Center for Biologics Evaluation and Research (CBER)

CBER Surveillance Program Biologics Effectiveness and Safety Initiative (BEST)

ADDENDUM
Validation of Algorithms to Identify Multisystem Inflammatory Syndrome in Children (MIS-C) in Administrative Claims Data

July 12, 2024

Note: Implementation of this protocol is on hold indefinitely. Please see protocol addendum.

STUDY TEAM

FDA/CBER	
Joann F. Gruber, PhD, MSPH Azadeh Shoaibi, PhD, MHS Patricia C. Lloyd, PhD, ScM Tainya C. Clarke, PhD, MPH, MSc	Sylvia Cho, PhD, MHS Richard A. Forshee, PhD Steven A. Anderson, PhD, MPP
Acumen, LLC	
Elizabeth Smith, BS Emily Lassman, MS Zhiruo Wan, MS Nirabh Koralia, BS Vincent Varvaro, MPH Sizhe Fan, BA	Mao Hu, BS Sandia Akhtar, BS Yixin Jiao, MS Yoganand Chillarige, MPA Myrna Cozen, PhD Thomas MaCurdy, PhD
Optum	
Kandace Amend, PhD, MPH Grace Yang, MPA, MA Lauren Peetluk, PhD, MPH Jie Deng, MS	Jennifer Song, MA, MURP C. Robin Clifford, MS John Seeger, DrPH, PharmD Elizabeth J. Bell, PhD, MPH
CVS Health	
Cheryl N. McMahill-Walraven, MSW, PhD Djeneba Audrey Djibo, PhD, MSBME Eugenio Abente, PhD Jon Deshazo, PhD, MPH	Ana M. Martinez-Baquero, MA Aparna Srikanti, MSc Vaibhav Sharma, MS
Carelon Research/IQVIA	
Daniel C. Beachler, PhD, MHS Alex Secora, PhD	Christian Reich, PhD, MD Michael Goodman, PhD

Note: Implementation of this protocol is on hold indefinitely. Please see protocol addendum.

VERSION CONTROL

Version	Description	Date
1.0	Final 508-remediated version of protocol for posting	10/18/2023
2.0	Added protocol addendum	07/12/2024

Note: Implementation of this protocol is on hold indefinitely. Please see protocol addendum.

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1. Background

The 2019 coronavirus respiratory illness (COVID-19) caused by the SARS-CoV-2 virus was first reported in December 2019.[1] While COVID-19 is typically mild in children, reports of children with elevated laboratory markers of inflammation similar to Kawasaki disease or toxic shock syndrome were first reported in April 2020 in the United Kingdom, followed shortly by reports of similar cases in other countries.[2,3,4] The condition became known as Multisystem Inflammatory Syndrome in Children (MIS-C), and in May 2020, the Centers for Disease Control and Prevention (CDC) issued a health advisory asking clinicians to report suspected cases to local, state, or territorial health department public health jurisdictions.[5]

MIS-C has since been characterized as a rare complication of COVID-19 in children, affecting <1% of children ages 21 years and younger with COVID-19.[6] There are currently no confirmatory laboratory tests available to diagnose MIS-C or to distinguish it from other inflammatory syndromes. Trends from ongoing surveillance have suggested that presenting features may include fever, elevated laboratory markers of inflammation, and multiple organ system dysfunction including cardiovascular, mucocutaneous, gastrointestinal, hematologic, neurologic, and renal involvement.[6] MIS-C patients often require admission to an intensive care unit (ICU) or extracorporeal membrane oxygenation (ECMO), and there has been an estimated 1-2% mortality rate among patients with MIS-C.[7]

Throughout the COVID-19 pandemic, observational research on MIS-C using administrative claims data has been limited, and no studies to date have validated claims-based algorithms for identifying MIS-C in claims databases using medical record review. This study aims to identify algorithms to select potential MIS-C cases in administrative claims databases and validate the algorithms through the objectives described in Section 2.

