Vaccines and Related Biological Products Advisory Committee October 14-15, 2021 Meeting Presentation Meeting

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Review of Post Authorization Safety Data for Janssen COVID-19 Vaccine

Narayan Nair, MD

Division Director– Division of Epidemiology,

Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, FDA

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Overview

- Passive Surveillance Safety Data from Vaccine Adverse Event Reporting System (VAERS)
  - Existing Safety Concerns
  - Potential Emerging Safety Concerns
- Summary of FDA Active Surveillance

Adverse Event Reporting under EUA

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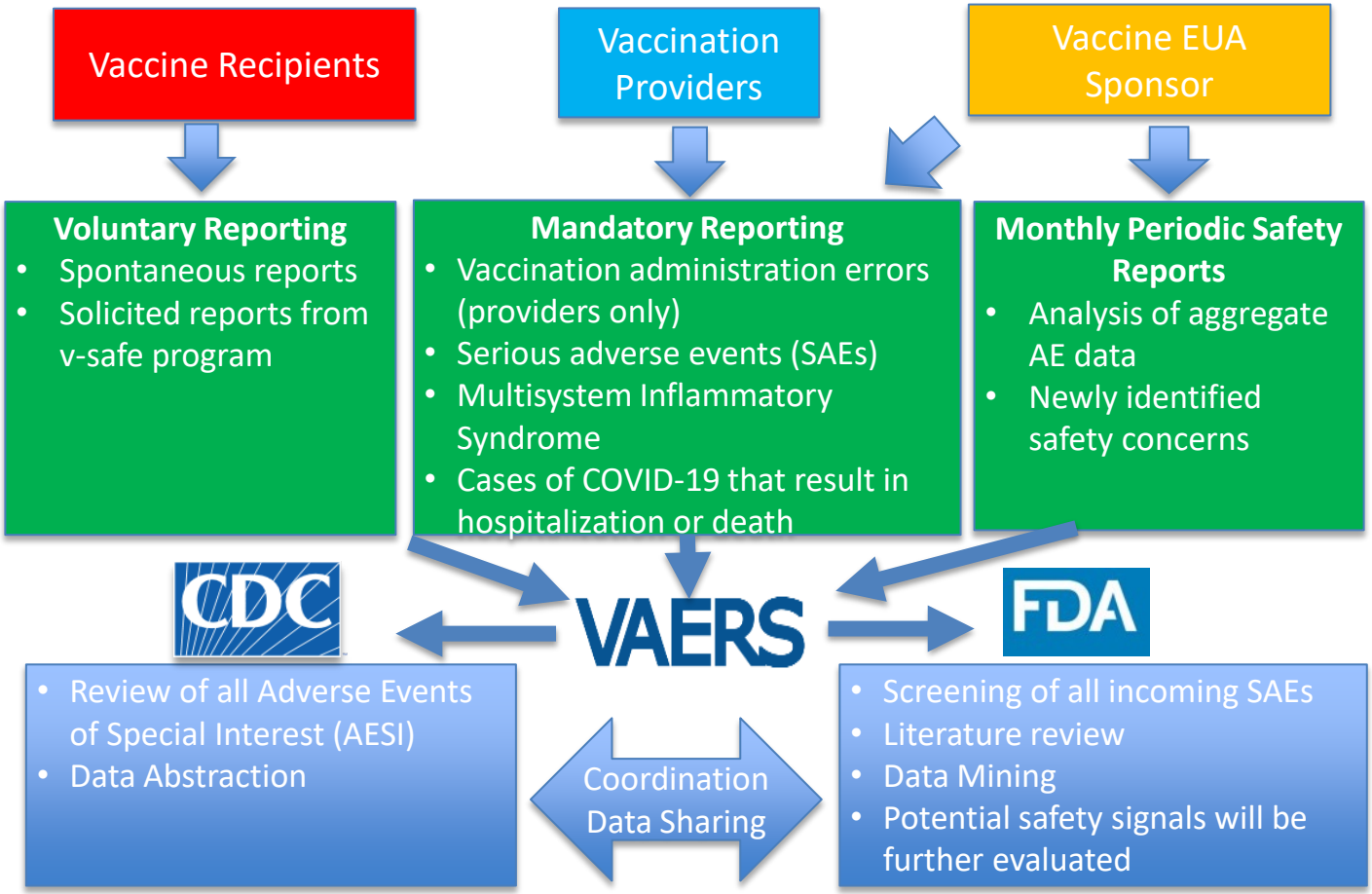

