ORIGINAL ARTICLE

Intervention to Reduce Transmission of Resistant Bacteria in Intensive Care

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ABSTRACT

BACKGROUND

Intensive care units (ICUs) are high-risk settings for the transmission of methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE).

METHODS

In a cluster-randomized trial, we evaluated the effect of surveillance for MRSA and VRE colonization and of the expanded use of barrier precautions (intervention) as compared with existing practice (control) on the incidence of MRSA or VRE colonization or infection in adult ICUs. Surveillance cultures were obtained from patients in all participating ICUs; the results were reported only to ICUs assigned to the intervention. In intervention ICUs, patients who were colonized or infected with MRSA or VRE were assigned to care with contact precautions; all the other patients were assigned to care with universal gloving until their discharge or until surveillance cultures obtained at admission were reported to be negative.

RESULTS

During a 6-month intervention period, there were 5434 admissions to 10 intervention ICUs, and 3705 admissions to 8 control ICUs. Patients who were colonized or infected with MRSA or VRE were assigned to barrier precautions more frequently in intervention ICUs than in control ICUs (a median of 92% of ICU days with either contact precautions or universal gloving [51% with contact precautions and 43% with universal gloving] in intervention ICUs vs. a median of 38% of ICU days with contact precautions in control ICUs, $P<0.001$). In intervention ICUs, health care providers used clean gloves, gowns, and hand hygiene less frequently than required for contacts with patients assigned to barrier precautions; when contact precautions were specified, gloves were used for a median of 82% of contacts, gowns for 77% of contacts, and hand hygiene after 69% of contacts, and when universal gloving was specified, gloves were used for a median of 72% of contacts and hand hygiene after 62% of contacts. The mean (±SE) ICU-level incidence of events of colonization or infection with MRSA or VRE per 1000 patient-days at risk, adjusted for baseline incidence, did not differ significantly between the intervention and control ICUs (40.4±3.3 and 35.6±3.7 in the two groups, respectively; $P=0.35$).

CONCLUSIONS

The intervention was not effective in reducing the transmission of MRSA or VRE, although the use of barrier precautions by providers was less than what was required. (Funded by the National Institute of Allergy and Infectious Diseases and others; STAR*ICU ClinicalTrials.gov number, NCT00100386.)

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Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococcus (VRE) are major causes of health care–associated infection.[1] Infections caused by these bacteria are usually preceded by colonization of mucous membranes, skin, wounds, or the gastrointestinal tract. Colonization occurs by means of indirect patient-to-patient transmission of MRSA and VRE through the hands of health care providers and through contaminated fomites and environmental surfaces[2,3] or, less commonly, by direct transmission from colonized health care providers.[4]

Standard interventions to prevent the transmission of MRSA and VRE in health care facilities include hand hygiene, the use of barrier precautions (gloves and gowns) in the care of colonized and infected patients, the use of dedicated instruments and equipment for these patients, and the placement of colonized or infected patients in single rooms or multibed rooms or areas reserved for such patients.[5,6] Additional interventions, including active surveillance — screening to identify asymptomatically colonized patients who may serve as undetected reservoirs of MRSA and VRE — and topical antimicrobial treatments, are supported by ecologic, observational, and quasi-experimental studies and mathematical models.[7-18]

We hypothesized that culture-based active surveillance for MRSA and VRE and the expanded use of barrier precautions, as compared with existing practice, would reduce the incidence of colonization or infection with MRSA or VRE in adult intensive care units (ICUs).

Methods

Design

We conducted an unmasked, cluster-randomized, controlled trial with the ICU as the unit of randomization and inference. The trial consisted of three periods: baseline (April through November 2005), randomization and implementation (December 2005 through February 2006), and intervention (March through August 2006). The intervention period began when the Web-based system for reporting the results of surveillance cultures was activated.

The study was designed and conducted by the authors with guidance from the principal investigators of the Bacteriology and Mycology Study Group and members of the Risk Group 4 Research Committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The staff at the coordinating center and the authors analyzed the data and vouch for the completeness and accuracy of the report. The commercial sponsors had no role in the design of the study, the accrual or analysis of the data, the reporting of the results, or the decision to submit the manuscript for publication. The protocol, including the statistical analysis plan, is available at NEJM.org.

Eligibility and Randomization

ICUs were eligible for inclusion in the study if they were adult medical, surgical, or medical–surgical ICUs with 1200 or more patient-days in a 6-month period and an estimated incidence of at least nine events of MRSA or VRE colonization or infection per 1000 patient-days as estimated on the basis of historical data. The study was approved by the physician and nurse directors in each ICU and the institutional review board at each participating site. The requirements for informed consent and for authorization by the federal Health Insurance Portability and Accountability Act (HIPAA) were waived on the basis of the criteria of Title 45, Section 46.116(d), of the Code of Federal Regulations and of Section 164.512(i) of the Privacy Rule, respectively. ICUs were randomly assigned, in a 1:1 ratio, to the intervention or to existing practice (control), with stratification according to type of ICU and the baseline incidence of MRSA or VRE colonization or infection.

