Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a multicentre intervention study

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Running head: MRSA control strategies in surgical patients

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Key words: meticillin resistant *Staphylococcus aureus*; methicillin resistant *Staphylococcus aureus*; screening; active surveillance cultures; hand hygiene; healthcare-associated infection

ABSTRACT

Objective: To compare the effect of two strategies (enhanced standard control versus meticillin resistant *Staphylococcus aureus* [MRSA] screening) on MRSA rates in surgical wards.

Design: Prospective, controlled, interventional study, with 6-month baseline, 12-month intervention, and 6-month washout phases.

Setting: 33 surgical wards in ten hospitals in nine countries in Europe and Israel.

Participants: All patients admitted to the enrolled wards for more than 24 hours.

Interventions: The two strategies compared were: 1) enhanced standard control emphasising hand hygiene (HH) promotion; and 2) universal MRSA screening with contact precautions and decolonisation (intranasal mupirocin and chlorhexidine bathing) of MRSA carriers. Four hospitals were assigned to each intervention and two hospitals combined both strategies, using targeted screening.

Outcome measures: Monthly rates of MRSA clinical cultures per 100 susceptible patients (primary outcome) and MRSA infections per 100 admissions (secondary outcome). Planned subgroup analysis for clean surgery wards was performed.

Results: There were a total of 126,750 admissions to the study wards. After adjusting for clustering and potential confounders, neither strategy when used alone was associated with changes in MRSA rates. Combining both strategies was associated with a reduction in the rate of MRSA clinical cultures of 12% per month (aIRR 0.88, 95% CI 0.79 to 0.98). In clean surgery wards, strategy 2 (MRSA screening, contact precautions, and decolonisation) was associated with decreasing rates of MRSA clinical cultures (15% monthly decrease, aIRR 0.85, 95% CI 0.74 to 0.97) and MRSA infections (17% monthly decrease, aIRR 0.83, 95% CI 0.69 to 0.99).

Conclusions: In surgical wards, a combination of standard and MRSA-specific infection control approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation was associated with significant reductions in MRSA clinical culture and infection rates.

Trial Registration: clinicaltrials.gov identifier: NCT00685867

ARTICLE SUMMARY

Article focus

- The relative effectiveness of different meticillin resistant *Staphylococcus aureus* (MRSA) control measures is controversial.
- This study directly compared the effect of two strategies (enhanced standard control versus MRSA screening) on MRSA rates in surgical wards.

Key messages

- Neither enhanced standard infection control measures (emphasising hand hygiene promotion) nor MRSA-specific control interventions (MRSA screening coupled with contact precautions and decolonisation therapy) when used alone for 12 months effectively reduced MRSA rates in surgical wards with relatively low MRSA rates.
- A combination of interventions, including targeted screening of high risk patients, did result in reduction in the rate of MRSA isolated from clinical cultures.
- In surgical subspecialties that perform clean surgery, MRSA screening coupled with contact precautions and decolonisation therapy effectively reduced both the rates of MRSA isolated from clinical cultures as well as MRSA infections.

Strengths and limitations of this study

- Unlike many previous studies, this was a large, prospective, multicentre, intervention study. The enrolled wards, from ten hospitals in Europe and Israel, varied in terms of infection control infrastructure and MRSA prevalence, thus the results are likely to be generalisable to other settings.
- Due to the nature of the quality improvement initiatives, investigators were not blinded to the allocated intervention.

INTRODUCTION

Healthcare associated infections affect hundreds of millions of patients worldwide every year and represent an important cause of patient mortality and a major financial burden to health systems.[1] Meticillin resistant *Staphylococcus aureus* (MRSA), now endemic in many healthcare facilities, is a leading cause of healthcare associated infections,[2] and patients in surgical units are at increased risk due to factors such as invasive procedures, antibiotic exposure, and prolonged healthcare contact. A number of countries mandate implementation of control measures, including MRSA screening.[3,4] Not all mandated interventions, however, are supported by robust evidence.

Studies evaluating MRSA control strategies show conflicting results, particularly with regards to the use of active surveillance cultures.[5-7] It is argued that broader infection control approaches, such as improving hand hygiene (HH) practices, may be as successful as MRSA-specific strategies.[8,9] There are limitations, however, to current evidence with few prospective, controlled studies,[10,11] and many studies have assessed multiple interventions simultaneously.[12] Quantifying the relative benefits of individual approaches is important, particularly as some strategies have significant cost implications, and will allow efficient use of limited resources.

Due to the ongoing debate concerning optimal approaches to MRSA control,[13,14] we performed a prospective, interventional, quality improvement study to directly compare the effect of an enhanced standard infection control strategy, emphasising HH adherence, to an MRSA screening, isolation and decolonisation strategy on the incidence rates of MRSA

clinical cultures and infections in surgical patients admitted to healthcare facilities across Europe and Israel.

METHODS

Study design and population

The study was a prospective, controlled, multicentre, interventional cohort study conducted between March 2008 and July 2010. Thirty-three surgical wards of ten hospitals in nine countries (Serbia, France, Spain [two hospitals], Italy, Greece, Scotland, Israel, Germany, and Switzerland) were enrolled. Wards included orthopaedic (8), vascular (6), cardiothoracic/cardiovascular (5), general (4), abdominal (4), urology (3), neurosurgery (2), and plastic surgery (1) subspecialties. Characteristics of the enrolled wards varied (table 1).

The study consisted of baseline (6 to 7 months), intervention (12 months), and washout (6 months) phases. During baseline and washout phases, wards employed their usual infection control practices. During the intervention phase, two strategies were investigated, with hospitals implementing one or both interventions in parallel.

Interventions

The first intervention, the Enhanced Standard Control (ESC) strategy, used the WHO multi-modal HH promotion method consisting of: 1) using alcohol-based handrub at the point of care, 2) training and education of healthcare workers, 3) observation and feedback of HH practices, 4) reminders in the workplace (e.g. posters), and 5) improving the safety climate in the institution with management support for the initiative.[15] Adherence to standard

precautions (e.g. gloves for body fluid contact) and isolation of MRSA patients according to local policies were encouraged.

The second intervention, the Active detection, Contact precautions and Decolonisation (ACD) strategy, consisted of screening patients admitted for more than 24 hours for MRSA, on admission (within 48 hours) then weekly. Patients were excluded from screening if they were undergoing ambulatory surgery or had already been screened within 5 days prior to admission to the surgical ward. The nares, perineum, and wounds (if present) were swabbed. Chromogenic agar screening was used with the addition of polymerase chain reaction (PCR) testing during the latter part of the intervention phase for patients who had risk factors for MRSA (e.g. hospitalisation in the last year) whose chromogenic agar results were unlikely to be available before surgery. MRSA carriers were placed on contact precautions (gown and gloves during patient contact), administered decolonisation therapy with twice daily intranasal mupirocin and daily chlorhexidine washes for five days, and perioperative prophylaxis was modified to reflect MRSA carriage. Chlorhexidine bathing was limited to identified MRSA carriers and not used as a unit-wide intervention. Pre-emptive isolation was not used as part of this strategy.

The hospital was the unit for assignment of interventions due to practical reasons and the nature of the strategies. Four hospitals were assigned to each intervention and two hospitals used a combination of both strategies (MIX arm) due to the introduction of national or local mandatory targeted MRSA screening policies (table 1). These assignments occurred prior to data collection.

Outcomes measures

The primary outcome measure was the monthly nosocomial MRSA isolation rate, defined as the number of MRSA clinical isolates (those from specimens collected other than for screening purposes, counting one isolate per patient per month), per 100 susceptible patients (not previously known to be MRSA colonised or infected). Isolates from specimens collected more than 48 hours after admission or within 30 days after discharge from study wards were considered nosocomial.

Secondary outcomes were the monthly rate of nosocomial MRSA infections per 100 admissions, and adherence to HH guidelines and contact precautions. Infections were defined using CDC criteria.[16] Adherence to HH guidelines was measured as the percentage of opportunities for HH in which staff used alcohol-based handrub and/or washed their hands according to the WHO method.[15] Adherence to contact precautions was measured as the percentage of randomly audited MRSA patients for whom precautions with gown and gloves during patient contact had been implemented.

Microbiological methods

Standardised laboratory manuals were provided to centres. Samples were processed in local laboratories using standard culture-based identification of MRSA from clinical specimens. In ACD hospitals, nasal and perineal swabs were pooled in the laboratory then plated directly onto chromogenic medium (BBL CHROMagar MRSA II, BD Diagnostics, Belgium) and also incubated overnight in an enrichment medium to increase test sensitivity.[17] Positive results could be reported within 24 to 48 hours.[18] PCR testing directly from pooled screening swabs was performed with the BD GeneOhm MRSA (BD Diagnostics, Belgium) or GeneXpert MRSA (Cepheid, Belgium) tests, which have turnaround times of 2 to 3 hours and 1.5 hours respectively (see online supplementary table A1).[18] Laboratories participated in an

external quality assurance program to evaluate their ability to detect, identify and perform antibiotic sensitivity testing on staphylococci from a variety of different specimens.[19] MRSA isolates were shipped to the central laboratory (University of Antwerp, Belgium) for confirmation of identification.

Data collection

Research personnel from each hospital were trained at the coordinating centre with regards to the study protocol and data collection tools. Local microbiology laboratory data were reviewed to obtain information regarding MRSA isolated from screening and clinical cultures. Infections were monitored by twice weekly ward visits to review medical records and interview staff. Surgical site infection surveillance occurred up to 30 days post-procedure (12 months after prosthetic device insertion). HH adherence was monitored by direct observation by research personnel who were independent of surgical ward staff.[15] All hospitals collected data for 100 HH opportunities per ward during baseline and washout phases. During the intervention phase, 100 HH opportunities per ward per month were observed in ESC and MIX wards only. Implementation of contact precautions, decolonisation therapy, and single room isolation of MRSA carriers was randomly audited each month. Signage of MRSA status and availability of gowns, gloves and alcohol-based handrub for contact with MRSA carriers was also audited. Data regarding admissions, patient-days, surgical procedures, and staffing were collected.

Ward-level data were submitted monthly to a central data management centre via a password protected secure online database which included range, consistency, and missing data checks. Meetings, site visits, and monthly teleconferences were held to review data, ensure adherence to study protocols, and address queries. Data were reviewed monthly for completeness and 6-

monthly for validity by teleconferences with individual study sites. Institutional review boards of all centres approved the study with a waiver of individual informed consent.

Statistical analysis

The study was designed to detect a 30% difference in nosocomial MRSA isolation rate assuming a baseline rate of 1.0 clinical isolate per 100 susceptible patients and an absolute difference of 10% between intervention arms. Sample size calculations assumed a two-sided test, a type I error rate of 0.05 and 80% power, taking the wards as the unit of analysis. A minimum of 15 wards was required per study arm.

Crude MRSA rates were calculated by study arm. Adjusted incidence rate ratios (aIRR) were calculated using multilevel Poisson segmented regression accounting for stepwise changes in MRSA level and changes in log-linear trends associated with the interventions.[20] This analysis allowed for two levels of random-effects: hospital-level variation in intercepts and baseline trends, and nested ward-level variation in intercepts. It adjusted for exposure given by the monthly number of susceptible patients or admissions per ward and allowed for extra-Poisson variation. Surgical subspecialty, baseline HH compliance, seasonal effects (using calendar month), and patient-to-nurse ratios were adjusted for. Autocorrelation was accounted for using a lagged dependent variable. A similar analysis was performed for HH compliance, but used segmented multilevel logistic regression, adjusting for ward-specific baseline levels and trends, professional category, HH indication, patient-to-nurse ratios, and monthly MRSA colonisation pressure (number of days patients known to be MRSA colonised/infected were in the wards each month).

Planned subgroup analyses were performed by hospital and for clean surgery wards (cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery) as studies have shown that intranasal mupirocin, which is active against gram-positive organisms, may be more effective for surgical site infection prevention in clean compared to clean-contaminated surgery (e.g. general or gastrointestinal surgery) where gram-negative and anaerobic organisms may play a larger role.[21] As screening intensity varied in the MIX arm, a planned exploratory analysis of MRSA outcome data was conducted to better quantify the intervention effects. It accounted for stepwise changes and log-linear trends in outcomes associated with the HH intervention, as well as the monthly proportion of patients screened and monthly cumulative screening rate on wards to account for changes in trends of outcomes associated with screening. Analyses were conducted with STATA 11.0 (STATA Corp, USA).

RESULTS

During the study period, there were a total of 126 750 admissions and 99 638 surgical procedures on the study wards. Baseline admission MRSA prevalence was 0.8% (269 of 33 608), ranging from 0.1% to 2.2% across surgical wards of each hospital. Baseline HH adherence varied between hospitals (39.5% overall, 95% CI 38.1% to 40.9%) as did use of targeted MRSA screening (0 to 30.9% of admissions) (table 1). Study characteristics are shown in table 2 and online supplementary table A2.

Adherence to hand hygiene guidelines

In ESC and MIX arms, HH compliance improved in all centres with overall compliance increasing from 49.3% (95% CI 47.2% to 51.4%) to 63.8% (95% CI 63.2% to 64.4%) from baseline to intervention phases (figure 1a). After multivariable analysis, commencing HH

promotion was associated with a significant immediate increase in HH compliance (adjusted odds ratio [aOR] 1.19, 95% CI 1.01 to 1.42) (see online supplementary table A3). However, this benefit was not sustained after cessation of the HH campaign with a significant decreasing trend in HH adherence of 9% per month (aOR for month post-intervention 0.91, 95% CI 0.85 to 0.97) during the washout phase. In ACD wards, where no HH promotion occurred, compliance remained low at 30.5% (95% CI 28.7% to 32.4%) at baseline and 23.9% (95% CI 22.0% to 25.9%) during the washout phase.

Active detection, contact precautions and decolonisation of MRSA carriers

During the intervention phase, 9250 (75.3%) of 12 279 patients were screened on admission to ACD wards. Admission MRSA prevalence was 2.1% (259 of 12 279), consisting of 27 patients (10.4%) with MRSA-positive clinical cultures and 232 patients (89.6%) identified by screening alone. PCR screening was used in addition to chromogenic agar cultures in 1047 (11.3%) of 9250 patients. Between baseline and intervention phases in ACD wards, the proportion of audited MRSA carriers placed on contact precautions increased (81.1% to 90.7%), as did administration of decolonisation therapy (34.4% to 69.8%) (figure 2). However, the proportion of audited MRSA carriers in single rooms decreased (67.8% to 40.1%), possibly due to a shortage of rooms for the higher number of identified MRSA carriers.

Screening occurred to a lesser extent in the other study arms (figure 1b). About 10% of admissions to ESC wards were screened throughout the study. In MIX wards, screening increased from 9.2% to 22.3%, then 36.9% during baseline, intervention, and washout phases respectively. In this arm, adherence to contact precautions was high throughout the study

(93.0% to 99.6%), but only 32.9% of MRSA patients at baseline and 35.9% of patients during the intervention phase received decolonisation therapy (figure 2).

Nosocomial MRSA isolation rate from clinical cultures

Crude MRSA isolation rates from clinical cultures decreased in all study arms during the intervention phase (ESC arm: 0.99 to 0.80; ACD arm: 0.47 to 0.23; MIX arm: 0.55 to 0.36; p=0.04; per 100 susceptible patients) (table 3). After adjusting for clustering and potential confounders with multilevel segmented Poisson regression (table 4 and see online supplementary table A4 for full model), commencement of HH promotion (ESC arm) was associated with an immediate non-significant increase in nosocomial MRSA isolation rate (aIRR 1.44, 95% CI 0.96 to 2.15) with no change in the trend in rates over time. In clean surgery wards, HH promotion was associated with a non-significant decreasing monthly MRSA isolation rate (aIRR 0.89, 95% CI 0.78 to 1.01) (table 5 and see online supplementary table A5 for full model).

Screening, contact precautions and decolonisation (ACD arm) was not associated with significant changes in MRSA isolation rates. However, in clean surgery, this intervention was associated with a reduction in MRSA clinical cultures of 15% per month (aIRR 0.85, 95% CI 0.74 to 0.97).

Combining HH promotion with targeted screening (MIX arm) was associated with a significant decreasing trend in MRSA isolation rate of 12% per month overall (aIRR 0.88, 95% CI 0.79 to 0.98), and 18% per month in clean surgery (aIRR 0.82, 95% CI 0.71 to 0.95). Observed and model-predicted MRSA isolation rates from clinical cultures are illustrated in figure 3a and online supplementary figure A1.

Nosocomial MRSA infection rates

There were 470 nosocomial MRSA infections in total (335 [71.3%] surgical site, 41 [8.7%] bloodstream, and 94 [20.0%] other infections). Crude infection rates decreased over time in all study arms (table 3). After multivariable analysis (table 4, figure 3b and see online supplementary table A4), HH promotion (ESC arm) was not associated with changes in MRSA infection rates. Both the screening/decolonisation and combined interventions resulted in non-significant decreasing trends in total MRSA infection (ACD arm: aIRR 0.93, 95% CI 0.82 to 1.05; MIX arm: aIRR 0.90, 95% CI 0.80 to 1.02) and surgical site infection rates (table 4, figure 3c and online supplementary table A4).

In clean surgery, the ACD screening strategy was associated with significant reductions in MRSA infection rate of 17% per month (aIRR 0.83, 95% CI 0.69 to 0.99) and MRSA surgical site infection rate of 19% per month (aIRR 0.81, 95% CI 0.66 to 1.00) (table 5 and online supplementary table A5).

Exploratory analysis to directly assess implemented interventions

The exploratory analysis did not show any significant effects of HH promotion on nosocomial MRSA isolation rates (see online supplementary table A6). The intensity of admission screening was associated with a decreasing trend in monthly MRSA isolation rate from clinical cultures (aIRR 0.91 per month with 100% compliance with screening, 95% CI 0.85 to 0.98). A similar effect was seen in the trend in MRSA infection rate (aIRR 0.92, 95% CI 0.85 to 0.99).

DISCUSSION

We found that as individual interventions, neither an enhanced standard control strategy using HH promotion nor universal MRSA screening with contact precautions and decolonisation of MRSA carriers were effective in reducing MRSA rates in surgical patients. However, using a combination of both HH promotion and targeted screening was associated with reduction in MRSA isolation rate from clinical cultures of 12% per month. In addition, when the interventions were specifically evaluated in the subgroup of clean surgery wards, the screening/decolonisation strategy was most effective. In these wards, this intervention was associated with significant reductions in both MRSA clinical culture isolation rate of 15% per month and MRSA infection rate of 17% per month.

This study is unique in that it directly compared strategies individually and in combination using a large, prospective, controlled design.[10] Interventions were assessed under operational conditions in ten heterogeneous hospitals across Europe and Israel with varying infection control practices, staffing, infrastructure, and MRSA epidemiology, increasing the generalisability of our findings.

Our analysis, which adjusted for confounders, seasonal effects and baseline MRSA trends, found no evidence that enhanced standard infection control measures were effective. MRSA rates are declining in many countries.[22] Failing to account for this would overestimate intervention effects. Overall baseline HH compliance was 49% in study wards that used the HH intervention. In settings where compliance is already above about 50%, modelling studies suggest that further increases in compliance will have rapidly diminishing returns for reducing MRSA transmission.[23] In facilities with lower HH compliance or higher MRSA rates, this intervention may be more effective than we were able to demonstrate. In addition,

HH campaigns involve education and behaviour change and are therefore unlikely to have a short term effect. Other studies have shown that they may be beneficial if activity is sustained over years.[24]

Active MRSA surveillance identifies asymptomatic carriers, enabling early implementation of contact precautions and decolonisation, which can reduce transmission.[25,26] With universal screening, we found that 90% of MRSA-positive patients would have been missed using clinical cultures alone. Our results suggest that selective (clean surgery) or targeted (high risk patient) screening may be more effective than universal screening. The relative burden of gram-positive infections is greater in clean compared to clean-contaminated surgery where other pathogens, including bowel flora, may be more important.[21] Thus MRSA-specific interventions would potentially have a greater impact in clean surgery. Indeed, intranasal mupirocin has been shown to reduce surgical site infections in cardiothoracic and orthopaedic surgery, but is less effective in general surgery.[21] The exploratory analysis suggests that screening intensity, rather than HH promotion, explained the intervention effects. It is curious, then, that universal screening did not perform better than HH promotion combined with targeted screening. Low baseline MRSA rates in the universal screening arm may have reduced our ability to detect significant effects. Shortage of isolation rooms may have also contributed. In addition, targeted screening may have been more effective if it identified "superspreaders",[27] facilitating more effective use of resources including limited single rooms.

This study adds to the conflicting literature regarding active surveillance cultures. Our results apply to surgical settings. The risk of MRSA infection in other wards, such as intensive care units or general medical wards, would differ due to variation in patient comorbidities and

exposure to invasive procedures or antibiotics. It is also important to note that previous studies have used a variety of interventions in combination with screening. In some cases, the use of pre-emptive isolation in both study arms[28] or lack of decolonisation strategies,[6] may have led to effect sizes that studies had insufficient power to detect. Comparison of rapid screening to conventional rather than no screening,[28] differences in screening methods,[10] variation in MRSA strains,[29] or limitations in study design and analyses[10,11] are other potential explanations for the conflicting results of screening studies.

There are some limitations to this study. Due to the nature of the interventions, investigators were not blinded to study assignment. Although allocation of interventions was not randomised, we accounted for differences in hospitals by adjusting for potential confounders and comparing outcomes between baseline and intervention phases within the same study arm. Decisions to take culture samples were initiated by treating physicians, not research personnel, and standardised definitions for infections were used, reducing the likelihood of bias from unblinded assessors. We used MRSA-positive clinical cultures as our primary outcome. Although this measure does not distinguish between colonisation and infection, it can be a more sensitive marker for changes in MRSA disease rates.[30] We found the results for MRSA clinical cultures similar to those for infections, suggesting that this measure was clinically relevant.

Conclusion

In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard infection control and MRSA-specific (targeted screening) approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening with contact precautions and decolonisation of

identified MRSA carriers was associated with significant reductions in MRSA clinical culture and infection rates. These findings are likely generalisable to other settings with varying infection control practices. Our results highlight the relative effectiveness of different MRSA control strategies, enabling optimisation of infection prevention approaches. Further research regarding the cost-effectiveness of these interventions will allow better utilisation of limited healthcare resources.

REFERENCES

1 WHO. Report on the burden of endemic health care-associated infection worldwide. http://whqlibdoc.who.int/publications/2011/9789241501507_eng.pdf (accessed 24 April 2013).

