

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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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

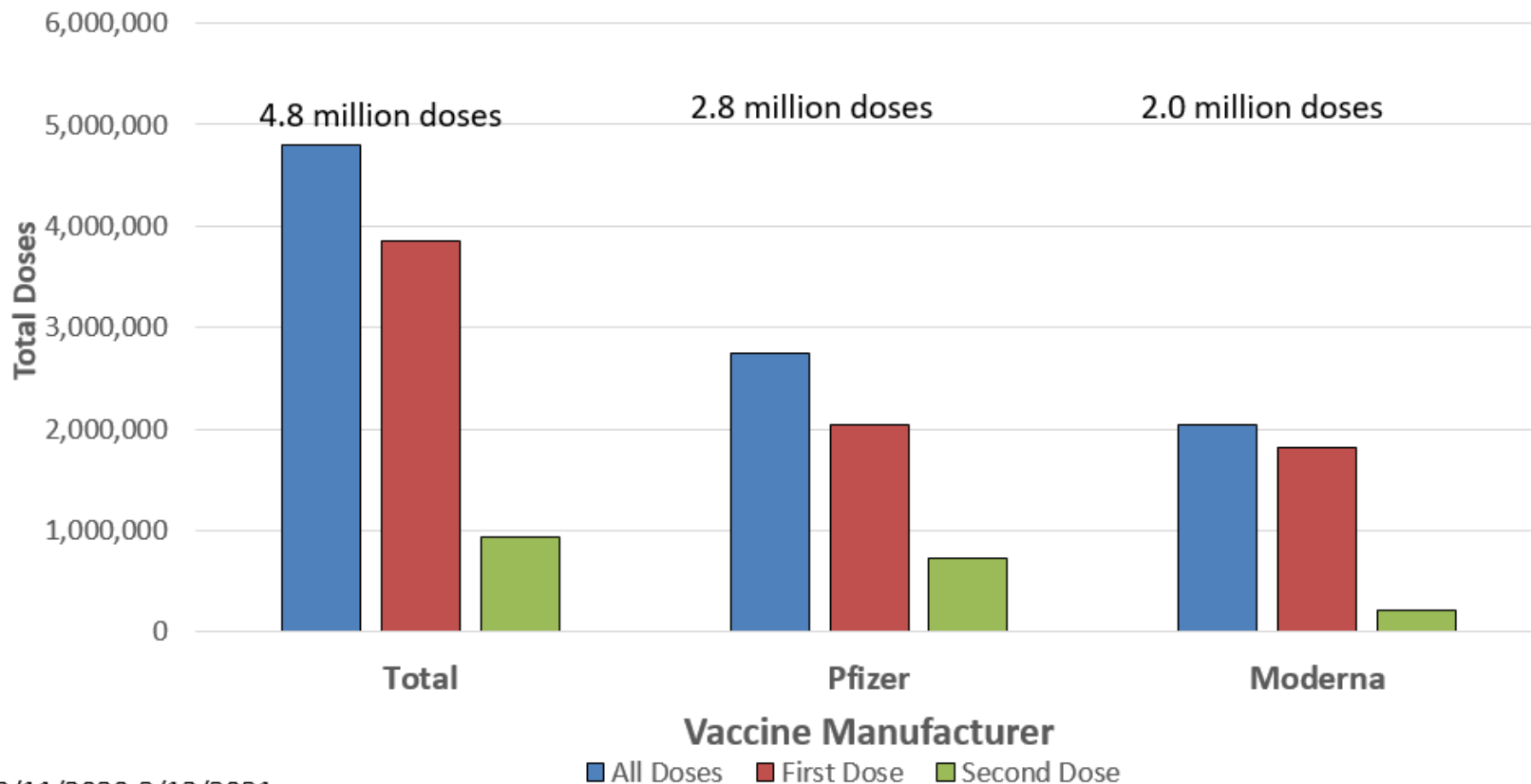
- **Guillain-Barré syndrome**
- **Bell's Palsy**
- **Encephalomyelitis**
- **Transverse myelitis**
- **Narcolepsy**
- **Appendicitis**
- **Hemorrhagic stroke**
- **Non-hemorrhagic stroke**
- **Acute myocardial infarction**
- **Myocarditis/pericarditis**
- **Immune thrombocytopenia (ITP)**
- **Disseminated 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 ≥ 65 yrs 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