Intervention

In intervention ICUs, nasal swabs for MRSA surveillance cultures and stool or perianal swabs for VRE surveillance cultures were obtained from patients within 2 days after their admission to the ICU, weekly thereafter, and within 2 days before or after their discharge from the ICU. Swabs were shipped overnight, 6 days a week, for processing at the Clinical Microbiology Laboratory of the National Institutes of Health Clinical Center. Broth enrichment and extended incubation were used to enhance the sensitivity of the culture methods (see Table 1 in the Supplementary Appendix).[19,20] Results were reported by means of an access-controlled, Web-based system.

In intervention ICUs, the assignment of a patient to care with contact precautions was made at the time of admission if a patient had been infected or colonized with MRSA or VRE during

the previous year and at any time during the ICU stay if a clinical or surveillance culture was reported to be positive for MRSA or VRE. Once contact precautions were initiated, they were continued for the entire ICU stay. All other patients were assigned to care with universal gloving from the time of admission until their discharge or until the results of surveillance cultures for both MRSA and VRE obtained at admission were reported to be negative, at which time they were assigned to standard precautions (unless isolation precautions were required for other conditions). The requirements for contact precautions, universal gloving, and standard precautions are specified in Table 1. No recommendations for the use of topical or systemic antimicrobial agents were provided.

In control ICUs, swabs for surveillance cultures were obtained and shipped with the use of procedures that were identical to those used in intervention ICUs, but the ICU staff did not have access to the results. Existing hospital procedures were used to identify patients who were colonized or infected with MRSA or VRE. Such patients were assigned to care with isolation precautions, which were generally consistent with contact precautions. All other patients were assigned to standard precautions (unless isolation precautions were required for other conditions).

Before randomization, all the ICUs received an aggregate report of the providers' use of standard precautions during the baseline period and a promotional program to improve the providers' use of standard precautions (see Additional Methods in the Supplementary Appendix). After randomization, intervention ICUs received training in the intervention, door signs describing each category of precautions, and an aggregate report on the providers' use of universal gloving during the first month of the intervention period.

In all the ICUs, monitors located in patients' rooms observed contacts between health care providers and patients or their immediate environment on random dates and times during daytime and evening hours and recorded the precaution category assigned to the patient, the type of contact, and the providers' use of hand hygiene, clean gloves, and a gown (Table 1 in the Supplementary Appendix).

MEASUREMENTS

Both patient-level and ICU-level data were collected (Table 1 in the Supplementary Appendix); all analyses were based on ICU-level aggregates, except as noted. A new event of colonization or infection was identified by a surveillance or clinical culture that was positive for MRSA or VRE. No attempt was made to distinguish colonization from infection. The event date was the date the earliest positive culture was obtained.

A patient was eligible to be considered as having a new event of colonization or infection if he or she had a length of stay in the ICU of at least 3 days, no history of colonization or infection during the previous year, no positive clinical culture within 2 days after admission to the ICU, and a negative surveillance culture obtained within 2 days after admission to the ICU. Days at risk were calculated from the date of the third ICU day through the event date or through either the date of discharge from the ICU or the date the last surveillance culture was obtained, whichever was later.

The primary outcome was the ICU-level incidence of new events of colonization or infection with MRSA or VRE per 1000 ICU patient-days at risk. Secondary ICU-level outcomes were the incidences of colonization or infection with MRSA and VRE calculated separately and the following implementation process measures: the percentage of ICU patient-days on which patients colonized or infected with MRSA or VRE were assigned to each of the precautions categories, the percentage of health care provider contacts with patients or their environment during which the provider performed hand hygiene before or after the contact or wore clean gloves or a gown (component measures), and the percentage of provider contacts during which the provider both wore clean gloves during the contact and performed hand hygiene after the contact (composite measure).

STATISTICAL ANALYSIS

We estimated the sample size on the basis of published data[22] and assumed a mean baseline incidence of MRSA or VRE colonization or infection of 30 per 1000 patient-days, a variance of 49 with a 20% reduction in that variance obtained from adjustment for baseline incidence, and a 25% reduction in incidence from baseline in both intervention and control ICUs, owing to the program promoting standard precautions. Using those assumptions, we estimated that with 10 ICUs in each group, the study would have at least 85% power to show an additional 40% reduction in incidence in intervention ICUs, with a two-sided

Table 1. Minimum Requirements for Hand Hygiene and Use of Gloves and Gowns by Health Care Providers during Contacts with Patients or Their Immediate Environment.*

Type of Contact†	Standard Precautions				Universal Gloving				Contact Precautions			
	Hand Hygiene‡		Gloves§	Gown§	Hand Hygiene‡		Gloves§	Gown§	Hand Hygiene‡		Gloves§	Gown§
	before contact	*after contact*			*before contact*	*after contact*			*before contact*	*after contact*		
Sterile	+	+	+	+	+	+	+	+	+	+	+	+
Contaminated	+	+	+		+	+	+		+	+	+	+
Blood or body fluid	+	+	+		+	+	+		+	+	+	+
Invasive device	+	+			+	+	+		+	+	+	+
Other patient	+	+			+	+	+		+	+	+	+
Environment only		+				+	+			+	+	+

* A plus sign indicates that the practice was required. Requirements for the room assignments of patients, the use of dedicated instruments and equipment, and the cleaning and disinfecting of contaminated items were specified by guidelines that were current when the trial was initiated.[21]

† Sterile contacts involved performing a sterile procedure; contaminated contacts involved potential contact with secretions, excretions, mucous membranes, non-intact skin, or items or surfaces that are likely to be contaminated with body secretions or excretions; blood or body-fluid contacts involved potential contact with blood or body fluids capable of transmitting bloodborne viruses; invasive-device contacts involved opening or accessing an invasive device that entered a sterile body site directly; and other patient contact involved contacts not included in the previously described categories. Environment-only contacts involved touching items or surfaces in the patient's immediate environment only. Examples of each type of contact are provided in Table 2 in the Supplementary Appendix.

