International Journal of Sciences: Basic and Applied Research (IJSBAR)

ISSN 2307-4531
(Print & Online)

http://gssrr.org/index.php?journal=JournalOfBasicAndApplied

Surveillance Analysis and Monitoring of Multidrug-Resistant Bacteria Incidence in an Intensive Care Unit: The Role of Cumulative Sum Control Charts

Isabela Pereira Rodrigues[a], Osiris Turnes[b*] , Celeste Aida Nogueira Silveira[c]

[a]*Infection Control Committee, University Hospital of Brasilia, SGAN 605, Av. L2 Norte, 70940-901 Brasilia, Brazil*

[b] *Department of Statistics, University of Brasilia, a/c SGAN 605, Av. L2 Norte, 70840-901 Brasilia, Brazil*

[c]*Tropical Medicine Nucleus, University of Brasilia, a/c SGAN 605, Av. L2 Norte, 70840-901 Brasilia, Brazil*

[b,c] *Retired professor, currently working as collaborator in the Infection Control Committee at University Hospital of Brasilia*

[a]*Email: isabelarodrigues67@gmail.com*

[b]*Email: osiris@unb.br*

[c]*Email: celeste@unb.br*

Abstract

Hospital surveillance programs focus mainly on detecting warning signs and epidemic events. Control charts are important quality control tools and are recommended for monitoring and improving a process. The aim of this article is to evaluate the role of the tabular cumulative sum control chart as an auxiliary tool to identify the onset of epidemics of multidrug-resistant bacteria in the intensive care unit for adults at the University Hospital of Brasilia, Brazil. A retrospective study is performed on the frequency of multidrug-resistant baterial epidemics. Days between positive cultures are statistically analysed. Cumulative sum control charts are described and applied. The six most prevalent bacterial species are studied.

---

* Corresponding author.

E-mail address: osiris@unb.br.

Cumulative sum control charts for methicillin resistant *Staphylococcus aureus* and *Klebsiella pneumoniae* are selected to illustrate situations in which the chart highlights possible changes in the state of the epidemic process. Special attention is given to the ability of the Cumulative sum control chart to identify how many periods it takes for an epidemic event to become an epidemic signal, with the aid of a counter named N^{-}. This counter gives indication of the period when the anomaly probably begins. The results indicate that analysis with the cumulative sum control chart is useful in providing warning signals of multidrug-resistant bacteria epidemics. The occurrence and spread of outbreaks, however, also depend on the immediate action by surveillance staff when a signal has been generated by the control chart.

Keywords: Cumulative sum control chart; days between positive cultures; intensive care unit; multidrug-resistant bacteria

1. Introduction

After the pioneering work of Shewhart [1] introducing and developing control charts, Page [2] introduced the cumulative sum (CUSUM) schemes. Many authors, see [3:29], extended Page's theory for a number of distributions. In 1985, Lucas [4] described the design and implementation procedures for count data CUSUM control charts based on the family of exponential distributions. Already in 1997, O'Brien & Christie [5] stated that "CUSUMs represents potentially useful adjunct to other surveillance methods in infection control". Later, numerous publications on the use of statistical process control in epidemiology [6-13] have considered the use of control charts in healthcare, and have discussed their theoretical design and properties. Three of these studies [9, 10, 13] focused on the CUSUM, exponential weighted moving average (EWMA) and moving average (MA) charts. Quesenberry [14] described methods that can be used with or without prior data and produce timely warnings of epidemic onset, and Woodall [15], reviewed the types of control charts used in healthcare. More recently, Woodall et al. [16:253] : "provided an overview of common uses of Statistical Process Control in healthcare and some guidance on the choice of appropriate charts for various applications", pointing out the superiority of CUSUM and EWMA control charts. Unkel et al. [17] dedicated a section to CUSUM charts in the detection of infection disease outbreaks.

The objective of this study is to discuss the role of the CUSUM control chart as an auxiliary instrument for immediate detection of multidrug-resistant bacteria (MDRB) outbreaks. This assessment is based on a retrospective study of MDRB days between positive cultures (DBPC) in the adult intensive care unit (ICU) of the University Hospital of Brasília (HUB) from January 2001 to December 2011.

The most important variable that appears in the specialized literature regarding time between events is Days Between Infections (DBI). According to Finison, Spencer and Finison [18] this measure provides greater measurement sensitivity and allows for the construction of charts in real time. To avoid any misunderstandings, and to include infection as well as colonization, a different acronym is adopted in this study: Days between positive cultures (DBPC). For example: if a positive culture for MRDB is recorded on the February 4th, and another following on the February 23rd, then DBPC equals19. Likewise, if two positive cultures occur on the same day, DBPC is zero.

CUSUM charts have undergone several adjustments and other algorithms have been developed to give better performance in early detection of abnormalities [19-24]. However, considering the type of distributions of our data sets and for meeting specific requirements, we chose the CUSUM charts adapted to the exponential family distributions, following Hawkins and Olwell's methodology [3].

