Epidemiology of Infectious Mononucleosis in Ambulatory Care Settings, United States, 2006–2019

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BACKGROUND

- Infectious mononucleosis (IM) is a contagious illness that can present clinically with fever, fatigue, sore throat, and lymphadenopathy; IM can also result in prolonged symptoms, hospitalization, and splenic rupture[1,2]
  - While numerous viruses can cause IM, the most frequent cause is Epstein-Barr virus (EBV),[1] accounting for approximately 90% of IM cases[3]
- IM incidence in the United States is commonly estimated at 500 cases per 100,000 persons per year,[4] although the reliability of this estimate is uncertain
  - Older community-based studies in the United States report dramatically lower estimates, ranging from 45 to 99 per 100,000 population[3]
  - A more recent study of adults in the US military estimated an incidence of 104 per 100,000 person-years[5]
- No recent studies have characterized the burden of IM in the general US population over time
  - Recent evidence supporting the possible role of EBV in multiple sclerosis[6] has prompted interest in further elucidating IM disease burden

OBJECTIVES

- To describe the frequency and rate of ambulatory care visits in which IM was diagnosed, and examine secular trends
- To describe the demographic characteristics of patients with IM-related visits
- To understand the proportion of visits resulting in hospital admissions, serving as a proxy for severity

METHODS

Study Design, Data Source, and Study Period

- Data from 2 ambulatory care surveys in the United States were utilized for this analysis:
  - National Ambulatory Medical Care Survey (NAMCS), which includes a sample of patient visits from non-federally employed office-based physicians
  - National Hospital Ambulatory Medical Care Survey (NHAMCS), which includes non-institutional general and short-stay hospital outpatient and emergency department (ED) visit data
- These surveys employ multi-stage probability sampling; application of weights allows for calculation of national estimates of ambulatory care visits
- The study period was 2006 to 2019; NAMCS and NHAMCS data were included based on availability
  - Data from 2006-2015 were examined from NAMCS, hereafter referred to as "freestanding ambulatory care"
  - Data from 2006-2019 were examined from NHAMCS; outpatient data (OPD) were available from 2006-2011 and ED data were available from 2006-2019
    - OPD and ED data were combined for better variance estimates from 2006-2011, hereafter referred to as "all hospital-based ambulatory care"
    - ED data were analyzed separately for 2012-2019 (after OPD collection ended), hereafter referred to as "ED-only care"

Case Definition and Study Outcomes

- Case definition of an IM visit was defined as presence of ≥1 diagnosis code for IM (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM]: 075; International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM]: B27.xx)
- Primary study outcomes included (analyzed in each dataset):
  - Weighted frequency and rate of IM visits by specified time periods
  - Secular trend in the rate of IM visits over time
  - Demographic characteristics of IM visits, including by age, sex, and race/ethnicity for all years combined
  - Proportion of visits that resulted in hospital admissions and corresponding discharge diagnoses for all years combined

Statistical Analyses

- The weighted frequency of IM-related visits and the corresponding rates per 10,000 visits were calculated by time period and database, and plotted by time period
- Unadjusted and adjusted restricted cubic spline models were used to assess time trends in the rate of IM-related visits by year
  - Covariates used for adjustment in the model were age (continuous variable), sex, and race/ethnicity

RESULTS

Rates of IM Visits

- From 2006-2015, using freestanding ambulatory care data, 9,612,613,670 physician office visits occurred; of these, 3,182,082 (0.03%) visits included an IM diagnosis (**Table 1**)
- From 2006-2011, using all hospital-based ambulatory care data, 1,385,553,358 outpatient and ED visits occurred; of these, 599,837 (0.04%) visits included an IM diagnosis (**Table 1**)
- From 2012-2019, using ED-only care data, 1,104,778,596 ED visits occurred; of these, 449,001 (0.04%) visits included an IM diagnosis (**Table 1**)
- For the overlapping years of 2006-2011, common across all databases, the average annual number of IM-related visits was 419,927 (**Table 1**)

Table 1. IM-Related Visits per 10,000 by Year and Database

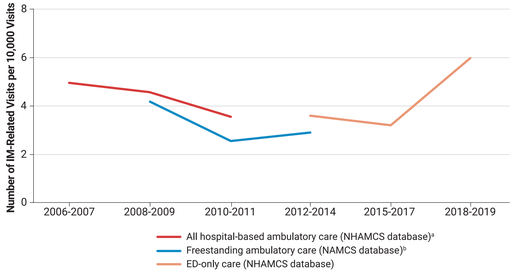
Year	Weighted N	IM-Related Visits (95% CI) per 10,000 Visits	SE per 10,000
Freestanding Ambulatory Care			
2006-2009	1,626,609	4.18 (3.02, 5.78)	0.69
2010-2012	746,918	2.55 (1.11, 5.86)	1.08
2013-2015	808,555	2.89 (1.40, 5.96)	1.07
All Hospital-Based Ambulatory Care[a]			
2006-2007	211,049	4.94 (3.41, 7.16)	0.93
2008-2009	213,397	4.58 (3.19, 6.57)	0.84
2010-2011	175,391	3.56 (2.33, 5.45)	0.77
ED-Only Care			
2012-2014	145,222	3.61 (2.30, 5.67)	0.83
2015-2017	135,879	3.22 (1.95, 5.32)	0.82
2018-2019	167,900	5.98 (3.20, 11.17)	1.90

CI, confidence interval; ED, emergency department; IM, infectious mononucleosis; OPD, outpatient data; SE, standard error.
[a]Includes both ED and OPD that is hospital based.

