ORIGINAL ARTICLE

Decolonization in Nursing Homes to Prevent Infection and Hospitalization

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ABSTRACT

BACKGROUND

Nursing home residents are at high risk for infection, hospitalization, and colonization with multidrug-resistant organisms.

METHODS

We performed a cluster-randomized trial of universal decolonization as compared with routine-care bathing in nursing homes. The trial included an 18-month baseline period and an 18-month intervention period. Decolonization entailed the use of chlorhexidine for all routine bathing and showering and administration of nasal povidone–iodine twice daily for the first 5 days after admission and then twice daily for 5 days every other week. The primary outcome was transfer to a hospital due to infection. The secondary outcome was transfer to a hospital for any reason. An intention-to-treat (as-assigned) difference-in-differences analysis was performed for each outcome with the use of generalized linear mixed models to compare the intervention period with the baseline period across trial groups.

RESULTS

Data were obtained from 28 nursing homes with a total of 28,956 residents. Among the transfers to a hospital in the routine-care group, 62.2% (the mean across facilities) were due to infection during the baseline period and 62.6% were due to infection during the intervention period (risk ratio, 1.00; 95% confidence interval [CI], 0.96 to 1.04). The corresponding values in the decolonization group were 62.9% and 52.2% (risk ratio, 0.83; 95% CI, 0.79 to 0.88), for a difference in risk ratio, as compared with routine care, of 16.6% (95% CI, 11.0 to 21.8; P<0.001). Among the discharges from the nursing home in the routine-care group, transfer to a hospital for any reason accounted for 36.6% during the baseline period and for 39.2% during the intervention period (risk ratio, 1.08; 95% CI, 1.04 to 1.12). The corresponding values in the decolonization group were 35.5% and 32.4% (risk ratio, 0.92; 95% CI, 0.88 to 0.96), for a difference in risk ratio, as compared with routine care, of 14.6% (95% CI, 9.7 to 19.2). The number needed to treat was 9.7 to prevent one infection-related hospitalization and 8.9 to prevent one hospitalization for any reason.

CONCLUSIONS

In nursing homes, universal decolonization with chlorhexidine and nasal iodophor led to a significantly lower risk of transfer to a hospital due to infection than routine care. (Funded by the Agency for Healthcare Research and Quality; Protect ClinicalTrials.gov number, NCT03118232.)

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An estimated 1.6 to 3.8 million health care–associated infections occur in U.S. nursing homes annually, leading to an estimated 150,000 hospital admissions and as many as 380,000 deaths.[1] Residents are at high risk for health care–associated infection owing to older age, wounds, medical devices, and coexisting medical conditions.[2,3] Nursing home infection prevention programs should identify strategies that provide safe care and prevent pathogen transmission because nursing home settings involve social activities, long stays, and limited resources.[4,5]

The prevalence of multidrug-resistant organism (MDRO) carriage in nursing homes (65%) is 4 to 6 times as high as that in hospitals (10 to 15%),[5-8] leading to increased risks of subsequent infection. For example, in residents carrying methicillin-resistant *Staphylococcus aureus* (MRSA), the risk of MRSA infection within 1 month after arrival is 10%, a risk that increases to up to 40% within 1 year.[9-11] Gram-negative MDROs continue to increase in prevalence, as extended-spectrum beta-lactamase (ESBL) producers spread and carbapenem-resistant Enterobacterales (CRE) emerge.[12,13]

Randomized trials have shown the benefit of decolonization in the prevention of health care–associated infection, including among all patients in intensive care units (ICUs),[14] non-ICU patients with devices,[15] and MRSA carriers after hospital discharge.[16] Targeted decolonization of patients carrying MDROs can reduce the risk of MDRO infection,[17,18] but routine cultures do not identify most patients with MDRO colonization.[19] In contrast, universal decolonization has been shown to reduce the risk of infection caused by multiple pathogens.[14,16,20,21] We performed a cluster-randomized trial of universal decolonization as compared with routine-care bathing in nursing homes to prevent infection and associated hospitalization.

METHODS

TRIAL DESIGN

The Protect trial was conducted at 28 nursing homes in Los Angeles and Orange counties in California; all the nursing homes provided skilled nursing care. Nursing homes were excluded if they were dedicated to pediatric, dementia, or psychiatric care or were already routinely performing decolonization. The trial was approved by the institutional review board of the University of California, Irvine (UCI), as a randomized quality-improvement trial, and the requirement for written informed consent was waived.

The trial included an 18-month baseline period (September 2015 through February 2017), a 4-month phase-in period (March through June 2017), and an 18-month intervention period (July 2017 through December 2018). The phase-in period was characterized by receipt of the intervention products and staff training in the nursing homes assigned to perform decolonization, with start dates predominantly falling in April.

