

Effectiveness of oral care for the prevention of non-ventilator hospital-acquired pneumonia (HAPPEN): a multicentre, stepped-wedge, cluster-randomised trial in Australia

Nicole M White, Philip L Russo, Georgia Matterson, Katrina Browne, Allen C Cheng, Martin Kiernan, Peta E Tehan, Andrew J Stewardson, Nicholas Graves, Auxillia Madhuvu, Helen Rawson, Jenny Sim, Sonja Dawson, Julee McDonagh, Caroline Marshall, Elizabeth Orr, Douglas Johnson, Irani Thevarajan, Pakhi Sharma, Rhonda Wilson, Brett G Mitchell



Summary

Background Non-ventilator hospital-acquired pneumonia (NV-HAP) is among the most prevalent health-care-associated infections, yet remains under-reported, understudied, and infrequently targeted by infection prevention strategies. Oral care is considered a key preventive measure; however, there are few high-quality randomised controlled trials conducted in hospital settings. The aim of this study is to evaluate whether an enhanced oral care intervention reduces the incidence of NV-HAP.

Methods The Hospital Acquired Pneumonia Prevention (HAPPEN) trial was an open-cohort, stepped-wedge, cluster-randomised trial conducted across three Australian hospitals. Large public or private hospitals were eligible. Simple randomisation was used to allocate nine wards (clusters) across three treatment sequences. All patients aged 18 years or older admitted to a trial cluster were eligible, with outcomes assessed for patients admitted for at least 48 h. The intervention comprised three components: enhanced delivery of oral care and provision of products, patient and staff education, and audit and feedback, delivered by dedicated research nurses. The control was usual practice—ie, oral care performed by health-care workers as per hospital policy. Primary and secondary outcomes were analysed in the intention-to-treat population. The primary outcome was NV-HAP incidence, defined according to European Centre for Disease Prevention and Control criteria. Secondary outcomes included hospital-acquired lower and upper respiratory tract infections and oral cavity infections. Outcomes were defined using established definitions and determined following a review of medical records. This study was single blinded, with data collectors masked to allocated treatment sequences. The completed trial is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12624000187549).

Findings The trial was conducted from June 3, 2024, to Aug 22, 2025. A total of 12 446 admitted patients were eligible to receive the intervention, 3336 of whom were excluded because they were admitted to a trial cluster for less than 48 h. A total of 8870 patients were analysed, with 4523 exposed to the control condition and 4347 exposed to the intervention condition. NV-HAP was confirmed in 78 (0.9%) of 8870 patients: 46 (1.0%) of 4523 under the control condition and 32 (0.7%) of 4347 under the intervention condition. Intervention exposure was associated with a cumulative hazard ratio of 0.40 (95% CI 0.19–0.82), representing a decrease from 1.00 to 0.41 infections per 100 admission-days at risk. Intervention exposure resulted in a cumulative hazard ratio of 1.64 (95% CI 0.61–4.39) for lower or upper respiratory tract infection, and 1.08 (0.66–1.77) for oral cavity infection. The proportion of participants who completed the oral care protocol increased from 474 (15.9%) of 2988 to 1727 (61.9%) of 2791 following intervention exposure.

Interpretation This multicentre randomised controlled trial demonstrates that improving oral care reduces NV-HAP incidence among hospitalised patients, compared with usual care. Our findings provide novel and clinically important evidence to inform future prevention guidelines and hospital infection control policy.

Funding Medical Research Future Fund.

Copyright © 2026 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license.

Introduction

Non-ventilator hospital-acquired pneumonia (NV-HAP) is a common health-care-associated infection; however, beyond point-prevalence studies, it is infrequently monitored or reported, and prevention strategies are

rarely implemented at either hospital or national levels.¹ Prevention is important due to the substantial clinical and economic burden of NV-HAP.² Patients who develop NV-HAP stay in hospital between 10 and 48 days longer,² and are estimated to be eight times more likely to die

Lancet Infect Dis 2026

Published Online
June 8, 2026
[https://doi.org/10.1016/S1473-3099\(26\)00235-5](https://doi.org/10.1016/S1473-3099(26)00235-5)

See Online/Comment
[https://doi.org/10.1016/S1473-3099\(26\)00282-3](https://doi.org/10.1016/S1473-3099(26)00282-3)

Australian Centre for Health Services Innovation and Centre for Healthcare Transformation, Faculty of Health, Queensland University of Technology, Brisbane, QLD, Australia (N M White PhD, P Sharma PhD); Nursing and Midwifery, Monash University, Melbourne, VIC, Australia (Prof P L Russo PhD, A Madhuvu PhD, Prof H Rawson PhD, Prof B G Mitchell PhD); Cabrini Health, Malvern, VIC, Australia (Prof P L Russo PhD); School of Nursing and Health, Avondale University, Cooranbong, NSW, Australia (Prof P L Russo PhD, G Matterson Biotech(Hons), M Kiernan M ClinRes, S Dawson PhD, Prof B G Mitchell PhD); School of Education and Science, Avondale University, Cooranbong, NSW, Australia (K Browne PhD); Infectious Diseases, Monash Health and School of Clinical Sciences, Monash University, Melbourne, VIC, Australia (Prof A C Cheng MBBS); Richard Wells Research Centre, University of West London, Brentford, UK (M Kiernan M ClinRes); Department of Surgery, School of Clinical Sciences, Monash University, Melbourne, VIC, Australia (P E Tehan PhD); Department of Infectious Diseases, The Alfred Hospital and Monash University School of Translational Medicine, Melbourne, VIC, Australia (A J Stewardson MBBS); Centre

