

# Annals of Internal Medicine

## A Cloud Adult: The *Staphylococcus aureus*-Virus Interaction Revisited

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**Background:** Nasal carriage of *Staphylococcus aureus* is common among health care workers, but outbreaks caused by such carriers are relatively uncommon. We previously reported outbreaks of *S. aureus* skin infections that affected newborn infants and were attributed to an *S. aureus* nasal carrier who had had an associated upper respiratory tract infection (URI) during the outbreak period.

**Objective:** To investigate the contribution of a nasal methicillin-resistant *S. aureus* (MRSA) carrier (physician 4) who contracted a URI to an outbreak of MRSA infections that involved 8 of 43 patients in a surgical intensive care unit during a 3-week period.

**Design:** An epidemiologic study of an outbreak of MRSA infections and a quantitative investigation of airborne dispersal of *S. aureus* associated with an experimentally induced rhinoviral infection.

**Setting:** A university hospital.

**Participants:** 43 patients in a surgical intensive care unit and 1 physician.

**Measurements:** Molecular typing was done, and risk factors for MRSA colonization were analyzed. Agar settle plates and volumetric air cultures were used to evaluate the airborne dispersal of *S. aureus* by physician 4 before and after a rhinoviral infection and with or without a surgical mask.

**Results:** A search for nasal carriers of MRSA identified a single physician (physician 4); molecular typing showed that the MRSA strain from physician 4 and those from the patients were identical. Multivariate logistic regression analysis identified exposure to physician 4 and duration of ventilation as independent risk factors for colonization with MRSA ( $P \leq 0.008$ ). Air cultures showed that physician 4 dispersed little *S. aureus* in the absence of a URI. After experimental induction of a rhinovirus URI, physician 4's airborne dispersal of *S. aureus* without a surgical mask increased 40-fold; dispersal was significantly reduced when physician 4 wore a mask ( $P \leq 0.015$ ).

**Conclusions:** Physician 4 became a "cloud adult," analogous to the "cloud babies" described by Eichenwald and coworkers who shed *S. aureus* into the air in association with viral URIs. Airborne dispersal of *S. aureus* in associa-

tion with a URI may be an important mechanism of transmission of *S. aureus*.

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Nosocomial outbreaks of *Staphylococcus aureus* infection have been well described. They occur most commonly in special care units, such as newborn nurseries (1-9), neonatal intensive care units (10-12), surgical intensive care units (13, 14), and burn units (15), and they have also been reported in patient wards (16, 17) and operating rooms (18, 19). Factors associated with nosocomial outbreaks of *S. aureus* include the overuse of antibiotic agents, inadequate handwashing, understaffing, and health care workers carrying the organism (1-19).

The nose (anterior nares) is the most common body site of colonization on health care workers; frequencies range between 20% and 90% (12, 20-22). Although many factors have been shown to increase *S. aureus* nasal colonization (23-29), nasal carriage alone does not cause outbreaks. If it did, the high frequency of nasal carriage of *S. aureus* by hospital personnel would be associated with a similarly high frequency of outbreaks. This is not the case, which suggests that other factors must modify the state of the nasal carrier of *S. aureus* for an outbreak to occur.

The likelihood that a nasal carrier of *S. aureus* will cause an outbreak may increase if the carrier acquires the ability to disperse the organism into the air. Airborne dispersal of *S. aureus* is uncommon and directly related to the quantity of *S. aureus* colonizing the anterior nares (30). No more than 10% of healthy nasal carriers of *S. aureus* disperse the organism into the air (17, 31), and males disperse more commonly than females (32). A viral



## Methods

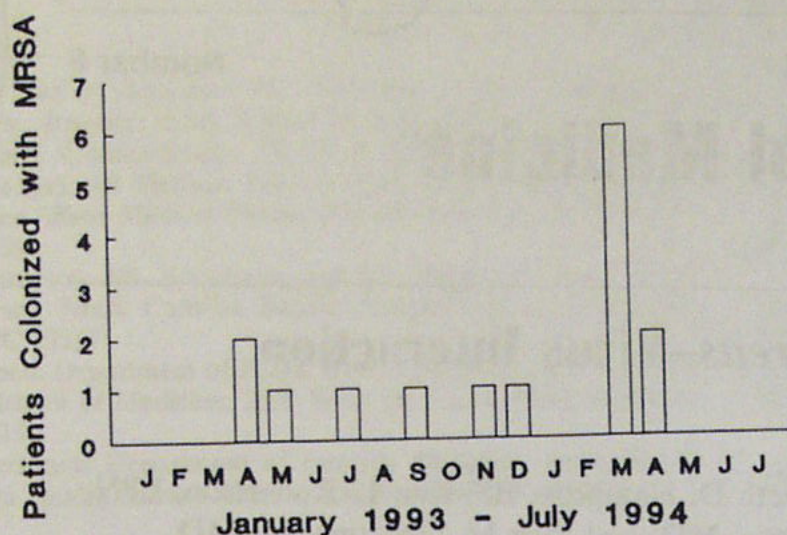


Figure 1. Epidemic curve for methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in a surgical intensive care unit. The eight colonizations that occurred during the outbreak period (March–April 1994) represent a statistically significant increase over the previous baseline ( $P < 0.05$ ).

upper respiratory tract infection (URI) was shown to change newborn infant nasal carriers of *S. aureus* from nondispersing to dispersing status, creating so-called “cloud babies” who can cause outbreaks (33). Similar studies have not been done in adults. We previously reported a nasal carrier of *S. aureus* who was linked to outbreaks in two newborn nurseries in association with URI, and we postulated the existence of a “cloud adult” (2).

