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Nursing Home Decolonization for Infection and Hospitalization Prevention

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BACKGROUND:

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

METHODS:

We performed a cluster-randomized trial of universal decolonization vs. standard-of-care bathing in 28 nursing homes involving an 18-month baseline and 18-month intervention period. Decolonization involved 1) chlorhexidine for all routine bathing and showering; 2) 5-days of nasal povidone-iodine on admission and biweekly. The primary outcome was transfer to a hospital due to infection. The secondary outcome was all-cause hospital transfer. As-randomized difference-in-differences for each outcome comparing intervention to baseline periods across groups were analyzed using generalized linear mixed models.

RESULTS:

A total of 28 nursing homes with 28,956 residents contributed data. Among control nursing homes, mean facility percent of hospital transfers due to infection was 62.2% during baseline and 62.6% during intervention (risk ratio (RR)=1.00, 95% CI:0.96-1.04). Among decolonization nursing homes, these proportions were 62.9% and 50.8%, respectively (RR=0.83, CI:0.79-0.88), for a relative risk reduction vs controls of 16.6% (CI:11.0%-21.8%, $p<0.001$). The proportion of all-cause hospital transfers among controls was 36.6% during baseline and 39.2% during intervention (RR=1.08, CI:1.04-1.12). In decolonization nursing homes, these proportions were 35.5% and 32.4%, respectively (RR=0.92, CI:0.88-0.96), for a relative reduction vs controls of 14.6% (CI:9.7%-19.2%). The number-needed-to-treat was 9.7 to prevent one infection-related hospitalization and 8.9 to prevent all-cause hospitalization.

CONCLUSION:

Universal nursing home decolonization with chlorhexidine and nasal iodophor significantly reduced the proportion of transfers to hospitals due to infection and proportion of all-cause transfers to hospitals. (Funded by the Agency for Healthcare Research and Quality; ClinicalTrials.gov number: NCT03118232)

Three million healthcare-associated infections (HAIs) occur in U.S. nursing homes (annually, causing an estimated 150,000 hospital admissions and 350,000 deaths.¹ Residents are at high risk for HAIs due to age, wounds, medical devices, and comorbidities.^{2,3} Nursing home infection prevention programs must identify strategies that provide safe care and prevent pathogen transmission when combining social activities, long stays, and limited resources.^{4,5}

Multidrug-resistant organism (MDRO) prevalence in ^{2,3} nursing homes (65%) is 4-6 times that of hospitals (10-15%),⁵⁻⁸ incurring risks for subsequent infection. For example, residents harboring methicillin-resistant *Staphylococcus aureus* (MRSA) have a 10% risk of MRSA infection within one month of arrival, and up to 40% within one year.⁹⁻¹¹ Gram-negative MDROs continue to increase in prevalence, as extended-spectrum beta-lactamase producers (ESBLs) spread and carbapenem-resistant Enterobacterales (CRE) emerge.^{12,13}

Randomized trials have demonstrated the benefit of decolonization in preventing HAIs, including MDRO and non-MDRO infections in intensive care unit (ICU) patients,¹⁴ non-ICU patients with devices,¹⁵ and MRSA carriers following hospital discharge.¹⁶ Targeted decolonization of patients harboring MDROs can reduce MDRO infections,^{17,18} but routine cultures fail to detect most MDRO-colonized patients.¹⁹ In contrast, universal decolonization reduces infections caused by multiple pathogens.^{14,16,20,21} We sought to perform a cluster-randomized trial of universal decolonization versus standard-of-care bathing in nursing homes to prevent infection and associated hospitalizations.

METHODS

The Protect Trial was a cluster-randomized trial of universal decolonization vs standard-of-care bathing (control) in 28 California nursing homes, all of which provided skilled nursing care, in Los Angeles and Orange Counties. nursing homes were excluded if they were dedicated to pediatric, dementia, or psychiatric care, or were already routinely using decolonization. The trial was approved by the University of California Irvine Institutional Review Board as a randomized comparison of a quality improvement strategy with a waiver of written informed consent.

The trial employed an 18-month baseline period (September 2015–February 2017), a 4-month phase-in period (March 2017–June 2017), and an 18-month intervention period (July 2017–December 2018). The phase-in period was characterized by receipt of product and staff training in decolonization nursing homes with product start dates predominantly in April.

Intervention

At time of randomization, no sites used routine topical chlorhexidine gluconate (CHG) or nasal decolonization. Sites randomized to the decolonization group adopted decolonization with 10% povidone-iodine (nasal iodophor) and CHG for bathing (see Supplement A and B). Nasal iodophor was given twice daily on admission for 5 days and then administered twice daily Monday through Friday every other week to all residents. CHG bathing (4% rinse-off CHG for showering, 2% no-rinse cloths for bed bathing) was performed on admission and thereafter for all routine bathing or showering.

Decolonization nursing homes were provided in-person training sessions, coaching calls, and a toolkit of protocols, training materials, and staff and resident handouts. Nursing homes

retained their usual bathing frequency throughout the trial regardless of study group. Iodophor compliance was assessed for all admissions and a rotating 25% sample of occupied beds once weekly. CHG compliance was assessed weekly (unannounced weekday) for the most recent bath or shower.

