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**Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)**
(b) (6)

PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM ADDENDUM

From: (b) (6)

To: (b) (6)
(OVRR), CBER, FDA

Through: (b) (6)
CBER, FDA

Subject: Labeling change to include new safety information for myocarditis and align with ongoing class safety labeling change (SLC) for approved mRNA COVID-19 vaccines
Safety-related postmarketing study milestone updates for PMR/PMCs

Sponsor: Moderna

Product: MNEXSPIKE (COVID-19 Vaccine, mRNA)

Application Type / Number BLA / STN 125835/0

1 OBJECTIVE

The purpose of this addendum is to review specific issues subsequent to and not addressed by the original pharmacovigilance review memorandum for MNEXSPIKE. Please refer to the original BLA pharmacovigilance review memorandum under STN125835/0, and to the Appendix for the list of materials reviewed.

2 CLASS SAFETY LABELING CHANGE (SLC) FOR NEW SAFETY INFORMATION (NSI)

As noted in the original BLA pharmacovigilance review memorandum under STN125835/0 and the SLC notification letter under STN125752/272, FDA notified Moderna of class SLC for approved mRNA COVID-19 vaccines including SPIKEVAX. FDA communicated comments and revisions to include new safety information (NSI) for myocarditis in the MNEXSPIKE package insert (PI) and patient package insert (PPI), and align with ongoing class safety labeling change (SLC) for approved mRNA COVID-19 vaccines (please see Table 1). These revisions for MNEXSPIKE were communicated to Moderna in information request (IR) number 47 dated May 5, 2025. The initial response for the SLC revisions was submitted to STN125835/0.55. Please see below table summarizing the revisions to the safety labeling language.

Table 1. Summary of Revisions to Safety Labeling Changes

Section	Applicant's Proposed Changes to FDA's Draft NSI (additions bolded and underlined, deletions in strikethrough)	FDA Responses to Applicant
Full Prescribing Information (FPI) – Warnings and Precautions	5.2 Myocarditis and Pericarditis Postmarketing data with authorized or approved mRNA COVID-19 vaccines have demonstrated increased risks of myocarditis and pericarditis, with onset of symptoms typically in the first week following vaccination. Based on analyses of commercial health insurance claims data from inpatient and outpatient settings, the estimated incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines in individuals 6 months through 64 years of <u>age was a very rare event (<1 case per 10,000 doses) with</u> approximately 8 cases per million doses. The highest estimated incidence was in males 16	See comments under IR #52 issued 5.27.2025 (Sponsor response submitted to STN125835/0.62), and IR# 55 issued May 29, 2025 (sponsor response submitted via email on May 30, 2025 and pending submission to EDR) and Appendices. Of note, IR# 55 included additional analyses from the (b) (6) [REDACTED] on the estimated incidence of myocarditis and/or pericarditis following

