Cover page

# STU00205629: A Retrospective Study to Understand the Risk Factors/Drivers of "Inappropriate" Antimicrobial Use and the Performance Evaluation of a Clinical Decision Support Tool that Facilitates Prediction of Outbreaks of Inappropriate Antibiotic Use

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|---|---|
| Entered IRB: | 8/2/2017 2:39 PM |
| Initial approval: | 10/26/2017 |
| Effective: | 2/7/2018 |
| Approval end: | 10/25/2018 |
| Last updated: | 2/7/2018 12:02 PM |

#STU00205629

**PROTOCOL TITLE:** *A Retrospective Study to Understand the Risk Factors/Drivers of "Inappropriate" Antimicrobial Use and the Performance Evaluation of a Clinical Decision Support Tool that Facilitates Prediction of Outbreaks of Inappropriate Antibiotic Use*

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**VERSION NUMBER: 2**

**VERSION DATE: 06/6/17**

**OBJECTIVES:**

Objective 1. The first objective of this study is to comprehensively classify and predict vancomycin never-events.

Vancomycin is selected as a prototypical broad-spectrum antibiotic that is regularly overused and is known to cause downstream harms (e.g., acute kidney injury). We will classify the proportion of vancomycin use in which potential for harm outweighs the potential benefit, herein referred to as "never events". We will categorize the rate of never events as a function of patient, provider, and disease/organism characteristics.

Objective 2. We will develop decision rules and thresholds (e.g. decision support tools) to predict time periods with frequent vancomycin never events based on antimicrobial consumption trends.

Objective 2a. Identify the relationship between clusters of high antibiotic use, herein referred to as "outbreaks," and occurrence of never events. We will use our previously published strategies to identify antibiotic outbreaks and correlate to vancomycin never events.

Objective 2b. Compare thresholds for prediction of never events based on Optimal Data Analysis (ODA) methodologies with exact statistics [3, 4] versus vancomycin never events.

**BACKGROUND:**

Appropriateness in antimicrobial prescribing has become a focal national and international issue. It has been estimated that upwards of 50% of antibiotic use is inappropriate [6-9]. With this backdrop, a national strategic goal has been set by the United States White House to decrease inappropriate antibiotic use by 20% and 50%, respectively for inpatient and outpatient settings [10]. In order to decrease inappropriate use, *drivers* of incorrect use must be identified at each local setting. The actual *drivers* of confirmed inappropriate use have been difficult to identify except when using time and resource intense chart reviews. Even the largest contemporary antibiotic consumption studies have not assessed appropriateness as it was 'outside of study scope' [11-13]. Further, there is no consensus or agreement on what constitutes inappropriate use. These apparent omissions underscore the difficulty and complexity in attributing appropriateness of use for antimicrobials. Importantly, this study will focus on the *MOST inappropriate use,* which we are defining as 'never events'. Never events represent the most clearly inappropriate use. By defining these never events unambiguously, electronic data capture strategies can quickly and accurately identify areas of antibiotic use concern.

Such novel methods are sorely needed to fill this gap and identify signals/signatures of inappropriate antimicrobial use so that strategies can be defined to improve use. This study will use an electronic data capture strategy to identify vancomycin consumption outbreaks and vancomycin never events. The latter will be confirmed by chart review to determine the correctness of the electronic strategy for defining never events. Our study is innovative since methods will use rapid electronic data capture strategies that can be tailored and scaled to many US hospitals; thus, providing conduits to conducting appropriateness assessments.

Our methods are expected to improve the status quo. To communicate effectively about antibiotic consumption and work towards improvement, there is a need for a benchmarking process that is validated, simple to perform, and uses common and persuasive language for reporting. Antimicrobial use can be measured in quality and/or quantity; however, the standard measures for benchmarking antimicrobial use are focused almost entirely on quantity. As shown by our group, both the CDC's

National Healthcare Safety Network Antibiotic Use (AU) and Resistance (R) module [1] [Scheetz, et al. ICHE, accepted article in-press] and the previous standard Days of Therapy (DOT) method perform well [14] for creating internal trend benchmarks. One challenge then, is determining thresholds of antimicrobial use that should be considered abnormal and used to trigger further evaluation. This study will identify *qualitative* vancomycin never events based on *quantitative thresholds*. Our group (including collaborators) is comprised of national leaders in antimicrobial stewardship (see PI and Co-I CVs) that are poised and eager to conduct these studies.