to Impact AMR, Monash University, Clayton, VIC, Australia (Prof P L Russo PhD, A J Stewardson MBBS); Duke-NUS Medical School, Singapore (Prof N Graves PhD); School of Nursing, Midwifery & Paramedicine, Australian Catholic University, North Sydney, NSW, Australia (Prof J Sim PhD); School of Nursing, Faculty of Science, Medicine and Health, University of Wollongong, Wollongong, NSW, Australia (J McDonagh PhD); Centre for Chronic & Complex Care Research (CCCCR), Blacktown Hospital, Western Sydney Local Health District, Blacktown, NSW, Australia (J McDonagh PhD); Infection Prevention and Surveillance Service, The Royal Melbourne Hospital, Parkville, VIC, Australia (C Marshall MBBS); The Department of Infectious Diseases, University of Melbourne at the Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia (C Marshall MBBS, I Thevarajan MBBS); Infection Prevention and Surveillance Service, The Royal Melbourne Hospital, Parkville, VIC, Australia (E Orr MPH); Department of General Medicine and Infectious Diseases, Royal Melbourne Hospital, Parkville, VIC, Australia (D Johnson MBBS); Department of Medicine, Royal Melbourne Hospital, Melbourne University, Parkville, VIC, Australia (D Johnson MBBS); Victorian Infectious Diseases Service, The Royal Melbourne Hospital, Parkville, VIC, Australia (I Thevarajan MBBS, D Johnson MBBS, C Marshall MBBS); Department of Nursing, School of Health and Biomedical Science, RMIT University, Melbourne, VIC, Australia (Prof R Wilson PhD); Central Coast Local Health District, Gosford Hospital, Gosford, NSW, Australia (Prof B G Mitchell PhD); Hunter Medical Research Institute, John Hunter Hospital, Newcastle, NSW, Australia (Prof B G Mitchell PhD)

Correspondence to: Prof Brett G Mitchell, School of Nursing and Health, Avondale University, Cooranbong, NSW 2265, Australia
brett.mitchell@avondale.edu.au

Research in context

Evidence before this study

Strategies to prevent non-ventilator hospital-acquired pneumonia (NV-HAP) include improving oral care, dysphagia screening and management, and patient mobilisation. A systematic review and meta-analysis conducted by Ehrenzeller and Klompas sought to determine whether daily toothbrushing is associated with lower rates of HAP. Keywords related to hospital, pneumonia, and oral care were used. 15 randomised controlled trials (RCTs) were included. Toothbrushing was associated with significantly lower risk for HAP (risk ratio 0.67, 95% CI 0.56–0.81). This review included ventilated and non-ventilated patients. We searched MEDLINE and Scopus for studies published between Jan 1, 1998, and March 31, 2026, using the terms “pneumonia”, “nosocomial”, “healthcare-associated”, and “prevention”, with the aim of identifying strategies specifically targeting the reduction of NV-HAP. The search was restricted to RCTs published in English. Eight RCTs met the inclusion criteria, of which five evaluated interventions focused exclusively on oral care for the prevention of NV-HAP. Among these, one trial was conducted in a single-centre hospital setting. Three of the five oral care-focused RCTs reported significant reductions in NV-HAP incidence associated with enhanced oral hygiene practices. An effectiveness–implementation study evaluating a bundle of NV-HAP interventions, including oral care, has been conducted by Wolfensberger and colleagues. This was a single-centre,

during their admission than comparable patients without NV-HAP.³ Despite this considerable burden, NV-HAP remains under-reported, understudied, and receives limited focus from policy makers and researchers.^{4,5} Furthermore, the evidence base informing prevention strategies is generally of low quality.^{4,6}

Current approaches to NV-HAP prevention typically include the provision of oral care, dysphagia screening and management, and patient mobilisation.^{4,6,7} A single-centre, non-randomised, hybrid effectiveness–implementation study conducted in Switzerland demonstrated that a bundled intervention incorporating these elements was associated with a reduction in NV-HAP incidence⁷ and has been the most robust hospital-based NV-HAP prevention study to date. Oral care is considered a key preventive measure, as reducing oral bacterial load can decrease the risk of aspiration-related pneumonia.⁸ In both ventilated and non-ventilated patients, evidence from a meta-analysis suggests that daily toothbrushing might be associated with significantly lower rates of HAP.⁹ However, oral care practices are often inconsistently or inadequately performed by both patients and nursing staff, with many implementation barriers.^{10–12} Existing evidence-based guidelines recommend daily toothbrushing for hospitalised patients, while acknowledging that the supporting evidence is largely derived from before-and-after studies, and that high-quality trials in hospital settings are

non-randomised study. There remains a paucity of RCTs addressing NV-HAP prevention in hospital settings. Evidence gaps for NV-HAP prevention have been underscored in previous literature, including a review by Rodrigues and colleagues and an evidence-based guideline by Klompas and colleagues, developed on behalf of leading infectious diseases and infection prevention organisations.

Added value of this study

This multicentre, cluster-randomised trial evaluated the effectiveness of improving oral care on the incidence of NV-HAP in hospitalised patients. The provision of oral care in hospitals is often deprioritised in busy environments. Our study builds on work by Wolfensberger and colleagues through its multicentre, randomised nature and focus on oral care for NV-HAP prevention. Our study provides evidence that improving oral care can reduce the risk of NV-HAP. We show that a strategy comprising provision of oral care products, patient and staff education, and audit and feedback is effective in increasing oral care frequency.

Implications of all the available evidence

A relatively simple intervention for increasing oral care led to important reductions in NV-HAP. The results contribute to a stronger evidence base for future NV-HAP prevention guidelines and initiatives, and they offer insights to inform clinical practice and local policy development.

lacking.^{6,13} The Hospital Acquired Pneumonia Prevention (HAPPEN) study is a multiphase research programme. Phase 1 refined the intervention by identifying implementation barriers and enablers through surveys, focus groups, and collaboration with consumers, health services, and professional organisations. Phase 2 was a randomised controlled trial. Phase 3 will optimise the resources developed and evaluated in the trial and make them open source (appendix pp 6–7). This paper reports the clinical effectiveness outcomes of phase 2 of the HAPPEN study, which aimed to evaluate whether an enhanced oral care intervention reduces the incidence of NV-HAP in hospital settings.

Methods

Study design and participants

The HAPPEN trial was an open-cohort, stepped-wedge, cluster-randomised trial conducted in three Australian hospitals. To be eligible, hospitals needed to be a principal referral, acute public group A, or acute private group A hospital as defined by the Australian Institute of Health and Welfare and have at least 50 000 overnight admissions each year. Inpatient wards within the hospitals, henceforth referred to as clusters, were eligible to participate if they provided care for adult patients in a designated stroke or medical service. Further details on eligibility are provided in the appendix (pp 10–13).

Three clusters were enrolled from each hospital; there were nine clusters in total. Clusters were randomly assigned into one of three treatment sequences. Treatment sequences were defined as four 3-monthly periods, beginning with an initial control period, followed by transitions to the intervention condition every 3 months after trial commencement. Due to the open-cohort design, participants assessed within a given month or period were assumed to include new admissions and continuing admissions.