Currently CUSUM charts are still being used in the ICU at HUB, and the results are satisfactory. There is a reasonable decrease in the number of MRDB positive cultures in the last three years. Besides, the charts themselves, and all the calculations involved, contain the memory of the process and allow the detection of at least two types of changes: the epidemiological one and those that occur due to the influence of extraordinary events such as changes in physical space, lack of laboratory, incoming materials, lack of records, etc. Recently, a program has been started to expand the use of control charts to support surveillance in other hospital units at HUB.

1.1. Ethical aspects

This research was conducted in compliance with the recommendations of the National Health Council, number 466/12 -Regulatory Guidelines and Standards for Research Involving Human Beings. It was approved by the Ethics Committee of the School of Medicine of the University of Brasilia, on November 21, 2011, under Project Registration: CEP-FM 055/2011.

1.2. Study constraints

The study was conducted on a teaching hospital laboratory data of positive cultures for MRDB in the adult ICU. One of the main constraints was that the records were on handwritten notes rather then in computer files, especially the microbiological exam results. For this reason, during data collection we had some difficulty in identifying which clinical departments requested the laboratory exams. To overcome this obstacle we established the following exclusion criteria to collect the data: 1. record books of the microbiological laboratory; 2. the admission and discharge books from the Intensive Care Office and 3.patients' identification files (without breaching confidentiality). We only moved on to the next step in case of lack of success on the previous step, and so on and so forth. This strategy was used to avoid bias during further statistical analyses. Confidentiality issues on the hospital records were strictly followed. Our graphical analysis was based on the graphical analysis of Hawkins and Olwell [3] and Montgomery [25]. Taking into consideration our data distribution and to fulfilling specific requirements, for instance, easy access to a free design software as well as its user friendly interaction, we then chose CUSUM charts based on the Hawkins and Olwell's methodology [3].

2. Methods

To monitor and control MDRB DBPC in the adult ICU-HUB, it was decided to adopt the CUSUM Control Chart. The design, development and interpretation of these charts are done according to the following operational steps:

- Dates of occurrences of MDRB are collected and statistically analyzed, using preliminary tabulation,

frequency distributions and graphical techniques to maximize the gathering of information hidden in observed values.

- The variable DBPC is computed. Statistical summaries, data tabulation, frequency distributions, and identification of probabilistic models are used to construct an appropriate CUSUM chart design.
- The CUSUM chart parameters are adjusted to obtain the best combination between the numbers of false and true alarms. The parameters are calculated using the *ANYGETH.EXE* software, developed by Hawkins and Olwell [3]. Warnings (points in which the curve slope changes) and alarms (points plotted outside the control limits or sequences of points showing a long downward trend) are flagged in the charts.
- CUSUM charts are interpreted.

2.1. CUSUM control chart

The CUSUM control chart, first proposed by Page [2], works, essentially, by accumulating deviations from a target value of a process. It was developed to monitor the mean of a normally distributed variable.

If μ_0 is the target value for the process mean, the algorithmic (tabular) CUSUM is generated by plotting the following statistics:

$$C_i^+ = \max[0, x_i - (\mu_0 + k) + C_{i-1}^+]$$

$$C_i^- = \max[0, (\mu_0 - k) - x_i + C_{i-1}^-] \ , \ \text{i} = 1, \ldots, \text{n}.$$

Where x_i is the observed value, μ_0 is the target value, k is the reference value (RV) and the starting values are as follows: $C_i^+ = C_i^- = 0$.

C^+ and C^-, which indicate upper-side and lower-side CUSUM, respectively, accumulate deviations from the target value that are greater than k with both quantities reset to zero upon becoming negative. If either C^+ or C_i^- exceed a decision interval h, the process is considered out of control. Parameters h and k are chosen to give a desired average run length (*ARL*) that represents the average number of points that must be plotted before a point indicates an out of control condition. The ideal is a high value of *ARL* when the process is at the endemic state (called $ARL_0 = 1/$Type I error*)* and a very low value of *ARL* (close to the unit) when the process is out of the endemic state (called ARL_1 = 1/(1- Type II error)). The *ARL* is a usual performance measure for control charts. In this work *ARL* means the desired number of occurrences acceptable until the chart records a point outside of the control limit. In other words: "to design a CUSUM control scheme, we first select the out of control state for which we would like maximum sensitivity. This determines the reference value *k*. We then select the desired in-control *ARL* to meet our particular needs" [3:44], at some acceptable level. "Once the *ARL* and *k* are determined, the value of the decision interval *h*, follows, and may be found from tables or software." [3:44].

Since the research work by Lucas [4], it is possible to find CUSUM approaches for other type of data modeling, for instance, for the exponential family of distributions [3]. Distributions belonging to this family have good inferential properties and, in that sense, play important role in statistical theory, due to their wide applications. Among the various distributions that are part of this family, the following may be cited: binomial, Poisson, negative binomial, gamma, normal inverse Gaussian. The Weibull distribution does not belong to this family, but according to [3] it can receive the same treatment as gamma, and the same routines can be applied. That is the approach adopted in this study. Detailed theoretical review of the CUSUM chart design for exponential family distributed random variables is given in the Appendix.