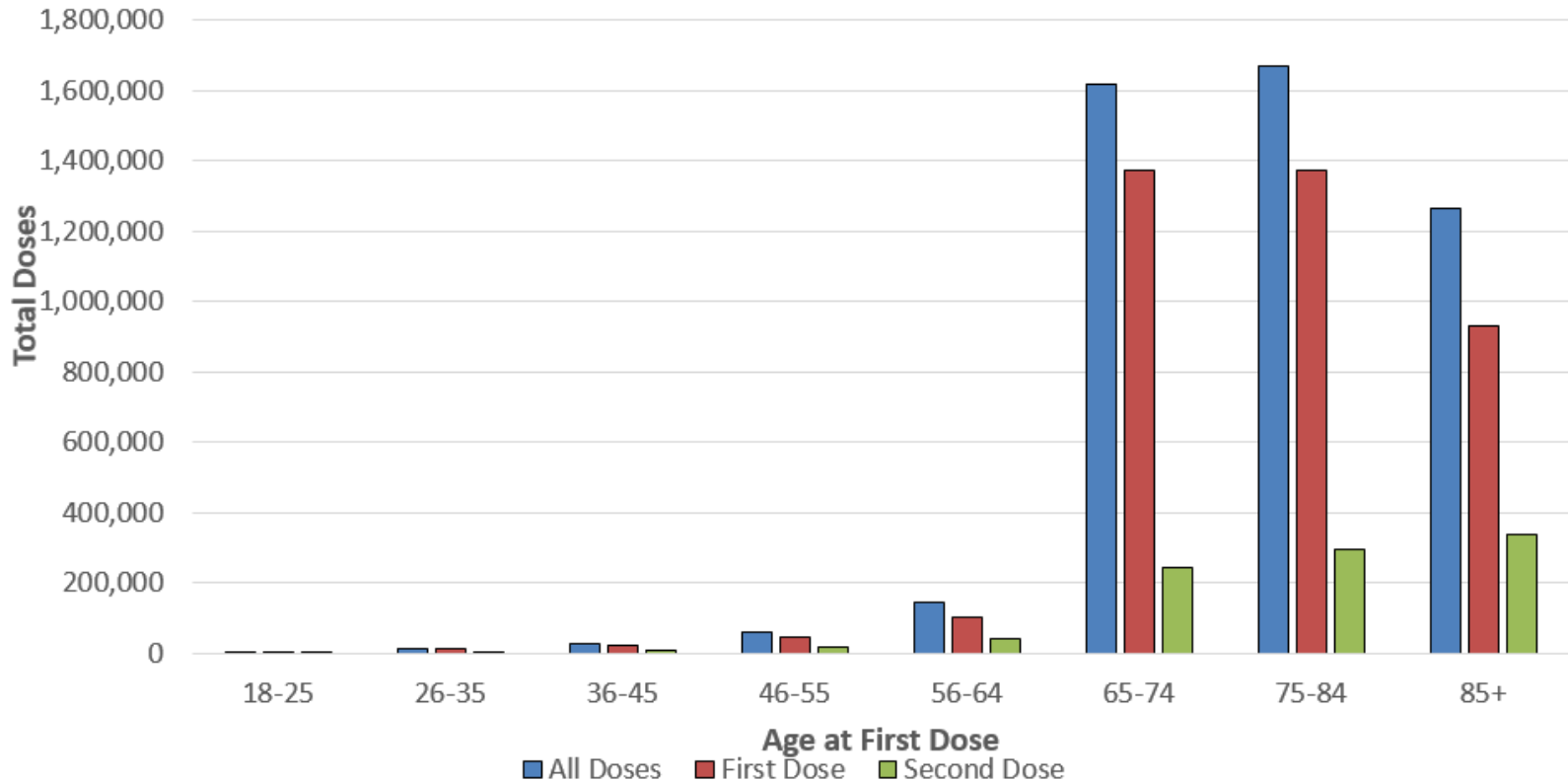


*12/11/2020-2/13/2021

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)