Sites randomized to the standard-of-care group continued their routine bathing practices.

Outcomes

Our primary outcome was hospitalization due to infection (among those hospitalized). We had 89% power to detect a two-tailed 15% difference between groups. Our secondary outcome was all-cause nursing home transfer to a hospital (among all nursing home discharges). Standardized nursing home and hospitalization datasets were used to assess outcomes (Supplement C).

Separate from specified trial outcomes, we evaluated pre- and end-intervention MDRO (specifically MRSA, vancomycin-resistant enterococci (VRE), ESBL, CRE) carriage. A one-day point-prevalence sample of 50 randomly-selected occupied beds was conducted at each nursing home during baseline (September 2016–January 2017) and end-intervention periods (August 2018–December 2018). To account for seasonality, each nursing home's two samples occurred within the same or adjacent calendar month in different years. Trained nurses from each nursing home swabbed the bilateral nares and bilateral axilla/groin of residents. Specimens were processed within 6 hours by the UCI Clinical Microbiology Laboratory. Nares

swabs were tested for MRSA, and axilla/groin swabs were processed for MRSA, VRE, ESBLs, and CRE, as previously described.¹⁹

Cluster Randomization

Nursing homes were randomized in pairs. To help balance key characteristics between groups, pairing used the Goldilocks Approach by calculating the Mahalanobis distance between facilities across baseline weighted key variables and choosing pairings with the minimum average within-pair distance.^{22,23} Further details on randomization and variables used for balancing groups are described in Supplement D.

Analysis

Main trial results were assessed using as-randomized, unadjusted analyses. Generalized linear mixed log-binomial regression models, clustering by nursing home, assessed the difference-in-differences using a group-by-period interaction term (Supplements E and F). We additionally conducted adjusted and as-treated analyses. Trial success was determined by the significance of the group-by-treatment period interaction, which assessed whether the difference in risk ratio (RR) between the baseline and intervention periods differed significantly between the groups. In adjusted models, variables evaluated included individual age, gender, race, ethnicity, insurance, and comorbidities including diabetes and cancer. As a conservative approach, analyses ignored pair-matching performed in randomization.²⁴ Phase-in period data were excluded from all analyses. We also calculated the number-needed-to-treat (NNT).

For the MDRO prevalence comparisons, we fit similar models comparing the intervention group to the control group. Models were clustered by nursing home. Analyses were performed using SAS 9.4 (SAS Institute, Cary NC).

RESULTS

We randomized 28 nursing homes, 14 per group (Figure 1). A total of 28,956 nursing home residents contributed data to the trial, 15,004 during baseline and 13,952 during intervention. Characteristics of residents and participating nursing homes were similar across groups and stable across periods (Table 1). One nursing home (decolonization) had a two-month closure in early 2018 for construction, which reduced accrued resident-days in that group.

One control and 3 decolonization nursing homes dropped from the trial; their data were included in the as-randomized analysis of primary and secondary outcomes. Reasons for dropout included administrative turnover and loss of support (control (1), decolonization (2)) and effort required during the phase-in period (decolonization (1)).

In the decolonization group, mean compliance with CHG admission bathing across participating nursing homes was 95.6% (SD=4.7; nursing home range:86.4%-100%) and for routine CHG bathing was 87.4% (SD=6.9; nursing home range:73.6%-98.2%). Mean compliance with nasal iodophor across participating nursing homes was 60.3% (SD=26.1; nursing home range:11%-95%) on admission and 67.4% (SD=17.7; nursing home range:42%-88%) for routine administration.

For the primary outcome, in the control group, the mean facility percent of hospitalizations due to infection was 62.2% during baseline and 62.6% during intervention; in the decolonization group, 62.9% during baseline and 50.8% during intervention (Table 2). When comparing intervention to baseline periods, the relative risk of hospital transfers due to infection was lower for the decolonization group (RR= 0.83 (0.79-0.88)) compared to controls (RR=1.00 (0.96-1.04)), for a relative reduction of 16.6% (11.0%-21.8%, $p<0.001$) (Table 2, Figure 2A). Odds of hospital transfer are provided in Supplement F.

For the secondary outcome, in the control group, the mean facility percent of all-cause transfers to hospitals was 36.6% during baseline and 39.2% during intervention; in the decolonization group, 35.5% during baseline and 32.4% during intervention (Table 2, Supplement G). When comparing intervention to baseline periods, the relative risk of all-cause hospital transfers was lower for the decolonization group (RR=0.92 (0.88-0.96)) compared to controls (RR=1.08 (1.04-1.12)), for a relative reduction of 14.6% (9.7%-19.2%). (Table 2, Figure 2B). As treated and adjusted results were similar (Table 2).

A post-hoc analysis (see Supplement F for details) of hospitalization due to infection per 1,000 resident days in control nursing homes was 2.11 (1,588/753,681) during the baseline and 2.31 (1,780/770,969) during the intervention period. In intervention nursing homes, it was 2.03 (1,653/813,844) and 1.61 (1,243/772,113), respectively, for a reduction of 30.9% (22.0%-38.7%) in hospitalization due to infection per 1,000 resident days attributed to decolonization. All-cause hospitalization due to per 1,000 resident days in control nursing homes was 3.37 (2,542/753,681) during the baseline and 3.71 (2,857/770,969) during the intervention period. In intervention nursing homes, it was 3.37 (2,743/813,844) and 3.09 (2,388/772,113),

respectively, for a reduction of 18.0% (9.7%-25.5%) in all-cause hospitalization per 1,000 resident days attributed to decolonization.

