## Disclaimer

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).

If you are using a web page screen reader and are unable to access this document, please contact the Mini-Sentinel Operations Center for assistance at info@sentinelsystem.org.

**Overview for Request MSY4_MPR57_V1**

**Request ID:** msy4_mpr57_v1, Report 2 of 2

**Request Description:** This report estimates the rate of re-admission to the hospital for a Clostridium difficile (C. difficle) infection (Identified using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 008.45) following treatment with oral vancomycin, fidaxomicin, or metronidazole.

**Sentinel Modular Program Tool Used:** Modular Program #3 (MP3)

**Data Source:** Data from January 1, 2000 to December 31, 2012 from 18 Data Partners contributing to the Mini-Sentinel Distributed Database (MSDD) were utilized for the two reports that encompass this request. This request was distributed to Data Partners on August 27, 2013. See Appendix A for a list of the dates of available data for each Data Partner. Report 1 contains results from the first run, which has a query period of May 1, 2011 to December 31, 2012. Report 2 has a query period of January 1, 2000 to December 31, 2012. Please see Appendix B for details into the exact parameters used in this request.

**Study Design:** This request identifies new users of oral vancomycin, fidaxomicin, or metronidazole who had an inpatient C. difficile diagnosis prior to treatment dispensing (i.e. a "pre-existing condition" of C. difficile in the 45 or 90 days prior); a subsequent inpatient C. difficile diagnosis is the outcome/event of interest. The number of users, dispensings, total days supplied, eligible members, member-days, and other counts are reported. Eight scenarios were examined; scenarios seven and eight are in this report: (7) vancomycin, 45 day look-back, and (8) metronidazole, 45 day look-back.

**Cohort Eligibility Criteria:** Patients of the following age groups were included in the cohort: 0-<20, 20-<45, 45-<65, 65-<75, 75-<85, and 85+ years.

**Limitation:** Algorithms to define exposures are imperfect and, therefore, they may be misclassified.

**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.

Mini-Sentinel

## Table of Contents

# Glossary of Terms in Modular Program 3*

**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

**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

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

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

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

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

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

**Minimum Episode Duration -** specifies a minimum number of days in length of the epsiode for it to be considered

**New Episodes -** new treatment episodes; length of episode is determined by days supplied in one dispensing (or consecutive

**New 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

**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 -** number of days supplied for all dispensings in qualifying treatment 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.

**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 types* will use the washout period to establish incidence, however *Single* will only consider the first treatment episode whereas *Multiple* will

**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*

*all terms may not be used in this report

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

**Table 1: Summary of Incident Metronidazole and Vancomycin Use and Clostridium Difficile in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2000 and December 31, 2012, by Drug Product**

| | New Users | New Episodes | Dispensings | Total Days Supplied | Years at Risk | New Events | Eligible Members | Member-Years | New Users / 1K Eligible Members | Days Supplied / User | Dispensings / User | Days Supplied / Dispensing | Events / 1K Years at Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Metronidazole | 36,681 | 37,093 | 43,235 | 457,488 | 3,636 | 6,008 | 109,325 | 11,034 | 335.52 | 12.47 | 1.18 | 10.58 | 1,652.17 |
| Vancomycin | 17,909 | 18,103 | 24,504 | 307,522 | 1,926 | 3,397 | 127,520 | 15,626 | 140.44 | 17.17 | 1.37 | 12.55 | 1,764.16 |

The pre-exisiting condition is an inpatient C. difficile diagnosis in the 45 or 90 days prior to treatment dispensing.
A subsequent inpatient C. difficile diagnosis, after treatment initiation, is the outcome/event of interest.

