs of age
  - Represents variety of healthcare settings – inpatient, outpatient, etc.
  - Consists of claims data with access to medical charts

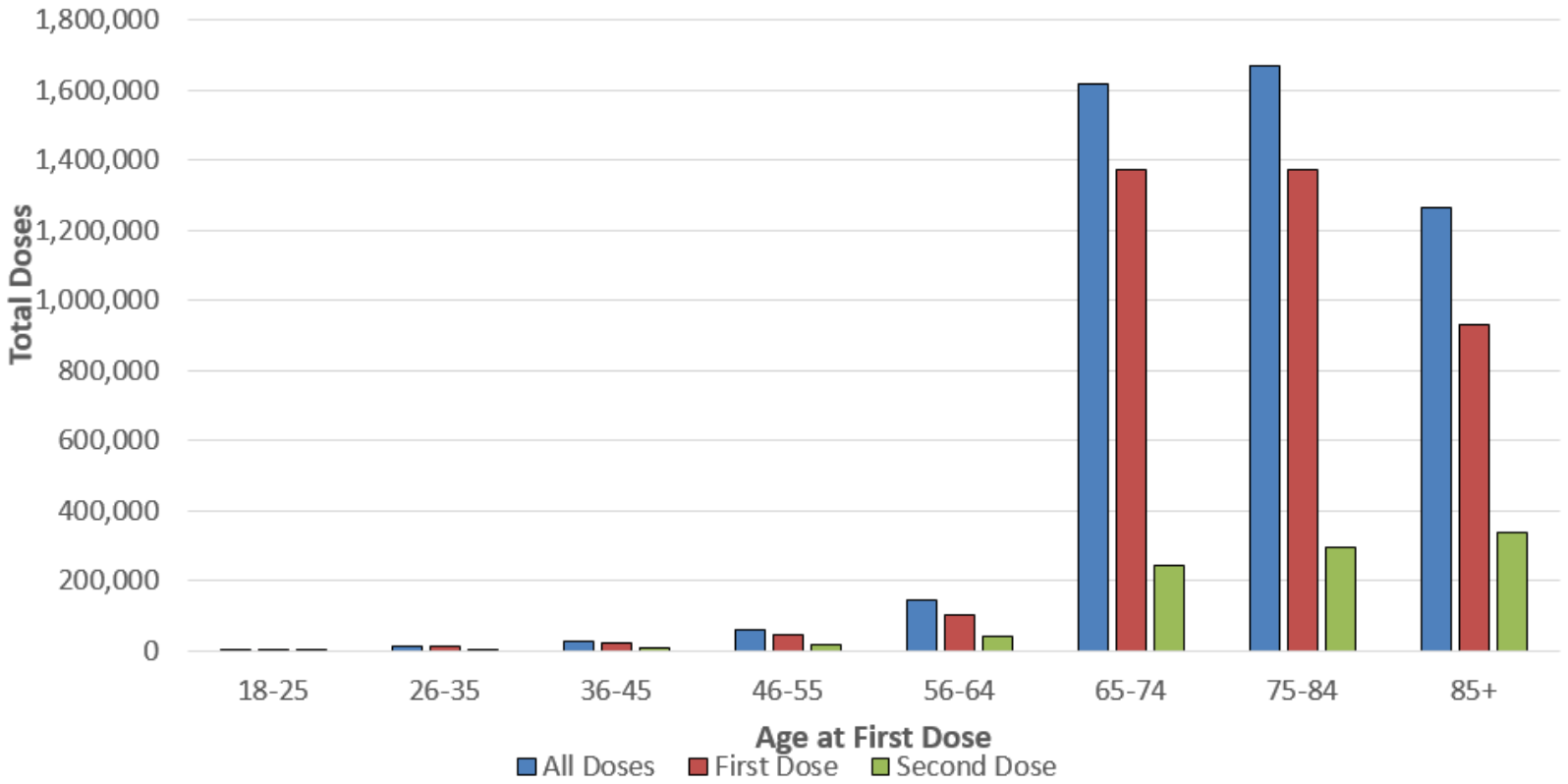
COVID-19 Vaccine Counts* in CMS Medicare Data