Using as-randomized data, the NNT was 9.7 to prevent one infection-related hospitalization and 8.9 to prevent any hospitalization; using as-treated data, NNTs were 6.8 and 5.8, respectively. In a typical nursing home with 100 occupants, the decolonization intervention would prevent 1.9 infection-related hospitalizations per month in both as-randomized (1.87) and as-treated (1.92) analyses.

Microbiologic outcomes from the 24 nursing homes that participated in both baseline and end-intervention samplings are summarized in Table 3. Findings represent 650 persons in control nursing homes and 550 in decolonization nursing homes. Baseline MDRO colonization prevalence was 48.3% in control nursing homes and 48.9% in decolonization nursing homes. By end-intervention, these percentages were 47.2% and 32.0%, respectively. Prevalence of any MDRO significantly decreased in decolonization vs. control nursing homes (RR=0.70, 95% CI:0.58-0.84, $P<0.001$) with reductions in MRSA (RR=0.73, 95% CI: 0.59-0.92, $P=0.007$), VRE (RR=0.29, 95% CI:0.14-0.62, $P=0.001$), and ESBL (RR=0.50, 95% CI:0.34-0.75, $P=0.001$). There was no meaningful difference in CRE, although only 20 cases were identified throughout the trial (14 in control nursing homes, 6 in decolonization nursing homes).

Thirty-five possible adverse events were reported by decolonization nursing homes during the 772,113 resident-day intervention period (Supplement H). These included 34 rashes potentially related to CHG and 1 sore throat potentially related to nasal iodophor. Rashes were mild and CHG was discontinued in 26 instances. The sole possible iodophor reaction did not result in discontinuation. Twenty-six of the 34 reported rashes occurred during phase-in with 12

reported by a single nursing home on the first day of product use and determined to represent pre-existing inguinal candidiasis.

DISCUSSION

There are over 15,000 nursing homes in the U.S. caring for 1.3 million residents annually.²⁵ These residents represent a vulnerable population at high risk for infection and infection-related hospitalization.^{19,26,27} An average 100-bed nursing home has 3,000 resident-days per month.²⁵ Using our baseline data, we would expect 10 hospitalizations per month per nursing home, with 61% due to infection. This trial found that the change in bathing soap to CHG antiseptic wash plus a 5-day biweekly nasal iodophor regimen reduced infection-related hospital transfers, all-cause transfers for hospitalization, and MDRO prevalence. These data suggest that a 100-bed nursing home could prevent 1.9 infection-related hospitalizations per month.

Our findings are consistent with universal decolonization studies in other healthcare settings.^{14,28,29} In ICUs, universal decolonization with CHG and nasal mupirocin reduced MRSA clinical cultures by 37% and all-cause bloodstream infections by 44%.¹⁴ In a non-trial setting, discontinuation of universal ICU MRSA decolonization was associated with increases in MRSA acquisition and bacteremia, which were reversed after reintroduction of universal decolonization.²⁸ Other trials have shown similarly large reductions from universal decolonization in non-ICU inpatients with devices (37% reduction in MDROs, 32% reduction in bloodstream infections)¹⁵ and a 30% reduction of MRSA infection when decolonizing MRSA carriers post-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 healthcare resources.

Universal decolonization has advantages for addressing MDROs compared to targeting only MDRO-colonized residents, 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 screening³¹ makes universal decolonization more appealing given that nursing home MDRO prevalence is 65% with multi-site sampling.¹⁹ Third, while nasal decolonization requires adoption, the switching of bathing soap is labor-neutral. Finally, similar to interventions using 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 study products and where increased attention to skin effects identified pre-existing conditions.

Mechanistically, reductions in infection were likely tied to CHG's ability to reduce skin bacterial bioburden better than soap³² and iodophor's ability to reduce MRSA nasal colonization.³³ We chose iodophor over mupirocin due to lower cost and potential for mupirocin-resistant *S. aureus*³⁴; subsequent trial evidence of mupirocin's superiority was not known 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 CHG rinse as has been done in other studies,^{16,36} due to added administration burden, challenges for residents to comply with rinsing, and evidence suggesting lesser benefit from oral decolonization.³⁷