	through 25 years of age (approximately 38 cases per million doses). Although some individuals with myocarditis and/or pericarditis following administration of mRNA COVID-19 vaccines have required intensive care support, available data suggest that individuals typically have resolution of symptoms within a few days with conservative management. Follow-up information on cardiovascular outcomes in hospitalized patients who had been diagnosed with COVID-19 vaccine-associated myocarditis is available from a longitudinal retrospective observational study. Most of these patients had received a two-dose primary series of an mRNA COVID-19 vaccine prior to their diagnosis. In this study, at a median follow-up of approximately 5 months post-vaccination, persistence of abnormal cardiac magnetic resonance imaging (CMR) findings that are a marker for myocardial injury was common. The clinical and prognostic significance of these CMR findings is not known (1) [see Adverse Reactions (6.2)]. Information is not yet available about potential long-term sequelae of myocarditis or pericarditis following administration of mRNA COVID-19 vaccines. The Centers for Disease Control and Prevention (CDC) has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html).	administration of the 2023-2024 Formula of mRNA COVID-19 vaccines to support the label changes were shared with the applicant on May 29, 2025, and this new analysis is attached to this memo.
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FPI – Postmarketing Experience	6.2 POSTMARKETING EXPERIENCE Postmarketing data with authorized or approved mRNA COVID-19 vaccines have demonstrated increased risks of myocarditis and pericarditis [see Warnings and Precautions (5.2)]. Cardiovascular outcomes in patients diagnosed with mRNA COVID-19 vaccine-associated myocarditis In a longitudinal retrospective observational cohort study across 38 hospitals in the U.S., information on cardiovascular outcomes was collected on 333 patients 5 through 29 years of age who had been diagnosed with COVID-19 vaccine-associated myocarditis. Among these patients, 322 were confirmed to have received an mRNA COVID-19 vaccine encoding the S glycoprotein of the Original SARS-CoV-2. Of 331 patients, 278 had onset of symptoms following the second dose of a primary series, 33 following the first dose of a primary series, and 20 following a first booster dose (1). Among 307 patients who had been diagnosed with COVID-19 vaccine-associated myocarditis for whom follow-up information was available, 89 reported cardiac symptoms at a median follow-up of 91 days (interquartile range 25-186 days) post vaccination (1). Initial gadolinium-enhanced cardiac magnetic resonance imaging (CMR) was performed on 216 patients, of whom 177 had late gadolinium enhancement (LGE), a marker of myocardial injury. Among 161 patients who had LGE on initial CMR and who had a follow-up gadolinium-enhanced CMR at a median follow up of 159 days (interquartile range 78-253	See comments under IR #52 Issued 5.27.2025 and Sponsor response submitted to STN125835/0.62.
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	days), 98 had persistence of LGE. Overall, the severity of LGE decreased during follow-up. The clinical and prognostic significance of these CMR findings is not known (1). Limitations of this study include potential selection bias towards patients with more severe myocarditis who are more likely to be hospitalized and have CMR, variability in diagnostic testing, and variability in follow up (1).	
Information for Recipients and Caregivers	Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received mRNA COVID-19 vaccines. In most of these people, symptoms began within a week following vaccination. Based on available data, <u>the estimated rate</u>reports of myocarditis and/or pericarditis from 1 through 7 days after getting a dose of the 2023-2024 Formula of mRNA COVID-19 vaccines was <u>were very rare with</u> approximately 8 <u>cases</u> per million doses in people 6 months through 64 years of age; the highest <u>estimated rate</u>occurrence was in males 16 through 25 years of age (<u>with</u> approximately 38 cases of myocarditis and/or pericarditis per million doses). In most people who have had myocarditis or pericarditis after receiving an mRNA COVID-19 vaccine, symptoms have gone away a few days after receiving treatment with medicines used to reduce inflammation. In a study, follow up information was collected on people who developed myocarditis after receiving the original formula of a COVID-19 vaccine; most people had received an mRNA COVID-19 vaccine. Some people in the study reported having heart symptoms	See comments under IR #52 Issued 5.27.2025 and Sponsor response submitted to STN125835/0.62.

	approximately 3 months after developing myocarditis. Some people in the study had heart MRIs (scans that show detailed images of the heart muscle) initially after developing myocarditis and again approximately 5 months later. The initial and follow-up heart MRIs commonly showed signs of injury to the heart muscle, with improvement over time in most people. It is not known if these heart MRI findings might predict long-term heart effects of myocarditis. Studies are underway to find out if there are long-term heart effects in people who have had myocarditis after receiving an mRNA COVID-19 vaccine.	
Sponsor revisions to the above comments were submitted to STN125835/0.62 and discussed below.		
FPI – Warnings and Precautions	5.2 Myocarditis and Pericarditis Postmarketing data with authorized or approved mRNA COVID-19 vaccines have demonstrated increased risks of myocarditis and pericarditis, with onset of symptoms typically in the first week following vaccination. <u>The observed risk has been highest in males 12 years through 24 years of age.</u> Based on analyses of commercial health insurance claims data from inpatient and outpatient settings, the estimated incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines in individuals 6 months through 64 years of age was approximately 8 cases per million doses. The highest estimated incidence was in males 16 years through 25 years of age (approximately 38 cases per million doses). Although some individuals with myocarditis and/or pericarditis following administration of mRNA COVID-19 vaccines have required intensive care	See comments under IR #55 Issued 5.29.2025