In the present study, we identified a nasal carrier of methicillin-resistant *S. aureus* (MRSA) as the probable cause of an outbreak of nosocomial MRSA infections in a surgical intensive care unit. During the outbreak period, this carrier had developed a URI. It was subsequently shown that this carrier could not disperse *S. aureus* into the air in the absence of a URI, but after infection with a rhinovirus, he began to disperse *S. aureus* into the air around him, thus becoming a “cloud adult.”

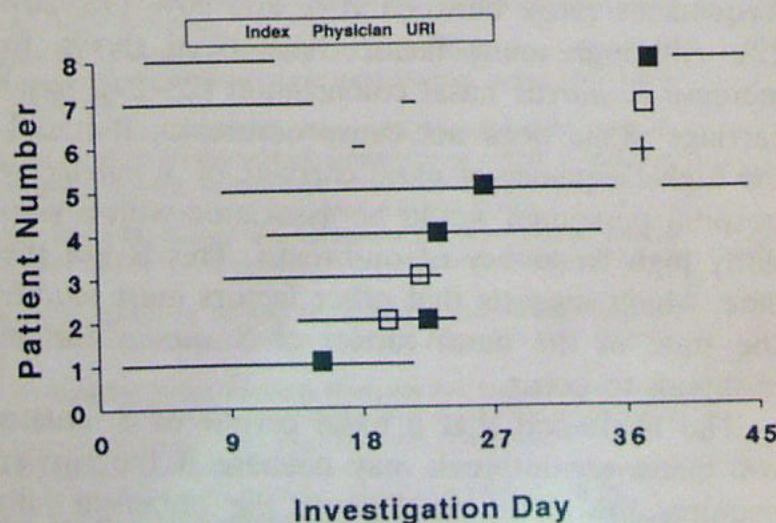


Figure 2. Relation between stay in a surgical intensive care unit and colonization with methicillin-resistant *Staphylococcus aureus* (MRSA). The horizontal lines after each patient number represent the time each patient spent in the surgical intensive care unit. Open squares represent lower respiratory tract colonization with MRSA, solid squares represent MRSA pneumonia, and the cross represents MRSA bacteremia. The bar at the top shows the duration of physician 4's upper respiratory tract infection (URI) relative to the times when patients were colonized with MRSA.

Our study had two major components. First, we investigated the epidemiology of an outbreak of MRSA infections, and our results suggested that a nasal carrier of MRSA who had an associated URI played a causative role. Second, we investigated the effect of an experimentally induced rhinovirus URI on this same nasal carrier's ability to disperse MRSA into the air.

### Outbreak Investigation

In early April 1994, the infection control department at our institution became aware of several cases of MRSA pneumonia in a surgical intensive care unit. A microbiology database query showed that, during a 3-week period in late March and early April 1994, 8 of 43 patients in the surgical intensive care unit had acquired MRSA. This was a clear increase from baseline (Figure 1).

The charts of all eight patients colonized with MRSA were reviewed using the Centers for Disease Control criteria for nosocomial infection (34). The temporal relations among the patients developing colonization or infection with MRSA are shown in Figure 2. Seven of the eight patients were from the same surgery service; all seven were intubated and had sputum samples growing MRSA; and five of these seven met criteria for MRSA nosocomial pneumonia. The eighth patient had leukemia, was on an internal medicine service, and developed nosocomial MRSA bacteremia (patient 6). The tight clustering of the first five cases and the fact that all surgical patients were colonized first in their respiratory tracts suggested a common mechanism of transmission.

Sixty-four of 70 (91%) clinical personnel (33 nurses, 13 physicians, and 18 respiratory therapists) who had worked in the surgical intensive care unit during the outbreak period were cultured for nasal carriage of MRSA. A sterile swab moistened with phosphate-buffered saline (pH, 7.2) was used to culture both anterior nares, was plated on tryptic soy agar (BBL, Cockeysville, Maryland) containing 4  $\mu$ g of oxacillin per mL, and was incubated at 37 °C for 48 hours. The identity of *S. aureus* was confirmed by using the slide coagulase test (Staphyloslide Test, Becton Dickinson, Cockeysville, Maryland). Resistance to methicillin was verified by using both an agar diffusion method (35) and a microtiter tube dilution method (36) at 35 °C; all isolates were resistant to methicillin and to several other antibiotic agents. Only physician 4, a resident in training, tested positive for MRSA.

Physician 4 was interviewed immediately after his *S. aureus* isolate was confirmed to be MRSA. He described having had a persistent URI during the



period in which the patients were colonized (1 March 1994 to 22 March 1994; Figure 2). The URI had lasted 3 weeks and had been characterized by extensive nasal discharge, coughing, and occasional sneezing. Physician 4 had received azithromycin during the last week of his illness. He reported washing his hands after sneezes and before sterile procedures; during this period, he wore a mask only during operating room procedures. Because he had already switched to a nonclinical elective at the time he was interviewed, removal from patient care activities was unnecessary. He received nasal treatment with mupirocin four times per day for 1 week in late June. Although the nasal culture done immediately after mupirocin treatment was negative for *S. aureus*, a culture done 18 days later was positive for methicillin-sensitive *S. aureus* (MSSA). No further infection control measures were taken, because no increase in MSSA infections had been detected. During 3 months of follow-up surveillance, no additional patients with MRSA infection or colonization in the surgical intensive care unit were identified (Figure 1).