Vaccine Adverse Event Reporting System

- Passive surveillance of vaccines
- Nation's early warning system for vaccine safety
- VAERS accepts all reports regardless of the plausibility of the vaccine causing the event or the clinical seriousness of the event

Strengths

- Rapidly detects potential safety problems
- Potential detection of rare adverse events
- Open-ended for hypothesis generation
- Geographic diversity
- Capability to monitor production lots

Limitations

- Missing and/or inaccurate data
- Reported diagnoses are not verified
- Under-reporting
- Reporting bias (stimulated reporting)
- Absence of unvaccinated control group
- Inability to assess causation
- Not likely to detect long latency events

Reports to VAERS after Janssen COVID-19 Vaccine - 14,688,615 doses of vaccine administered (as of October 7, 2021)

Type of Reports	N
Serious non-fatal	12,699
U.S.	6,504
Foreign	6,195
Deaths	1,367
U.S.	957
Foreign	410
Non-serious	48,778
U.S.	48,672
Foreign	106
Total	62,844

Note: Serious non-fatal adverse events include life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability, or otherwise medically important conditions (OMIC).

Most Commonly Reported Adverse Events to VAERS after Janssen COVID-19 Vaccine - 14,688,615 doses of vaccine administered (data as of 10/7/21)

Adverse Event (MedDRA Preferred Term)*	N (%)
Headache	16,408 (26.1)
Pyrexia	13,939 (22.2)
Chills	11,717 (18.6)
Fatigue	11,202 (17.8)
Pain	10,553 (16.8)
Nausea	8,495 (13.5)
Dizziness	8,469 (13.5)
Pain In Extremity	6,265 (10.0)
Myalgia	4,931 (7.8)
Dyspnoea	4,230 (6.7)

*Terms are not mutually exclusive

Summary of Existing Safety Concerns - Thrombosis with Thrombocytopenia Syndrome

- Post authorization surveillance in VAERS identified reports of cerebral venous sinus thrombosis (CVST) and thrombosis with thrombocytopenia syndrome (TTS) after Janssen COVID-19 Vaccine*
- On 4/13/21, use of the vaccine in the US was paused because of concerns about a potential association with the vaccine.
- On 4/23/21, the Fact Sheets were updated to include a Warning about TTS and the pause was lifted
- As of 10/5/21, 47 cases of TTS have been confirmed after Janssen COVID-19 Vaccine
- Evaluation of this safety issue is ongoing

*See I, Su JR, Lale A, Woo EJ, Guh AY, Shimabukuro TT, Streiff MB, Rao AK, Wheeler AP, Beavers SF, Durbin AP. US case reports of cerebral venous sinus thrombosis with thrombocytopenia after Ad26. COV2. S vaccination, March 2 to April 21, 2021. JAMA. 2021 Apr 30

Summary of Existing Safety Concerns - Guillain-Barré Syndrome (GBS)

- Post-authorization surveillance in VAERS identified 130 reports of GBS after Janssen vaccine as of 7/24/2021
  - Observed reports > expected across multiple age groups, without respect to Brighton Collaboration criteria
  - Reporting rate for GBS is higher for Janssen than for mRNA vaccines
- Estimated observed-to-expected rate ratio was 4.18*
- On 7/12/21, EUA Fact Sheets were updated to include new information about GBS

* Woo EJ, Mba-Jonas A, Dimova RB, Alimchandani M, Zinderman CE, Nair N. Association of Receipt of the Ad26.COV2.S COVID-19 Vaccine With Presumptive Guillain-Barré Syndrome, February-July 2021. JAMA.