	support, available data suggest that individuals typically have resolution of symptoms within a few days with conservative management. Follow-up information on cardiovascular outcomes in hospitalized patients who had been diagnosed with COVID-19 vaccine-associated myocarditis is available from a longitudinal retrospective observational study. Most of these patients had received a two-dose primary series of an mRNA COVID-19 vaccine prior to their diagnosis. In this study, at a median follow-up of approximately 5 months post-vaccination, persistence of abnormal cardiac magnetic resonance imaging (CMR) findings that are a marker for myocardial injury was common. The clinical and prognostic significance of these CMR findings is not known (1) [see Adverse Reactions (6.2)]. Information is not yet available about potential long-term sequelae of myocarditis or pericarditis following administration of mRNA COVID-19 vaccines. The Centers for Disease Control and Prevention (CDC) has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html).	
FPI – Postmarketing Experience	6.2 POSTMARKETING EXPERIENCE Postmarketing data with authorized or approved mRNA COVID-19 vaccines have demonstrated increased risks of myocarditis and pericarditis [see Warnings and Precautions (5.2)].	See comments under IR #55 Issued 5.29.2025

	Cardiovascular outcomes in patients diagnosed with mRNA COVID-19 vaccine-associated myocarditis In a longitudinal retrospective observational cohort study across 38 hospitals in the U.S., information on cardiovascular outcomes was collected on 333 patients 5 <u>years</u> through 29 years of age who had been diagnosed with COVID-19 vaccine-associated myocarditis. Among these patients, 322 were confirmed to have received an mRNA COVID-19 vaccine encoding the S glycoprotein of the Original SARS-CoV-2. Of 331 patients, 278 had onset of symptoms following the second dose of a primary series, 33 following the first dose of a primary series, and 20 following a first booster dose (1). Among 307 patients who had been diagnosed with COVID-19 vaccine-associated myocarditis for whom follow-up information was available, 89 reported cardiac symptoms at a median follow-up of 91 days (interquartile range 25-186 days) post-vaccination (1). Initial gadolinium-enhanced cardiac magnetic resonance imaging (CMR) was performed on 216 patients, of whom 177 had late gadolinium enhancement (LGE), a marker of myocardial injury. Among 161 patients who had LGE on initial CMR and who had a follow-up gadolinium-enhanced CMR at a median follow-up of 159 days (interquartile range 78-253 days), 98 had persistence of LGE. Overall, the severity of LGE decreased during follow-up. The clinical and prognostic significance of these CMR findings is not known (1). Limitations of this study include potential selection bias towards patients with more	
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	severe myocarditis who are more likely to be hospitalized and have CMR, variability in diagnostic testing, and variability in follow-up ⁽¹⁾ .	
Information for Recipients and Caregivers	Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received mRNA COVID-19 vaccines. <u>Myocarditis and pericarditis following mRNA COVID-19 vaccines have occurred most commonly in males 12 years through 24 years of age.</u> In most of these people, symptoms began within a week following vaccination. Based on available data, the estimated rate of myocarditis and/or pericarditis from 1 through 7 days after getting a dose of the 2023-2024 Formula of mRNA COVID-19 vaccines was approximately 8 <u>cases</u> per million doses in people 6 months through 64 years of age; the highest estimated rate was in males 16 <u>years</u> through 25 years of age (approximately 38 cases of myocarditis and/or pericarditis per million doses). In most people who have had myocarditis or pericarditis after receiving an mRNA COVID-19 vaccine, symptoms have gone away a few days after receiving treatment with medicines used to reduce inflammation. In a study, follow-up information was collected on people who developed myocarditis after receiving the original formula of a COVID-19 vaccine; most people had received an mRNA COVID-19 vaccine. Some people in the study reported having heart symptoms approximately 3 months after developing myocarditis. Some people in the study had heart MRIs (scans that show detailed images of the heart muscle) initially after developing myocarditis and again approximately 5 months later. The initial	See comments under IR #55 Issued 5.29.2025