We reviewed the charts of all 43 patients who were present in the surgical intensive care unit during the period in which physician 4 had the URI to determine whether contact with physician 4 or any other physician was an independent risk factor for MRSA colonization. Physician contacts were determined by counting the number of times that the physician operated on, examined, or did a procedure on a patient (counts were based on the presence of the physician's signature or name in the patient's chart). Additional data collected from the charts included age, sex, duration of hospitalization before admission to the surgical intensive care unit, duration of stay in the surgical intensive care unit before the URI period, duration of stay in the intensive care unit during the URI period, number of invasive procedures, Glasgow coma score at the time of admission to the surgical intensive care unit, number of different antibiotics used during the URI period, number of days receiving each antibiotic during the URI period, number of contacts with each physician during the URI period, wound debridement, intubation, abdominal surgery, thoracic surgery, abdominal trauma, chest trauma, previous hospitalizations, previous nursing home residences, MSSA colonization or infection, and death.

#### Effect of Rhinoviral Infection on Airborne Dispersal of *Staphylococcus aureus*

After we obtained approval from our institutional review board, physician 4 gave informed consent to participate in a study to determine the effect of an experimental rhinovirus URI on physician 4's ability to disperse *S. aureus* into the air. All air cultures

were done in a small conference room (20 ft × 16 ft × 8 ft [2560 ft<sup>3</sup>]; 6 air changes/h). Air cultures were done before the physician entered the room (baseline) and then with the physician in the room both before and after rhinoviral infection and with and without a surgical mask (Anago, Fort Worth, Texas). In the period before the rhinoviral infection, air cultures were done at 10 a.m. (with no mask) or 2 p.m. (with mask), or both, after the room had been occupied for other purposes.

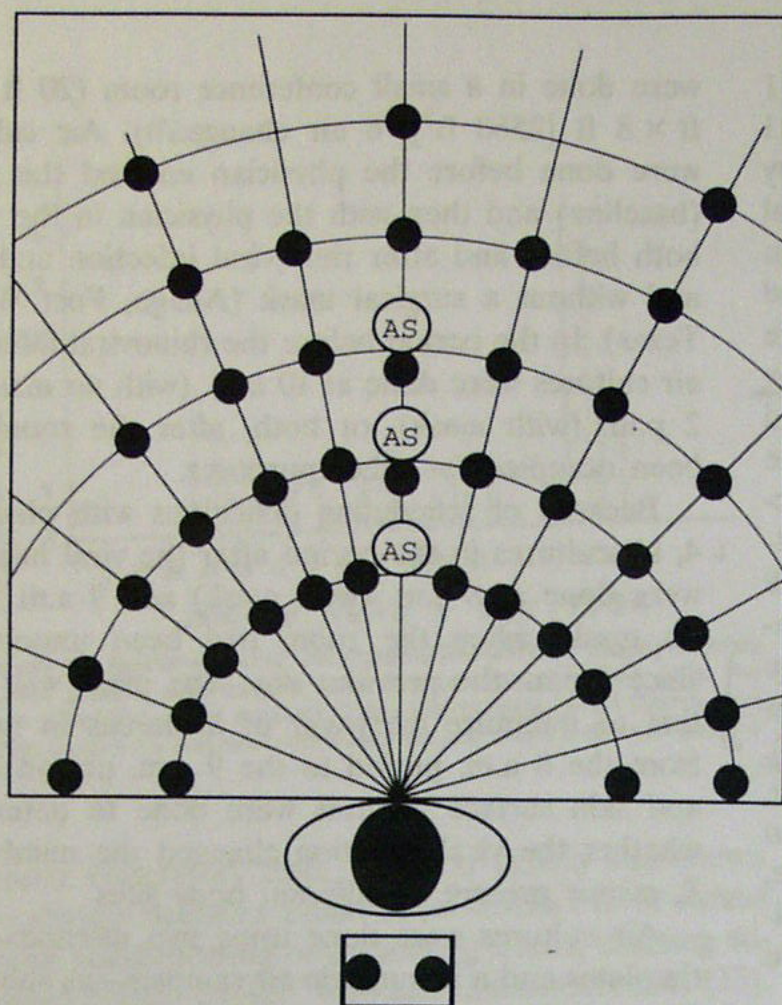
Because of scheduling difficulties with physician 4, air cultures in the period after the viral infection were done at 8 a.m. (with mask) and 9 a.m. (with no mask) when the room had been unoccupied since 5 p.m. the previous day. The mask was worn first to minimize carryover of *S. aureus* in the air from the 8 a.m. period to the 9 a.m. period. Nose and skin surface cultures were done to determine whether the viral infection changed the number of *S. aureus* present at different body sites.

Air cultures were done using two methods—settle plates and a volumetric air sampler—as shown in Figure 3. Forty-one agar plates (Columbia agar with 5% sheep blood, Carr-Scarborough Microbiologicals, Stone Mountain, Georgia) were placed on top of a conference table (8 ft × 8 ft) in the middle of the room for 1 hour to culture *S. aureus* that settled out of the air. In addition, a two-stage volumetric air sampler (Graseby Andersen, Atlanta, Georgia) containing two blood agar plates was used for three 20-minute periods to culture organisms that might have been too small to fall onto the settle plates (Figure 3). The air sampler cultures 1 ft<sup>3</sup>/minute. All agar plates were incubated for 48 hours at 37°C, and all colonies with morphology consistent with *S. aureus* were tested for coagulase activity and methicillin susceptibility, as described above. All isolates identified as *S. aureus* were saved for subsequent typing.

#### Quantitative Mucosal and Skin Surface Cultures

Cultures of physician 4 at two mucosal sites (anterior nares and posterior pharynx) and selected skin sites (midline anterior chest, midline abdomen, axilla, and groin) were done using sterile cotton swabs moistened with phosphate-buffered saline. For skin cultures, a sterile template (5 cm × 5 cm) was placed on the skin, and a moistened cotton swab was rubbed twice over the area. Each swab was placed in 5 mL of sterile tryptic soy broth (BBL), sonicated for 1 minute, vortexed for 15 seconds, and then serially diluted and surface plated (0.1 mL) on blood agar. Colonies with typical *S. aureus* morphology were further evaluated as described above.





