



Modular Program Report

The following report(s) provides findings from an FDA-initiated query using its Mini-Sentinel pilot. While Mini-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 Mini-Sentinel, and seeking to better understand the capabilities of the Mini-Sentinel pilot.

Data obtained through Mini-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 the Mini-Sentinel pilot in the public domain as soon as possible. Any public health actions taken by FDA regarding products involved in Mini-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 | |
|-----------------------------------|---|
| <u>Request Description</u> | <p>FDA requested use of Modular Program (MP) #3 (version2.3) to investigate diagnosis of progressive multifocal leukoencephalopathy (PML - ICD-9 code 046.3) following exposure to natalizumab or efalizumab. MP #5 (version 2.0) was also run to produce background rates of PML events among all eligible members. The query was run against the Mini-Sentinel Distributed Database for the years 01/01/2003 to 12/31/2011 (query period) and distributed to Data Partners on May 7, 2012. This report contains data from 15 Data Partners. Two Data Partners were excluded due to unresolved data issues at the time of data gathering.</p> <p>Results of MP #5 provide counts of prevalent PML patients and those with a new PML event, PML events for these PML patients, eligible members (denominator), and member days. Prevalent PML patients are members with at least one day of medical benefit enrollment and one or more diagnoses of PML during the query period. The number of PML events for these patients are the total number of events occurring on or after the index date of PML diagnosis. A new PML patient was defined as a person with a PML event during the query period and no PML events during any observed time (including before the start of the query period) before the qualifying PML event. Care in the outpatient (AV), inpatient (IP), and emergent care (ED) settings were included. MP #5 results are presented in Table 1, Figure 1, Table 2, and Figure 2.</p> <p>Results of MP #3 provide counts of new users of natalizumab and efalizumab and associated exposures (dispensings/injections), days supplied, treatment episodes, eligible members (denominator), and member days. Days supplied are from the MSCDM outpatient pharmacy table for records identified using valid NDC codes (for any form, e.g., tablet, vial, topical). Outpatient injections identified from the MSCDM procedure table were automatically given a one day supply. Counts of PML events and days at risk following exposure to natalizumab and efalizumab are also presented. A natalizumab or efalizumab user was considered new if no prior use was found in the user's entire observed history. In addition, the entire available post-exposure histories of users were scanned for PML events. PML events in the outpatient (AV), inpatient (IP), and emergent (ED) settings were included. MP #3 results are presented in Table 3, Figure 3, Table 4, Figure 4, Table 5, and Figure 5.</p> |
| <u>Request ID</u> | msy3_mpr16 |
| <u>Specifications</u> | Program parameter inputs and scenarios |
| <u>Glossary</u> | Glossary of key terms in the context of MP #3 and MP #5 |
| <u>Tables 1a & b</u> | Tables of Number of Prevalent and Incident Progressive Multifocal Leukoencephalopathy (PML) Patients, Incident Starts (Incident Patients only), PML Events, Eligible Members, and Member Days Overall and by Age Group, Sex, and Year - 2003-2011 |
| <u>Figures 1a - d</u> | Four figures depicting the information from Tables 1a & b |
| <u>Table 2</u> | Table of Number of Prevalent and Incident PML Patients per 1 Million Eligible Members and PML Events per Patient Overall and by Age Group, Sex, and Year - 2003-2011 |
| <u>Figures 2a - d</u> | Four figures depicting the information from Table 2 |
| <u>Table 3</u> | Table of Number of Incident Users, Exposures (dispensings/injections), Total Days Supplied, Episodes, Eligible Members, and Member Days by Drug Product Overall and by Age Group, Sex, and Year - 2003-2011 |
| <u>Figure 3a - j</u> | Ten figures depicting the information from Table 3 |
| <u>Table 4</u> | Table of Number of Exposures (dispensings/injections) per Incident User, Days Supplied per Incident User, Days Supplied per Exposure, and Rates of Incident Users per 1 Million Eligible Members by Drug Product Overall and by Age Group, Sex, and Year - 2003-2011 |

| | |
|-----------------------------|--|
| Overview cont. | |
| <u>Figure 4a - h</u> | Eight figures depicting the information from Table 4 |
| <u>Table 5</u> | Table of Number of Incident Users (from Table 3), Events, Days at Risk, and Rates of Events per 1 Million Days at Risk by Drug Product Overall and by Age Group, Sex, and Year - 2003-2011 |
| Notes: | Please contact the Mini-Sentinel Operations Center (MSOC_Requests@harvardpilgrim.org) for questions and to provide comments/suggestions for future enhancements to this document. |

MP #5 Specifications

The three parameters below apply to all scenarios:

Enrollment gap = 45 days

Query Period 01/01/2003 to 03/31/2011

Age Group: 0-39 40-64 65+

| Scenario | Drug/Exposure | | | | | |
|----------|-------------------|------------------------|----------------|---------------|--------------|--------------|
| | Incident exposure | Incident w/respect to: | Washout (days) | Washout Type* | Care Setting | Principal Dx |
| 1 | PML | PML | 1 | Min | IP, ED, AV | NO |

MP #3 Specifications

The three parameters below apply to all scenarios:

Enrollment gap = 45 days

Query Period 01/01/2003 to 03/31/2011

Age Group: 0-39 40-64 65+

| Scenario | Drug/Exposure | | | | | | | Event/Outcome | | | | | | |
|----------|-------------------|-------------------------|----------------|--------------|-------------|------------------|----------------------|-------------------|----------------|----------------|--------------|--------------|--------------|-----------------|
| | Incident exposure | Incident w/ respect to: | Washout (days) | Washout Type | Episode gap | Extension period | Min episode duration | Min days supplied | Event/ Outcome | Washout (days) | Washout Type | Care Setting | Principal Dx | Blackout Period |
| 1 | Efalizumab | Efalizumab | 14 | Min | 4000 | 4000 | 1 | 1 | PML | 1 | Min | ED, IP, AV | NO | 0 |
| 2 | Natalizumab | Natalizumab | 14 | Min | 4000 | 4000 | 1 | 1 | PML | 1 | Min | ED, IP, AV | NO | 0 |

Glossary of Terms

Modular Program 5 Terms:

Prevalent Patients - number of members with exposure/event of interest during the query period

Prevalent Events - total number of exposures/events of interest during the query period for prevalent patients

Prevalent Eligible Members - number of members with at least one day of medical benefit enrollment during the query period

Prevalent Member-Days - sum of all the medical coverage days eligible members are enrolled in during the query period

Incident Patients - number of members with an incident exposure/event of interest during the query period

Incident Events - total number of events during the query period for incident patients

Incident Eligible Members - number of members with at least one day of medical benefit enrollment during the query period

Incident Member-Days - sum of all the medical coverage days eligible members are enrolled in during the query period

Washout Type - to establish incidence, minimum washout type will consider the first event in the query period as long as it is the first event in the patient's entire available history. Multiple washout type will use the washout period to establish incidence and will consider all qualifying incident events

Washout Period - number of days a patient is required to have no evidence of a prior event and continuous medical coverage prior to an incident event

Modular Program 3 Terms:

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)

Days at Risk - number of days supplied plus any episode gaps and exposure extension periods

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

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

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

Exposures - number of dispensings of the drug of interest in all incident episodes

Exposure Extension Period - number of days post treatment period in which the outcomes/events are counted for a treatment episode

Lookback Period (pre-existing condition) - number of days wherein a member is required to have evidence of pre-existing condition (diagnosis/procedure/drug dispensing)

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

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

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

New (Incident) Users - number of members with incident 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

Principal Diagnosis - diagnosis or condition established to be chiefly responsible for admission of the patient to the hospital. YES will only consider diagnoses flagged as Principal

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

Total Days Supplied - total number of days supplied for all dispensings in qualifying incident episodes

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

Glossary of Terms

Washout Type (drug/exposure) - *minimum washout type* will consider the first treatment episode in the query period as long as it is the first treatment episode in the user's entire available history. *Single* and *multiple washout type* will use the washout period to establish incidence, however *single* will only consider the first treatment episode whereas *multiple* will consider all qualifying incident treatment episodes

Washout Type (event/outcome) - *minimum washout type* considers the first event in a valid episode as long as it is the first event in the user's entire available history. *Multiple washout type* uses the washout period to establish incidence and considers all qualifying incident treatment episodes. The program will only consider one event per episode, but the *multiple washout type* will consider more than one event per user if a user has more than one incident episode

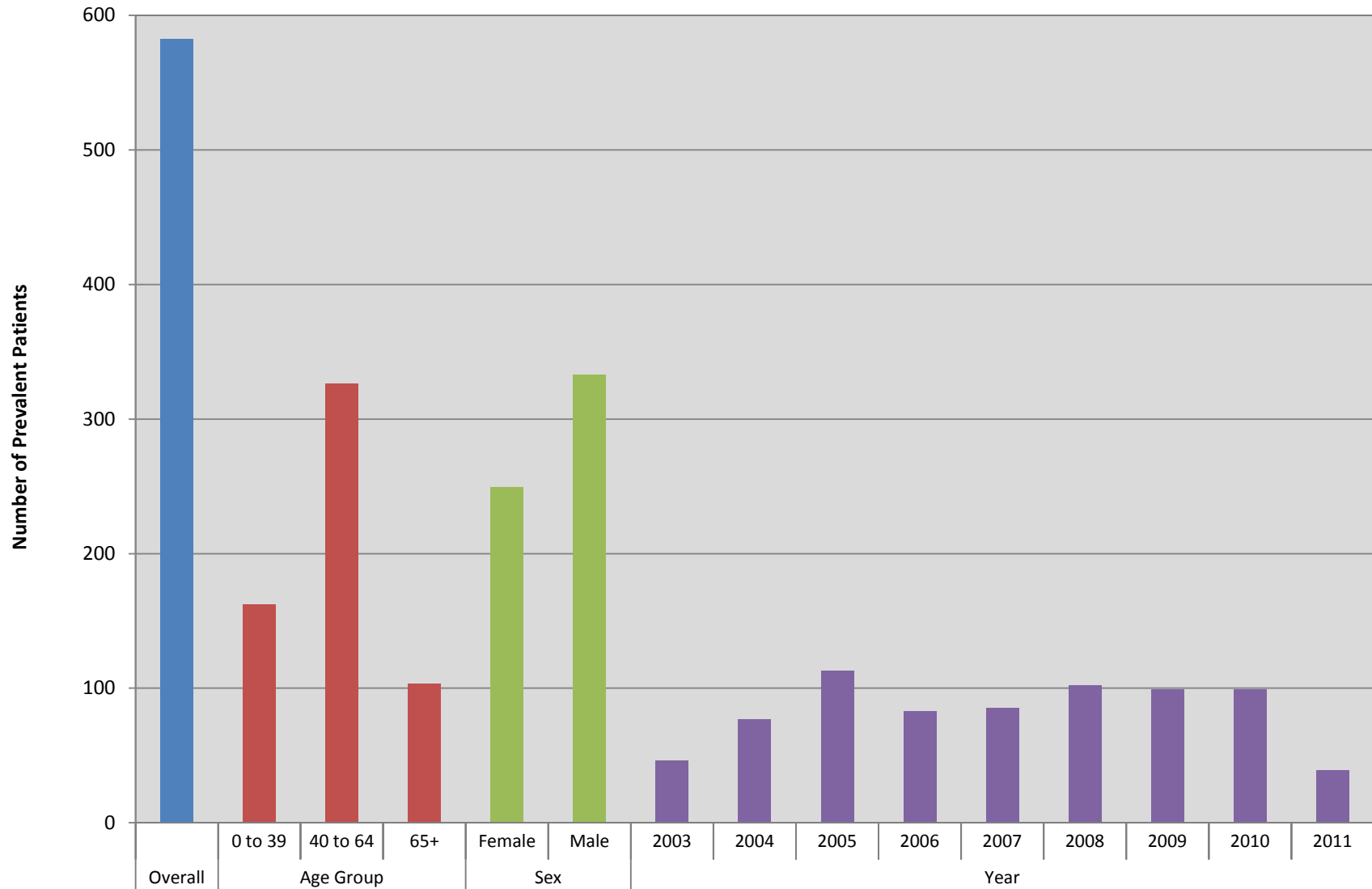
Table 1a. Number of Prevalent Progressive Multifocal Leukoencephalopathy (PML) Patients, PML Events, Eligible Members, and Member Days, by Age Group, Sex, and Year

| | | Prevalant Patients | Prevalant Events | Prevalant Eligible Members | Member-Days |
|-----------|----------------|--------------------|------------------|----------------------------|----------------|
| OVERALL | | 582 | 1,650 | 65,120,354 | 63,300,249,958 |
| AGE GROUP | 0 to 39 years | 162 | 481 | 39,581,733 | 33,545,340,388 |
| | 40 to 64 years | 326 | 895 | 22,796,318 | 22,729,792,385 |
| | 65+ years | 103 | 274 | 6,594,201 | 7,025,117,185 |
| SEX | Female | 249 | 591 | 33,098,356 | 32,670,260,151 |
| | Male | 333 | 1,059 | 31,933,880 | 30,523,827,675 |
| | Unknown | 0 | 0 | 88,118 | 106,162,132 |
| YEAR | 2003 | 46 | 99 | 9,240,701 | 2,929,307,510 |
| | 2004 | 77 | 175 | 24,680,826 | 7,313,526,704 |
| | 2005 | 113 | 180 | 25,371,119 | 7,481,676,551 |
| | 2006 | 83 | 140 | 26,905,534 | 8,029,473,598 |
| | 2007 | 85 | 195 | 30,276,534 | 8,694,377,749 |
| | 2008 | 102 | 201 | 30,768,252 | 8,877,121,481 |
| | 2009 | 99 | 210 | 29,028,078 | 8,837,245,739 |
| | 2010 | 99 | 357 | 29,304,577 | 8,918,943,616 |
| | 2011 | 39 | 93 | 23,363,422 | 2,218,577,010 |

Table 1b. Number of Incident Progressive Multifocal Leukoencephalopathy (PML) Patients, PML Events, Eligible Members, and Member Days, by Age Group, Sex, and Year

| | | Incident Patients | Incident Events | Incident Eligible Members | Member-Days |
|-----------|----------------|-------------------|-----------------|---------------------------|----------------|
| OVERALL | | 561 | 1,503 | 64,988,019 | 63,162,166,165 |
| AGE GROUP | 0 to 39 years | 155 | 404 | 39,484,346 | 33,459,270,204 |
| | 40 to 64 years | 309 | 820 | 22,751,353 | 22,687,820,969 |
| | 65+ years | 97 | 262 | 6,591,120 | 7,015,074,992 |
| SEX | Female | 248 | 551 | 33,050,764 | 32,600,279,991 |
| | Male | 313 | 952 | 31,849,164 | 30,456,007,252 |
| | Unknown | 0 | 0 | 88,091 | 105,878,922 |
| YEAR | 2003 | 34 | 69 | 9,237,962 | 2,918,371,586 |
| | 2004 | 65 | 144 | 24,665,078 | 7,279,240,612 |
| | 2005 | 96 | 146 | 25,358,575 | 7,469,042,013 |
| | 2006 | 69 | 106 | 26,891,976 | 8,013,919,707 |
| | 2007 | 64 | 118 | 30,257,831 | 8,675,424,462 |
| | 2008 | 75 | 145 | 30,751,685 | 8,862,473,615 |
| | 2009 | 71 | 148 | 28,972,594 | 8,824,527,083 |
| | 2010 | 69 | 231 | 29,245,255 | 8,905,128,879 |
| | 2011 | 18 | 38 | 23,351,067 | 2,214,038,208 |

Figure 1a. Number of Prevalent PML Patients, Overall and by Age Group, Sex, and Year



| | | | | | | | | | | | | | | | |
|--------------------|-----|-----|-----|-----|-----|-----|----|----|-----|----|----|-----|----|----|----|
| Prevalent Patients | 582 | 162 | 326 | 103 | 249 | 333 | 46 | 77 | 113 | 83 | 85 | 102 | 99 | 99 | 39 |
|--------------------|-----|-----|-----|-----|-----|-----|----|----|-----|----|----|-----|----|----|----|