	and follow-up heart MRIs commonly showed signs of injury to the heart muscle, with improvement over time in most people. It is not known if these heart MRI findings might predict long-term heart effects of myocarditis. Studies are underway to find out if there are long-term heart effects in people who have had myocarditis after receiving an mRNA COVID-19 vaccine.	
Sponsor revisions to the above comments were submitted by email on May 30, 2025.		
FPI – Warnings and Precautions	5.2 Myocarditis and Pericarditis Postmarketing data with authorized or approved mRNA COVID-19 vaccines have demonstrated increased risks of myocarditis and pericarditis, with onset of symptoms typically in the first week following vaccination. The observed risk has been highest in males 12 years through 24 years of age. Based on analyses of commercial health insurance claims data from inpatient and outpatient settings, the estimated unadjusted incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines was approximately 8 cases per million doses in individuals 6 months through 64 years of age and approximately 25 cases per million doses in males 12 years through 25 years of age. Although some individuals with myocarditis and/or pericarditis following administration of mRNA COVID-19 vaccines have required intensive care support, available data suggest that individuals typically have resolution of symptoms within a few days with conservative management. Follow-up information on cardiovascular outcomes in hospitalized patients who	Not applicable.

	had been diagnosed with COVID-19 vaccine-associated myocarditis is available from a longitudinal retrospective observational study. Most of these patients had received a two-dose primary series of an mRNA COVID-19 vaccine prior to their diagnosis. In this study, at a median follow-up of approximately 5 months post-vaccination, persistence of abnormal cardiac magnetic resonance imaging (CMR) findings that are a marker for myocardial injury was common. The clinical and prognostic significance of these CMR findings is not known¹ [see Adverse Reactions (6.2)]. Information is not yet available about potential long-term sequelae of myocarditis or pericarditis following administration of mRNA COVID-19 vaccines. The Centers for Disease Control and Prevention (CDC) has published considerations related to myocarditis and pericarditis after vaccination, including for vaccination of individuals with a history of myocarditis or pericarditis (https://www.cdc.gov/vaccines/covid-19/clinical-considerations/myocarditis.html).	
FPI – Postmarketing Experience	Not applicable. Only minor formatting changes were made.	Not applicable.
Information for Recipients and Caregivers	Not applicable. The Sponsor accepted the revisions proposed by FDA in IR #55 Issued 5.29.2025.	Not applicable.

3 POSTMARKETING STUDIES

IR number 51 dated May 21, 2025 communicated FDA's expectation for an updated indication for MNEXSPIKE that is consistent with FDA's current policy position on COVID-19 vaccines. In the response to FDA's April 11, 2025 IR number 37 submitted to STN125835/0.43 on April 18, 2025, the Sponsor acknowledged two Postmarketing Requirement (PMR) studies and one Postmarketing Commitment (PMC) study. The

Sponsor was requested to confirm the milestones or revise if needed for each of these studies based on the May 21, 2025 IR number 51 for a revised indication. In the IR response submitted to STN125835/0.62, the Sponsor proposed to revise the milestones for the PMR study mRNA-1283-P901 *Postmarketing safety of the mRNA-1283 vaccine in the United States* to ensure the feasibility of obtaining three full seasons with lags in the databases included in the protocol. The revised milestones are as follows:

Final Protocol Submission: June 30, 2025

Study Completion Date: March 30, 2029

Final Study Submission: September 30, 2029

Reviewer comment: The Sponsor's proposed milestone revisions are acceptable. The milestones for the other two postmarketing studies are unchanged as documented in the (b) (6) Pharmacovigilance memorandum under STN125835/0.

4 (b) (6) ASSESSMENT AND RECOMMENDATIONS

No changes to the Pharmacovigilance Plan are warranted. Please see the (b) (6) Pharmacovigilance memorandum under STN125835/0 for the pharmacovigilance recommendations, and the final version of the package insert submitted by the sponsor for the final agreed-upon language for the label.