In hospital infection control, the occurrence of a false positive result (Type I error) is less harmful than a false negative (Type II error). This justifies, in our scheme, a certain tolerance in defining the number of observations admitted until the occurrence of a false alarm (see ARL_0 values shown just below Figures 2 and 3).

Since we are interested in detecting only decreases in the DBPC, we based our analysis on a one-sided CUSUM. The parameters for the charts of this work were obtained using the program *ANYGETH.EXE* developed by the same authors in 2005, available at http:/www.stat.edu/~doug/software.html.

There are other statistic programs that can be used, like “Surveillance”; it is a powerful software developed in the R language which provides, among other programs, an approximate CUSUM method for time varying Poisson means, as documented in Rossi et al [26]. A comparative study between the results obtained in this work based on [3] and the method developed in the Surveillance package in the R language [27] could be the target of a future research.

Furthermore, if a shift is signaled then the most recent epoch *i*, at which $C_i^- = 0$, gives the maximum likelihood estimate of the last instant before the mean shift [28]. Indeed, the tabular CUSUM chart indicates it by means of a counter called N^- [25]. This counter records the number of consecutive periods since the lower-side CUSUM, C^-, assumed zero for the last time, i.e.

$$N^- = \begin{cases} 0, \text{ when } C_i^- = 0 \\ N_{i-1}^- + 1, \text{ when } C_i^- < 0 \end{cases} \qquad i=1,2,...$$

For example: in Figure 1, $N^- = 4$ at the 16th occurrence, then it can be concluded that the process was last in control (C^- assumed zero for the last time) at period 16-4 = 12, so the shift likely occurred approximately there.

There are four situations:

1) in control : $C^- = 0 \Rightarrow N^- = 0$. See occurrences number 1 to 5.

2) alert: one or two decreasing values of $C^- \Rightarrow 1 \le N^- \le 2$. See occurrences number 7 and 8.

3) alarm: a decreasing sequence of C^- values $\Rightarrow N^- \geq 3$. See occurrences number 13 to16.

4) alert: C^- plotted outside of the low control limit. Occurrence number 19.

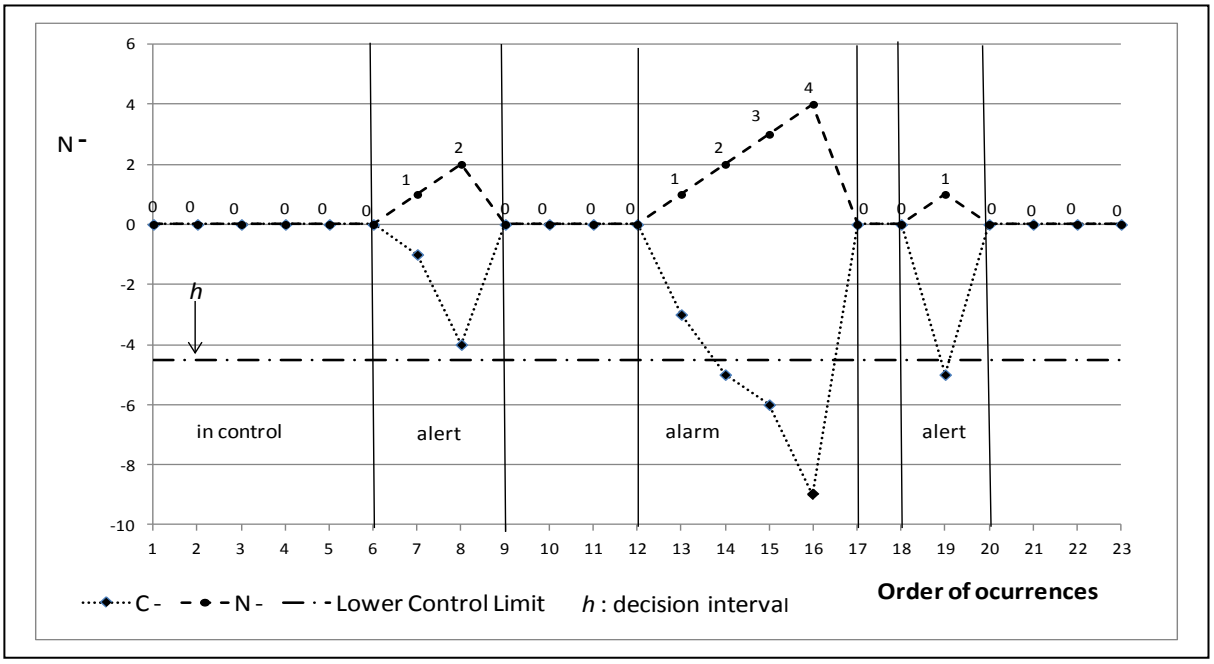

Figure 1: Relation between N^- and C^- values and illustration of the decision criteria

When a sequence of decreasing points is plotted inside or outside the control limit, the process is assumed to be in an alarm: this happens when intervals between infections are far below the expected value of DBPC. Some conclusions must be made regarding their causes. Very short intervals between positive cultures can occur due to careless surveillance by healthcare workers. For example: technical failures in the implementation of Standard Precautions and cross-contamination due to lack of isolation of infected or colonized inpatients. These types of intervals may also occur when hospitals are overcrowded.