**Table 2: Summary of Incident Metronidazole and Vancomycin Use and Clostridium Difficile in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2000 and December 31, 2012, by Drug Product and Age Group**

| | New Users | New Episodes | Dispensings | Total Days Supplied | Years at Risk | New Events | Eligible Members | Member-Years | New Users / 1K Eligible Members | Days Supplied / User | Dispensings / User | Days Supplied / Dispensing | Events / 1K Years at Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Metronidazole** | | | | | | | | | | | | | |
| 0 to 19 Years | 1,611 | 1,631 | 1,846 | 19,329 | 167 | 184 | 3,888 | 342 | 414.35 | 12.00 | 1.15 | 10.47 | 1,104.27 |
| 20 to 44 Years | 4,783 | 4,819 | 5,438 | 59,086 | 498 | 479 | 9,643 | 776 | 496.01 | 12.35 | 1.14 | 10.87 | 961.22 |
| 45 to 64 Years | 11,826 | 11,966 | 13,746 | 146,953 | 1,211 | 1,617 | 28,528 | 2,604 | 414.54 | 12.43 | 1.16 | 10.69 | 1,334.95 |
| 65 to 74 Years | 7,165 | 7,229 | 8,415 | 88,048 | 696 | 1,298 | 21,883 | 2,277 | 327.42 | 12.29 | 1.17 | 10.46 | 1,864.32 |
| 75 to 84 Years | 7,433 | 7,495 | 9,014 | 93,389 | 704 | 1,539 | 28,246 | 3,060 | 263.15 | 12.56 | 1.21 | 10.36 | 2,185.59 |
| 85+ Years | 3,923 | 3,953 | 4,776 | 50,683 | 360 | 891 | 18,443 | 1,975 | 212.71 | 12.92 | 1.22 | 10.61 | 2,476.41 |
| **Vancomycin** | | | | | | | | | | | | | |
| 0 to 19 Years | 403 | 405 | 539 | 6,208 | 45 | 45 | 4,526 | 561 | 89.04 | 15.40 | 1.34 | 11.52 | 994.33 |
| 20 to 44 Years | 2,582 | 2,607 | 3,443 | 41,669 | 284 | 361 | 12,244 | 1,330 | 210.88 | 16.14 | 1.33 | 12.10 | 1,271.58 |
| 45 to 64 Years | 6,367 | 6,418 | 8,564 | 104,470 | 690 | 1,025 | 34,308 | 3,979 | 185.58 | 16.41 | 1.35 | 12.20 | 1,484.66 |
| 65 to 74 Years | 3,280 | 3,307 | 4,485 | 57,388 | 346 | 675 | 25,534 | 3,204 | 128.46 | 17.50 | 1.37 | 12.80 | 1,949.18 |
| 75 to 84 Years | 3,506 | 3,546 | 4,891 | 62,785 | 371 | 833 | 32,050 | 4,046 | 109.39 | 17.91 | 1.40 | 12.84 | 2,243.97 |
| 85+ Years | 1,795 | 1,820 | 2,582 | 35,002 | 188 | 458 | 20,614 | 2,506 | 87.08 | 19.50 | 1.44 | 13.56 | 2,429.80 |

The pre-exisiting condition is an inpatient C. difficile diagnosis in the 45 or 90 days prior to treatment dispensing.
A subsequent inpatient C. difficile diagnosis, after treatment initiation, is the outcome/event of interest.

**Table 3: Summary of Incident Metronidazole and Vancomycin Use and Clostridium Difficile in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2000 and December 31, 2012, by Drug Product and Sex**

| | New Users | New Episodes | Dispensings | Total Days Supplied | Years at Risk | New Events | Eligible Members | Member-Years | New Users / 1K Eligible Members | Days Supplied / User | Dispensings / User | Days Supplied / Dispensing | Events / 1K Years at Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Metronidazole** | | | | | | | | | | | | | |
| Female | 21,485 | 21,748 | 25,428 | 267,540 | 2,129 | 3,573 | 62,424 | 6,235 | 344.18 | 12.45 | 1.18 | 10.52 | 1,678.03 |
| Male | 15,194 | 15,343 | 17,805 | 189,933 | 1,507 | 2,435 | 46,899 | 4,800 | 323.97 | 12.50 | 1.17 | 10.67 | 1,615.87 |
| Unknown | 2 | 2 | 2 | 15 | 0 | 0 | 2 | 0 | 1000.00 | 7.50 | 1.00 | 7.50 | 0.00 |
| **Vancomycin** | | | | | | | | | | | | | |
| Female | 11,149 | 11,271 | 15,454 | 191,127 | 1,203 | 2,084 | 73,700 | 8,960 | 151.28 | 17.14 | 1.39 | 12.37 | 1,731.92 |
| Male | 6,760 | 6,832 | 9,050 | 116,395 | 722 | 1,313 | 53,817 | 6,666 | 125.61 | 17.22 | 1.34 | 12.86 | 1,817.87 |
| Unknown | 0 | 0 | 0 | 0 | 0 | 0 | 3 | 0 | 0.00 | --- | --- | --- | --- |

The pre-exisiting condition is an inpatient C. difficile diagnosis in the 45 or 90 days prior to treatment dispensing.
A subsequent inpatient C. difficile diagnosis, after treatment initiation, is the outcome/event of interest.