Summary of Potential Emerging Safety Concerns – Myocarditis and Pericarditis

- Post authorization surveillance of VAERS has identified a potential emerging safety concern regarding myocarditis and pericarditis
- As of 8/27/21, 93 reports of myocarditis/pericarditis in VAERS following the Janssen COVID-19 Vaccine (non-adjudicated)
- Based on preliminary review, the estimated observed-to-expected values were elevated for all adults 18 and older, with significant elevations in both sexes, various age strata, different risk windows, and different background rates with reporting rate ratio of 4.14 (3.20, 5.27)
- There were five death reports, all in people 30 or older and three in women
- Evaluation of myocarditis and pericarditis is ongoing

Summary of Potential Emerging Safety Concerns – Thromboembolic Events (TEE)

- Post authorization surveillance of VAERS has identified a potential emerging safety concern regarding TEE
- As described in the Fact Sheets, section 6.1 Clinical Trials Experience, numerical imbalances, with more events in vaccine than placebo recipients, were observed for TEE (deep vein thrombosis; pulmonary embolism; transverse sinus thrombosis with thrombocytopenia).
- As of 10/4/2021, 2,792 reports of TEE in VAERS following the Janssen COVID-19 Vaccine (non-adjudicated)
- At their meeting September 27, 2021, the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) concluded that there is a reasonable possibility that rare cases of venous thromboembolism are linked with Janssen COVID-19 Vaccine
- Evaluation of TEE is ongoing

Summary of Potential Emerging Safety Concerns – Immune Thrombocytopenia (ITP)

- Post authorization surveillance of VAERS has identified a potential emerging safety concern regarding ITP
- As of 10/4/2021, 185 reports of ITP in VAERS following the Janssen COVID-19 Vaccine (non-adjudicated)
- FDA preliminary analysis found the number observed exceeded the number expected with reporting rate ratio of 1.37 (1.18, 1.58)
- At their meeting September 27, 2021, the EMA PRAC assessed cases of ITP following the Janssen COVID-19 Vaccine and AstraZeneca COVID-19 Vaccine, and recommended updating the product information of both vaccines to include ITP
- Evaluation of ITP reports is ongoing

Active Surveillance in FDA BEST System: Near Real-Time Surveillance of Janssen COVID-19 Vaccine

Adverse Event of Special Interest (AESI)	Risk Window	Number of AESI post-vaccination (Number of Janssen Vaccine Doses)			Signal in Testing		
		CMS* (406,451)	Optum (197,553)	HCI (224,609)	CMS*	Optum	HCI
Guillan-Barre Syndrome	1-42	N<11	N<11	N<11	No	No	No
Unusual site thromboses** with thrombocytopenia	1-28	N<11	N<11	N<11	No	No	No
Common site thromboses*** with thrombocytopenia	1-28	139	N<11	N<11	No	No	No
Deep vein thrombosis	1-28	397	39	31	No	No	No
Pulmonary embolism	1-28	296	32	28	No	No	No
Myocarditis/Pericarditis	1-42	39	N<11	11	No	No	No
Immune thrombocytopenia	1-42	57	11	N<11	No	No	No

Data cutoff: Optum: 9/18; Health Core (HCI) :7/10, Medicare FFS (CMS): 9/11
Risk Window: An interval during which occurrence of the AESI will be included in the analyses
*CMS – 65 years and older
**cerebral and abdominal
***acute myocardial infraction, deep vein thrombosis, pulmonary embolism, hemorrhagic stroke, non-hemorrhagic stroke

Pharmacovigilance Plan

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

- ❑ Important identified risks
  - Anaphylaxis
  - Thrombosis with thrombocytopenia syndrome
  - Guillain-Barré syndrome
- ❑ Important potential risks
  - Vaccine-associated enhanced disease, including vaccine-associated enhanced respiratory disease
  - Venous thromboembolism
  - Immune thrombocytopenia
- ❑ 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

Summary of Post-authorization Safety Data following the Janssen Vaccine

- FDA and CDC continue to follow cases of GBS, and TTS reported to VAERS following Janssen COVID-19 vaccination
  - Information regarding these adverse events are currently communicated in EUA Fact Sheets
- FDA and CDC continue to assess cases of myocarditis, pericarditis, ITP, TEE reported to VAERS following Janssen COVID-19 vaccination
  - Preliminary analysis of unadjudicated cases in VAERS reveal an increased observed to expected ratio of myocarditis/pericarditis, and ITP
- FDA Near Real-Time Surveillance of 16 potential outcomes does not reveal safety signals for these adverse events at this time