‡ Hand hygiene involved rubbing hands with a waterless, alcohol-based hand rub or washing hands with soap and water.

§ Sterile gloves and gowns were needed for sterile contacts; otherwise clean nonsterile gloves and gowns were sufficient.

type I error of 0.05. On the basis of observed factors, the 18-site study had a post hoc power of 80% to detect a 30% reduction in the incidence of MRSA or VRE colonization or infection in intervention ICUs.

The primary analysis was a comparison of the primary outcome between the intervention and control ICUs during the intervention period, with the use of an ICU-level analysis-of-covariance model with adjustment for baseline incidence and with the use of an F-test, with a two-sided P value of 0.05. We used similar models to evaluate the secondary outcomes and the relationship between the primary outcome and implementation process measures. ICU-level and patient-level variables and implementation process measures were compared between the groups within the baseline and intervention periods with the use of Wilcoxon rank-sum tests and between periods within groups with the use of Wilcoxon signed-rank tests, with no adjustment for multiple comparisons.

Patient-level exploratory analyses were performed with time from admission to a new event of colonization or infection with MRSA or VRE as the outcome, with the use of Cox proportional-hazards models with adjustment for within-ICU correlation.[23] Data were censored at the time of a patient's discharge from the ICU or at the end of the study in the case of patients who were still in the ICU and were negative for both MRSA and VRE colonization or infection. ICU-level and patient-level variables were evaluated as possible confounders with the use of paired models that examined the effect of the intervention on the risk of a new colonization or infection event with and without the variable. We generated a "best fit" multivariable model using backward elimination and including all potential confounders with P values of less than 0.10. This model was also used to assess the effect of the intervention by month.

RESULTS

CHARACTERISTICS OF ICUs AND PATIENTS

Figure 1 shows the random assignment of ICUs to the intervention or control group and the follow-up of patients in the intervention and control ICUs. There were no significant differences in key characteristics between patients in the intervention ICUs and those in the control ICUs, except with respect to the prescription of some topical and systemic antimicrobial agents (Table 2, and Table 3 in the Supplementary Appendix).

RESULTS OF SURVEILLANCE CULTURES

In intervention ICUs, the mean (±SD) number of days from the time a surveillance culture was obtained until the time it was reported was 5.2±1.4.

