*Title Page (with author details)

Increased Use of Alcohol-based Hand Sanitizers and Successful Eradication of Methicillin-Resistant Staphylococcus aureus from a Neonatal Intensive Care Unit –A Multivariate Time Series Analysis—

Fumie Sakamoto, BSN, MPH, CIC
Division of Safety Management, St. Luke's International Hospital, Tokyo, Japan
Hiroko Yamada, BSN
Coronary Care Unit, St. Luke's International Hospital, Tokyo, Japan
Chieko Suzuki, RN
Neonatal Intensive Care Unit, St. Luke's International Hospital, Tokyo, Japan
Hideko Sugiura, MT
Clinical Laboratory Department, St. Luke's International Hospital, Tokyo, Japan
Yasuharu Tokuda, MD, MPH
Mito Medical Center, Institute of Clinical Medicine, University of Tsukuba, Mito, Ibaraki, Japan

Address correspondence to Fumie Sakamoto, BSN, MPH, CIC, Division of Safety Management, St. Luke's International Hospital, 9-1 Akashicho, Chuoku, Tokyo, Japan 104-8560. E-mail: fumienum@luke.or.jp

Increased Use of Alcohol-based Hand Sanitizers and Successful Eradication of Methicillin-Resistant Staphylococcus aureus from a Neonatal Intensive Care Unit –A Multivariate Time Series Analysis—

Background: We analyzed time series data to investigate factors that contributed to the gradual decrease and eventual eradication of Methicillin Resistant Staphylococcus aureus (MRSA) from our Neonatal Intensive Care Unit (NICU).

Methods: A multivariate adjusted auto-regressive integrated moving average (ARIMA) model was used for time series analyses of monthly MRSA incidence density rates and their predictors in the NICU from July 2003 to July 2009.

Results: Based on our ARIMA (0,1,1) model, the monthly pooled mean of the amount of alcohol-based hand sanitizer used for one patient per day (lag time 0 month, p=0.011) was the only factor significantly associated with the MRSA incidence density rates. MRSA colonization pressure, patient-to-nurse ratios and bed occupancy rates were not associated with MRSA acquisition in the NICU. Active surveillance, which had been practiced since the late 1980s, alone was not sufficient to control the spread of MRSA until it was accompanied by enhanced hand hygiene.

Conclusion: Increasing the use of alcohol-based hand sanitizers by improving accessibility and providing periodic hand-hygiene training sessions to health-care workers is strongly recommended for decreasing the risk of MRSA acquisition among neonates in NICU settings.

Since first noted in a Neonatal Intensive Care Unit (NICU) in 1981[1], Methicillin Resistant Staphylococcus aureus (MRSA) has become one of the most common causes of healthcare-associated infections in neonates[2)-5)]. In order to prevent and control the spread of the organism in NICUs, different measures such as active surveillance cultures, strict contact precautions and topical decolonization therapy have been tried and achieved various degrees of success[6)-10)].

Many studies published to date have compared MRSA colonization or infection rates before and after the implementation of preventive strategies to evaluate their effectiveness[11)-19)]. However, a statistically significant reduction in MRSA rates does not necessarily indicate a continuous downward trend. In fact, the observed change in the post-intervention phase may only be transient. We, therefore, analyzed time series data to investigate factors that contributed to the gradual decrease and eventual eradication of MRSA from our NICU. Specifically, we evaluated the relationship between MRSA colonization or infection incidence density rates and MRSA prevalence rates (colonization pressure), amount of alcohol-based hand sanitizers used for patients, patient-to-nurse ratios, and bed occupancy rates.

Methods

＜Study Population＞

This prospective study was conducted from July 2003 to July 2009, in the 33-bed NICU at St.

Luke's International Hospital, an acute care hospital providing primary to tertiary care to a population of about 400,000 in Tokyo, Japan.

During the study period, there were a total of 1,229 admissions to the NICU. The median number of annual admissions to the NICU was 195.5 (range 168-256). The average length of stay was 24.2 days (range 12.0-40.4 days).