**Figure 3.** Location of the air culture plates in relation to physician 4. The large rectangle represents a table; the small rectangle is an elevated platform just behind physician 4 at nose height. Each small black circle is an agar settle plate. The settle plates are arranged along arcs 2, 3, 4, 5, and 6 feet from physician 4 at approximately 15-degree intervals on the table. The circles labeled AS are volumetric air samplers located 2, 3, and 4 feet directly in front of physician 4.

### Rhinoviral Infection

Physician 4 was screened for contraindications to rhinoviral infection (37). The rhinovirus used was a strain of type 39 that had been safety tested (38) and used in volunteer studies at the University of Virginia (39, 40). A serum sample drawn from physician 4 before infection had a neutralizing antibody titer to rhinovirus type 39 of less than 1:2. The virus inoculum contained 100 tissue culture infectious doses<sub>50</sub> in a 1 mL volume (41) and was administered through intranasal drops (0.25 mL per nostril) on two occasions 10 minutes apart using a sterile 1-mL pipette.

The illness was defined by a modification (37) of the scoring method of Jackson and coworkers (41). Symptoms were evaluated daily for 5 days by using a nine-item questionnaire. A clinical cold was defined as a total symptom score greater than 6 and either the subjective impression of having developed a cold or 3 or more days of self-reported rhinorrhea. Nasal washings were collected 2 days before and 3 and 19 days after viral inoculation for viral culture in human embryonic lung cells (WI38). Physician 4 refused more frequent nasal wash collections. Serum specimens taken before and 6 weeks

after viral inoculation were tested for homotypic neutralizing antibody.

### *Staphylococcus aureus* Typing by Analysis of Chromosomal DNA

Isolates of *S. aureus* were stored in 20% milk at  $-70^{\circ}\text{C}$  after verification that each organism was *S. aureus*. Typing was done by using a modification of the method of Goering and Duensing (42, 43). Chromosomal DNA was isolated by plating *S. aureus* on tryptic soy agar and incubating overnight at  $37^{\circ}\text{C}$ . Cells were centrifuged at 1900 g for 15 minutes, the cell pellet was suspended in 1 mL of 0.85% NaCl, and 20  $\mu\text{L}$  was transferred to a tube containing 400  $\mu\text{L}$  of EC buffer (6 mmol/L tromethamine, 1 mol/L NaCl, 100 mmol/L ethylenediaminetetraacetic acid [EDTA], 0.5% Brij 58, 0.2% deoxycholate, 0.5% sarkosyl at pH 7.5). In rapid succession, 20  $\mu\text{L}$  of lyso-staphin (20 mg/mL; Applied Microbiology, New York, New York) and 450  $\mu\text{L}$  of 2% InCert agarose (FMC, Rockland, Maine) were added with agitation. The mixture was poured into a plug mold, cut into 1-mm thick slices, and incubated in EC buffer at  $37^{\circ}\text{C}$  for 4 hours. The slices were washed with Tris-EDTA buffer (100 mmol/L of tromethamine and 100 mmol/L of EDTA) for three 20-minute periods, then 1 mL of EDTA-sarkosyl buffer (0.4 mol/L EDTA [pH 9.3] and 1% sarkosyl) and 50  $\mu\text{L}$  of proteinase K (20 mg/mL; Promega, Madison, Wisconsin) were added, and the slices were incubated overnight at  $50^{\circ}\text{C}$ . The slices were washed with Tris-EDTA buffer for three 20-minute periods and stored at  $4^{\circ}\text{C}$ .

For restriction endonuclease digestion, slices were washed in buffer as suggested by the manufacturer (25 mmol/L tromethamine-acetate [pH 7.8], 50 mmol/L of potassium acetate, and 10 mmol/L of magnesium acetate; Promega) for three 20-minute periods. A 4 mm  $\times$  4 mm  $\times$  1 mm piece was then cut, placed in a 96-well microtiter plate containing 50  $\mu\text{L}$  of digestion buffer that contained 12 units of *Sma* I (Promega), and incubated at  $25^{\circ}\text{C}$  for 8 hours. The plugs were incorporated into a 1% agarose gel (SeaKem LE, FMC). Electrophoresis was done using a CHEF DR-II apparatus (BioRad, Hercules, California) using 0.5  $\times$  tris-borate-EDTA buffer at  $13^{\circ}\text{C}$ , a pulse ramp of 5 to 50 seconds, and a run time of 23 hours. Lambda ladder pulsed field gel electrophoresis marker (New England Biolabs, Beverly, Massachusetts) was used as a molecular weight standard. Gels were stained with ethidium bromide (0.5  $\mu\text{g/mL}$ ) and photographed using ultraviolet light. Banding patterns were compared by visual inspection. For organisms with the same antibiotic susceptibilities, different strains were defined as having more than three band differences.



## Data Analysis

Data from the 8 patients colonized with MRSA were compared with data from the 35 noncolonized patients in several ways. Univariate analysis was done by using the Fisher exact test, the chi-square test (Epistat Services, Richardson, Texas), the Student *t*-test, or the Mann-Whitney rank-sum test (Minitab, State College, Pennsylvania). Because of the small number of total patients, it was not possible to use all of the variables in a multivariate logistic regression model (Statistical Analysis System, SAS Institute, Cary, North Carolina) at one time. Therefore, only variables that were statistically significant by univariate analysis plus age, sex, and Glasgow coma scale at the time of admission to the surgical intensive care unit were analyzed further using a forward stepwise approach.