2 Cosgrove SE, Qi Y, Kaye KS, et al. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 2005;26:166-74.

3 Weber SG, Huang SS, Oriola S, et al. Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: Position statement from the Joint SHEA and APIC Task Force. *Am J Infect Control* 2007;35:73-85.

4 UK Department of Health. MRSA Screening - Operational Guidance 2. http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_092844 (accessed 24 April 2013).

5 Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. *Ann Intern Med* 2008;148:409-18.

6 Huskins WC, Huckabee CM, O'Grady NP, et al. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med* 2011;364:1407-18.

7 Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 2008;299:1149-57.

8 Edmond MB, Ober JF, Bearman G. Active surveillance cultures are not required to control MRSA infections in the critical care setting. *Am J Infect Control* 2008;36:461-3.

9 Wenzel RP, Bearman G, Edmond MB. Screening for MRSA: a flawed hospital infection control intervention. *Infect Control Hosp Epidemiol* 2008;29:1012-8.

10 Tacconelli E, De Angelis G, de Waure C, et al. Rapid screening tests for meticillin-resistant *Staphylococcus aureus* at hospital admission: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:546-54.

11 Loveday HP, Pellowe CM, Jones SR, et al. A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant *Staphylococcus aureus* (1996-2004): report to the Joint MRSA Working Party (Subgroup A). *J Hosp Infect* 2006;63 Suppl 1:S45-70.

12 Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med* 2011;364:1419-30.

13 Farr BM, Jarvis WR. Searching many guidelines for how best to control methicillin-resistant *Staphylococcus aureus* healthcare-associated spread and infection. *Infect Control Hosp Epidemiol* 2009;30:808-9.

14 Nijssen S, Bonten MJ, Weinstein RA. Are active microbiological surveillance and subsequent isolation needed to prevent the spread of methicillin-resistant *Staphylococcus aureus*? *Clin Infect Dis* 2005;40:405-9.

15 WHO. WHO Guidelines on Hand Hygiene in Health Care. World Alliance for Patient Safety. Geneva: WHO Press Geneva, 2009.

16 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32.

17 Van Heirstraeten L, Cortinas Abrahantes J, Lammens C, et al. Impact of a short period of pre-enrichment on detection and bacterial loads of methicillin-resistant *Staphylococcus aureus* from screening specimens. *J Clin Microbiol* 2009;47:3326-8.

18 Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.
19 Gazin M, Lee A, Derde L, et al. Culture-based detection of methicillin-resistant *Staphylococcus aureus* by a network of European laboratories: an external quality assessment study. *Eur J Clin Microbiol Infect Dis* 2012;31:1765-70.
20 Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis* 2007;45:901-7.
21 Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005;26:916-22.
22 Struelens MJ, Monnet DL. Prevention of methicillin-resistant *Staphylococcus aureus* infection: is Europe winning the fight? *Infect Control Hosp Epidemiol* 2010;31 Suppl 1:S42-4.
23 Cooper BS, Medley GF, Scott GM. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J Hosp Infect* 1999;43:131-47.
24 Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. *Lancet* 2000;356:1307-12.
25 Lee AS, Huttner B, Harbarth S. Control of methicillin-resistant Staphylococcus aureus. *Infect Dis Clin North Am* 2011;25:155-79.
26 Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis* 2009;48:922-30.
27 Lloyd-Smith JO, Schreiber SJ, Kopp PE, et al. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005;438:355-9.
28 Jeyaratnam D, Whitty CJ, Phillips K, et al. Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008;336:927-30.
29 Cooper BS, Kypraios T, Batra R, et al. Quantifying type-specific reproduction numbers for nosocomial pathogens: evidence for heightened transmission of an Asian sequence type 239 MRSA clone. *PLoS Comput Biol* 2012;8:e1002454.
30 Walker S, Peto TE, O'Connor L, et al. Are there better methods of monitoring MRSA control than bacteraemia surveillance? An observational database study. *PLoS One* 2008;3:e2378.

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Competing interests

SH is a member of the speakers' bureau for bioMérieux and Pfizer, and the scientific advisory board of Destiny Pharma, DaVolterra, and bioMérieux. He has received financial support for MRSA research activities from Geneva University Hospitals, B.Braun, and Pfizer. AP is a member of the speakers' bureau for Cubist and has received financial support for MRSA research activities from BD. There were no other financial or non-financial relationships, or interests that may be relevant to the submitted work.

Author contributions

Conceived and designed the experiments: SH CBB. Analysed the data: ASL BSC. Contributed reagents/materials: SMK HG. Wrote the first draft of the manuscript: ASL. Contributed to the writing of the manuscript: ASL SH BSC CBB AC GLD CF BC SL SMK JAM CMA AP GP BR HG. ICMJE criteria for authorship read and met: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Agree with manuscript results and conclusions: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Enrolled patients: ASL AC GLD CF BC SL JAM CMA AP GP BR. Statistical support: BSC.

Data sharing

The dataset is available from the corresponding author at stephan.harbarth@hcuge.ch.

FIGURE LEGENDS

Figure 1 Implementation of the interventions

Figure 1 Legend
The top panel (A) shows the monthly hand hygiene compliance rates for hospitals that used hand hygiene promotion campaigns. The solid dots represent the observed compliance rates while the lines represent the predicted compliance rates based on the regression model. The bottom panel (B) shows the proportion of patients screened on admission to the study wards by study arm. ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using meticillin resistant *Staphylococcus aureus* [MRSA] screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).

Figure 2 Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers

Figure 2 Legend
This figure shows the distribution of monthly adherence to infection control measures for randomly audited patients known to be colonised or infected with meticillin resistant *Staphylococcus aureus* (MRSA) for each study arm. The top panel (A) shows adherence to implementation of contact precautions, decolonisation therapy, and isolation in single rooms. The middle panel (B) shows the presence of signage of MRSA status on the patients' room, bed, or nursing chart. The bottom panel (C) shows the availability of gowns, gloves, and alcohol-based handrub in or at the entrance of the room. The horizontal line in each box represents the median, the box represents the interquartile range and the vertical lines represent the minimum and maximum values. MRSA, meticillin resistant *Staphylococcus aureus*; ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).

Figure 3 Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm

Figure 3 Legend
The top panel (A) shows the nosocomial meticillin resistant *Staphylococcus aureus* (MRSA) isolaton rates from clinical specimens. The middle panel (B) shows the nosocomial MRSA infection rates. The bottom panel (C) shows the nosocomial MRSA surgical site infection rates. The solid dots represent the observed MRSA rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*; ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).

TABLES

Table 1: Baseline phase characteristics of hospitals and wards enrolled in the study

	Hospital characteristics			Study ward characteristics							
Hospital	Total beds (n)	Total number of single rooms (%)	Ratio of infection control nurses to beds	Surgical subspecialties	Total beds (n)	Total admissions during baseline phase (n)	Mean patient-to-nurse ratio (SD)*	Percent hand hygiene compliance (95% CI)	Number of patients screened on admission (%)	Number identified MRSA positive on admission (%)†	Study arm
1	3611	45 (1.2)	1:240	Abdominal Cardiovascular Orthopaedic	588	8018	6.4 (1.2)	18.8 (15.1 to 22.9)	0 (0)	9 (0.1)	Enhanced Standard Control
2	317	235 (74.1)	1:160	Cardiothoracic Orthopaedic Vascular	72	1613	4.1 (1.8)	75.4 (70.3 to 80.0)	29 (1.8)	20 (1.2)	Active Detection
3	850	135 (15.9)	1:425	Cardiovascular General Orthopaedic	75	1841	5.6 (0.7)	26.8 (24.4 to 29.4)	14 (0.8)	11 (0.6)	Active Detection
4	822	0 (0)	1:137	Abdominal Orthopaedic Urology Vascular	230	6574	3.7 (0.9)	39.3 (34.6 to 44.1)	182 (2.8)	21 (0.3)	Combined‡
5	545	89 (16.3)	1:272	General Neurosurgery Orthopaedic Vascular	121	1938	5.8 (1.5)	14.3 (11.3 to 17.6)	56 (2.9)	4 (0.2)	Active Detection
6	547	4 (0.7)	1:274	General Orthopaedic Vascular	93	1300	16.8 (2.5)	25.1 (20.7 to 30.1)	0 (0)	5 (0.4)	Active Detection
7	902	62 (6.9)	1:180	Abdominal General Vascular	84	1963	6.1 (1.5)	76.5 (71.3 to 81.1)	607 (30.9)	41 (2.1)	Combined‡
8	850	202 (23.8)	1:567	Orthopaedic Urology Vascular	87	2434	5.5 (0.6)	50.2 (44.6 to 55.8)	0 (0)	3 (0.1)	Enhanced Standard Control

9	1350	150 (11.1)	1:260	Cardiothoracic Neurosurgery Plastic surgery	164	1561	10.0 (2.2)	67.0 (61.4 to 72.3)	17 (1.1)	15 (1.0)	Enhanced Standard Control
10	2044	402 (19.7)	1:204	Abdominal Cardiovascular Orthopaedic Urology	302	6366	4.8 (0.4)	55.9 (51.2 to 60.5)	1666 (26.2)	140 (2.2)	Enhanced Standard Control
Overall	11 838	1324 (11.2)			1816	33 608	6.6 (3.8)	39.5 (38.1 to 40.9)	2571 (7.6)	269 (0.8)	

MRSA, meticillin resistant *Staphylococcus aureus*.
*Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
†By screening or clinical culture.
‡Screening in hospitals in the Combined arm was performed according to locally introduced policies. Hospital 4 used targeted screening of patients who were previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. Hospital 7 introduced universal screening in two of three study wards and targeted screening in the third ward. In this ward, patients who were previously known to be MRSA-positive, nursing home residents, patients admitted to the hospital in the last three months, contacts of MRSA-positive patients, and patients transferred from another ward or healthcare facility were screened.

Table 2: Study characteristics by study period

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Total patient-days (n)	264 035	496 975	249 119
Total surgical procedures (n)	27 768	49 747	22 123
Procedures in clean surgery wards (n)†	12 916	21 463	8787
Procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Number positive by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Number positive by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the Active Detection arm and one hospital in each of the Enhanced Standard Control and Combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table 3: Crude nosocomial meticillin resistant *Staphylococcus aureus* incidence rates and incidence rate ratios by study arm for each study period*

Outcome	Baseline phase	Intervention phase	Washout phase	Crude IRR (95% CI) for intervention vs. baseline phases	Crude IRR (95% CI) for washout vs. intervention phases
MRSA isolation rate from clinical cultures (no. per 100 susceptible patients)					
Enhanced Standard Control	0.99 (181/183.47)	0.80 (279/349.50)	0.65 (106/163.83)	0.81 (0.67 to 0.98)	0.81 (0.65 to 1.01)
Active Detection	0.47 (31/66.61)	0.23 (28/122.56)	0.26 (17/66.04)	0.49 (0.29 to 0.82)	1.13 (0.62 to 2.06)
Combined	0.55 (47/85.35)	0.36 (60/165.23)	0.13 (8/63.04)	0.66 (0.45 to 0.97)	0.35 (0.17 to 0.73)
MRSA infection rate (no. per 100 admissions)					
Enhanced Standard Control	0.58 (106/183.79)	0.50 (175/349.96)	0.45 (74/164.13)	0.87 (0.68 to 1.10)	0.90 (0.69 to 1.18)
Active Detection	0.24 (16/66.92)	0.19 (23/122.79)	0.17 (11/66.15)	0.78 (0.41 to 1.48)	0.89 (0.43 to 1.82)
Combined	0.29 (25/85.37)	0.19 (32/165.35)	0.13 (8/63.04)	0.66 (0.39 to 1.12)	0.66 (0.30 to 1.42)
MRSA surgical site infection rate (no. per 100 surgical procedures)					
Enhanced Standard Control	0.60 (79/132.27)	0.49 (123/250.03)	0.42 (54/127.06)	0.82 (0.62 to 1.09)	0.86 (0.63 to 1.19)
Active Detection	0.26 (14/54.00)	0.15 (15/99.63)	0.16 (8/50.74)	0.58 (0.28 to 1.20)	1.05 (0.44 to 2.47)
Combined	0.20 (18/91.41)	0.14 (21/147.81)	0.07 (3/43.43)	0.72 (0.38 to 1.35)	0.49 (0.15 to 1.63)
MRSA bloodstream infection rate (no. per 10 000 patient-days)					
Enhanced Standard Control	0.93 (14/15.0757)	0.56 (16/28.6667)	0.44 (6/13.5745)	0.60 (0.29 to 1.23)	0.79 (0.31 to 2.02)
Active Detection	0.17 (1/5.7754)	0.18 (2/11.2971)	0.17 (1/5.8473)	1.02 (0.09 to 11.28)	0.97 (0.09 to 10.65)
Combined	0.18 (1/5.5524)	0.00 (0/9.7337)	0.00 (0/5.4901)	-	-

IRR, incidence rate ratio; MRSA, meticillin resistant *Staphylococcus aureus*.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward.

Table 4: Multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced Standard Control	1.44	0.96 to 2.15	0.076	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
Active Detection	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.070	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced Standard Control	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Active Detection	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.162
Combined	0.88	0.79 to 0.98	0.016	0.90	0.80 to 1.02	0.096	0.86	0.74 to 1.01	0.059
Washout phase									
Change in level	1.90	0.91 to 3.95	0.087	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.

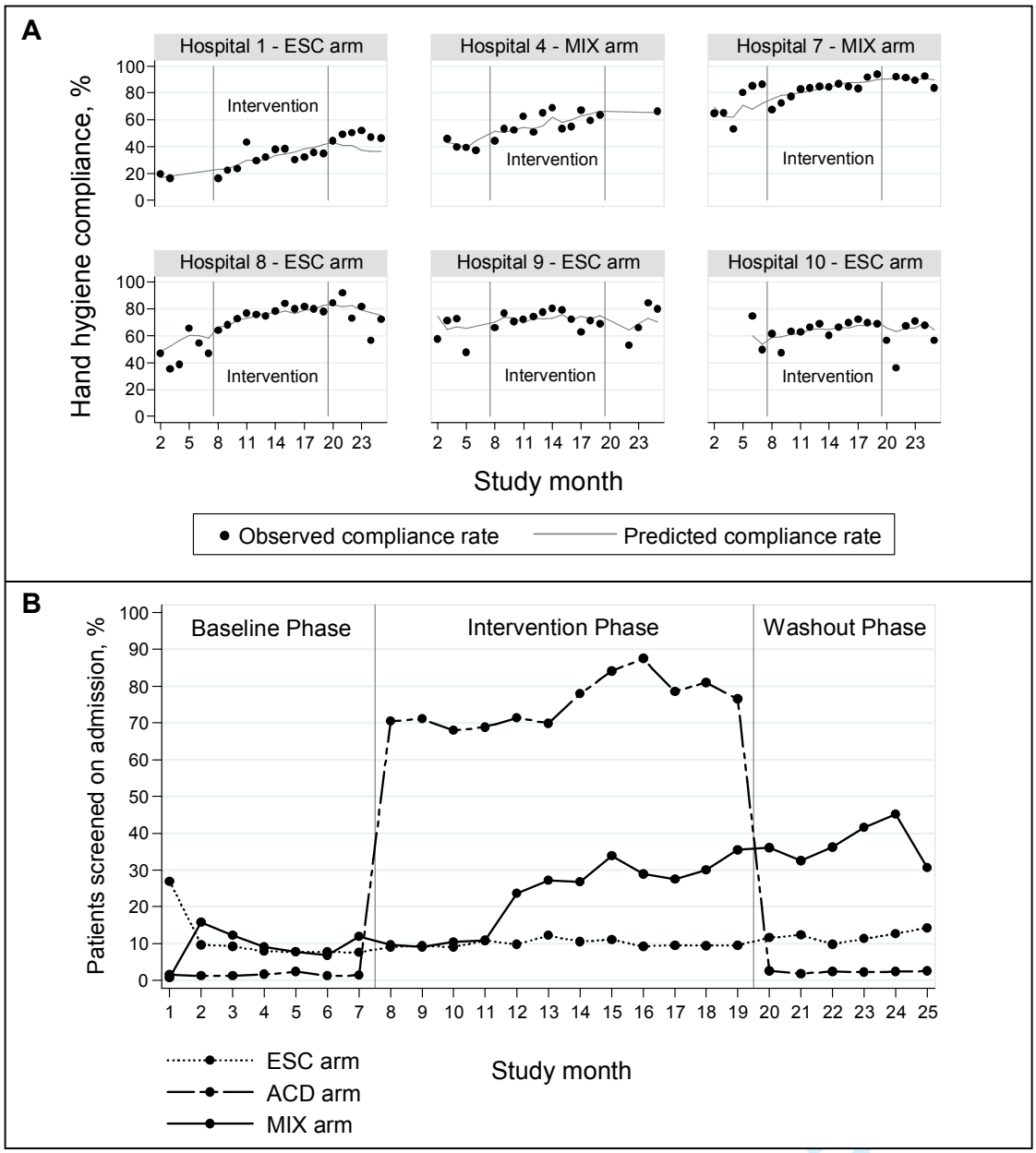
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

Table 5: Multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced Standard Control	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Active Detection	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.121	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced Standard Control	0.89	0.78 to 1.01	0.063	0.88	0.75 to 1.04	0.127	0.89	0.73 to 1.07	0.21
Active Detection	0.85	0.74 to 0.97	0.019	0.83	0.69 to 0.99	0.041	0.81	0.66 to 1.00	0.054
Combined	0.82	0.71 to 0.95	0.007	0.84	0.70 to 1.00	0.055	0.84	0.68 to 1.03	0.095
Washout phase									
Change in level	3.01	1.05 to 8.63	0.041	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21

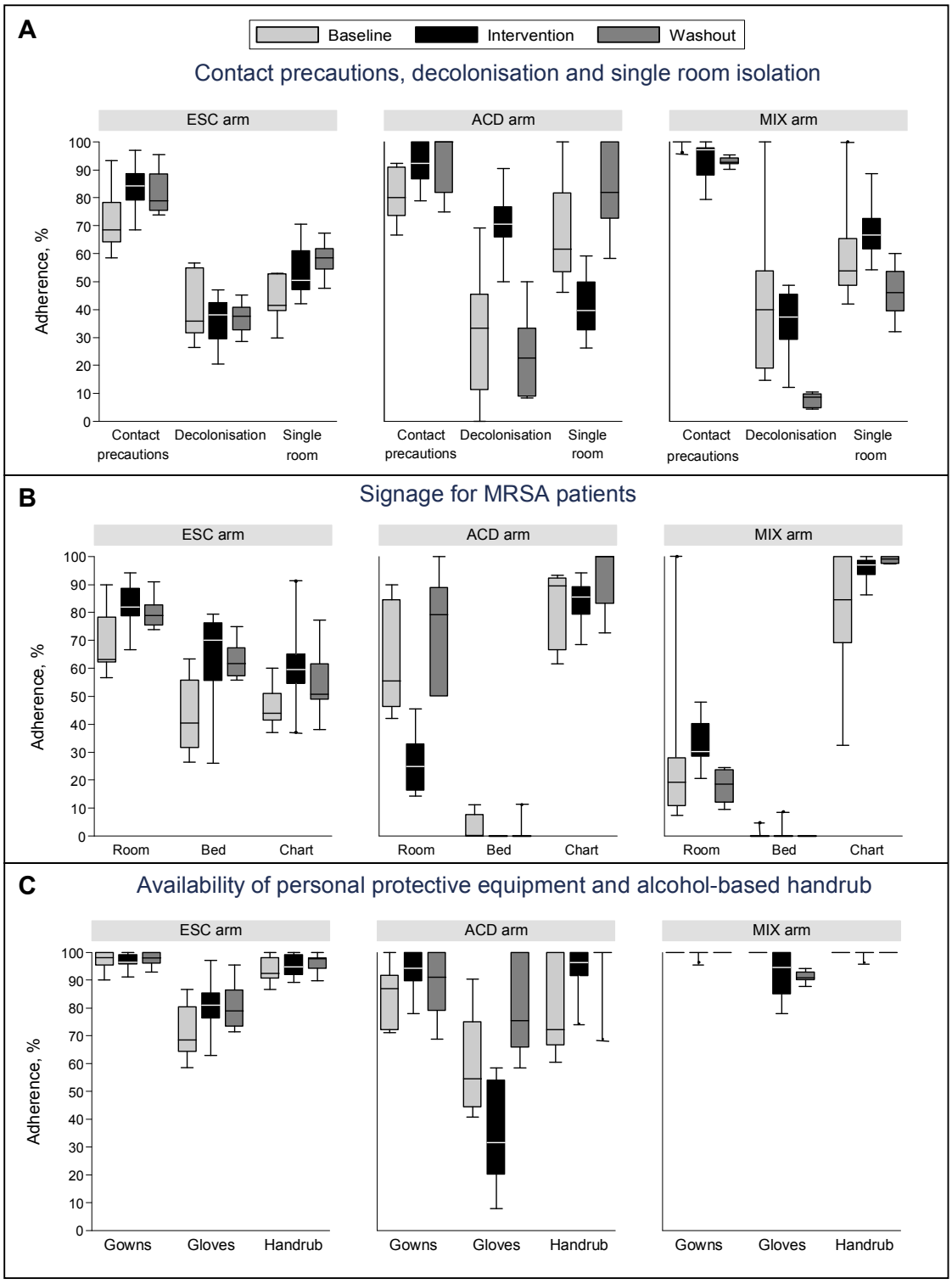
MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

Figure 1: Implementation of the interventions



The top panel (A) shows the monthly hand hygiene compliance rates for hospitals that used hand hygiene promotion campaigns. The solid dots represent the observed compliance rates while the lines represent the predicted compliance rates based on the regression model. The bottom panel (B) shows the proportion of patients screened on admission to the study wards by study arm. ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using meticillin resistant *Staphylococcus aureus* [MRSA] screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).