A Quick Take is available at NEJM.org

INTERVENTION

At the time of randomization, none of the sites routinely used topical chlorhexidine gluconate or performed nasal decolonization. The sites that were assigned to the routine-care group continued their usual bathing practices. The sites in the decolonization group implemented decolonization with 10% povidone–iodine (nasal iodophor) and chlorhexidine for bathing (see the protocol and Section S1 in the Supplementary Appendix, both of which are available with the full text of this article at NEJM.org). Nasal iodophor was administered to all residents twice daily for 5 days (Monday through Friday) every other week; newly admitted residents received nasal iodophor twice daily for the first 5 days after admission. Chlorhexidine (4% chlorhexidine rinse-off antiseptic wash for showering and 2% chlorhexidine no-rinse cloths for bed bathing) was used for bathing on admission and then for all routine bathing or showering.

The nursing homes in the decolonization group were provided in-person training sessions, coaching calls, and a toolkit of protocols, training materials, and staff and resident handouts. The usual frequency of bathing was retained throughout the trial regardless of the trial-group assignment. Adherence to the iodophor course during the initial admission period was assessed in all residents and once weekly in a rotating 25% sample of residents occupying a bed. Adherence to chlorhexidine use was assessed among residents on a weekly basis (on an unannounced weekday) with respect to their most recent bath or shower.

OUTCOMES

The primary outcome was transfer to a hospital due to infection, as assessed among all residents who were hospitalized. The secondary outcome was transfer to a hospital for any reason, as assessed among all residents who were discharged

from the nursing home. Standardized nursing home and hospitalization data sets were used to assess outcomes (Section S2).

In a another analysis, we evaluated the carriage of MDROs (specifically, MRSA, vancomycin-resistant enterococci [VRE], ESBL producers, and CRE). A 1-day point-prevalence survey of 50 randomly selected residents was conducted at each nursing home during the baseline period (September 2016 through January 2017) and during 5 months near the end of the intervention period (August 2018 through December 2018). To account for seasonality, the two surveys at each nursing home were performed within the same or an adjacent calendar month in different years. Trained nurses at each nursing home obtained swab samples from both nostrils and from the left and right axillae and groin areas (combined samples). The samples were processed in the UCI Clinical Microbiology Laboratory within 6 hours after collection. The swab samples from the nostrils were tested for MRSA, and axilla and groin swabs were tested for MRSA, VRE, EBSL producers, and CRE, as described previously.[19]

CLUSTER RANDOMIZATION

Nursing homes were randomly assigned in pairs. To help balance key characteristics between the groups, pairing was performed with the Goldilocks approach, whereby the Mahalanobis distance between facilities was calculated across baseline-weighted key variables, and the nursing homes with the minimum average within-pair distance were chosen as pairs.[22,23] Further details on randomization and the variables used for balancing the trial groups are described in Section S3.

STATISTICAL ANALYSIS

The main results of the trial were assessed in intention-to-treat (as-assigned), unadjusted analyses. Generalized linear mixed log-binomial regression models, with clustering by nursing home, were used to assess the difference in differences with a group-by-period interaction term (see the statistical analysis plan, available with the protocol, and Section S4). We additionally conducted adjusted and as-treated analyses. Trial success was determined by the significance of the group-by-period interaction, which was used to assess whether the difference in the risk ratio between the baseline and intervention periods differed significantly between the trial groups.

The trial had 89% power to detect a two-tailed 15% difference in the primary outcome between the trial groups. The variables that were evaluated in adjusted models included individual age, sex, race, ethnic group, insurance, and coexisting conditions, including diabetes and cancer. As a conservative approach, pair-matching performed in randomization was ignored in the analyses.[24] Data from the phase-in period were excluded from all analyses. We also calculated the number needed to treat. For the comparisons of the prevalence of MDRO carriage, we fit similar models comparing the decolonization group with the routine-care group. Analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

RANDOMIZATION AND ADHERENCE

A total of 28 nursing homes underwent randomization; 14 were assigned to the decolonization group and 14 to the routine-care group (Fig. 1). A total of 28,956 nursing home residents contributed data to the trial — 15,004 during the baseline period and 13,952 during the intervention period. Characteristics of residents and participating nursing homes were similar in the trial groups and stable across the trial periods (Table 1). One nursing home in the decolonization group had a 2-month closure in early 2018 for construction, which reduced accrued resident-days in that group.

One nursing home in the routine-care group and 3 in the decolonization groups were dropped from the trial; the data collected from these facilities were included in the as-assigned analysis of the primary and secondary outcomes. Reasons for dropout included administrative turnover and loss of support (1 nursing home in the routine-care group and 2 in the decolonization group) and effort required during the phase-in period (1 in the decolonization group).

Among the nursing homes in the decolonization group, the mean (±SD) adherence to chlorhexidine bathing was 95.6±4.7% (range, 86.4 to 100) at admission and 87.4±6.9% (range, 73.6 to 98.2) for routine bathing. The mean adherence to nasal iodophor was 60.3±26.1% (range, 11 to 95) at admission and 67.4±17.7% (range, 42 to 88) for routine administration.