＜MRSA Surveillance and Prevention Strategies＞

Active surveillance for MRSA in the NICU began in the late 1980s and was conducted throughout the study period. All neonates were screened on admission and weekly thereafter for MRSA colonization using conventional plate culture methods. Culture samples were taken with a single swab from the nares, umbilicus, ear and throat.

Signs were posted on cots or incubators of culture positive neonates for identification, and gloves and gowns were required for health care workers caring for these neonates. Cohorting of MRSA positive neonates was not implemented due to shortage in nursing staff. NICU staff and visitors were asked to perform hand hygiene upon entry into the NICU and before and after touching the neonates. During the first three years of the study period, NICU staff had mainly used five hand washing sinks and several alcohol-based hand sanitizer dispensers, placed in each corner of the NICU, for hand hygiene. In July 2006, to facilitate the use of alcohol-based hand sanitizers, infection prevention liaison nurses in the NICU placed one dispenser beside each cot/incubator. They also started to offer short training sessions on the importance and methods of

hand hygiene to NICU staff twice a year.

＜Data Collection＞

The number of infants with at least one MRSA positive sample was recorded in the hospital's microbiology database. Only the first positive culture results were counted. MRSA detected more than 48 hours after admission were considered nosocomial and counted as incident cases. MRSA detected within 48 hours of admission were considered imported but counted as prevalent cases.

The incidence of MRSA colonization or infection per 1,000 patient days was calculated each month during the study period.

Monthly MRSA prevalence rates, which indicate colonization pressure, were calculated by dividing the patient-days of MRSA-positive neonates during a month by the total patient-days of the same month.

The monthly pooled mean of the amount of alcohol-based hand sanitizers used for one patient per day was calculated by dividing the total amount of alcohol-based hand sanitizers in milliliters delivered to the NICU from the pharmacy each month by the patient-days of the same month.

The monthly pooled mean of patient-to-nurse ratios was calculated by dividing the total number of patients in the NICU at midnight during a month by the total number of nurses working at midnight during the same month.

Monthly bed occupancy rates were calculated by dividing the total number of patients in the NICU at midnight during a month by the number of NICU beds multiplied by the number of days

in the same month.

＜Statistical Analyses＞

We conducted a time series analysis to identify significant predictors of MRSA incidence density rates in the NICU using a multivariate adjusted auto-regressive integrated moving average (ARIMA) model. The three main parameters selected when fitting the ARIMA model were the order of auto-regression (p), the order of integration (d), and the order of moving-average (q).

The best-fit model for our time series data with the generalized least squares regression was ARIMA(0,1,1), which is a non-seasonal and non-stationary moving average model. In our model, we included four independent variables as potential predictors: Monthly MRSA prevalence rates (colonization pressure), monthly pooled mean of the amount of alcohol-based hand sanitizers used for one patient per day, monthly pooled mean of patient-to-nurse ratios, and monthly bed occupancy rates.

Lag time in the ARIMA model indicated the time interval (months) between the occurrence of a significant independent variable and the dependent variable. A beta coefficient is the slope of the regression surface constructed using the fitted model where a positive beta coefficient indicates a positive correlation and a negative beta coefficient indicates a negative correlation. All p values are two-sided, and $p<.05$ is considered statistically significant. We used SPSS 15.0J (Tokyo, Japan) for all statistical analyses.

Results

During the 73-month study period, 223 (18.1%) of the 1,229 neonates admitted to the NICU were MRSA positive. Two of the 233 MRSA-positive neonates had been transferred from other hospitals and were positive on the day of admission. The MRSA incidence, therefore, was 221, and the overall MRSA incidence density rate was 7.5 per 1,000 patient days. The average time from admission to the acquisition of MRSA was 11.3 days (range 3-162 days) for the incident cases.