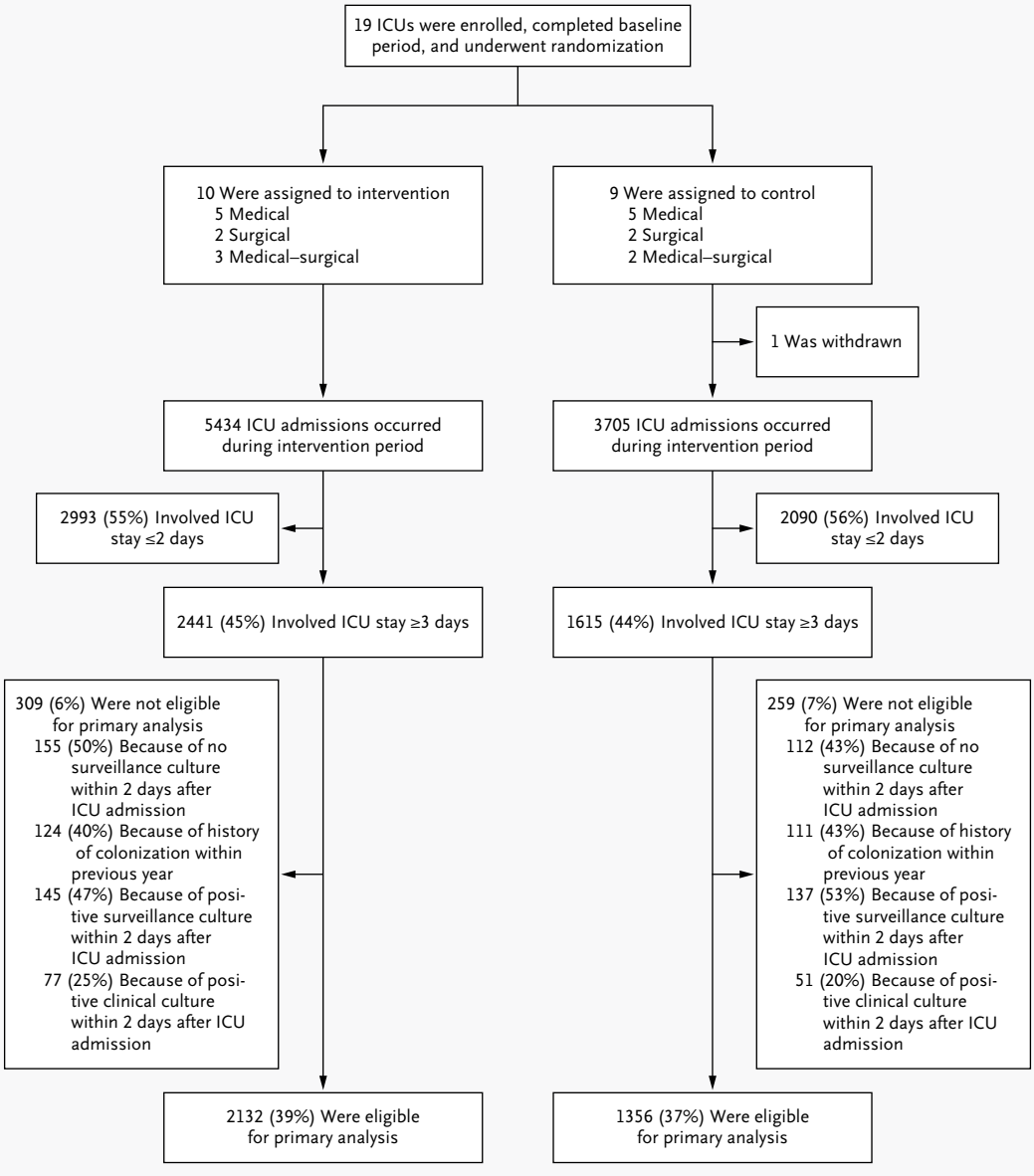

Figure 1. Randomization of Intensive Care Units (ICUs) and Follow-up of Patients.

The ICU-level percentage of patients with multiple admissions was 7.6% among all ICU stays and 6.1% among ICU stays of 3 days or more; therefore, each admission was treated as an independent event. A total of 20 ICUs were eligible for the study, of which 19 participated. In addition, 1 medical ICU assigned to the control group was withdrawn from the study owing to a failure to collect surveillance cultures according to the study protocol. Data from this ICU were excluded from all analyses. During the intervention period, there were 24,484 total ICU patient-days in the intervention ICUs and 16,579 total ICU patient-days in the control ICUs. A total of 18,136 ICU patient-days at risk (74% of total ICU patient-days) in the intervention group and 11,827 ICU patient-days at risk (71% of total ICU patient-days) in the control group were included in the primary analysis. ICU stays could have multiple reasons for not being eligible for the primary analysis.

Among patients with an ICU stay of 3 days or more, 41% (range, 30 to 66) of all ICU patient-days coincided with or followed the day on which the results of surveillance cultures were reported. In a substantial proportion of patients in all ICUs who were colonized or infected with MRSA or VRE at the time of admission or who had new colonization or infection events during their stay in the

ICU, MRSA or VRE was detected only by means of surveillance cultures, with no evidence of a significant difference between intervention and control ICUs. The median proportions of patients with positive surveillance cultures were 46% (range, 16 to 56) in intervention ICUs and 38% (range, 14 to 77) in control ICUs for detection of MRSA at admission (P=0.81); 62% (range, 29 to 83) and 77% (range, 43 to 92) in the two groups, respectively, for detection of VRE at admission (P=0.18); 77% (range, 43 to 96) and 86% (range, 24 to 100) in the respective groups for detection of a new MRSA event (P=0.30); and 100% (range, 91 to 100) and 99% (range, 80 to 100) in the respective groups for detection of a new VRE event (P=0.51) (Table 4 in the Supplementary Appendix).

ASSIGNMENT OF PRECAUTIONS CATEGORIES

Patients who were colonized or infected with MRSA or VRE were assigned to expanded barrier precautions more frequently in intervention ICUs than in control ICUs. In the intervention ICUs, these patients were assigned to contact precautions for a median of 51% (range, 30 to 85) of