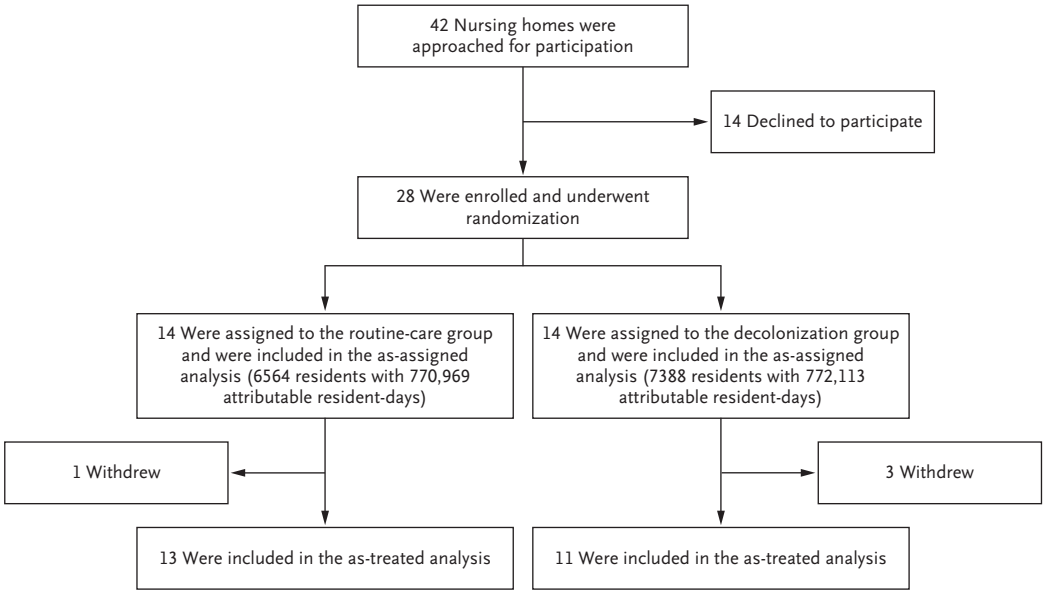

Figure 1. Enrollment, Randomization, Retention, and Analysis.

OUTCOMES

In the as-assigned, unadjusted analysis of the primary outcome, among the transfers to a hospital in the routine-care group, 62.2% (the mean across facilities) were due to infection during the baseline period and 62.6% were due to infection during the intervention period (risk ratio, 1.00; 95% confidence interval [CI], 0.96 to 1.04). The corresponding values in the decolonization group were 62.9% and 52.2% (risk ratio, 0.83; 95% CI, 0.79 to 0.88) (Table 2), for a difference in risk ratio, as compared with routine care, of 16.6% (95% CI, 11.0 to 21.8; P<0.001) (Table 2 and Fig. 2A). The data on the odds of hospital transfer are provided in Section S4.

In the as-assigned, unadjusted analysis of the secondary outcome, among the discharges from the nursing home in the routine-care group, transfer to a hospital for any reason accounted for 36.6% during the baseline period and for 39.2% during the intervention period (risk ratio, 1.08; 95% CI, 1.04 to 1.12). The corresponding values in the decolonization group were 35.5% and 32.4% (risk ratio, 0.92; 95% CI, 0.88 to 0.96) (Table 2 and Section S5), for a difference in risk ratio, as compared with routine care, of 14.6% (95% CI, 9.7 to 19.2) (Table 2 and Fig. 2B). The results of the as-treated and adjusted analyses were similar to those of the as-assigned, unadjusted analysis (Table 2).

In a post hoc analysis, the number of transfers to a hospital due to infection per 1000 resident days in the routine-care group was 2.11 (1588 of 753,681 resident days) during the baseline period and 2.31 (1780 of 770,969) during the intervention period. The corresponding values in the decolonization group were 2.03 (1653 of 813,844) and 1.61 (1243 of 772,113), for a relative reduction, as compared with routine care, of 30.9% (95% CI, 22.0 to 38.7). The number of transfers to a hospital for any reason per 1000 resident days among the nursing homes in the routine-care group was 3.37 (2542 of 753,681 resident days) during the baseline period and 3.71 (2857 of 770,969) during the intervention period. The corresponding values in the decolonization group were 3.37 (2743 of 813,844) and 3.09 (2388 of 772,113), for a relative reduction, as compared with routine care, of 18.0% (95% CI, 9.7 to 25.5).

On the basis of the data from the as-assigned analysis, the number needed to treat was 9.7 to prevent one infection-related hospitalization and 8.9 to prevent one hospitalization for any reason, and the values based on data from the as-treated analysis were 6.8 and 5.8, respectively. In a typical nursing home with 100 occupants, the decoloni-