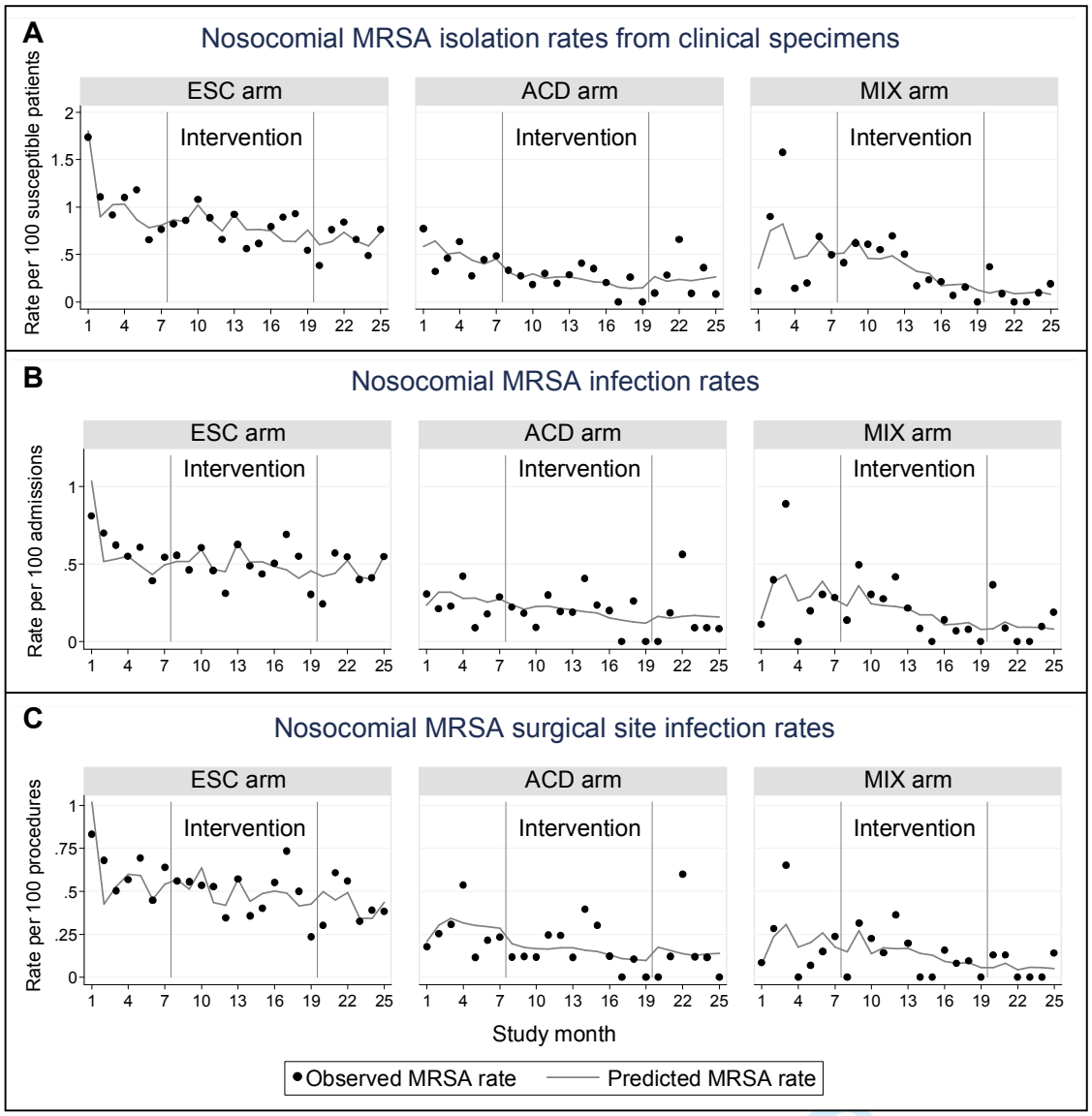
Figure 2: Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers



This figure shows the distribution of monthly adherence to infection control measures for randomly audited patients known to be colonised or infected with meticillin resistant *Staphylococcus aureus* (MRSA) for each study arm. The top panel (A) shows adherence to implementation of contact precautions, decolonisation therapy

and isolation in single rooms. The middle panel (B) shows the presence of signage of MRSA status on the patients' room, bed, or nursing chart. The bottom panel (C) shows the availability of gowns, gloves, and alcohol-based handrub in or at the entrance of the room. The horizontal line in each box represents the median, the box represents the interquartile range and the vertical lines represent the minimum and maximum values. MRSA, meticillin resistant *Staphylococcus aureus*; ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).

Figure 3: Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm



The top panel (A) shows the nosocomial meticillin resistant *Staphylococcus aureus* (MRSA) isolaton rates from clinical specimens. The middle panel (B) shows the nosocomial MRSA infection rates. The bottom panel (C) shows the nosocomial MRSA surgical site infection rates. The solid dots represent the observed MRSA rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*; ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).

SUPPLEMENTARY DATA FOR MANUSCRIPT:

Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a multicentre intervention study

Table A1: Meticillin resistant *Staphylococcus aureus* screening methods used in study centres in the Active Detection and Combined arms

Table A2: Study characteristics by study period and study arm

Table A3: Multiple segmented multilevel logistic regression model showing factors associated with monthly hand hygiene compliance rates

Table A4: Full model results for the multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates

Table A5: Full model results for the multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only

Table A6: Exploratory analysis using multiple segmented multilevel Poisson regression models including interventions implemented by centres as covariates in the model

Figure A1: Nosocomial meticillin resistant *Staphylococcus aureus* isolation rates from clinical specimens by hospital

Table A1: Meticillin resistant *Staphylococcus aureus* screening methods used in study centres in the Active Detection and Combined arms

Study arm	Hospital	Chromogenic medium used	Minimum time to detection (days)*	Months during intervention phase test used†	Molecular assay used	Total assay time (hours)*	Months during intervention phase test used†‡
Active Detection	2	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	1 to 10
					GeneXpert (Cepheid)	<1.5	7 to 12
	3	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneXpert (Cepheid)	<1.5	6 to 12
	5	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	10 to 12
	6	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneXpert (Cepheid)	<1.5	8 to 12
Combined	4	MRSA Select (Bio-Rad Laboratories)	1.35	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	1 to 12
	7	ChromID (bioMérieux)	1.65	1 to 12	Not used	-	-

*From Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.
†Screening for meticillin resistant *Staphylococcus aureus* occurred during all study phases for centres in the Combined arm using existing local methods.
‡For the Active Detection arm, molecular assays were introduced during the latter part of the intervention phase. In one centre in this arm (Hospital 2) a locally available molecular assay was used from the commencement of the intervention phase.

Table A2: Study characteristics by study period and study arm

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Enhanced Standard Control	18 379	34 996	16 413
Active Detection	6692	12 279	6615
Combined	8537	16 535	6304
Total patient-days (n)	264 035	496 975	249 119
Enhanced Standard Control	150 757	286 667	135 745
Active Detection	57 754	112 971	58 473
Combined	55 524	97 337	54 901
Total surgical procedures (n)	27 768	49 747	22 123
Enhanced Standard Control	13 227	25 003	12 706
Active Detection	5400	9963	5074
Combined	9141	14 781	4343
Surgical procedures in clean surgery wards (n)†	12 916	21 463	8787
Enhanced Standard Control	5160	9102	4693
Active Detection	1310	2551	1185
Combined	6446	9810	2909
Surgical procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Enhanced Standard Control	8067	15 901	8013
Active Detection	4090	7412	3889
Combined	2695	4971	1434
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Enhanced Standard Control	6.46 (2.35)	6.73 (2.11)	6.99 (2.57)
Active Detection	7.68 (5.11)	7.96 (4.74)	8.31 (5.52)
Combined	4.65 (1.62)	4.14 (1.17)	3.96 (1.30)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Enhanced Standard Control	167 (0.9)	272 (0.8)	136 (0.8)
Active Detection	40 (0.6)	259 (2.1)	13 (0.2)
Combined	62 (0.7)	193 (1.2)	79 (1.3)
Number of patients MRSA positive on admission by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Enhanced Standard Control	32 (0.2)	46 (0.1)	30 (0.2)
Active Detection	31 (0.5)	27 (0.2)	11 (0.2)
Combined	2 (0.02)	12 (0.1)	0 (0)
Number of patients MRSA positive on admission by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)
Enhanced Standard Control	135 (0.7)	226 (0.6)	106 (0.6)
Active Detection	9 (0.1)	232 (1.9)	2 (0.03)
Combined	60 (0.7)	181 (1.1)	79 (1.3)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the Active Detection arm and one hospital in each of the Enhanced Standard Control and Combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table A3: Multiple segmented multilevel logistic regression model showing factors associated with monthly hand hygiene compliance rates*

Variable	Adjusted odds ratio	95% CI	p Value
Baseline phase			
Trend	1.04	0.98 to 1.10	0.24
Intervention phase			
Change in level	1.19	1.01 to 1.42	0.04
Change in trend	1.03	0.97 to 1.09	0.30
Washout phase			
Change in level	1.17	0.82 to 1.68	0.39
Change in trend	0.91	0.85 to 0.97	0.004
Professional category			
Physician	1.00	-	-
Nurse	1.37	1.28 to 1.46	<0.001
Auxiliary nurse	1.27	1.16 to 1.39	<0.001
Other	1.11	0.99 to 1.24	0.06
Indication for hand hygiene			
Before touching patient	1.00	-	-
Before clean/aseptic procedure	1.20	1.09 to 1.32	<0.001
After body fluid exposure	4.95	4.47 to 5.48	<0.001
After touching patient	2.79	2.60 to 3.00	<0.001
After touching patient surroundings	1.52	1.41 to 1.65	<0.001
Patient-to-nurse ratio (per 1-unit increment)†	0.91	0.89 to 0.94	<0.001
MRSA colonisation pressure‡			
0 to 0.7%	1.00	-	-
0.8 to 3.2%	0.86	0.79 to 0.94	<0.001
3.3 to 8.2%	0.90	0.81 to 1.01	0.07
>8.2%	0.78	0.68 to 0.90	<0.001

MRSA, meticillin resistant *Staphylococcus aureus*.
*Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all statistically significant, though baseline trends and intercepts showed no evidence of correlation.
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.
‡Calculated by dividing the patient-days of subjects known to be colonised or infected with meticillin resistant *Staphylococcus aureus* by the total number of patient-days in the ward in any given study month. This variable was divided into quartiles for the analysis.

Table A4: Full model results for the multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced Standard Control	1.44	0.96 to 2.15	0.08	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
Active Detection	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.07	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced Standard Control	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Active Detection	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.16
Combined	0.88	0.79 to 0.98	0.02	0.90	0.80 to 1.02	0.10	0.86	0.74 to 1.01	0.06
Washout phase									
Change in level	1.90	0.91 to 3.95	0.09	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53
Patient-to-nurse ratio (per 1-unit increment)†	1.01	0.94 to 1.08	0.87	1.01	0.93 to 1.09	0.84	1.04	0.96 to 1.14	0.33
Calendar month									
January	1.00	-	-	1.00	-	-	1.00	-	-
February	0.83	0.54 to 1.28	0.41	0.89	0.53 to 1.50	0.67	0.76	0.40 to 1.45	0.41
March	1.16	0.78 to 1.72	0.47	1.49	0.94 to 2.35	0.09	1.34	0.76 to 2.37	0.31
April	0.93	0.61 to 1.43	0.75	1.16	0.70 to 1.90	0.57	0.81	0.42 to 1.55	0.52
May	1.19	0.78 to 1.83	0.42	1.33	0.80 to 2.21	0.27	1.31	0.71 to 2.41	0.39
June	1.40	0.92 to 2.12	0.11	1.40	0.84 to 2.33	0.19	1.45	0.79 to 2.64	0.23
July	1.31	0.86 to 1.99	0.21	1.44	0.88 to 2.38	0.15	1.52	0.83 to 2.77	0.17
August	1.20	0.78 to 1.84	0.40	1.14	0.67 to 1.94	0.63	1.22	0.65 to 2.30	0.54
September	1.40	0.92 to 2.13	0.11	1.39	0.84 to 2.32	0.20	1.41	0.77 to 2.58	0.27
October	0.89	0.59 to 1.34	0.58	1.06	0.65 to 1.72	0.81	1.19	0.67 to 2.10	0.55
November	1.04	0.70 to 1.55	0.85	1.13	0.70 to 1.82	0.63	1.11	0.62 to 1.98	0.72
December	1.29	0.87 to 1.90	0.21	1.34	0.84 to 2.14	0.23	1.33	0.75 to 2.35	0.32
Surgical subspecialty									
Orthopaedics	1.00	-	-	1.00	-	-	1.00	-	-
Vascular	2.91	1.44 to 5.88	0.003	2.07	0.98 to 4.37	0.06	1.90	0.73 to 4.92	0.19
Cardiothoracic	1.10	0.52 to 2.34	0.80	1.16	0.55 to 2.45	0.70	1.35	0.55 to 3.27	0.51
General	1.65	0.70 to 3.89	0.26	1.92	0.81 to 4.55	0.14	2.06	0.72 to 5.88	0.18
Abdominal	1.51	0.69 to 3.29	0.30	1.44	0.67 to 3.13	0.35	1.30	0.52 to 3.27	0.58
Urology	0.82	0.33 to 2.05	0.67	0.63	0.24 to 1.64	0.34	0.90	0.29 to 2.86	0.87
Neurosurgery	0.79	0.22 to 2.78	0.71	0.85	0.23 to 3.07	0.80	0.53	0.10 to 2.71	0.44
Plastic surgery	0.75	0.13 to 4.41	0.75	0.59	0.08 to 4.38	0.60	0.54	0.06 to 4.51	0.57
Baseline HH compliance rate (per increment from 0 to 100%)	1.56	0.32 to 7.53	0.58	1.11	0.20 to 6.06	0.91	1.29	0.18 to 9.27	0.80

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio; HH, hand hygiene.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.

Table A5: Full model results for the multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced Standard Control	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Active Detection	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.12	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced Standard Control	0.89	0.78 to 1.01	0.06	0.88	0.75 to 1.04	0.13	0.89	0.73 to 1.07	0.21
Active Detection	0.85	0.74 to 0.97	0.02	0.83	0.69 to 0.99	0.04	0.81	0.66 to 1.00	0.05
Combined	0.82	0.71 to 0.95	0.01	0.84	0.70 to 1.00	0.06	0.84	0.68 to 1.03	0.10
Washout phase									
Change in level	3.01	1.05 to 8.63	0.04	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21
Patient-to-nurse ratio (per 1-unit increment)†	0.99	0.91 to 1.07	0.73	0.99	0.90 to 1.09	0.81	0.99	0.88 to 1.12	0.90
Calendar month									
January	1.00	-	-	1.00	-	-	1.00	-	-
February	1.06	0.54 to 2.07	0.86	1.58	0.66 to 3.81	0.31	1.22	0.45 to 3.28	0.69
March	1.13	0.60 to 2.16	0.70	1.68	0.72 to 3.95	0.23	1.51	0.60 to 3.84	0.38
April	1.32	0.68 to 2.57	0.41	2.12	0.89 to 5.03	0.09	1.52	0.57 to 4.09	0.41
May	2.00	1.06 to 3.76	0.03	3.07	1.34 to 7.04	0.01	2.61	1.04 to 6.52	0.04
June	2.34	1.25 to 4.39	0.01	3.33	1.43 to 7.74	0.01	3.06	1.22 to 7.65	0.02
July	2.19	1.16 to 4.15	0.02	3.20	1.35 to 7.57	0.01	2.94	1.14 to 7.59	0.03
August	2.25	1.18 to 4.26	0.01	2.80	1.18 to 6.65	0.02	2.77	1.08 to 7.10	0.03
September	2.35	1.26 to 4.39	0.01	2.88	1.24 to 6.72	0.01	2.89	1.15 to 7.26	0.02
October	1.49	0.81 to 2.73	0.20	2.66	1.20 to 5.90	0.02	2.39	1.00 to 5.72	0.05
November	1.70	0.93 to 3.09	0.09	2.52	1.12 to 5.67	0.03	1.86	0.75 to 4.62	0.18
December	1.96	1.06 to 3.60	0.03	2.44	1.06 to 5.66	0.04	2.02	0.80 to 5.08	0.14
Surgical subspecialty									
Orthopaedics	1.00	-	-	1.00	-	-	1.00	-	-
Vascular	2.14	1.00 to 4.58	0.05	1.57	0.70 to 3.54	0.27	1.29	0.50 to 3.33	0.60
Cardiothoracic	1.22	0.55 to 2.72	0.62	1.25	0.58 to 2.68	0.57	1.51	0.68 to 3.38	0.31
Neurosurgery	0.72	0.21 to 2.40	0.59	0.87	0.22 to 3.42	0.84	0.78	0.17 to 3.62	0.75
Plastic surgery	0.57	0.11 to 3.03	0.51	0.50	0.07 to 3.88	0.51	0.53	0.07 to 3.83	0.53
Baseline HH compliance rate (per increment from 0 to 100%)	2.07	0.45 to 9.53	0.35	1.37	0.29 to 6.53	0.69	2.15	0.34 to 13.60	0.42

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio; HH, hand hygiene.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular

surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

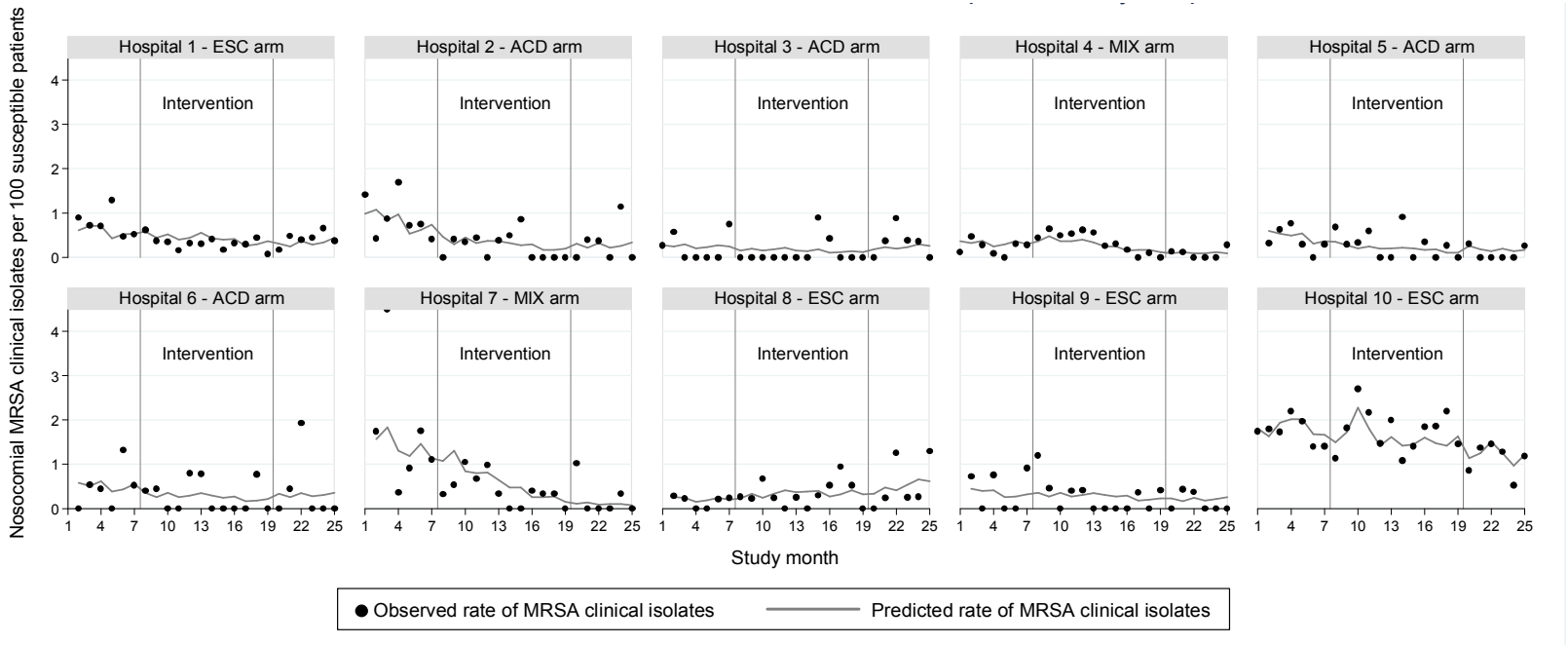
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.

Table A6: Exploratory analysis using multiple segmented multilevel Poisson regression models including interventions implemented by centres as covariates in the model*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase						
Trend	1.00	0.95 to 1.05	0.92	1.00	0.95 to 1.06	0.92
Hand Hygiene Promotion						
Change in level	1.05	0.87 to 1.27	0.63	1.03	0.83 to 1.28	0.80
Change in trend	0.98	0.92 to 1.04	0.47	0.99	0.92 to 1.06	0.68
MRSA screening						
Change in level	0.71	0.40 to 1.26	0.24	0.95	0.49 to 1.84	0.88
Change in trend†	0.91	0.85 to 0.98	0.01	0.92	0.85 to 0.99	0.03

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*The models used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, though there was no evidence that baseline trends significantly correlated with intercepts.
†Each additional month with x% compliance with admission screening would be associated with a reduction in the MRSA isolation rate by a factor of $aIRR^{x/100}$.

Figure A1 Nosocomial meticillin resistant *Staphylococcus aureus* isolation rates from clinical specimens by hospital



The solid dots represent the observed meticillin resistant *Staphylococcus aureus* (MRSA) rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*; ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).