Figure 1 shows the monthly number of MRSA positive neonates as well as MRSA incidence density rates during the study period. For the first three and a half years, the rates fluctuated around 15 per 1,000 patient days. After rising to 20.0 per 1,000 patient days in August 2006, MRSA incidence density rates started to decline gradually, which then reached zero in October 2008. No MRSA positive neonate has been detected in our NICU thereafter until the end of the study period (July 2009).

The overall MRSA prevalence rate, or colonization pressure (CP), was 34.8% (range 0.0-72.6%). During the first three years of the study period, CP often exceeded 60%. After reaching its second highest peak of 71.3% in August 2006, CP started to fall. However, the average CP during the next 12 months continued to remain as high as 40.7%. When the incidence reached zero in October 2008, CP was still vacillating around 10% until it finally became zero six months later.

The pooled mean of alcohol-based hand sanitizers used (ml) for one patient per day during the study period was 11.6 ml/patient/day. The monthly amount stayed below 10 ml/patient/day until it rose sharply to 22.0 ml/patient/day in April 2005, one month after the MRSA incidence had

reached its highest level of 25.9 per 1,000 patient days. The amount then rose and fell in accordance with MRSA incidence density rates until July 2006 when one dispenser was placed beside each cot/incubator in the NICU. Thereafter, the monthly amount constantly stayed around 15.0 ml/patient/day even after the MRSA incidence had reached zero (Figure 2).

All nurses working in the NICU are registered nurses. The number of full-time equivalent (FTE) nurses increased from 15 in 2003 to 22 in 2009. The number of part-time nurses employed each year ranged from 1 to 4. The ratio of FTE nurses to part-time nurses was constant throughout the study period. The monthly pooled mean of patient-to-nurse ratios was highest in 2004 when it reached 5.0, then slowly fell. It remained below 3.0 in the final year of the study period.

The average bed occupancy rate was 85.8% for the entire study period. Monthly bed occupancy rates had often exceeded 100% in the NICU and newborn nursery until October 2007 when the hospital started to limit admissions to the Labor and Delivery Unit to alleviate overcrowding.

Based on our ARIMA (0,1,1) model, the amount of alcohol-based hand sanitizer used for one patient per day (lag time 0 month, $p=0.011$) was the only factor significantly associated with the MRSA incidence density rates. MRSA colonization pressure, patient-to-nurse ratios and bed occupancy rates were not associated with MRSA acquisition in the NICU (Table 1).

Discussion

Unlike previous studies that compared pre- and post-intervention MRSA rates, time series

analyses enable identification of factors that influence the long term trend of MRSA transmission after adjusting auto-correlation and cross correlation of time-series data. To our knowledge, this is the first study that used time series data to identify significant factors associated with MRSA acquisition in a NICU.

The incidence of MRSA in a NICU may be influenced by the prevalence of the organism in the entire hospital or the population the hospital serves. Unfortunately, there is currently no national or local benchmark data on the incidence density rates of MRSA colonization and infection in Japan. In our hospital, the NICU is the only unit that conducts active surveillance, so the true MRSA incidence for the entire hospital is unknown. For this reason, it is difficult to ascertain how the hospital-wide and local prevalence of MRSA has influenced the incidence in our NICU. Nevertheless, the fact that all MRSA cases, except for the two transferred cases, were detected more than 78 hours after admission suggests that the widespread MRSA transmission occurred almost exclusively within the NICU and not from cases imported from other facilities or from the community. Thus, it is also likely that factors associated with the elimination of MRSA existed within rather than outside the NICU.

Our study shows that monthly pooled mean of the amount of alcohol-based hand sanitizer used for each patient per day is significantly associated with a decrease in MRSA incidence density rates. From the beginning of the study period until mid-2006, NICU staff had used five hand-washing sinks and several alcohol hand sanitizer dispensers, placed in each corner of the NICU, for hand hygiene. During the same period, the monthly amount of alcohol-based hand

sanitizer used rose and fell almost simultaneously with MRSA incidence rates, indicating that adherence to hand hygiene improved temporarily when staff were alerted to the rise in MRSA incidence. After the placement of one alcohol-based hand sanitizer dispenser per cot/incubator in July 2006, we began to observe a steady decline in MRSA incidence density rates as well as an increase in the amount of alcohol-based hand sanitizers used, which remained at a high level even after elimination of MRSA from the NICU in October 2008.