The air culture data were analyzed by using a general linear model (SAS Institute) controlling for day, use of a mask, distance of plate from physician 4, and plate location. Only days when data were collected both with and without a mask were analyzed: days 1 and 3 (before viral infection) and 6 through 10 (after viral infection). We conservatively adjusted *P* values using the Dunn-Sidak method, a slight variation on the Bonferroni method.

## Results

### Risk Factors for Methicillin-Resistant *Staphylococcus aureus* Colonization

The results of univariate analysis of MRSA risk factors are shown in Table 1. Factors that were significantly different ( $P < 0.05$ ) between MRSA-colonized and noncolonized patient groups included duration of stay in the surgical intensive care unit during the URI period, number of invasive procedures during the URI period, number of different antibiotic agents used during the URI period, number of days receiving antibiotic agents during the URI period, number of intubation days during the URI period, and number of physician contacts. Physicians 1, 2, 3, and 4 had the most contacts with the patients in the surgical intensive care unit, and they were all significantly associated ( $P < 0.05$ ) with case-patients. They were all surgical residents and were all said by their supervising attending physicians to have good aseptic technique. A total of 15 physicians had contact with patients in the surgical intensive care unit during the URI period; none of the other 11 physicians had significantly greater contacts with the MRSA-colonized patient group than did physicians 1, 2, 3, and 4 ( $P > 0.05$ ).

Forward stepwise regression analysis was then used to determine which of the factors associated

**Table 1. Risk Factors for Methicillin-Resistant *Staphylococcus aureus* Colonization in the Surgical Intensive Care Unit during the Upper Respiratory Tract Infection Period\***

Variable	Patients Colonized with Methicillin-Resistant <i>S. aureus</i> (n = 8)	Noncolonized Patients (n = 35)	P Value
Age, y	52 ± 22	51 ± 18	0.95†
Male sex, %	87.5	74.3	0.66‡
Duration of hospital stay before admission to SICU, d	8 ± 19	1.4 ± 3.2	0.36†
Duration of stay in SICU before URI period, d	5 ± 2.8	1.8 ± 5.3	0.74§
Duration of stay in SICU during URI period, d	10.3 ± 6.2	2.8 ± 3.3	0.0006†
Glasgow coma scale score on admission to SICU	8.9 ± 5.4	11.4 ± 4.4	0.14§
Invasive procedures during URI period, n	2.6 ± 1.7	0.9 ± 0.9	0.029†
Antibiotics used during URI period, n	4.6 ± 2.1	1.3 ± 1.4	0.003†
Days receiving antibiotic agents during URI period	28 ± 12	7.1 ± 12	0.001†
Intubation during URI period, %	100	86	0.34¶
Duration of intubation during URI period, d	13.5 ± 8.9	2.7 ± 5.1	0.01†
Death, %	12.5	20.0	0.47‡
Physician contacts, n			
Physician 1	5.5 ± 3.2	2.0 ± 2.3	0.008§
Physician 2	4.4 ± 2.6	2.3 ± 2.5	0.039§
Physician 3	6.3 ± 3.8	2.6 ± 2.5	0.01§
Physician 4	3.8 ± 2.7	1.0 ± 1.4	0.002§
Wound debridement, %	0	5.7	0.66¶
Abdominal surgery, %	12.5	5.7	0.47¶
Thoracic surgery, %	0	0	NS
Abdominal trauma, %	0	0	NS
Chest trauma, %	0	11.4	0.42¶
Previous hospitalization (within 5 y), %	25	20	0.54‡
Previous residence in a nursing home, %	0	0	NS
Methicillin-sensitive <i>S. aureus</i> colonization or infection, %	25	11.4	0.31‡

\* NS = not significant. SICU = surgical intensive care unit; URI = upper respiratory tract infection. Values are given as mean ± SD.

† By the Student *t*-test.

‡ By the chi-square test.

§ By the Mann-Whitney rank-sum test.

|| Seven patients colonized with methicillin-resistant *S. aureus* had Glasgow coma scale score; 32 noncolonized patients had Glasgow coma scale scores.

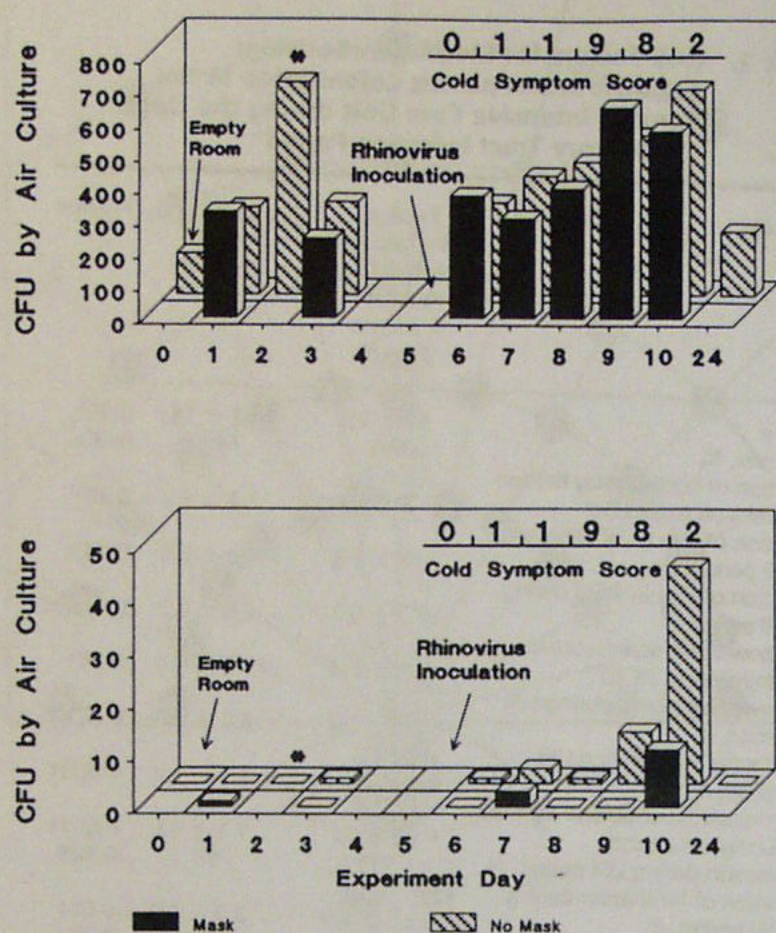
¶ By the Fisher exact test.