ORION Checklist of items to include when reporting an outbreak or intervention study of a nosocomial organism

	Item No.	Descriptor	Reported on page no.
Title & Abstract	1	Description of paper as outbreak report or intervention study. Design of intervention study (eg Randomised Controlled Trial , Cluster Randomised Controlled Trial, Interrupted Time Series, Cohort study etc). Brief description of intervention and main outcomes.	1,2
Introduction Background	2	Scientific and/or local clinical background and rationale. Description of organism as epidemic, endemic or epidemic becoming endemic.	5, 6
Type of paper	3	Description of paper as Intervention study or an Outbreak Report. If an outbreak report, report the number of outbreaks.	5
Dates	4	Start and finish dates of the study or report.	6
Objectives	5	Objectives for outbreak reports. Hypotheses for intervention studies	5, 6
Methods Design	6	Study design. Use of EPOC classification recommended (RCT or CRCT, CBA, or ITS) Whether study was retrospective, prospective or ambidirectional. Whether decision to report or intervene was prompted by any outcome data. Whether study was formally implemented with predefined protocol and endpoints.	6-10
Participants	7	Number of patients admitted in study or outbreak. Summaries of distributions of age and lengths of stays. If possible, proportion admitted from other wards, hospitals, nursing homes or from abroad. Where relevant, potential risk factors for acquiring the organism. Eligibility criteria for study. Case definitions for outbreak report.	6, 7, 11, 27
Setting	8	Description of the unit, ward or hospital and, if a hospital, the units included. Number of beds, the presence and staffing levels of an infection control team.	6, 25, 26
Interventions	9	Definition of phases by major change in specific infection control practice (with start and stop dates). A summary table is strongly recommended with precise details of interventions, how and when administered in each phase.	6, 7
Culturing & Typing	10	Details of culture media, use of selective antibiotics and local and /or reference typing. Where relevant, details of environmental sampling.	8, 9
Infection-related outcomes	11	Clearly defined primary and secondary outcomes (eg incidence of infection, colonisation , bacteraemia) at regular time intervals (eg daily, weekly, monthly) rather than as totals for each phase, with at least three data points per phase and, for many two phase studies, 12 or more monthly data points per phase. Denominators (eg numbers admissions or discharges, patient bed days). If possible, prevalence of organism and incidence of colonisation on admission at same time intervals. Criteria for infection, colonisation on admission and directly attributable mortality. For short studies or outbreak reports, use of charts with duration patient stay & dates organism detected may be useful (see text)	8, 9
Economic outcomes	12	If a formal economic study done, definition of outcomes to be reported, description of resources used in interventions, with costs broken down to basic units, stating important assumptions.	Not applicable
Potential Threats to internal validity	13	Which potential confounders were considered, recorded or adjusted for (eg: changes in length of stay, case mix, bed occupancy, staffing levels, hand-hygiene compliance, antibiotic use, strain type, processing of isolates, seasonality). Description of measures to avoid bias including blinding & standardisation of outcome assessment & provision of care.	9-11
Sample size	14	Details of power calculations, where appropriate	10
Statistical methods	15	Description of statistical methods to compare groups or phases. Methods for any subgroup or adjusted analyses, distinguishing between planned and unplanned (exploratory) analysis. Unless outcomes are independent, statistical approaches able to account for dependencies in the outcome data should be used, adjusting, where necessary, for potential confounders. For outbreak reports statistical analysis may be inappropriate.	10, 11
Results Recruitment	16	For relevant designs the dates defining periods of recruitment and follow-up. A flow diagram is recommended to describe participant flow in each stage of study.	6, 11, 27
Outcomes & estimation	17	For the main outcomes, the estimated effect size and its precision (usually using confidence intervals). A graphical summary of the outcome data is often appropriate for dependent data (such as most time series).	13, 14, 29, Fig 3
Ancillary analyses	18	Any subgroup analyses should be reported and it should be stated whether or not it was planned (specified in the protocol) and possible confounders adjusted for	11,13,14,30
Adverse events	19	Pre-specified categories of adverse events and occurrences of these in each intervention group . This might include drug side effects, crude or disease specific mortality in antibiotic policy studies or opportunity costs in isolation studies.	Not applicable
Discussion Interpretation	20	For intervention studies an assessment of evidence for/against hypotheses, accounting for potential threats to validity of inference including regression to mean effects and reporting bias. For outbreak reports, consider clinical significance of observations and hypotheses generated to explain them.	15-17
Generalisability	21	External validity of the findings of the intervention study i.e. to what degree can results be expected to generalise to different target populations or settings.	15
Overall evidence	22	General interpretation of results in context of current evidence.	17, 18

Abbreviations: RCT: randomised controlled trial CRCT : Cluster Randomised Controlled Trial CBA: controlled before and after study ITS: interrupted time series

Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a multicentre intervention study

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Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a multicentre intervention study

Running head: MRSA control strategies in surgical patients

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Key words: meticillin resistant *Staphylococcus aureus*; methicillin resistant *Staphylococcus aureus*; screening; active surveillance cultures; hand hygiene; healthcare-associated infection

ABSTRACT

Objective: To compare the effect of two strategies (enhanced hand hygiene versus meticillin resistant *Staphylococcus aureus* [MRSA] screening and decolonisation) alone and in combination on MRSA rates in surgical wards.

Design: Prospective, controlled, interventional cohort study, with 6-month baseline, 12-month intervention, and 6-month washout phases.

Setting: 33 surgical wards in ten hospitals in nine countries in Europe and Israel.

Participants: All patients admitted to the enrolled wards for more than 24 hours.

Interventions: The two strategies compared were: 1) enhanced hand hygiene promotion; and 2) universal MRSA screening with contact precautions and decolonisation (intranasal mupirocin and chlorhexidine bathing) of MRSA carriers. Four hospitals were assigned to each intervention and two hospitals combined both strategies, using targeted MRSA screening.

Outcome measures: Monthly rates of MRSA clinical cultures per 100 susceptible patients (primary outcome) and MRSA infections per 100 admissions (secondary outcome). Planned subgroup analysis for clean surgery wards was performed.

Results: After adjusting for clustering and potential confounders, neither strategy when used alone was associated with significant changes in MRSA rates. Combining both strategies was associated with a reduction in the rate of MRSA clinical cultures of 12% per month (aIRR 0.88, 95% CI 0.79 to 0.98). In clean surgery wards, strategy 2 (MRSA screening, contact precautions, and decolonisation) was associated with decreasing rates of MRSA clinical cultures (15% monthly decrease, aIRR 0.85, 95% CI 0.74 to 0.97) and MRSA infections (17% monthly decrease, aIRR 0.83, 95% CI 0.69 to 0.99).

Conclusions: In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard and MRSA-specific infection control approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation was associated with significant reductions in MRSA clinical culture and infection rates.

Trial Registration: clinicaltrials.gov identifier: NCT00685867

ARTICLE SUMMARY

Article focus

- The relative effectiveness of different meticillin resistant *Staphylococcus aureus* (MRSA) control measures is controversial.
- This study directly compared the effect of two strategies (enhanced hand hygiene versus MRSA screening and decolonisation, alone and in combination) on MRSA rates in surgical wards.

Key messages

- Neither enhanced standard infection control measures (emphasising hand hygiene promotion) nor MRSA-specific control interventions (MRSA screening coupled with contact precautions and decolonisation therapy) when used alone for 12 months effectively reduced MRSA rates in surgical wards with relatively low MRSA rates.
- A combination of interventions, including targeted screening of high risk patients, did result in reduction in the rate of MRSA isolated from clinical cultures.
- In surgical subspecialties that perform clean surgery, MRSA screening coupled with contact precautions and decolonisation therapy effectively reduced both the rates of MRSA isolated from clinical cultures as well as MRSA infections.

Strengths and limitations of this study

- Unlike many previous studies, this was a large, prospective, multicentre, intervention study. The enrolled wards, from ten hospitals in Europe and Israel, varied in terms of infection control infrastructure and MRSA prevalence, thus the results are likely to be generalisable to other settings.
- Due to the nature of the quality improvement initiatives, investigators were not blinded to the allocated intervention. Interventions were not randomly allocated.

INTRODUCTION

Healthcare associated infections affect hundreds of millions of patients worldwide every year and represent an important cause of patient mortality and a major financial burden to health systems.[1] Meticillin resistant *Staphylococcus aureus* (MRSA), now endemic in many healthcare facilities, is a leading cause of healthcare associated infections,[2] and patients in surgical units are at increased risk due to factors such as invasive procedures, antibiotic exposure, and prolonged healthcare contact. A number of countries mandate implementation of control measures, including MRSA screening.[3,4] Not all mandated interventions, however, are supported by robust evidence.

Studies evaluating MRSA control strategies show conflicting results, particularly with regards to the use of active surveillance cultures.[5-7] It is argued that broader infection control approaches, such as improving hand hygiene (HH) practices, may be as successful as MRSA-specific strategies.[8,9] There are limitations, however, to current evidence with few prospective, controlled studies,[10,11] and many studies have assessed multiple interventions simultaneously.[12] Quantifying the relative benefits of individual approaches is important, particularly as some strategies have significant cost implications, and will allow efficient use of limited resources.

Due to the ongoing debate concerning optimal approaches to MRSA control,[13,14] we performed a prospective, interventional, quality improvement study to compare the effect of an enhanced HH promotion strategy to an MRSA screening, isolation and decolonisation strategy when used alone and in combination on the incidence rates of MRSA clinical cultures and infections in surgical patients admitted to healthcare facilities across Europe and

Israel. We also aimed to specifically assess these interventions in clean surgery wards where their benefits may be expected to be more pronounced.

METHODS

Study design and population

This prospective, controlled, multicentre, interventional cohort study with a three phase interrupted time series design was conducted between March 2008 and July 2010. Thirty-three surgical wards of ten hospitals in nine countries (Serbia, France, Spain [two hospitals], Italy, Greece, Scotland, Israel, Germany, and Switzerland) were enrolled. Wards included orthopaedic (8), vascular (6), cardiothoracic/cardiovascular (5), general (4), abdominal (4), urology (3), neurosurgery (2), and plastic surgery (1) subspecialties. Characteristics of the enrolled wards varied (table 1).

The study consisted of baseline (6 to 7 months), intervention (12 months), and washout (6 months) phases. During baseline and washout phases, wards employed their usual infection control practices. During the intervention phase, two strategies were investigated, with hospitals implementing one or both interventions in parallel (figure 1).

Interventions

The first intervention, the enhanced HH strategy, used the WHO multi-modal HH promotion method consisting of: 1) using alcohol-based handrub at the point of care, 2) training and education of healthcare workers, 3) observation and feedback of HH practices, 4) reminders in the workplace (e.g. posters), and 5) improving the safety climate in the institution with management support for the initiative.[15] Adherence to standard precautions (e.g. gloves for

body fluid contact) and isolation of MRSA patients according to local policies were encouraged.

The second intervention, the screening and decolonisation strategy, consisted of screening patients admitted for more than 24 hours for MRSA, on admission (within 48 hours) then weekly. Patients were excluded from screening if they were undergoing ambulatory surgery or had already been screened within 5 days prior to admission to the surgical ward. The nares, perineum, and wounds (if present) were swabbed. Chromogenic agar screening was used with the addition of polymerase chain reaction (PCR) testing during the latter part of the intervention phase for patients who had risk factors for MRSA (e.g. hospitalisation in the last year) whose chromogenic agar results were unlikely to be available before surgery. MRSA carriers were placed on contact precautions (gown and gloves during patient contact), administered decolonisation therapy with twice daily intranasal mupirocin and daily chlorhexidine washes for five days, and perioperative prophylaxis was modified to reflect MRSA carriage. Chlorhexidine bathing was limited to identified MRSA carriers and not used as a unit-wide intervention. Pre-emptive isolation was not used as part of this strategy.

The hospital was the unit for assignment of interventions due to practical reasons and the nature of the strategies. Four hospitals were assigned to each intervention and two hospitals used a combination of both strategies (the combined strategy) due to the introduction of national or local mandatory targeted MRSA screening policies (table 1). These assignments occurred prior to data collection.

Outcomes measures

The primary outcome measure was the monthly nosocomial MRSA isolation rate, defined as the number of MRSA clinical isolates (those from specimens collected other than for screening purposes, counting one isolate per patient per month), per 100 susceptible patients (not previously known to be MRSA colonised or infected). Isolates from specimens collected more than 48 hours after admission or within 30 days after discharge from study wards were considered nosocomial.

Secondary outcomes were the monthly rate of nosocomial MRSA infections per 100 admissions, and adherence to HH guidelines and contact precautions. Infections were defined using CDC criteria.[16] Adherence to HH guidelines was measured as the percentage of opportunities for HH in which staff used alcohol-based handrub and/or washed their hands according to the WHO method.[15] Adherence to contact precautions was measured as the percentage of randomly audited MRSA patients for whom precautions with gown and gloves during patient contact had been implemented.

Microbiological methods

Standardised laboratory manuals were provided to centres. Samples were processed in local laboratories using standard culture-based identification of MRSA from clinical specimens. In hospitals assigned to the screening and decolonisation arm, nasal and perineal swabs were pooled in the laboratory then plated directly onto chromogenic medium (BBL CHROMagar MRSA II, BD Diagnostics, Belgium) and also incubated overnight in an enrichment medium to increase test sensitivity.[17] Positive results could be reported within 24 to 48 hours.[18] PCR testing directly from pooled screening swabs was performed with the BD GeneOhm MRSA (BD Diagnostics, Belgium) or GeneXpert MRSA (Cepheid, Belgium) tests, which have turnaround times of 2 to 3 hours and 1.5 hours respectively (see online supplementary table

A1).[18] All laboratories participated in an external quality assurance program to evaluate their ability to detect, identify and perform antibiotic sensitivity testing on staphylococci from a variety of different specimens.[19] MRSA isolates were shipped to the central laboratory (University of Antwerp, Belgium) for confirmation of identification.

Data collection

Research personnel from each hospital collected data and implemented the interventions at their study site. These personnel were from departments that supervise infection control activities at the participating hospitals, including Infection Control, Infectious Diseases and Hospital Epidemiology departments. They were trained at the study coordinating centre with regards to the study protocol, the outcome definitions and the use of the data collection tools prior to the commencement of the study to ensure consistency of data collection across the hospitals. Local microbiology laboratory data were reviewed to obtain information regarding MRSA isolated from screening and clinical cultures. Infections were monitored by twice weekly ward visits to review medical records and interview staff. Surgical site infection surveillance occurred up to 30 days post-procedure (or 12 months after prosthetic device insertion).

HH adherence was monitored by the research personnel who had been trained and validated in the WHO method of direct observation at the study coordinating centre.[15] A standardised observation form was used by all centres. All hospitals collected data for 100 HH opportunities per ward during baseline and washout phases.[20] HH observers were specifically instructed not to provide feedback to healthcare workers concerning their HH practices during these study phases, and the observers were independent of surgical ward staff, reducing the likelihood of the Hawthorne effect, in which staff improve their practices when

they are aware that they are being observed.[21] During the intervention phase, there was intensive monitoring of HH practices in wards using the enhanced HH and combined strategies. In these wards, 100 HH opportunities per ward per month were observed as part of the intervention. Implementation of contact precautions, decolonisation therapy, and single room isolation for MRSA carriers was randomly audited each month. Signage of MRSA status and availability of gowns, gloves and alcohol-based handrub for contact with MRSA carriers was also audited.

Data regarding numbers of admissions, patient-days, surgical procedures, and level of staffing were collected. Ward-level data were submitted monthly to a central data management centre via a password protected secure online database which included range, consistency, and missing data checks. Meetings, site visits, and monthly teleconferences were held to review data, ensure adherence to study protocols, and address queries. Data were reviewed monthly for completeness and 6-monthly for validity by teleconferences with individual study sites. Institutional review boards of all centres approved the study with a waiver of individual informed consent.

Statistical analysis

The study was designed to detect a 30% difference in nosocomial MRSA isolation rate assuming a baseline rate of 1.0 clinical isolate per 100 susceptible patients and an absolute difference of 10% between intervention arms. Sample size calculations assumed a two-sided test, a type I error rate of 0.05 and 80% power, taking the wards as the unit of analysis. A minimum of 15 wards was required per study arm.

Crude MRSA rates were calculated by study arm. Adjusted incidence rate ratios (aIRR) were calculated using multilevel Poisson segmented regression accounting for stepwise changes in MRSA level and changes in log-linear trends associated with the interventions.[22] This analysis allowed for two levels of random-effects: hospital-level variation in intercepts and baseline trends, and nested ward-level variation in intercepts. It adjusted for exposure given by the monthly number of susceptible patients or admissions per ward and allowed for extra-Poisson variation. Surgical subspecialty, baseline HH compliance, seasonal effects (using calendar month), and patient-to-nurse ratios were adjusted for. Autocorrelation was accounted for using a lagged dependent variable. A similar analysis was performed for HH compliance, but used segmented multilevel logistic regression, adjusting for ward-specific baseline levels and trends, professional category, HH indication, patient-to-nurse ratios, and monthly MRSA colonisation pressure (number of days patients known to be MRSA colonised/infected were in the wards each month).

Planned subgroup analyses were performed by hospital and for clean surgery wards (cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery) as studies have shown that intranasal mupirocin, which is active against Gram-positive organisms, may be more effective for surgical site infection prevention in clean compared to clean-contaminated surgery (e.g. general or gastrointestinal surgery) where Gram-negative and anaerobic organisms may play a larger role.[23] As screening intensity varied in the combined arm, a planned exploratory analysis of MRSA outcome data was conducted to better quantify the intervention effects. It accounted for stepwise changes and log-linear trends in outcomes associated with the HH intervention, as well as the monthly proportion of patients screened and monthly cumulative screening rate on wards to account for changes in trends of outcomes associated with screening. Analyses were conducted with STATA 11.0 (STATA Corp, USA).

RESULTS

During the study period, there were a total of 126 750 admissions and 99 638 surgical procedures on the study wards. Baseline admission MRSA prevalence, without systematic screening of all admitted patients, was 0.8% (269 of 33 608), ranging from 0.1% to 2.2% across surgical wards of each hospital. Baseline HH adherence varied between hospitals (39.5% overall, 95% CI 38.1% to 40.9%) as did use of targeted MRSA screening (0 to 30.9% of admissions) (table 1). Study characteristics are shown in table 2 and online supplementary table A2.

Adherence to hand hygiene guidelines

In the enhanced HH and combined arms, HH compliance improved in all centres with overall compliance increasing from 49.3% (95% CI 47.2% to 51.4%) to 63.8% (95% CI 63.2% to 64.4%) from baseline to intervention phases (figure 2a). After multivariable analysis, commencing HH promotion was associated with a significant immediate increase in HH compliance (adjusted odds ratio [aOR] 1.19, 95% CI 1.01 to 1.42) (see online supplementary table A3). However, this benefit was not sustained after cessation of the HH campaign with a significant decreasing trend in HH adherence of 9% per month (aOR for month post-intervention 0.91, 95% CI 0.85 to 0.97) during the washout phase. In wards in the screening and decolonisation arm, where no HH promotion occurred, compliance remained low at 30.5% (95% CI 28.7% to 32.4%) at baseline and 23.9% (95% CI 22.0% to 25.9%) during the washout phase.

Screening, contact precautions and decolonisation of MRSA carriers

During the intervention phase, 9250 (75.3%) of 12 279 patients were screened on admission to wards in the screening and decolonisation arm. Admission MRSA prevalence was 2.1% (259 of 12 279), consisting of 27 patients (10.4%) with MRSA-positive clinical cultures and 232 patients (89.6%) identified by screening alone. PCR screening was used in addition to chromogenic agar cultures in 1047 (11.3%) of 9250 patients. Between baseline and intervention phases in screening and decolonisation wards, the proportion of audited MRSA carriers placed on contact precautions increased (81.1% to 90.7%), as did administration of decolonisation therapy (34.4% to 69.8%) (figure 3). However, the proportion of audited MRSA carriers in single rooms decreased (67.8% to 40.1%), possibly due to a shortage of rooms for the higher number of identified MRSA carriers. Reasons for non-adherence to decolonisation therapy included discharge prior to an MRSA-positive result, discharge prior to commencement of decolonisation therapy or the patient declining the intervention.

Screening occurred to a lesser extent in the other study arms (figure 2b). About 10% of admissions to wards in the enhanced HH arm were screened throughout the study. In wards in the combined arm, screening increased from 9.2% to 22.3%, then 36.9% during baseline, intervention, and washout phases respectively. In this arm, adherence to contact precautions was high throughout the study (93.0% to 99.6%), but only 32.9% of MRSA patients at baseline and 35.9% of patients during the intervention phase received decolonisation therapy (figure 3).

Nosocomial MRSA isolation rate from clinical cultures

Crude MRSA isolation rates from clinical cultures decreased in all study arms during the intervention phase (enhanced HH arm: 0.99 to 0.80; screening and decolonisation arm: 0.47 to 0.23; combined arm: 0.55 to 0.36; p=0.04; per 100 susceptible patients) (table 3). After

adjusting for clustering and potential confounders with multilevel segmented Poisson regression (table 4 and see online supplementary table A4 for full model), commencement of HH promotion in the enhanced HH arm was associated with an immediate non-significant increase in nosocomial MRSA isolation rate (aIRR 1.44, 95% CI 0.96 to 2.15) with no change in the trend in rates over time. In clean surgery wards, HH promotion was associated with a non-significant decreasing monthly MRSA isolation rate (aIRR 0.89, 95% CI 0.78 to 1.01) (table 5 and see online supplementary table A5 for full model).

In the screening and decolonisation arm, there were no significant changes in MRSA isolation rates. However, in clean surgery, this intervention was associated with a reduction in MRSA clinical cultures of 15% per month (aIRR 0.85, 95% CI 0.74 to 0.97).

In the combined arm (wards that used a combination of HH promotion with targeted screening), there was a significant decreasing trend in MRSA isolation rate of 12% per month overall (aIRR 0.88, 95% CI 0.79 to 0.98), and 18% per month in clean surgery (aIRR 0.82, 95% CI 0.71 to 0.95). Observed and model-predicted MRSA isolation rates from clinical cultures are illustrated in figure 4a and online supplementary figure A1.

During the washout phase, MRSA clinical culture isolation rates increased, particularly in clean surgery wards. This was due to an abrupt increase in the level of MRSA clinical cultures on cessation of the intervention phase in all study arms, but particularly with the conclusion of the intensive HH promotion campaign in the combined arm (data not shown).

Nosocomial MRSA infection rates

There were 470 nosocomial MRSA infections in total (335 [71.3%] surgical site, 41 [8.7%] bloodstream, and 94 [20.0%] other infections). Crude infection rates decreased over time in all study arms (table 3). After multivariable analysis (table 4, figure 4b and see online supplementary table A4), enhanced HH promotion alone was not associated with changes in MRSA infection rates. Both the screening/decolonisation and combined interventions resulted in non-significant decreasing trends in total MRSA infection (screening and decolonisation arm: aIRR 0.93, 95% CI 0.82 to 1.05; combined arm: aIRR 0.90, 95% CI 0.80 to 1.02) and surgical site infection rates (table 4, figure 4c and online supplementary table A4).

In clean surgery, the screening and decolonisation strategy was associated with significant reductions in total MRSA infection rate of 17% per month (aIRR 0.83, 95% CI 0.69 to 0.99) and MRSA surgical site infection rate of 19% per month (aIRR 0.81, 95% CI 0.66 to 1.00) (table 5 and online supplementary table A5).

Exploratory analysis to directly assess implemented interventions

The exploratory analysis did not show any significant effects of HH promotion on nosocomial MRSA isolation rates (see online supplementary table A6). The intensity of admission screening was associated with a decreasing trend in monthly MRSA isolation rate from clinical cultures (aIRR 0.91 per month with 100% compliance with screening, 95% CI 0.85 to 0.98). A similar effect was seen in the trend in MRSA infection rate (aIRR 0.92, 95% CI 0.85 to 0.99).

DISCUSSION

We found that as individual interventions, neither an enhanced HH promotion strategy nor universal MRSA screening with contact precautions and decolonisation of MRSA carriers were effective in reducing MRSA rates in surgical patients. However, using a combination of both HH promotion and targeted screening was associated with a reduction in MRSA isolation rate from clinical cultures of 12% per month. When the interventions were specifically evaluated in the subgroup of clean surgery wards, the screening and decolonisation strategy was most effective. In these wards, this intervention was associated with significant reductions in both MRSA clinical culture isolation rate of 15% per month and MRSA infection rate of 17% per month.