Pittet et al. reported that hand hygiene adherence was associated with lower MRSA colonization rates[19]. Bischoff et al. also observed that improved accessibility to alcohol based hand sanitizers enhanced adherence to hand hygiene[20]. Our study not only confirms these results but also demonstrates the long-term preventive effect of improved accessibility to alcohol-based hand sanitizers on MRSA incidence. Our time series analyses show a negative correlation between MRSA incidence and the amount of hand sanitizers used; in other words, using more hand sanitizers resulted in fewer MRSA cases in the long run.

Previous studies have shown a statistically significant association between the incidence of multidrug-resistant organisms and their colonization pressure (CP) [21)-23)]. For example, Merrer et al. found weekly MRSA CP above 30% increased the risk of MRSA acquisition approximately fivefold[21]. Similarly, Williams et al. reported the relative risk of MRSA acquisition to be 7.64 when the CP was above 6.7%[22]. We, however, did not observe such an association. In fact, in September 2006, the month after CP hit its second highest peak of 71.3%, the incidence began to decrease rather than increase. During the next 12 months, incidence rates continued to fall

despite a CP average of above 40%. As our data show, maintaining a high level of alcohol hand sanitizer use by improving access and periodically holding training sessions on hand hygiene may have reduced the risk of MRSA transmission even during periods of high CP.

Even though the patient-to-nurse ratios and bed occupancy rates decreased steadily toward the end of the study period, they were not statistically significant predictors of MRSA acquisition in the NICU. Previous studies have found that understaffing and overcrowding hindered hand hygiene adherence[24-27] and resulted in outbreaks of MRSA and other organisms in NICUs[28-30]. Our results may suggest that, in NICUs with bed occupancy rates and nurse-to-patient ratios similar to ours, facilitating the use of alcohol-based hand sanitizers may help counteract the unfavorable effects of nursing shortage and overcrowding.

Our study is subject to at least four limitations. First, we used pharmacy records to estimate the monthly pooled mean of the amount of alcohol-based hand sanitizers used for each patient per day, but the data may not reflect the actual amount used in the NICU. Second, since there were only two MRSA-positive cases transferred from other facilities to our NICU, our results may not be generalized to NICUs with higher proportion of MRSA-positive neonates admitted from other facilities or community. Third, there may be factors associated with MRSA transmission in the NICU other than colonization pressure, nurse-to-patient-ratios and bed occupancy rates evaluated in this study. Lastly, preventive measures that had already been in place before the start of the study may have influenced MRSA incidence density rates, but we were not able to identify their individual effects. It should be noted that, even though active surveillance had been

practiced since the late 1980s, MRSA incidence density rates had constantly been high at around 15.0 per 1000 patient days until it started to decline in the fall of 2006. In our NICU, active surveillance was not sufficient to control the spread of MRSA until it was accompanied by enhanced and sustained performance of hand hygiene.

Conclusion

Our time series analyses showed that increasing the amount of alcohol-based hand sanitizer usage by improving accessibility and providing periodic hand-hygiene training sessions to health-care workers was associated with a statistically significant and sustained downward trend in MRSA incidence density rates in our NICU. Increasing the use of alcohol-based hand sanitizers is strongly recommended for decreasing the risk of MRSA acquisition among neonates in NICU settings.

References

1. Weeks JL, Garcia-Prats JA, Baker CJ. Methicillin-resistant Staphylococcus aureus osteomyelitis in a neonate. JAMA 1981;245:1662-4.
2. Carey AJ, Duchon J, Della-Latta P, Saiman L. The epidemiology of methicillin-susceptible and methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit, 2000-2007. J Perinatol Published online 27 August 2009.
3. Gregory ML, Eichenwald EC, Puopolo KM. Seven-year experience with a surveillance

program to reduce methicillin-resistant Staphylococcus aureus colonization in a neonatal intensive care unit. Pediatrics 2009;123:790-6.