2. Objectives

The protocol describes the methods to achieve the following study objectives:

- To evaluate the positive predictive value (PPV) of claims-based algorithms for MIS-C in the commercially insured population aged 21 years old or younger
- To describe demographic and clinical characteristics of identified and chart-confirmed MIS-C cases

3. Data Sources

The current study will use administrative claims databases contributing to the CBER Biologics Effectiveness and Safety (BEST) Initiative, including those from CVS Health, Optum (pre-adjudicated claims), and Carelon Research. Table 1 summarizes some select characteristics of the administrative claims data sources used in this study.

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Table 1. Description of Administrative Claims Data Sources

Data Source	Claims Type	Update Frequency	Data Lag*	Population Enrolled Ages 0-21 Years**
CVS Health	Fully Adjudicated	Monthly	Approximately 80% data completeness in 3-4 months for inpatient claims, 2-3 months for outpatient claims, and 1-2 months for professional claims	0-4 years: > 0.8 million 5-11 years: > 1.2 million 12-17 years: > 1.2 million 18-25 years: > 2.8 million
Optum pre-adjudicated claims	Pre-Adjudicated	Bi-Weekly	Approximately 80% data completeness in 1-2 months for inpatient, outpatient, and professional claims	0-4 years: > 0.8 million 5-11 years: > 1.1 million 12-17 years: > 1.0 million 18-21 years: > 0.6 million
Carelon Research	Fully Adjudicated	Monthly	Approximately 80% data completeness in 2-3 months for inpatient claims and 1-2 months for outpatient and professional claims	0-4 years: > 1.0 million 5-11 years: > 1.7 million 12-17 years: > 1.6 million 18-25 years: > 2.8 million

** Data lag is based on 2020 claims delay distribution*

*** Enrollment numbers from CVS Health and Carelon Research are from 2021 and enrollment numbers from Optum are from 2022; enrollment information from CVS Health and Carelon Research contains numbers of enrollees through age 25 years*

4. Study Period

The beginning of the study period will be March 1, 2020, corresponding to the approximate acknowledged start of the COVID-19 pandemic in the United States. The study period will continue through the date for which 90% complete claims data are available for each data source at the time of data extraction. Due to lack of historical MIS-C data, 90% completeness will be estimated using a different outcome identified in the inpatient setting for which historical data are available.

5. Study Population

The study population will include people aged 0–21 years who are enrolled in the aforementioned commercial insurance plans who meet the criteria for the MIS-C claims-based algorithms (Section 6) during the study period and have at least 180 days of continuous enrollment prior to the record of the MIS-C diagnosis code in the claims databases.

6. Claims-Based Algorithms for MIS-C

We have identified two algorithms that we will use to select potential cases of MIS-C in administrative claims databases using International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes available for MIS-C (Table 2).

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Table 2. ICD-10-CM Diagnosis Codes for MIS-C

ICD-10-CM Code	Description	Effective Date
M35.8	Other specified systemic involvement of connective tissue	Prior to January 1, 2021
M35.81	Multisystem Inflammatory Syndrome	January 1, 2021
M35.89	Other specified systemic involvement of connective tissue	January 1, 2021

The first algorithm will be used to capture cases between March and December 2020. This algorithm uses the only diagnosis code that was available during this time period to identify potential MIS-C cases in claims data (i.e., ICD-10-CM code M35.8). Beginning in January 1, 2021, an additional and more specific code for MIS-C (i.e., ICD-10-CM code M35.81) became available (Table 2).

Feasibility analyses demonstrated quick uptake of the M35.81 code after it came into effect. Thus, the second algorithm will use the newer, more specific code during its approved period. Both algorithms will be restricted to diagnoses in the inpatient setting to align with the 2023 Council of State and Territorial Epidemiologists (CSTE)/CDC standardized case definition for MIS-C that requires severe disease resulting in hospitalization or death. Each algorithm is described in more detail below:

- Algorithm 1:
  - No ICD-10-CM code for MIS-C (Table 2) in the prior 180 days, and
  - The ICD-10-CM M35.8 diagnosis code in the inpatient setting between the study start date of March 1, 2020 and December 31, 2020
- Algorithm 2:
  - No ICD-10-CM code for MIS-C (Table 2) in the prior 180 days, and
  - The ICD-10-CM M35.81 diagnosis code in the inpatient setting between January 1, 2021 and the database-specific study end date

7. Case Sampling

Because Algorithm 2 (Section 6) will be used for future identification of MIS-C cases, we will begin the study by completing a one-time request of 50 medical records for cases identified in claims databases by Algorithm 2 during 2023. Based on the value and precision of the PPV estimates for Algorithm 2, we will determine if the study will continue with additional records requests for cases identified by either Algorithm 1 or Algorithm 2.

