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Disclaimer

The following report(s) provides findings from an FDA-initiated query using Sentinel. While Sentinel queries may be undertaken to assess potential medical product safety risks, they may also be initiated for various other reasons. Some examples include determining a rate or count of an identified health outcome of interest, examining medical product use, exploring the feasibility of future, more detailed analyses within Sentinel, and seeking to better understand Sentinel capabilities.

Data obtained through Sentinel are intended to complement other types of evidence such as preclinical studies, clinical trials, postmarket studies, and adverse event reports, all of which are used by FDA to inform regulatory decisions regarding medical product safety. The information contained in this report is provided as part of FDA's commitment to place knowledge acquired from Sentinel in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Sentinel queries will continue to be communicated through existing channels.

FDA wants to emphasize that the fact that FDA has initiated a query involving a medical product and is reporting findings related to that query does not mean that FDA is suggesting health care practitioners should change their prescribing practices for the medical product or that patients taking the medical product should stop using it. Patients who have questions about the use of an identified medical product should contact their health care practitioners.

The following report contains a description of the request, request specifications, and results from the modular program run(s).

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Overview

Date Run: December 29, 2016

Request Description: This purpose of this report was to compare the frequency of diagnoses for angioedema using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) versus International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes. ICD-10-CM code definitions were determined by mapping from ICD-9-CM code definitions using the Centers for Medicare and Medicaid Services (CMS) General Equivalence Mappings (GEMs). Simple forward mapping (SFM) and forward-backward mapping (FBM) were used to map ICD-9-CM to ICD-10-CM codes.[1]

Sentinel Modular Program Tool Used: Cohort Identification and Descriptive Analysis (CIDA) tool, version 3.3.2

Data Source: This request was run against data from 11 Data Partners contributing to the Sentinel Distributed Database (SDD). Data from October 1, 2010 to August 31, 2016 were included in this report. The report includes three separate time periods: 1) October 1, 2010 to August 31, 2016 2) January 1, 2015 to March 31, 2015 and 3) January 1, 2016 to March 31, 2016. See Appendix A for a list of the dates of available data for each Data Partner.

Study Design: We examined the incidence of angioedema across the ICD-9-CM era (October 2010 - September 2015) and the ICD-10-CM era (October 2015 - September 2016) in the US. See Appendices B, C, and D for specific codes.

Cohort Eligibility Criteria: Members included in the cohort were required to be continuously enrolled in plans with medical coverage for at least 6 months (183 days) before their diagnosis date, during which gaps in coverage of up to 45 days were allowed. The following age groups were included in the cohort: 0-17, 18-49, 50-64, 65+ years.

Limitations: Algorithms used to define outcomes are imperfect; thus, it is possible that there may be misclassification. Therefore, data should be interpreted with this limitation in mind.

Please refer to Appendix E for detailed specifications of parameters used in the analyses for this request.

Notes: Please contact the Sentinel Operations Center Query Fulfillment Team (qf@sentinelsystem.org) for questions and to provide comments/suggestions for future enhancements to this document.

[1]Fung, K. W., et al. (2016). "Preparing for the ICD-10-CM Transition: Automated Methods for Translating ICD Codes in Clinical Phenotype Definitions." EGEMS (Wash DC) 4(1): 1211.

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Glossary of Terms for Analyses Using Cohort Identification and Descriptive Analysis (CIDA) Tool*

Amount Supplied - number of units (pills, tablets, vials) dispensed. Net amount per NDC per dispensing. This is equivalent to the "RxAmt" value in the Sentinel Common Data Model.

Blackout Period - number of days at the beginning of a treatment episode that events are to be ignored. If an event occurs during the blackout period, the episode is excluded.

Care Setting - type of medical encounter or facility where the exposure, event, or condition code was recorded. Possible care settings include: Inpatient Hospital Stay (IP), Non-Acute Institutional Stay (IS), Emergency Department (ED), Ambulatory Visit (AV), and Other Ambulatory Visit (OA). For laboratory results, possible care settings include: Emergency department (E), Home (H), Inpatient (I), Outpatient (O), or Unknown or Missing (U). Along with the Principal Diagnosis Indicator, forms the Care Setting/PDX parameter.