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Backup Slides

VAERS Data after additional dose of Janssen COVID-19 vaccine - 8770 doses administered (data as of October 7)

Characteristics	n = 282
Sex[a]	
Male	136 (49%)
Female	143 (51%)
Seriousness[b]	
Serious	18 (6%)
Died	5 (1.8%)
Non-serious	264(94%)

[a] One report had missing sex, information.
[b] Serious adverse events include death, life-threatening events, hospitalization, prolongation of hospitalization, congenital anomaly, significant disability, or otherwise medically important conditions.

Most Commonly Reported Adverse Events after additional dose of Janssen COVID-19 vaccine - 8770 doses administered (data as of October 7, n=282)

Non-Serious Adverse Event (MedDRA Preferred Term)	N (%)
Interchange of vaccine products	69 (24%)
Extra dose administered	42 (15%)
No Adverse Event	42 (15%)
Headache	34 (12%)
Dizziness	25 (9%)

Description of Commercial Claims Data Sources in BEST Initiative

	Optum	HealthCore (HCI)
Overall description	Health insurance enrollment, demographic, and longitudinal health information for commercially insured and Medicare Advantage enrollees	Health insurance enrollment, demographic, medical claims, pharmacy claims and laboratory results from the HealthCore Integrated Research Environment (HIRE), which contains longitudinal health information for Anthem insured and Medicare Advantage enrolled individuals
Health plans	Optum affiliated health plans	Anthem
Time period	December 2017-Present	2010-Present
Average Number of Annual Enrollees	~14.5 million	20-25 million
Data lag	~ 2 months for IP at 90% completeness	The data lag is 3 months for complete data and is 1-3 months for pharmacy dispensings and early settled outpatient claims
Limitations	Claims data was sourced before the adjudication process (which allowed for data to be analyzed more quickly – data is available for claims with dates of service through 9/18)	Data is currently only available for claims with dates of service through 7/10 for the RCA and through 8/5 for the descriptive analysis of booster vaccinations

FDA BEST Initiative: Booster Vaccinations

Brand and Dose	CMS (Data through 9/4)		Optum (Data through 9/18)		HCI (Data through 8/5)	
	Number of Vaccinations	Percentage of Total Booster Vaccinations*	Number of Vaccinations	Percentage of Total Booster Vaccinations*	Number of Vaccinations	Percentage of Number of Vaccinations*
Total Booster Vaccinations	***82,129***	***100***	***67,698***	***100***	***6,603***	***100***
Dose 2 following Janssen	**2,242**	**2.6**	**5,163**	**7.6**	**963**	**14.6**
Janssen	1,051	1.2	1,275	1.9	179	2.7
Moderna	603	0.7	1,546	2.3	409	6.2
Pfizer	588	0.7	2,342	3.5	375	5.7
Dose 3 following Moderna Dose 2	**44,014**	**51.7**	**28,514**	**42.1**	**3,255**	**49.3**
Janssen	274	0.3	115	0.2	37	0.6
Moderna	42,085	49.4	27,130	40.1	2,876	43.6
Pfizer	1,655	1.9	1,269	1.9	342	5.2
Dose 3 following Pfizer Dose 2	**38,873**	**45.7**	**34,021**	**50.3**	**2,385**	**36.1**
Janssen	330	0.4	138	0.2	37	0.6
Moderna	1,619	1.9	1,435	2.1	769	11.6
Pfizer	36,924	43.4	32,448	47.9	1,579	23.9

*Strata percentages may not sum to 100% due to rounding

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 Follow-up for Safety:

- Post-authorization, observational studies to assess the safety of Ad26.COV2.S using electronic health record (EHR) databases in Europe and the US
- Objective: to assess the occurrence of pre-specified AESIs within specific risk periods

❑ Real World Effectiveness Study:

- Prospective cohort study [info pending]
- Evaluate vaccine effectiveness [info pending]
- Vaccinated subjects: receipt of Janssen COVID-19 Vaccine in 2021
- Comparator group: [info pending]