Specifications will be anchored on the relevant diagnosis date. All records from providers with MIS-C diagnoses will be requested from 3 days prior to 90 days following the claims-based MIS-C diagnosis date. Cases will be identified from the study start date through 90 days prior to study end date to allow for sufficient capture of treatment and follow-up care. The time period used for records requests may be modified based on availability of information in records during a preliminary record review.

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8. Case Definition

Cases identified in claims databases will be validated using the 2023 CSTE/CDC standardized MIS-C case definition.[8] This definition uses clinical, laboratory, epidemiologic, and/or vital records criteria (Table 3) to classify cases (Table 4).

Table 3. Description of the CSTE/CDC Case Definition Criteria Used in Classification

Criteria	Description[9,10]

Clinical	An illness characterized by ***all*** of the following, in the absence of a more likely alternative diagnosis*:
	• Subjective or documented fever (temperature ≥38.0^{o} C)
	• Clinical severity requiring hospitalization or resulting in death
	• Evidence of systemic inflammation indicated by C-reactive protein ≥3.0 mg/dL (30 mg/L)
	• New onset manifestations in at least two of the following categories:
	• Cardiac involvement indicated by:
	  ○ Left ventricular ejection fraction <55% OR
	  ○ Coronary artery dilatation, aneurysm, or ectasia, OR
	  ○ Troponin elevated above laboratory normal range, or indicated as elevated in a clinical note
	• Mucocutaneous involvement indicated by:
	  ○ Rash, OR
	  ○ Inflammation of the oral mucosa (e.g., mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue), OR
	  ○ Conjunctivitis or conjunctival injection (redness of the eyes), OR
	  ○ Extremity findings (e.g., erythema [redness] or edema [swelling] of the hands or feet)
	• Shock**
	• Gastrointestinal involvement indicated by:
	  ○ Abdominal pain, OR
	  ○ Vomiting, OR
	  ○ Diarrhea
	• Hematologic involvement indicated by:
	  ○ Platelet count <150,000 cells/µL, OR
	  ○ Absolute lymphocyte count (ALC) <1,000 cells/µL

Laboratory	• Detection of SARS-CoV-2 RNA in a clinical specimen*** up to 60 days prior to or during hospitalization, or in a post-mortem specimen using a diagnostic molecular amplification test (e.g., polymerase chain reaction [PCR]), OR • Detection of SARS-CoV-2 specific antigen in a clinical specimen*** up to 60 days prior to or during hospitalization, or in a post-mortem specimen, OR • Detection of SARS-CoV-2 specific antibodies^ in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization
Epidemiologic Linkage	• Close contact‡ with a confirmed or probable case of COVID-19 disease in the 60 days prior to hospitalization
Vital Records	• A person whose death certificate lists MIS-C or multisystem inflammatory syndrome as an underlying cause of death or a significant condition contributing to death

** If documented by the clinical treatment team, a final diagnosis of Kawasaki disease should be considered an alternative diagnosis. These cases should not be reported to national MIS-C surveillance*

*** Clinician documentation of shock meets this criterion*

**** Positive molecular or antigen results from self-administered testing using over-the-counter test kits meet laboratory criteria*

^ Includes a positive serology test regardless of COVID-19 vaccination status. Detection of anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, while anti-spike protein antibody may be induced either by COVID-19 vaccination or by SARS-CoV-2 infection
‡ Close contact is generally defined as being within 6 feet for at least 15 minutes (cumulative over a 24-hour period). However, it depends on the exposure level and setting; for example, in the setting of an aerosol-generating procedure in healthcare settings without proper personal protective equipment (PPE), this may be defined as any duration