Table 1. Characteristics of the Nursing Home Residents and Facilities.*

Characteristic	Routine Care		Decolonization	
	Baseline Period	Intervention Period	Baseline Period	Intervention Period
Residents				
Residents — no.	6993	6564	8011	7388
Attributable resident-days	753,681	770,969	813,844	772,113†
Age — yr	77.3±5.4	76.6±5.8	75.3±4.8	75.7±4.2
Length of stay — days	278.6±153.0	240.1±119.1	308.5±432.8	278.3±341.7
Length of stay ≥100 days — no. (%)‡	1504 (21.5)	1569 (23.9)	1638 (20.4)	1608 (21.8)
Transfer to a hospital due to infection — no./total no. of transfers for any reason (%)‡	1588/2542 (62.5)	1780/2857 (62.3)	1653/2743 (60.3)	1243/2388 (52.1)
Transfer to a hospital for any reason — no./total no. of discharges from the nursing home (%)‡§	2542/8081 (31.5)	2857/7939 (36.0)	2743/9261 (29.6)	2388/8647 (27.6)
Deaths among all residents — no./total no. of discharges from the nursing home (%)	562/8081 (7.0)	511/7939 (6.4)	590/9261 (6.4)	478/8647 (5.5)
Deaths among all current nursing home residents — no./total no. (%)	562/6993 (8.0)	511/6564 (7.8)	590/8011 (7.4)	478/7388 (6.5)
Male sex — no. (%)	3003 (42.9)	2962 (45.1)	3451 (43.1)	3208 (43.4)
Race — no. (%)¶				
White	3124 (44.7)	2666 (40.6)	4062 (50.7)	3749 (50.7)
Black	1035 (14.8)	1042 (15.9)	939 (11.7)	841 (11.4)
Asian	1328 (19.0)	1312 (20.0)	1152 (14.4)	1042 (14.1)
Other or unknown	1506 (21.5)	1544 (23.5)	1858 (23.2)	1756 (23.8)
Hispanic ethnic group — no. (%)¶	1343 (19.2)	1349 (20.6)	1603 (20.0)	1581 (21.4)
Insurance — no. (%)				
Medicaid only	2814 (40.2)	2811 (42.8)	3404 (42.5)	3013 (40.8)
Medicare only	1154 (16.5)	1085 (16.5)	1333 (16.6)	1149 (15.6)
Dual-eligible status‖	2138 (30.6)	2152 (32.8)	2248 (28.5)	1994 (27.0)
Other or unknown	887 (12.7)	516 (7.9)	1026 (12.8)	1232 (16.7)
Highly compromised or late loss of ADLs — no. of activities‡**	2.6±1.4	2.6±1.4	2.7±1.4	2.7±1.4
Elixhauser comorbidity score‡††	3.52±0.64	3.94±0.53	3.59±0.46	3.76±0.53
Coexisting conditions — no. (%)				
Diabetes	3083 (44.1)	3103 (47.3)	3222 (40.2)	3064 (41.5)
Chronic pulmonary disease	1862 (26.6)	1664 (25.4)	2118 (26.4)	1961 (26.5)
Renal failure	1456 (20.8)	1435 (21.9)	1589 (19.8)	1483 (20.1)
Liver disease	183 (2.6)	204 (3.1)	285 (3.6)	259 (3.51)
Cancer	789 (11.3)	752 (11.5)	855 (10.7)	859 (11.6)
Facilities‡‡				
Nursing homes — no.	14	14	14	14
Licensed beds — no.	114.6±55.8	114.6±55.8	117.9±36.4	117.9±36.4
Daily census — no. of residents‡	102.0±36.6	103.6±37.0	109.4±35.8	105.3±37.0
Attributable resident-days	53,834±20,632	55,069±21,271	58,132±19,354	55,151±19,408
Age of residents — yr	77.1±5.4	76.6±5.8	74.8±5.2	75.8±4.1
Length of stay among residents — days	217.8±16.4	219.7±14.3	216.2±29.9	216.4±29.8
Length of stay ≥100 days — % of residents‡	29.5±14.6	29.5±13.1	29.3±25.1	30.9±25.9
Transfer to a hospital due to infection — % of residents‡	62.2±5.2	62.6±5.6	62.9±8.1	52.2±5.1
Transfer to a hospital for any reason — % of residents‡	36.6±16.4	39.2±17.4	35.5±20.8	32.4±18.5
Frequency of routine bathing at baseline — baths/wk‡§§	3.2±1.6	—	4.4±2.0	—

Table 1. (Continued.)