*12/11/2020-2/13/2021

COVID-19 Vaccine Counts* in CMS Medicare Data

(Total Doses = 4.8 million)



*12/11/2020-2/13/2021

Background Rate Analyses

Background Rates for AESI

- Background rates provide information on expected rates or estimate of a baseline for comparison
- COVID-19 vaccines are new - lack of historical information
- Require new background rates generation for the deliberate selection of the comparator group(s)
  - Unlike active monitoring for influenza vaccines which has a strong historical base on background rates for the comparator groups
- AESIs (n=15-18) background rates may vary by population and time period
  - Populations: adults aged 65+ years vs. influenza vaccinees 65+ years
  - Time periods: pre-COVID-19 vs. peri-COVID-19

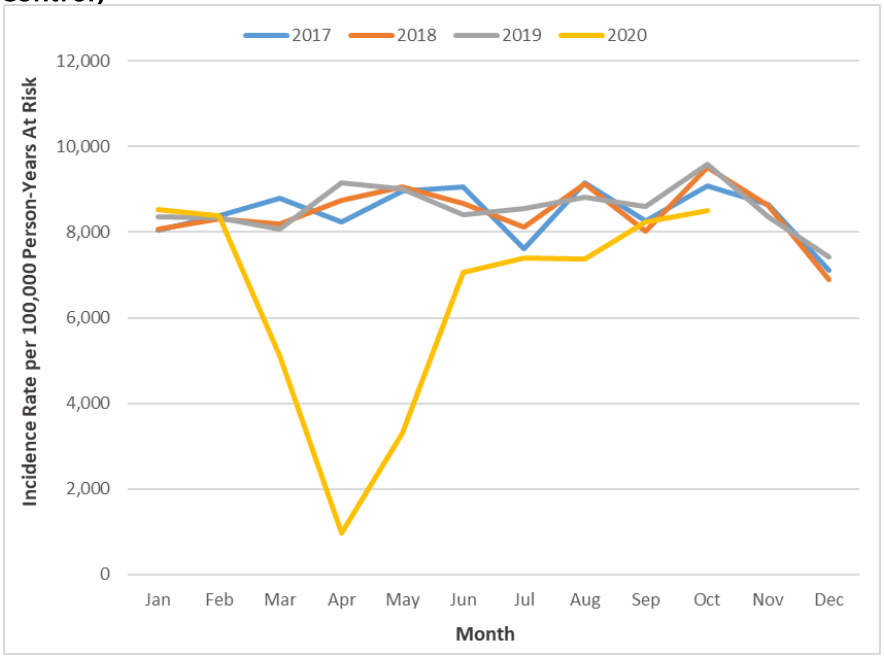
Background Rates for AESI (cont'd)

- COVID-19 pandemic may impact healthcare utilization and AESI rates during peri-COVID-19 period (March – October 2020)
- Evaluation for populations and time periods allows for more reliable safety signal detection and generation
- Assessment of background rates allows approximation of the true AESI rates