Our trial had limitations. We dedicated four months to staff training, troubleshooting, and coaching. Despite these efforts, three of 14 intervention sites did not implement decolonization, mostly due to lost support from leadership turnover. Several sites had low adherence to iodophor, especially on admission, due to 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 might improve adoption. Similar to the process for universal CHG bathing that is widespread in hospital ICUs, audit and feedback were needed to enhance compliance, and CHG incompatible skin care products needed to be exchanged for CHG compatible ones (Supplement A for protocol toolkit).¹⁴ Furthermore, the decolonization training process may have enhanced measured and unmeasured nursing home infection prevention processes and affected trial results. Nevertheless, prior decolonization trials in ICU settings where bathing protocols are standardized have demonstrated benefit attributable to CHG and nasal decolonization.^{14,16,20,21} Finally, nursing home laundry is performed on-site and does not reach the high temperatures achieved by outsourced laundry facilities. Decolonization nursing homes switched from chlorine to peroxide bleach to avoid the chemical interaction between chlorine and CHG 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 (n=28) which might not have adequately balanced confounders. Nevertheless, measured variables were well-matched between groups and the study design comparing each facility's intervention period to its own baseline helps address imbalance in measured or unmeasured confounders. In addition,

participating nursing homes were located in a single region, although participating facilities represented a mix of owners and their pre-intervention practices and processes were varied. Notably, demographic and clinical characteristics of our nursing home population were similar to national nursing home data.³⁸ Nationally, mean age is in the 70s, with >55% females, and similar proportions of co-morbidities. The only notable difference is that the proportion of Hispanics in our population (approximately 20%) differs from national data (5.7%).³⁸ Finally, our pragmatic trial used publicly-reported hospitalization and nursing home data to measure study outcomes and was dependent on the accuracy of ICD-10 coding, although randomization would have helped errors be non-differential across the groups.

There are strengths to this cluster-randomized trial. Participating sites were diverse in processes, staffing, resident populations, and corporate structures, reflecting the heterogeneity of community-based nursing homes rather than a coordinated effort within a single health system. Second, the diverse facilities demonstrated real-life potential for adopting decolonization; thus, this intervention is likely feasible in the nursing home setting and, given observed reductions in infection-related hospitalizations, the cost-benefit ratio is likely very favorable. Third, compliance was reasonably high, suggesting the feasibility of implementation. Fourth, the intervention products used, CHG and nasal iodophor, are relatively inexpensive. CHG comes in multiple commercial formulations such as liquid and impregnated cloths, providing options for economy and/or ease of use, depending on the needs and resources of facilities and individual residents. Finally, we observed a biologically-plausible mechanism, reduction in MDRO colonization, that lends support that differences in our primary outcome

are related to true infection reduction and not differences in nursing home resident management between groups.

In summary, an over-the-counter topical universal decolonization strategy of CHG bathing and nasal iodophor was associated with reductions in infection-related and all-cause hospitalization in nursing homes. Our findings suggest preventability of serious infection outcomes can be achieved with a relatively simple intervention in nursing homes.

Disclosure forms provided by the authors are available with the full text of this article at
NEJM.org.

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REFERENCES

1. Koch AM, Eriksen HM, Elstrom P, Aavitsland P, Harthug S. Severe consequences of healthcare-associated infections among residents of nursing homes: a cohort study. *J Hosp Infect* 2009;71(3):269-74. DOI: 10.1016/j.jhin.2008.10.032.
2. Jeon CY, Neidell M, Jia H, Sinisi M, Larson E. On the role of length of stay in healthcare-associated bloodstream infection. *Infect Control Hosp Epidemiol* 2012;33(12):1213-8. DOI: 10.1086/668422.
3. Eilers R, Veldman-Ariesen MJ, Haenen A, van Benthem BH. Prevalence and determinants associated with healthcare-associated infections in long-term care facilities (HALT) in the Netherlands, May to June 2010. *Euro Surveill* 2012;17(34) (<https://www.ncbi.nlm.nih.gov/pubmed/22939212>).
4. Smith PW, Bennett G, Bradley S, et al. SHEA/APIC guideline: infection prevention and control in the long-term care facility, July 2008. *Infect Control Hosp Epidemiol* 2008;29(9):785-814. DOI: 10.1086/592416.
5. Murphy CR, Quan V, Kim D, et al. Nursing home characteristics associated with methicillin-resistant *Staphylococcus aureus* (MRSA) Burden and Transmission. *BMC Infect Dis* 2012;12:269. DOI: 10.1186/1471-2334-12-269.
6. Jarvis WR, Jarvis AA, Chinn RY. National prevalence of methicillin-resistant *Staphylococcus aureus* in inpatients at United States health care facilities, 2010. *Am J Infect Control* 2012;40(3):194-200. DOI: 10.1016/j.ajic.2012.02.001.

7. McKinnell JA, Singh RD, Miller LG, et al. The SHIELD Orange County Project: Multidrug-resistant Organism Prevalence in 21 Nursing Homes and Long-term Acute Care Facilities in Southern California. *Clin Infect Dis* 2019;69(9):1566-1573. DOI: 10.1093/cid/ciz119.
8. Huang SS, Rifas-Shiman SL, Warren DK, et al. Improving methicillin-resistant *Staphylococcus aureus* surveillance and reporting in intensive care units. *J Infect Dis* 2007;195(3):330-8. DOI: 10.1086/510622.
9. Bradley SF, Terpenning MS, Ramsey MA, et al. Methicillin-resistant *Staphylococcus aureus*: colonization and infection in a long-term care facility. *Ann Intern Med* 1991;115(6):417-22. DOI: 10.7326/0003-4819-115-6-417.
10. Mulhausen PL, Harrell LJ, Weinberger M, Kochersberger GG, Feussner JR. Contrasting methicillin-resistant *Staphylococcus aureus* colonization in Veterans Affairs and community nursing homes. *Am J Med* 1996;100(1):24-31. DOI: 10.1016/s0002-9343(96)90007-8.
11. Muder RR, Brennen C, Wagener MM, et al. Methicillin-resistant staphylococcal colonization and infection in a long-term care facility. *Ann Intern Med* 1991;114(2):107-12. DOI: 10.7326/0003-4819-114-2-1-107.
12. Hansen GT. Continuous Evolution: Perspective on the Epidemiology of Carbapenemase Resistance Among Enterobacterales and Other Gram-Negative Bacteria. *Infect Dis Ther* 2021;10(1):75-92. DOI: 10.1007/s40121-020-00395-2.
13. Zhou R, Fang X, Zhang J, et al. Impact of carbapenem resistance on mortality in patients infected with Enterobacteriaceae: a systematic review and meta-analysis. *BMJ Open* 2021;11(12):e054971. DOI: 10.1136/bmjopen-2021-054971.

14. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. N Engl J Med 2013;368(24):2255-65. (In eng). DOI: 10.1056/NEJMoa1207290.
15. Huang SS, Septimus E, Kleinman K, et al. Chlorhexidine versus routine bathing to prevent multidrug-resistant organisms and all-cause bloodstream infections in general medical and surgical units (ABATE Infection trial): a cluster-randomised trial. Lancet 2019;393(10177):1205-1215. DOI: 10.1016/S0140-6736(18)32593-5.
16. Huang SS, Singh R, McKinnell JA, et al. Decolonization to Reduce Postdischarge Infection Risk among MRSA Carriers. N Engl J Med 2019;380(7):638-650. DOI: 10.1056/NEJMoa1716771.
17. Perl TM, Cullen JJ, Wenzel RP, et al. Intranasal mupirocin to prevent postoperative Staphylococcus aureus infections. N Engl J Med 2002;346(24):1871-7.
(http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12063371).
18. Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. N Engl J Med 2010;362(1):9-17. DOI: 10.1056/NEJMoa0808939.
19. McKinnell JA, Miller LG, Singh RD, et al. High Prevalence of Multidrug-Resistant Organism Colonization in 28 Nursing Homes: An "Iceberg Effect". J Am Med Dir Assoc 2020;21(12):1937-1943 e2. DOI: 10.1016/j.jamda.2020.04.007.
20. Climo MW, Yokoe DS, Warren DK, et al. Effect of daily chlorhexidine bathing on hospital-acquired infection. N Engl J Med 2013;368(6):533-42. DOI: 10.1056/NEJMoa1113849.

21. Milstone AM, Elward A, Song X, et al. Daily chlorhexidine bathing to reduce bacteraemia in critically ill children: a multicentre, cluster-randomised, crossover trial. *Lancet* 2013;381(9872):1099-106. DOI: 10.1016/S0140-6736(12)61687-0.
22. Mahalanobis PC. On the generalised distance in statistics. *Proceedings of the National Institute of Sciences of India* 1936;2(2):49-55.
23. Sturdevant SG, Huang SS, Platt R, Kleinman K. Matching in cluster randomized trials using the Goldilocks Approach. *Contemp Clin Trials Commun* 2021;22:100746. DOI: 10.1016/j.conctc.2021.100746.
24. Diehr P, Martin DC, Koepsell T, Cheadle A. Breaking the matches in a paired t-test for community interventions when the number of pairs is small. *Stat Med* 1995;14(13):1491-504. DOI: 10.1002/sim.4780141309.
25. Centers for Disease Control and Prevention. Nursing Home Care, found at <https://www.cdc.gov/nchs/fastats/nursing-home-care.htm>, Accessed August 30, 2022.
26. Sloane PD, Zimmerman S, Nace DA. Progress and Challenges in the Management of Nursing Home Infections. *J Am Med Dir Assoc* 2020;21(1):1-4. DOI: 10.1016/j.jamda.2019.11.025.
27. Jacobs Slifka KM, Kabbani S, Stone ND. Prioritizing Prevention to Combat Multidrug Resistance in Nursing Homes: A Call to Action. *J Am Med Dir Assoc* 2020;21(1):5-7. DOI: 10.1016/j.jamda.2019.11.024.
28. Bradley CW, Wilkinson MA, Garvey MI. The Effect of Universal Decolonization With Screening in Critical Care to Reduce MRSA Across an Entire Hospital. *Infect Control Hosp Epidemiol* 2017;38(4):430-435. DOI: 10.1017/ice.2017.4.