Characteristic	Routine Care		Decolonization	
	Baseline Period	Intervention Period	Baseline Period	Intervention Period
Antibiotic treatment that was started at the nursing home at baseline — % of residents‡	2.9±1.1	—	3.4±2.2	—
Highly compromised or late loss of ADLs — no. of activities‡††	2.2±0.3	2.2±0.2	2.1±0.4	2.0±0.4
Prevalence of MDRO carriage at baseline — %‡	48.3±10.4	—	48.9±12.6	—
CMS overall star rating at baseline‡¶¶	3.2±1.4	3.2±1.3	3.5±1.2	3.5±1.0
Male sex — % of residents	41.9±10.2	44.5±9.5	42.8 ±5.8	43.2±6.7
Race — % of residents¶				
White	44.1±20.3	39.9±17.8	51.6±17.5	52.2±14.9
Black	15.7±13.8	16.6±15.0	12.4±11.2	11.1±9.6
Asian	19.0±25.3	20.5±20.6	14.6±14.9	13.2±11.1
Other or unknown	21.3±14.5	23.1±12.7	21.4±8.0	23.5±8.5
Hispanic ethnic group — % of residents¶	19.5±12.7	20.3±13.7	20.6±10.0	20.6±10.5
Insurance — % of residents				
Medicaid only	31.8±16.6	33.1±14.8	30.4±22.0	32.4±25.0
Medicare only	14.4±12.9	14.0±14.5	13.7±13.5	13.5±12.9
Dual-eligible status‖	30.6±24.6	32.7±22.4	28.0±22.8	27.0±20.7
Other or unknown	23.3±18.8	20.1±18.5	27.9±22.4	27.2±21.8
Elixhauser comorbidity score among residents‡††	3.6±0.6	3.7±0.4	3.6±0.4	3.6±0.5
Coexisting conditions among residents — %				
Diabetes	40.0±7.0	40.5±7.8	37.7±6.3	37.0±8.2
Chronic pulmonary disease	26.8±12.6	25.4±12.4	26.2±14.6	26.4±11.9
Kidney failure	21.0±6.8	21.1±4.8	20.1±5.8	19.2±6.0
Liver disease	2.7±2.0	2.9±2.3	3.61±1.7	3.5 ±1.0
Cancer	8.8±3.1	8.5±3.2	8.81±3.7	8.7±3.1

* Plus–minus values are means ±SD. All the data are based on the residents and facilities in the intention-to-treat (as-assigned) analysis, including the four nursing homes (one in the routine-care group and three in the decolonization group) that dropped out of the trial. ADLs denotes activities of daily living, CMS Centers for Medicare and Medicaid Services, and MDRO multidrug-resistant organism.

† The slightly lower number of attributable resident-days in the intervention period in the decolonization group is due in part to the partial closure of one of the decolonization facilities during January and February 2018 due to urgent construction needs. During this time, there were no resident-days or transfers.

‡ The variables of "length of stay ≥100 days," "transfer to a hospital due to infection," "transfer to a hospital for any reason," "frequency of routine bathing," "highly compromised or late loss of activities of daily living," "daily census," "antibiotic treatment that was started at the nursing home," "prevalence of MDRO carriage," and CMS overall star rating" were balanced by means of constructing pairs of nursing homes for randomization. Variables were selected to account for the facility characteristics (volume, baseline outcome event rates), as well as the nursing home case mix that could affect the likelihood of hospitalization or infection (i.e., antibiotic use, prevalence of MDRO carriage, coexisting conditions, activities of daily living, and percentage of long-stay vs. post–acute-care residents).

§ The total number of transfers exceeds the number of residents because some residents were hospitalized more than once during the trial period.

¶ Race and Hispanic ethnic group were determined with the use of the minimum data set provided by the Centers for Medicare and Medicaid Services.

‖ Dual-eligible status for nursing home residents denotes those who are dually enrolled to receive Medicare and Medicaid benefits, as defined according to payment source in the CMS records.

** Highly compromised or late loss of ADLs was defined as residents who were in need of extensive assistance or were totally dependent on others with respect to bed mobility, transferring, eating, or toileting.

†† The Elixhauser comorbidity score ranges from 0 to 29, with higher values indicating a greater number of chronic coexisting conditions.

‡‡ Facility-level data including demographics represent the mean proportion of that characteristic (e.g., race or ethnic group) in each nursing home averaged over the 14 nursing homes in that category.

§§ The frequency of bathing in nursing homes across trial groups and trial periods was three times per week on average.

¶¶ The CMS star rating is a measure of nursing home quality on a scale from 1 (lowest score) to 5 (highest rating). Of note, CMS describes their scores as follows: "Nursing homes with 5 stars are considered to have much above average quality and nursing homes with 1 star are considered to have quality much below average" (www.cms.gov/medicare/health-safety-standards/certification-compliance/five-star-quality-rating-system).

Table 2. Trial Outcomes According to Trial Group and Trial Period.