> **Ambulatory Visit (AV) -** includes visits at outpatient clinics, same-day surgeries, urgent care visits, and other same-day ambulatory hospital encounters, but excludes emergency department encounters.
>
> **Emergency Department (ED) -** includes ED encounters that become inpatient stays (in which case inpatient stays would be a separate encounter). Excludes urgent care visits.
>
> **Inpatient Hospital Stay (IP) -** includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date.
>
> **Non-Acute Institutional Stay (IS) -** includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
>
> **Other Ambulatory Visit (OA) -** includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

Cohort Definition (drug/exposure) - indicates how the cohort will be defined: (1) 01: Cohort includes only the first valid treatment episode during the query period; (2) 02: Cohort includes all valid treatment episodes during the query period; (3) 03: Cohort includes all valid

Days Supplied - number of days supplied for all dispensings in qualifying treatment episodes.

Eligible Members - number of members eligible for an incident treatment episode (defined by the drug/exposure and event washout periods) with drug and medical coverage during the query period.

Episodes - treatment episodes; length of episode is determined by days supplied in one dispensing or consecutive dispensings bridged by

Enrollment Gap - number of days allowed between two consecutive enrollment periods without breaking a “continuously enrolled”

Episode Gap - number of days allowed between two (or more) consecutive exposures (dispensings/procedures) to be considered the same

Event Deduplication - specifies how events are counted by the MP algorithm: (0) 0: Counts all occurrences of an HOI during an exposure episode; (1) 1: de-duplicates occurrences of the same HOI code and code type on the same day; (2) 2: de-duplicates occurrences of the same HOI group on the same day (e.g., de-duplicates at the group level).

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode. Extensions days are added after any episode gaps have been bridged.

Exposure Episode Length - number of days after exposure initiation that is considered "exposed time."

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition

Maximum Episode Duration - truncates exposure episodes after a requester-specified number of exposed days. Applied after any gaps are

Member-Years - sum of all days of enrollment with medical and drug coverage** in the query period preceded by an exposure washout

Minimum Days Supplied - specifies a minimum number of days in length of the days supplied for the episode to be considered.

Minimum Episode Duration - specifies a minimum number of days in length of the episode for it to be considered. Applied after any gaps are bridged and extension days added to the length of the exposure episode.

Principal Diagnosis (PDX) - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. 'P' = principal diagnosis, 'S' = secondary diagnosis, 'X' = unspecified diagnosis, '.' = blank. Along with the Care Setting values, forms the

Query Period - period in which the modular program looks for exposures and outcomes of interest.

Treatment Episode Truncation Indicator - indicates whether observation of the incident query code during follow-up requires truncation of valid treatment episodes. A value of Y indicates that the treatment episodes should be truncated at the first occurrence of an incident query code. A value of N indicates that the treatment episodes should not be truncated at the occurrence of the incident query code.

Users - number of members with exposure during the query period. Member must have no evidence of exposure(s) of interest (defined by incidence criteria) in the prior washout period. A user may only be counted once in a query period.

Washout Period (drug/exposure) -** number of days a user is required to have no evidence of prior exposure (drug dispensing/procedure) and continuous drug and medical coverage prior to an incident treatment episode.

Washout Period (event/outcome) -** number of days a user is required to have no evidence of a prior event (procedure/diagnosis) and continuous drug and medical coverage prior to an incident treatment episode.

Years at Risk - number of days supplied plus any episode gaps and exposure extension periods all divided by 365.25.