with MRSA colonization by univariate analysis were independent risk factors for MRSA colonization. When all 43 patients were considered, only two variables were found to be independently associated with MRSA colonization: duration of ventilation ( $P = 0.007$ ) and contact with physician 4 ( $P = 0.008$ ). When data from the 42 surgical patients (excluding the patient on the medical service) were analyzed in the same way, physician 4 was still independently associated with MRSA colonization ( $P = 0.002$ ).

### Rhinovirus Cold of Physician 4

Nasal cultures taken from physician 4 three days after viral inoculation grew rhinovirus type 39. Cultures taken 2 days before and 19 days after viral inoculation were negative for virus. Physician 4 also





**Figure 4.** Air culture results from a single volunteer (physician 4) nasally colonized with *Staphylococcus aureus*. Each bar represents a 1-hour culture period using a combination of agar settle plates (41) and volumetric air cultures (6), arranged as shown in Figure 3. Striped bars show the total number of colonies isolated from all 47 plates when physician 4 was not wearing a mask; black bars show the same data when physician 4 was wearing a mask. The Cold Symptom Score summarizes the severity of physician 4's cold symptoms after nasal inoculation with a rhinovirus ( $>6$  = a cold). On one occasion, the room was cultured when physician 4 was absent. The asterisk denotes that physician 4 was talking during most of the period. **Top.** All bacteria. **Bottom.** Only *S. aureus* of the same molecular type as physician 4's nasal strains. CFU = colony-forming units.

had a greater than fourfold increase in serum neutralizing antibody (from  $<1:2$  to  $1:16$ ) to rhinovirus type 39. He met the criteria for a common cold 3 and 4 days after viral inoculation (Figure 4); his illness consisted of sneezing, a runny nose, nasal stuffiness, a mild sore throat, and occasional coughing. His symptom score on the last day that air cultures were done was only 2. Notably, during the time that air cultures were done, physician 4 did not cough or sneeze.

#### Mucosal and Skin Cultures of Physician 4

The results of physician 4's nasal cultures for *S. aureus* during the period of experimental rhinoviral infection are shown in Table 2. From the anterior nares, MSSA was isolated every time, but MRSA was isolated only once. In contrast, during the outbreak investigation, when agar containing oxacillin was used for cultures, MRSA was found each of the two times the nose was cultured, suggesting that the presence of MSSA obscured the detection of MRSA during the rhinovirus experiment. The throat and skin sites were cultured on 5 different days (1, 3, 6, 8, and 10 June). No MRSA isolates were detected, and MSSA was found on only three occasions (on 3

June in the abdomen and on 10 June in the left axilla and in the abdomen). The three MSSA skin isolates were typed, and all were identical to the MSSA strain found in the nose.

#### Airborne Dispersal of *Staphylococcus aureus* from Physician 4

The air around physician 4 was cultured 17 different times for periods of 1 hour. From 797 plates, a total of 6554 colony-forming units (CFUs) of bacteria were isolated. Of these, 69 isolates (1.5%) were *S. aureus*. Organisms other than *S. aureus* were not defined at the species level. The pattern of isolation of all bacterial species (Figure 4, top) showed several interesting points. During the baseline period before the rhinoviral infection, approximately twice as many organisms were isolated in one culture interval (day 2) than in the other two sampling periods. On that day (Figure 4, top), physician 4 talked on the telephone most of the hour; he did not talk at all during any other culture periods. After viral infection, the number of CFUs isolated showed a clear upward trend whether physician 4 was (correlation coefficient,  $r = 0.81$ ) or was not ( $r = 0.98$ ) wearing a mask. No evidence suggested that wearing a mask decreased the total number of CFUs in the air.

The volumetric air sample plates grew 5 to 10 times as many bacteria as the settle plates in a 1-hour period. The volumetric air cultures had 2 to 3 times as many organisms on the smaller particle size plates ( $<5$  microns, bottom plate) as were found on the larger particle size plates ( $>5$  microns, top plate). When physician 4 was in the room, a clear gradient of organisms was in the air; that is, the number of organisms decreased as the distance from physician 4 increased. The mean numbers of CFUs detected by the top plate were  $16.7 \pm 10.0$  CFUs (mean  $\pm$  SD) at 2 feet from physician 4 and  $8.3 \pm 4.7$  CFUs at 4 feet ( $P = 0.009$ , Student *t*-test). For the bottom plate, the mean numbers of CFUs were  $32.0 \pm 13.7$  CFUs at 2 feet compared with  $21.9 \pm 11.1$  CFUs at 4 feet ( $P = 0.04$ , Student *t*-test).