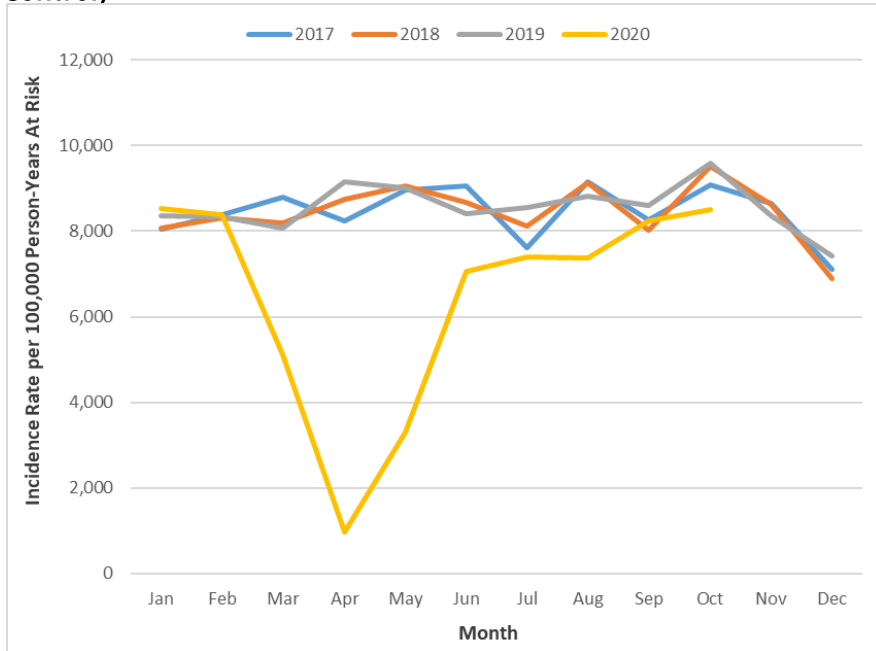
- COVID-19 pandemic may impact healthcare utilization and AESI rates during peri-COVID-19 period (March – October 2020)
- Evaluation for populations and time periods allows for more reliable safety signal detection and generation
- Assessment of background rates allows approximation of the true AESI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

Background Rates

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

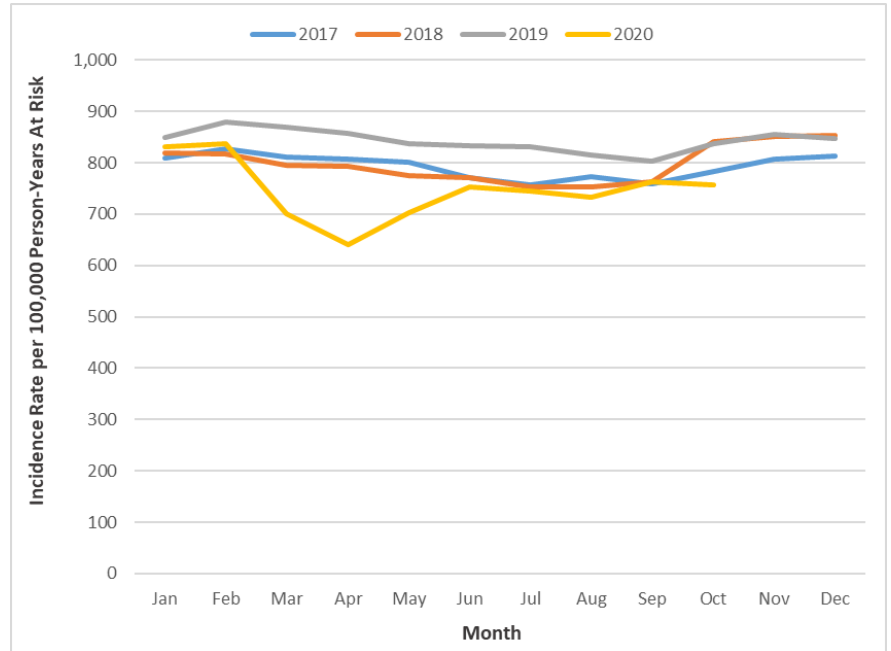


Colonoscopies for colorectal cancer screening (Negative Control)



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

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

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
 - Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease
 - anaphylaxis
 - thromboembolic events

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