Trends in IM-Related Visits

- Across databases and years, there were no significant linear trends in IM-related visits in adjusted or unadjusted models (**Figure 1**)

Figure 1. Rates of US Ambulatory Care Visits With an IM Diagnosis (per 10,000 Visits) by Database and Year



ED, emergency department; IM, infectious mononucleosis; NAMCS, National Ambulatory Medical Care Survey; NHAMCS, National Hospital Ambulatory Medical Care Survey.
[a]Hospital-based ambulatory care includes both ED and outpatient visits associated with a hospital facility.
[b]Freestanding ambulatory care dates covered 2006-2009, 2010-2012, and 2013-2015.

Demographic Characteristics of IM Visits

- The mean age (standard error) of patients in each cohort was 29.4 (4.59) years, 18.0 (0.72) years, and 17.5 (1.53) years in freestanding ambulatory care, all hospital-based ambulatory care, and ED-only care, respectively.
- Persons aged 10 to 30 years comprised most IM-related visits: 61% in the freestanding ambulatory care dataset, 88% in the all hospital-based ambulatory care dataset, and 85% in the ED-only care dataset (**Table 2**)
- While 66% of IM visits were made by females in freestanding ambulatory care, this proportion was lower in all hospital-based ambulatory care (58%) and ED-only care (51%; **Table 2**)
- Most IM-related visits were among non-Hispanic White patients: 92%, 87%, and 67% in freestanding ambulatory care, all hospital-based ambulatory care, and ED-only care, respectively (**Table 2**)

Table 2. Demographics of IM Visits

	Freestanding Ambulatory Care, 2006-2015 (N=3,182,082)		All Hospital-Based Ambulatory Care,[a] 2006-2011 (N=599,837)		ED-Only Care, 2012-2019 (N=449,001)	
Characteristic	**Weighted N**	**Proportion (95% CI)**	**Weighted N**	**Proportion (95% CI)**	**Weighted N**	**Proportion (95% CI)**
Age Category						
0-9 years	220,501	6.93 (3.86, 12.13)	43,866	7.31 (3.77, 13.72)	53,595	11.94 (5.26, 24.87)
10-15 years	523,220	16.44 (9.32, 27.36)	183,515	30.59 (21.05, 42.16)	115,430	25.71 (15.38, 39.72)
16-20 years	986,576	31.00 (19.85, 44.92)	234,988	39.18 (29.59, 49.67)	183,301	40.82 (29.36, 53.38)
21-30 years	418,984	13.17 (6.90, 23.67)	107,797	17.97 (10.99, 27.99)	83,574	18.61 (9.69, 32.76)
≥31 years	1,032,801	32.46 (17.21, 52.62)	29,671	4.95 (2.41, 9.89)	13,101	2.92 (0.42, 17.80)
Sex						
Female	2,090,342	65.69 (54.17, 75.62)	345,074	57.53 (47.22, 67.22)	226,757	50.50 (36.34, 64.58)
Male	1,091,740	34.31 (24.38, 45.83)	254,763	42.47 (32.78, 52.78)	222,244	49.50 (35.42, 63.66)
Race/Ethnicity						
Non-Hispanic White	2,913,488	91.56 (85.20, 95.34)	522,299	87.07 (79.95, 91.92)	302,802	67.44 (54.09, 78.46)
Non-Hispanic Black	92,997	2.92 (1.13, 7.35)	36,786	6.13 (3.15, 11.60)	61,110	13.61 (7.55, 23.31)
Hispanic	132,163	4.15 (1.71, 9.75)	27,521	4.59 (2.07, 9.84)	75,469	16.81 (8.43, 30.73)
Non-Hispanic Other	43,434	1.36 (0.39, 4.62)	13,231	2.21 (0.67, 7.04)	9,619	2.14 (0.57, 7.70)

CI, confidence interval; ED, emergency department; IM, infectious mononucleosis; OPD, outpatient data; SE, standard error.
[a]Includes both ED and OPD that is hospital based.

Hospital Admissions

- In the datasets containing all hospital-based ambulatory care and ED-only care, most patients at IM-related visits were not admitted to the hospital; 93.48% and 92.48% of visits, respectively, did not result in hospital admission
- Among visits that led to hospital admission, IM was the most common discharge diagnosis: 67.63% in all hospital-based ambulatory care and 48.74% in ED-only care, respectively
  - Other discharge diagnoses included acute and subacute necrosis of liver, erythema multiforme, enlargement of lymph nodes, unspecified anemia, dehydration, other abnormal blood chemistry, and unspecified polyneuropathy

CONCLUSIONS

- Our estimates suggest that the IM burden in the United States is lower than published estimates
  - The published estimate of 500 cases per 100,000 persons per year[4] translates to 1.69M new IM cases annually in the United States vs approximately 420,000 annual ambulatory care visits for IM in our study
- Demographic patterns in our study were largely consistent with known IM epidemiology for age,[2,3,5] gender,[2,3] and race/ethnicity[5]
- This study provides the first known hospital admission proportion data for IM from a nationally representative US study
- Strengths of our study include use of a large, nationally representative sample and underlying reliance on patient medical records
- Limitations of our study include potential for overestimation or underestimation of cases because of:
  - Possible undetected repeat visits and inclusion of cases in which IM was not the primary diagnosis
  - Estimation of IM from any diagnosis field position
  - Estimation of medically attended IM only, as opposed to the full universe of disease occurrence
- In addition, the etiology of IM diagnosis (eg, EBV or cytomegalovirus) was not gathered
- This study informs the current epidemiology knowledge base for IM in the United States using recent, nationally representative data

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Disclosures

RM, RP, PB, SC, and SH are employees of Moderna, Inc., and hold stock/stock options in the company.