4. Raymond J, Aujard Y. Nosocomial infections in pediatric patients: a European, multicenter prospective study. Infect Control Hosp Epidemiol 2000;21:260-3.

5. Babazono A, Kitajima H, Nishimaki S, Nakamura T, Shiga S, Hayakawa M, et al. Risk factors for nosocomial infection in the neonatal intensive care unit by the Japanese nosocomial infection surveillance (JANIS). Acta Med Okayama 2008;62:261-8.

6. Lepelletier D, Corvec S, Caillon J, Reynaud A, Rozé JC, Gras-Leguen C. Eradication of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit: which measures for which success? Am J Infect Control 2009;37:195-200.

7. Khoury J, Jones M, Grim A, Dunne WM Jr, Fraser V. Eradication of methicillin-resistant Staphylococcus aureus from a neonatal intensive care unit by active surveillance and aggressive infection control measures. Infect Control Hosp Epidemiol 2005;26:616-21.

8. Back NA, Linnemann CC, Staneck JL, Kotagal UR. Control of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit: use of intensive microbiologic surveillance and mupirocin, Infect Control Hosp Epidemiol 1996;17:227-31.

9. Saiman L, Cronquist A, Wu F, Zhou J, Rubenstein D, Eisner W, et al. An outbreak of methicillin-resistant Staphylococcus aureus in a neonatal intensive care unit. Infect Control Hosp Epidemiol 2003;24:317-21.

10. Haley RW, Cushion NB, Tenover FC, Bannerman TL, Dryer D, Ross J, et al. Eradication of

endemic methicillin-resistant Staphylococcus aureus infections from a neonatal intensive care unit. J Infect Dis 1995;17:614-24.

11. Lederer JW Jr, Best D, Hendrix V. A comprehensive hand hygiene approach to reducing MRSA health care-associated infections. Jt Comm J Qual Patient Saf 2009;35:180-5.
12. Gill CJ, Mantaring JB, Macleod WB, Mendoza M, Mendoza S, Huskins WC, et al. Impact of enhanced infection control at 2 neonatal intensive care units in the Philippines. Clin Infect Dis. 2009;48:13-21.
13. Pofahl WE, Goettler CE, Ramsey KM, Cochran MK, Nobles DL, Rotondo MF. Active surveillance screening of MRSA and eradication of the carrier state decreases surgical-site infections caused by MRSA. J Am Coll Surg 2009;208:981-6.
14. Sandri AM, Dalarosa MG, Ruschel de Alcantara L, da Silva Elias L, Zavascki AP. Reduction in incidence of nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection in an intensive care unit: role of treatment with mupirocin ointment and chlorhexidine baths for nasal carriers of MRSA. Infect Control Hosp Epidemiol 2006;27:185–7.
15. Shitrit P, Gottesman BS, Katzir M, Kilman A, Ben-Nissan Y, Chowers M. Active surveillance for methicillin-resistant Staphylococcus aureus (MRSA) decreases the incidence of MRSA bacteremia. Infect Control Hosp Epidemiol 2006;27:1004-8.
16. West TE, Guerry C, Hiott M, Morrow N, Ward K, Salgado CD. Effect of targeted surveillance for control of methicillin-resistant Staphylococcus aureus in a community hospital system. Infect Control Hosp Epidemiol 2006;27:233-8.

17. Lucet JC, Paoletti X, Lolom I, Paugam-Burtz C, Trouillet JL, Timsit JF, et al. Successful long-term program for controlling methicillin-resistant Staphylococcus aureus in intensive care units. Intensive Care Med 2005;31:1051-7.