APPENDIX

Materials Reviewed

Table A1: Materials reviewed in support of this assessment

Date	Source	Document Type	Document(s) Reviewed
May 8, 2025	Sponsor	STN125835/0.55	Module 1.11.3, Response to Myocarditis/Pericarditis Labeling Changes Dated 08May2025 Module 1.114.1.3 Draft Prescribing Information; Draft Patient Information
May 28, 2025	Sponsor	STN125835/0.62	Module 1.11.3, Response to IR#52 Module 1.114.1.3 Draft Prescribing Information; Draft Patient Information
May 30, 2025	Sponsor	Email	Revised Prescribing Information and Patient Information

FDA responses during labeling negotiations to include NSI for myocarditis in Mnexspike USPI

IR #52 (issued 5.27.2025; response received 5.28.25)

We refer to your response document “Sponsor Response to Requested Safety Labeling Sections for mRNA-1283” submitted on 8 May 2025 under Amendment 55 (Seq 0056) to STN 125835/0 for MNEXSPIKE in response to our Information Request #47 issued on 6 May 2025.

1. In your 8 May 2025 response document, you request that “the Agency provide additional supporting data for the proposed modifications, including the adjustment of the age group with the highest risk of myocarditis and/or pericarditis following administration of mRNA COVID-19 2023–2024 Formula from 18–24 years to 16–25 years, and the frequency of COVID-19 vaccine-associated myocarditis and/or pericarditis for the mRNA COVID-19 2023 – 2024 vaccine.”

CBER Comment:

The estimated incidence rates of myocarditis and/or pericarditis from (b) (6) are not intended as an “adjustment of the age group with the highest risk of myocarditis and/or pericarditis.” Rather, they provide numerical estimates of the incidence of myocarditis and/or pericarditis following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines which we think is important to clinical decision making and should be included in the Prescribing Information. FDA is actively discussing the most appropriate age range for the analyses of incidence rates and we will provide additional information shortly.

Please note that we do not concur with your further qualification of incidence rates. Non-specific terms such as “very rare” can be misleading and should be avoided in characterizing adverse reactions in Prescribing Information.

Upon further consideration, we request that in Highlights, Warnings and Precautions and in the Full Prescribing Information Section 5.2, before the estimated incidence rates from (b) (6) you include the following statement:

“The observed risk has been highest in males 12 years through 24 years of age.”

We also request that in the Patient Package Insert, you include the following statement after “Myocarditis (inflammation of the heart muscle) and pericarditis (inflammation of the lining outside the heart) have occurred in some people who have received mRNA COVID-19 vaccines:”

“Myocarditis and pericarditis following mRNA COVID-19 vaccines have occurred most commonly in males 12 years through 24 years of age.”

2. Regarding the findings from Cardiac manifestations and outcomes of COVID-19 vaccine-associated myocarditis in the young in the USA: longitudinal results from the Myocarditis After COVID Vaccination (MACiV) multicenter study (Jain et al., 2024):
 - a. You indicate in your 8 May 2025 response document that “The Sponsor has carefully reviewed the Agency’s request to include findings from the study referenced in Jain 2024 as new safety information (NSI). The Sponsor notes that this study has important limitations (which are clearly acknowledged by the authors) that significantly impact the applicability and interpretations of its findings, particularly within product information for providers.”

CBER Comment:

Limitations of the MACiV study, including selection bias, the retrospective study design, and the unknown clinical significance of CMR findings, have been acknowledged in the safety labeling change (SLC) language that was provided to you by FDA. Please see FDA proposed language in:

- Section 5.2 Myocarditis and Pericarditis:
 - “The clinical and prognostic significance of these CMR findings is not known (1) [see Adverse Reactions (6.2)].”
 - “Information is not yet available about potential long-term sequelae of myocarditis or pericarditis following administration of mRNA COVID-19 vaccines.”
- Section 6.2 Postmarketing Experience: “The clinical and prognostic significance of these CMR findings is not known (1). Limitations of this study include potential selection bias towards patients with more severe myocarditis who are more likely to be hospitalized and have CMR, variability in diagnostic testing, and variability in follow-up (1).”