All patients aged 18 years or older admitted to a cluster during the trial were assessed for eligibility. Eligible patients were continuously recruited and assigned to control or intervention according to their cluster's allocated treatment sequence. Upon transition from control to intervention, all participants received the intervention until discharge from the same trial cluster.

Following trial commencement, an unforeseen delay in required approvals at one trial hospital led to an 11-week delay in starting the control period. Treatment sequences allocated to affected clusters were shifted to accommodate this delay, with no changes to the duration of control and intervention period or the number of periods (figure 1).

The trial was approved by the Hunter New England Human Research Ethics Committee (2023/ETH02447). A waiver of consent was granted, consistent with the Australian National Statement on Ethical Conduct in Human Research. Rationale for a waiver included the overall risk–benefit profile of the study, as this study aimed to enhance existing care by putting in measures to help facilitate this. The research posed negligible additional risks to participants compared with usual care. Site-specific authorisation for the study was granted by each of the participating hospitals (appendix pp 11–13). There was no data safety monitoring board; this was not deemed necessary as the intervention is enhancement of existing care. The study protocol and statistical analysis plan are provided in the appendix. This trial is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12624000187549), and is complete.

Randomisation and masking

Randomisation was undertaken by the trial statistician on May 22, 2024, after all clusters had been recruited to the trial and before the start of the control period. Simple randomisation was used at each hospital to allocate clusters to treatment sequences (1, 2, or 3), using a set seed in R statistical software (version 4.0.0). This randomisation method was chosen for logistical reasons to allow for sequential intervention roll-out at each trial hospital. The trial statistician, principal investigator, and research coordinator were not masked to the treatment sequences and were not involved in data collection. Study team members responsible for collecting outcome data were masked to allocated treatment sequences and, therefore, did not know when a cluster transitioned from

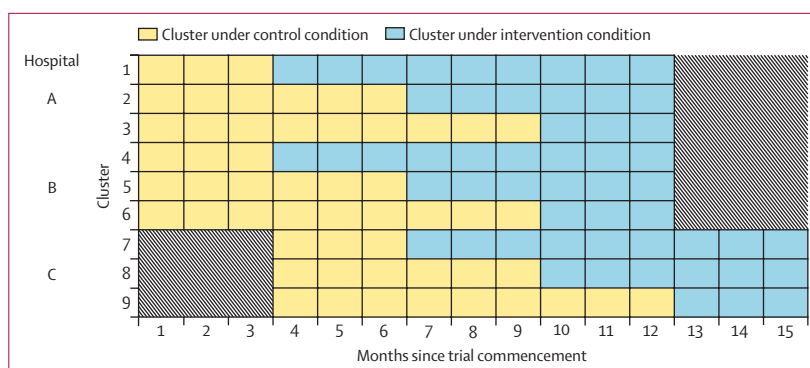


Figure 1: Stepped-wedge trial design for the HAPPEN trial at Hospitals A, B, and C
Clusters (1–9) sequentially cross from control (yellow) to intervention (blue) at regular intervals until full implementation (15 months) is achieved. The trial was delayed in Hospital C for 3 months.

the control period to the intervention period, or how long each cluster had been exposed to the intervention. Those responsible for data collection were research nurses and only reviewed medical records relevant to determining the outcome. Nursing staff working in clusters were informed of their treatment sequence allocation 4 weeks before their intervention start date, to allow for initial education activities. It was not possible to mask participants or nursing staff working in clusters following exposure to the intervention given their involvement in implementation.

See Online for appendix

Procedures

The intervention aimed to improve oral care for participants. To achieve this, the intervention consisted of three components: the provision of oral care products and oral care to participants, education of participants and staff, and audit and feedback. These components were developed in consultation with consumers and partner organisations, and the development was informed by research conducted as part of phase 1 of the HAPPEN study.^{11,12} Further detailed information regarding the intervention is provided in the appendix (pp 13–30). Dedicated research nurses were employed to deliver the intervention at each hospital.

In addition to standard ward staffing, research nurses were employed for 20 h per week, per cluster, focusing on delivering oral care initiatives as part of the trial. Oral care included moisturising lips and cleaning of teeth or dentures and tongue with a suitable toothbrush and toothpaste containing sodium bicarbonate and fluoride. The research nurses engaged with participants as early as possible after their admission to the intervention ward. They provided education on the importance of oral care and how to undertake oral care. Where needed, nurses assisted participants in performing oral care. Each patient was provided with a HAPPEN biodegradable bag containing a toothbrush and toothpaste, as well as further information via a dedicated trial website. No antiseptic mouthwash was provided. The provision of the

bag facilitated a conversation about the importance of oral care. The provided toothbrush had printed wording on the exterior to prompt participants to perform oral care. The wording was developed by the consumer advisory group. See the appendix (pp 17–20) for additional details on the delivery of oral care and products.

Educational materials supporting the intervention were developed by the research team and informed by consumers and previous research.^{11,12} The trial website, which contained information about performing oral care, was made available to participants and clinicians on participating intervention wards (appendix pp 22–27). During the intervention, research nurses visited participating wards approximately three times per week to provide training to nursing staff. Nursing staff worked on dedicated wards, so contamination is unlikely.

During the control and intervention periods, a data collector (separate from the research nurses) assessed the electronic medical records of every participant from their last full day of admission, to audit whether oral care was documented and how frequently. During the intervention phase, results from the oral care audit were reported to HAPPEN research nurses via a monthly email.

During the control phase, oral care was performed by participants themselves or provided by health-care workers as per hospital policy. No change in usual nursing routines occurred. No additional education, product, or information was provided. The research nurses provided no support. Remote auditing of medical records occurred to locate and record oral care documentation during the control, but no feedback was provided to staff. Any adverse events from the trial intervention were reported using existing hospital reporting processes, which included notification to the research team.

Data were collected for all participants aged 18 years or older during the study period. A designated, experienced data collector at each site was responsible for collecting data throughout the trial to maintain consistency. An inter-rater reliability assessment was undertaken before trial commencement, as well as validation processes during data collection (appendix pp 32–33). Following a review of medical, pathology, and microbiology records, infection outcomes were determined using a developed electronic algorithm (REDCap, hosted by Hunter Medical Research Institute) applying health-care-associated infection definitions piloted and previously used in other studies.^{14,15} During the study, NV-HAP, lower respiratory tract infection (LRTI), upper respiratory tract infection (URTI), and oral cavity infection (eye, ear, nose, throat, or mouth [EENT]-Oral) data were collected. Microbiology data were available and thus collected only for a small number of patients.