Figure 1b. Number of PML Events among Prevalent PML Patients, Overall and by Age Group, Sex, and Year

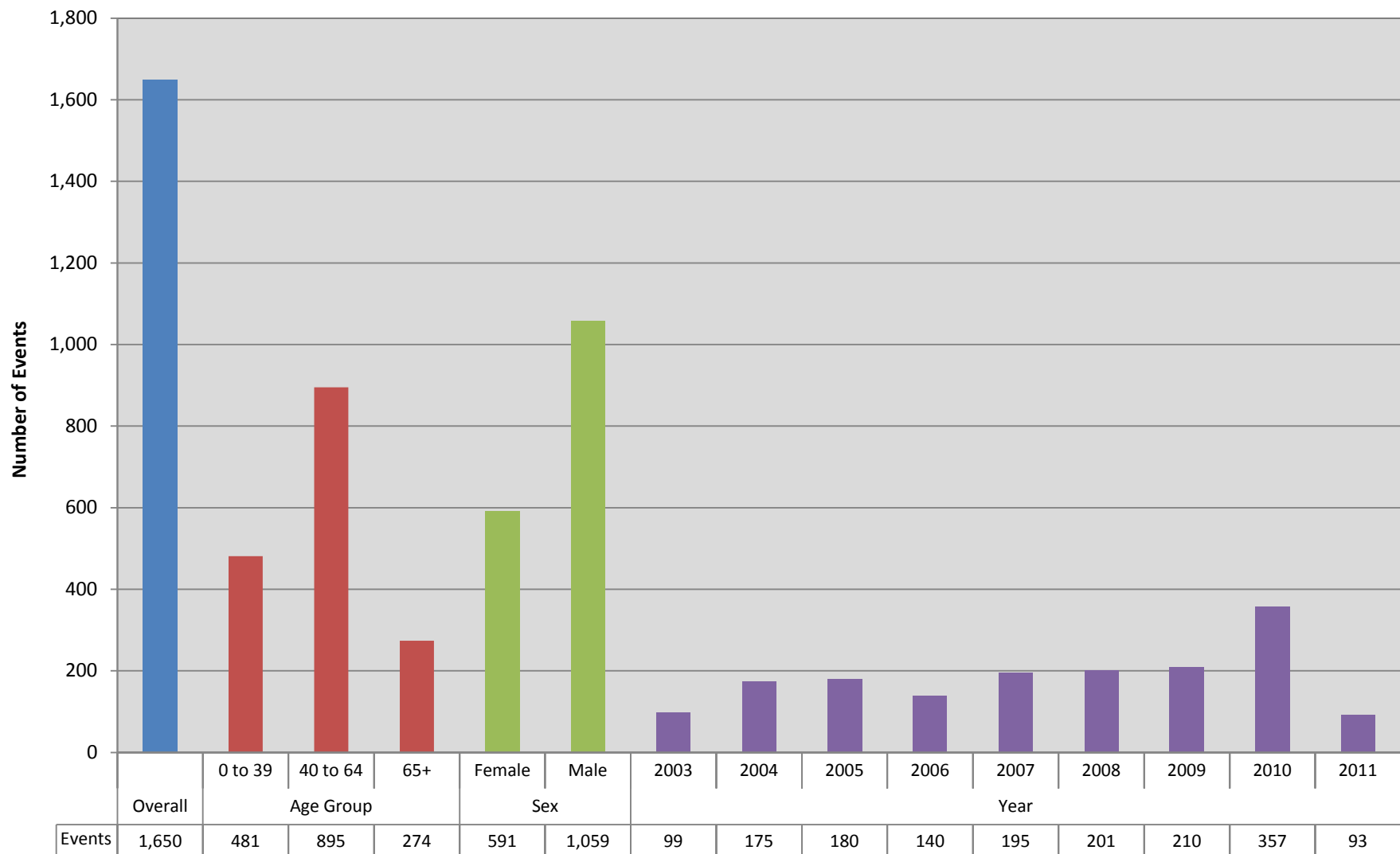


Figure 1c. Number of Incident PML Patients, Overall and by Age Group, Sex, and Year

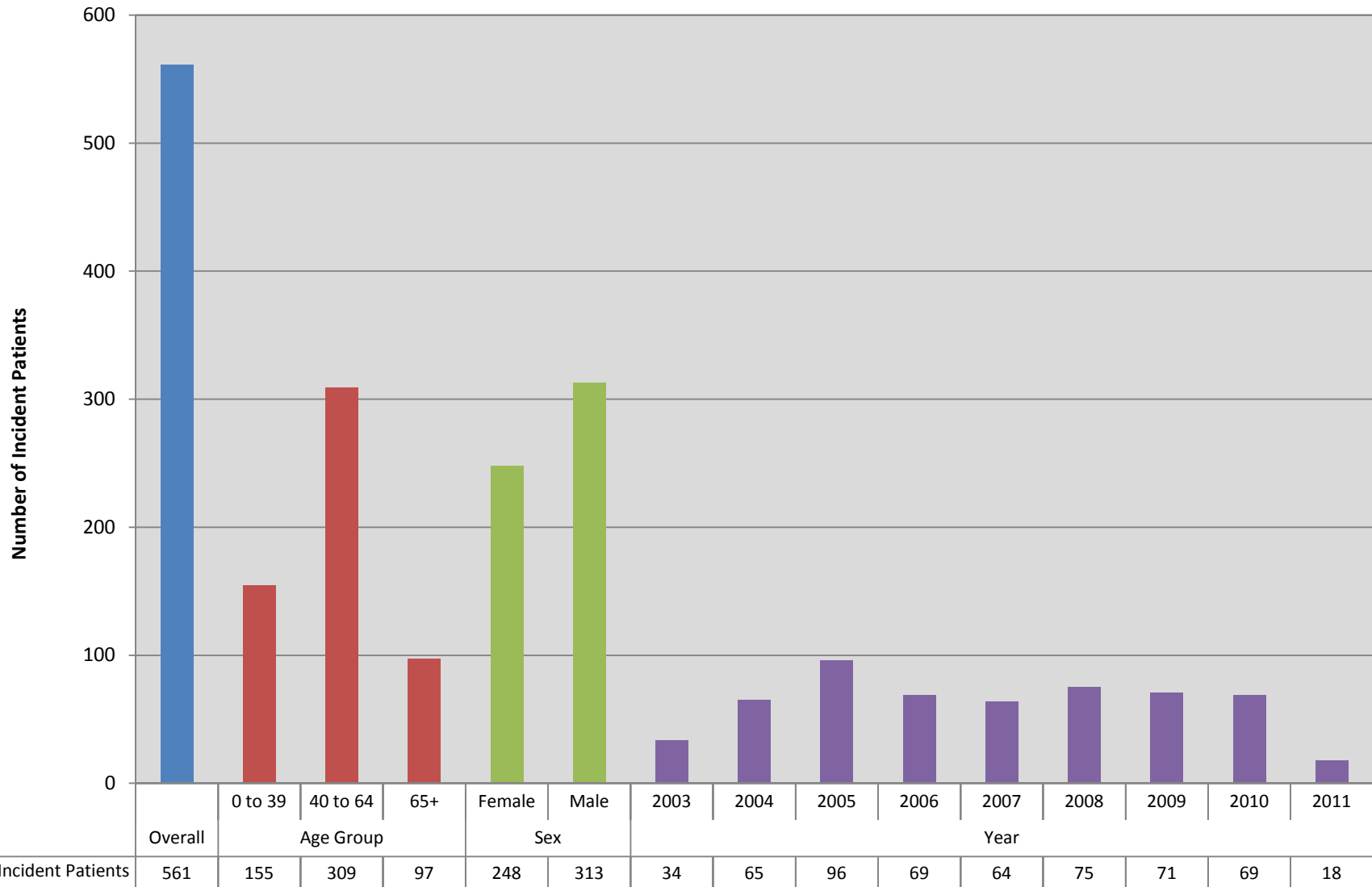


Figure 1d. Number of PML Events for Incident PML Patients, Overall and by Age Group, Sex, and Year

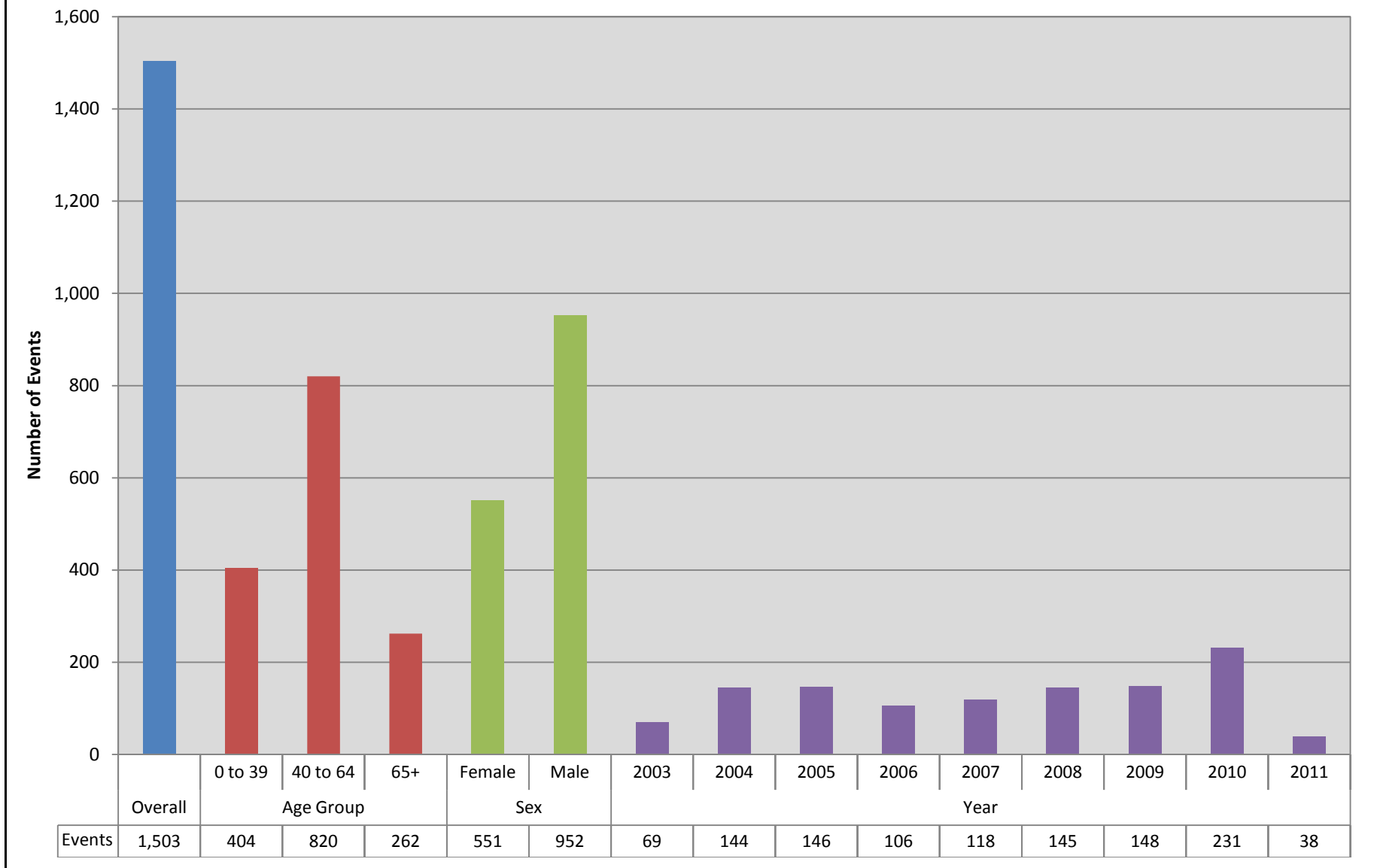
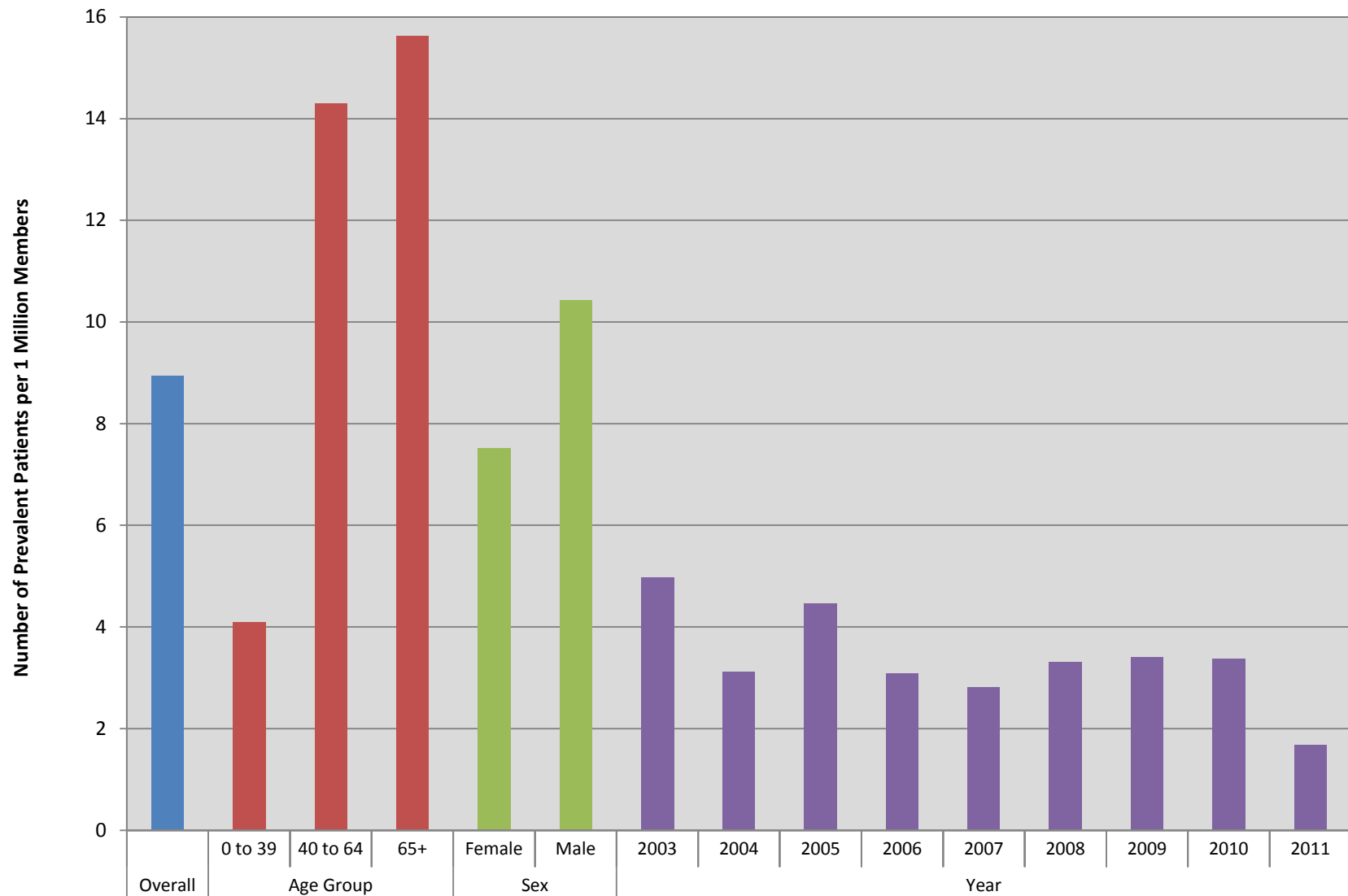