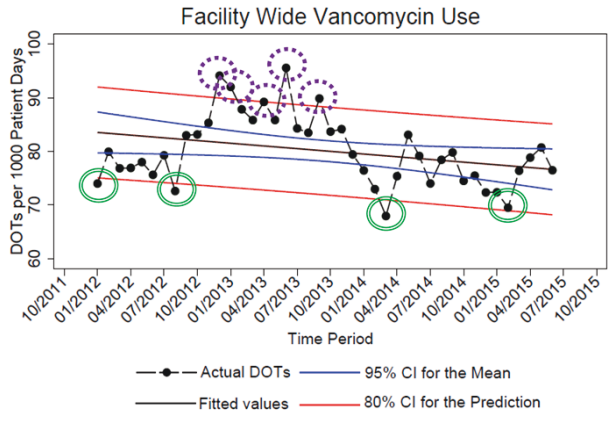
**RATIONALE.** While antimicrobial consumption trends are part of routine tracking and reporting for antimicrobial stewardship programs, consumption metrics like days of therapy are not well understood outside of ASPs themselves. To move away from relying on quantitative factors like drug consumption and cost, there is a considerable need for measures that reflect patient safety and outcome, as these considerations are more likely to resonate with clinicians and health system leaders. Vancomycin is chosen as a prototypical antimicrobial that is widely and indiscriminately used and has been closely associated with a common adverse effect (i.e. nephrotoxicity). As vancomycin is one of the most frequently prescribed antibiotics in US hospitals [13, 15], results of this research will be widely applicable immediately. Further, the method can be transferred to other antibiotics, allowing individual hospitals to tailor antimicrobial stewardship efforts.

**SIGNIFICANCE.** While antimicrobial use tracking and reporting is widely recommended, this data is inconsistently applied in real time to facilitate measurable improvements in antimicrobial use. One considerable barrier to this is the lack of a consistent approach for identifying and reporting trends that represent inappropriate or unsafe antimicrobial use. The proposed work will provide a framework to identify vancomycin never events using only vancomycin consumption data and ultimately provide pragmatic targets for antimicrobial stewardship intervention. After creating antibiotic use thresholds that predict antibiotic never events, the next logical step will be to implement these real-time threshold decision support tools in a prospective quality improvement study.

**PRELIMINARY DATA.** Our group has demonstrated that quantifying antibiotic consumption via the AUR methodology performs well compared to the old standard, DOT methodology [14]. That is, there is a high level of correlation between AUR and DOT estimates of antibiotic use within an individual hospital. Hence, either metric can be used for creating internal trend benchmarks at the hospital level. We have also described methods for individual hospitals to track antibiotic use and predict anomalies of use. Normal use is comprised of the hospital's usual consumption of an antibiotic for appropriate indications plus some small random amount of "inappropriate" use. However, periods exist when use rises beyond normal variation (i.e. presumed inappropriate use), and we have defined these periods as antibiotic outbreaks [1]. The definition is similar to The World Health Organization definition of a disease outbreak: "the occurrence of cases of disease in excess of what would normally be expected in a defined community, geographical area or season" [16]. The proposed study will define the environment/triggers in which vancomycin never events occur and establish thresholds of vancomycin outbreaks that predict time periods with frequent 'never events'.

Our method for describing anomalies of antibiotic use (i.e. antibiotic outbreaks) follows [1] [Scheetz et al., ICHE, accepted in press]. In brief, linear regressive strategies can be automated based on user parameters. DOTs can be trended according to time (in months) as the dependent variable (Figure 1). Typical linear regressive strategies can define a mean regression line and a confidence interval (most typically 95%) for the mean trend. However, it is also possible to define prediction intervals. Prediction intervals are highly useful as they determine the likelihood of the result at any given month, instead of

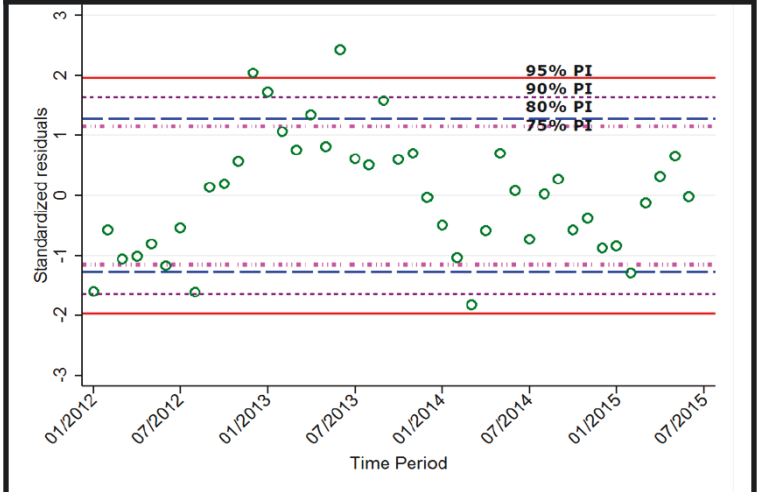
Figure 1. Time trended antibiotic use.