Outcomes

The primary outcome was NV-HAP, as defined by the European Centre for Disease Prevention and Control.¹⁶

Secondary outcomes were hospital-acquired LRTI and URTI (excluding COVID-19) and EENT-Oral. The appendix contains details on the criteria used for each infection type (appendix pp 33–37). Tertiary outcomes included combined infections (one or more of NV-HAP, LRTI or URTI, and EENT-Oral) and monitoring of oral care. For each participant, the frequency of oral care was documented. Adverse events were recorded by hospitals as per their usual reporting procedures.

Outcomes for each eligible participant were assessed after discharge from a trial cluster. Confirmed infections in each cluster were attributed to trial conditions and time steps using predefined rules based on the date(s) of infection onset and the trial dates (appendix pp 37–38). The attribution of an infection to the cluster was confirmed if the infection resulted directly or indirectly from hospital admission, with symptoms occurring more than 48 h after admission to the cluster.¹⁷

Our study protocol included other secondary outcomes not reported in this paper: description of patients' experience with NV-HAP and clinicians' experience of implementing the intervention, evaluation of the cost-effectiveness of adopting the intervention, and estimation of excess attributable length of stay in hospital associated with NV-HAP. Given the detail required to adequately report these secondary outcomes, they will be reported in future publications.

Statistical analysis

Primary, secondary, and tertiary outcomes were analysed using eligible participant data from all trial clusters and observed intervention timings, using an intention-to-treat approach. Sensitivity analyses assessed the contribution of single clusters and trial hospitals to estimated intervention effectiveness. We have published the statistical analysis plan.¹⁷ Analyses were undertaken in R version 4.4.1.

Sample size calculations based on the trial design were informed by published estimates of NV-HAP incidence and clinically relevant effect sizes for intervention effectiveness.^{17,18} Assumptions about within-cluster and between-cluster variation were informed by previous cluster-randomised trials in infection control and expected monthly variation in recruitment. Under the planned trial design (figure 1), 125 participants per cluster-month provided an expected 80% power to detect a decrease in the primary outcome from 0.07 (7%) to 0.049 (4.9%). Calculations assumed an exchangeable correlation structure, an intra-cluster correlation coefficient of 0.02,¹⁹ a coefficient of variation in cluster sizes of 0.5, and a two-sided 0.05 alpha level.²⁰

Generalised linear mixed models estimated the within-cluster change in outcomes associated with intervention exposure as a binary fixed effect, after accounting for clustering and time since trial commencement. A random effect per cluster accounted for between-cluster variation in outcomes. A fixed effect for each month since trial commencement was specified to account for secular

trends. Admission-days at risk from cluster admission until infection or discharge if uninfected were included in each model as an offset term, with its coefficient fixed at 1. Planned analyses aimed to estimate intervention effectiveness at the patient level and cluster level. Patient-level outcomes were binary and analysed as a Bernoulli distribution with a complementary log-log link function to model cumulative infection incidence during cluster admission for primary and secondary outcomes, and a logit link to estimate the odds of acquired one or more infections during cluster admission for the tertiary infection outcome. Cluster-level analysis modelled the expected number of infections per 100 admission-days at risk as a Poisson distribution with a log link function.

Model results for primary and secondary outcomes were reported as cumulative hazard ratios for patient-level analysis and incidence rate ratios for cluster-level analysis, with 95% CIs. Tertiary infection outcome results were reported as odds ratios and incidence rate ratios. We did not conduct post-hoc analysis. There was a delay in Hospital C commencing the trial, which was a deviation from our protocol.

Sensitivity analysis updated models to include a random intervention effect per trial hospital. Cluster-level sensitivity analyses further explored the influence of time at risk by redefining the outcome as the total number of infections per 100 admissions. A leave-one-cluster-out analysis examined the potential influence of data from individual clusters on effectiveness estimates.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The trial was conducted from June 3, 2024, to May 30, 2025 in Hospitals A and B, and from Aug 26, 2024, to Aug 22, 2025 in Hospital C. Hospitals A and B are located in the state of New South Wales, Hospital C in the state of Victoria, Australia. The first cluster commenced the intervention on Sept 2, 2024 (appendix p 8). A total of 12446 admitted patients were eligible to receive the intervention in the nine clusters. At outcome assessment, 3336 patients were excluded because they were admitted to a trial cluster for less than 48 h, and 240 patients were excluded due to a lack of medical record availability or insufficient data needed to define time at risk. The final sample analysed included 8870 admissions, with 4523 participants exposed to the control condition (ie, admitted to a cluster while it was under the control condition) and 4347 exposed to the intervention condition (ie, admitted to a cluster while it was under the intervention condition). 54 infections were excluded because they were acquired before or within 48 h of cluster admission, or because they met the criteria for ventilator-associated pneumonia (figure 2).