Outcome	Transfer to a Hospital in the Routine-Care Group		Transfer to a Hospital in the Decolonization Group		Risk Ratio (95% CI)*		Difference in Risk Ratio (95% CI), Decolonization vs. Routine Care
	Baseline (N=6993)	Intervention (N=6564)	Baseline (N=8011)	Intervention (N=7388)	Routine Care	Decolonization	
	number/total number (percent)						*percent*
As-assigned, unadjusted analysis							
Transfer to a hospital due to infection†	1588/2542 (62.5)	1780/2857 (62.3)	1653/2743 (60.3)	1243/2388 (52.1)	1.00 (0.96–1.04)	0.83 (0.79–0.88)	16.6 (11.0–21.8)‡
Transfer to a hospital for any reason§	2542/8081 (31.5)	2857/7939 (36.0)	2743/9261 (29.6)	2388/8647 (27.6)	1.08 (1.04–1.12)	0.92 (0.88–0.96)	14.6 (9.7–19.2)
As-assigned, adjusted analysis¶							
Transfer to a hospital due to infection†	1588/2542 (62.5)	1780/2857 (62.3)	1653/2743 (60.3)	1243/2388 (52.1)	1.00 (0.96–1.04)	0.83 (0.79–0.88)	16.6 (11.0–21.8)
Transfer to a hospital for any reason§	2542/8081 (31.5)	2857/7939 (36.0)	2743/9261 (29.6)	2388/8647 (27.6)	1.05 (1.01–1.09)	0.93 (0.89–0.96)	11.6 (6.8–16.1)
As-treated, unadjusted analysis							
Transfer to a hospital due to infection†	1476/2337 (63.2)	1653/2615 (63.2)	1250/1990 (62.8)	916/1779 (51.5)	1.00 (0.96–1.05)	0.80 (0.76–0.85)	20.1 (14.3–25.6)
Transfer to a hospital for any reason§	2337/7740 (30.2)	2615/7602 (34.4)	1990/7548 (26.4)	1779/7125 (25.0)	1.06 (1.02–1.22)	0.95 (0.90–1.00)	10.5 (4.3–16.3)
As-treated, adjusted analysis¶							
Transfer to hospital due to infection†	1476/2337 (63.2)	1653/2615 (63.2)	1250/1990 (62.8)	916/1779 (51.4)	1.00 (0.96–1.04)	0.80 (0.76–0.85)	19.8 (13.9–25.4)
Transfer to hospital for any reason§	2337/7740 (30.2)	2615/7602 (34.4)	1990/7548 (26.4)	1779/7125 (25.0)	1.03 (0.99–1.07)	0.96 (0.91–1.01)	7.0 (0.9–12.6)

* The risk ratios reflect the risk of transfer to a hospital during the intervention period relative to the baseline period in each trial group.
† Transfer to a hospital due to infection (primary outcome) was assessed among all the residents who had been hospitalized.
‡ P<0.001.
§ Transfer to a hospital for any reason (secondary outcome) was assessed among the residents who had been discharged from the nursing home.
¶ The adjusted models accounted for individual age, sex, race, ethnic group, insurance, diabetes, and cancer.

Table 3. Prevalence of MDRO Carriage during the Baseline Period and near the End of the Intervention Period.*

MDRO or Sample	Prevalence in the Routine-Care Group		Prevalence in the Decolonization Group		Risk Ratio (95% CI)†
	Baseline Period (N=700)	Intervention Period (N=650)	Baseline Period (N=700)	Intervention Period (N=550)	
	percent (number of positive samples)				
Any MDRO	48.3 (338)	47.2 (307)	48.9 (342)	32.0 (176)	0.70 (0.58–0.84)
Any MRSA	37.6 (263)	36.9 (240)	36.4 (255)	25.1 (138)	0.73 (0.59–0.92)
Nostril swab sample	29.1 (203)	27.1 (176)	29.9 (209)	22.0 (121)	0.81 (0.62–1.05)
Skin swab sample	26.1 (183)	25.4 (165)	22.6 (158)	11.6 (64)	0.58 (0.42–0.79)
VRE	5.9 (41)	5.1 (33)	8.3 (58)	2.2 (12)	0.29 (0.14–0.62)
ESBL producer	15.9 (111)	17.9 (116)	16.7 (117)	9.2 (51)	0.50 (0.34–0.75)
CRE	1.4 (10)	0.6 (4)	0.4 (3)	0.4 (3)	3.53 (0.44–28.52)

* Prevalence is shown as the mean percentage of positive samples across the facilities in each trial group. CRE denotes carbapenem-resistant Enterobacterales, ESBL extended-spectrum beta-lactamase, MRSA methicillin-resistant *Staphylococcus aureus*, and VRE vancomycin-resistant enterococci.

† We modeled the difference in differences between the changes observed in the decolonization group and those observed in the routine-care group. Models were clustered at the facility level and controlled for trial phase (intervention period vs. baseline period), trial group (decolonization group vs. routine-care group), and the interaction term for trial phase by trial group. The results of unadjusted models were very similar to those of the adjusted models that accounted for bed-bound status, diabetes, and number of licensed beds in the nursing home. The results of the unadjusted models are reported here.

zation intervention would prevent 1.9 infection-related hospitalizations per month in both as-assigned and as-treated analyses (1.87 and 1.92, respectively).

Microbiologic outcomes from the 24 nursing homes that participated in sample collection during the baseline period and near the end of the intervention are summarized in Table 3. The findings are based on samples that were obtained from 650 nursing home residents in the routine-care group and from 550 nursing home residents in the decolonization group. During the baseline period, the prevalence of MDRO carriage was 48.3% in the routine-care group and 48.9% in the decolonization group. Near the end of the intervention, the prevalence was 47.2% in the routine-care group and 32.0% in the decolonization group. The risk ratio in the decolonization group, as compared with the routine-care group, was 0.70 (95% CI, 0.58 to 0.84) for MDRO carriage, 0.73 (95% CI, 0.59 to 0.92) for MRSA carriage, 0.29 (95% CI, 0.14 to 0.62) for VRE carriage, and 0.50 (95% CI, 0.34 to 0.75) for EBSL-producer carriage. The prevalence of CRE carriage did not differ meaningfully between the trial groups, although only 20 cases were identified throughout the trial (in 14 residents among the nursing homes in the routine-care group and in 6 residents among the nursing homes in the decolonization group).