29. Pallotto C, Fiorio M, De Angelis V, et al. Daily bathing with 4% chlorhexidine gluconate in intensive care settings: a randomized controlled trial. Clin Microbiol Infect 2019;25(6):705-710. DOI: 10.1016/j.cmi.2018.09.012.
30. Cherkaoui A, Renzi G, Martischang R, Harbarth S, Vuilleumier N, Schrenzel J. Impact of Total Laboratory Automation on Turnaround Times for Urine Cultures and Screening Specimens for MRSA, ESBL, and VRE Carriage: Retrospective Comparison With Manual Workflow. Front Cell Infect Microbiol 2020;10:552122. DOI: 10.3389/fcimb.2020.552122.
31. McKinnell JA, Huang SS, Eells SJ, Cui E, Miller LG. Quantifying the impact of extranasal testing of body sites for methicillin-resistant Staphylococcus aureus colonization at the time of hospital or intensive care unit admission. Infection Control & Hospital Epidemiology 2013;34(2):161-70.
32. Russell AD, Day MJ. Antibacterial activity of chlorhexidine. J Hosp Infect 1993;25(4):229-38. DOI: 10.1016/0195-6701(93)90109-d.
33. Phillips M, Rosenberg A, Shopsin B, et al. Preventing surgical site infections: a randomized, open-label trial of nasal mupirocin ointment and nasal povidone-iodine solution. Infect Control Hosp Epidemiol 2014;35(7):826-32. DOI: 10.1086/676872.
34. McDanel JS, Murphy CR, Diekema DJ, et al. Chlorhexidine and mupirocin susceptibilities of methicillin-resistant staphylococcus aureus from colonized nursing home residents. Antimicrob Agents Chemother 2013;57(1):552-8. DOI: 10.1128/AAC.01623-12.
35. Huang SS, Septimus E, Kleinman K, et al. Hospital Cluster-Randomized Trial of Mupirocin-Chlorhexidine vs Iodophor-Chlorhexidine for Universal Decolonization in

- Intensive Care Units (ICUs) (Mupirocin Iodophor Swap Out Trial) Open Forum Infectious Diseases 2021;8:Supplement 1:S3-S4. DOI: <https://doi.org/10.1093/ofid/ofab466.004>.
36. Bebko SP, Green DM, Awad SS. Effect of a preoperative decontamination protocol on surgical site infections in patients undergoing elective orthopedic surgery with hardware implantation. JAMA Surg 2015;150(5):390-5. DOI: 10.1001/jamasurg.2014.3480.
37. Poyraz O, Sater MRA, Miller LG, et al. Modelling methicillin-resistant Staphylococcus aureus decolonization: interactions between body sites and the impact of site-specific clearance. J R Soc Interface 2022;19(191):20210916. DOI: 10.1098/rsif.2021.0916.
38. Sengupta M, Lendon JP, Caffrey C, Melekin A, Singh P. Post-acute and Long-term Care Providers and Services Users in the United States, 2017-2018. Vital Health Stat 3 2022(47):1-93. (<https://www.ncbi.nlm.nih.gov/pubmed/35604771>).

Figure 1: CONSORT Diagram

CONSORT diagram for the Protect nursing home cluster-randomized trial detailing the enrollment of facilities, allocation to treatment, retention, and analysis.

Figure 2: Impact of Decolonization Intervention on Hospitalization Among Nursing Home Residents

In this figure, each nursing home is represented by a circle. The size of the circle is proportional to the number of residents contributing data to the trial. The y-axis represents the intervention vs. baseline risk ratio (RR). Each nursing home's circle is plotted at the y-value for that nursing home's deviation from the overall RR for their group represented by the black dot. Size and location of the circles, as well as the black dot representing RR with confidence limits, come from the model results.

Panel A compares the probability that a transfer to a hospital was due to infection; Panel B compares the probability that a nursing home transfer was to a hospital for any cause. The p values represent the significance of the difference in the relative risk between groups (the trial effect). See text for further details.

Table 1. Characteristics of Protect Trial Nursing Home Resident Population and Facilities (As Randomized)^a

Resident Characteristics				
	Control Group		Decolonization Group	
	Baseline Period, N (%)	Intervention Period, N (%)	Baseline Period, N (%)	Intervention Period, N (%)
Residents	6,993	6,564	8,011	7,388
Attributable Resident Days	753,681	770,969	813,844	772,113 ^b
Age in Years (Mean, SD)	77.3 (5.4)	76.6 (5.8)	75.3 (4.8)	75.7 (4.2)
Length-Of-Stay in Days (Mean, SD)	278.6 (153.0)	240.1 (119.1)	308.5 (432.8)	278.3 (341.7)
Length-Of-Stay ≥100 Days ^c	1504 (21.5%)	1569 (23.9%)	1638 (20.4%)	1608 (21.8%)
Number of Residents Transferred to Hospital Due to Infection/All Hospital Transfers (%) ^c	1,588/2,542 (62.5%)	1,780/2,857 (62.3%)	1,653/2,743 (60.3%)	1,243/2,388 (52.1%)
Number of Residents Transferred to a Hospital for Any Reason/All NH Transfers (%) ^{c, d}	2,542/8,081 (31.5%)	2,857/7,939 (36.0%)	2,743/9,261 (29.6%)	2,388/8,647 (27.6%)
Number of Residents Who Died/All NH Transfers (%)	562/8,081 (7.0%)	511/7,939 (6.4%)	590/9,261 (6.4%)	478/8,647 (5.5%)
Number of Residents Who Died/All NH Residents (%)	562/6,993 (8.0%)	511/6,564 (7.8%)	590/8,011 (7.4%)	478/7,388 (6.5%)
Male Sex	3003 (42.9%)	2962 (45.1%)	3451 (43.1%)	3208 (43.4%)
Race: 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/Unknown	1506 (21.5%)	1544 (23.5%)	1858 (23.2%)	1756 (23.8%)
Hispanic Ethnicity	1343 (19.2%)	1349 (20.6%)	1603 (20.0%)	1581 (21.4%)
Insurance: 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 ^e	2138 (30.6%)	2152 (32.8%)	2248 (28.5%)	1994 (27.0%)
Other/Unknown	887 (12.7%)	516 (7.9%)	1026 (12.8%)	1232 (16.7%)
Mean Number of Highly Compromised Late Loss Activities of Daily Living ^{c, f}	2.6 (1.4)	2.6 (1.4)	2.7 (1.4)	2.7 (1.4)
Elixhauser Score (Mean, SD) ^c	3.52 (0.64)	3.94 (0.53)	3.59 (0.46)	3.76 (0.53)
Comorbidities				
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%)