*all terms may not be used in this report

**incident treatment episodes must be incident to both the exposure and the event

Table 1. Comparison of Incident Angioedema Diagnoses* in the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Eras (January 1, 2015 - March 31, 2015 and January 1, 2016 - March 31, 2016)

	Number of Incident Diagnoses	Number of Diagnoses	Eligible Members	Member-Years	Incident Diagnoses per 1,000 Eligible Members
Angioedema					
ICD-9-CM: January 1, 2015 - March 31, 2015					
	19,486	19,486	57,677,701	13,565,531.3	0.34
ICD-10-CM: January 1, 2016 - March 31, 2016					
	15,020	15,020	57,465,350	13,790,285.6	0.26

*Incidence defined by 90 day washout

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Figure 1. Incidence of Angioedema Diagnoses per 1,000 Eligible Members from October 2010 - August 2016 by Code Type, 183-Day Washout

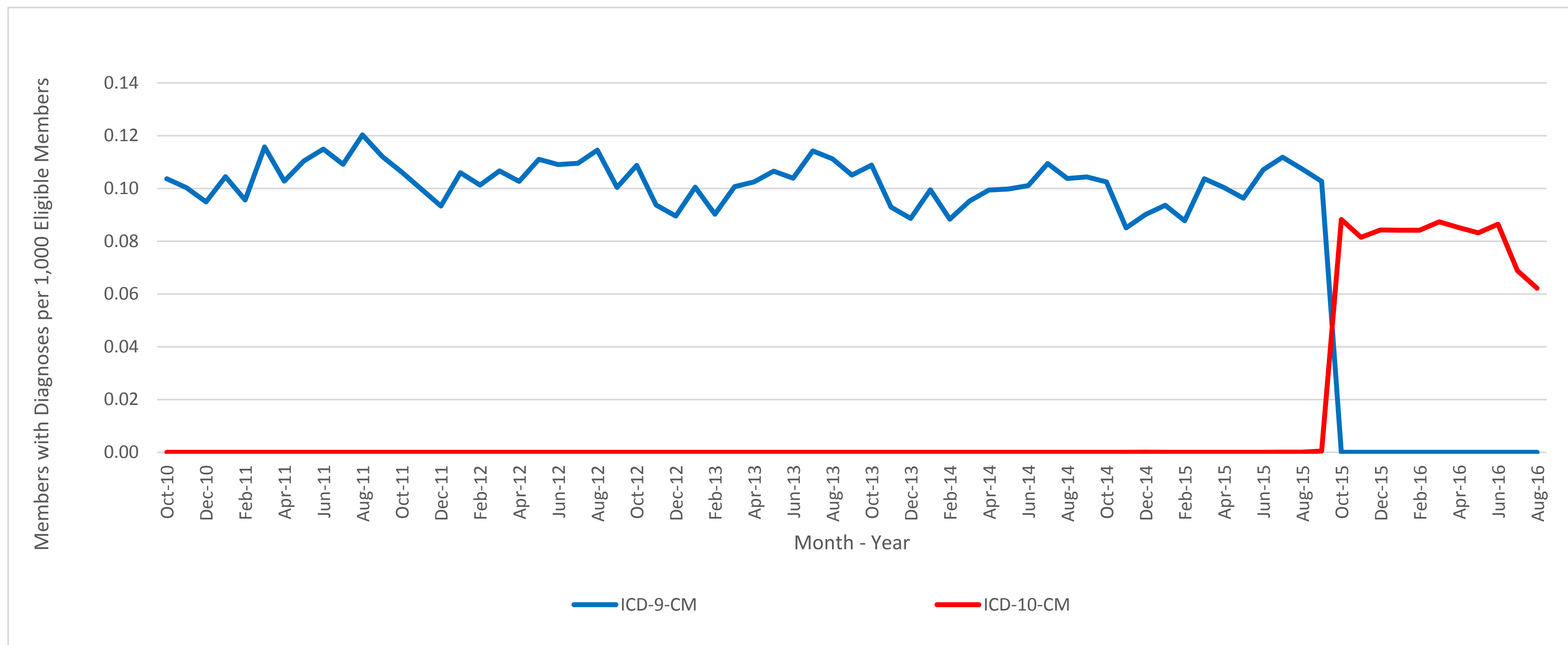

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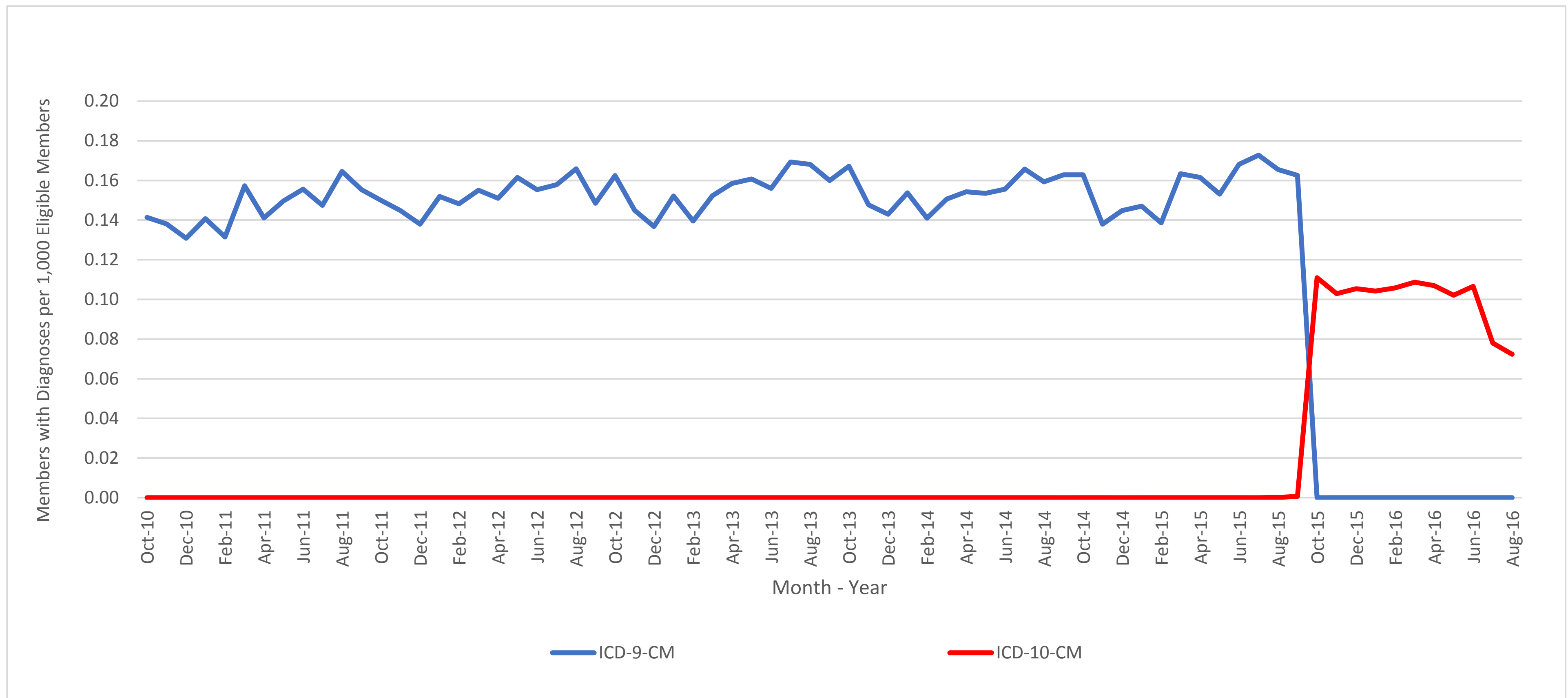
Figure 2. Prevalence of Angioedema Diagnoses per 1,000 Eligible Members from October 2010 - August 2016 by Code Type, 0-Day Washout



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Appendix A. Dates of Available Data for Each Data Partner in the Sentinel Distributed Database (SDD) as of Request End Date (August 31, 2016)