Background Rates

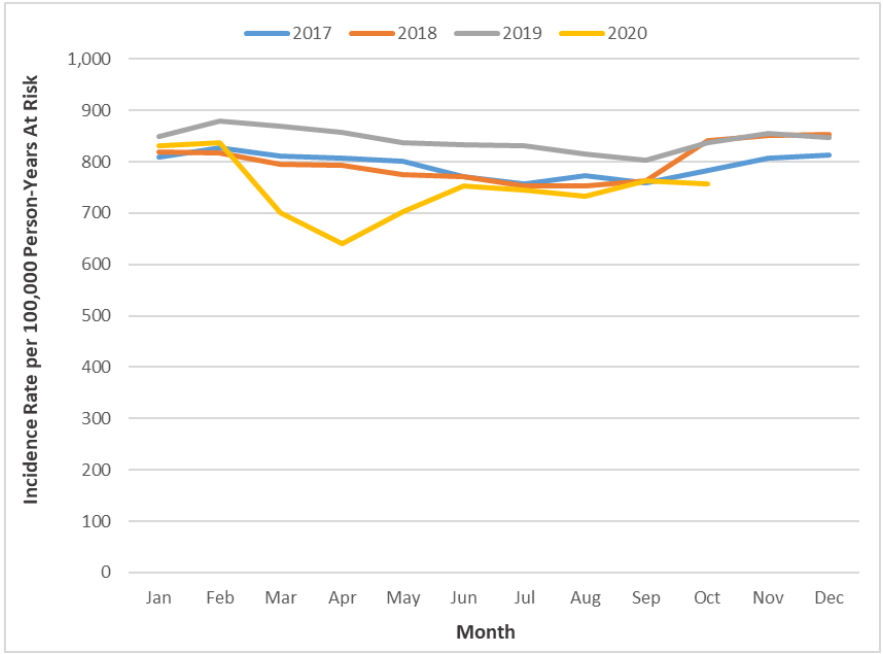
Monthly incidence rates per 100,000 person-years at risk among adults aged 65+ years, CMS Medicare, 2017-2020

Colonoscopies for colorectal cancer screening (Negative Control)



Non-hemorrhagic stroke (Potential AESI*)

This AESI has not been associated with COVID-19 vaccines based on available pre-licensure evidence.



Background Rates for AESI

Implications from Background Rates Assessment

- For the majority of AESIs, we select pre-COVID-19 background rates among adults 65+ years.
- For a few AESIs (n<5) where AESI rates did not recover to pre-COVID-19 levels, we select peri-COVID-19 background rates among adults 65+ years.
- Background rates will be standardized to the distribution of COVID-19 vaccinees by select demographic characteristics (e.g., age).
- Potential seasonality for some AESIs (n<10) will be evaluated.

FDA RCA using CMS data

- Foundational work on counts monitoring, background rates are completed
- Preliminary runs underway – FDA is evaluating early results
- Conduct runs every one to two weeks to achieve near real-time monitoring

Surveillance Study Protocols

Surveillance Study Protocols

1. Background Rates of AESI for COVID-19 Vaccine Safety Monitoring
    - Final protocol posted*; Study completed

2. COVID-19 Vaccine Safety Surveillance: Active Monitoring Master Protocol
    - Final protocol posted*;
    - Analysis underway with input from background rates study;
    - Weekly vaccine counts updates

3. COVID-19 Vaccine Safety Surveillance: Inferential Study Master Protocol
    - Protocol to be posted

4. Performance of Claims-based COVID-19 Diagnosis Code Using SARS-CoV-2 Nucleic Acid Amplification Test Results
    - Protocol to be posted

*Posted at www.bestinitiative.org

Surveillance Study Protocols (cont'd)

Future Protocols (in development)

1. COVID-19 Vaccine Safety Study to verify potential vaccine safety signals
   - Based on the Inferential Study Master Protocol;
   - Study designs depends on AESIs

2. COVID-19 Vaccine Effectiveness Study
   - Effectiveness by vaccine, Comparative effectiveness
   - By dose, durations between doses
   - Duration of protection, etc.

Next Steps

Next steps for Active Safety Monitoring

- **≥ 65 years:** active monitoring analyses underway in CMS Medicare
  - Background rates analyses completed

- **18-64 years:** Additional Rapid Cycle Analyses – development work underway
  - Planned use of FDA BEST commercial insurance claims to be used:
    - Optum pre-adjudicated claims
    - CVS/Healthagen claims
    - Others
  - Plan to start in late March

Next steps for Active Safety Monitoring (cont'd)

- For each AESI
  - Brand specific analyses
  - Risk intervals – consensus from vaccine experts and clinicians
  - Database-specific background rates input to estimate expected counts in active monitoring analyses

- Quality Assurance
  - Compare with signals from other national safety surveillance systems
  - Temporal clustering analyses, patient profile analyses, etc.