Table 4. Criteria for Case Classification Using the 2023 CSTE/CDC Standardized MIS-C Case Definition

Case Classification	CSTE/CDC Definition Criteria[9]
Confirmed	*Meets **clinical and laboratory** criteria*
Probable	*Meets **clinical** and **epidemiologic linkage** criteria*
Suspect	*Meets **vital records** criteria*
Not a Case	Sufficient information in the medical records received to determine that the patient does not meet the case definition ***or*** evidence of an alternative diagnosis is present
Indeterminate	Insufficient information in the medical records received to determine if the case definition is met

9. Record Adjudication

Each case will be adjudicated independently by two clinicians. Each clinician will independently abstract and adjudicate medical records using a standardized case report form. The case report form will include patient information, details on presentation of symptoms, medical history, COVID-19 diagnosis information, diagnostic study and laboratory findings, and hospital discharge information. Each case identified in claims will be classified as confirmed, probable, suspect, not a case, or indeterminate using the 2023 CSTE/CDC standardized MIS-C case definition as described in Table 4. If the two clinicians disagree on a case classification, then a third clinician will act as a tie-breaker in adjudication. Example tables representing the attrition of medical records can be found below in Table 5. Initially, the table will only be completed for Algorithm 2 and may be updated if additional records are requested and reviewed for Algorithm 1 or Algorithm 2.

Table 5. Example Table – Attrition of Medical Charts

	Number of Cases (%)		
	Algorithm 1	**Algorithm 2**	**Total Cases**
Potential cases identified by algorithm	N	N	N
Potential cases with medical records requested	N (%*)	N (%*)	N (%*)
Potential cases with medical records available	N (%*)	N (%*)	N (%*)
Potential cases with sufficient information in medical records to determine outcome	N (%*)	N (%*)	N (%*)

**Denominator is potential cases identified by algorithm*

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10. Analyses

Among all claims-based cases with records returned and reviewed, the count and proportion of individuals will be reported by case status according to the 2023 CSTE/CDC case definition (Table 4). Example tables representing the proposed case classification summaries can be found below in Table 6. Initially, the table will only be completed for Algorithm 2 and may be updated if additional records are requested and reviewed for Algorithm 1 or Algorithm 2.

Table 6. Example Table – Summary of Case Classifications by Algorithm

Case Classification	Algorithm 1	Algorithm 2
Total Cases Reviewed		
Confirmed Case		
Probable Case		
Suspect Case		
Not a Case		
Indeterminate Case		

10.1 Evaluate Performance of Algorithms

To estimate the proportion of true cases identified, PPVs will be estimated for each algorithm for MIS-C in the commercially insured population aged 21 years old or younger, and 95% confidence intervals (CIs) will be calculated using the Wilson score interval method.[11] True cases will be defined using two approaches: 1) confirmed and 2) confirmed or probable cases based on the case classifications determined by clinician adjudicators using the CSTE/CDC standardized case definition. Individuals whose medical records did not have information to determine case status will be excluded from the PPV estimates.

10.1.1 Primary Analysis

PPVs will be calculated by the following categories, and will be estimated by algorithm. The denominator for calculating PPV estimates will include the total number of cases classified as confirmed, probable, suspect, and not a case. The numerator will include 1) number of confirmed cases and 2) number of confirmed and probable cases.

An example table representing the proposed summaries can be found below in Table 7. Initially, the table will only be completed for Algorithm 2 and may be updated if additional records are requested and reviewed for Algorithm 1 or Algorithm 2.

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Table 7. Example Table – PPVs for Confirmed and Probable Cases by Algorithm

Category	PPV (95% CI)	
	Algorithm 1	Algorithm 2
Confirmed Cases		
Confirmed or Probable Cases		

10.1.2 Sensitivity Analysis

In order to better understand the lower and upper bounds of our PPV estimates, sensitivity analyses will be conducted where 1) indeterminate cases will be assigned as not cases and will be included in the denominator for PPV calculations and 2) indeterminate cases will be assigned as confirmed or probable cases and will be included in the numerator and denominator for PPV calculations.