Table 2. Characteristics of Patient Populations.*

Characteristic	Baseline Period			Intervention Period		
	Intervention ICUs (N=10)	Control ICUs (N=8)	P Value†	Intervention ICUs (N=10)	Control ICUs (N=8)	P Value†
	median (range)‡			*median (range)‡*		
Colonization or infection during previous year — %						
MRSA	6.6 (1.9–16.2)	5.7 (2.7–13.9)	0.97	6.5 (3.1–13.4)	5.8 (2.0–14.7)	1.00
VRE	4.0 (0.0–14.4)	4.3 (1.4–8.5)	0.46	4.4 (1.6–16.8)	4.4 (0.7–10.5)	0.90
Positive clinical culture on admission — %§						
MRSA	4.0 (1.1–19.2)	3.1 (1.1–9.4)	0.97	3.0 (1.7–14.2)	2.8 (0.4–7.0)	0.70
VRE	1.9 (0.0–23.1)	0.9 (0.7–3.0)	0.41	1.5 (0.4–23.0)	1.5 (0.0–7.4)	0.70
Positive surveillance culture on admission — %§						
MRSA	9.5 (6.3–14.8)	12.4 (8.7–24.3)	0.08	10.6 (8.3–19.8)	12.6 (6.2–17.6)	0.97
VRE	13.6 (6.9–24.4)	17.2 (8.9–26.2)	0.57	16.9 (7.9–39.9)	22.1 (12.3–34.4)	0.63
Use of topical antimicrobial agent — %						
Any	9.0 (2.3–33.3)	4.2 (0.2–11.3)	0.10	12.0 (2.5–36.1)	3.2 (0.3–13.0)	0.07
Bacitracin	3.6 (0.9–7.6)	2.2 (0.0–3.7)	0.10	2.8 (0.1–11.8)	1.2 (0.2–8.6)	0.41
Mupirocin¶	0.3 (0.0–24.5)	0.1 (0.0–1.1)	0.48	0.1 (0.0–24.4)	0.0 (0.0–0.5)	0.33
Chlorhexidine gluconate¶	0.0 (0.0–25.3)	0.0 (0.0–1.6)	0.71	0.0 (0.0–30.9)	0.0 (0.0–8.4)	0.71
Vancomycin, enteric	0.0 (0.0–0.5)	0.4 (0.0–2.9)	0.02	0.0 (0.0–1.3)	0.5 (0.0–3.6)	0.04
Use of systemic antimicrobial agent — %						
Regimen with anti-anaerobic activity	35.8 (19.5–48.4)	41.9 (31.8–55.0)	0.41	35.4 (21.6–46.2)	43.8 (34.9–52.9)	0.01
Vancomycin	24.6 (11.8–33.8)	28.0 (18.0–39.6)	0.46	23.8 (12.8–40.0)	32.0 (18.8–37.2)	0.17
Piperacillin–tazobactam	15.2 (0.0–27.0)	24.6 (6.9–36.8)	0.10	13.6 (0.0–19.9)	22.6 (6.4–28.9)	0.03
Cefepime	11.2 (0.0–25.8)	1.1 (0.0–8.6)	0.03	13.4 (0.0–23.2)	3.5 (0.0–20.0)	0.09
Levofloxacin	12.7 (0.0–24.2)	0.1 (0.0–27.8)	0.82	9.9 (0.0–23.7)	0.2 (0.0–23.8)	0.55
Metronidazole	7.3 (1.4–21.4)	11.1 (0.0–19.8)	0.83	6.6 (4.8–19.9)	13.3 (5.8–25.3)	0.20

* A complete list of the characteristics of the intensive care units (ICUs) and the patient populations is provided in Table 2 in the Supplementary Appendix. MRSA denotes methicillin-resistant *Staphylococcus aureus,* and VRE vancomycin-resistant enterococcus.
† P values were calculated with the use of the Wilcoxon rank-sum test.
‡ Values are ICU-level estimates.
§ Cultures were obtained within 2 days after admission to the ICU.
¶ Mupirocin was almost always administered by intranasal application, and chlorhexidine by intraoral application.

all ICU patient-days, universal gloving for 43% (range, 9 to 56) of ICU patient-days, and either contact precautions or universal gloving for 92% (range, 80 to 95) of ICU patient-days. In control ICUs, these patients were assigned to contact precautions for a median of 38% (range, 12 to 59) of all ICU patient-days; universal gloving was not used (P<0.001 for the comparison of either contact precautions or universal gloving in intervention ICUs with contact precautions in control ICUs) (Table 5 in the Supplementary Appendix).

HEALTH CARE PROVIDERS' USE OF HAND HYGIENE, CLEAN GLOVES, AND GOWNS

Across all contacts, regardless of the type or category of precautions, the composite measure of providers' use of both clean gloves during the contact and hand hygiene after the contact was higher in intervention ICUs than in the control ICUs by a factor of almost 2 (a median of 47% of contacts [range, 26 to 63] vs. 25% of contacts [range, 4 to 61], P=0.02). For contacts with patients assigned to contact precautions, providers in intervention ICUs used clean gloves and a gown and performed hand hygiene after contact less frequently than required, but marginally more frequently, and with less site-to-site variability, than did providers in control ICUs (Fig. 2A and 2C). Clean gloves were used for a median of 82% of contacts (range, 55 to 87) in intervention ICUs, as compared with 72% (range, 27 to 95) in control ICUs; gowns, for 77% of contacts (range, 60 to 88) in intervention ICUs, as compared with 59% (range, 0 to 93) in control ICUs; and hygiene after contact, for 69% of contacts (range, 38 to 77) in intervention ICUs, as compared with 59% (range, 20 to 88) in control ICUs. For contacts with patients assigned to universal gloving in intervention ICUs, providers used clean gloves and performed hand hygiene after contact less frequently than required and marginally less frequently than for contacts with patients assigned to contact precautions (Fig. 2B); clean gloves were used for a median of 72% of contacts (range, 46 to 77), and hygiene after contact for 62% of contacts (range, 38 to 82). Regardless of the precautions category or the ICU group assignment, providers used clean gloves and a gown and performed hygiene after contact less frequently for contacts with the environment than for all other contact types (Fig. 2). Individual ICU data are provided in Tables 6 through 11 in the Supplementary Appendix.