2.1.2 *Decision criteria*

As illustrated in Figure1, for detecting non-random patterns on DBPC behaviour, the following set of decision rules was adopted:

- While the points are plotting on the central line, there is evidence that the process is in-control.
- When a point plots outside the control limit, there is evidence that the process is going out of control and is considered an alert.
- N^- sequences are used as flags:

o After updating the chart, if $1 \leq N^- \leq 2$, a warning signal is triggered because the process is probably at a changing state.

- When a sequence of points shows a long downward trend ($N^- \geq 3$), strong evidence is provided that the process is out of control and is considered an alarm.

3. Results

After appropriate adjustments, 453 samples of MDRB were analysed. The bacterial species most frequently identified were: methicillin-resistant *Staphylococcus aureus* (MRSA; 24.50%), *Acinetobacterbaumannii* (20.53%), *Pseudomonas aeruginosa* (16.56%), *Klebsiella pneumoniae* (*K.Pneumoniae*; 16.11%), *Staphylococcus epidermidis* (8.61%) and *Enterobacter spp*. (5.08%). These species represented 91.39% of the isolates. We focused on MRSA and *K. pneumoniae* because the behaviour of these two bacteria is sufficient to evaluate the performance of CUSUM chart analysis.

The behaviour of variable DBPC for MRSA has been recorded since 2003, but the chart currently covers only the period from 2007 to 2011(n=36 cases). This filtering resulted from a required update on the average DBPC because of the increased gaps between positive cultures for MRSA during the last five years. This procedure is typical for statistical process control whenever significant changes occur in the average behaviour of a variable. A similar update was performed for *K. pneumoniae*. Therefore, the corresponding chart covers records from 2009 to 2011 (n=50 cases).

In addition, a study on the type of probability distribution that best fits each data set was performed according to the coefficients of the Anderson–Darling and Cramér–von Mises tests and respective *P* values [29-30](Table 1).

Table 1: MRSA (2007–2011) and *K. pneumoniae* (2009–2011) probability distribution fitness tests for DBPC-Adult ICU at HUB.

MDRB	DBPC		Probability Distribution	*P* value
	Mean	SD		
MRSA	50.20	59.91	Exponential	.08[a]
				.14[b]
K. pneumoniae	17.50	16.94	Weibull	.23[a]
				>.25[b]

[a]Anderson–Darling test, [b]Cramér–von Mises test,
MRSA: methicillin-resistant *Staphylococcus aureus*;
DBPC: days between positive cultures
MDRB: multidrug-resistant bacteria;
SD: standard deviation

Based on these results, and considering that the *P*-values do not reject the hypothesis that the data approximately follow the specified distributions, the CUSUM charts are determined according to the methodology [3]

described in Section 2.1 and in the Appendix.

Figures 2 and 3 show the CUSUM charts for MRSA and *K. pneumoniae*. The chart performance measures, which represent the average number of points plotted before an alarm sign (ARL_0 and ARL_1), are shown just below the figures.