Nursing Home Characteristics ^g				
	Control Group Facilities		Decolonization Group Facilities	
	Baseline Period Mean (SD)	Intervention Period Mean (SD)	Baseline Period Mean (SD)	Intervention Period Mean (SD)
Nursing Homes	14	14	14	14
Licensed Beds	114.6 (55.8)	114.6 (55.8)	117.9 (36.4)	117.9 (36.4)
Daily Census ^c	102.0 (36.6)	103.6 (37.0)	109.4 (35.8)	105.3 (37.0)
Attributable Resident Days	53,834.4 (20,631.6)	55,069.2 (21,270.8)	58,131.7 (19,353.7)	55,150.9 (19,407.7)
Age in Years	77.1 (5.4)	76.6 (5.8)	74.8 (5.2)	75.8 (4.1)
Length-Of-Stay in Days	217.8 (16.4)	219.7 (14.3)	216.2 (29.9)	216.4 (29.8)
% Length-Of-Stay ≥100 Days ^c	29.5 (14.6)	29.5 (13.1)	29.3 (25.1)	30.9 (25.9)
% of Hospital Transfers Due To Infection ^c	61.2 (5.2)	62.6 (5.6)	62.9 (8.1)	50.8 (4.2)
% of NH Transfers to a Hospital For Any Reason ^c	36.6 (16.4)	39.2 (17.4)	35.5 (20.8)	32.4 (18.5)
Baseline Frequency Of Routine Bathing (Baths/Week) ^{c, h}	3.2 (1.6)	.	4.4 (2.0)	.
Baseline % of Residents on an Antibiotic Started at the NH ^c	2.9 (1.1)	.	3.4 (2.2)	.
Mean Number of Highly Compromised Late Loss Activities of Daily Living ^{c, f}	2.2 (0.3)	2.2 (0.2)	2.1 (0.4)	2.0 (0.4)
Baseline MDRO Prevalence ^c	48.3 (10.4)	.	48.9 (12.6)	.
Baseline CMS Overall Star Rating ^c	3.2 (1.4)	3.2 (1.3)	3.5 (1.2)	3.5 (1.0)
% Male	41.9 (10.2)	44.5 (9.5)	42.8 (5.8)	43.2 (6.7)
Race: % 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 Ethnicity	19.5 (12.7)	20.3 (13.7)	20.6 (10.0)	20.6 (10.5)
Insurance: % 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 ^e	30.6 (24.6)	32.7 (22.4)	28.0 (22.8)	27.0 (20.7)
% Other/Unknown	23.3 (18.8)	20.1 (18.5)	27.9 (22.4)	27.2 (21.8)
Elixhauser Score (Mean, SD) ^c	3.6 (0.6)	3.7 (0.4)	3.6 (0.4)	3.6 (0.5)
Comorbidities				
% 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)
% Renal 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)
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Abbreviations: SD = Standard Deviation, NH = nursing home

^a All numbers represent as-randomized residents and facilities, including the 3 nursing homes (1 control, 3 decolonization) that dropped out of the trial.

^b The slightly lower number of attributable resident days in the intervention period in the decolonization group is in part due 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 patient days or resident transfers.

^c Variable balanced in constructing nursing home pairs for randomization. Variables were selected to account for nursing home characteristics (volume, baseline outcome event rates) as well as nursing home case mix that could affect likelihood of hospitalization or infection (antibiotic use, prevalence of multidrug-resistant organisms, comorbidities, activities of daily living, and proportion of long-stay versus post-acute residents).

^d Total transfers exceed number of residents because some residents were hospitalized more than once in the study period

^e Dual-eligible represents NH residents who are dually enrolled to receive Medicare and Medicaid benefits, defined by payment source in CMS records

^f Defined as residents requiring “extensive assistance” and/or “total dependence” for bed mobility, transferring, eating, or toileting

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

^h The frequency for bathing in nursing homes across both arms and study periods was 3x/week on average