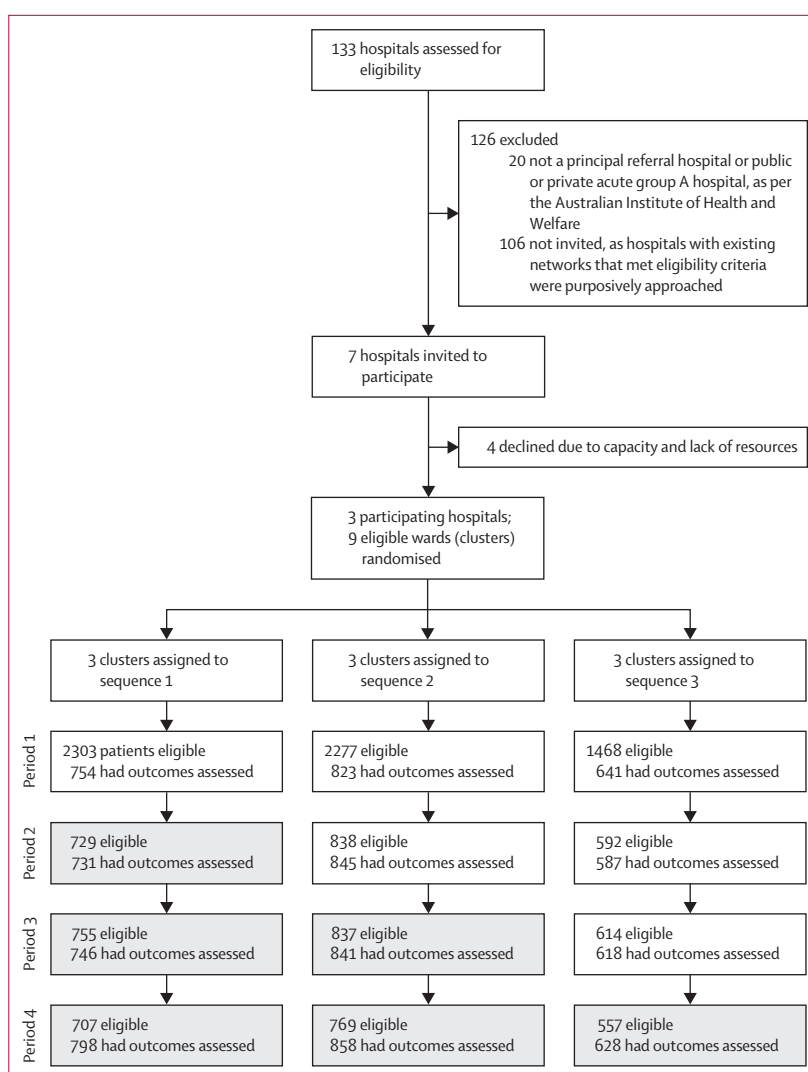


Figure 2: Trial profile

Figure shows screening and enrolment of hospitals ($n=3$), allocation of nine clusters across three sequences, and numbers of eligible patients and outcomes assessed in each stepped-wedge period ($n=4$). Grey boxes define periods when the intervention was implemented. Periods 1–4 are defined from the start of the control condition in each hospital (A, B, C). Hospitals A and B commenced on June 3, 2024. Hospital C commenced on Aug 26, 2024. “Eligible” refers to patients eligible to receive the intervention. “Outcomes assessed” refers to patients who stayed on the ward for >48 h with a medical record available and sufficient data to define time at risk at the time of outcome assessment.

Participants spent a median of 7 days in a trial cluster (table 1). The average age of trial participants was 72 years (SD 17), and 4587 (51.7%) of 8870 were female. Baseline characteristics by trial hospital and treatment sequence allocation were similar (appendix pp 38–39). In terms of potential confounders, risk factors for NV-HAP were relatively balanced between the control and intervention groups, except for antimicrobial use. More than half of the participants received antimicrobial therapy (excluding surgical prophylaxis) during their admission, with higher percentages observed under the control (3070 [67.9%] of 4523) than the intervention

	All admissions (n=8870)	Control (n=4523)	Intervention (n=4347)	No NV-HAP (n=8792)	NV-HAP (n=78)
Age, years					
Mean (SD)	72.5 (17.0)	72.4 (17.4)	72.7 (16.6)	72.5 (17.1)	74.7 (13.2)
Median (IQR)	76 (6–85)	77 (63–85)	76 (64–85)	76 (64–85)	78 (66–85)
Sex					
Female	4587 (51.7%)	2356 (52.1%)	2231 (51.3%)	4544 (51.7%)	43 (55.1%)
Male	4283 (48.3%)	2167 (47.9%)	2116 (48.7%)	4248 (48.3%)	35 (44.9%)
Cluster length of stay, days					
Mean (SD)	9.5 (12.5)	10.4 (15.1)	8.6 (8.9)	9.4 (12.4)	24.5 (15.7)
Median (IQR)	6 (4–11)	6 (4–12)	6 (4–10)	6 (4–11)	20 (13–33)
Antimicrobial therapy excluding surgical prophylaxis	5647 (63.7%)	3070 (67.9%)	2577 (59.3%)	5570 (63.4%)	77 (98.7%)
Documented fever	1379 (15.5%)	780 (17.2%)	599 (13.8%)	1337 (15.2%)	42 (53.8%)
Proton pump inhibitor	3198/5780 (55.3%)	1761/3137 (56.1%)	1437/2643 (54.4%)	3138/5702 (55%)	60/78 (76.9%)
History of dementia	714/5780 (12.4%)	429/3317 (13.7%)	285/2643 (10.8%)	701/5702 (12.3%)	13/78 (16.7%)
History of dysphagia	1294/5780 (22.4%)	709/3317 (22.6%)	585/2643 (22.1%)	1263/5702 (22.2%)	31/78 (39.7%)
History of stroke	863/5780 (14.9%)	430/3317 (13.7%)	433/2643 (16.4%)	846/5702 (14.8%)	17/78 (21.8%)
Outcome of admission					
Discharged	6032 (68.0%)	3143 (69.5%)	2889 (66.4%)	5986 (68.1%)	46 (59.0%)
Died	446 (5.0%)	248 (5.5%)	198 (4.6%)	432 (4.9%)	14 (17.9%)
Transferred	2392 (27.0%)	1132 (25.0%)	1260 (29.0%)	2374 (27.0%)	18 (23.1%)

Data are n (%) or n/N (%) unless otherwise specified. Patient assignment to control and intervention conditions was defined by trial cluster admission date for describing baseline characteristics. NV-HAP=non-ventilator hospital-acquired pneumonia.

Table 1: Baseline characteristics by trial condition and primary outcome

	Control condition (n=4523)	Intervention condition (n=4347)	Hazard ratio (95% CI)*	Incidence rate ratio (95% CI)†
Primary outcome: non-ventilator hospital-acquired pneumonia	46 (1.0%)	32 (0.7%)	0.40 (0.19–0.82)	0.41 (0.20–0.84)
Secondary outcome: lower or upper respiratory tract infections	18 (0.4%)	21 (0.5%)	1.64 (0.61–4.39)	1.63 (0.64–4.19)
Secondary outcome: EENT-Oral	127 (2.8%)	101 (2.3%)	1.08 (0.66–1.77)	1.07 (0.66–1.76)

Data are n (%) unless otherwise specified. Control and intervention condition estimates represent observed numbers and percentages unadjusted for clustering, time step, and admission-days at risk. EENT=eye, ear, nose, throat, or mouth (EENT-Oral=oral cavity infection as defined by European Centre for Disease Prevention and Control¹⁶).

*Patient-level analysis for outcome incidence adjusted for admission-days at risk. †Incidence defined as total infections per 100 admission-days at risk.