This study is unique in that it directly compared strategies individually and in combination using a large, prospective, controlled design.[10] In addition, we used a planned exploratory analysis to separate out the individual effects of the HH and MRSA screening strategies. Interventions were implemented and assessed under operational conditions in ten heterogeneous hospitals across Europe and Israel with widely varying infection control practices, staffing, infrastructure, and MRSA epidemiology, increasing the generalisability of our findings. This study has been reported using standard reporting guidelines that are designed to maximise transparency and scientific rigor of intervention studies of healthcare associated infection.[24]

Our analysis, which adjusted for confounders, seasonal effects and baseline MRSA trends, found no evidence that enhanced HH promotion was effective. MRSA rates are declining in many countries.[25] Failing to account for this would overestimate intervention effects. Overall baseline HH compliance was 49% in study wards that used the HH intervention. In settings where compliance is already above about 50%, modelling studies suggest that further

increases in compliance will have rapidly diminishing returns for reducing MRSA transmission.[26] In facilities with lower HH compliance or higher MRSA rates, this intervention may be more effective than we were able to demonstrate. In addition, HH campaigns involve education and behaviour change and are therefore unlikely to have a short term effect. Other studies have shown that they may be beneficial if activity is sustained over years.[27,28] Although we did not detect any intervention effects of the HH promotion strategy, cessation of this intervention was associated with an increase in MRSA rates in our study, suggesting that discontinuing activities to optimise HH practices may be detrimental.

Active MRSA surveillance identifies the reservoir of asymptomatic carriers, enabling early implementation of contact precautions and decolonisation, which can reduce transmission.[29,30] With universal screening, we found that 90% of MRSA-positive patients would have been missed using clinical cultures alone. However, our results suggest that rather than universal screening of all surgical patients, selective screening in clean surgery wards or a combination of HH promotion and targeted screening of high risk patients may be more effective strategies. The relative burden of Gram-positive infections is greater in clean compared to clean-contaminated surgery where other pathogens, including bowel flora, may be more important.[23,31] Thus it is biologically plausible that MRSA-specific interventions would potentially have a greater impact in clean surgery. Indeed, intranasal mupirocin has been shown to reduce surgical site infections in cardiothoracic and orthopaedic surgery, but is less effective in general surgery.[23] The commencement of such decolonisation regimens prior to surgical procedures, which can be facilitated by rapid detection of *S. aureus* carriage with molecular tests, is likely a key factor in the success of this approach.[32] The use of molecular tests in the latter part of the intervention phase in our study could have significantly

contributed to the reduction in MRSA rates seen over the period of the intervention phase, particularly in clean surgery wards.

The exploratory analysis suggests that screening intensity, rather than HH promotion, explained the intervention effects. It is curious, then, that universal screening did not perform better than HH promotion combined with targeted screening. A significant reduction in MRSA clinical cultures was seen with the combined strategy despite the enrolment of only two hospitals in this study arm. This suggests that the effect of the combined intervention was robust. Although the universal screening arm enrolled four hospitals, low baseline MRSA rates in this arm may have reduced our ability to detect significant effects. Shortage of isolation rooms may have also contributed. In addition, targeted screening may have been more effective if it identified "superspreaders",[33] facilitating more efficient use of resources including limited single rooms. Modelling studies also demonstrate that targeted screening has the advantage of increased cost-effectiveness compared to universal screening for reducing healthcare associated MRSA infections.[34]

This study adds to the conflicting literature regarding active surveillance cultures. Our results apply to surgical settings. The risk of MRSA infection in other wards, such as intensive care units or general medical wards, would differ due to variation in patient comorbidities and exposure to invasive procedures or antibiotics. It is also important to note that previous studies have used a variety of interventions in combination with screening. In some cases, the use of pre-emptive isolation in both study arms[35] or lack of decolonisation strategies,[6] may have led to effect sizes that studies had insufficient power to detect. Comparison of rapid screening to conventional rather than no screening,[35] differences in screening methods,[10]

variation in MRSA strains,[36] or limitations in study design and analyses[10,11] are other potential explanations for the conflicting results of screening studies.

There are some limitations to this study. Due to the nature of the interventions, which involved HH audits, promotion and feedback and/or implementation of MRSA screening, investigators were not blinded to study assignment. Although allocation of interventions was not randomised, we accounted for differences in hospitals by adjusting for potential confounders and comparing outcomes between baseline and intervention phases within the same study arm. Decisions to take culture samples were initiated by treating physicians, not research personnel, and standardised definitions for infections were used, reducing the likelihood of bias in the measurement of the study outcomes by unblinded assessors. We used MRSA-positive clinical cultures as our primary outcome. Although this measure does not distinguish between colonisation and infection, it can be a more sensitive marker for changes in MRSA disease rates.[37] We found the results for MRSA clinical cultures similar to those for infections, suggesting that this measure was clinically relevant. Patient-level data, such as age, comorbidities and length of stay, and antibiotic use were not measured for this study. However, results were similar when each centre was excluded in turn from the analysis (data not shown) so changes in factors in individual centres are unlikely to have had a major effect on study outcomes.

Conclusion

In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard infection control measures emphasising HH promotion and MRSA-specific (targeted screening) approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening

coupled with contact precautions and decolonisation of identified MRSA carriers was associated with significant reductions in MRSA clinical culture and infection rates. These findings are likely generalisable to other settings with varying infection control practices. In addition, the HH promotion strategy implemented in this study is already being used in many parts of the world. Therefore our study, which provides evidence that this intervention alone is not sufficient to reduce MRSA rates, potentially has widespread implications for best clinical practice recommendations and policy change. Further research regarding the cost-effectiveness of these interventions will allow better utilisation of limited healthcare resources.

REFERENCES

1 WHO. Report on the burden of endemic health care-associated infection worldwide. http://whqlibdoc.who.int/publications/2011/9789241501507_eng.pdf (accessed 24 April 2013).

2 Cosgrove SE, Qi Y, Kaye KS, et al. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 2005;26:166-74.

3 Weber SG, Huang SS, Oriola S, et al. Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: Position statement from the Joint SHEA and APIC Task Force. *Am J Infect Control* 2007;35:73-85.

4 UK Department of Health. MRSA Screening - Operational Guidance 2. http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_092844 (accessed 24 April 2013).

5 Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. *Ann Intern Med* 2008;148:409-18.

6 Huskins WC, Huckabee CM, O'Grady NP, et al. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med* 2011;364:1407-18.

7 Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 2008;299:1149-57.

8 Edmond MB, Ober JF, Bearman G. Active surveillance cultures are not required to control MRSA infections in the critical care setting. *Am J Infect Control* 2008;36:461-3.

9 Wenzel RP, Bearman G, Edmond MB. Screening for MRSA: a flawed hospital infection control intervention. *Infect Control Hosp Epidemiol* 2008;29:1012-8.

10 Tacconelli E, De Angelis G, de Waure C, et al. Rapid screening tests for meticillin-resistant *Staphylococcus aureus* at hospital admission: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:546-54.

11 Loveday HP, Pellowe CM, Jones SR, et al. A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant *Staphylococcus aureus* (1996-2004): report to the Joint MRSA Working Party (Subgroup A). *J Hosp Infect* 2006;63 Suppl 1:S45-70.

12 Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med* 2011;364:1419-30.

13 Farr BM, Jarvis WR. Searching many guidelines for how best to control methicillin-resistant *Staphylococcus aureus* healthcare-associated spread and infection. *Infect Control Hosp Epidemiol* 2009;30:808-9.

14 Nijssen S, Bonten MJ, Weinstein RA. Are active microbiological surveillance and subsequent isolation needed to prevent the spread of methicillin-resistant *Staphylococcus aureus*? *Clin Infect Dis* 2005;40:405-9.

15 WHO. WHO Guidelines on Hand Hygiene in Health Care. World Alliance for Patient Safety. Geneva: WHO Press Geneva, 2009.

16 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32.

17 Van Heirstraeten L, Cortinas Abrahantes J, Lammens C, et al. Impact of a short period of pre-enrichment on detection and bacterial loads of methicillin-resistant *Staphylococcus aureus* from screening specimens. *J Clin Microbiol* 2009;47:3326-8.

18 Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.
19 Gazin M, Lee A, Derde L, et al. Culture-based detection of methicillin-resistant *Staphylococcus aureus* by a network of European laboratories: an external quality assessment study. *Eur J Clin Microbiol Infect Dis* 2012;31:1765-70.
20 Lee A, Chalfine A, Daikos GL, et al. Hand hygiene practices and adherence determinants in surgical wards across Europe and Israel: a multicenter observational study. *Am J Infect Control* 2011;39:517-20.
21 Harbarth S, Pittet D, Grady L, et al. Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. *Pediatr Infect Dis J* 2002;21:489-95.
22 Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis* 2007;45:901-7.
23 Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005;26:916-22.
24 Stone SP, Cooper BS, Kibbler CC, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007;7:282-8.
25 Struelens MJ, Monnet DL. Prevention of methicillin-resistant *Staphylococcus aureus* infection: is Europe winning the fight? *Infect Control Hosp Epidemiol* 2010;31 Suppl 1:S42-4.
26 Cooper BS, Medley GF, Scott GM. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J Hosp Infect* 1999;43:131-47.
27 Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. *Lancet* 2000;356:1307-12.
28 Stone SP, Fuller C, Savage J, et al. Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. *BMJ* 2012;344:e3005.
29 Lee AS, Huttner B, Harbarth S. Control of methicillin-resistant Staphylococcus aureus. *Infect Dis Clin North Am* 2011;25:155-79.
30 Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis* 2009;48:922-30.
31 Huttner B, Robicsek AA, Gervaz P, et al. Epidemiology of methicillin-resistant Staphylococcus aureus carriage and MRSA surgical site infections in patients undergoing colorectal surgery: a cohort study in two centers. *Surg Infect (Larchmt)* 2012;13:401-5.
32 Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. *N Engl J Med* 2010;362:9-17.
33 Lloyd-Smith JO, Schreiber SJ, Kopp PE, et al. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005;438:355-9.
34 Hubben G, Bootsma M, Luteijn M, et al. Modelling the costs and effects of selective and universal hospital admission screening for methicillin-resistant Staphylococcus aureus. *PLoS One* 2011;6:e14783.

35 Jeyaratnam D, Whitty CJ, Phillips K, et al. Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008;336:927-30.
36 Cooper BS, Kypraios T, Batra R, et al. Quantifying type-specific reproduction numbers for nosocomial pathogens: evidence for heightened transmission of an Asian sequence type 239 MRSA clone. *PLoS Comput Biol* 2012;8:e1002454.
37 Walker S, Peto TE, O'Connor L, et al. Are there better methods of monitoring MRSA control than bacteraemia surveillance? An observational database study. *PLoS One* 2008;3:e2378.

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Competing interests

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Author contributions

Conceived and designed the experiments: SH CBB. Analysed the data: ASL BSC. Contributed reagents/materials: SMK HG. Wrote the first draft of the manuscript: ASL. Contributed to the writing of the manuscript: ASL SH BSC CBB AC GLD CF BC SL SMK JAM CMA AP GP BR HG. ICMJE criteria for authorship read and met: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Agree with manuscript results and conclusions: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Enrolled patients: ASL AC GLD CF BC SL JAM CMA AP GP BR. Statistical support: BSC.

Data sharing

The dataset is available from the corresponding author at stephan.harbarth@hcuge.ch.

FIGURE LEGENDS

Figure 1 Flow of study wards through each phase of the study

Figure 1 Legend
Ten hospitals in nine countries were enrolled and were allocated to one of three study arms during the intervention phase. The enhanced hand hygiene arm used hand hygiene promotion; the screening and decolonisation arm used universal meticillin resistant *Staphylococcus aureus* (MRSA) screening coupled with contact precautions and decolonisation therapy with intranasal mupirocin and chlorhexidine body washes for identified MRSA carriers; the combined arm used a combination of hand hygiene promotion and targeted MRSA screening.

Figure 2 Implementation of the interventions

Figure 2 Legend
The top panel (A) shows the monthly hand hygiene compliance rates for hospitals in the enhanced hand hygiene and combined arms that used hand hygiene promotion campaigns. The solid dots represent the observed compliance rates while the lines represent the predicted compliance rates based on the regression model. The bottom panel (B) shows the proportion of patients screened on admission to the study wards by study arm. HH, hand hygiene.

Figure 3 Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers

Figure 3 Legend
This figure shows the distribution of monthly adherence to infection control measures for randomly audited patients known to be colonised or infected with meticillin resistant *Staphylococcus aureus* (MRSA) for each study arm. The top panel (A) shows adherence to implementation of contact precautions, decolonisation therapy, and isolation in single rooms. The middle panel (B) shows the presence of signage of MRSA status on the patients' room, bed, or nursing chart. The bottom panel (C) shows the availability of gowns, gloves, and alcohol-based handrub in or at the entrance of the room. The horizontal line in each box represents the median, the box represents the interquartile range and the vertical lines represent the minimum and maximum values. MRSA, meticillin resistant *Staphylococcus aureus*.

Figure 4 Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm

Figure 4 Legend
The top panel (A) shows the nosocomial meticillin resistant *Staphylococcus aureus* (MRSA) isolaton rates from clinical specimens. The middle panel (B) shows the nosocomial MRSA infection rates. The bottom panel (C) shows the nosocomial MRSA surgical site infection rates. The solid dots represent the observed MRSA rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*.

TABLES

Table 1: Baseline phase characteristics of hospitals and wards enrolled in the study

	Hospital characteristics			Study ward characteristics						
Hospital	Total beds (n)	Total number of single rooms (%)	Ratio of infection control nurses to beds	Surgical subspecialties	Total beds (n)	Total admissions during baseline phase (n)	Mean patient-to-nurse ratio (SD)*	Percent hand hygiene compliance (95% CI)	Number of patients screened on admission (%)	Number identified MRSA positive on admission (%)†	Study arm
1	3611	45 (1.2)	1:240	Abdominal Cardiovascular Orthopaedic	588	8018	6.4 (1.2)	18.8 (15.1 to 22.9)	0 (0)	9 (0.1)	Enhanced hand hygiene
2	317	235 (74.1)	1:160	Cardiothoracic Orthopaedic Vascular	72	1613	4.1 (1.8)	75.4 (70.3 to 80.0)	29 (1.8)	20 (1.2)	Screening and decolonisation
3	850	135 (15.9)	1:425	Cardiovascular General Orthopaedic	75	1841	5.6 (0.7)	26.8 (24.4 to 29.4)	14 (0.8)	11 (0.6)	Screening and decolonisation
4	822	0 (0)	1:137	Abdominal Orthopaedic Urology Vascular	230	6574	3.7 (0.9)	39.3 (34.6 to 44.1)	182 (2.8)	21 (0.3)	Combined‡
5	545	89 (16.3)	1:272	General Neurosurgery Orthopaedic Vascular	121	1938	5.8 (1.5)	14.3 (11.3 to 17.6)	56 (2.9)	4 (0.2)	Screening and decolonisation
6	547	4 (0.7)	1:274	General Orthopaedic Vascular	93	1300	16.8 (2.5)	25.1 (20.7 to 30.1)	0 (0)	5 (0.4)	Screening and decolonisation
7	902	62 (6.9)	1:180	Abdominal General Vascular	84	1963	6.1 (1.5)	76.5 (71.3 to 81.1)	607 (30.9)	41 (2.1)	Combined‡

8	850	202 (23.8)	1:567	Orthopaedic Urology Vascular	87	2434	5.5 (0.6)	50.2 (44.6 to 55.8)	0 (0)	3 (0.1)	Enhanced hand hygiene
9	1350	150 (11.1)	1:260	Cardiothoracic Neurosurgery Plastic surgery	164	1561	10.0 (2.2)	67.0 (61.4 to 72.3)	17 (1.1)	15 (1.0)	Enhanced hand hygiene
10	2044	402 (19.7)	1:204	Abdominal Cardiovascular Orthopaedic Urology	302	6366	4.8 (0.4)	55.9 (51.2 to 60.5)	1666 (26.2)	140 (2.2)	Enhanced hand hygiene
Overall	11 838	1324 (11.2)			1816	33 608	6.6 (3.8)	39.5 (38.1 to 40.9)	2571 (7.6)	269 (0.8)	

MRSA, meticillin resistant *Staphylococcus aureus*.
*Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
†By screening or clinical culture.
‡Screening in hospitals in the combined arm was performed according to locally introduced policies. Hospital 4 used targeted screening of patients who were previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. Hospital 7 introduced universal screening in two of three study wards and targeted screening in the third ward. In this ward, patients who were previously known to be MRSA-positive, nursing home residents, patients admitted to the hospital in the last three months, contacts of MRSA-positive patients, and patients transferred from another ward or healthcare facility were screened.

Table 2: Study characteristics by study period

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Total patient-days (n)	264 035	496 975	249 119
Total surgical procedures (n)	27 768	49 747	22 123
Procedures in clean surgery wards (n)†	12 916	21 463	8787
Procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Number positive by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Number positive by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the screening and decolonisation arm and one hospital in each of the enhanced hand hygiene and combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table 3: Crude nosocomial meticillin resistant *Staphylococcus aureus* incidence rates and incidence rate ratios by study arm for each study period*

Outcome	Baseline phase	Intervention phase	Washout phase	Crude IRR (95% CI) for intervention vs. baseline phases	Crude IRR (95% CI) for washout vs. intervention phases
MRSA isolation rate from clinical cultures (no. per 100 susceptible patients)					
Enhanced hand hygiene	0.99 (181/183.47)	0.80 (279/349.50)	0.65 (106/163.83)	0.81 (0.67 to 0.98)	0.81 (0.65 to 1.01)
Screening and decolonisation	0.47 (31/66.61)	0.23 (28/122.56)	0.26 (17/66.04)	0.49 (0.29 to 0.82)	1.13 (0.62 to 2.06)
Combined	0.55 (47/85.35)	0.36 (60/165.23)	0.13 (8/63.04)	0.66 (0.45 to 0.97)	0.35 (0.17 to 0.73)
MRSA infection rate (no. per 100 admissions)					
Enhanced hand hygiene	0.58 (106/183.79)	0.50 (175/349.96)	0.45 (74/164.13)	0.87 (0.68 to 1.10)	0.90 (0.69 to 1.18)
Screening and decolonisation	0.24 (16/66.92)	0.19 (23/122.79)	0.17 (11/66.15)	0.78 (0.41 to 1.48)	0.89 (0.43 to 1.82)
Combined	0.29 (25/85.37)	0.19 (32/165.35)	0.13 (8/63.04)	0.66 (0.39 to 1.12)	0.66 (0.30 to 1.42)
MRSA surgical site infection rate (no. per 100 surgical procedures)					
Enhanced hand hygiene	0.60 (79/132.27)	0.49 (123/250.03)	0.42 (54/127.06)	0.82 (0.62 to 1.09)	0.86 (0.63 to 1.19)
Screening and decolonisation	0.26 (14/54.00)	0.15 (15/99.63)	0.16 (8/50.74)	0.58 (0.28 to 1.20)	1.05 (0.44 to 2.47)
Combined	0.20 (18/91.41)	0.14 (21/147.81)	0.07 (3/43.43)	0.72 (0.38 to 1.35)	0.49 (0.15 to 1.63)
MRSA bloodstream infection rate (no. per 10 000 patient-days)					
Enhanced hand hygiene	0.93 (14/15.0757)	0.56 (16/28.6667)	0.44 (6/13.5745)	0.60 (0.29 to 1.23)	0.79 (0.31 to 2.02)
Screening and decolonisation	0.17 (1/5.7754)	0.18 (2/11.2971)	0.17 (1/5.8473)	1.02 (0.09 to 11.28)	0.97 (0.09 to 10.65)
Combined	0.18 (1/5.5524)	0.00 (0/9.7337)	0.00 (0/5.4901)	-	-

IRR, incidence rate ratio; MRSA, meticillin resistant *Staphylococcus aureus*.

*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward.

Table 4: Multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced hand hygiene	1.44	0.96 to 2.15	0.076	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
Screening and decolonisation	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.070	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced hand hygiene	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Screening and decolonisation	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.162
Combined	0.88	0.79 to 0.98	0.016	0.90	0.80 to 1.02	0.096	0.86	0.74 to 1.01	0.059
Washout phase									
Change in level	1.90	0.91 to 3.95	0.087	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

Table 5: Multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced hand hygiene	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Screening and decolonisation	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.121	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced hand hygiene	0.89	0.78 to 1.01	0.063	0.88	0.75 to 1.04	0.127	0.89	0.73 to 1.07	0.21
Screening and decolonisation	0.85	0.74 to 0.97	0.019	0.83	0.69 to 0.99	0.041	0.81	0.66 to 1.00	0.054
Combined	0.82	0.71 to 0.95	0.007	0.84	0.70 to 1.00	0.055	0.84	0.68 to 1.03	0.095
Washout phase									
Change in level	3.01	1.05 to 8.63	0.041	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.

*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a multicentre intervention study

Running head: MRSA control strategies in surgical patients

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Key words: meticillin resistant *Staphylococcus aureus*; methicillin resistant *Staphylococcus aureus*; screening; active surveillance cultures; hand hygiene; healthcare-associated infection

ABSTRACT

Objective: To compare the effect of two strategies (enhanced ~~standard control~~hand hygiene versus meticillin resistant *Staphylococcus aureus* [MRSA] screening and decolonisation) alone and in combination on MRSA rates in surgical wards.

Design: Prospective, controlled, interventional cohort study, with 6-month baseline, 12-month intervention, and 6-month washout phases.

Setting: 33 surgical wards in ten hospitals in nine countries in Europe and Israel.

Participants: All patients admitted to the enrolled wards for more than 24 hours.

Interventions: The two strategies compared were: 1) enhanced hand hygiene~~standard control emphasising hand hygiene (HH)~~ promotion; and 2) universal MRSA screening with contact precautions and decolonisation (intranasal mupirocin and chlorhexidine bathing) of MRSA carriers. Four hospitals were assigned to each intervention and two hospitals combined both strategies, using targeted MRSA screening.

Outcome measures: Monthly rates of MRSA clinical cultures per 100 susceptible patients (primary outcome) and MRSA infections per 100 admissions (secondary outcome). Planned subgroup analysis for clean surgery wards was performed.