COLONIZATION OR INFECTION WITH MRSA OR VRE

The monthly ICU-level incidence of MRSA or VRE colonization or infection varied considerably within both ICU groups during the baseline and intervention periods (Fig. 3; see also the figure and Table 12 in the Supplementary Appendix). The percentage change from baseline in the incidence of colonization or infection during the intervention period varied widely in both ICU groups — a median change in the intervention ICUs of 30% (range, −29 to 105) in the incidence of MRSA or VRE, of 10% (range, −43 to 148) in the incidence of MRSA, and of 35% (range, −32 to 197) in the incidence of VRE; and a median change in the control ICUs of 5% (range, −40 to 36) in the incidence of MRSA or VRE, of −9% (range, −52 to 75) in the incidence of MRSA, and of 13% (range, −27 to 90) in the incidence of VRE.

The mean (±SE) ICU-level incidence of events of colonization or infection with MRSA or VRE per 1000 patient-days at risk, adjusted for baseline incidence, did not differ significantly between the intervention and control ICUs (40.4±3.3 and 35.6±3.7 in the two groups, respectively; P=0.35), nor did the ICU-level incidence of MRSA or VRE considered separately (16.0±1.8 and 13.5±2.1 in the two groups, respectively, for MRSA; P=0.39; and 38.9±5.6 and 33.4±6.3 in the two groups, respectively, for VRE; P=0.53).

The ICU-level incidence of MRSA or VRE colonization or infection was not significantly associated with the percentage of ICU patient-days on which colonized or infected patients were assigned to contact precautions (P=0.26) or the percentage of health care provider contacts during which the provider both wore clean gloves during the contact and performed hand hygiene after the contact, either when caring for patients assigned to all precaution categories (P=0.61) or when caring for patients assigned to contact precautions (P=0.92).

The patient-level risk of MRSA or VRE colonization or infection showed little evidence of confounding between patient-level and ICU-level covariates and the intervention (unadjusted hazard ratio for care in an intervention ICU, 1.17; 95% confidence interval [CI], 0.88 to 1.54; P=0.28, with adjusted hazard ratios in bivariable models ranging from 1.04 to 1.25; P>0.13 for all models) (Table 13 in the Supplementary Appendix). An adjusted multivariable model including all potential confounders showed no evidence of an inter-

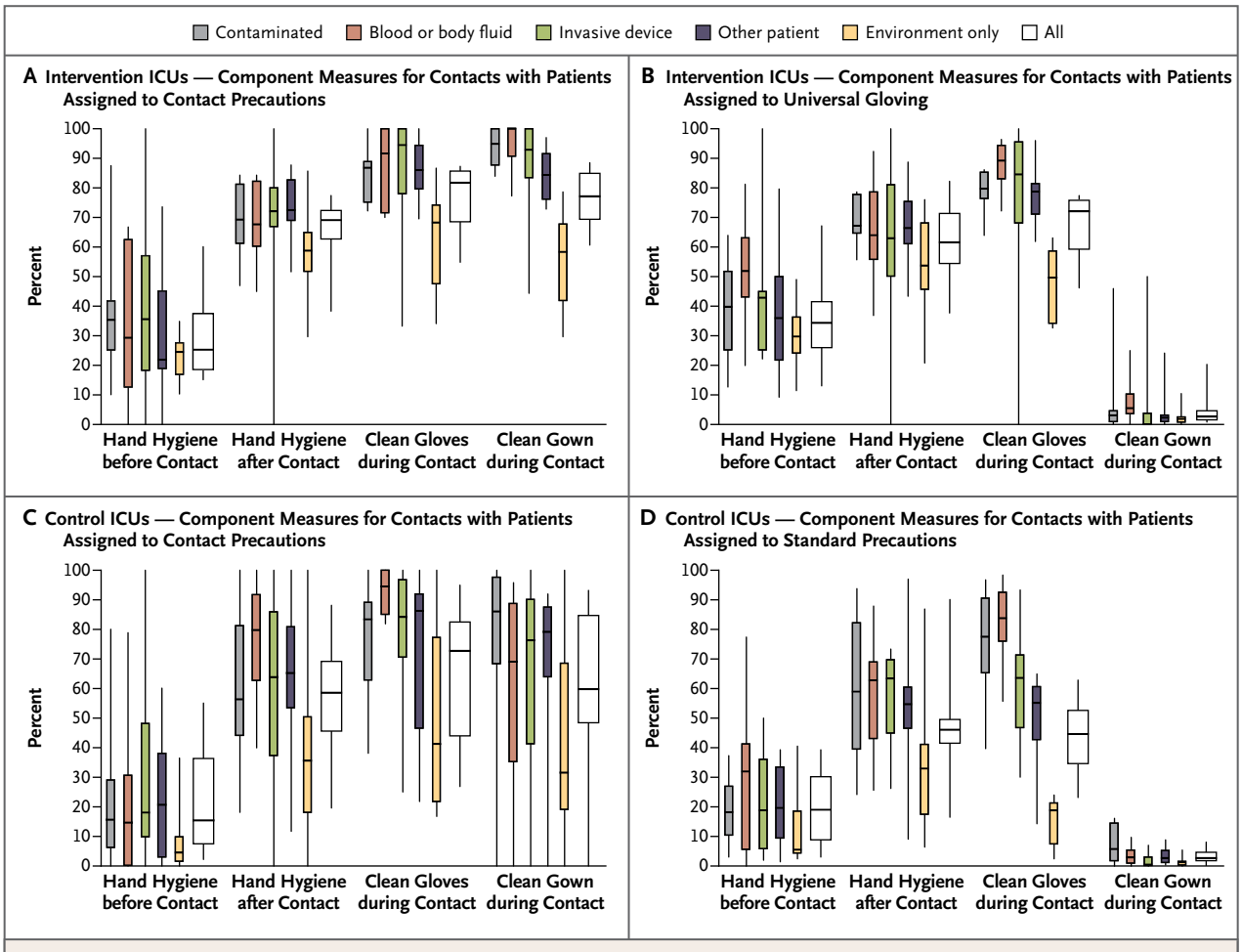

Figure 2. Use of Hand Hygiene, Gloves, and Gowns by Health Care Providers in Intensive Care Units (ICUs) during Contacts with Patients or Their Immediate Environment.