18. Pan A, Carnevale G, Catenazzi P, Colombini P, Crema L, Dolcetti L, et al. Trends in methicillin-resistant Staphylococcus aureus (MRSA) bloodstream infections: effect of the MRSA "search and isolate" strategy in a hospital in Italy with hyperendemic MRSA. Infect Control Hosp Epidemiol 2005;26:127-33.

19. Pittet D, Hugonnet S, Harbarth S, Mourouga P, Sauvan V, Touveneau S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Lancet 2000;356:1307-12.

20. Bischoff WE, Reynolds TM, Sessler CN, Edmond MB, Wenzel RP. Handwashing compliance by health care workers: the impact of introducing an accessible, alcohol-based hand antiseptic. Arch Intern Med 2000;160:1017-2.

21. Merrer J, Santoli F, Appéré de Vecchi C, Tran B, De Jonghe B, Outin H. "Colonization pressure" and risk of acquisition of methicillin-resistant Staphylococcus aureus in a medical intensive care unit. Infect Control Hosp Epidemiol 2000;21:718-23.

22. Williams VR, Callery S, Vearncombe M, Simor AE. The role of colonization pressure in nosocomial transmission of methicillin-resistant Staphylococcus aureus. Am J Infect Control 2009;37:106-110.

23. Bonten MJ, Slaughter S, Ambergen AW, Hayden MK, van Voorhis J, Nathan C, et al. The role

of "colonization pressure" in the spread of vancomycin-resistant enterococci: an important infection control variable. Arch Intern Med. 1998;158:1127-32.

24. Grundmann H, Hori S, Winter B, Tami A, Austin DJ. Risk factors for the transmission of methicillin-resistant Staphylococcus aureus in an adult intensive care unit: fitting a model to the data. J Infect Dis 2002;185:481-8.

25. Nijssen S, Bonten MJ, Franklin C, Verhoef J, Hoepelman AI, Weinstein RA. Relative risk of physicians and nurses to transmit pathogens in a medical intensive care unit. Arch Intern Med 2003;163:2785-6.

26. Pittet D, Mourouga P, Perneger TV. Compliance with handwashing in a teaching hospital. Ann Intern Med 1999;130:126-30.

27. Pittet D, Simon A, Hugonnet S, Pessoa-Silva CL, Sauvan V, Perneger TV. Hand hygiene among physicians: performance, beliefs, and perceptions. Ann Intern Med 2004;141:1-8.

28. Andersen BM, Lindemann R, Bergh K, Nesheim BI, Syversen G, Solheim N, et al. Spread of methicillin-resistant Staphylococcus aureus in a neonatal intensive unit associated with understaffing, overcrowding and mixing of patients. J Hosp Infect 2002;50:18-24.

29. Haley R, Bregman D. The role of understaffing and overcrowding in recurrent outbreaks of staphylococcal infections in a neonatal special-care unit. J Infect Dis 1982;145: 875-85.

30. Smith PJ, Brookfield DS, Shaw DA, Gray J. An outbreak of Serratia marcescens infections in a neonatal unit. Lancet 1984;1:151-3.

Figures1&2

Click here to download Figure(s): Figures1and2.doc

Figure 1

Monthly MRSA incidence and incidence density rates in the NICU, July 2003-July 2009