Additionally, regarding variability in imaging protocols across study sites, the CMR findings underwent additional verification by site co-investigators with expertise with this modality. Furthermore, the lead author of the study is a noted national expert on CMR and its use in the pediatric population. The absence of biopsy data is acknowledged in the publication which is referenced in the SLC.

- b. Regarding “Information around the outcomes of C-VAM is already included in the mRNA-1283 product information, “Although some individuals with myocarditis and/or pericarditis following administration of mRNA COVID-19 vaccines have required intensive care support, available data suggest that individuals typically have resolution of symptoms within a few days with conservative management.*

Information is not yet available about potential long-term sequelae of myocarditis or pericarditis following administration of mRNA COVID-19 vaccines.

Adding further information, particularly around cardiac magnetic resonance imaging (CMR) findings such as late gadolinium enhancement (LGE) without a clear understanding of its long-term prognostic value could create unnecessary concern among healthcare providers and lead to additional, potentially unwarranted, testing in patients. The current body of evidence does not establish a clinically actionable correlation between LGE and adverse outcomes in postvaccination myocarditis. It is also important to note that Gadolinium carries with it risks (e.g., nephrogenic systemic fibrosis, anaphylaxis), making it difficult to rationalize the need for additional gadolinium-enhanced MRIs if there are no persistence symptoms, and/or if follow up CMR data is considered normal.”

CBER Comment:

In addition to information on clinical follow-up within a few days postvaccination, the MACiV study provides important NSI on longer-term follow-up of individuals diagnosed with myocarditis following administration of mRNA COVID-19 vaccines, namely information on cardiac symptoms at a median follow-up of 91 days postvaccination and information on CMR findings at a median follow-up of 159 days.

As noted in the publication by Jain et al, in other conditions, including viral myocarditis, LGE by CMR can be a harbinger of poor outcomes in the future. The publication also notes that LGE by CMR is increasingly used to characterize acute myocardial injury and chronic scarring in childhood myocarditis. Thus, although there are uncertainties about the clinical and prognostic significance of the CMR findings (as conveyed in the SLC language we provided), we think it is important to convey the findings in the Prescribing Information. The SLC language we provided does not include any recommendations on use of CMR in diagnosis or follow-up of patients who present with myocarditis following administration mRNA COVID-19 vaccines. Such decisions should be made by healthcare providers for individual patients.

While we acknowledge study limitations, we believe the study findings meet criteria for NSI and we strongly urge you to include FDA proposed language for the class SLC for mRNA COVID-19 vaccines (as conveyed in the April 18, 2025, Safety Labeling Change Notification letter for SPIKEVAX), in the MNEXSPIKE USPI. Following the completion of Moderna conducted studies to further characterize myocarditis and pericarditis, and review of the final study reports, additional updates to the USPI may be considered in the future.

IR #55 (issued 5.29.2025; response received 5.30.25)

FDA provided the applicant with the attached presentation, which includes additional analyses from the (b) (6) on the estimated incidence of myocarditis and/or pericarditis following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines to support the label changes below.

In PI, section 5.2, FDA asked the applicant to **replace**:

“Based on analyses of commercial health insurance claims data from inpatient and outpatient settings, the estimated incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA

COVID-19 vaccines in individuals 6 months through 64 years of age was approximately 8 cases per million doses. The highest estimated incidence was in males 16 years through 25 years of age (approximately 38 cases per million doses)."

with:

"Based on analyses of commercial health insurance claims data from inpatient and outpatient settings, the estimated unadjusted incidence of myocarditis and/or pericarditis during the period 1 through 7 days following administration of the 2023-2024 Formula of mRNA COVID-19 vaccines was approximately 8 cases per million doses in individuals 6 months through 64 years of age and approximately 25 cases per million doses in males 12 through 25 years of age."