the trend. That is, a 75% prediction interval will define the likelihood that the number of DOTs in any single month (e.g. December 2016) will fall within the range. Since stewardship programs are more interested in individual events (e.g. is the amount of vancomycin being used in December of 2016 beyond expected?), the prediction interval has a natural interpretation and may be of great value to programs seeking to address antibiotic outbreaks. We have suggested that that the prediction interval has more meaning and translative capacity than the more commonly reported 95% confidence interval for the mean [1]. These concepts can be visually appreciated in Figure 1. The confidence interval for the mean predicts where the mean prediction would fall with 95% confidence. The purple dashed circles represent potential outbreaks and green double lined circles are potential under-utilizations. Residuals (i.e. difference between observed and predicted) can be plotted and those that are outside of the 75% prediction interval of interest can be visually and mathematically identified (Figure 2). It is important to note that the optimal prediction interval for identifying specific events (such as thresholds for antibiotic outbreaks that predict never events) has not yet been established. Our proposed research will do this.

Our strategy [1] has received much attention. It has been presented 1) on a CDC / AU Option partner quarterly call, 2) at the American Society of Health System Pharmacists meeting with over 900 presentation attendees, and 3) the abstract/manuscript has been downloaded over 5000 times since the electronic release in May 2016. However, identifying anomalies in antibiotic use is just the first step to predicting antibiotic inappropriateness and antibiotic never events. The ultimate utility of these methods will be realized when strategies based only on antibiotic use are linked to the more concerning antibiotic never events. This is important since identifying the environment of overuse that gives rise to never events will facilitate root-cause analyses at individual institutions. These strategies will lay the groundwork for data-driven solutions to mitigate inappropriate antibiotic prescribing.

Figure 2. Standardized residuals, visualizing prediction intervals




**INCLUSION AND EXCLUSION CRITERIA:**

The retrospective study population will be based on all inpatient intravenous vancomycin used during the proposed 36-month study period. Vancomycin ordered for any other route of administration or for outpatient use will be excluded. We will not collect variables that identify:

- Adults unable to consent
- Individuals who are not yet adults (infants, children, teenagers)
- Pregnant women
- Prisoners

**Age Range:**

Adults 18 years of age or older and less than 90 years of age.

**Indicate if this is a retrospective and/or prospective chart review**

**__X__ Retrospective Chart Review** (Retrospective means the data is already in existence when the project is submitted to the IRB for initial review.

__NA___ **Prospective Chart Review** (Prospective means the data is not in existence when the project is submitted to the IRB for initial review)

**STUDY-WIDE NUMBER OF PARTICIPANTS:**
2000

**STUDY-WIDE RECRUITMENT METHODS:**
Subjects will not be recruited for this study as it is retrospective.

**MULTI-SITE RESEARCH:**
This study will be conducted at Northwestern Memorial Hospital, Chicago, IL and Midwestern University, Downers Grove, IL (PI: Marc Scheetz); Wayne State University and Henry Ford Hospital, Detroit, MI (Co-I: Susan Davis); University of Michigan, Ann Arbor, MI (Co-I: Keith Kaye). Study coordination will occur at Midwestern University under the direction of Dr. Scheetz. IRB approval ~~from all sites (coordinated by NU) is required.~~ will be required individually from all sites. MWU will serve as Lead site. NU will be a performance site, where data will be collected.

All sites will have the most current version of the protocol. IRB is required from all sites before data may be sent to Dr. Scheetz. A waiver of consent and Waiver of HIPAA Authorization are required from each site. Individual IRB approval will verify that:

- All required approvals have been obtained at each site (including approval by the site's IRB of record).
- All engaged participating sites will safeguard data as required by local information security policies.
- All local site investigators conduct the study appropriately.
- All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

The study will be discussed on semi-annual conference calls and all problems will be reported to Dr. Scheetz via email (within 48 hours of actionable event).