ADVERSE EVENTS

A total of 35 possible adverse events were reported by the nursing homes in the decolonization group during the 772,113 resident-day intervention period (Section S6). These events included 34 rashes potentially related to chlorhexidine and 1 sore throat potentially related to nasal iodophor. Rashes were mild, and chlorhexidine was discontinued in 26 instances. The sole possible reaction to iodophor did not result in discontinuation. Of the 34 reported rashes, 26 occurred during the phase-in period, 12 of which were reported by a single nursing home on the first day of product use and were determined by a trial investigator to be related to preexisting inguinal candidiasis.

DISCUSSION

More than 15,000 nursing homes, in which approximately 1.3 million residents are cared for annually, are located in the United States.[25] These residents represent a vulnerable population at

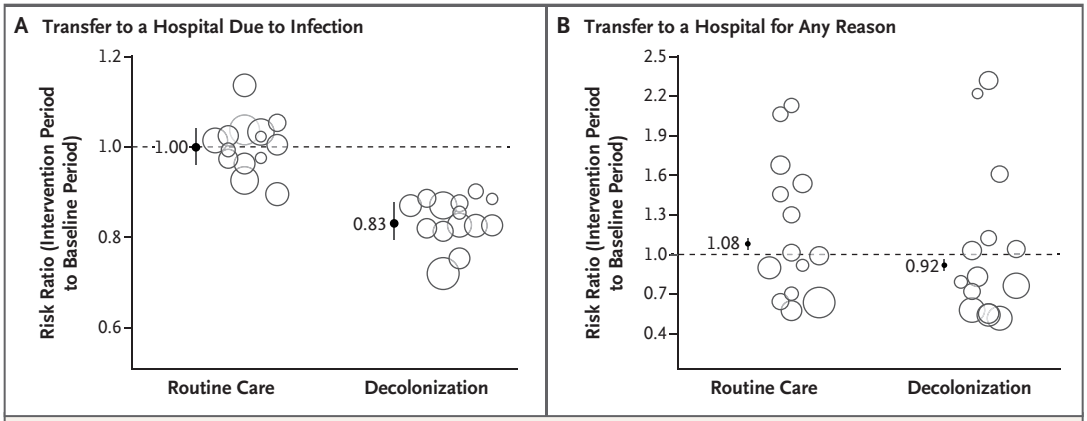

Figure 2. Effect of Decolonization on the Risk of Transfer to a Hospital among Nursing Home Residents.

Shown are the risk ratios for transfer to a hospital due to infection (Panel A) and for any reason (Panel B) between the intervention period and the baseline period. Each nursing home is represented by an open circle, and the size of the open circle is proportional to the number of residents contributing data to the trial. Each open circle is plotted at the y axis value that represents the deviation of that nursing home from the overall risk ratio in the trial group (solid circle, with I bars indicating the 95% confidence interval). The size and location of the open circles are based on the results of the unadjusted model.

high risk for infection and infection-related hospitalization.[19,26,27] An average 100-bed nursing home has 3000 resident-days per month.[25] On the basis of our baseline data, we would expect 10 transfers to a hospital per month per nursing home, with 61% of the transfers being due to infection. This trial showed that switching routine bathing soap with chlorhexidine antiseptic wash plus the twice-daily administration of nasal iodophor for 5 consecutive days every other week significantly reduced the risk of transfer to a hospital due to infection. These data suggest that a 100-bed nursing home could prevent 1.9 infection-related hospitalizations per month. The results of the analyses of the secondary and microbiologic outcomes (not adjusted for multiple testing) suggest that decolonization led to a reduction in the risk of transfer to a hospital for any reason and a reduction in the prevalence of MDRO carriage.

Our findings are consistent with those from universal decolonization studies in other health care settings.[14,28,29] In ICUs, universal decolonization with chlorhexidine and nasal mupirocin reduced the risk of an MRSA-positive clinical culture by 37% and of all-cause bloodstream infection by 44%.[14] In a nontrial setting, discontinuation of universal MRSA decolonization in the ICU was associated with increases in MRSA acquisition and bacteremia, which were reversed after the reintroduction of universal decolonization.[28] Other trials have shown similarly large reductions from universal decolonization in non-ICU inpatients with medical devices (a 37% reduction in the risk of an MDRO-positive clinical culture and a 32% reduction in the incidence of bloodstream infection)[15] and a 30% reduction in the incidence of MRSA infection when MRSA carriers were decolonized after discharge.[16] Given the large and increasing numbers of persons cared for in nursing homes, this intervention could prevent a substantial amount of hospitalization-associated morbidity and save health care resources.