**Table 4: Summary of Incident Metronidazole and Vancomycin Use and Clostridium Difficile in the Mini-Sentinel Distributed Database (MSDD) between January 1, 2000 and December 31, 2012, by Drug Product and Year**

| | New Users | New Episodes | Dispensings | Total Days Supplied | Years at Risk | New Events | Eligible Members | Member-Years | New Users / 1K Eligible Members | Days Supplied / User | Dispensings / User | Days Supplied / Dispensing | Events / 1K Years at Risk |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Metronidazole** | | | | | | | | | | | | | |
| 2000 | 384 | 384 | 434 | 4,105 | 38 | 41 | 954 | 65 | 402.52 | 10.69 | 1.13 | 9.46 | 1,074.42 |
| 2001 | 797 | 798 | 929 | 8,931 | 81 | 85 | 2,028 | 151 | 393.00 | 11.21 | 1.17 | 9.61 | 1,055.74 |
| 2002 | 1,059 | 1,059 | 1,198 | 11,331 | 105 | 99 | 2,473 | 178 | 428.22 | 10.70 | 1.13 | 9.46 | 940.02 |
| 2003 | 1,106 | 1,108 | 1,272 | 12,397 | 109 | 142 | 2,624 | 190 | 421.49 | 11.21 | 1.15 | 9.75 | 1,304.79 |
| 2004 | 1,322 | 1,323 | 1,549 | 16,150 | 132 | 191 | 3,325 | 253 | 397.59 | 12.22 | 1.17 | 10.43 | 1,444.87 |
| 2005 | 1,582 | 1,584 | 1,859 | 18,986 | 156 | 243 | 4,187 | 335 | 377.84 | 12.00 | 1.18 | 10.21 | 1,556.93 |
| 2006 | 1,957 | 1,958 | 2,321 | 25,222 | 195 | 329 | 5,954 | 486 | 328.69 | 12.89 | 1.19 | 10.87 | 1,688.38 |
| 2007 | 2,841 | 2,845 | 3,401 | 36,754 | 291 | 411 | 9,663 | 852 | 294.01 | 12.94 | 1.20 | 10.81 | 1,411.92 |
| 2008 | 4,880 | 4,885 | 5,777 | 61,123 | 479 | 859 | 16,271 | 1,471 | 299.92 | 12.53 | 1.18 | 10.58 | 1,792.33 |
| 2009 | 5,374 | 5,379 | 6,327 | 67,768 | 537 | 815 | 18,007 | 1,647 | 298.44 | 12.61 | 1.18 | 10.71 | 1,516.31 |
| 2010 | 5,387 | 5,393 | 6,270 | 67,249 | 522 | 981 | 18,248 | 1,687 | 295.21 | 12.48 | 1.16 | 10.73 | 1,878.86 |
| 2011 | 5,436 | 5,443 | 6,271 | 67,130 | 530 | 923 | 19,856 | 1,910 | 273.77 | 12.35 | 1.15 | 10.70 | 1,741.97 |
| 2012 | 4,930 | 4,934 | 5,627 | 60,342 | 461 | 889 | 18,686 | 1,808 | 263.83 | 12.24 | 1.14 | 10.72 | 1,929.91 |
| **Vancomycin** | | | | | | | | | | | | | |
| 2000 | 115 | 115 | 160 | 1,725 | 12 | 20 | 1,220 | 113 | 94.26 | 15.00 | 1.39 | 10.78 | 1,680.08 |
| 2001 | 226 | 226 | 343 | 3,385 | 24 | 25 | 2,409 | 249 | 93.81 | 14.98 | 1.52 | 9.87 | 1,048.36 |
| 2002 | 285 | 285 | 399 | 4,177 | 31 | 37 | 2,944 | 304 | 96.81 | 14.66 | 1.40 | 10.47 | 1,193.63 |
| 2003 | 247 | 247 | 356 | 3,500 | 25 | 49 | 3,229 | 339 | 76.49 | 14.17 | 1.44 | 9.83 | 1,967.16 |
| 2004 | 385 | 385 | 551 | 5,649 | 41 | 62 | 3,984 | 414 | 96.64 | 14.67 | 1.43 | 10.25 | 1,510.81 |
| 2005 | 538 | 542 | 743 | 7,967 | 54 | 126 | 5,083 | 537 | 105.84 | 14.81 | 1.38 | 10.72 | 2,347.68 |
| 2006 | 861 | 862 | 1,208 | 14,856 | 92 | 173 | 7,069 | 716 | 121.80 | 17.25 | 1.40 | 12.30 | 1,875.08 |
| 2007 | 1,543 | 1,544 | 2,131 | 25,900 | 166 | 275 | 11,462 | 1,181 | 134.62 | 16.79 | 1.38 | 12.15 | 1,660.09 |
| 2008 | 2,729 | 2,732 | 3,619 | 44,996 | 291 | 517 | 19,090 | 2,010 | 142.95 | 16.49 | 1.33 | 12.43 | 1,777.56 |
| 2009 | 2,907 | 2,912 | 4,045 | 53,183 | 319 | 532 | 21,336 | 2,276 | 136.25 | 18.29 | 1.39 | 13.15 | 1,665.96 |
| 2010 | 2,904 | 2,907 | 3,992 | 51,645 | 312 | 579 | 21,809 | 2,367 | 133.16 | 17.78 | 1.37 | 12.94 | 1,855.96 |
| 2011 | 2,765 | 2,770 | 3,666 | 47,762 | 300 | 502 | 23,700 | 2,636 | 116.67 | 17.27 | 1.33 | 13.03 | 1,674.80 |
| 2012 | 2,573 | 2,576 | 3,291 | 42,777 | 259 | 500 | 22,302 | 2,485 | 115.37 | 16.63 | 1.28 | 13.00 | 1,927.60 |