**STUDY TIMELINES:**

This is a retrospective study that will analyze date from 1/1/14-10/1/17. All events have already occurred. It is estimated that the study will take approximately 18 months to complete (i.e. official protocol development, IRB coordination for all sites through a central IRB (i.e. MWU), data collection, data review/cleaning and data analysis).

It is anticipated that it will take 3 months to draft and revise a manuscript, including incorporation of input from all study authors

**STUDY ENDPOINTS:**

1. Descriptive level antimicrobial use (containing no PHI)

2. Patient level demographics (intermediary, not study endpoint)
    a. Age (if between 18-89, >90 will be classified categorically only)
    b. Gender
    c. Infecting organism
    d. Infecting organism susceptibility
    e. Antibiotic indication
    f. Duration of therapy
    g. Duration of time between identification of pathogen/susceptibility and vancomycin discontinuation
    h. Hospital location

3. Provider demographics
    a. Ordering provider classification (i.e. medical resident, PGY1, 2, 3; medical
    b. fellow; attending physician; other (e.g. Nurse practitioner).
    c. Number of years since terminal clinical training.
    d. Specialty (e.g. critical care, infectious diseases, internal medicine).
    e. Average monthly patient census during prescription

4. Patient level outcomes data including:
    a. Length of stay
    b. Duration of therapy
    c. Discharge disposition
    d. 30-day readmission

**STUDY METHODS**

A retrospective, non-interventional study will be completed.

**SOURCE (LOCATION) OF RECORDS TO BE REVIEWED:**

See Section (MULTISITE RESEARCH)

**DESCRIBE HOW THE CHARTS TO BE REVIEWED WILL BE IDENTIFIED:**

Charts will be identified from electronic data sources (e.g. EDW, Powerchart, Theradoc) on the basis of having received vancomycin while inpatient at NMH

**DESCRIBE WHO WILL IDENTIFY CHARTS TO BE REVIEWED:**

Charts to be reviewed will be identified by the principal investigator, Dr. Marc Scheetz.

**CONFIDENTIALITY OF DATA**

**DESCRIBE HOW DATA (BOTH PAPER AND ELECTRONIC) WILL BE STORED TO SAFE-GUARD CONFIDENTIALITY (E.G. IN A LOCKED CABINET, PASSWORD PROTECTED COMPUTER):**

Redcap will be used for data confidentiality. De-identification will be maintained through their site. The Redcap data collection tool is being built based on the documents submitted to the IRB. Patient-specific data will be kept behind NM firewalls.

**SPECIFY WHO WILL HAVE ACCESS TO HARVESTED PATIENT DATA:**

Patient name and MRN will be entered into RedCap. The coded identifier will only ever be opened behind NM firewalls. No patient identifying information will be co-located on research databases for analysis.

**CLARIFY LONG HARVESTED PATIENT DATA WILL BE STORED AND HOW IT WILL BE DESTROYED WHEN NO LONGER NEEDED:**

Data will be stored in RedCap. It is the investigator's responsibility to retain study essential documents for at least 3 years after the study is completed. After that, the records can be shipped to off-site storage or destroyed at the investigator's discretion.

**CONSENT:**

A waiver of consent is sought.

**RISKS AND BENEFITS: (MODIFY AS NEEDED)**

**RISKS:**

There is minimal, but measurable, risk of a confidentiality breach in chart review research

**BENEFITS:**

The subject's whose charts are reviewed are not likely to receive any benefit from the proposed research; however, society and investigators will benefit from the knowledge gained.

**STATISTICAL CONSIDERATIONS**

**PROPOSED SAMPLE SIZE (NUMBER OF RECORDS TO BE REVIEWED):**

We expect to enroll about 2000 subjects between the 3 sites. Locally, we expect approximately 1000 subjects

**PROPOSED TIME PERIOD TO BE EVALUATED:**

36 months (minimum over the requested time period).

**SPECIFY HOW DATA WILL BE ANALYZED AND BY WHOM:**

The PI, Dr. Scheetz, will be responsible for the statistical analysis in Objective 1 and 2a. Objective 2b will be analyzed by Dr. Paul Yarnold. Dr. Yarnold will receive a completely de-identified dataset.