Table 2. Number of Prevalent and Incident PML Patients per 1 Million Eligible Members and PML Events per Patient, Overall and by Age Group, Sex, and Year

| | | PREVALENT | | INCIDENT | |
|-----------|----------------|---------------------|----------------|---------------------|----------------|
| | | Patients/1M Members | Events/Patient | Patients/1M Members | Events/Patient |
| OVERALL | | 8.9 | 2.8 | 8.6 | 2.7 |
| AGE GROUP | 0 to 39 years | 4.1 | 3.0 | 3.9 | 2.6 |
| | 40 to 64 years | 14.3 | 2.7 | 13.6 | 2.7 |
| | 65+ years | 15.6 | 2.7 | 14.7 | 2.7 |
| SEX | Female | 7.5 | 2.4 | 7.5 | 2.2 |
| | Male | 10.4 | 3.2 | 9.8 | 3.0 |
| | Unknown | 0.0 | . | 0.0 | . |
| YEAR | 2003 | 5.0 | 2.2 | 3.7 | 2.0 |
| | 2004 | 3.1 | 2.3 | 2.6 | 2.2 |
| | 2005 | 4.5 | 1.6 | 3.8 | 1.5 |
| | 2006 | 3.1 | 1.7 | 2.6 | 1.5 |
| | 2007 | 2.8 | 2.3 | 2.1 | 1.8 |
| | 2008 | 3.3 | 2.0 | 2.4 | 1.9 |
| | 2009 | 3.4 | 2.1 | 2.5 | 2.1 |
| | 2010 | 3.4 | 3.6 | 2.4 | 3.3 |
| | 2011 | 1.7 | 2.4 | 0.8 | 2.1 |

Figure 2a. Number of Prevalent PML Patients per 1 Million Eligible Members, Overall and by Age Group, Sex, and Year



| | | | | | | | | | | | | | | | |
|---------------------|-----|-----|------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|
| Patients/1M Members | 8.9 | 4.1 | 14.3 | 15.6 | 7.5 | 10.4 | 5.0 | 3.1 | 4.5 | 3.1 | 2.8 | 3.3 | 3.4 | 3.4 | 1.7 |
|---------------------|-----|-----|------|------|-----|------|-----|-----|-----|-----|-----|-----|-----|-----|-----|

Figure 2b. Number of PML Events per Prevalent PML Patient, Overall and by Age Group, Sex, and Year

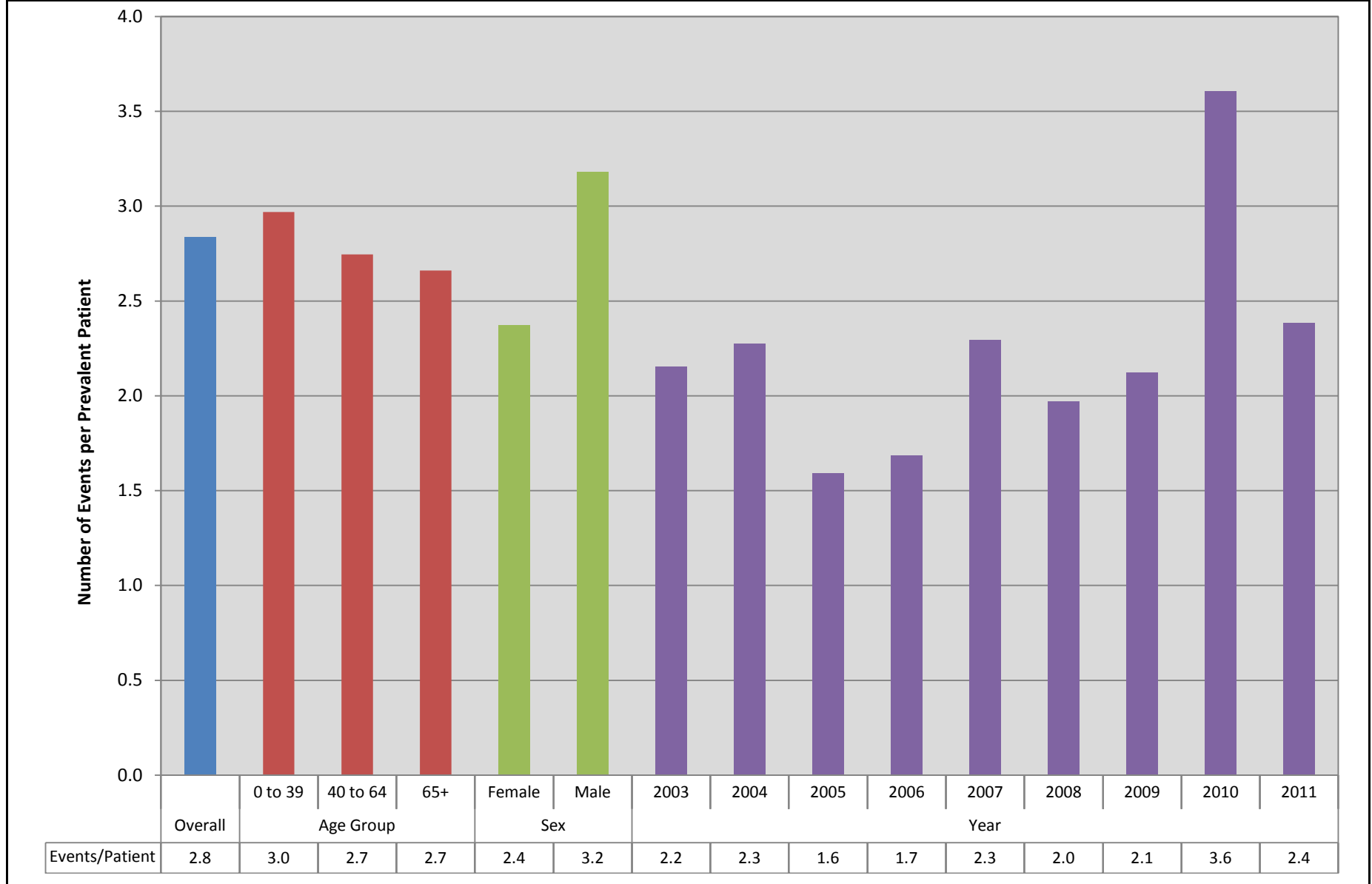


Figure 2c. Number of Incident PML Patients per 1 Million Eligible Members, Overall and by Age Group, Sex, and Year

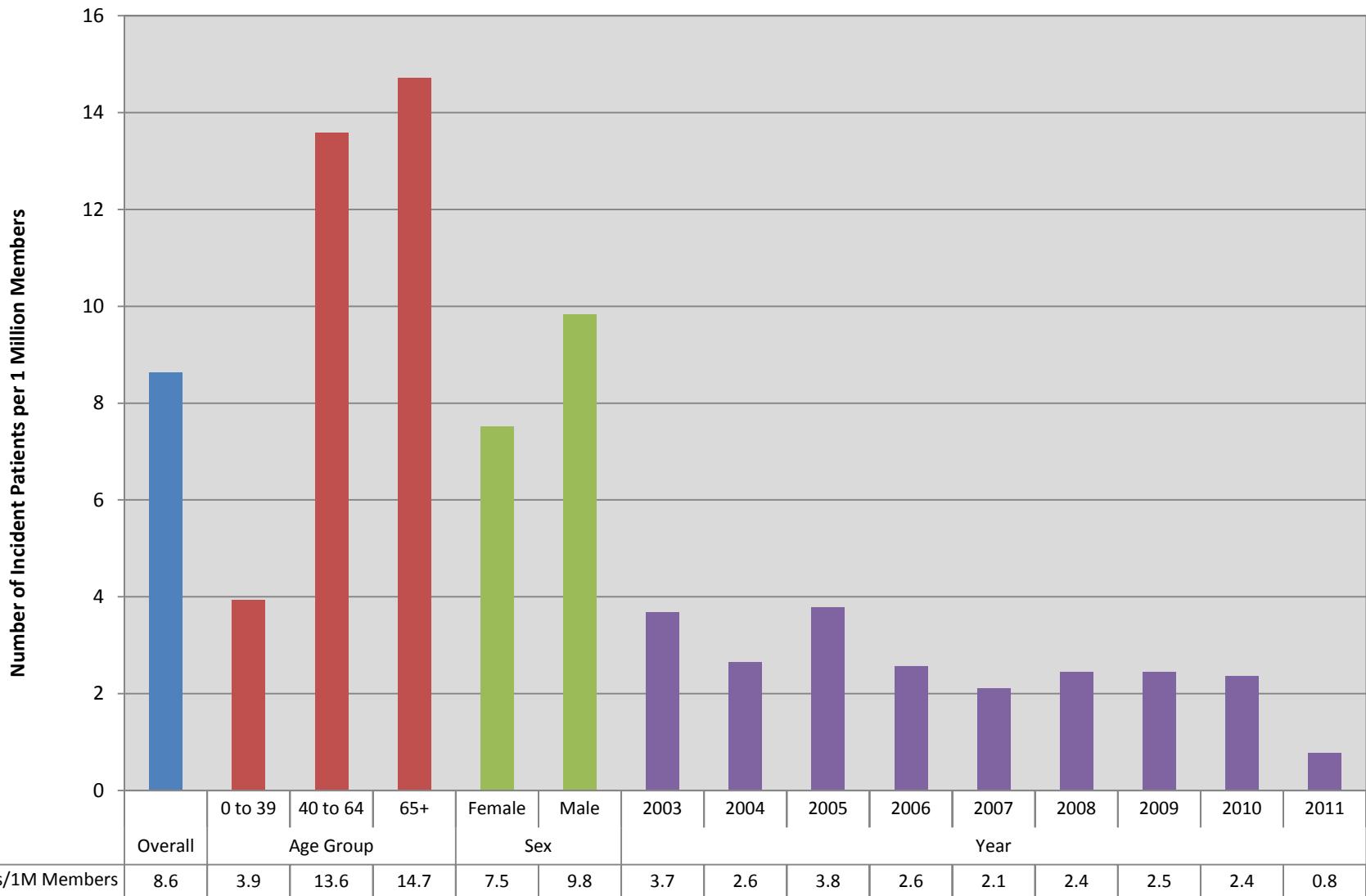


Figure 2d. Number of PML Events per Incident PML Patient, Overall and by Age Group, Sex, and Year

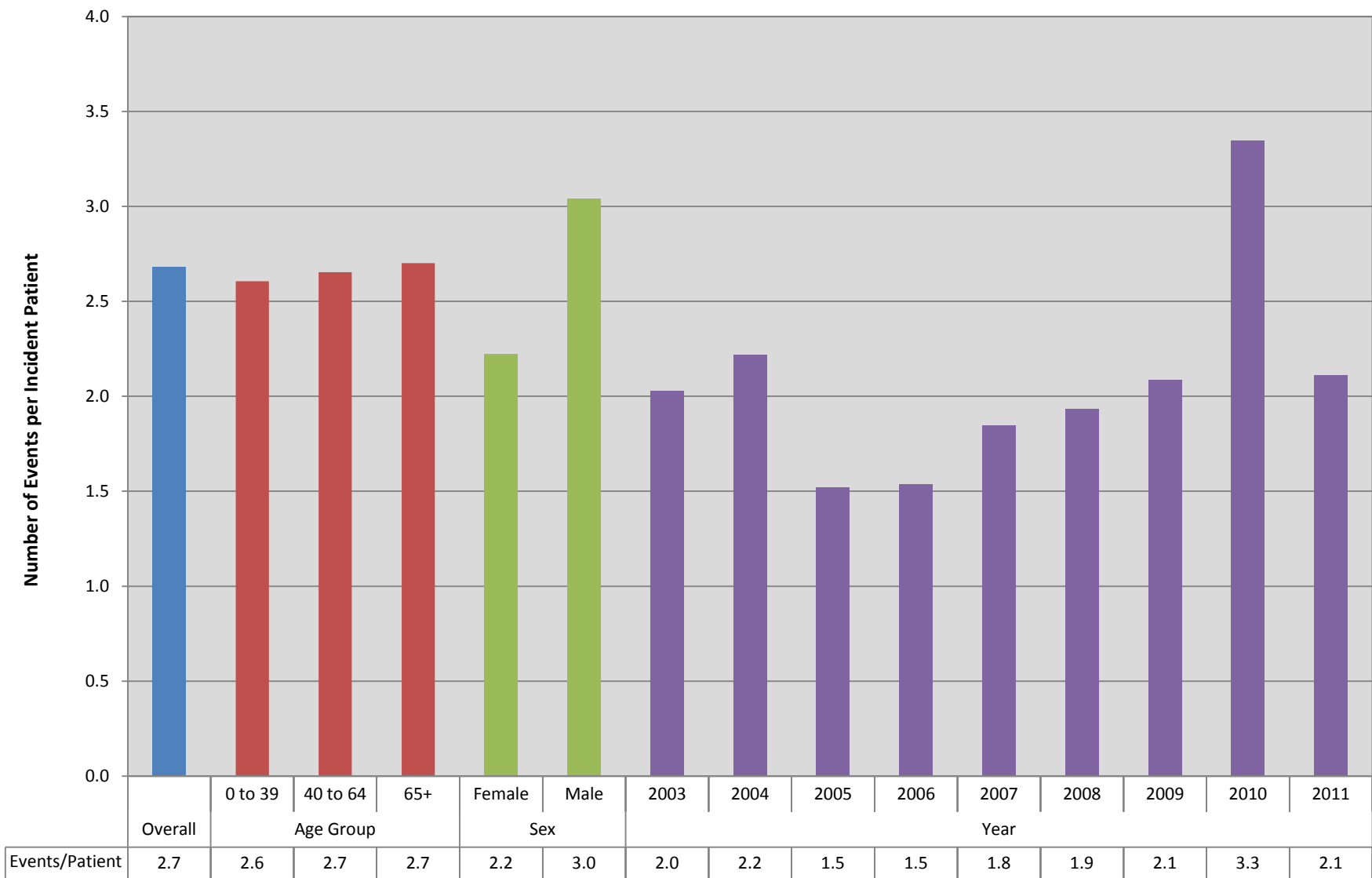
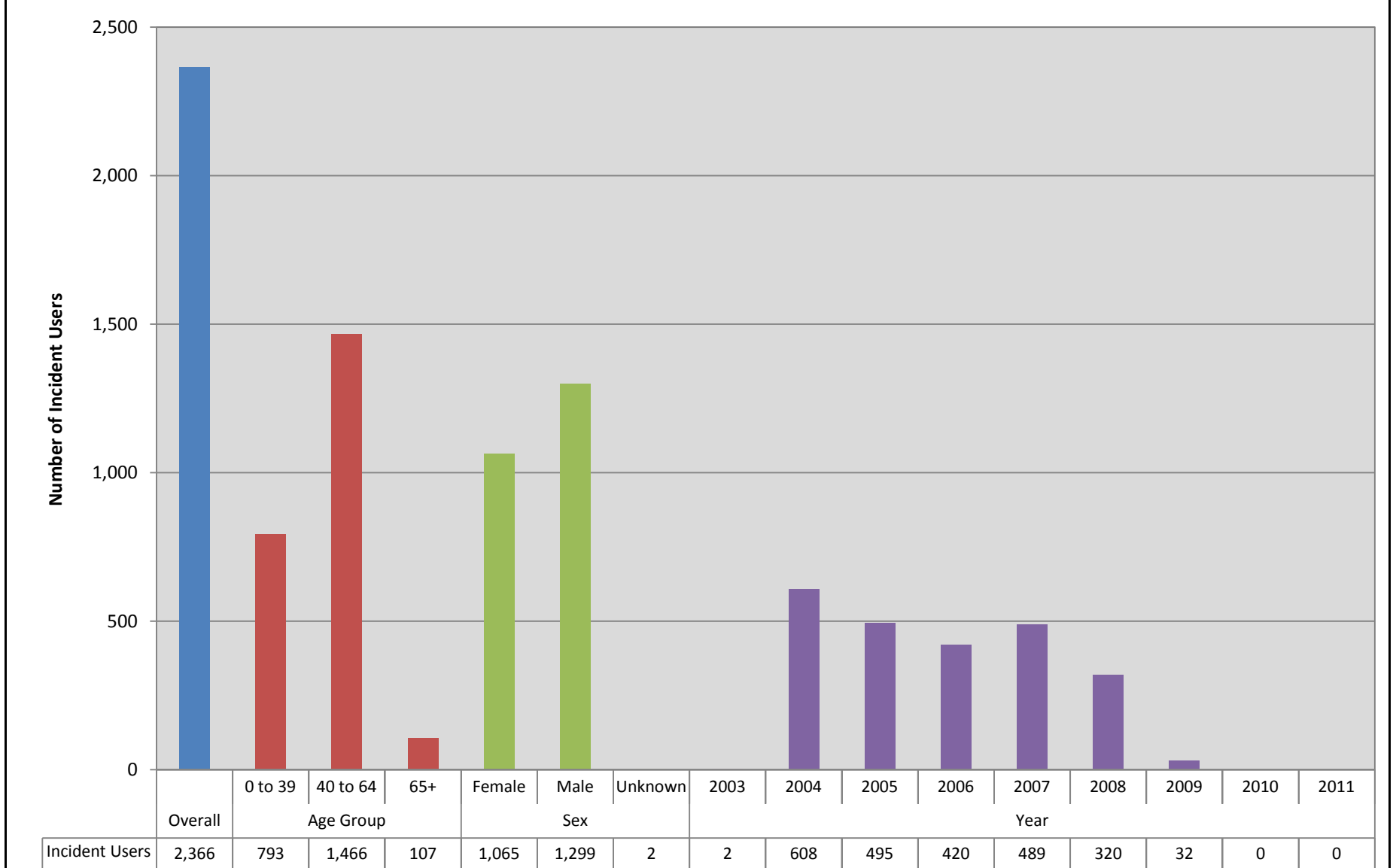