Results: ~~There were a total of 126,750 admissions to the study wards.~~ After adjusting for clustering and potential confounders, neither strategy when used alone was associated with significant changes in MRSA rates. Combining both strategies was associated with a reduction in the rate of MRSA clinical cultures of 12% per month (aIRR 0.88, 95% CI 0.79 to 0.98). In clean surgery wards, strategy 2 (MRSA screening, contact precautions, and decolonisation) was associated with decreasing rates of MRSA clinical cultures (15% monthly decrease, aIRR 0.85, 95% CI 0.74 to 0.97) and MRSA infections (17% monthly decrease, aIRR 0.83, 95% CI 0.69 to 0.99).

Conclusions: In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard and MRSA-specific infection control approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation was associated with significant reductions in MRSA clinical culture and infection rates.

Trial Registration: clinicaltrials.gov identifier: NCT00685867

ARTICLE SUMMARY

Article focus

- The relative effectiveness of different meticillin resistant *Staphylococcus aureus* (MRSA) control measures is controversial.
- This study directly compared the effect of two strategies (enhanced ~~standard control~~hand hygiene versus MRSA screening and decolonisation, alone and in combination) on MRSA rates in surgical wards.

Comment [AL1]: Reviewer 3 clarification point 4

Key messages

- Neither enhanced standard infection control measures (emphasising hand hygiene promotion) nor MRSA-specific control interventions (MRSA screening coupled with contact precautions and decolonisation therapy) when used alone for 12 months effectively reduced MRSA rates in surgical wards with relatively low MRSA rates.
- A combination of interventions, including targeted screening of high risk patients, did result in reduction in the rate of MRSA isolated from clinical cultures.
- In surgical subspecialties that perform clean surgery, MRSA screening coupled with contact precautions and decolonisation therapy effectively reduced both the rates of MRSA isolated from clinical cultures as well as MRSA infections.

Strengths and limitations of this study

- Unlike many previous studies, this was a large, prospective, multicentre, intervention study. The enrolled wards, from ten hospitals in Europe and Israel, varied in terms of infection control infrastructure and MRSA prevalence, thus the results are likely to be generalisable to other settings.
- Due to the nature of the quality improvement initiatives, investigators were not blinded to the allocated intervention. Interventions were not randomly allocated.

INTRODUCTION

Healthcare associated infections affect hundreds of millions of patients worldwide every year and represent an important cause of patient mortality and a major financial burden to health systems.[1] Meticillin resistant *Staphylococcus aureus* (MRSA), now endemic in many healthcare facilities, is a leading cause of healthcare associated infections,[2] and patients in surgical units are at increased risk due to factors such as invasive procedures, antibiotic exposure, and prolonged healthcare contact. A number of countries mandate implementation of control measures, including MRSA screening.[3,4] Not all mandated interventions, however, are supported by robust evidence.

Studies evaluating MRSA control strategies show conflicting results, particularly with regards to the use of active surveillance cultures.[5-7] It is argued that broader infection control approaches, such as improving hand hygiene (HH) practices, may be as successful as MRSA-specific strategies.[8,9] There are limitations, however, to current evidence with few prospective, controlled studies,[10,11] and many studies have assessed multiple interventions simultaneously.[12] Quantifying the relative benefits of individual approaches is important, particularly as some strategies have significant cost implications, and will allow efficient use of limited resources.

Due to the ongoing debate concerning optimal approaches to MRSA control,[13,14] we performed a prospective, interventional, quality improvement study to ~~directly~~ compare the effect of an enhanced ~~standard infection control~~HH promotion strategy~~, emphasising HH adherence,~~ to an MRSA screening, isolation and decolonisation strategy when used alone and in combination on the incidence rates of MRSA clinical cultures and infections in surgical

patients admitted to healthcare facilities across Europe and Israel. We also aimed to specifically assess these interventions in clean surgery wards where their benefits may be expected to be more pronounced.

Comment [AL2]: Reviewer 3 clarification point 3

METHODS

Study design and population

This~~e study was a~~ prospective, controlled, multicentre, interventional cohort study with a three phase interrupted time series design was conducted between March 2008 and July 2010.

Comment [AL3]: Reviewer 3 comment 1

Thirty-three surgical wards of ten hospitals in nine countries (Serbia, France, Spain [two hospitals], Italy, Greece, Scotland, Israel, Germany, and Switzerland) were enrolled. Wards included orthopaedic (8), vascular (6), cardiothoracic/cardiovascular (5), general (4), abdominal (4), urology (3), neurosurgery (2), and plastic surgery (1) subspecialties. Characteristics of the enrolled wards varied (table 1).

The study consisted of baseline (6 to 7 months), intervention (12 months), and washout (6 months) phases. During baseline and washout phases, wards employed their usual infection control practices. During the intervention phase, two strategies were investigated, with hospitals implementing one or both interventions in parallel (figure 1).

Interventions

The first intervention, ~~the E~~the enhanced HH~~Standard Control (ESC)~~ strategy, used the WHO multi-modal HH promotion method consisting of: 1) using alcohol-based handrub at the point of care, 2) training and education of healthcare workers, 3) observation and feedback of HH practices, 4) reminders in the workplace (e.g. posters), and 5) improving the

safety climate in the institution with management support for the initiative.[15] Adherence to standard precautions (e.g. gloves for body fluid contact) and isolation of MRSA patients according to local policies were encouraged.

The second intervention, the screening and decolonisation~~Active detection, Contact precautions and Decolonisation (ACD)~~ strategy, consisted of screening patients admitted for more than 24 hours for MRSA, on admission (within 48 hours) then weekly. Patients were excluded from screening if they were undergoing ambulatory surgery or had already been screened within 5 days prior to admission to the surgical ward. The nares, perineum, and wounds (if present) were swabbed. Chromogenic agar screening was used with the addition of polymerase chain reaction (PCR) testing during the latter part of the intervention phase for patients who had risk factors for MRSA (e.g. hospitalisation in the last year) whose chromogenic agar results were unlikely to be available before surgery. MRSA carriers were placed on contact precautions (gown and gloves during patient contact), administered decolonisation therapy with twice daily intranasal mupirocin and daily chlorhexidine washes for five days, and perioperative prophylaxis was modified to reflect MRSA carriage. Chlorhexidine bathing was limited to identified MRSA carriers and not used as a unit-wide intervention. Pre-emptive isolation was not used as part of this strategy.

The hospital was the unit for assignment of interventions due to practical reasons and the nature of the strategies. Four hospitals were assigned to each intervention and two hospitals used a combination of both strategies (~~MIX arm~~the combined strategy) due to the introduction of national or local mandatory targeted MRSA screening policies (table 1). These assignments occurred prior to data collection.

Comment [AL4]: Reviewer 3 comment 1. Reviewer 3 clarification point 5b.

Outcomes measures

The primary outcome measure was the monthly nosocomial MRSA isolation rate, defined as the number of MRSA clinical isolates (those from specimens collected other than for screening purposes, counting one isolate per patient per month), per 100 susceptible patients (not previously known to be MRSA colonised or infected). Isolates from specimens collected more than 48 hours after admission or within 30 days after discharge from study wards were considered nosocomial.

Secondary outcomes were the monthly rate of nosocomial MRSA infections per 100 admissions, and adherence to HH guidelines and contact precautions. Infections were defined using CDC criteria.[16] Adherence to HH guidelines was measured as the percentage of opportunities for HH in which staff used alcohol-based handrub and/or washed their hands according to the WHO method.[15] Adherence to contact precautions was measured as the percentage of randomly audited MRSA patients for whom precautions with gown and gloves during patient contact had been implemented.

Comment [AL5]: Reviewer 2 comment 3

Microbiological methods

Standardised laboratory manuals were provided to centres. Samples were processed in local laboratories using standard culture-based identification of MRSA from clinical specimens. In ~~ACD~~ hospitals assigned to the screening and decolonisation arm, nasal and perineal swabs were pooled in the laboratory then plated directly onto chromogenic medium (BBL CHROMagar MRSA II, BD Diagnostics, Belgium) and also incubated overnight in an enrichment medium to increase test sensitivity.[17] Positive results could be reported within 24 to 48 hours.[18] PCR testing directly from pooled screening swabs was performed with the BD GeneOhm MRSA (BD Diagnostics, Belgium) or GeneXpert MRSA (Cepheid, Belgium)

tests, which have turnaround times of 2 to 3 hours and 1.5 hours respectively (see online supplementary table A1).[18] All ~~L~~laboratories participated in an external quality assurance program to evaluate their ability to detect, identify and perform antibiotic sensitivity testing on staphylococci from a variety of different specimens.[19] MRSA isolates were shipped to the central laboratory (University of Antwerp, Belgium) for confirmation of identification.

Data collection

Research personnel from each hospital collected data and implemented the interventions at their study site. These personnel were from departments that supervise infection control activities at the participating hospitals, including Infection Control, Infectious Diseases and Hospital Epidemiology departments. They were trained at the study coordinating centre with regards to the study protocol, the outcome definitions and the use of the data collection tools prior to the commencement of the study to ensure consistency of data collection across the hospitals. Local microbiology laboratory data were reviewed to obtain information regarding MRSA isolated from screening and clinical cultures. Infections were monitored by twice weekly ward visits to review medical records and interview staff. Surgical site infection surveillance occurred up to 30 days post-procedure (or 12 months after prosthetic device insertion).

HH adherence was monitored by the ~~direct observation by~~ research personnel ~~who were independent of surgical ward staff.[15]~~ who had been trained and validated in the WHO method of direct observation at the study coordinating centre.[15] A standardised observation form was used by all centres. All hospitals collected data for 100 HH opportunities per ward during baseline and washout phases.[20] HH observers were specifically instructed not to provide feedback to healthcare workers concerning their HH practices during these study phases, and

Comment [AL6]: Reviewer 3 clarification point 1.

Comment [AL7]: Reviewer 2 comment 3.

the observers were independent of surgical ward staff, reducing the likelihood of the Hawthorne effect, in which staff improve their practices when they are aware that they are being observed.[21] During the intervention phase, there was intensive monitoring of HH practices in wards using the enhanced HH and combined strategies. In these wards, 100 HH opportunities per ward per month were observed as part of the intervention ~~in ESC and MIX wards only~~. Implementation of contact precautions, decolonisation therapy, and single room isolation ~~of~~for MRSA carriers was randomly audited each month. Signage of MRSA status and availability of gowns, gloves and alcohol-based handrub for contact with MRSA carriers was also audited.

Data regarding numbers of admissions, patient-days, surgical procedures, and level of staffing were collected.

Ward-level data were submitted monthly to a central data management centre via a password protected secure online database which included range, consistency, and missing data checks. Meetings, site visits, and monthly teleconferences were held to review data, ensure adherence to study protocols, and address queries. Data were reviewed monthly for completeness and 6-monthly for validity by teleconferences with individual study sites. Institutional review boards of all centres approved the study with a waiver of individual informed consent.

Comment [AL8]: Reviewer 1 comment 2. Reviewer 2 comment 4.

Comment [AL9]: Reviewer 2 comment 3.

Statistical analysis

The study was designed to detect a 30% difference in nosocomial MRSA isolation rate assuming a baseline rate of 1.0 clinical isolate per 100 susceptible patients and an absolute difference of 10% between intervention arms. Sample size calculations assumed a two-sided

test, a type I error rate of 0.05 and 80% power, taking the wards as the unit of analysis. A minimum of 15 wards was required per study arm.

Crude MRSA rates were calculated by study arm. Adjusted incidence rate ratios (aIRR) were calculated using multilevel Poisson segmented regression accounting for stepwise changes in MRSA level and changes in log-linear trends associated with the interventions.[22] This analysis allowed for two levels of random-effects: hospital-level variation in intercepts and baseline trends, and nested ward-level variation in intercepts. It adjusted for exposure given by the monthly number of susceptible patients or admissions per ward and allowed for extra-Poisson variation. Surgical subspecialty, baseline HH compliance, seasonal effects (using calendar month), and patient-to-nurse ratios were adjusted for. Autocorrelation was accounted for using a lagged dependent variable. A similar analysis was performed for HH compliance, but used segmented multilevel logistic regression, adjusting for ward-specific baseline levels and trends, professional category, HH indication, patient-to-nurse ratios, and monthly MRSA colonisation pressure (number of days patients known to be MRSA colonised/infected were in the wards each month).

Planned subgroup analyses were performed by hospital and for clean surgery wards (cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery) as studies have shown that intranasal mupirocin, which is active against Gg~~g~~ram-positive organisms, may be more effective for surgical site infection prevention in clean compared to clean-contaminated surgery (e.g. general or gastrointestinal surgery) where ~~g~~Gram-negative and anaerobic organisms may play a larger role.[23] As screening intensity varied in the combined~~MIX~~ arm, a planned exploratory analysis of MRSA outcome data was conducted to better quantify the intervention effects. It accounted for stepwise changes and log-linear trends in outcomes

associated with the HH intervention, as well as the monthly proportion of patients screened and monthly cumulative screening rate on wards to account for changes in trends of outcomes associated with screening. Analyses were conducted with STATA 11.0 (STATA Corp, USA).

RESULTS

During the study period, there were a total of 126 750 admissions and 99 638 surgical procedures on the study wards. Baseline admission MRSA prevalence, without systematic screening of all admitted patients, was 0.8% (269 of 33 608), ranging from 0.1% to 2.2% across surgical wards of each hospital. Baseline HH adherence varied between hospitals (39.5% overall, 95% CI 38.1% to 40.9%) as did use of targeted MRSA screening (0 to 30.9% of admissions) (table 1). Study characteristics are shown in table 2 and online supplementary table A2.

Adherence to hand hygiene guidelines

In the enhanced HH and combined~~ESC and MIX~~ arms, HH compliance improved in all centres with overall compliance increasing from 49.3% (95% CI 47.2% to 51.4%) to 63.8% (95% CI 63.2% to 64.4%) from baseline to intervention phases (figure ~~1~~2a). After multivariable analysis, commencing HH promotion was associated with a significant immediate increase in HH compliance (adjusted odds ratio [aOR] 1.19, 95% CI 1.01 to 1.42) (see online supplementary table A3). However, this benefit was not sustained after cessation of the HH campaign with a significant decreasing trend in HH adherence of 9% per month (aOR for month post-intervention 0.91, 95% CI 0.85 to 0.97) during the washout phase. In ~~ACD~~ wards in the screening and decolonisation arm, where no HH promotion occurred,

compliance remained low at 30.5% (95% CI 28.7% to 32.4%) at baseline and 23.9% (95% CI 22.0% to 25.9%) during the washout phase.

Screening~~Active detection~~, contact precautions and decolonisation of MRSA carriers

During the intervention phase, 9250 (75.3%) of 12 279 patients were screened on admission to ~~ACD~~ wards in the screening and decolonisation arm. Admission MRSA prevalence was 2.1% (259 of 12 279), consisting of 27 patients (10.4%) with MRSA-positive clinical cultures and 232 patients (89.6%) identified by screening alone. PCR screening was used in addition to chromogenic agar cultures in 1047 (11.3%) of 9250 patients. Between baseline and intervention phases in ~~ACD~~screening and decolonisation wards, the proportion of audited MRSA carriers placed on contact precautions increased (81.1% to 90.7%), as did administration of decolonisation therapy (34.4% to 69.8%) (figure ~~2~~3). However, the proportion of audited MRSA carriers in single rooms decreased (67.8% to 40.1%), possibly due to a shortage of rooms for the higher number of identified MRSA carriers. Reasons for non-adherence to decolonisation therapy included discharge prior to an MRSA-positive result, discharge prior to commencement of decolonisation therapy or the patient declining the intervention.

Comment [AL10]: Reviewer 1 comment 3.

Screening occurred to a lesser extent in the other study arms (figure ~~1~~2b). About 10% of admissions to ~~ESC~~ wards in the enhanced HH arm were screened throughout the study. In ~~MIX~~ wards in the combined arm, screening increased from 9.2% to 22.3%, then 36.9% during baseline, intervention, and washout phases respectively. In this arm, adherence to contact precautions was high throughout the study (93.0% to 99.6%), but only 32.9% of MRSA patients at baseline and 35.9% of patients during the intervention phase received decolonisation therapy (figure ~~3~~2).

Nosocomial MRSA isolation rate from clinical cultures

Crude MRSA isolation rates from clinical cultures decreased in all study arms during the intervention phase (enhanced HH~~ESC~~ arm: 0.99 to 0.80; ~~ACD~~screening and decolonisation arm: 0.47 to 0.23; ~~MIX~~ combined arm: 0.55 to 0.36; p=0.04; per 100 susceptible patients) (table 3). After adjusting for clustering and potential confounders with multilevel segmented Poisson regression (table 4 and see online supplementary table A4 for full model), commencement of HH promotion in the enhanced HH ~~(ESC~~ arm~~)~~ was associated with an immediate non-significant increase in nosocomial MRSA isolation rate (aIRR 1.44, 95% CI 0.96 to 2.15) with no change in the trend in rates over time. In clean surgery wards, HH promotion was associated with a non-significant decreasing monthly MRSA isolation rate (aIRR 0.89, 95% CI 0.78 to 1.01) (table 5 and see online supplementary table A5 for full model).

In the screening and decolonisation arm~~Screening, contact precautions and decolonisation (ACD arm)~~, there were no ~~was not associated with~~ significant changes in MRSA isolation rates. However, in clean surgery, this intervention was associated with a reduction in MRSA clinical cultures of 15% per month (aIRR 0.85, 95% CI 0.74 to 0.97).

In the combined arm (wards that used a combination of ~~Combining~~ HH promotion with targeted screening), ~~(MIX arm) was associated with~~there was a significant decreasing trend in MRSA isolation rate of 12% per month overall (aIRR 0.88, 95% CI 0.79 to 0.98), and 18% per month in clean surgery (aIRR 0.82, 95% CI 0.71 to 0.95). Observed and model-predicted MRSA isolation rates from clinical cultures are illustrated in figure 4~~3~~a and online supplementary figure A1.

During the washout phase, MRSA clinical culture isolation rates increased, particularly in clean surgery wards. This was due to an abrupt increase in the level of MRSA clinical cultures on cessation of the intervention phase in all study arms, but particularly with the conclusion of the intensive HH promotion campaign in the combined arm (data not shown).

Comment [AL11]: Reviewer 3 comment 2.

Nosocomial MRSA infection rates

There were 470 nosocomial MRSA infections in total (335 [71.3%] surgical site, 41 [8.7%] bloodstream, and 94 [20.0%] other infections). Crude infection rates decreased over time in all study arms (table 3). After multivariable analysis (table 4, figure 43b and see online supplementary table A4), enhanced HH promotion alone~~(ESC arm)~~ was not associated with changes in MRSA infection rates. Both the screening/decolonisation and combined interventions resulted in non-significant decreasing trends in total MRSA infection (screening and decolonisation~~ACD~~ arm: aIRR 0.93, 95% CI 0.82 to 1.05; ~~MIX~~ combined arm: aIRR 0.90, 95% CI 0.80 to 1.02) and surgical site infection rates (table 4, figure 43c and online supplementary table A4).

In clean surgery, the ~~ACD~~ screening and decolonisation strategy was associated with significant reductions in total MRSA infection rate of 17% per month (aIRR 0.83, 95% CI 0.69 to 0.99) and MRSA surgical site infection rate of 19% per month (aIRR 0.81, 95% CI 0.66 to 1.00) (table 5 and online supplementary table A5).

Exploratory analysis to directly assess implemented interventions

The exploratory analysis did not show any significant effects of HH promotion on nosocomial MRSA isolation rates (see online supplementary table A6). The intensity of

admission screening was associated with a decreasing trend in monthly MRSA isolation rate from clinical cultures (aIRR 0.91 per month with 100% compliance with screening, 95% CI 0.85 to 0.98). A similar effect was seen in the trend in MRSA infection rate (aIRR 0.92, 95% CI 0.85 to 0.99).

DISCUSSION

We found that as individual interventions, neither an enhanced HH promotion ~~standard control~~ strategy ~~using HH promotion~~ nor universal MRSA screening with contact precautions and decolonisation of MRSA carriers were effective in reducing MRSA rates in surgical patients. However, using a combination of both HH promotion and targeted screening was associated with a reduction in MRSA isolation rate from clinical cultures of 12% per month. ~~In addition, w~~When the interventions were specifically evaluated in the subgroup of clean surgery wards, the screening and ~~/~~decolonisation strategy was most effective. In these wards, this intervention was associated with significant reductions in both MRSA clinical culture isolation rate of 15% per month and MRSA infection rate of 17% per month.

This study is unique in that it directly compared strategies individually and in combination using a large, prospective, controlled design.[10] In addition, we used a planned exploratory analysis to separate out the individual effects of the HH and MRSA screening strategies. Interventions were implemented and assessed under operational conditions in ten heterogeneous hospitals across Europe and Israel with widely varying infection control practices, staffing, infrastructure, and MRSA epidemiology, increasing the generalisability of our findings. This study has been reported using standard reporting guidelines that are

Comment [AL12]: Reviewer 4 comment 2.

designed to maximise transparency and scientific rigor of intervention studies of healthcare associated infection.[24]

Our analysis, which adjusted for confounders, seasonal effects and baseline MRSA trends, found no evidence that enhanced ~~standard infection control measures~~ HH promotion was~~were~~ effective. MRSA rates are declining in many countries.[25] Failing to account for this would overestimate intervention effects. Overall baseline HH compliance was 49% in study wards that used the HH intervention. In settings where compliance is already above about 50%, modelling studies suggest that further increases in compliance will have rapidly diminishing returns for reducing MRSA transmission.[26] In facilities with lower HH compliance or higher MRSA rates, this intervention may be more effective than we were able to demonstrate. In addition, HH campaigns involve education and behaviour change and are therefore unlikely to have a short term effect. Other studies have shown that they may be beneficial if activity is sustained over years.[27,28] Although we did not detect any intervention effects of the HH promotion strategy, cessation of this intervention was associated with an increase in MRSA rates in our study, suggesting that discontinuing activities to optimise HH practices may be detrimental.

Active MRSA surveillance identifies the reservoir of asymptomatic carriers, enabling early implementation of contact precautions and decolonisation, which can reduce transmission.[29,30] With universal screening, we found that 90% of MRSA-positive patients would have been missed using clinical cultures alone. However, ~~O~~our results suggest that rather than universal screening of all surgical patients, ~~that~~ selective screening in ~~(~~clean surgery~~)~~ wards or a combination of HH promotion and targeted ~~(high risk patient)~~ screening of high risk patients may be more effective strategies ~~than universal screening~~. The relative

Comment [AL13]: Reviewer 3 clarification point 7.

Comment [AL14]: Reviewer 3 clarification point 8.

Comment [AL15]: Reviewer 3 clarification point 9.