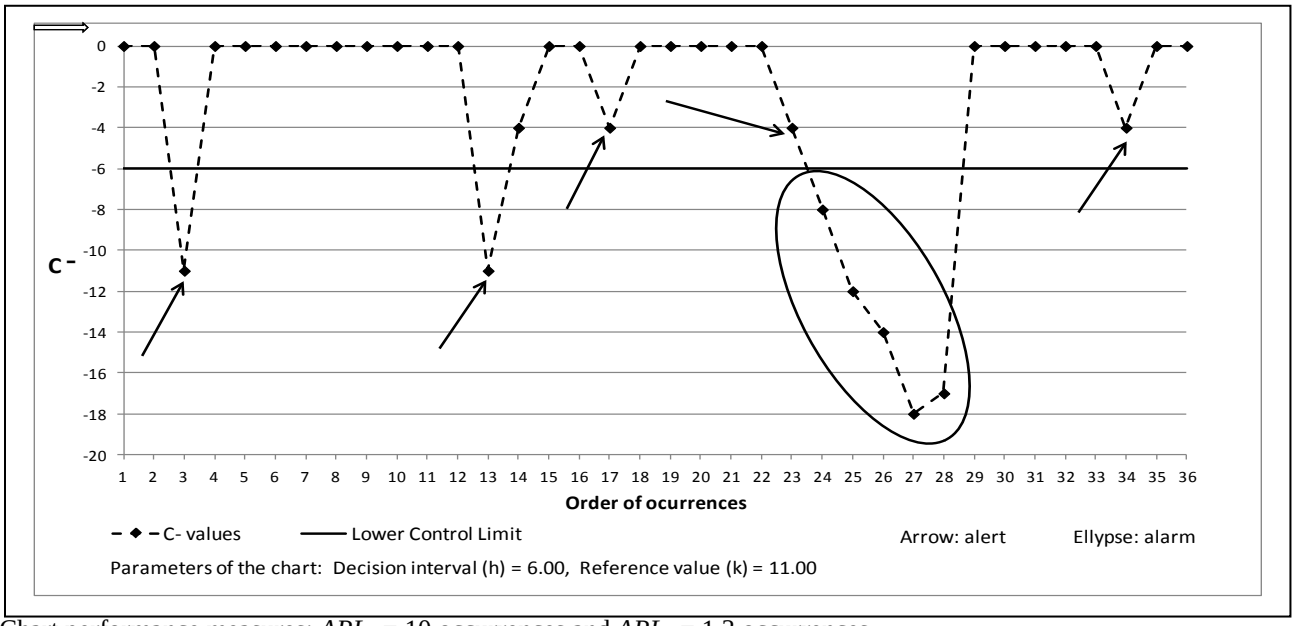

Chart performance measures: ARL_0 = 10 occurrences and ARL_1 = 1.3 occurrences.

Figure 2: The CUSUM chart of DBPC related to MRSA in the adult ICU-HUB (2007–2011)

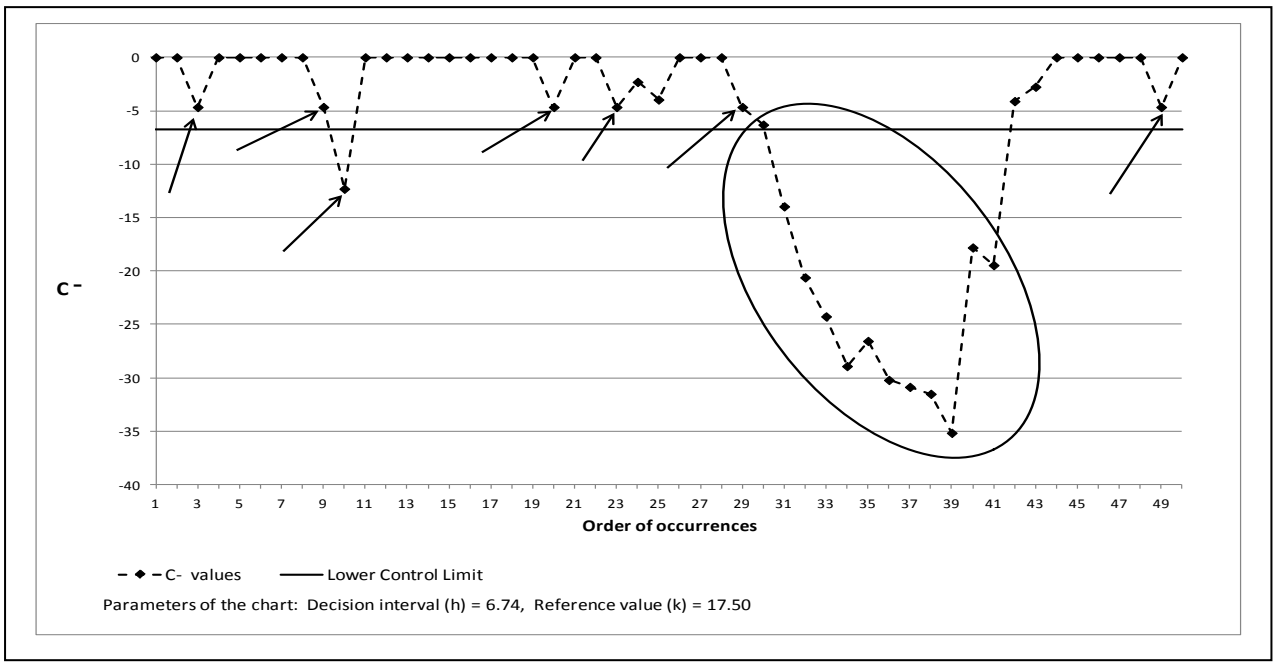

Chart performance measures*:* ARL_0 = 10 occurrences and ARL_1 = 2.5 occurrences

Figure 3: CUSUM chart of the DBPC for K. pneumoniae in the ICU-HUB (2009–2011)

The arrows in Figure 2 indicate that $1 \leq N^{-} \leq 2$, five times, pointing out warning signs. An undesirable sequence of positive cultures for MRSA occurred between June and July 2010 (see occurrence orders 23–28). The penultimate arrow indicates the observation where the change in the process may have started. The ellipse shows the subsequent cases that were not avoided. There were 7, 7, 7, 9, 7 and 12 DBPC in a strong downward trend.