10.2 Demographic and Clinical Characteristics of Children with MIS-C

To describe demographic and clinical characteristics of identified and chart-confirmed MIS-C cases, descriptive summaries will be produced. Descriptive summaries of demographic characteristics available in claims data will be produced for cases for which medical records were reviewed, stratified by case classification as described in Table 8, but additional characteristics may be added based on literature review. Initially, the table will only be completed for Algorithm 2 and may be updated if additional records are requested and reviewed for Algorithm 1 or Algorithm 2.

Table 8. Descriptive Summary of Characteristics Using Claims Data for Children with Medical Records Reviewed with Potential MIS-C Cases

Patient Characteristics	Case Classification									
	Confirmed		Probable		Suspect		Not a Case		Indeterminate	
	N	%	N	%	N	%	N	%	N	%
Total Cases Identified										
Age (years)										
<1 year										
1-4 years										
5-11 years										
12-15 years										
16-17 years										
18-21 years										
Sex										
Male										
Female										
Missing/Unknown										
HHS Region										
Region 1										

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Patient Characteristics	Case Classification									
	Confirmed		Probable		Suspect		Not a Case		Indeterminate	
	N	%	N	%	N	%	N	%	N	%
Region 2										
Region 3										
Region 4										
Region 5										
Region 6										
Region 7										
Region 8										
Region 9										
Region 10										
Missing/Unknown										

For the subset of cases classified as confirmed and probable MIS-C cases through chart review and adjudication, further clinical and demographic characteristics will be summarized from the medical record data. A literature review will be conducted to determine clinical characteristics of interest. An example list of the characteristics that will be summarized include:

- Race:
  - American Indian/Alaska Native
  - Asian/Pacific Islander
  - Black/African American
  - White/Caucasian
  - Another race not listed
  - Unknown
- Ethnicity:
  - Hispanic
  - Non-Hispanic
  - Unknown
- Organ system involvement:
  - Cardiac
  - Dermatologic
  - Gastrointestinal
  - Hematologic
  - Hypertension/shock
  - Mucocutaneous
  - Neurologic
  - Renal
  - Respiratory
- Clinical features:

  - Shock
  - Criteria for Kawasaki disease met
  - Myocardial dysfunction
  - Arrhythmia
  - Acute respiratory failure requiring noninvasive or invasive ventilation
  - Acute kidney injury
  - Serositis
  - Hepatitis or hepatomegaly
  - Encephalopathy, seizures, coma, or meningoencephalitis
- Measures of disease activity:
  - Elevated BNP or NT-proBNP or troponin
  - Neutrophilia, lumphopenia, or thrombocytopenia
  - Evidence of cardiac involvement by echocardiography or physical stigmata of heart failure
- Laboratory evidence of inflammation, including elevated levels of:
  - Erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)
  - Ferritin
  - Lactic Acid Dehydrogenase (LDH)
- Comorbidities:
  - Obesity
  - Asthma/respiratory
  - Seizure disorder
  - Neurological/neuromuscular
  - Cardiovascular
  - Other
- Treatments for MIS-C:
  - Intravenous immune globulin (IVIG)
  - Glucocorticoids
  - Steroid therapy
- Hospitalization measures:
  - Length of inpatient stay
  - ICU admission (as available)
  - Ventilation status (as available)
  - ECMO
  - Hospital discharge status
  - In-hospital mortality (as available)
- COVID-19 information:
  - Documented SARS-CoV-2 test results: NAAT, anti-spike protein, anti-nucleocapsid antibody, unknown type
  - Epidemiologic link/documented exposure to suspected or confirmed case of COVID-19
  - SARS-CoV-2 vaccination

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11. References

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Note: Implementation of this protocol is on hold indefinitely. Please see protocol addendum.

12. Addendum

Given competing priorities, FDA is diverting resources to high priority surveillance activities. Consequently, the implementation of this protocol, *Validation of Algorithms to Identify Multisystem Inflammatory Syndrome in Children (MIS-C) in Administrative Claims Data*, has been placed on hold indefinitely. If priorities shift as it relates to the content of this protocol, we may re-initiate implementation.