All 69 *S. aureus* isolates from physician 4 were

**Table 2.** Quantitative Nose Cultures for *Staphylococcus aureus* Shown as Log<sub>10</sub> Colony-Forming Units\*

Body Site	Experiment Day†								
	1	3	6	7	8	9	10	24	31
Right nares									
MRSA	3.3	<1.7	<1.7	<1.7	<1.7	<1.7	<1.7	<1.7	<1.7
MSSA	3.9	3.0	4.5	2.4	3.3	3.3	3.3	3.0	0
Left nares									
MRSA	0	0	0	0	0	0	0	0	<1.7
MSSA	4.4	4.3	4.0	3.0	2.8	3.0	0	3.0	0

\* MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-sensitive *S. aureus*.

† Experiment day corresponds to the days shown in Figure 4.

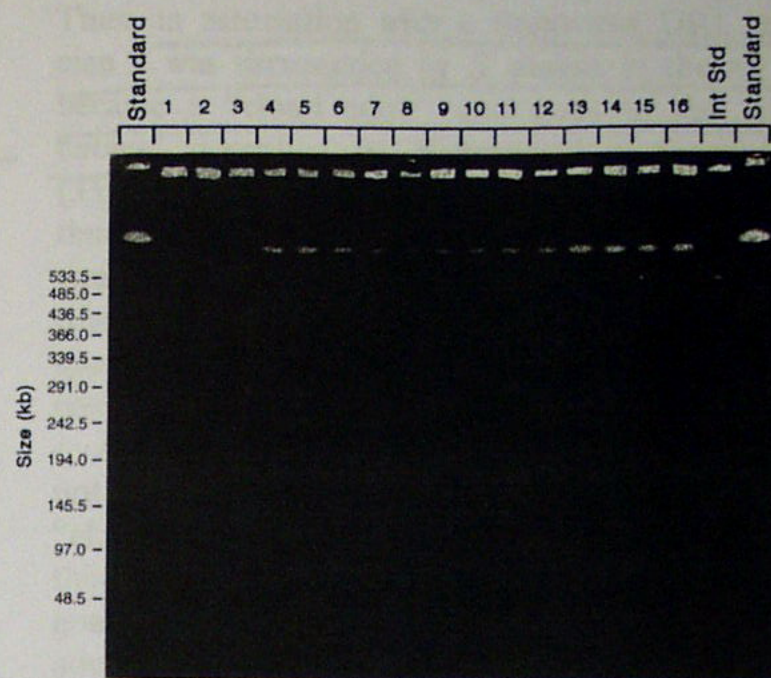


tested for susceptibility to oxacillin; 4 isolates (5.8%) were resistant (all from day 9; Figure 4, bottom). Twenty-seven of these organisms were studied using molecular typing, and representative strains are shown in Figure 5. In the period before viral infection, all 8 *S. aureus* organisms isolated were typed. Only 2 of 8 isolates came from physician 4. The baseline cultures were done immediately after periods in which persons worked in the conference room. The *S. aureus* from the baseline period that were not from physician 4 probably came from personnel working in the conference room just before the culture periods. Only the two *S. aureus* strains that came from physician 4 were used for further analysis (Figure 4, bottom).

Sixty-one *S. aureus* organisms were grown in the period after the viral infection. Nineteen isolates were chosen for typing (see Figure 4, bottom): all 8 isolates from days 6 through 8, 3 of 10 isolates from day 9 without mask, 4 of 43 isolates from day 10 without mask, and 4 of 10 isolates from day 10 with mask. The strains of all 19 *S. aureus* isolates were shown to be the same as those isolated from physician 4. In our subsequent analysis and in producing Figure 4, we assumed that the 42 remaining *S. aureus* isolates also came from physician 4. The lack of "background noise" (*S. aureus* not attributable to physician 4) in the period after viral infection was attributed to the fact that no one had been in the conference room for at least 12 hours.

The *S. aureus* data from days 1, 3, and 6 through 10 were further analyzed using a general linear model. The dependent variable was the number of *S. aureus* CFUs attributable to physician 4 that was detected on each agar plate. When physician 4 did not wear a mask, the number of *S. aureus* CFUs per plate was significantly greater when physician 4 was infected with rhinovirus on day 10 than when he was not infected on days 1 and 3 ( $0.83 \pm 0.14$  CFUs compared with  $0.0 \pm 0.0$  CFUs; adjusted  $P \leq 0.015$ ). On day 10 during the rhinoviral infection period, the mean number of *S. aureus* CFUs per plate was significantly less when physician 4 wore the mask than when he did not ( $0.14 \pm 0.06$  CFUs compared with  $0.83 \pm 0.14$  CFUs; adjusted  $P \leq 0.015$ ). Not surprisingly (Figure 4, top), the effect of the mask was significantly different on different days ( $P \leq 0.0001$ ).

On day 10 when physician 4 was not wearing a mask, the distribution of the *S. aureus* isolates from air cultures was remarkable. Twenty-nine of the 47 agar plates (61.7%), including all settle plates at the extremes of distance from physician 4, grew *S. aureus*. The 6 volumetric culture plates grew 9 *S. aureus* isolates, and 23 settle plates grew 34 *S. aureus* isolates. Nineteen days after viral inoculation, physician 4 had no *S. aureus* detectable by air culture.



**Figure 5.** Pulsed field gel electrophoresis of different strains of *Staphylococcus aureus*. Lanes 1 to 3 = air culture isolates not attributable to physician 4; lanes 4 and 5 = methicillin-resistant *S. aureus* (MRSA) nasal isolates from physician 4 (March and June 1994); lanes 6 to 11 = patient MRSA isolates (patients 2, 3, 4, 5, 7, 8); lane 12 = MRSA air culture isolate (day 9; Figure 4, bottom); lanes 13 and 14 = methicillin-sensitive *S. aureus* (MSSA) nasal isolates from physician 4 (May and June 1994); and lanes 15 and 16 = MSSA air culture isolates (days 1 and 10; Figure 4, bottom).