Table 3. Number of Incident Users, Exposures, Total Days Supplied, Episodes, Eligible Members, and Member Days by Drug Product, Overall and by Age Group, Sex, and Year

| | | Incident Users | Exposures | Total Days Supplied | Episodes | Eligible Members | Member-Days | |
|-------------|-----------|----------------|-----------|---------------------|----------|------------------|----------------|----------------|
| EFALIZUMAB* | OVERALL | 2,366 | 25,655 | 692,719 | 2,366 | 64,950,138 | 63,232,483,127 | |
| | AGE GROUP | 0 to 39 years | 793 | 8,168 | 208,667 | 793 | 39,453,362 | 33,503,740,430 |
| | | 40 to 64 years | 1,466 | 16,665 | 457,425 | 1,466 | 22,732,452 | 22,708,386,690 |
| | | 65+ years | 107 | 822 | 26,627 | 107 | 6,590,466 | 7,020,362,408 |
| | SEX | Female | 1,065 | 10,753 | 289,638 | 1,065 | 33,036,644 | 32,636,177,110 |
| | | Male | 1,299 | 14,876 | 402,353 | 1,299 | 31,825,406 | 30,490,288,398 |
| | | Unknown | 2 | 26 | 728 | 2 | 88,088 | 106,017,619 |
| | YEAR | 2003 | 2 | 34 | 904 | 2 | 9,232,956 | 2,927,736,707 |
| | | 2004 | 608 | 8,891 | 233,817 | 608 | 24,658,907 | 7,296,273,384 |
| | | 2005 | 495 | 6,407 | 169,339 | 495 | 25,351,469 | 7,475,094,062 |
| | | 2006 | 420 | 4,574 | 132,301 | 420 | 26,883,632 | 8,021,326,115 |
| | | 2007 | 489 | 3,817 | 107,409 | 489 | 30,245,817 | 8,684,435,601 |
| | | 2008 | 320 | 1,813 | 47,071 | 320 | 30,738,845 | 8,869,310,389 |
| 2009 | | 32 | 119 | 1,878 | 32 | 28,961,184 | 8,830,415,752 | |
| 2010 | | 0 | 0 | 0 | 0 | 29,235,054 | 8,911,638,455 | |
| 2011 | | 0 | 0 | 0 | 0 | 23,347,627 | 2,216,252,662 | |
| NATALIZUMAB | OVERALL | 4,097 | 53,935 | 238,050 | 4,097 | 64,950,053 | 63,232,138,332 | |
| | AGE GROUP | 0 to 39 years | 1,397 | 17,956 | 79,508 | 1,397 | 39,453,338 | 33,503,641,243 |
| | | 40 to 64 years | 2,611 | 34,966 | 154,968 | 2,611 | 22,732,307 | 22,708,094,346 |
| | | 65+ years | 89 | 1,013 | 3,574 | 89 | 6,590,497 | 7,020,409,143 |
| | SEX | Female | 2,965 | 38,801 | 172,337 | 2,965 | 33,036,614 | 32,635,330,884 |
| | | Male | 1,130 | 15,108 | 65,687 | 1,130 | 31,825,349 | 30,490,787,907 |
| | | Unknown | 2 | 26 | 26 | 2 | 88,090 | 106,019,541 |
| | YEAR | 2003 | 0 | 0 | 0 | 0 | 9,232,895 | 2,927,712,713 |
| | | 2004 | 8 | 231 | 2,283 | 8 | 24,658,848 | 7,296,355,236 |
| | | 2005 | 122 | 1,028 | 15,714 | 122 | 25,351,902 | 7,475,287,504 |
| | | 2006 | 248 | 5,109 | 28,886 | 248 | 26,884,310 | 8,021,615,458 |
| | | 2007 | 888 | 15,541 | 67,409 | 888 | 30,246,526 | 8,684,604,957 |
| | | 2008 | 1,047 | 16,608 | 63,926 | 1,047 | 30,739,048 | 8,869,225,667 |
| 2009 | | 732 | 8,948 | 33,647 | 732 | 28,960,718 | 8,830,123,103 | |
| 2010 | | 826 | 5,719 | 22,755 | 826 | 29,234,056 | 8,911,147,337 | |
| 2011 | | 226 | 751 | 3,430 | 226 | 23,346,275 | 2,216,066,357 | |

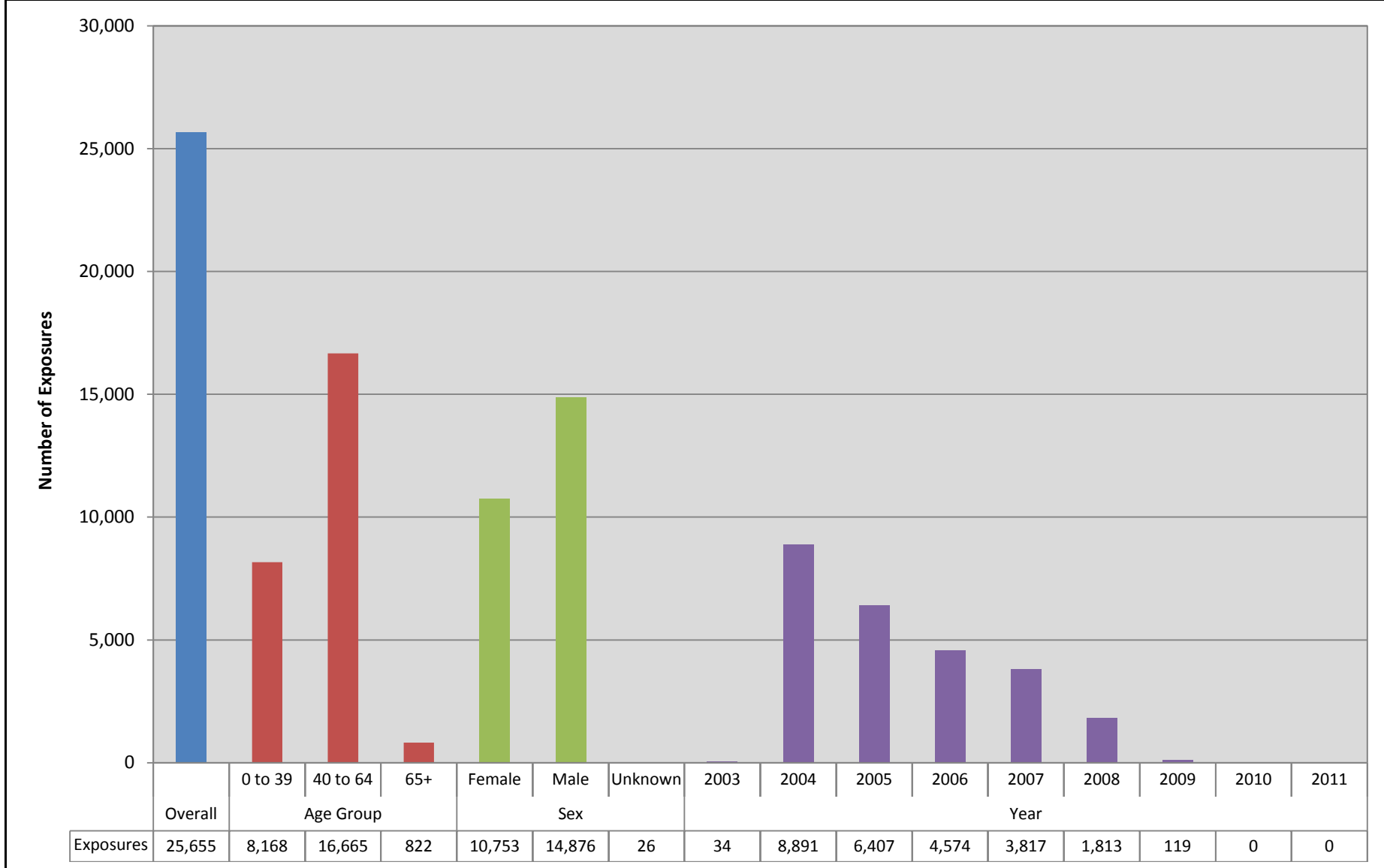
*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 3a. Number of Incident Efalizumab* Users, Overall and by Age Group, Sex, and Year



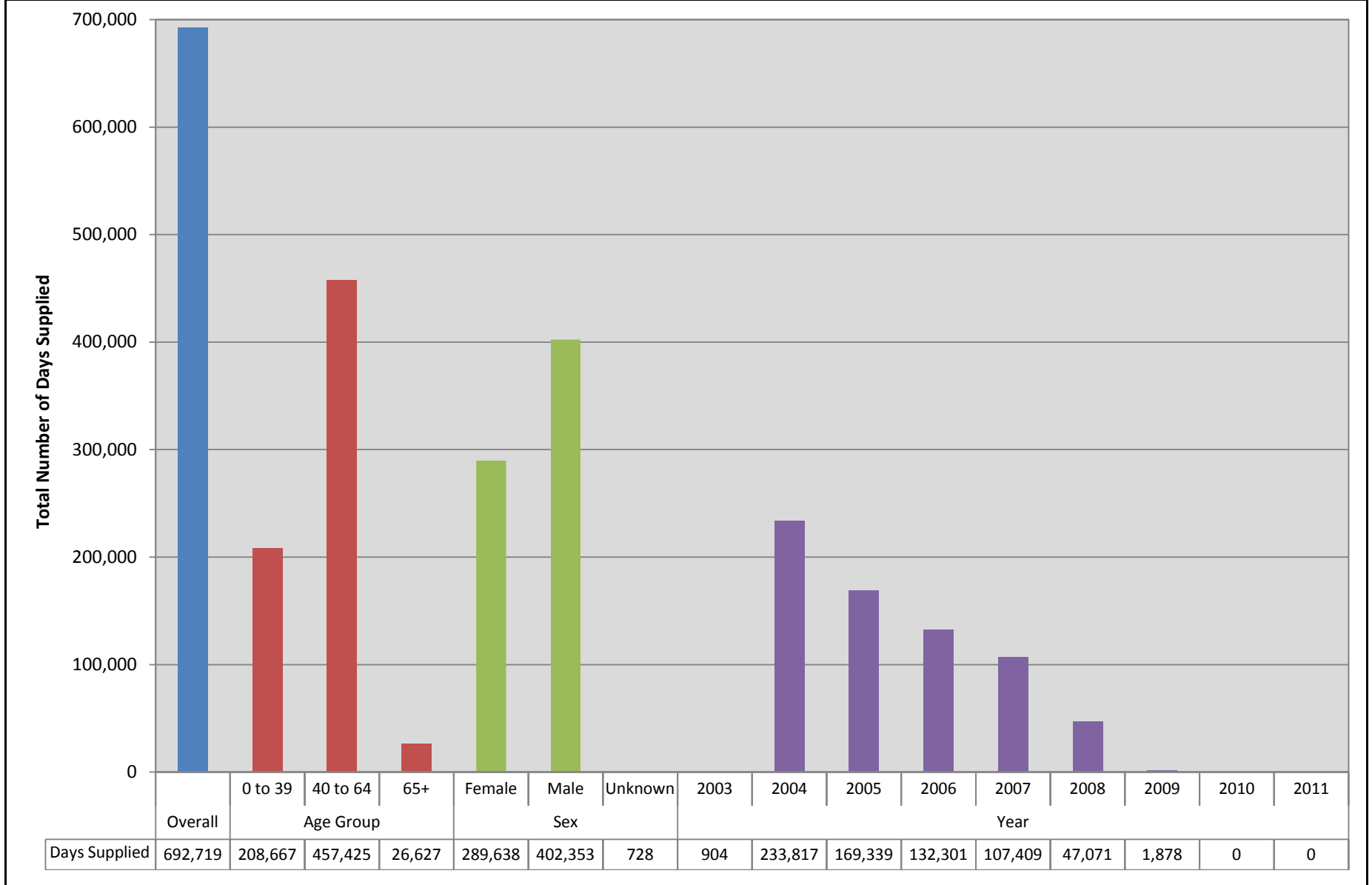
*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 3b. Number of Exposures (Dispensings/Injections) for Incident Efalizumab* Users, Overall and by Age Group, Sex, and Year