Universal decolonization, as compared with targeting only residents with MDRO colonization, has advantages for addressing MDROs, particularly in nursing homes. First, screening for MDROs is labor-intensive, costly, and takes days for results.[30] Second, the contagiousness of MDROs and the insensitivity of screening[31] make universal decolonization more appealing, given that the prevalence of MDRO carriage in nursing homes is 65% with multisite sampling.[19] Third, although nasal decolonization requires adoption, switching routine bathing soap with chlorhexidine antiseptic wash is labor-neutral. Finally, similar to interventions with the same or similar products in other settings,[15,16] the intervention was associated with few adverse events, which were mild and mostly occurred during the phase-in period, when

staff were relatively unfamiliar with the trial products and increased attention to skin effects led to the identification of preexisting conditions.

The mechanistic basis for the reductions in the incidence of infection is probably tied to the ability of chlorhexidine to reduce skin bacterial bioburden better than soap[32] and the ability of iodophor to reduce MRSA nasal colonization.[33] We chose iodophor over mupirocin because of the lower cost and the potential for mupirocin-resistant *S. aureus*[34]; subsequent trial evidence of the superiority of mupirocin was not available at the time.[35] We note that our intervention did not change the bathing frequency in nursing homes. Each center continued its routine bathing schedule, typically three times weekly with additional partial wipe-downs for "freshening up," as requested. We also did not use an oral chlorhexidine rinse (which has been used in other studies[16,36]) owing to the added administration burden, challenges for residents to adhere to an oral rinsing, and evidence suggesting lesser benefit from oral decolonization.[37]

Our trial has several limitations. We dedicated 4 months to staff training, troubleshooting, and coaching. Despite these efforts, 3 of 14 intervention sites did not implement decolonization, mostly because of the loss of support due to leadership turnover. Several sites had low adherence to iodophor, especially at admission, because of the requirement that nurses, rather than nursing assistants, administer iodophor to residents. Iodophor is an over-the-counter product, so a regulatory change to allow nursing assistants to apply topical nasal products may improve adoption. Similar to the process needed to successfully implement universal chlorhexidine bathing in hospital ICUs, which is now a widespread practice, audit and feedback were needed to improve adherence, and skin-care products that were incompatible with chlorhexidine needed to be exchanged for compatible ones (see the protocol toolkit in the protocol).[14] Furthermore, the decolonization training process may have enhanced measured and unmeasured processes for infection prevention in nursing homes and affected the trial results. Nevertheless, previous decolonization trials in ICU settings where bathing protocols are standardized have shown a benefit that is attributable to chlorhexidine and nasal decolonization.[14,16,20,21] Finally, laundering is performed on-site in nursing homes and does not reach the high temperatures attained by outsourced laundry facilities. The nursing homes in the decolonization group switched from chlorine to peroxide bleach to avoid the chemical interaction between chlorine and chlorhexidine, which causes irreversible brown stains at lower temperatures. Nevertheless, these implementation steps were achieved by most decolonization nursing homes.

Additional limitations included the limited number of sites (28 nursing homes), which might not have adequately balanced the trial groups with respect to confounders. Nevertheless, measured variables were well-matched between the two groups, and the trial design that allowed for a comparison between the intervention period and the baseline period at each facility helped address imbalance in measured or unmeasured confounders. In addition, even though nursing homes were located in a single region, they were owned by different entities with varied practices and processes. It is notable that the demographic and clinical characteristics of our nursing home population were similar to those of the national nursing home population.[38] Among nursing home residents nationwide, the mean age is in the 70s, more than 55% are women, and the prevalence of coexisting medical conditions is similar to that in our trial. The only notable difference is that the percentage of Hispanic residents in our population (approximately 20%) differs from that in national data (5.7%).[38] Finally, our pragmatic trial used publicly reported hospitalization and nursing home data to measure trial outcomes and was dependent on the accuracy of coding according to the *International Classification of Diseases, 10th Revision*, although randomization would have helped in making potential coding errors more nondifferential between the trial groups.

This trial has several strengths. Participating sites were diverse with respect to processes, staffing, resident populations, and corporate structures, a feature that reflects the heterogeneity of community-based nursing homes rather than a coordinated effort within a single health system. Second, the diverse facilities showed real-life potential for adopting decolonization; thus, this intervention is probably feasible in the nursing home setting and, given observed reductions in infection-related hospitalizations, the cost–benefit ratio is likely to be very favorable. Third, ad-

herence was reasonably high, a finding that suggests the feasibility of implementation. Fourth, the intervention products that were used (chlorhexidine and nasal iodophor) are relatively inexpensive. Chlorhexidine comes in multiple commercial formulations, such as liquid and impregnated cloths, that provide options for economy, ease of use, or both, depending on the needs and resources of facilities and individual residents. Finally, we observed a biologically plausible mechanism — a reduction in the prevalence of MDRO colonization — that lends support to the hypothesis that the differences observed in the incidence of transfers to the hospital due to infection (our primary outcome) are related to a true reduction in the incidence of infection and not to between-group differences in the care of nursing home residents.

In this cluster-randomized trial, a universal decolonization strategy of using over-the-counter topical chlorhexidine for bathing and nasal iodophor in nursing homes was associated with a lower risk of transfer to the hospital due to infection. Our findings suggest that the prevention of serious infection in nursing homes can be facilitated with a relatively simple intervention with a low number needed to treat.

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APPENDIX

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