DP ID	Start Date	End Date
DP0001	10/1/2010	6/30/2016
DP0002	10/1/2010	4/30/2016
DP0003	10/1/2010	6/30/2016
DP0004	10/1/2010	7/31/2016
DP0005	10/1/2010	7/31/2016
DP0006	10/1/2010	6/30/2016
DP0007	10/1/2010	5/31/2016
DP0008	10/1/2010	7/31/2016
DP0009	10/1/2010	8/31/2016
DP0010	10/1/2010	3/31/2016
DP0011	10/1/2010	4/30/2016

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Appendix B. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM Codes used to Define Angioedema, Algorithm (Incident)[1]

Code	Description	Code Type
995.1	Angioneurotic edema not elsewhere classified	ICD-9-CM
T78.3XXA	Angioneurotic edema, initial encounter	ICD-10-CM

[1]ICD-10-CM codes from Algorithm include codes used in countries outside of the US, as they started using ICD-10-CM codes prior to their use in the US.

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Appendix C. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM Codes used to Define Angioedema, Algorithm (Incidence Definition)

Code	Description	Code Type
995.1	Angioneurotic edema not elsewhere classified	ICD-9-CM
T78.3XXA	Angioneurotic edema, initial encounter	ICD-10-CM
T78.3XXD	Angioneurotic edema, subsequent encounter	ICD-10-CM
T78.3XXS	Angioneurotic edema, sequela	ICD-10-CM

Appendix D. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and ICD-10-CM Codes used to Define Angioedema, Simple Forward Mapping (SFM) and Forward Backward Mapping (FBM)

Code	Description	Code Type
995.1	Angioneurotic edema not elsewhere classified	ICD-9-CM
T78.3XXA	Angioneurotic edema, initial encounter	ICD-10-CM

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Appendix E. Specifications for Parameters for this Request

Sentinel's Cohort Identification and Descriptive Analysis (CIDA) tool, version 3.3.2, was used to compare the frequency of diagnoses for a selection of health outcomes using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) versus ICD-10-CM codes.

Enrollment Gap: 45 Days
Age Groups: 0-17, 18-49, 50-64, 65+ years
Enrollment Requirement: 183 Days
Coverage Requirement: Medical Coverage

Scenario	Code Source	Query Start Date	Query End Date	Event					
				Event	Care Setting	Incident w/ respect to:	Washout (days)	Incident w/ respect to Care Setting	Cohort Definition
1	ICD-9-CM Code Search	1/1/2015	3/31/2015	Angioedema diagnosis (**only** ICD-9-CM code 995.1)	Any	Angioedema diagnosis (**only** ICD-9-CM code 995.1)	90	Any	01
2	SFM and FBM	1/1/2016	3/31/2016	Angioedema diagnosis (**only** ICD-10-CM code T78.3XXA)	Any	Angioedema diagnosis (**only** ICD-10-CM code T78.3XXA)	90	Any	01
3	ICD-9-CM Code Search	10/1/2010	8/31/2016	Angioedema diagnosis (**only** ICD-9-CM code 995.1)	Any	Angioedema diagnosis (ICD-9-CM: 995.1 **or** ICD-10-CM[1]: T78.3XXA, T78.3XXD, T78.3XXS)	183	Any	01
4	SFM and FBM	10/1/2010	8/31/2016	Angioedema diagnosis (**only** ICD-10-CM code T78.3XXA)	Any	Angioedema diagnosis (ICD-9-CM: 995.1 **or** ICD-10-CM: T78.3XXA)	183	Any	01
5	ICD-9-CM Code Search	10/1/2010	8/31/2016	Angioedema diagnosis (**only** ICD-9-CM code 995.1)	Any	NA	0	Any	02
6	SFM and FBM	10/1/2010	8/31/2016	Angioedema diagnosis (**only** ICD-10-CM code T78.3XXA)	Any	NA	0	Any	02

ICD-9-CM and ICD-10-CM are provided by Optum360. ICD-10-CM codes were mapped from ICD-9-CM codes using the Centers for Medicare and Medicaid Services General Equivalence Mappings.

[1]ICD-10-CM codes from Algorithm include codes used in countries outside of the US, as they started using ICD-10-CM codes prior to their use in the US.