The arrows in Figure 3 indicate that $1 \leq N^{-} \leq 2$, seven times, pointing out warning signs. The sixth arrow is followed by an ellipse, showing a long sequence of short gaps between positive cultures for *K.pneumoniae* during June and July 2011 (see occurrence orders 29–39). There were 3, 6, 0, 1, 4, 3, 10, 4, 7, 7 and 4 DBPC showing a sharp decrease in the C^{-} curve.

4. Discussion

The CUSUM charts designed for this study performed well (see *ARL* values below Figures 2 and 3), confirming that they are a good alternative when the detection of the onset of epidemics is important. The counter N^{-} plays an important role in signalling a likely earlier state change. Note that MRSA was continuously monitored with the help of these charts in the adult ICU at HUB since 2003, and its frequency was observed in this timeline. Furthermore, from 2007, a feedback system was implemented between the Infection Control Committee (ICC) and the ICU, and a more effective control of the occurrences of positive cultures for MRSA was observed. Nevertheless, in 2010, there was a non-infectious outbreak, (all isolates positive for MRSA derived from surveillance swabs, which are defined as colonization). However, it appears that there were failures in surveillance service at that time because interventions were only implemented during the outbreak.

The data for *K. pneumoniae* reveals a different scenario on changes in the number of occurrences. We observed an outbreak during June and July 2011. In the same period, an outbreak of *K. pneumoniae* carbapenemase was in progress in Brasília. For this reason, the ICU was already performing accurate surveillance cultures to monitor the outbreak. In 2011, this bacterium was not being monitored with the aid of the CUSUM chart. The used monitoring system showed that all positive cases resulted from surveillance cultures, thereby characterizing a non-infectious outbreak. Moreover, in the absence of the CUSUM chart, the precaution measures were implemented late, and it was not possible to prevent the spread of *K. pneumoniae* among inpatients.

The relevance of CUSUM charts is strongly supported by the current findings. Moreover, the use of CUSUM charts to monitor health events such as occurrences of MDRB is advantageous when compared with using other charts. Furthermore, it favours the implementation of corrective actions, aiming to stop the spread of these infectious agents among inpatients.

5. Conclusion

The use of the CUSUM control chart, which was developed for variables that approximately follow exponential family distributions, indicates that this method may be recommended for monitoring DBPC for MDRB in a hospital ICU. Individual analysis of the CUSUM control charts for MRSA and *K.pneumoniae* shows that they

pointed out possible outbreaks. Therefore, the implementation of the use of the charts may lead to better decision-making when linked to the local surveillance team. The CUSUM chart successfully detects any slight early deviation in the process and the counter N^{-} fulfils its role. The charts are helpful as an auxiliary tool to monitor hospital infections according to the control of MDRB. However, the prompt reaction of the surveillance team to the signal generated by the charts is the key for improving the control system. The epidemiological surveillance system for MDRB depends on multidisciplinary interactions and adherence by the majority of health professionals. Besides, the graphical method and application might be extended to the entire hospital. Its application would include an initial project design to create an adequate flow of actions for the implementation of statistical monitoring in an effort to improve quality in health care. The analysis was restricted to the dataset obtained from the ICU at HUB data under study. Finally, feedback strategies associated with statistical control are recommended and may gradually improve process performance and make surveillance more agile.

Acknowledgments: We thank our colleagues Robert Wayne Samohyl and Ana Maria Nogales Vasconcelos for their valuable comments that greatly improved the manuscript. We are also grateful to Sandra Pereira for the scientific translation.

References

[1] W.A.Shewhart. *Economic Control of Quality Manufactured Product.* New York: Van Nostrand, 1931.

[2] E.S. Page. “Continuous Inspection Schemes.” *Biometrika*, vol. 41, pp.100–15, 1954.

[3] D.M. Hawkins, D.H. Olwell. *Cumulative sum charts and charting for quality improvement*. New York: Springer-Verlag, 1998.

[4] J.M. Lucas. “Counted data CUSUM’s.” *Technometrics*, vol. 27, pp. 129-44, 1985.

[5] S.J. O’Brien, P. Christie. “Do CuSums have a role in routine communicable disease surveillance?.” *Public Health*, vol. 11, pp. 255-88, 1997.

[6] J.C. Benneyan. “Statistical Quality Control Methods in Infection Control and Hospital Epidemiology, Part I: Introduction and Basic Theory.” *Infection Control and Hospital Epidemiology*, vol. 19, pp.194–214, 1998.

[7] J.C. Benneyan.” Statistical Quality Control Methods in Infection Control and Hospital Epidemiology, Part II: Chart use, Statistical Properties, and Research Issues.” *Infection Control and Hospital Epidemiology*, vol. 19, pp. 265–83, 1998a.

[8] T.L.Gustafson. “Practical risk-adjusted quality control charts for infection control.” *American Journal of Infection Control*, vol. 28, pp. 406–14, 2000.