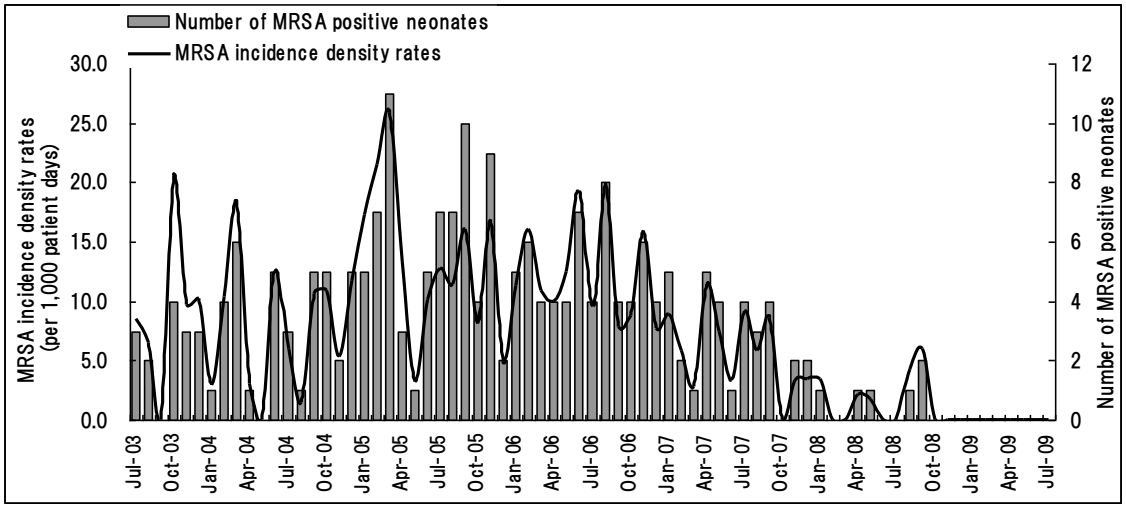

Figure 2

Monthly MRSA incidence density rates (black line) and corresponding pooled mean amount of alcohol-based hand sanitizers used for one patient per day in the NICU, July 2003-July 2009

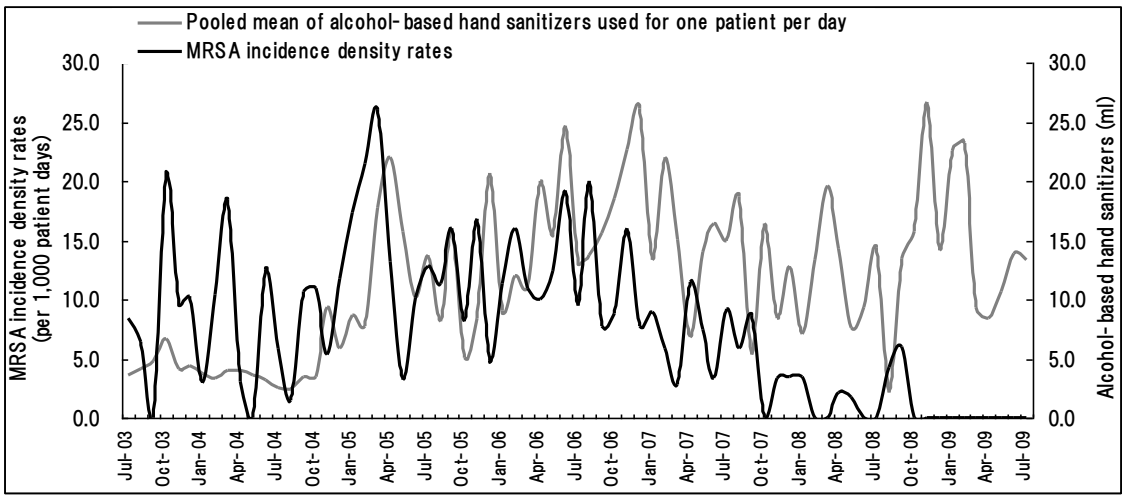

Table 1

Multivariate ARIMA (0,1,1) model for MRSA incidence density rates in the NICU, July 2003-July 2009

Independent Variables	Lag time	Beta coefficient	SE	t statistic	p value
Alcohol-based hand sanitizer used(ml) for one patient per day	0	-0.052	0.020	-2.616	0.011
MRSA prevalence rates (colonization pressure; %)	0	0.006	0.011	0.570	0.571
Bed occupancy rates	0	0.033	0.025	1.296	0.199
Patient-to-nurse ratio	0	-0.769	0.728	-1.057	0.295

ARIMA= auto-regressive integrated moving average

MRSA= Methicillin-Resistant Staphylococcus aureus

NICU= Neonatal Intensive Care Unit

SE= standard error