The box plot diagram shows the distribution of ICU-level percentages for the use of component measures for all contacts (white boxes) and according to type of contact (colored boxes). The box represents the interquartile range and the horizontal line inside the box the median; vertical lines represent the maximum and minimum percentages. Contaminated refers to actual or potential contact with secretions, excretions, mucous membranes, non-intact skin, or items or surfaces that are likely to be contaminated with body secretions or excretions. Data regarding sterile contacts in both ICU groups and the use of standard precautions in intervention ICUs are not presented because of the small number of observed contacts. The distributions of types of contacts across all precaution categories were as follows: in intervention ICUs, contaminated, 15%; blood or body fluid, 8%; invasive device, 6%; any other patient, 34%; and environment only, 37%; in control ICUs, contaminated, 15%; blood or body fluid, 8%; invasive device, 8%; any other patient, 32%; and environment only, 37%. Data for individual ICUs are provided in Tables 6 through 11 in the Supplementary Appendix.

vention effect overall (adjusted hazard ratio for care in an intervention ICU, 1.05; 95% CI, 0.81 to 1.36; P=0.72) (Table 14 in the Supplementary Appendix) or a consistent effect over time (adjusted hazard ratio for care in an intervention ICU, 0.86; 95% CI, 0.56 to 1.22; P=0.50 for month 1 of the intervention period; hazard ratio, 1.59; 95% CI, 1.14 to 2.22; P=0.006 for month 2; hazard ratio, 1.73; 95% CI, 1.09 to 2.74; P=0.02 for month 3; hazard ratio, 0.98; 95% CI, 0.62 to 1.54; P=0.92 for month 4; hazard ratio, 1.16; 95% CI, 0.63 to 2.16; P=0.63 for month 5; and hazard ratio, 0.76; 95% CI, 0.35 to 1.63; P=0.48 for month 6).

DISCUSSION

In this trial, an intervention that included culture-based active surveillance and the expanded use of

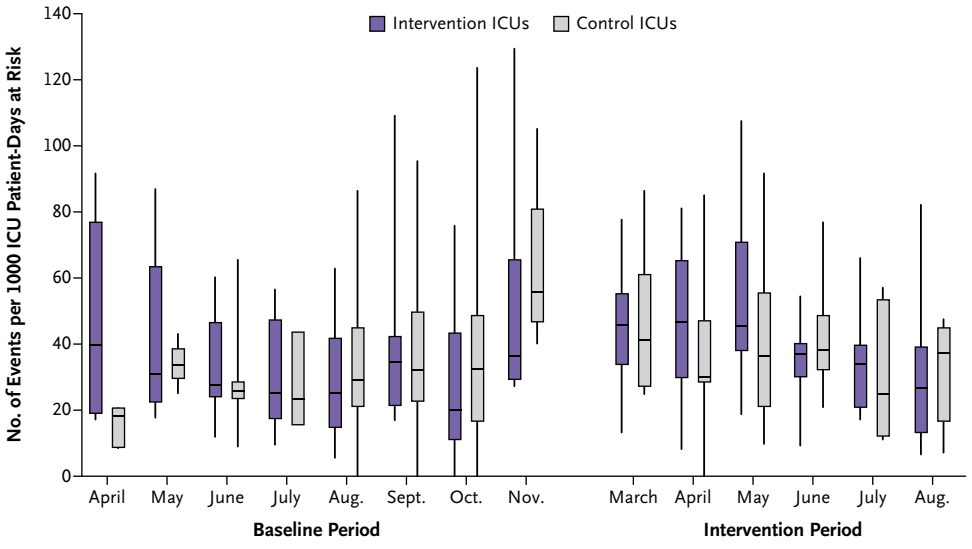

Figure 3. Monthly Incidence of Colonization or Infection with Methicillin-Resistant *Staphylococcus aureus* (MRSA) or Vancomycin-Resistant Enterococcus (VRE) among Patients in Intensive Care Units (ICUs).