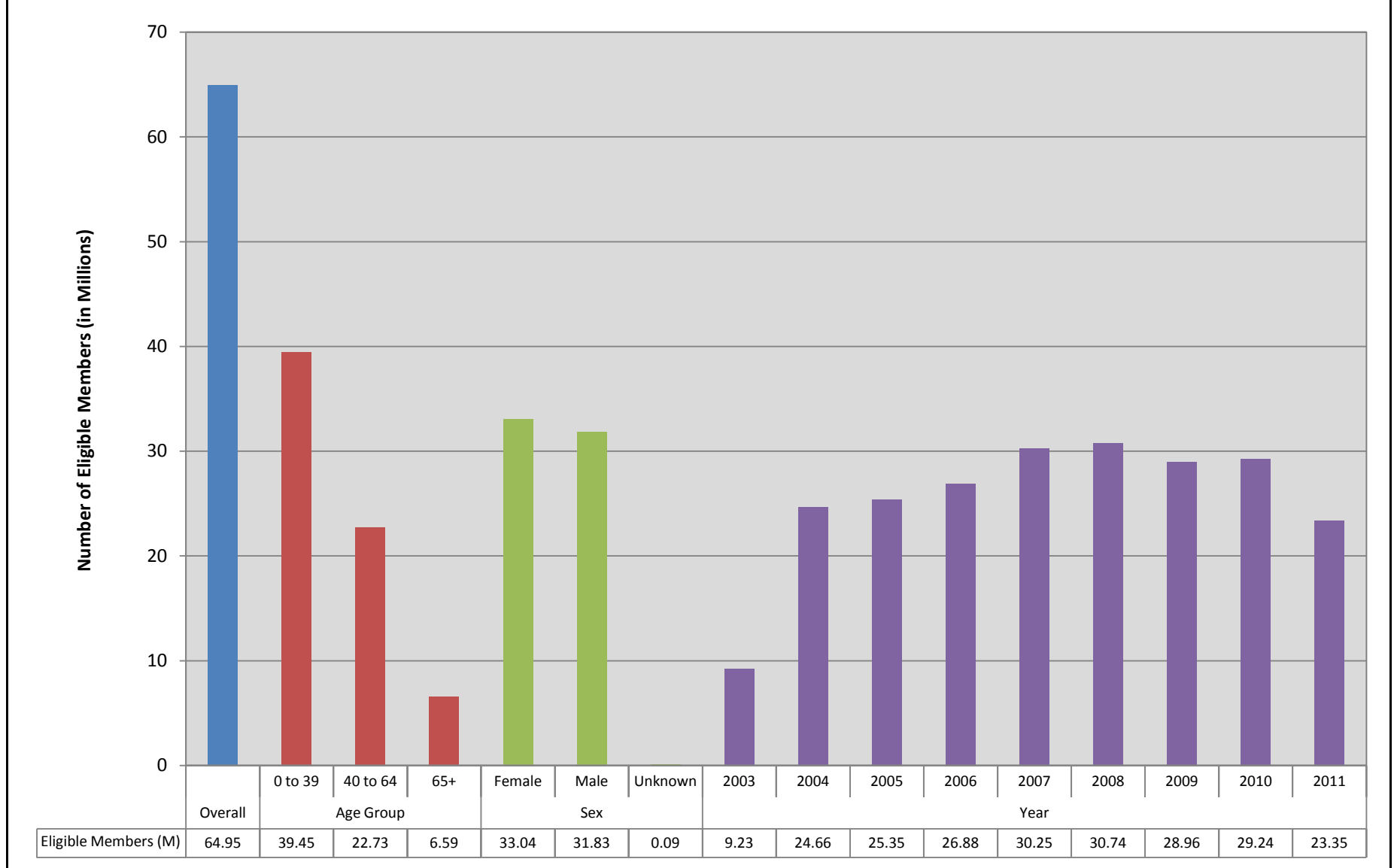
*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 3c. Number of Days Supplied for Incident Efalizumab* Users, Overall and by Age Group, Sex, and Year



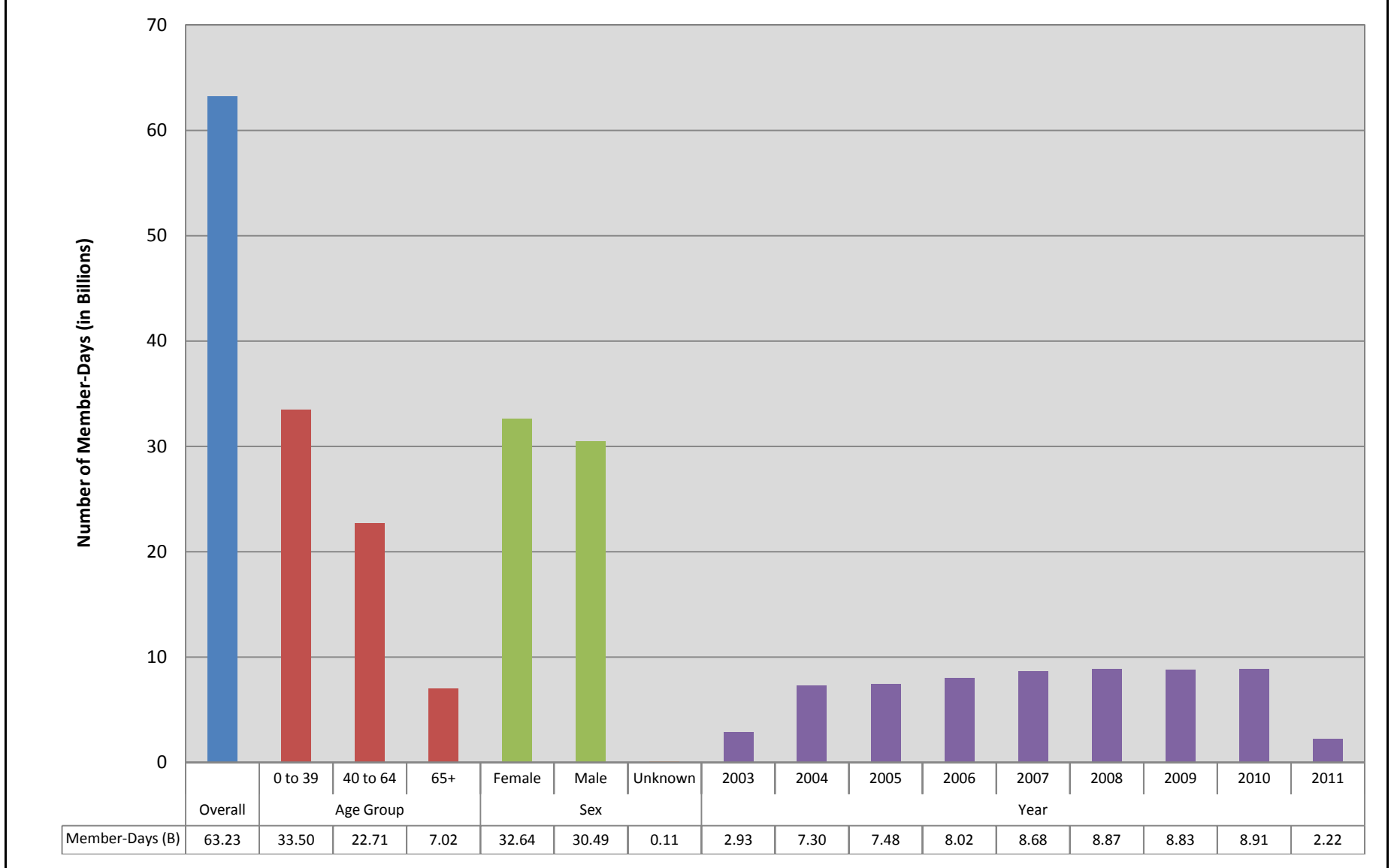
*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 3d. Number of Members Eligible for Efalizumab* Use, Overall and by Age Group, Sex, and Year



*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 3e. Number of Member-Days for Members Eligible for Efalizumab* Use, Overall and by Age Group, Sex, and Year



*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 3f. Number of Incident Natalizumab Users, Overall and by Age Group, Sex, and Year

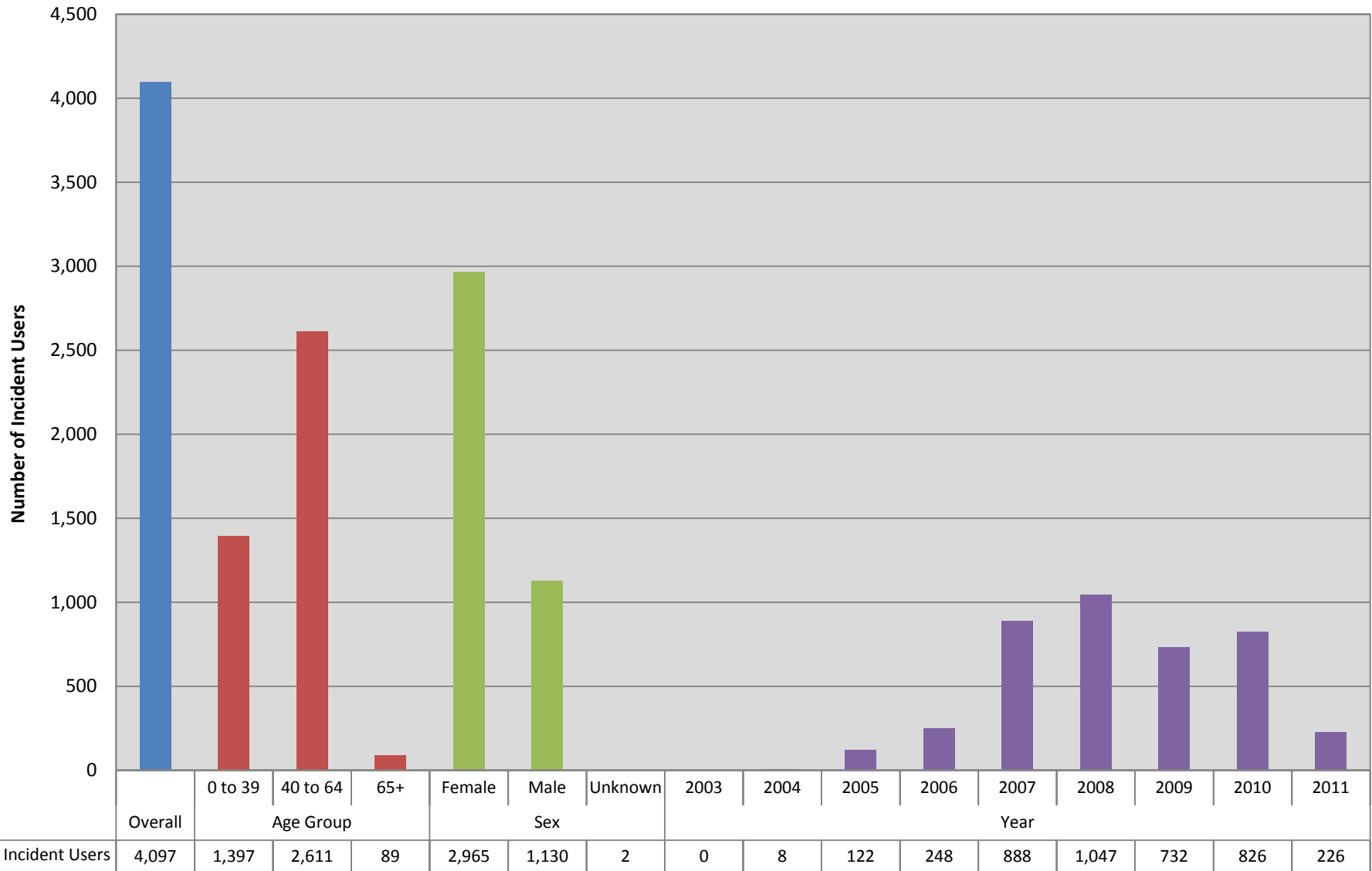


Figure 3g. Number of Exposures (Dispensings/Injections) for Incident Natalizumab Users, Overall and by Age Group, Sex, and Year

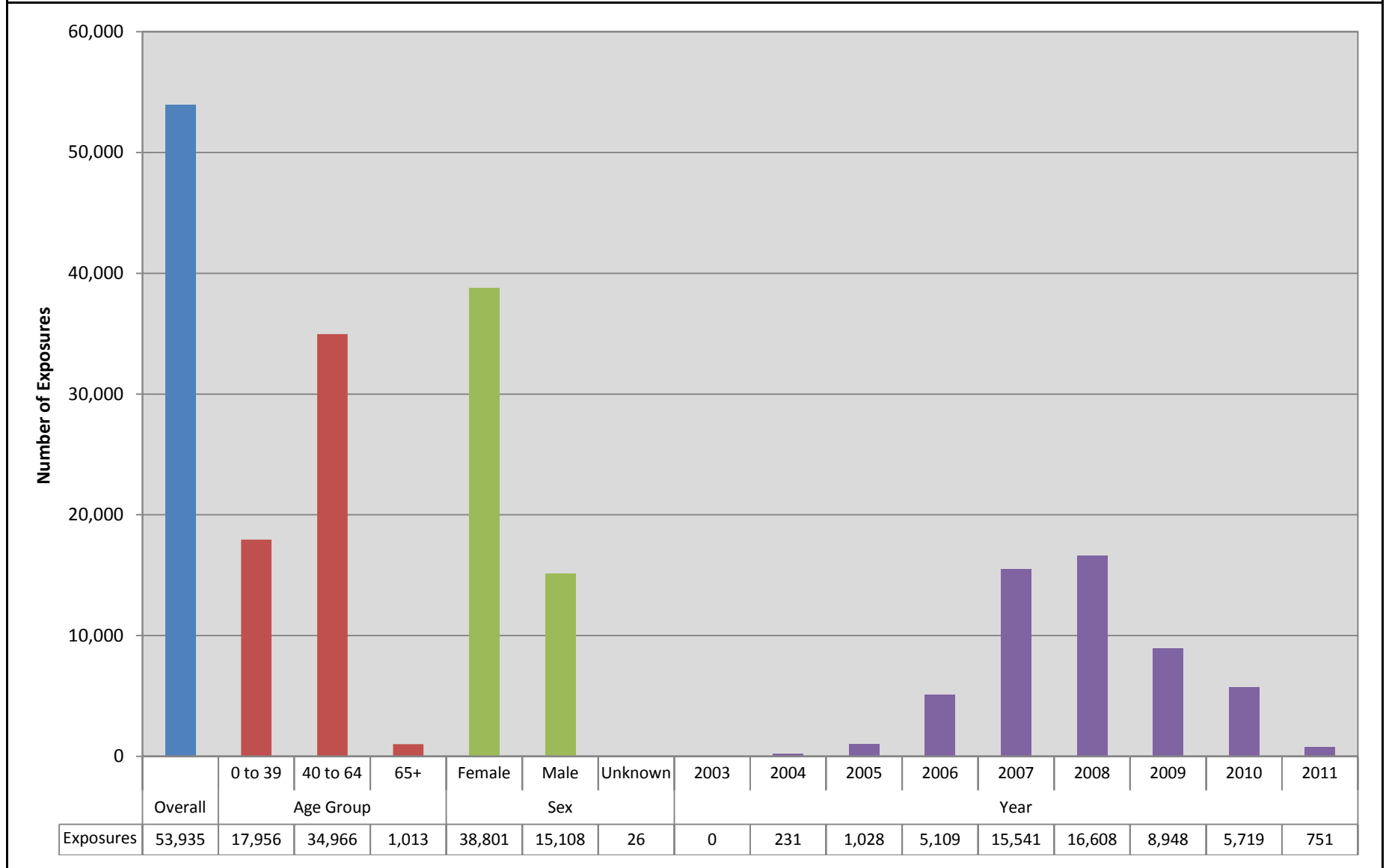


Figure 3h. Number of Days Supplied for Incident Natalizumab Users, Overall and by Age Group, Sex, and Year