#### Relatedness of *Staphylococcus aureus* isolates from Physician 4 and Patients

Physician 4 had two strains of *S. aureus* in his nose: one MSSA strain and one MRSA strain. His nasal carriage of these two organisms was stable during a 3-month period (Figure 5). Strains of MRSA were available from 6 of 8 patients, and all 6 had the same type as the MRSA strain found in physician 4's nose.

#### Discussion

We investigated an outbreak of MRSA infections in a surgical intensive care unit; this outbreak had several unique features. It was tightly clustered in time (3 weeks) and anatomical site of infection (seven of eight cases involved the lower respiratory tract), suggesting a common mechanism of acquisition of organisms. Nearly all physicians, nurses, and respiratory therapists working with the patients in the surgical intensive care unit during this period were cultured to identify nasal carriers of MRSA, and only one was found: physician 4. By using molecular typing, physician 4's MRSA strain was found to be identical to the MRSA strain colonizing the patients. Chart review and multivariate logistic regression analysis showed that exposure to physician 4 was an independent risk factor for MRSA colonization. These findings strongly suggested that physician 4 was the source of the outbreak organism.

Given that physician 4 had nasal colonization with MSSA and MRSA simultaneously, it is inter-



esting that no outbreak of MSSA infections occurred. This was probably related to the fact that almost all patients in the surgical intensive care unit during the MRSA outbreak period received parenteral antibiotics, either prophylactically or therapeutically, that were active against MSSA but not MRSA. The azithromycin received by physician 4 while he had a URI may also have suppressed the MSSA, but not the MRSA, in his nose.

The most interesting feature of this outbreak was that physician 4 acquired a URI during the time he was thought to have transmitted *S. aureus* to patients. Subsequent efforts in our investigation focused on whether the URI may have increased the likelihood of transmission. Most existing evidence suggests that *S. aureus* is transmitted in the hospital setting through direct contact with the hands of personnel (22). We previously speculated (2) that airborne transmission of *S. aureus* from a nasal carrier might occur in association with a URI. This same consideration was raised by Nahmias and coworkers (44) in their investigation of an outbreak of *S. aureus* surgical site infections attributed to a single surgeon and by Boyce and colleagues (17) in connection with an MRSA outbreak associated with a respiratory therapist who had chronic MRSA sinusitis. The best evidence supporting this mechanism was provided by Eichenwald and coworkers (33), who showed that a viral URI caused babies who carried nasal *S. aureus* to disperse the organism into the air and become "cloud babies" with the ability to cause outbreaks.

Our baseline air cultures showed that few *S. aureus* organisms were shed into the air around physician 4 under resting conditions. Hare and Thomas (45) found that when agar plates were held directly under the nose of resting nasal *S. aureus* carriers for 5 minutes, no organisms were detectable. Using a more sensitive volumetric air sampler method to culture the air inside a closed chamber containing a volunteer, Bethune and coworkers (32) found that few nasal carriers of *S. aureus* dispersed organisms into the air, even when exercising. Notably, extensive talking by physician 4 did not affect *S. aureus* dispersal, although it essentially doubled the total number of organisms other than *S. aureus* that were isolated from the air (Figure 4).

After rhinoviral infection, the total number of bacteria in the air around physician 4 increased steadily, but little effect on *S. aureus* was seen until the second day of physician 4's symptomatic cold, when the number of dispersed *S. aureus* CFUs increased. One day later, when cold symptoms had started to wane, the number of *S. aureus* CFUs in the air increased even more. These *S. aureus* organisms were widely dispersed around physician 4; 62% of all agar plates were growing the organism, and all

plates at maximum distances to the front, side, and back of physician 4 were growing the organisms. Thus, in association with a rhinovirus URI, physician 4 was surrounded by *S. aureus* in the air and became a "cloud adult" analogous to the "cloud babies" described by Eichenwald and coworkers (33). The mechanism for this effect is unclear at this time, although it may be as simple as the URI swelling the nasal turbinates, resulting in very narrow air passages. This, in turn, would lead to high-speed, turbulent air flow over a wet surface, which could create an aerosol.

Although it is unfortunate that physician 4 was not cultured longer so that the duration of the "cloud adult" effect could be clearly defined, lack of this later culture data does not detract from our goal, which was to determine whether "cloud adults" existed. We have confirmed this possibility, and it is now important to investigate the incidence of "cloud adults," the duration of the phenomenon in those who manifest it, whether the phenomenon occurs with all or just certain URIs, and which preventive interventions need to be considered for health care workers or patients with URIs. Until more data are available, our findings should not be extrapolated to other health care workers.

If further studies show that the "cloud adult" phenomenon is generalizable to most nasal *S. aureus* carriers, then the potential implications of these findings would be far reaching. Twenty percent to 90% of health care workers who care for patients are nasally colonized with *S. aureus* (12, 19-22). Because adults average two colds per year (46), "cloud adults" may be working around patients all year long. If this is so, then interventions to minimize the spread of *S. aureus* to patients are necessary. Our results suggest one possible intervention. The statistically significant reduction in the number of *S. aureus* CFUs found when physician 4 wore a mask, in combination with the fact that none of the patients on whom physician 4 operated during the outbreak period developed surgical site infections, suggest that surgical masks may interrupt the airborne transmission of *S. aureus* from the nose. This phenomenon could also be relevant to the transmission of other bacterial pathogens that colonize the nose (47), such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Neisseria meningitidis* (48, 49).

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