[9] A.P. Morton, M. Whitby,M.L. McLaws, A. Dobson, S. Mc Elwain, D. Looke et al. “The application of statistical process control charts to the detection and monitoring of hospital acquired infections.” *Journal of Quality in Clinical Practice*, vol. 21, pp.112–7, 2001.

[10] S.M. Brown, J.C. Benneyan, D.A. Theobald, K. Sands, M.T. Kahn, G.A. Potter-Bynoe et al.. “Binary cumulative sum and moving averages in nosocomial infection cluster detection.” *Emerging Infectious Diseases*, vol . 8, pp. 1426–32, 2002.

[11] E.T. Curran ET, J.C. Benneyan, J. Hood. “Controlling methicillin-resistant Staphylococcus aureus: a

feedback approach using annotated statistical process control charts." *Infection Control and Hospital Epidemiology*, vol. 23, pp. 13–8, 2002.

[12] N.A. Ismail NA, A.N. Pettitt AN, R.A. Webster RA. "'Online' monitoring and retrospective analysis of hospital outcomes based on a scan statistic." *Statistics in Medicine*, vol. 22, pp. 2861–76, 2003.

[13] C.M. Burns, C.J. Bennett, C.T. Myers, M. Ward. "The use of CUSUM analysis in the early detection and management of hospital bed occupancy crises." *Medical Journal of Australia*, vol. 183, pp. 291–4, 2005.

[14] C.P. Quesenberry. "Statistical Process Control Geometric Q-Chart for Nosocomial Infection Surveillance." *American Journal of Infection Control*, vol. 28, pp. 314–20, 2000.

[15] W.H. Woodall. "Use of control charts in health care monitoring and public health surveillance." *Journal of Quality Technology*, vol. 38, pp. 89–104, 2006.

[16] W.H. Woodall, B.M. Adams, J.C. Benneyan , "VISN 1 Engineering Resource Center The Use of Control charts in Healthcare," in *Statistical Methods in Healthcare*, F. Faltin, R. Kenett, F. Ruggeri, eds., Wiley: New York, 2012.

[17] S. Unkel, C.P. Farrington, P.H. Garthwaite, C. Robertson, N. Andrews. "Statistical Methods for the Prospective Detection of Infections Disease Outbreaks: a Review." *Journal of the Royal Statistical Society, Series A*, vol. 175, pp. 49-82, 2012.

[18] L.J. Finison, M. Spencer, K.S. Finison. "Total quality measurement in healthcare using individual charts in infection control." *ASQC Quality Congress Transactions*, vol. 47, pp. 349-59, 1993.

[19] B.C.P. Farrington, N.J. Andrews, A.D. Beale, M.A. Catchpole. "A statistical algorithm for the early detection of outbreaks of infectious disease." *Journal of the Royal Statistical Society, Series A*, vol. 159, pp. 547-63, 1996.

[20] L.C. Hutwagner, E.K. Maloney, N.H. Bean, L. Slutsker, S.M. Martin. "Using laboratory-based surveillance data for prevention: an algorithm for detecting *Salmonella* outbreaks." *Emerging Infectious Diseases*, vol. .3, pp. 395-400, 1997.

[21] L.C. Hutwagner, T. Browne, G.M. Seeman, T. Fleischauer. "Comparing aberration detection methods with simulated data." *Emerging Infectious Diseases*, vol. 11, pp. 314-6, 2005.

[22] D.A. Axelrod, M.K. Guidinger, R.A. Metzger, R.H. Wiesner, R.L. Webb, R.M. Merion. "Transplant center quality assessment using continuously updatable, risk-adjusted technique (CUSUM)." *American Journal of Transplantation*, vol. 6, pp. 313-23, 2006.

[23] M. Hoehle. "Surveilllance: an R package for the monitoring of infectious diseases." *Computational Statistics* , vol. 22, pp. 571-82, 2007.

[24] C. Polanco, J.A. Castanón-Gonzalez, A.E. Macias, J.L. Samaniego, T. Busche, S. Villanueva-Martinez. "Detection of severe respiratory disease epidemic outbreaks by CUSUM- based-overcrowd-severe-respiratory-disease-Index Model." *Computational and Mathematical Methods in Medicine* 2013, Article ID 213206, 9 pages.

[25] D.C. Montgomery. *Introduction to statistical quality control*. John Wiley and Sons: New York, 2004.

[26] G. Rossi, L. Lampagnani, M. Marchi. "An approximate CUSUM procedure for surveillance of health events". *Statistics in Medicine*, vol. 18, pp. 2111-22, 1999.

[27] M. Hoehle, S. Meyer, M. Paul. "Temporal and Spatio-Temporal Modeling and Monitoring of

Epidemic Phenomena," Version 1.8.0, Internet: cran.r-project.org/web/packages/surveillance/surveillance.pdf.2014. [09/10/14].

[28] T.L. Lai. "Sequential Analysis: Some Classical Problems and New Challenges." *Statistica Sinica*, vol. 11, pp. 303-350, 2001.