Table 2. Protect Trial Outcomes by Group and Period

	Hospital Transfer Events by Trial Group and Phase				Risk Ratios (95% CI) ^a		Difference-in-Differences (95% CI)
	Control (Routine Care)		Decolonization		Control (Routine Care)	Decolonization	
	Baseline	Intervention	Baseline	Intervention			
Number of Residents, N	6,993	6,564	8,011	7,388	.	.	.
As-Randomized, Unadjusted							
Hospital transfer due to infection ^b	1,588/2,542 (62.5%)	1,780/2,857 (62.3%)	1,653/2,743 (60.3%)	1,243/2,388 (52.1%)	1.00 (0.96-1.04)	0.83 (0.79-0.88)	16.6% (11.0%-21.8%) decrease with decolonization vs routine care
Hospital transfer for any reason ^c	2,542/8,081 (31.5%)	2,857/7,939 (36.0%)	2,743/9,261 (29.6%)	2,388/8,647 (27.6%)	1.08 (1.04-1.12)	0.92 (0.88-0.96)	14.6% (9.7%-19.2%) decrease with decolonization vs routine care
As-Randomized, Adjusted ^c							
Hospital transfer due to infection ^b	1,588/2,542 (62.5%)	1,780/2,857 (62.3%)	1,653/2,743 (60.3%)	1,243/2,388 (52.1%)	1.00 (0.96-1.04)	0.83 (0.79-0.88)	16.6% (11.0%-21.8%) decrease with decolonization vs routine care
Hospital transfer for any reason ^c	2,542/8,081 (31.5%)	2,857/7,939 (36.0%)	2,743/9,261 (29.6%)	2,388/8,647 (27.6%)	1.05 (1.01-1.09)	0.93 (0.89-0.96)	11.6% (6.8%-16.1%) decrease with decolonization vs routine care

As-Treated, Unadjusted							
Hospital transfer due to infection ^b	1,476/2,337 (63.2%)	1,653/2,615 (63.2%)	1,250/1,990 (62.8%)	916/1,779 (51.5%)	1.00 (0.96-1.05)	0.80 (0.76-0.85)	20.1% (14.3%-25.6%) decrease with decolonization vs routine care
Hospital transfer for any reason ^c	2,337/7,740 (30.2%)	2,615/7,602 (34.4%)	1,990/7,548 (26.4%)	1,779/7,125 (25.0%)	1.06 (1.02-1.22)	0.95 (0.90-1.00)	10.5% (4.3%-16.3%) decrease with decolonization vs routine care
As-Treated, Adjusted ^d							
Hospital transfer due to infection ^b	1,476/2,337 (63.2%)	1,653/2,615 (63.2%)	1,250/1,990 (62.8%)	916/1,779 (51.4%)	1.00 (0.96-1.04)	0.80 (0.76-0.85)	19.8% (13.9%-25.4%) decrease with decolonization vs routine care
Hospital transfer for any reason ^c	2,337/7,740 (30.2%)	2,615/7,602 (34.4%)	1,990/7,548 (26.4%)	1,779/7,125 (25.0%)	1.03 (0.99-1.07)	0.96 (0.91-1.01)	7.0% (0.9%-12.6%) decrease with decolonization vs routine care

^a Risk ratios reflect the risk of hospital transfer in the intervention period relative to the baseline period, within randomized group.

^b Primary outcome is transfer from the nursing home to a hospital due to infection (numerator) divided by transfers from the nursing home to the hospital due to any cause (denominator).

^c Secondary outcome is transfer from the nursing home to the hospital for any cause (numerator) divided by the total number of transfers from the nursing home to any destination (denominator).

^d Adjusted models accounted for individual age, gender, race, ethnicity, insurance, and comorbidities including diabetes and cancer.

Table 3: Multidrug-resistant organism (MDRO) Prevalence During Baseline and End-intervention Sampling Periods

	Routine Care Group Positive Samples % (N)		Decolonization Group Positive Samples % (N)		Risk Ratios* (95% CI)	P-value
	Baseline Period	Intervention Period	Baseline Period	Intervention Period		
# Residents	700	650	700	550		
Any MDRO	48.3% (338)	47.2% (307)	48.9% (342)	32.0% (176)	0.70 (0.58-0.84)	<0.001
Any MRSA	37.6% (263)	36.9% (240)	36.4% (255)	25.1% (138)	0.73 (0.59-0.92)	0.007
Nares	29.1% (203)	27.1% (176)	29.9% (209)	22.0% (121)	0.81 (0.62-1.05)	0.11
Skin	26.1% (183)	25.4% (165)	22.6% (158)	11.6% (64)	0.58 (0.42-0.79)	0.001
VRE	5.9% (41)	5.1% (33)	8.3% (58)	2.2% (12)	0.29 (0.14-0.62)	0.001
ESBL	15.9% (111)	17.9% (116)	16.7% (117)	9.2% (51)	0.50 (0.34-0.75)	0.001
CRE	1.4% (10)	0.6% (4)	0.4% (3)	0.4% (3)	3.53 (0.44-28.52)	0.24

Table 3 Legend

Abbreviations:

MDRO = multidrug-resistant organism

MRSA = methicillin-resistant *Staphylococcus aureus*

VRE = vancomycin-resistant enterococci

ESBL = extended-spectrum beta-lactamase producer

CRE = carbapenem-resistant Enterobacterales

Data are mean prevalence (N) across facilities.

*Models reflect a difference in differences between changes seen in the intervention group compared to the control group. Models are clustered at the facility level while controlling for study phase (intervention vs baseline), trial group (decolonization vs routine care), and the interaction term for phase*group. Unadjusted models were highly similar to adjusted models accounting for bedbound status, diabetes, and nursing home number of licensed beds; unadjusted models are reported here.