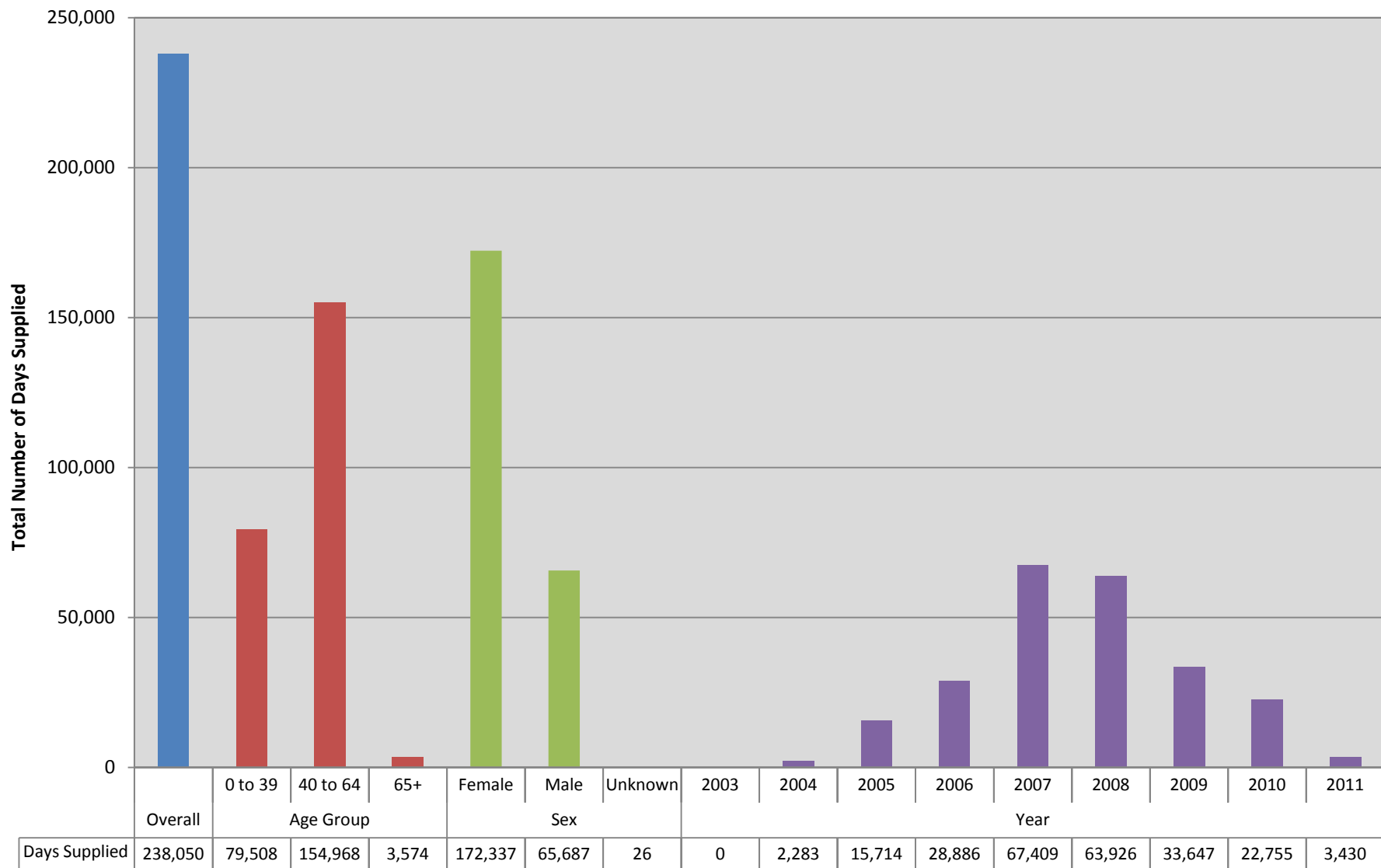


Figure 3i. Number of Members Eligible for Natalizumab Use, Overall and by Age Group, Sex, and Year

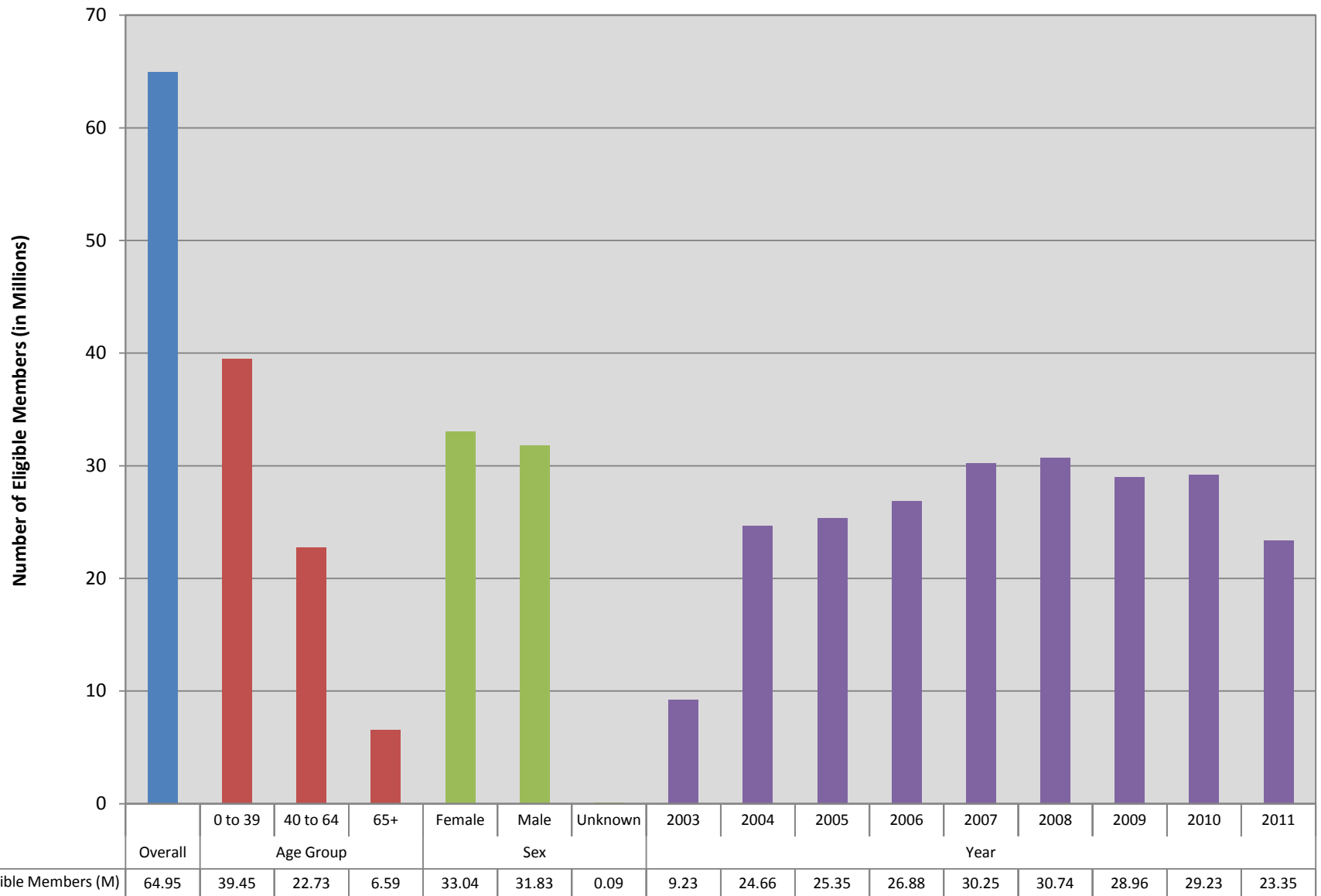


Figure 3j. Number of Member-Days for Members Eligible for Natalizumab Use, Overall and by Age Group, Sex, and Year

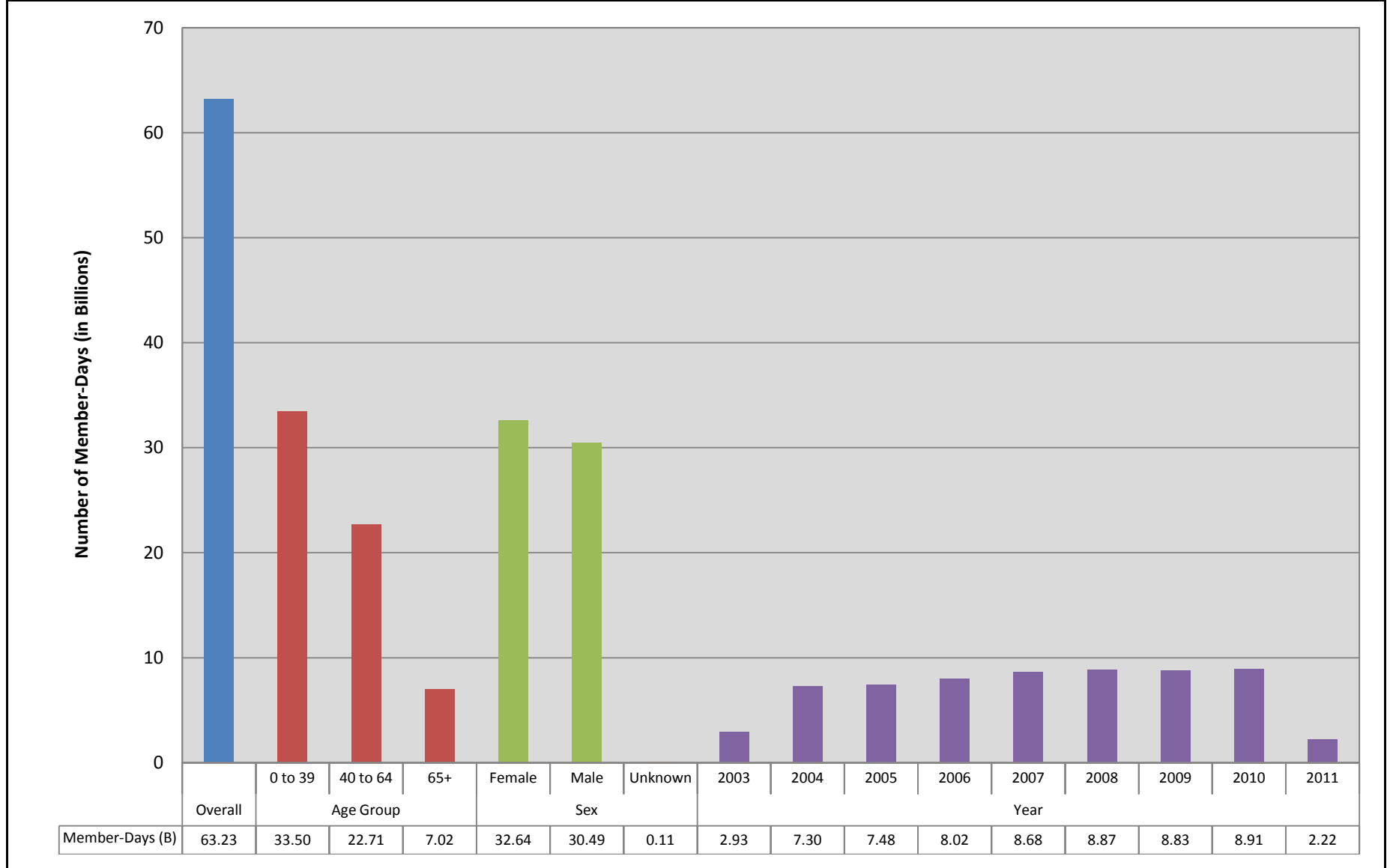
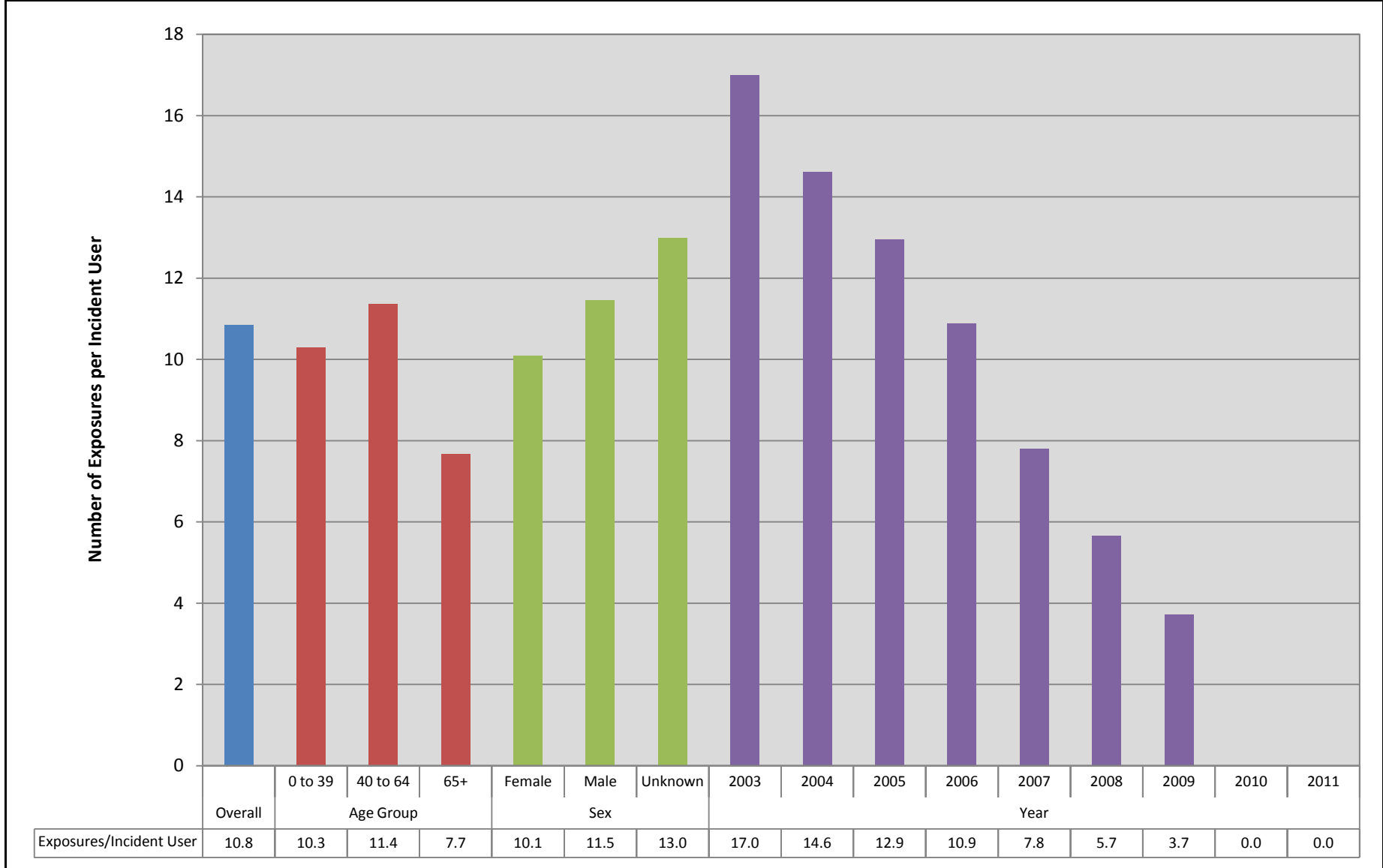


Table 4. Number of Exposures per Incident User, Days Supplied per Incident User, Days Supplied per Exposure, and Rates of Incident Users per 1 Million Eligible Members by Drug Product, Overall and by Age Group, Sex, and Year

| | | Exposures/Incident User | Days Supplied/Incident User | Days Supplied/Exposure | Incident Users/ 1M Eligible Members | |
|-------------|-----------|-------------------------|-----------------------------|------------------------|--|--------|
| EFALIZUMAB* | OVERALL | 10.84 | 292.78 | 27.00 | 36.43 | |
| | AGE GROUP | 0 to 39 years | 10.30 | 263.14 | 25.55 | 20.10 |
| | | 40 to 64 years | 11.37 | 312.02 | 27.45 | 64.49 |
| | | 65+ years | 7.68 | 248.85 | 32.39 | 16.24 |
| | SEX | Female | 10.10 | 271.96 | 26.94 | 32.24 |
| | | Male | 11.45 | 309.74 | 27.05 | 40.82 |
| | | Unknown | 13.00 | 364.00 | 28.00 | 22.70 |
| | YEAR | 2003 | 17.00 | 452.00 | 26.59 | 0.22 |
| | | 2004 | 14.62 | 384.57 | 26.30 | 24.66 |
| | | 2005 | 12.94 | 342.10 | 26.43 | 19.53 |
| | | 2006 | 10.89 | 315.00 | 28.92 | 15.62 |
| | | 2007 | 7.81 | 219.65 | 28.14 | 16.17 |
| | | 2008 | 5.67 | 147.10 | 25.96 | 10.41 |
| 2009 | | 3.72 | 58.69 | 15.78 | 1.10 | |
| 2010 | | . | . | . | . | |
| 2011 | | . | . | . | . | |
| NATALIZUMAB | OVERALL | 13.16 | 58.10 | 4.41 | 63.08 | |
| | AGE GROUP | 0 to 39 years | 12.85 | 56.91 | 4.43 | 35.41 |
| | | 40 to 64 years | 13.39 | 59.35 | 4.43 | 114.86 |
| | | 65+ years | 11.38 | 40.16 | 3.53 | 13.50 |
| | SEX | Female | 13.09 | 58.12 | 4.44 | 89.75 |
| | | Male | 13.37 | 58.13 | 4.35 | 35.51 |
| | | Unknown | 13.00 | 13.00 | 1.00 | 22.70 |
| | YEAR | 2003 | . | . | . | . |
| | | 2004 | 28.88 | 285.38 | 9.88 | 0.32 |
| | | 2005 | 8.43 | 128.80 | 15.29 | 4.81 |
| | | 2006 | 20.60 | 116.48 | 5.65 | 9.22 |
| | | 2007 | 17.50 | 75.91 | 4.34 | 29.36 |
| | | 2008 | 15.86 | 61.06 | 3.85 | 34.06 |
| 2009 | | 12.22 | 45.97 | 3.76 | 25.28 | |
| 2010 | | 6.92 | 27.55 | 3.98 | 28.25 | |
| 2011 | | 3.32 | 15.18 | 4.57 | 9.68 | |