**APPENDICES: THE FOLLOWING APPENDICES MUST BE ATTACHED TO THE PROTOCOL**

**APPENDIX A: DATA COLLECTION FORM (THIS FORM SHOULD LIST THE DATA ELEMENTS THAT WILL BE COLLECTED FROM THE MEDICAL RECORD. IT SHOULD NOT CONTAIN ANY DIRECT OR INDIRECT IDENTIFIERS EXCEPT FOR A UNIQUE SUBJECT CODE.)**

**APPENDIX B: CODED IDENTIFIER LIST (THIS FORM SHOULD SERVE AS THE LINK BETWEEN THE UNIQUE SUBJECT CODE AND ANY IDENTIFIERS YOU WILL NEED TO CONDUCT THIS CHART REVIEW STUDY [E.G., NAME , MEDICAL RECORD NUMBER, DATE OF BIRTH, ADDRESS, TELEPHONE NUMBER, SOCIAL SECURITY NUMBER])**

**PROCEDURES INVOLVED:**
NA

**DATA AND SPECIMEN BANKING:**
Data banking in RedCap as described above.

**DATA AND SPECIMEN MANAGEMENT:**
Data management in RedCap as described above.

**PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF PARTICIPANTS:**
NA

**WITHDRAWAL OF PARTICIPANTS:**
NA

**RISKS TO PARTICIPANTS:**
Risks to the subjects are loss of data confidentiality. To minimize this risk, patient specific data will be kept secure in RedCap. De-identified data will be utilized for analyses.

**POTENTIAL BENEFITS TO PARTICIPANTS:**
There is no direct benefit to study participants.

**VULNERABLE POPULATIONS:**
NA

**COMMUNITY-BASED PARTICIPATORY RESEARCH:**
NA

**SHARING OF RESULTS WITH PARTICIPANTS:**
No results will be shared with study participants. Notifying them could increase the risk of confidentiality breach and there is no common medium to contact them as all events occurred in the past.

**SETTING:**
This study will be conducted at Northwestern Memorial Hospital, Chicago, IL and Midwestern University, Downers Grove, IL (PI: Marc Scheetz); Wayne State University and Henry Ford Hospital, Detroit, MI (Co-I: Susan Davis); University of Michigan, Ann Arbor, MI (Co-I: Keith Kaye). Study coordination will occur at Midwestern University under the direction of Dr. Scheetz. IRB approval from all sites (coordinated by NU) is required.

**RESOURCES AVAILABLE:**
Dr. Scheetz is an internationally recognized researcher and holds an appointment at Northwestern Medicine. Hi PI status has been approved (see attachment), and he has adequate time for study oversight. This study is similar to those regularly conducted by Dr. Scheetz and his team at NMH.

https://www.ncbi.nlm.nih.gov/sites/myncbi/1Bw-VFHOUgI53/bibliography/46519885/public/?sort=date&direction=descending

https://scholar.google.com/citations?user=4-dax_DquKAC&hl=en

All study personnel will have access to the protocol. It will be reviewed with Dr. Scheetz. Dr. Scheetz is available 24/7 for questions related to the protocol (from any study personnel). He can be called at 312.545.7943.

**PRIOR APPROVALS:**
NA

**RECRUITMENT METHODS:**
Subjects are not recruited.

**NUMBER OF LOCAL PARTICIPANTS:**
We expect to enroll ~2000 subjects between the 3 sites. Locally, we expect ~1000.

**CONFIDENTIALITY:**
Redcap will be used for data confidentiality. De-identification will be maintained at each local study site. MRNs and subject identifying numbers will be removed completely for analysis documents. All dates will be scrambled in RedCap when downloaded for analysis to maintain confidentiality.

**PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF PARTICIPANTS:**
PHI will be accessed for retrospective events. Privacy will be protected as described under heading 'Confidentiality'.