Acknowledgments

- CDC Colleagues – sharing of slides
- Richard Forshee
- Azadeh Shoaibi
- Hui-Lee Wong
- CBER Surveillance Team
- Manette Niu
- CBER OBE Colleagues
- CMS Colleagues
- VA Colleagues
- FDA Partners: Acumen, IBM Watson – and new partners in FY2021

U.S. FOOD & DRUG ADMINISTRATION

Thank you!

Questions?

Backup

Table B. Adverse Outcomes of Special Interest

AESI	Age Group of Interest	Setting	Clean Window	Risk Window
Primary Outcomes				
General Population Outcomes				
Guillain-Barré syndrome	All	IP- primary position only	365 days	1-42 days
Bell's Palsy	All	IP, OP/PB	183 days	1-42 days
Anaphylaxis	All	IP, OP-ED	30 days	0-1 days
Encephalomyelitis	All	IP	183 days	1-42 days
Narcolepsy	All	IP, OP/PB	365 days	1-42 days
Appendicitis	All	IP, OP-ED	365 days	1-42 days
Non-hemorrhagic Stroke	All	IP	365 days	1-28 days
Hemorrhagic Stroke	All	IP	365 days	1-28 days
Acute myocardial infarction	All	IP	365 days	1-28 days
Myocarditis/Pericarditis	All	IP, OP/PB	365 days	1-42 days
Deep Vein Thrombosis (DVT)	All	IP, OP/PB	365 days	1-28 days
Pulmonary Embolism (PE)	All	IP, OP/PB	365 days	1-28 days
Disseminated intravascular coagulation (DIC)	All	IP, OP-ED	365 days	1-28 days
Immune thrombocytopenia (ITP)	All	IP, OP/PB	365 days	1-42 days
Transverse Myelitis	All	IP, OP-ED	365 days	1-42 days
Multisystem Inflammatory Syndrome	All	IP, OP-ED	365 days	1-42 days

Biologics Effectiveness and Safety (BEST) Initiative

2a. FDA Biologics Effectiveness and Safety (BEST) System

- Several partners – Acumen, IBM Watson, IQVIA, OHDSI, HealthCore, Humana, Optum, Healthagen, MedStar, OneFlorida, and Academic organizations
- Represents variety of healthcare settings – inpatient, emergency department, outpatient, etc.
- Emphasis on inclusion of Electronic Health Record (EHR) data, some claims data and linked Claims-EHR data
- Emphasis on detection of vaccine rare vaccine adverse events (>1/50,000 or lower)

Pharmacovigilance Plan

The applicant submitted a pharmacovigilance plan to monitor safety concerns associated with the Janssen COVID-19 Vaccine. The safety specifications of the pharmacovigilance plan are:

- ❑ Important potential risk
  - o Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease
  - o anaphylaxis
  - o thromboembolic events

- ❑ Important missing information
  - o Use in pregnant and breast-feeding women
  - o Use in immunocompromised patients
  - o Use in patients with autoimmune or inflammatory disorders
  - o Use in frail patients with comorbidities
  - o Interaction with other vaccines
  - o Long-term safety
  - o Use in the pediatric population

Surveillance Studies

❑ Pregnancy study

- Post-authorization pregnancy exposure study: multi-country, observational, prospective cohort study of pregnant women administered with Ad26.COV2.S and including follow-up of liveborn infants to one year of age
- Objective: To assess the occurrence of obstetric, neonatal, and infant outcomes among women administered with Ad26.COV2.S during pregnancy

❑ Active surveillance study: safety

- The Sponsor is planning to conduct a retrospective, observational propensity-scored matched cohort study using health insurance claims and electronic health records (pending feasibility studies), in order to assess the risk of developing pre-specified adverse events of special interest (AESIs) during specific risk windows following administration of Ad26.COV2.S.

❑ Active surveillance study: effectiveness

- The Sponsor is planning to conduct a retrospective, observational propensity-scored matched cohort study using health insurance claims and electronic health records (pending feasibility studies), in order to estimate the effectiveness of Ad26.COV2.S to prevent medically-attended COVID-19 in individuals who were vaccinated according to the national immunization recommendations.