Table 2: Primary and secondary outcomes

condition (2577 [59.3%] of 4347). There were 446 deaths reported by clusters during the trial period not related to the intervention (control, 248 [5.5%] of 4523; intervention, 198 [4.6%] of 4347). A total of 327 (3.7%) of 8870 eligible participants acquired one or more target infections during trial admission. Participants who acquired one or more infections were admitted to trial clusters for a median of 17 days (IQR 10–28), with higher reported rates of fever and antimicrobial therapy (appendix pp 39–40). Missing data reflected the availability of reported medical histories, for a subset of patients assessed (table 1; control, 1206 [26.7%] of 4523 missing; intervention, 1704 [39.2%] of 4347 missing).

NV-HAP was confirmed in 78 (0.9%) of the 8870 participants: 46 (1.0%) of 4523 under the control condition and 32 (0.7%) of 4347 under the intervention condition (table 2). Cumulative incidence functions for time to NV-HAP from cluster admission were similar between control and intervention conditions; observed cumulative incidences at 30 days were 4.1% (95% CI 2.56–5.75) and 1.7% (0.79–2.61) for control and intervention conditions, respectively (appendix p 47). After accounting for time at risk and background time trends, exposure to the intervention was associated with a cumulative hazard ratio of 0.40 (95% CI 0.19–0.82) for NV-HAP, corresponding to an incidence rate ratio of 0.41 (95% CI 0.20–0.84) or a reduction from 1.00 (95% CI 0.55–1.45) to 0.41 (0.21–0.60) infections per 100 admission-days at risk (table 2).

For LRTIs and URTIs, exposure to the intervention resulted in a cumulative hazard ratio of 1.64 (95% CI 0.61–4.4) at the patient level and an incidence rate ratio of 1.63 (95% CI 0.64–4.19) for infections per 100 admission-days at risk at the cluster level (table 2). Similarly, the estimated cumulative hazard ratio for EENT-Oral infections associated with the intervention was 1.08 (0.66–1.77). The corresponding incidence rate ratio per 100 admission-days at risk was 1.07 (0.66–1.76; table 2; appendix pp 50–54).

In tertiary outcome analysis, the estimated odds ratio for acquiring one or more infections during admission was 0.92 (95% CI 0.61–1.37), and the corresponding

incidence rate ratio was 0·96 (95% CI 0·65–1·42). Oral care on the last day of cluster admission was documented for 5779 participants. The proportion of participants who completed the oral care protocol increased from 473 (15·8%) of 2988 to 1727 (61·9%) of 2791 following exposure to the intervention (appendix p 56).

Sensitivity analysis is presented in the appendix (pp 51–56). Estimated effectiveness remained consistent for the primary outcome during sensitivity analysis. In patients with NV-HAP, pathogens were identified in nine cases, the most common being mixed growth ($n=4$). Further data are provided in the appendix (pp 57–58). Microbiological data were limited to a small number of patients, so results should be interpreted with caution. No policy changes, such as changes to oral care practice or other educational initiatives, were commenced during the trial. There were no reported outbreaks. No adverse events were reported.

Discussion

This multicentre, cluster-randomised trial demonstrated that ward-based implementation of a strategy to improve oral care was effective in reducing the incidence of NV-HAP among hospitalised patients compared with usual care, which involved infrequent oral care during the control period, with improvements identified during the intervention. There were no reductions for LRTIs or URTIs or EENT-Oral infections associated with the intervention. Our study reinforces the benefits of enhanced oral care in hospital settings. The benefit of oral care has previously been demonstrated only in randomised trials conducted in long-term care settings,⁴ and one single-centre hospital-based trial.²¹ A high-quality, non-randomised hybrid effectiveness–implementation study, which used multiple strategies to reduce NV-HAP, including oral care, also identified reductions in NV-HAP.⁷

We identified infrequent oral care, as documented, during the control phase, a finding consistent with observations reported in other studies.^{7,22} Such low frequency suggests that oral care is not prioritised or recorded, or that barriers to implementation exist.²³ These issues were also highlighted in our research informing this trial.^{11,12} To address these challenges, we collaborated with a range of professional partners, professional associations, and consumer representatives to develop strategies aimed at improving oral care frequency. These strategies included direct support for intervention delivery, onsite education delivered to clinical staff, patient engagement activities, timely on-demand resources, and the provision of essential oral care products such as toothbrushes and toothpaste. Oral care frequency was assessed through audits of medical records. We did not collect data on, and were unable to estimate, how frequently assistance was provided to participants by our study nurses, as opposed to participants independently undertaking this themselves. Although direct observation of oral care would have

provided more precise data, it would also have introduced a substantial risk of observer bias, a potential Hawthorn effect.

Our study reinforces the importance of providing oral care to hospitalised patients. The results contribute to a stronger evidence base for future NV-HAP prevention guidelines and initiatives, and they offer insights to inform clinical practice and local policy development. The study population is broadly representative of patients at elevated risk of NV-HAP, as the selected wards primarily comprise general medicine units, including stroke units. In resource-constrained settings, our results show that oral care should remain a clinical priority. Although our study focused on the impact of improved oral care on NV-HAP incidence, additional benefits likely include the relief of dry mouth, enhanced patient comfort, and earlier identification of complications such as oral thrush.^{24,25} Our results are consistent with the estimated effectiveness of oral care conducted in other randomised trials in long-term care settings.^{26,27} Similarly, a cluster-randomised trial involving four units in one hospital identified a 56% reduction in the incidence rate per 1000 patient-days associated with an approximate doubling in oral care frequency.²¹

As antimicrobial use was available only at baseline and exposure likely varied over the course of admission, in addition to us not capturing antimicrobial start and end dates, we chose not to explore this post hoc. To ensure transparency and to allow interpretation of risk reduction at both the patient and cluster levels, the research team prespecified two analytic approaches for the primary outcome. This analysis plan was reported before commencing data analysis. We did not find strong evidence of differences in LRTIs or URTIs associated with the intervention. Primary routes of viral transmission, such as inhalation or direct deposition of infectious aerosols, might not be mitigated by oral care; thus, improvements in oral hygiene might not be expected to reduce viral infection risk. This could explain why we found no difference in secondary outcomes such as LRTIs or URTIs and EENT-Oral infections. However, we do not have evidence from our study to support this hypothesis.