Comment [AL16]: Reviewer 3 clarification point 10a, 10b.

burden of ~~g~~Gram-positive infections is greater in clean compared to clean-contaminated surgery where other pathogens, including bowel flora, may be more important.[23,31] Thus it is biologically plausible that MRSA-specific interventions would potentially have a greater impact in clean surgery. Indeed, intranasal mupirocin has been shown to reduce surgical site infections in cardiothoracic and orthopaedic surgery, but is less effective in general surgery.[23] The commencement of such decolonisation regimens prior to surgical procedures, which can be facilitated by rapid detection of *S. aureus* carriage with molecular tests, is likely a key factor in the success of this approach.[32] The use of molecular tests in the latter part of the intervention phase in our study could have significantly contributed to the reduction in MRSA rates seen over the period of the intervention phase, particularly in clean surgery wards.

Comment [AL17]: Reviewer 3 clarification point 5a

Comment [AL18]: Reviewer 1 comment 1.

The exploratory analysis suggests that screening intensity, rather than HH promotion, explained the intervention effects. It is curious, then, that universal screening did not perform better than HH promotion combined with targeted screening. A significant reduction in MRSA clinical cultures was seen with the combined strategy despite the enrolment of only two hospitals in this study arm. This suggests that the effect of the combined intervention was robust. Although the universal screening arm enrolled four hospitals, ~~L~~low baseline MRSA rates in this~~e universal screening~~ arm may have reduced our ability to detect significant effect~~s~~s. Shortage of isolation rooms may have also contributed. In addition, targeted screening may have been more effective if it identified "superspreaders",[33] facilitating more eff~~ective~~icient use of resources including limited single rooms. Modelling studies also demonstrate that targeted screening has the advantage of increased cost-effectiveness compared to universal screening for reducing healthcare associated MRSA infections.[34]

Comment [AL19]: Reviewer 3 clarification point 10c.

Comment [AL20]: Reviewer 3 clarification point 10a

This study adds to the conflicting literature regarding active surveillance cultures. Our results apply to surgical settings. The risk of MRSA infection in other wards, such as intensive care units or general medical wards, would differ due to variation in patient comorbidities and exposure to invasive procedures or antibiotics. It is also important to note that previous studies have used a variety of interventions in combination with screening. In some cases, the use of pre-emptive isolation in both study arms[35] or lack of decolonisation strategies,[6] may have led to effect sizes that studies had insufficient power to detect. Comparison of rapid screening to conventional rather than no screening,[35] differences in screening methods,[10] variation in MRSA strains,[36] or limitations in study design and analyses[10,11] are other potential explanations for the conflicting results of screening studies.

There are some limitations to this study. Due to the nature of the interventions, which involved HH audits, promotion and feedback and/or implementation of MRSA screening, investigators were not blinded to study assignment. Although allocation of interventions was not randomised, we accounted for differences in hospitals by adjusting for potential confounders and comparing outcomes between baseline and intervention phases within the same study arm. Decisions to take culture samples were initiated by treating physicians, not research personnel, and standardised definitions for infections were used, reducing the likelihood of bias in the measurement of the study outcomes ~~from~~by unblinded assessors. We used MRSA-positive clinical cultures as our primary outcome. Although this measure does not distinguish between colonisation and infection, it can be a more sensitive marker for changes in MRSA disease rates.[37] We found the results for MRSA clinical cultures similar to those for infections, suggesting that this measure was clinically relevant. Patient-level data, such as age, comorbidities and length of stay, and antibiotic use were not measured for this study. However, results were similar when each centre was excluded in turn from the analysis

Comment [AL21]: Reviewer 2 comment 1
Reviewer 3 comment 3

(data not shown) so changes in factors in individual centres are unlikely to have had a major effect on study outcomes.

Comment [AL22]: Reviewer 2 comment 1. Reviewer 3 comment 4.

Conclusion

In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard infection control measures emphasising HH promotion and MRSA-specific (targeted screening) approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation of identified MRSA carriers was associated with significant reductions in MRSA clinical culture and infection rates. These findings are likely generalisable to other settings with varying infection control practices. In addition, the HH promotion strategy implemented in this study is already being used in many parts of the world. Therefore our study, which provides evidence that this intervention alone is not sufficient to reduce MRSA rates, potentially has widespread implications for best clinical practice recommendations and policy change. ~~Our results highlight the relative effectiveness of different MRSA control strategies, enabling optimisation of infection prevention approaches.~~ Further research regarding the cost-effectiveness of these interventions will allow better utilisation of limited healthcare resources.

Comment [AL23]: Reviewer 3 clarification point 5a.

Comment [AL24]: Reviewer 3 clarification point 11a.

Comment [AL25]: Reviewer 3 clarification point 11b.

REFERENCES

1 WHO. Report on the burden of endemic health care-associated infection worldwide. http://whqlibdoc.who.int/publications/2011/9789241501507_eng.pdf (accessed 24 April 2013).

2 Cosgrove SE, Qi Y, Kaye KS, et al. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 2005;26:166-74.

3 Weber SG, Huang SS, Oriola S, et al. Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: Position statement from the Joint SHEA and APIC Task Force. *Am J Infect Control* 2007;35:73-85.

4 UK Department of Health. MRSA Screening - Operational Guidance 2. http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_092844 (accessed 24 April 2013).

5 Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. *Ann Intern Med* 2008;148:409-18.

6 Huskins WC, Huckabee CM, O'Grady NP, et al. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med* 2011;364:1407-18.

7 Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 2008;299:1149-57.

8 Edmond MB, Ober JF, Bearman G. Active surveillance cultures are not required to control MRSA infections in the critical care setting. *Am J Infect Control* 2008;36:461-3.

9 Wenzel RP, Bearman G, Edmond MB. Screening for MRSA: a flawed hospital infection control intervention. *Infect Control Hosp Epidemiol* 2008;29:1012-8.

10 Tacconelli E, De Angelis G, de Waure C, et al. Rapid screening tests for meticillin-resistant *Staphylococcus aureus* at hospital admission: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:546-54.

11 Loveday HP, Pellowe CM, Jones SR, et al. A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant *Staphylococcus aureus* (1996-2004): report to the Joint MRSA Working Party (Subgroup A). *J Hosp Infect* 2006;63 Suppl 1:S45-70.

12 Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med* 2011;364:1419-30.

13 Farr BM, Jarvis WR. Searching many guidelines for how best to control methicillin-resistant *Staphylococcus aureus* healthcare-associated spread and infection. *Infect Control Hosp Epidemiol* 2009;30:808-9.

14 Nijssen S, Bonten MJ, Weinstein RA. Are active microbiological surveillance and subsequent isolation needed to prevent the spread of methicillin-resistant *Staphylococcus aureus*? *Clin Infect Dis* 2005;40:405-9.

15 WHO. WHO Guidelines on Hand Hygiene in Health Care. World Alliance for Patient Safety. Geneva: WHO Press Geneva, 2009.

16 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32.

17 Van Heirstraeten L, Cortinas Abrahantes J, Lammens C, et al. Impact of a short period of pre-enrichment on detection and bacterial loads of methicillin-resistant *Staphylococcus aureus* from screening specimens. *J Clin Microbiol* 2009;47:3326-8.

18 Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.
19 Gazin M, Lee A, Derde L, et al. Culture-based detection of methicillin-resistant *Staphylococcus aureus* by a network of European laboratories: an external quality assessment study. *Eur J Clin Microbiol Infect Dis* 2012;31:1765-70.
20 Lee A, Chalfine A, Daikos GL, et al. Hand hygiene practices and adherence determinants in surgical wards across Europe and Israel: a multicenter observational study. *Am J Infect Control* 2011;39:517-20.
21 Harbarth S, Pittet D, Grady L, et al. Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. *Pediatr Infect Dis J* 2002;21:489-95.
22 Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis* 2007;45:901-7.
23 Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005;26:916-22.
24 Stone SP, Cooper BS, Kibbler CC, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007;7:282-8.
25 Struelens MJ, Monnet DL. Prevention of methicillin-resistant *Staphylococcus aureus* infection: is Europe winning the fight? *Infect Control Hosp Epidemiol* 2010;31 Suppl 1:S42-4.
26 Cooper BS, Medley GF, Scott GM. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J Hosp Infect* 1999;43:131-47.
27 Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. *Lancet* 2000;356:1307-12.
28 Stone SP, Fuller C, Savage J, et al. Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. *BMJ* 2012;344:e3005.
29 Lee AS, Huttner B, Harbarth S. Control of methicillin-resistant Staphylococcus aureus. *Infect Dis Clin North Am* 2011;25:155-79.
30 Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis* 2009;48:922-30.
31 Huttner B, Robicsek AA, Gervaz P, et al. Epidemiology of methicillin-resistant Staphylococcus aureus carriage and MRSA surgical site infections in patients undergoing colorectal surgery: a cohort study in two centers. *Surg Infect (Larchmt)* 2012;13:401-5.
32 Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of Staphylococcus aureus. *N Engl J Med* 2010;362:9-17.
33 Lloyd-Smith JO, Schreiber SJ, Kopp PE, et al. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005;438:355-9.
34 Hubben G, Bootsma M, Luteijn M, et al. Modelling the costs and effects of selective and universal hospital admission screening for methicillin-resistant Staphylococcus aureus. *PLoS One* 2011;6:e14783.

35 Jeyaratnam D, Whitty CJ, Phillips K, et al. Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008;336:927-30.
36 Cooper BS, Kypraios T, Batra R, et al. Quantifying type-specific reproduction numbers for nosocomial pathogens: evidence for heightened transmission of an Asian sequence type 239 MRSA clone. *PLoS Comput Biol* 2012;8:e1002454.
37 Walker S, Peto TE, O'Connor L, et al. Are there better methods of monitoring MRSA control than bacteraemia surveillance? An observational database study. *PLoS One* 2008;3:e2378.

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Competing interests

SH is a member of the speakers' bureau for bioMérieux and Pfizer, and the scientific advisory board of Destiny Pharma, DaVolterra, and bioMérieux. He has received financial support for MRSA research activities from Geneva University Hospitals, B.Braun, and Pfizer. AP is a member of the speakers' bureau for Cubist and has received financial support for MRSA research activities from BD. There were no other financial or non-financial relationships, or interests that may be relevant to the submitted work.

Author contributions

Conceived and designed the experiments: SH CBB. Analysed the data: ASL BSC. Contributed reagents/materials: SMK HG. Wrote the first draft of the manuscript: ASL. Contributed to the writing of the manuscript: ASL SH BSC CBB AC GLD CF BC SL SMK JAM CMA AP GP BR HG. ICMJE criteria for authorship read and met: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Agree with manuscript results and conclusions: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Enrolled patients: ASL AC GLD CF BC SL JAM CMA AP GP BR. Statistical support: BSC.

Data sharing

The dataset is available from the corresponding author at stephan.harbarth@hcuge.ch.

FIGURE LEGENDS

Figure 1 Flow of study wards through each phase of the study

Figure 1 Legend
Ten hospitals in nine countries were enrolled and were allocated to one of three study arms during the intervention phase. The enhanced hand hygiene arm used hand hygiene promotion; the screening and decolonisation arm used universal meticillin resistant *Staphylococcus aureus* (MRSA) screening coupled with contact precautions and decolonisation therapy with intranasal mupirocin and chlorhexidine body washes for identified MRSA carriers; the combined arm used a combination of hand hygiene promotion and targeted MRSA screening.

Figure ~~1~~2 Implementation of the interventions

Figure ~~1~~2 Legend
The top panel (A) shows the monthly hand hygiene compliance rates for hospitals in the enhanced hand hygiene and combined arms that used hand hygiene promotion campaigns. The solid dots represent the observed compliance rates while the lines represent the predicted compliance rates based on the regression model. The bottom panel (B) shows the proportion of patients screened on admission to the study wards by study arm. HH, hand hygiene.~~ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using meticillin resistant *Staphylococcus aureus* [MRSA] screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening).~~

Figure ~~2~~3 Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers

Figure ~~2~~3 Legend
This figure shows the distribution of monthly adherence to infection control measures for randomly audited patients known to be colonised or infected with meticillin resistant *Staphylococcus aureus* (MRSA) for each study arm. The top panel (A) shows adherence to implementation of contact precautions, decolonisation therapy, and isolation in single rooms. The middle panel (B) shows the presence of signage of MRSA status on the patients' room, bed, or nursing chart. The bottom panel (C) shows the availability of gowns, gloves, and alcohol-based handrub in or at the entrance of the room. The horizontal line in each box represents the median, the box represents the interquartile range and the vertical lines represent the minimum and maximum values. MRSA, meticillin resistant *Staphylococcus aureus*~~; ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening)~~.

Figure ~~3~~4 Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm

Figure ~~3~~4 Legend
The top panel (A) shows the nosocomial meticillin resistant *Staphylococcus aureus* (MRSA) isolaton rates from clinical specimens. The middle panel (B) shows the nosocomial MRSA infection rates. The bottom panel (C) shows the nosocomial MRSA surgical site infection rates. The solid dots represent the observed MRSA rates while the lines represent the

predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*~~; ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening)~~.

TABLES

Table 1: Baseline phase characteristics of hospitals and wards enrolled in the study

	Hospital characteristics			Study ward characteristics							
Hospital	Total beds (n)	Total number of single rooms (%)	Ratio of infection control nurses to beds	Surgical subspecialties	Total beds (n)	Total admissions during baseline phase (n)	Mean patient-to-nurse ratio (SD)*	Percent hand hygiene compliance (95% CI)	Number of patients screened on admission (%)	Number identified MRSA positive on admission (%)†	Study arm
1	3611	45 (1.2)	1:240	Abdominal Cardiovascular Orthopaedic	588	8018	6.4 (1.2)	18.8 (15.1 to 22.9)	0 (0)	9 (0.1)	Enhanced hand hygiene~~Standard Control~~
2	317	235 (74.1)	1:160	Cardiothoracic Orthopaedic Vascular	72	1613	4.1 (1.8)	75.4 (70.3 to 80.0)	29 (1.8)	20 (1.2)	~~Active Detection~~Screening and decolonisation
3	850	135 (15.9)	1:425	Cardiovascular General Orthopaedic	75	1841	5.6 (0.7)	26.8 (24.4 to 29.4)	14 (0.8)	11 (0.6)	Screening and decolonisation~~Active Detection~~
4	822	0 (0)	1:137	Abdominal Orthopaedic Urology Vascular	230	6574	3.7 (0.9)	39.3 (34.6 to 44.1)	182 (2.8)	21 (0.3)	Combined‡
5	545	89 (16.3)	1:272	General Neurosurgery Orthopaedic Vascular	121	1938	5.8 (1.5)	14.3 (11.3 to 17.6)	56 (2.9)	4 (0.2)	Screening and decolonisation~~Active Detection~~
6	547	4 (0.7)	1:274	General Orthopaedic	93	1300	16.8 (2.5)	25.1 (20.7 to 30.1)	0 (0)	5 (0.4)	Screening and decolonisation~~Active Detection~~

7	902	62 (6.9)	1:180	Vascular Abdominal General	84	1963	6.1 (1.5)	76.5 (71.3 to 81.1)	607 (30.9)	41 (2.1)	Combined‡
8	850	202 (23.8)	1:567	Vascular Orthopaedic Urology	87	2434	5.5 (0.6)	50.2 (44.6 to 55.8)	0 (0)	3 (0.1)	Enhanced ~~Standard Control~~hand hygiene
9	1350	150 (11.1)	1:260	Vascular Cardiothoracic Neurosurgery Plastic surgery	164	1561	10.0 (2.2)	67.0 (61.4 to 72.3)	17 (1.1)	15 (1.0)	Enhanced ~~Standard Control~~hand hygiene
10	2044	402 (19.7)	1:204	Abdominal Cardiovascular Orthopaedic Urology	302	6366	4.8 (0.4)	55.9 (51.2 to 60.5)	1666 (26.2)	140 (2.2)	Enhanced ~~Standard Control~~hand hygiene
Overall	11 838	1324 (11.2)			1816	33 608	6.6 (3.8)	39.5 (38.1 to 40.9)	2571 (7.6)	269 (0.8)	

MRSA, meticillin resistant *Staphylococcus aureus*.
*Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
†By screening or clinical culture.
‡Screening in hospitals in the ~~C~~combined arm was performed according to locally introduced policies. Hospital 4 used targeted screening of patients who were previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. Hospital 7 introduced universal screening in two of three study wards and targeted screening in the third ward. In this ward, patients who were previously known to be MRSA-positive, nursing home residents, patients admitted to the hospital in the last three months, contacts of MRSA-positive patients, and patients transferred from another ward or healthcare facility were screened.

Table 2: Study characteristics by study period

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Total patient-days (n)	264 035	496 975	249 119
Total surgical procedures (n)	27 768	49 747	22 123
Procedures in clean surgery wards (n)†	12 916	21 463	8787
Procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Number positive by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Number positive by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the ~~Active Detection~~screening and decolonisation arm and one hospital in each of the enhanced hand hygiene~~Enhanced Standard Control~~ and ~~C~~combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table 3: Crude nosocomial meticillin resistant *Staphylococcus aureus* incidence rates and incidence rate ratios by study arm for each study period*

Outcome	Baseline phase	Intervention phase	Washout phase	Crude IRR (95% CI) for intervention vs. baseline phases	Crude IRR (95% CI) for washout vs. intervention phases
MRSA isolation rate from clinical cultures (no. per 100 susceptible patients)					
Enhanced ~~Standard Control~~hand hygiene	0.99 (181/183.47)	0.80 (279/349.50)	0.65 (106/163.83)	0.81 (0.67 to 0.98)	0.81 (0.65 to 1.01)
~~Active Detection~~Screening and decolonisation	0.47 (31/66.61)	0.23 (28/122.56)	0.26 (17/66.04)	0.49 (0.29 to 0.82)	1.13 (0.62 to 2.06)
Combined	0.55 (47/85.35)	0.36 (60/165.23)	0.13 (8/63.04)	0.66 (0.45 to 0.97)	0.35 (0.17 to 0.73)
MRSA infection rate (no. per 100 admissions)					
Enhanced ~~Standard Control~~hand hygiene	0.58 (106/183.79)	0.50 (175/349.96)	0.45 (74/164.13)	0.87 (0.68 to 1.10)	0.90 (0.69 to 1.18)
Screening and decolonisation~~Active Detection~~	0.24 (16/66.92)	0.19 (23/122.79)	0.17 (11/66.15)	0.78 (0.41 to 1.48)	0.89 (0.43 to 1.82)
Combined	0.29 (25/85.37)	0.19 (32/165.35)	0.13 (8/63.04)	0.66 (0.39 to 1.12)	0.66 (0.30 to 1.42)
MRSA surgical site infection rate (no. per 100 surgical procedures)					
Enhanced ~~Standard Control~~hand hygiene	0.60 (79/132.27)	0.49 (123/250.03)	0.42 (54/127.06)	0.82 (0.62 to 1.09)	0.86 (0.63 to 1.19)
Screening and decolonisation~~Active Detection~~	0.26 (14/54.00)	0.15 (15/99.63)	0.16 (8/50.74)	0.58 (0.28 to 1.20)	1.05 (0.44 to 2.47)
Combined	0.20 (18/91.41)	0.14 (21/147.81)	0.07 (3/43.43)	0.72 (0.38 to 1.35)	0.49 (0.15 to 1.63)
MRSA bloodstream infection rate (no. per 10 000 patient-days)					
Enhanced ~~Standard Control~~hand hygiene	0.93 (14/15.0757)	0.56 (16/28.6667)	0.44 (6/13.5745)	0.60 (0.29 to 1.23)	0.79 (0.31 to 2.02)
Screening and decolonisation~~Active Detection~~	0.17 (1/5.7754)	0.18 (2/11.2971)	0.17 (1/5.8473)	1.02 (0.09 to 11.28)	0.97 (0.09 to 10.65)
Combined	0.18 (1/5.5524)	0.00 (0/9.7337)	0.00 (0/5.4901)	-	-

IRR, incidence rate ratio; MRSA, meticillin resistant *Staphylococcus aureus*.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward.

Table 4: Multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

Variable	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
	aIRR	95% CI	p Value	aIRR	95% CI	p Value	aIRR	95% CI	p Value
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced ~~Standard Control~~hand hygiene	1.44	0.96 to 2.15	0.076	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
Screening and decolonisation~~Active Detection~~	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.070	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced ~~Standard Control~~hand hygiene	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Screening and decolonisation~~Active Detection~~	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.162
Combined	0.88	0.79 to 0.98	0.016	0.90	0.80 to 1.02	0.096	0.86	0.74 to 1.01	0.059
Washout phase									
Change in level	1.90	0.91 to 3.95	0.087	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.