The pre-exisiting condition is an inpatient C. difficile diagnosis in the 45 or 90 days prior to treatment dispensing.
A subsequent inpatient C. difficile diagnosis, after treatment initiation, is the outcome/event of interest.

**Appendix A: Available Data in the Sentinel Distributed Database (SDD) for Each Data Partner as of Request Send Date (August 27, 2013)**

| Data Partner ID | Start Date | End Date |
|---|---|---|
| DP001 | 1/2/2008 | 11/30/2012 |
| DP002 | 1/2/2006 | 3/30/2013 |
| DP003 | 1/31/2004 | 4/30/2013 |
| DP004 | 1/1/2000 | 4/30/2012 |
| DP005 | 1/2/2000 | 12/31/2011 |
| DP006 | 1/1/2000 | 12/31/2011 |
| DP007 | 1/2/2000 | 6/30/2012 |
| DP008 | 1/2/2000 | 6/30/2012 |
| DP009 | 6/2/2007 | 10/31/2012 |
| DP010 | 1/2/2000 | 3/31/2013 |
| DP011 | 1/2/2000 | 5/31/2013 |
| DP012 | 1/2/2005 | 12/31/2012 |
| DP013 | 1/31/2000 | 12/31/2012 |
| DP014 | 1/31/2000 | 5/31/2013 |
| DP015 | 1/2/2008 | 9/30/2012 |
| DP016 | 1/2/2000 | 12/31/2012 |
| DP017 | 1/1/2000 | 12/31/2012 |
| DP018 | 1/1/2000 | 12/31/2012 |