**COMPENSATION FOR RESEARCH-RELATED INJURY:**
No compensation is being offered.

**ECONOMIC BURDEN TO PARTICIPANTS:**
NA

**CONSENT PROCESS:**
NA

***Waiver or Alteration of Consent Process***:
A waiver of consent is requested.

**DRUGS OR DEVICES:**
NA

**REFERENCES**

[1] M.H. Scheetz, P.E. Crew, C. Miglis, E.M. Gilbert, S.H. Sutton, J.N. O'Donnell, M. Postelnick, T. Zembower, N.J. Rhodes, Investigating the Extremes of Antibiotic Use with an Epidemiologic Framework, Antimicrob Agents Chemother, 60 (2016) 3265-3269.
[2] https://psnet.ahrq.gov/primers/primer/3/never-events. accessed 03/16/17, DOI.
[3] P.R. Yarnold, R.C. Soltysik, Refining two-group multivariable classification models using univariate optimal discriminant analysis., Decision Sciences, 22 (1991) 1158-1164.
[4] P.R. Yarnold, R.C. Soltysik, Maximizing Predictive Accuracy, ODA Books2016.
[5] N.J. Rhodes, J.N. O'Donnell, B.D. Lizza, M.M. McLaughlin, J.S. Esterly, M.H. Scheetz, Tree-Based Models for Predicting Mortality in Gram-Negative Bacteremia: Avoid Putting the CART before the Horse, Antimicrob Agents Chemother, 60 (2016) 838-844.
[6] A. Cusini, S.K. Rampini, V. Bansal, B. Ledergerber, S.P. Kuster, C. Ruef, R. Weber, Different patterns of inappropriate antimicrobial use in surgical and medical units at a tertiary care hospital in Switzerland: a prevalence survey, PLoS One, 5 (2010) e14011.
[7] R.C. Glowacki, D.N. Schwartz, G.S. Itokazu, M.F. Wisniewski, P. Kieszkowski, R.A. Weinstein, Antibiotic combinations with redundant antimicrobial spectra: clinical epidemiology and pilot intervention of computer-assisted surveillance, Clin Infect Dis, 37 (2003) 59-64.
[8] M.T. Hecker, D.C. Aron, N.P. Patel, M.K. Lehmann, C.J. Donskey, Unnecessary use of antimicrobials in hospitalized patients: current patterns of misuse with an emphasis on the antianaerobic spectrum of activity, Arch Intern Med, 163 (2003) 972-978.
[9] K.E. Fleming-Dutra, A.L. Hersh, D.J. Shapiro, M. Bartoces, E.A. Enns, T.M. File, Jr., J.A. Finkelstein, J.S. Gerber, D.Y. Hyun, J.A. Linder, R. Lynfield, D.J. Margolis, L.S. May, D. Merenstein, J.P. Metlay, J.G. Newland, J.F. Piccirillo, R.M. Roberts, G.V. Sanchez, K.J. Suda, A. Thomas, T.M. Woo, R.M. Zetts, L.A. Hicks, Prevalence of Inappropriate Antibiotic Prescriptions Among US Ambulatory Care Visits, 2010-2011, JAMA, 315 (2016) 1864-1873.
[10] National Strategy for Combatting Antibiotic Resistant Bacteria. https://www.cdc.gov/drugresistance/pdf/carb_national_strategy.pdf. Official White House communication. 2014, DOI.
[11] T. Kelesidis, N. Braykov, D.Z. Uslan, D.J. Morgan, S. Gandra, B. Johannsson, M.L. Schweizer, S.A. Weisenberg, H. Young, J. Cantey, E. Perencevich, E. Septimus, A. Srinivasan, R. Laxminarayan, Indications and Types of Antibiotic Agents Used in 6 Acute Care Hospitals, 2009-2010: A Pragmatic Retrospective Observational Study, Infect Control Hosp Epidemiol, 37 (2016) 70-79.
[12] S.S. Magill, J.R. Edwards, Z.G. Beldavs, G. Dumyati, S.J. Janelle, M.A. Kainer, R. Lynfield, J. Nadle, M.M. Neuhauser, S.M. Ray, K. Richards, R. Rodriguez, D.L. Thompson, S.K. Fridkin, I. Emerging Infections Program Healthcare-Associated, T. Antimicrobial Use Prevalence Survey, Prevalence of antimicrobial use in US acute care hospitals, May-September 2011, JAMA, 312 (2014) 1438-1446.
[13] J. Baggs, S.K. Fridkin, L.A. Pollack, A. Srinivasan, J.A. Jernigan, Estimating National Trends in Inpatient Antibiotic Use Among US Hospitals From 2006 to 2012, JAMA Intern Med, 176 (2016) 1639-1648.
[14] N.J. Rhodes, J.L. Wagner, E.M. Gilbert, P.E. Crew, S.L. Davis, M.H. Scheetz, Days of Therapy and Antimicrobial Days: Similarities and Differences Between Consumption Metrics, Infect Control Hosp Epidemiol, DOI 10.1017/ice.2016.109(2016) 1-3.
[15] T. Kelesidis, N. Braykov, D.Z. Uslan, D.J. Morgan, S. Gandra, B. Johannsson, M.L. Schweizer, S.A. Weisenberg, H. Young, J. Cantey, E. Perencevich, E. Septimus, A. Srinivasan, R. Laxminarayan, Indications and Types of Antibiotic Agents Used in 6 Acute Care Hospitals, 2009-2010: A Pragmatic Retrospective Observational Study, DOI.
[16] The World Health Organization. Health Topics: Disease Outbreaks, 2015.