Our study was designed as an effectiveness trial rather than an implementation study. Its primary purpose was to generate robust evidence on whether improving oral care reduces NV-HAP. We deliberately invested resources and structured processes to enhance oral care frequency, recognising this as a major challenge in previous research. However, the delivery of the intervention by research nurses might not represent the most feasible or scalable model for routine hospital implementation. Further implementation-focused studies will be required, similar to those conducted by Wolfensberger and colleagues.⁷ Cost-effectiveness is also a critical consideration for implementation, and the economic evaluation of the HAPPEN trial will be reported separately.

Cluster-randomised trials have become increasingly common for evaluating changes to health-care delivery, including the effectiveness of individual-level interventions. For the HAPPEN trial, our stepped-wedge design supported the sequential roll-out of the intervention within each hospital, to make the most of available resources and promote fidelity. Beyond supporting intervention delivery, cluster-randomised trials can reduce the risk of contamination compared with individual randomisation. This benefit was an important consideration as HAPPEN trial participants could not be masked to receiving the intervention, yet it came at the expense of a larger target sample size compared with individual randomisation. Due to the time-dependent nature of our trial design, a potential source of contamination was participant admissions across both control and intervention conditions, which might complicate outcome assessment. We carefully considered how patient movement between clusters is accounted for, to mitigate contamination and subsequent risk of bias in estimated intervention effectiveness. We proactively managed this possibility by predefining rules for attributing confirmed infections to control or intervention conditions based on the standard 48-h period commonly used in infection control surveillance.²⁸ Secular trends in outcomes unrelated to the intervention were also explicitly modelled, in line with best practices for stepped-wedge designs.²⁹ It is noted that parameter estimates for secular trends can reflect a combination of factors unrelated to the intervention, including seasonality; however, seasonal effects could not be estimated separately given the 12-month trial duration.

We acknowledge the limitations of our study. Evidence generated by this study was based on a relatively small number of clusters and short exposure times. Reported oral care during the control condition should also be considered when contextualising trial findings. Larger-scale trials at the hospital level would provide further evidence on adherence with oral care over the full course of patient admission and use methods other than documentation. We did not collect data on vaccination status or antimicrobial duration. Although baseline differences in antimicrobial use were observed, we did not plan to adjust for this in our prespecified analysis plan. Nursing staff worked on dedicated wards, so while contamination is unlikely, it is possible. We fell short of our sample size estimate. The trial design precluded ongoing enrolment to achieve the target number of individual participants, but we were able to get close to achieving the prespecified 125 observations per cluster-month (ie, 12 446 vs 13 500). Our sample size calculations were based on the incidence of all admissions, using data available at the planning stage. Although our sample size was based on a dichotomous outcome (NV-HAP yes or no), analysis accounted for time at risk and considered count outcomes, which are expected to increase power. A post-hoc sample size estimate was not considered in

line with recommended practice. Microbiological confirmation was obtained for a small number of patients and we did not collect or report ethnicity data.

In conclusion, we report a large-scale study that demonstrates that improving oral care can reduce the risk of NV-HAP, compared with the control. Our study reinforces the importance of providing oral care to hospitalised patients. Findings contribute to a stronger evidence base for future NV-HAP prevention guidelines and practice. In future work, we will update the resources used in our study and make these available open source. Cost-effectiveness evaluations and qualitative work exploring the patients' and clinicians' experience of the trial are planned.

Contributors

BGM, PLR, ACC, MK, AJS, and NMW developed the concept. BGM was the chief investigator. BGM acquired funding for the study. Methodology was designed by BGM, PLR, AJS, ACC, and NMW. KB was the study coordinator responsible for project administration and implementation. BGM, PLR, and KB supervised the study. Study visualisation was performed by NMW. Software was managed by PET, NMW, and KB. Investigation was performed by GM, KB, and BGM. Data validation was performed by KB and GM. BGM and NMW curated the data. BGM and NMW had access to the raw data. Formal analysis was performed by NMW. Data verification was performed by NMW and BGM. BGM, NMW, and GM wrote the first draft of the manuscript. ACC, MK, PET, AJS, NG, AM, HR, JS, SD, JM, CM, EO, DJ, IT, PS, KB, and RW revised the draft critically for important intellectual content. All authors approved the final version of the Article. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

BGM declares grants from the Medical Research Future Fund and the National Health and Medical Research Council paid to his institution; honoraria for his role as Editor-in-Chief of *Infection, Disease and Health* from the Australasian College for Infection Prevention and Control; royalties from a textbook from Elsevier made to him; and payment for expert testimony from Herbert Smith Freehills Kramer paid to his institution and him. PET declares consulting fees from Convatec Australia Advisory Board paid to her; and annual honoraria as the Editor-in-Chief of *Wound Practice and Research* from Wounds Australia paid to her. PLR declares consulting fees from Arnold Block Leibler lawyers paid to him, Minter Ellinson lawyers paid to him, and Johnson & Johnson paid to his institution; expert testimony from Minter Ellinson lawyers paid to his institution; royalties from a textbook from Elsevier paid to him; and being a recent Board Member of the Australasian College for Infection Prevention and Control, with this role having ended in 2024. All other authors declare no competing interests.

Data sharing

Participant data reported in this Article are subject to ethics and privacy restrictions. The conditions of ethics approval do not allow us to distribute or make available these data directly to other parties. Applications for data access should be made by contacting the chief investigator and corresponding author BGM, Avondale University. However, the statistical analysis plan and associated resources are freely available online for researchers to access (<http://www.happenstudy.com>). We have posted the coding for our analysis on GitHub (<https://github.com/nicolewhite/HAPPEN>).

Acknowledgments

This project was funded by a Medical Research Future Fund grant, awarded to BGM, administered by Avondale University (MRF2022645). We acknowledge Hunter Research Medical Institute, Newcastle, NSW, Australia, for their support. We would like to thank the 12 research nurses across the sites for their hard work and dedication to this study. Similarly, we thank the consumers who provided valuable input into this study, as well as our partner organisations: Australasian College for

Infection Prevention and Control, Cabrini Health, Central Coast Local Health District, Mid-North Coast Local Health District, Clinical Excellence Commission (New South Wales), Australian College of Nursing, and Sigma Nursing. We would also like to thank two experts, Alistair McGregor and Jason Kwong, for critically reviewing our paper before submission. Finally, we sincerely thank the hospital volunteers (Margaret Harland, Lorraine Bullivant, and Sue-Ann Walter) who helped pack the HAPPEN bags for patients.