## Appendix B: Modular Program Specifications MSY4_MPR57_v1

Modular Program #3 was used to estimate the rate of hospital re-admission with Clostridium difficile (C. difficile) infection (identified using International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code 008.45) following treatment with oral vancomycin, fidaxomicin, or metronidazole. In total, eight different scenarios were examined in this request with differing exposures of interest, blackout periods, and inclusion/exclusion criteria. This report contains results from scenarios 7 and 8, where the query period was from January 1, 2000 to December 31, 2012. A second report (MS_Brief_Report_MSY4_MPR57_r1.xls) contains results from scenarios 1 through 6, where the query period was from May 1, 2011 to December, 2012. See below for a description of each of these scenarios.

| | |
|---|---|
| Enrollment Gap | 45 Days |
| Age Groups | 0-<20, 20-<45, 45-<65, 65-<75, 75-<85, and 85+ years |
| Query Period | Scenarios 1-6: May 1, 2011 - December 31, 2012 |
| | Scenarios 7-8 : January 1, 2000 - December 31, 2012 |

| | Drug/Exposure | | | | | | | | Pre-Existing Condition | | | | | Event/Outcome | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Scenario | Incident exposure | Incident w/ respect to: | Washout (days) | Washout Type | Episode Gap | Exposure Extension Period | Min Episode Duration | Min Days Supplied | Pre-Existing Condition | Include or Exclude | Lookback Start | Lookback End | Care Setting | Event/ Outcome | Care Setting | Incident w/ respect to: | Incident Only Care Setting | Washout (days) | Washout Type | Blackout Period |
| 1 | *Vancomycin* | *Vancomycin* | *183* | *MULT* | *10* | *30* | *0* | *0* | *C. Diff infection* | *Include* | *-45* | *-1* | *IP** | *C. Diff infection* | *IP** | *C. Diff infection* | *IP** | *0* | *MULT* | *0* |
| 2 | *Vancomycin* | *Vancomycin* | *183* | *MULT* | *10* | *30* | *0* | *0* | *C. Diff infection* | *Include* | *-90* | *-1* | *IP** | *C. Diff infection* | *IP** | *C. Diff infection* | *IP** | *0* | *MULT* | *0* |
| 3 | *Fidaxomicin* | *Fidaxomicin* | *183* | *MULT* | *10* | *30* | *0* | *0* | *C. Diff infection* | *Include* | *-45* | *-1* | *IP** | *C. Diff infection* | *IP** | *C. Diff infection* | *IP** | *0* | *MULT* | *0* |
| 4 | *Fidaxomicin* | *Fidaxomicin* | *183* | *MULT* | *10* | *30* | *0* | *0* | *C. Diff infection* | *Include* | *-90* | *-1* | *IP** | *C. Diff infection* | *IP** | *C. Diff infection* | *IP** | *0* | *MULT* | *0* |
| 5 | *Metronidazole* | *Metronidazole* | *183* | *MULT* | *10* | *30* | *0* | *0* | *C. Diff infection* | *Include* | *-45* | *-1* | *IP** | *C. Diff infection* | *IP** | *C. Diff infection* | *IP** | *0* | *MULT* | *0* |
| 6 | *Metronidazole* | *Metronidazole* | *183* | *MULT* | *10* | *30* | *0* | *0* | *C. Diff infection* | *Include* | *-90* | *-1* | *IP** | *C. Diff infection* | *IP** | *C. Diff infection* | *IP** | *0* | *MULT* | *0* |
| 7 | Vancomycin | Vancomycin | 183 | MULT | 10 | 30 | 0 | 0 | C. Diff infection | Include | -45 | -1 | IP* | C. Diff infection | IP* | C. Diff infection | IP* | 0 | MULT | 0 |
| 8 | Metronidazole | Metronidazole | 183 | MULT | 10 | 30 | 0 | 0 | C. Diff infection | Include | -45 | -1 | IP* | C. Diff infection | IP* | C. Diff infection | IP* | 0 | MULT | 0 |

National Drug Codes (NDC codes) checked against First Data Bank's "National Drug Data File (NDDF®) Plus"
ICD-9-CM diagnosis and procedure codes checked against "Ingenix 2012 ICD-9-CM Data File" provided by OptumInsight
Healthcare Common Procedure Coding System (HCPCS) codes checked against "Optum 2012 HCPCS Level II Data File" provided by OptumInsight
Current Procedural Terminology (CPT) codes checked against "Optum 2012 Current Procedure Codes & Relative Values Data File" provided by OptumInsight