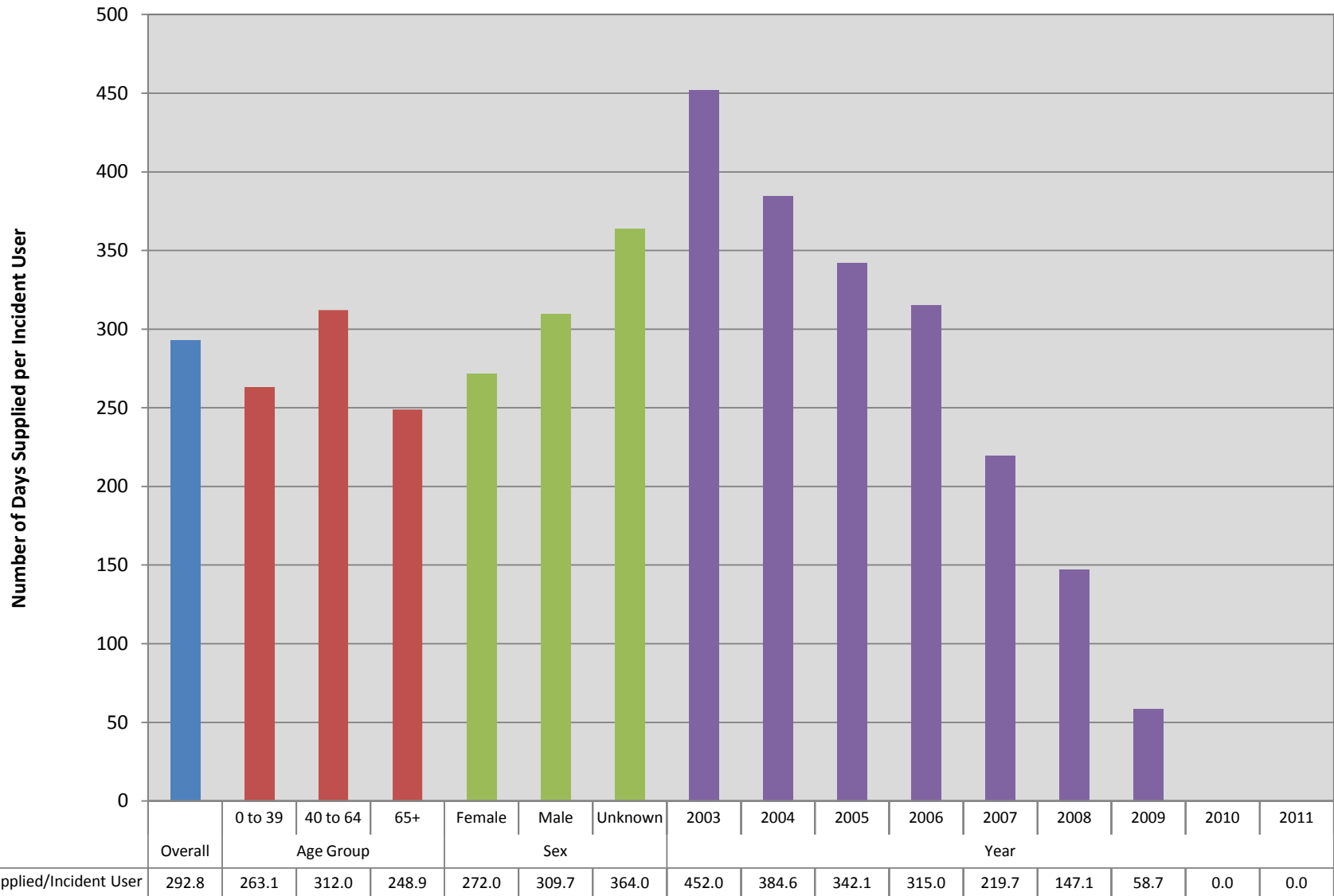
*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 4a. Number of Exposures per Incident Efalizumab* User, Overall and by Age Group, Sex, and Year



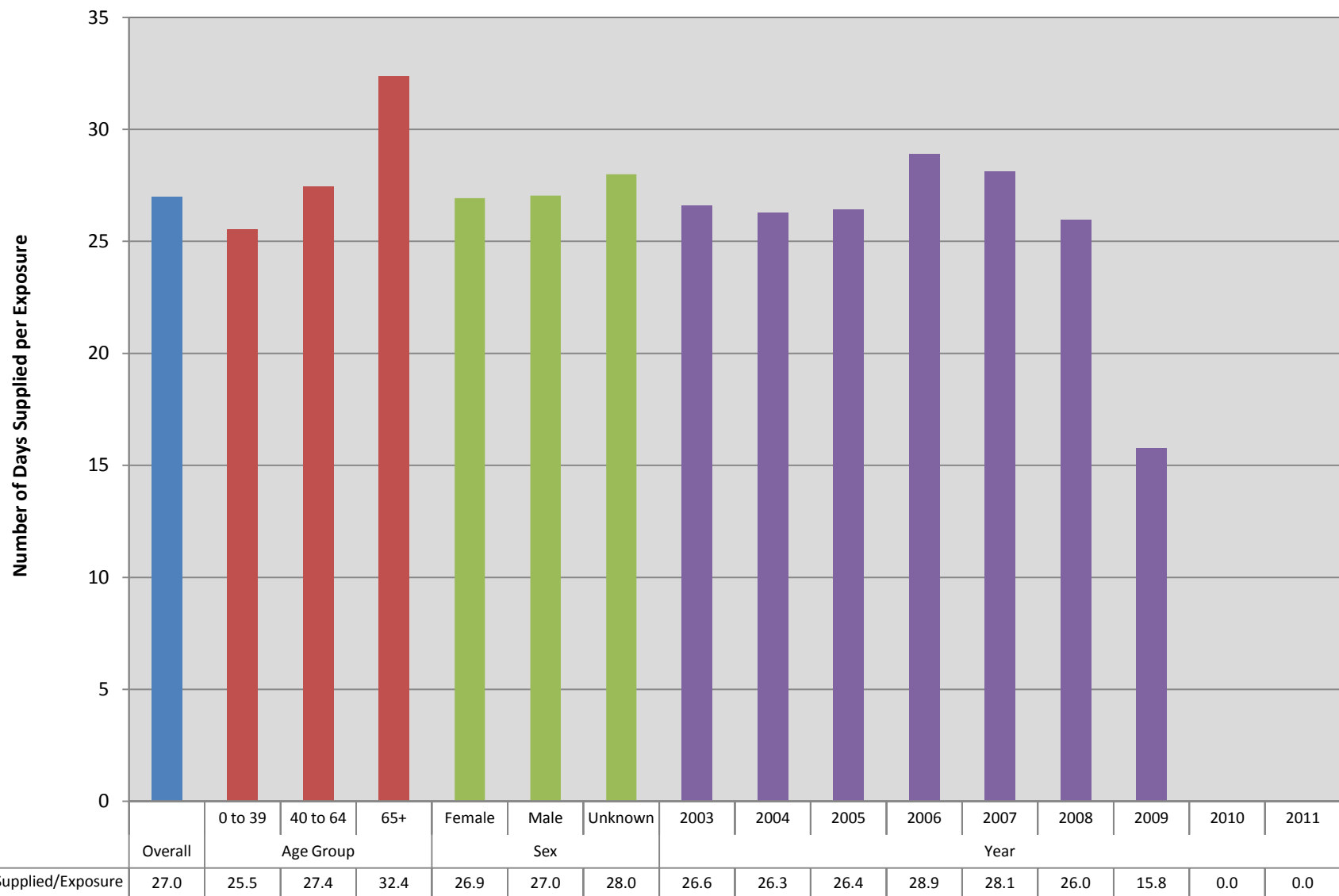
*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 4b. Number of Days Supplied per Incident Efalizumab* User, Overall and by Age Group, Sex, and Year



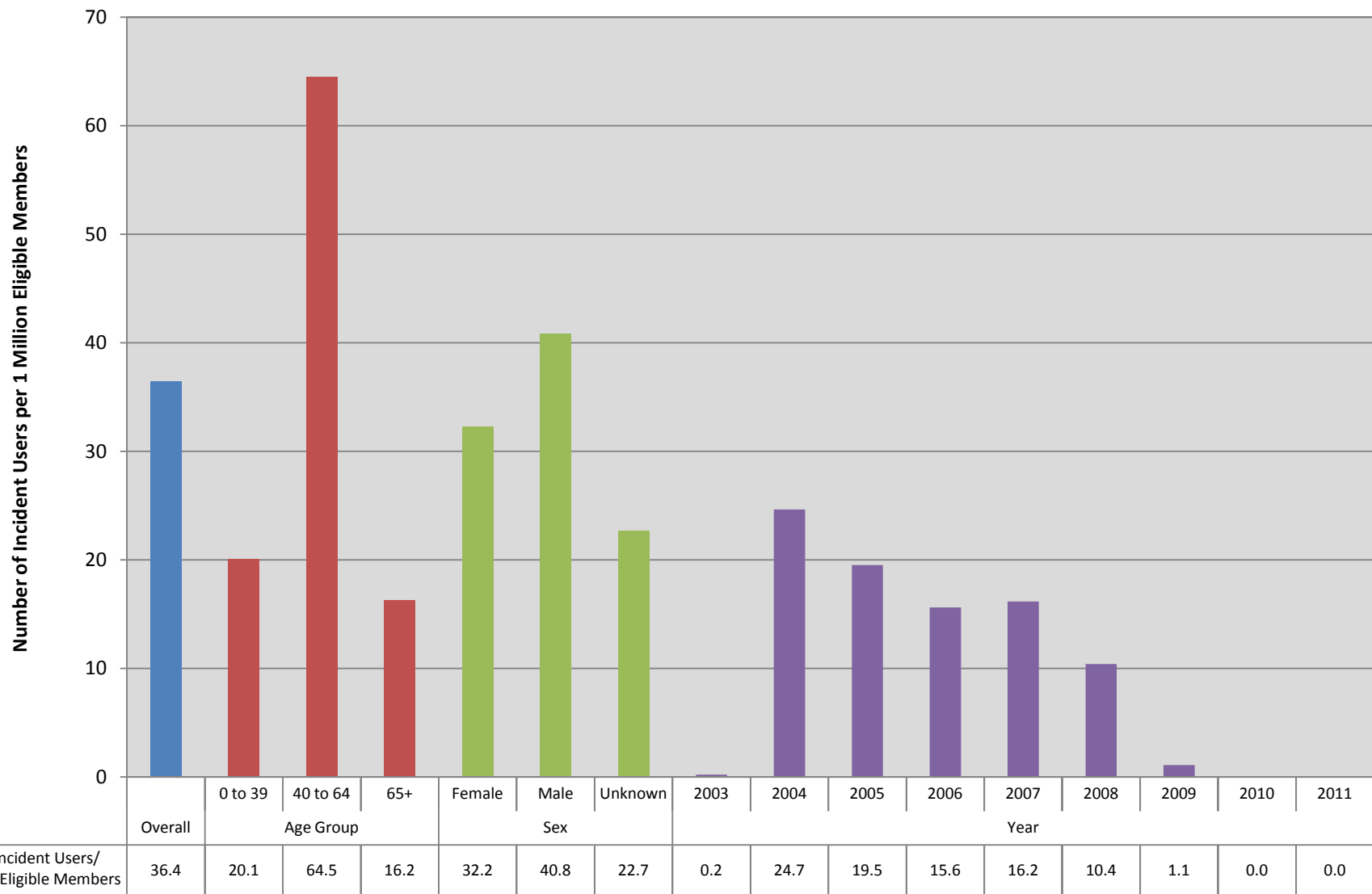
*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 4c. Number of Days Supplied per Exposure of Efalizumab*, Overall and by Age Group, Sex, and Year



*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 4d. Rates of Incident Efalizumab* Users per 1 Million Eligible Members, Overall and by Age Group, Sex, and Year



*Withdrawn from market in 2009 and unavailable in 2010 and 2011

Figure 4e. Number of Exposures per Incident Natalizumab User, Overall and by Age Group, Sex, and Year

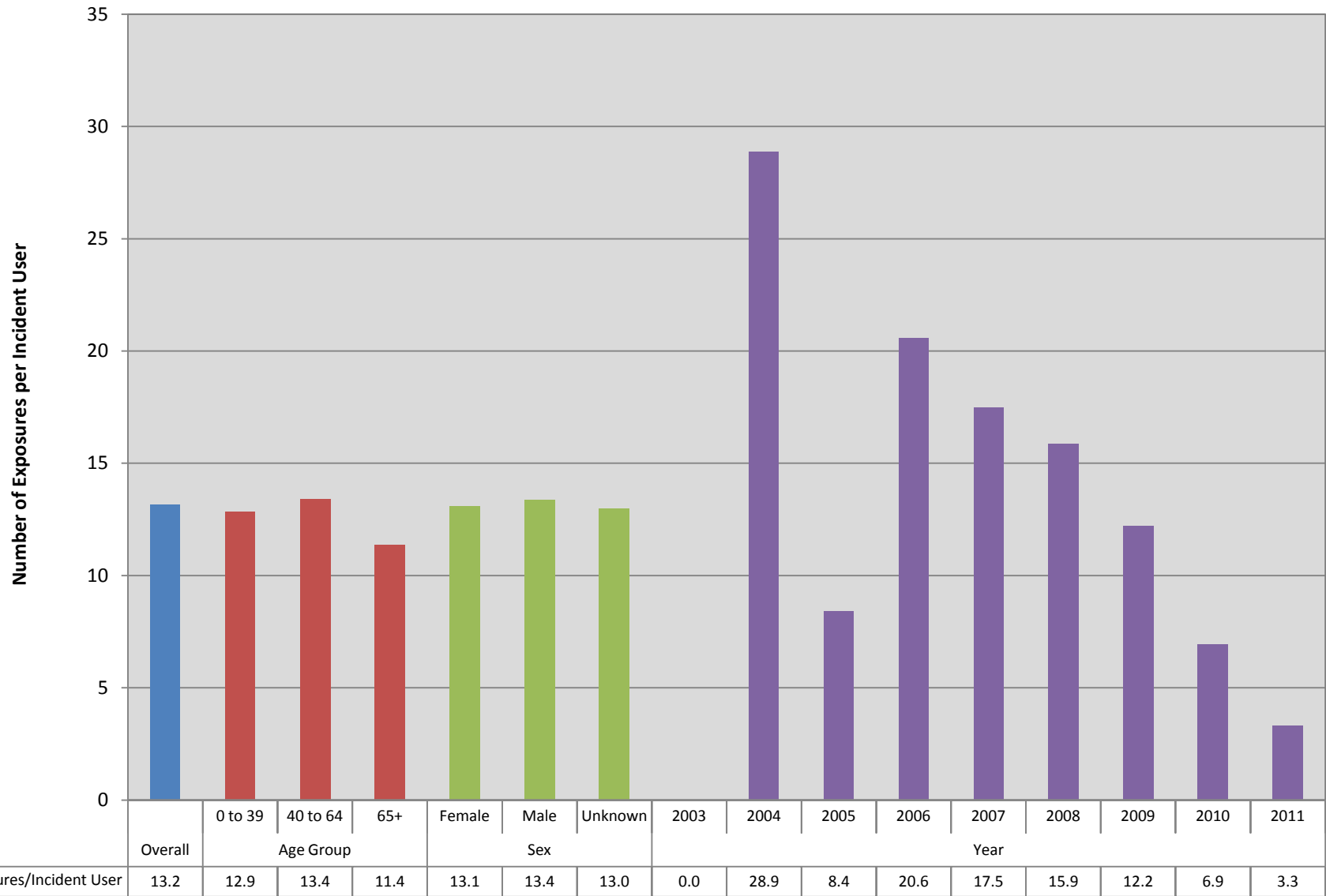


Figure 4f. Number of Days Supplied per Incident Natalizumab User, Overall and by Age Group, Sex, and Year