References

- Munro SC, Baker D, Giuliano KK, et al. Nonventilator hospital-acquired pneumonia: a call to action. *Infect Control Hosp Epidemiol* 2021; **42**: 991–96.
- Chalker MA, Browne K, Russo PL, Mitchell BG. Impact of non-ventilator healthcare-associated pneumonia on mortality and additional length of stay in adults admitted to an acute care hospital: a systematic review. *J Hosp Infect* 2026; **170**: 122–38.
- Micek ST, Chew B, Hampton N, Kollef MH. A case-control study assessing the impact of nonventilated hospital-acquired pneumonia on patient outcomes. *Chest* 2016; **150**: 1008–14.
- Mitchell BG, Russo PL, Cheng AC, et al. Strategies to reduce non-ventilator-associated hospital-acquired pneumonia: a systematic review. *Infect Dis Health* 2019; **24**: 229–39.
- Ewan VC, Witham MD, Kiernan M, Simpson AJ. Hospital-acquired pneumonia surveillance—an unmet need. *Lancet Respir Med* 2017; **5**: 771–72.
- Klompas M, Branson R, Cawcutt K, et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 update. *Infect Control Hosp Epidemiol* 2022; **43**: 687–713.
- Wolfensberger A, Clack L, von Felten S, et al. Prevention of non-ventilator-associated hospital-acquired pneumonia in Switzerland: a type 2 hybrid effectiveness-implementation trial. *Lancet Infect Dis* 2023; **23**: 836–46.
- Ewan V, Hellyer T, Newton J, Simpson J. New horizons in hospital acquired pneumonia in older people. *Age Ageing* 2017; **46**: 352–58.
- Ehrenzeller S, Klompas M. Association between daily toothbrushing and hospital-acquired pneumonia: a systematic review and meta-analysis. *JAMA Intern Med* 2024; **184**: 131–42.
- McNally E, Krisciunas GP, Langmore SE, Crimlisk JT, Pisegna JM, Massaro J. Oral care clinical trial to reduce non-intensive care unit, hospital-acquired pneumonia: lessons for future research. *J Healthc Qual* 2019; **41**: 1–9.
- Tehan PE, Browne K, Matterson G, et al. Oral care practices and hospital-acquired pneumonia prevention: a national survey of Australian nurses. *Infect Dis Health* 2024; **29**: 212–17.
- Rawson H, Dawson S, Madhuvu A, et al. Nurses' experiences of providing oral care to hospitalised patients: a qualitative study. *Infect Dis Health* 2025; **30**: 343–52.
- Rodrigues DS, de Souza PTDR, Orsi JSR, Souza PHC, Azevedo-Alanis LR. Oral care to reduce costs and increase clinical effectiveness in preventing nosocomial pneumonia: a systematic review. *J Evid Based Dent Pract* 2023; **23**: 101834.
- Browne K, White NM, Russo PL, et al. Investigating the effect of enhanced cleaning and disinfection of shared medical equipment on health-care-associated infections in Australia (CLEEN): a stepped-wedge, cluster randomised, controlled trial. *Lancet Infect Dis* 2024; **24**: 1347–56.
- Russo PL, Stewardson AJ, Cheng AC, Bucknall T, Mitchell BG. The prevalence of healthcare associated infections among adult inpatients at nineteen large Australian acute-care public hospitals: a point prevalence survey. *Antimicrob Resist Infect Control* 2019; **8**: 114.
- European Centre for Disease Prevention and Control. Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals – protocol version 6.1. Stockholm: European Centre for Disease Prevention and Control, 2022.
- White NM, Cheng A, Stewardson A, Russo PL, Mitchell B. Hospital Acquired Pneumonia Prevention (HAPPEN) study: statistical analysis plan. *medRxiv* 2025; published online Aug 16. <https://doi.org/10.1101/2025.08.14.25333719> (preprint).
- Brogan E, Langdon C, Brookes K, Budgeon C, Blacker D. Respiratory infections in acute stroke: nasogastric tubes and immobility are stronger predictors than dysphagia. *Dysphagia* 2014; **29**: 340–45.
- O'Hara LM, Blanco N, Leekha S, et al, and the CDC Prevention Epicenters Program. Design, implementation, and analysis considerations for cluster-randomized trials in infection control and hospital epidemiology: a systematic review. *Infect Control Hosp Epidemiol* 2019; **40**: 686–92.
- Hemming K, Kasza J, Hooper R, Forbes A, Taljaard M. A tutorial on sample size calculation for multiple-period cluster randomized parallel, cross-over and stepped-wedge trials using the Shiny CRT Calculator. *Int J Epidemiol* 2020; **49**: 979–95.
- Giuliano KK, Penoyer D, Middleton A, Baker D. Original research: oral care as prevention for nonventilator hospital-acquired pneumonia: a four-unit cluster randomized study. *Am J Nurs* 2021; **121**: 24–33.
- Tsui PK, Chau PH, Wong JYH, et al. Oral care knowledge, attitude and practice among nursing staff in acute hospital settings in Hong Kong. *PLoS One* 2023; **18**: e0289953.
- van Noort HHJ, Witteman BJM, den Hertog-Voortman R, Everaars B, Vermeulen H, Huisman-de Waal G. A context analysis on how oral care is delivered in hospitalised patients: a mixed-methods study. *J Clin Nurs* 2020; **29**: 1991–2003.
- Hewson V, Wood C. Mouth care: why it matters—highlighting a neglected care need. *Br J Nurs* 2023; **32**: S4–6.
- Australian Commission on Safety and Quality in Health Care. Oral health care for adult inpatients: recommendations. Sydney: Australian Commission on Safety and Quality in Health Care, 2023.
- Adachi M, Ishihara K, Abe S, Okuda K, Ishikawa T. Effect of professional oral health care on the elderly living in nursing homes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2002; **94**: 191–95.
- Yoneyama T, Yoshida M, Ohru T, et al, and the Oral Care Working Group. Oral care reduces pneumonia in older patients in nursing homes. *J Am Geriatr Soc* 2002; **50**: 430–33.
- Torgerson DJ. Contamination in trials: is cluster randomisation the answer? *BMJ* 2001; **322**: 355–57.
- Hemming K, Haines TP, Chilton PJ, Girling AJ, Lilford RJ. The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting. *BMJ* 2015; **350**: h391.