The box plot diagram shows the distribution of ICU-level incidences of colonization or infection with MRSA or VRE. The box represents the interquartile range, and the horizontal line inside the box the median; vertical lines represent the maximum and minimum percentages. The median number of incidences of colonization or infection according to period were as follows: in intervention ICUs during the baseline period, 30.1 (range, 14.5 to 76.1) for MRSA or VRE, 11.9 (range, 6.8 to 19.6) for MRSA, and 25.7 (range, 9.7 to 78.2) for VRE, and in intervention ICUs during the intervention period, 40.3 (range, 20.8 to 54.9) for MRSA or VRE, 14.6 (range, 6.8 to 21.8) for MRSA, and 36.8 (range, 6.6 to 87.0) for VRE; in control ICUs during the baseline period, 32.5 (range, 12.3 to 58.4) for MRSA or VRE, 13.2 (range, 3.8 to 39.4) for MRSA, and 27.1 (range 9.9 to 53.4) for VRE, and in control ICUs during the intervention period, 32.6 (range, 15.8 to 60.7) for MRSA or VRE, 11.1 (range, 6.6 to 48.9) for MRSA, and 29.9 (range, 11.1 to 71.1) for VRE. Individual ICU data are provided in the figure and Table 2 in the Supplementary Appendix.

barrier precautions, as compared with existing hospital practice, was not effective in reducing the incidence of MRSA or VRE colonization or infection in adult ICUs. This finding was surprising, given that surveillance cultures identified a sizable subgroup of colonized patients who were not otherwise recognized and that colonized or infected patients were assigned to either contact precautions or universal gloving for nearly all their ICU patient-days. Several factors may explain this result.

Studies with less rigorous designs may have overestimated the effectiveness of MRSA and VRE control programs. Indeed, systematic reviews have identified major methodologic weaknesses in many previous studies, including the lack of concurrent control groups.[6,24,25] More recent studies have yielded mixed results.[14,26]

The expanded use of barrier precautions may have been insufficient to reduce the transmission of MRSA or VRE for two reasons. First, the turnaround time for reporting a positive result on a surveillance culture was prolonged, which increased the proportion of days that patients who were colonized or infected with MRSA or VRE were assigned to universal gloving instead of contact precautions. Contact precautions are recommended for the care of colonized or infected patients because these precautions specify the use of gowns to prevent contamination of clothing and the use of dedicated instruments and equipment.[5,6] In addition, the practice of hand hygiene and the use of gloves by providers may be enhanced.[27] However, the evidence that gowns prevent transmission of MRSA or VRE or that contact precautions increase the practice of hand hygiene or the use of gloves is mixed.[27-32] We observed that providers used gloves only marginally more often when they cared for patients assigned to contact precautions than when they cared for

patients assigned to universal gloving (Fig. 2), and we found no evidence of an inverse relationship between the percentage of ICU patient-days that colonized or infected patients were assigned to contact precautions and the primary outcome.

Second, the use by health care providers of the required components of contact precautions and universal gloving was less than required (Fig. 2), particularly with respect to contacts with the environment only, and may have been overestimated because monitoring was not surreptitious and was performed only during daytime and evening hours. However, we found no evidence of an inverse relationship between providers' use of both gloves during contact and hand hygiene after contact with patients or their environment and the primary outcome. Nonetheless, faster turnaround time for reporting the results of surveillance cultures and exemplary performance with respect to providers' use of barrier precautions and hand hygiene may reduce transmission more effectively.

Colonized patients who were not identified at the time of admission could have served as persistent reservoirs of MRSA or VRE and could have been misclassified as having incident events later in their ICU stay. Detection of MRSA colonization in patients is enhanced when body sites in addition to the anterior nares are cultured, including the pharynx, open wounds, skin, respiratory secretions, and the rectum or stool.[33,34] We performed surveillance cultures for MRSA and VRE from single body sites only but used broth enrichment and extended incubation to enhance the sensitivity of our culture methods.[19,20] This probably explains why the prevalence of colonization at the time of ICU admission in this trial was 15% higher for MRSA and 64% higher for VRE than that reported previously.[11,12]

MRSA and VRE may have been transmitted by routes other than those the intervention was designed to interrupt, such as by contaminated instruments or equipment or by colonized health care workers.[4] However, these events were unlikely to have been frequent enough across multiple ICUs to account for the findings.

The intervention period may not have been long enough to show an effect. Previous studies have observed that a reduction in the incidence of MRSA infection may not be evident until a year or more after initiation of an intervention.[13,14] However, the trial design and methods make a delayed intervention effect unlikely, and there was no evidence of a small effect by month that might have become significant if the intervention period had been longer.

Additional interventions that reduce the density of colonization of body sites or contamination of the environment may be necessary. Intranasal mupirocin, coupled with other systemic and topical agents, reduces MRSA colonization in the short term, but its long-term effect is limited and is associated with the development of mupirocin resistance.[35] Daily bathing of patients with chlorhexidine and improved environmental cleaning have, in quasi-experimental studies, shown promise in reducing the incidence of MRSA and VRE colonization among ICU patients.[15,16,36] Treatment with systemic antibiotics that have antianaerobic activity promotes high-density colonization of VRE in the gastrointestinal tract, and the use of fluoroquinolone has been associated with increased rates of MRSA colonization or infection.[37,38] Efforts to reduce the unnecessary use of these agents may complement other interventions.

The results of this trial indicate that merely improving the identification of colonized patients and expanding the use of barrier precautions, at least as achieved during this trial, are measures that are not likely to be broadly effective. If transmission of MRSA and VRE in health care facilities is to be decreased substantially, improvement in reliable, sustainable adherence to isolation precautions is important and may need to be complemented by interventions to reduce the density of MRSA or VRE colonization of body sites and to decrease environmental contamination.

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