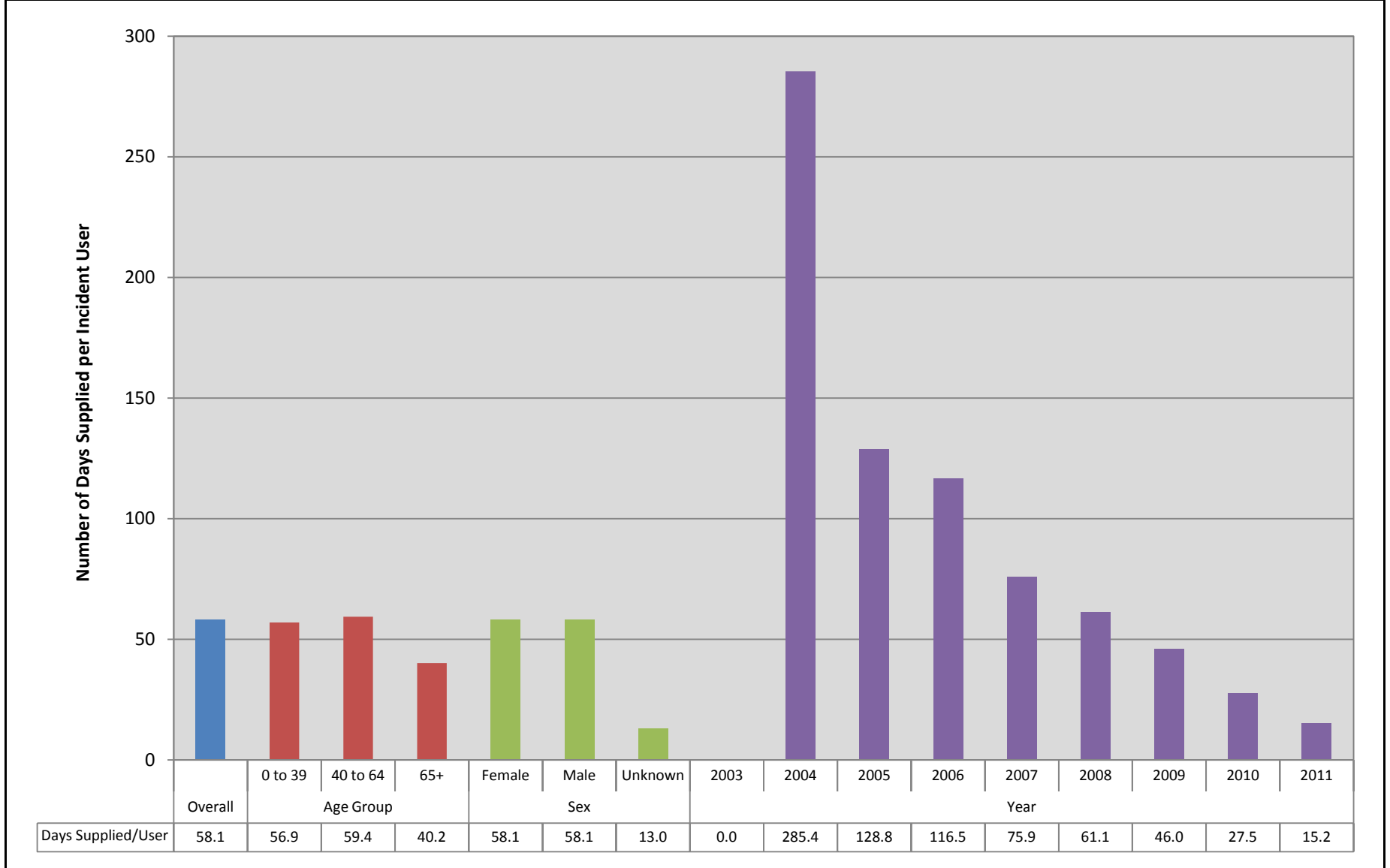
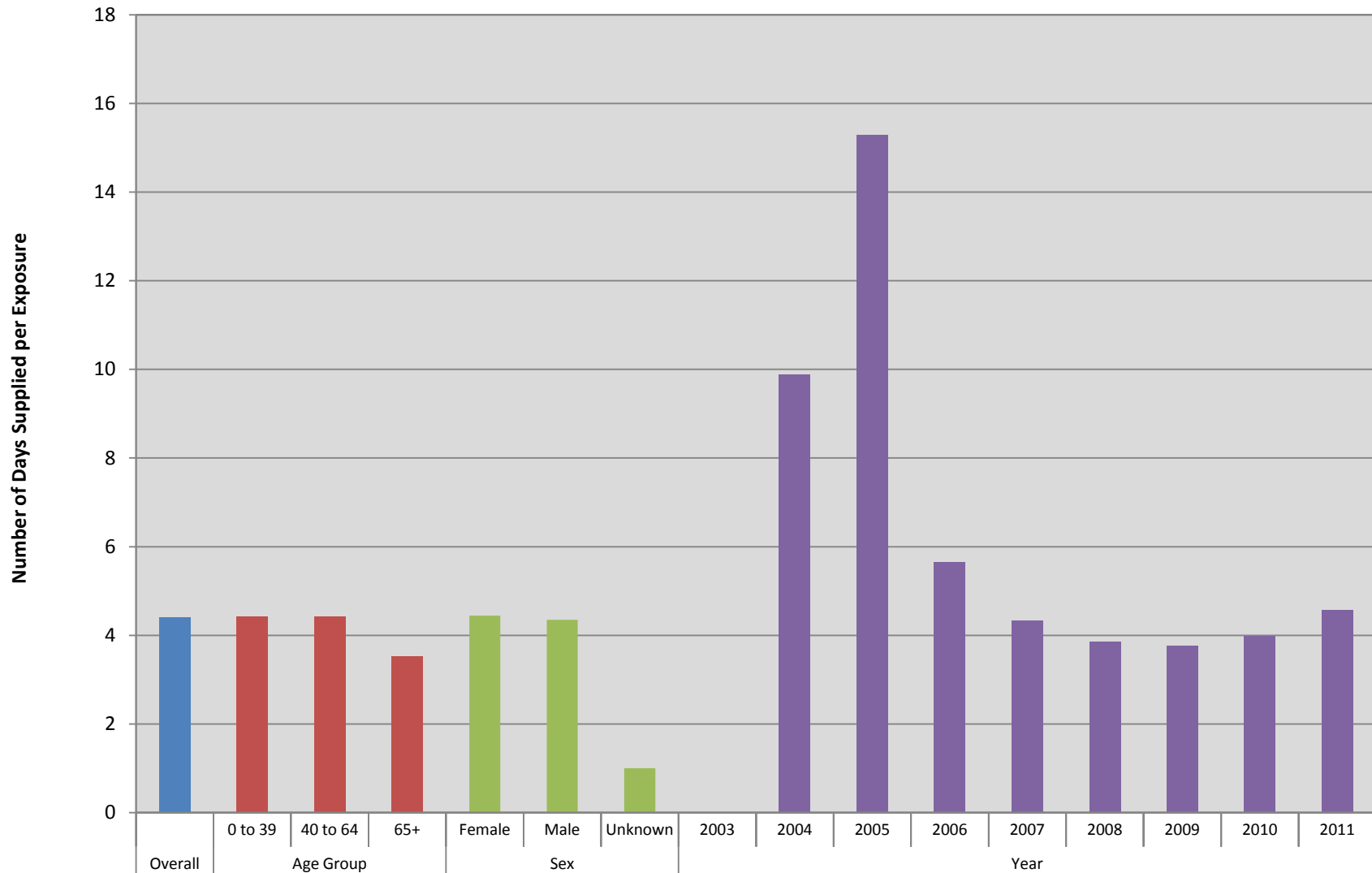


Figure 4g. Number of Days Supplied per Exposure of Natalizumab, Overall and by Age Group, Sex, and Year



| | | | | | | | | | | | | | | | | |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|
| Days Supplied/Exposure | 4.4 | 4.4 | 4.4 | 3.5 | 4.4 | 4.3 | 1.0 | 0.0 | 9.9 | 15.3 | 5.7 | 4.3 | 3.8 | 3.8 | 4.0 | 4.6 |
|------------------------|-----|-----|-----|-----|-----|-----|-----|-----|-----|------|-----|-----|-----|-----|-----|-----|

Figure 4h. Rates of Incident Natalizumab Users per 1 Million Eligible Members, Overall and by Age Group, Sex, and Year

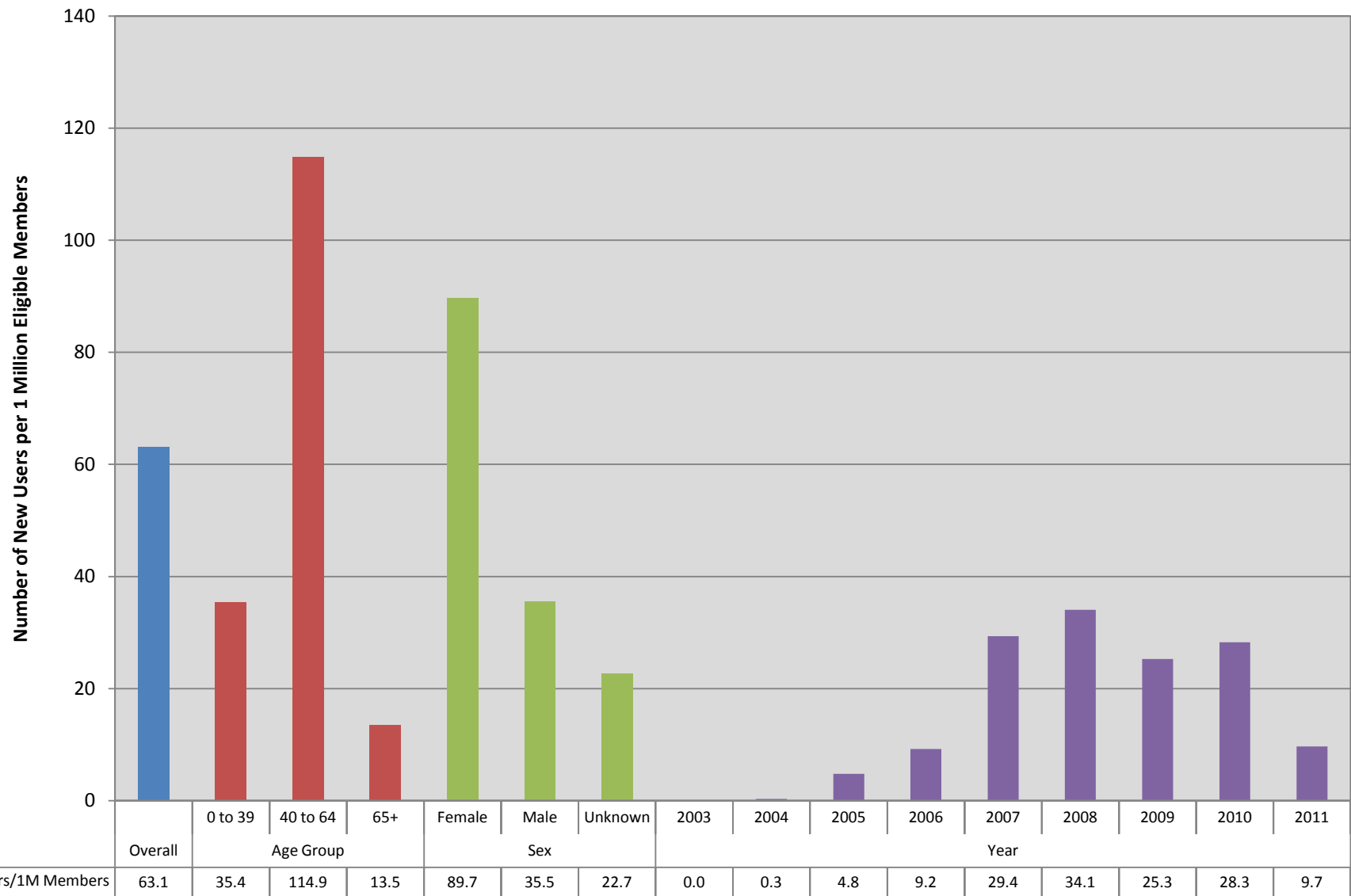


Table 5. Number of Incident Users (from Table 3), PML Events, Days at Risk, and Rates of PML Events per 1 Million Days at Risk by Drug Product, Overall and by Age Group, Sex, and Year

| | | Incident Users | PML Events | Days at Risk | PML Events/1M Days at Risk | |
|-------------|-----------|----------------|------------|--------------|----------------------------|------|
| EFALIZUMAB* | OVERALL | 2,366 | 0 | 2,435,342 | 0 | |
| | AGE GROUP | 0 to 39 years | 793 | 0 | 753,724 | 0 |
| | | 40 to 64 years | 1,466 | 0 | 1,573,976 | 0 |
| | | 65+ years | 107 | 0 | 107,642 | 0 |
| | SEX | Female | 1,065 | 0 | 1,077,405 | 0 |
| | | Male | 1,299 | 0 | 1,356,554 | 0 |
| | | Unknown | 2 | 0 | 1,383 | 0 |
| | YEAR | 2003 | 2 | 0 | 1,175 | 0 |
| | | 2004 | 608 | 0 | 798,700 | 0 |
| | | 2005 | 495 | 0 | 568,142 | 0 |
| | | 2006 | 420 | 0 | 419,916 | 0 |
| | | 2007 | 489 | 0 | 403,468 | 0 |
| | | 2008 | 320 | 0 | 227,098 | 0 |
| 2009 | | 32 | 0 | 16,843 | 0 | |
| 2010 | | . | . | . | . | |
| 2011 | | . | . | . | . | |
| NATALIZUMAB | OVERALL | 4,097 | 7 | 2,560,370 | 2.73 | |
| | AGE GROUP | 0 to 39 years | 1,397 | 5 | 811,778 | 6.16 |
| | | 40 to 64 years | 2,611 | 2 | 1,687,932 | 1.18 |
| | | 65+ years | 89 | 0 | 60,660 | 0.00 |
| | SEX | Female | 2,965 | 5 | 1,846,533 | 2.71 |
| | | Male | 1,130 | 2 | 711,943 | 2.81 |
| | | Unknown | 2 | 0 | 1,894 | 0.00 |
| | YEAR | 2003 | 0 | 0 | 0 | . |
| | | 2004 | 8 | 0 | 13,449 | 0.00 |
| | | 2005 | 122 | 0 | 151,666 | 0.00 |
| | | 2006 | 248 | 0 | 225,918 | 0.00 |
| | | 2007 | 888 | 1 | 759,524 | 1.32 |
| | | 2008 | 1,047 | 1 | 791,605 | 1.26 |
| 2009 | | 732 | 4 | 381,844 | 10.48 | |
| 2010 | | 826 | 1 | 210,666 | 4.75 | |
| 2011 | | 226 | 0 | 25,698 | 0.00 | |

*Withdrawn from market in 2009 and unavailable in 2010 and 2011