[29] W.J. Conover. *Practical Nonparametric Statistics*. John Wiley and Sons: New York, 1998.

[30] SAS system for Windows. Release 9.2, SAS Institute, Inc. Cary, NC.

[31] D. Brook, D.A. Evans. "An Approach to the Probability Distribution of CUSUM Run Length." *Biometrika*, vol. 59, pp. 539-49, 1972.

Appendix

Design for exponential family distributed random variables

According to [3], the density function of any member of the exponential family (with one parameter) can be written as:

$$F(y|\theta) = \exp(\{a(y)b(\theta) + c(y) + d(\theta)\} \quad (1)$$

Where $a(.)$, $b(.)$, $c(.)$ and $d(.)$ are known functions; θ is the parameter, and y the random variable. As an example, the density function of a normal distribution expressed like (1) is

$$F(y|\theta) = \exp\left[\frac{y\mu}{\sigma^2} - \frac{y^2}{2\sigma^2} - \ln\left(\sigma\sqrt{2\pi}\right) - \frac{\mu^2}{2\sigma}\right] \quad (2)$$

with $a(y) = y$; $b(\mu) = \frac{\mu}{\sigma^2}$; $d(\mu) = -\frac{\mu^2}{2\sigma^2}$

To test whether the process has shifted from the in control parameter θ_0 to an out of control parameter θ_1, the behavior of the "score" variables Z_i (see [3:135-136]) are defined as follows:

$$Z_i = \ln\left(\frac{f_1(Y_i)}{f_0(Y_i)}\right) = a(y_i)\{b(\theta_1) - b(\theta_0)\} + \{d(\theta_1) - d(\theta_0)\} \quad (3)$$

A general way to monitor the process using a CUSUM chart is the statistic D_n obtained recursively, as follows:

$$D_n = \max(0, D_{n-1} + Z_n) = \max(0, D_{n-1} + a(y_n)\{b(\theta_1) - b(\theta_0)\} + \{d(\theta_1) - d(\theta_0)\}) \quad (4)$$

The process is considered out of control when $D_n > A$.

The constant A is determined by deciding on the Type I error probability.

$$\text{Let } X_n = a(y_n) \text{ and } k = -\frac{d(\theta_1) - d(\theta_0)}{b(\theta_1) - b(\theta_0)} \tag{5}$$

The expression (5) is known as a reference value. Note that (5) is completely determined as a function of the process parameters under control and out of control. For illustration, consider the density function given by (2) keeping σ fixed and μ variable; the reference value takes the form:

$$k = -\frac{\mu_1^2 + \mu_0^2 / \left(2\sigma^2\right)}{\left(\mu_1 - \mu_0\right)/\sigma^2} = \frac{\mu_1 + \mu_2}{2} \tag{6}$$

In the case of monitoring possible changes in σ maintaining μ fixed, the reference value is given by:

$$k = \frac{\ln \sigma_1 - \ln \sigma_0}{\left(2\sigma_1^2\right)^{-1} - \left(2\sigma_0^2\right)^{-1}} \tag{7}$$

Details on the reference value *k* for other distributions of the exponential family can be found in [30].

If $b(\theta_1) - b(\theta_0) > 0$ in (5), expression (4) can be rescaled to

$$C_n^+ = \frac{D_n}{b(\theta_1) - b(\theta_0)} = \max\left(o, C_{n-1}^+ + X_n - k\right), \tag{8}$$

and if $b(\theta_1) - b(\theta_0) < 0$, then (4) is:

$$C_n^- = \frac{D_n}{b(\theta_1) - b(\theta_0)} = \min\left(0, C_{n-1}^- + X_n - k\right) \tag{9}$$

The process is considered out of control if

$$C_n^+ > h^+ = \frac{A}{b(\theta_1) - b(\theta_0)} \quad \text{or} \quad C_n^- < -h^- = \frac{A}{b(\theta_1) - b(\theta_0)}, \text{ with } C_0^+ = C_0^- = 0$$

Decision interval h^+ and h^- determines the distance between the central line and the control limit and is usually fixed by deciding on the minimum tolerable in control average run length (*ARL*). There are many methods to determine the *ARL* of a control scheme. One of these methods consists in converting the range of possible values of (8) in *M* discrete states; the state "zero" corresponds to the start of the monitoring process or after an adjusting stop and $C^+ = C^- = 0$. The state (*M+1*) occurs when (8) exceeds the decision interval. Thus it is possible to determine the probability transition matrix among the states, and the probability of transition from the state (*M+1*) to the state zero is 1. (i.e. when (8) exceeds the decision interval, the cycle begins again). Employing the properties of Markov chains, one can obtain the stationary distribution $\boldsymbol{\pi} = \pi_1, \pi_2, ..., \pi_M, \pi_{M+1}$, and $ARL = 1/\pi_{M+1}$. This modeling was introduced by [31].