*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

Table 5: Multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced ~~Standard Control~~hand hygiene	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Screening and decolonisation~~Active Detection~~	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.121	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced ~~Standard Control~~hand hygiene	0.89	0.78 to 1.01	0.063	0.88	0.75 to 1.04	0.127	0.89	0.73 to 1.07	0.21
Screening and decolonisation~~Active Detection~~	0.85	0.74 to 0.97	0.019	0.83	0.69 to 0.99	0.041	0.81	0.66 to 1.00	0.054
Combined	0.82	0.71 to 0.95	0.007	0.84	0.70 to 1.00	0.055	0.84	0.68 to 1.03	0.095
Washout phase									
Change in level	3.01	1.05 to 8.63	0.041	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

Figure 1: Flow of study wards through each phase of the study

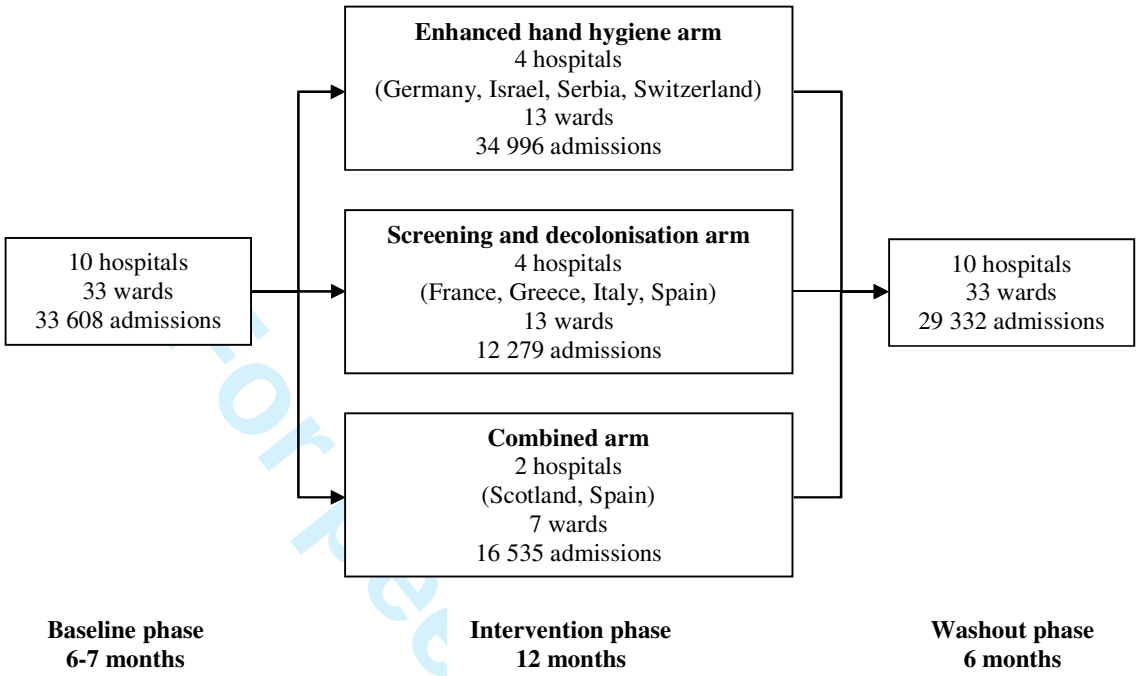


Figure ~~1~~2: Implementation of the interventions

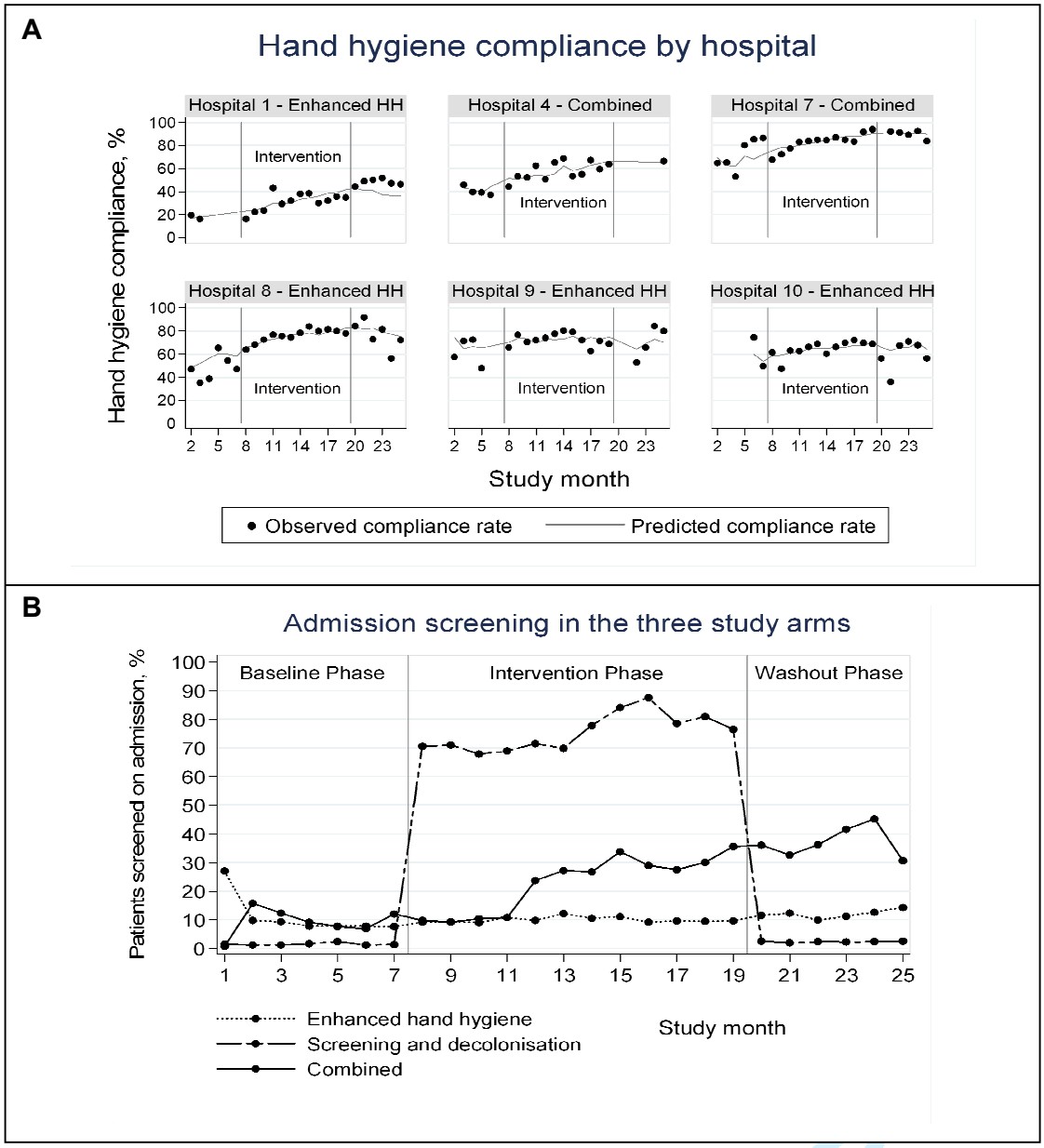


Figure ~~2~~3: Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers

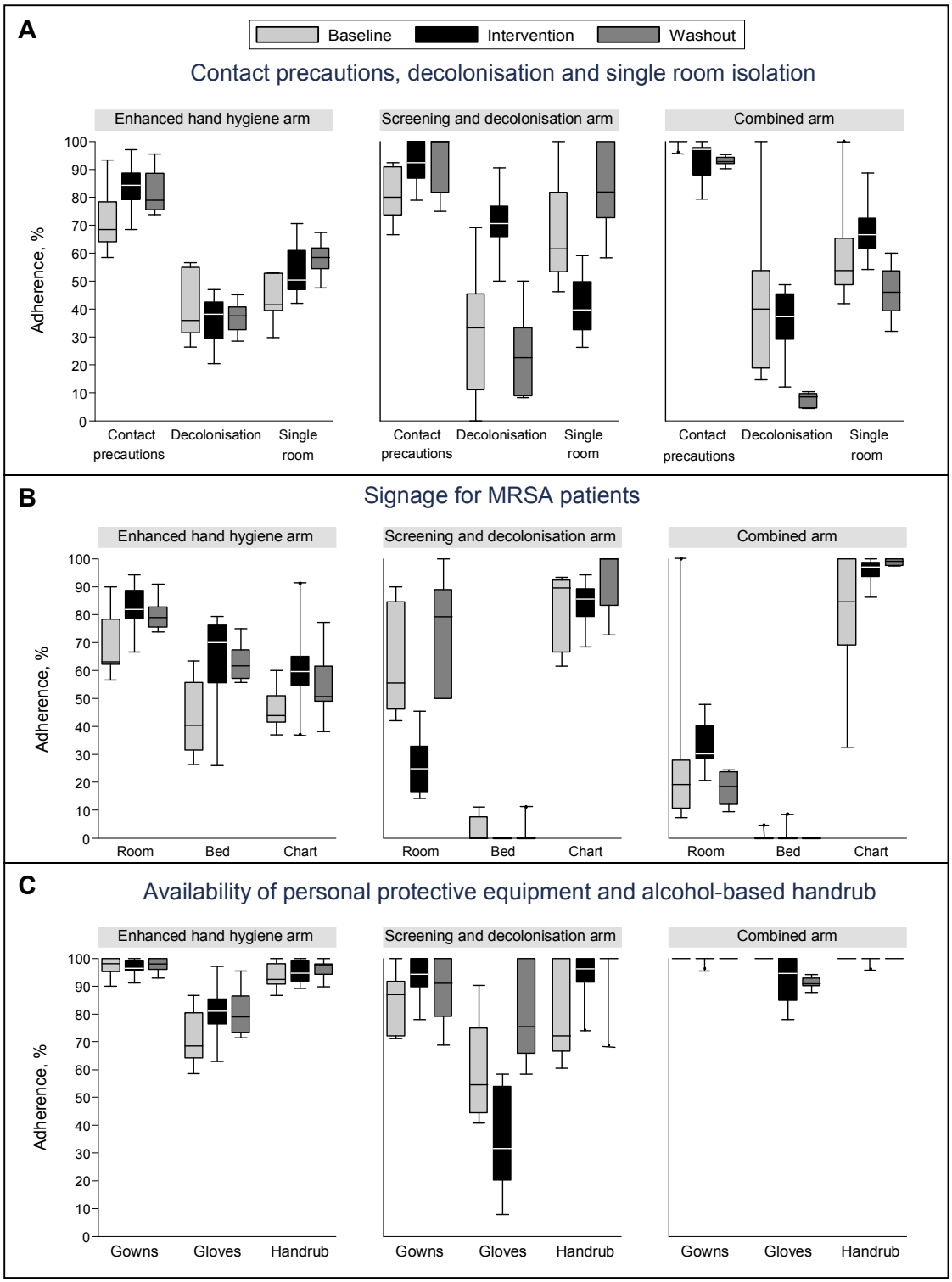
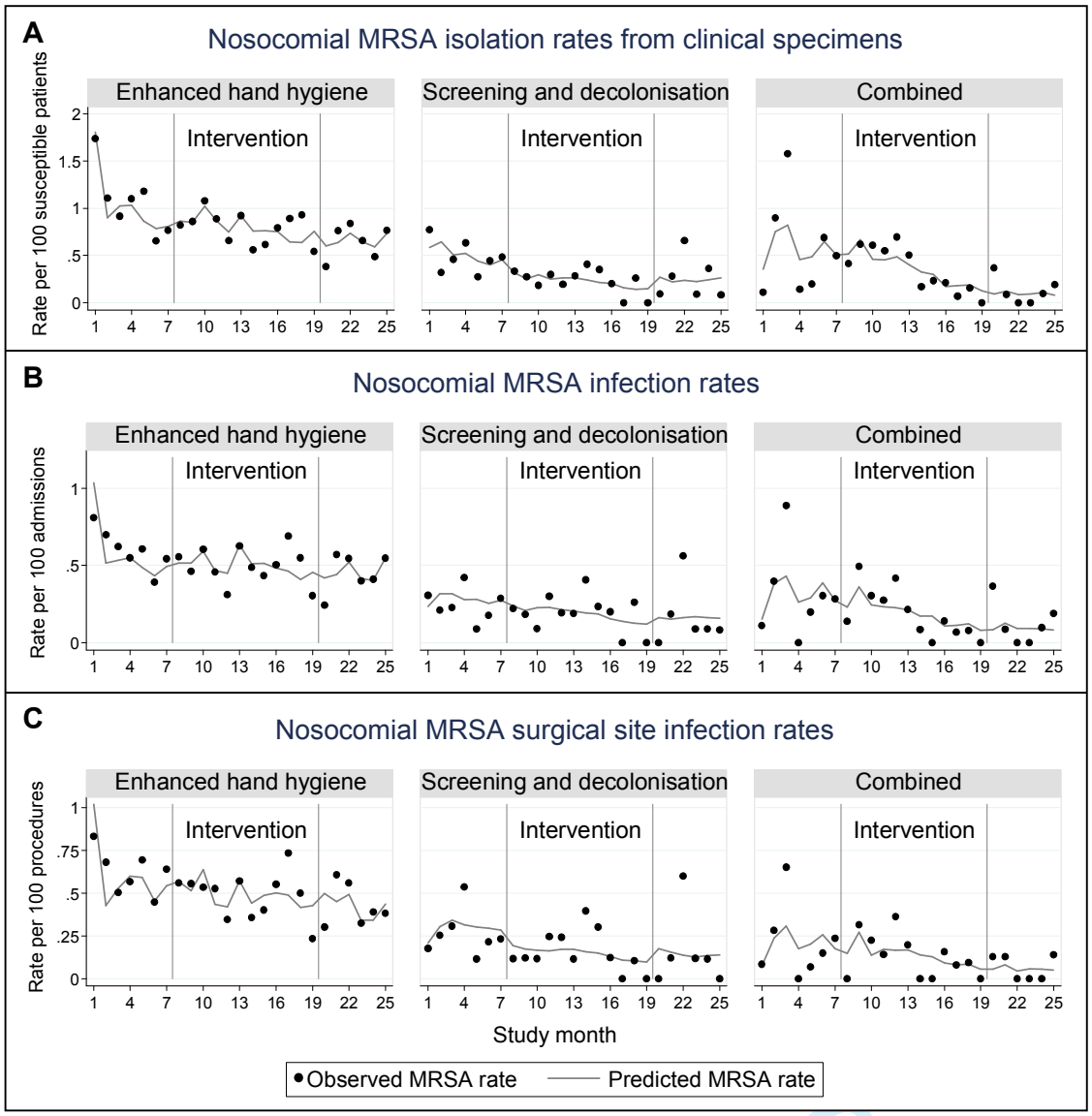


Figure ~~3~~4: Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm



SUPPLEMENTARY DATA FOR MANUSCRIPT:

Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a multicentre intervention study

Table A1: Meticillin resistant *Staphylococcus aureus* screening methods used in study centres in the screening and decolonisation arm and combined arm~~Active Detection and Combined arms~~

Table A2: Study characteristics by study period and study arm

Table A3: Multiple segmented multilevel logistic regression model showing factors associated with monthly hand hygiene compliance rates

Table A4: Full model results for the multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates

Table A5: Full model results for the multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only

Table A6: Exploratory analysis using multiple segmented multilevel Poisson regression models including interventions implemented by centres as covariates in the model

Figure A1: Nosocomial meticillin resistant *Staphylococcus aureus* isolation rates from clinical specimens by hospital

Table A1: Meticillin resistant *Staphylococcus aureus* screening methods used in study centres in the screening and decolonisation arm~~Active Detection~~ and ~~C~~combined arm~~s~~

Study arm	Hospital	Chromogenic medium used	Minimum time to detection (days)*	Months during intervention phase test used†	Molecular assay used	Total assay time (hours)*	Months during intervention phase test used†‡
~~Active Detection~~Screening and decolonisation	2	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	1 to 10
					GeneXpert (Cepheid)	<1.5	7 to 12
	3	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneXpert (Cepheid)	<1.5	6 to 12
	5	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	10 to 12
	6	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneXpert (Cepheid)	<1.5	8 to 12
Combined	4	MRSA Select (Bio-Rad Laboratories)	1.35	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	1 to 12
	7	ChromID (bioMérieux)	1.65	1 to 12	Not used	-	-

*From Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.

†Screening for meticillin resistant *Staphylococcus aureus* occurred during all study phases for centres in the ~~C~~combined arm using existing local methods.

‡For the ~~Active Detection~~screening and decolonisation arm, molecular assays were introduced during the latter part of the intervention phase. In one centre in this arm (Hospital 2) a locally available molecular assay was used from the commencement of the intervention phase.

Table A2: Study characteristics by study period and study arm

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Enhanced ~~Standard Control~~hand hygiene	18 379	34 996	16 413
~~Active Detection~~Screening and decolonisation	6692	12 279	6615
Combined	8537	16 535	6304
Total patient-days (n)	264 035	496 975	249 119
Enhanced hand hygiene~~Standard Control~~	150 757	286 667	135 745
Screening and decolonisation~~Active Detection~~	57 754	112 971	58 473
Combined	55 524	97 337	54 901
Total surgical procedures (n)	27 768	49 747	22 123
Enhanced hand hygiene~~Standard Control~~	13 227	25 003	12 706
Screening and decolonisation~~Active Detection~~	5400	9963	5074
Combined	9141	14 781	4343
Surgical procedures in clean surgery wards (n)†	12 916	21 463	8787
Enhanced hand hygiene~~Standard Control~~	5160	9102	4693
Screening and decolonisation~~Active Detection~~	1310	2551	1185
Combined	6446	9810	2909
Surgical procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Enhanced hand hygiene~~Standard Control~~	8067	15 901	8013
Screening and decolonisation~~Active Detection~~	4090	7412	3889
Combined	2695	4971	1434
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Enhanced hand hygiene~~Standard Control~~	6.46 (2.35)	6.73 (2.11)	6.99 (2.57)
Screening and decolonisation~~Active Detection~~	7.68 (5.11)	7.96 (4.74)	8.31 (5.52)
Combined	4.65 (1.62)	4.14 (1.17)	3.96 (1.30)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Enhanced hand hygiene~~Standard Control~~	167 (0.9)	272 (0.8)	136 (0.8)
Screening and decolonisation~~Active Detection~~	40 (0.6)	259 (2.1)	13 (0.2)
Combined	62 (0.7)	193 (1.2)	79 (1.3)
Number of patients MRSA positive on admission by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Enhanced hand hygiene~~Standard Control~~	32 (0.2)	46 (0.1)	30 (0.2)
Screening and decolonisation~~Active Detection~~	31 (0.5)	27 (0.2)	11 (0.2)
Combined	2 (0.02)	12 (0.1)	0 (0)
Number of patients MRSA positive on admission by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)
Enhanced hand hygiene~~Standard Control~~	135 (0.7)	226 (0.6)	106 (0.6)
Screening and decolonisation~~Active Detection~~	9 (0.1)	232 (1.9)	2 (0.03)
Combined	60 (0.7)	181 (1.1)	79 (1.3)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the ~~Active Detection~~screening and decolonisation arm and one hospital in each of the ~~E~~enhanced hand hygiene~~Standard Control~~ and ~~C~~combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table A3: Multiple segmented multilevel logistic regression model showing factors associated with monthly hand hygiene compliance rates*

Variable	Adjusted odds ratio	95% CI	p Value
Baseline phase			
Trend	1.04	0.98 to 1.10	0.24
Intervention phase			
Change in level	1.19	1.01 to 1.42	0.04
Change in trend	1.03	0.97 to 1.09	0.30
Washout phase			
Change in level	1.17	0.82 to 1.68	0.39
Change in trend	0.91	0.85 to 0.97	0.004
Professional category			
Physician	1.00	-	-
Nurse	1.37	1.28 to 1.46	<0.001
Auxiliary nurse	1.27	1.16 to 1.39	<0.001
Other	1.11	0.99 to 1.24	0.06
Indication for hand hygiene			
Before touching patient	1.00	-	-
Before clean/aseptic procedure	1.20	1.09 to 1.32	<0.001
After body fluid exposure	4.95	4.47 to 5.48	<0.001
After touching patient	2.79	2.60 to 3.00	<0.001
After touching patient surroundings	1.52	1.41 to 1.65	<0.001
Patient-to-nurse ratio (per 1-unit increment)†	0.91	0.89 to 0.94	<0.001
MRSA colonisation pressure‡			
0 to 0.7%	1.00	-	-
0.8 to 3.2%	0.86	0.79 to 0.94	<0.001
3.3 to 8.2%	0.90	0.81 to 1.01	0.07
>8.2%	0.78	0.68 to 0.90	<0.001

MRSA, meticillin resistant *Staphylococcus aureus*.
*Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all statistically significant, though baseline trends and intercepts showed no evidence of correlation.
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.
‡Calculated by dividing the patient-days of subjects known to be colonised or infected with meticillin resistant *Staphylococcus aureus* by the total number of patient-days in the ward in any given study month. This variable was divided into quartiles for the analysis.

Table A4: Full model results for the multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced hand hygiene~~Standard Control~~	1.44	0.96 to 2.15	0.08	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
~~Active Detection~~Screening and decolonisation	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.07	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced hand hygiene~~Standard Control~~	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Screening and decolonisation~~Active Detection~~	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.16
Combined	0.88	0.79 to 0.98	0.02	0.90	0.80 to 1.02	0.10	0.86	0.74 to 1.01	0.06
Washout phase									
Change in level	1.90	0.91 to 3.95	0.09	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53
Patient-to-nurse ratio (per 1-unit increment)†	1.01	0.94 to 1.08	0.87	1.01	0.93 to 1.09	0.84	1.04	0.96 to 1.14	0.33
Calendar month									
January	1.00	-	-	1.00	-	-	1.00	-	-
February	0.83	0.54 to 1.28	0.41	0.89	0.53 to 1.50	0.67	0.76	0.40 to 1.45	0.41
March	1.16	0.78 to 1.72	0.47	1.49	0.94 to 2.35	0.09	1.34	0.76 to 2.37	0.31
April	0.93	0.61 to 1.43	0.75	1.16	0.70 to 1.90	0.57	0.81	0.42 to 1.55	0.52
May	1.19	0.78 to 1.83	0.42	1.33	0.80 to 2.21	0.27	1.31	0.71 to 2.41	0.39
June	1.40	0.92 to 2.12	0.11	1.40	0.84 to 2.33	0.19	1.45	0.79 to 2.64	0.23
July	1.31	0.86 to 1.99	0.21	1.44	0.88 to 2.38	0.15	1.52	0.83 to 2.77	0.17
August	1.20	0.78 to 1.84	0.40	1.14	0.67 to 1.94	0.63	1.22	0.65 to 2.30	0.54
September	1.40	0.92 to 2.13	0.11	1.39	0.84 to 2.32	0.20	1.41	0.77 to 2.58	0.27
October	0.89	0.59 to 1.34	0.58	1.06	0.65 to 1.72	0.81	1.19	0.67 to 2.10	0.55
November	1.04	0.70 to 1.55	0.85	1.13	0.70 to 1.82	0.63	1.11	0.62 to 1.98	0.72
December	1.29	0.87 to 1.90	0.21	1.34	0.84 to 2.14	0.23	1.33	0.75 to 2.35	0.32
Surgical subspecialty									
Orthopaedics	1.00	-	-	1.00	-	-	1.00	-	-
Vascular	2.91	1.44 to 5.88	0.003	2.07	0.98 to 4.37	0.06	1.90	0.73 to 4.92	0.19
Cardiothoracic	1.10	0.52 to 2.34	0.80	1.16	0.55 to 2.45	0.70	1.35	0.55 to 3.27	0.51
General	1.65	0.70 to 3.89	0.26	1.92	0.81 to 4.55	0.14	2.06	0.72 to 5.88	0.18
Abdominal	1.51	0.69 to 3.29	0.30	1.44	0.67 to 3.13	0.35	1.30	0.52 to 3.27	0.58
Urology	0.82	0.33 to 2.05	0.67	0.63	0.24 to 1.64	0.34	0.90	0.29 to 2.86	0.87
Neurosurgery	0.79	0.22 to 2.78	0.71	0.85	0.23 to 3.07	0.80	0.53	0.10 to 2.71	0.44
Plastic surgery	0.75	0.13 to 4.41	0.75	0.59	0.08 to 4.38	0.60	0.54	0.06 to 4.51	0.57
Baseline HH compliance rate (per increment from 0 to 100%)	1.56	0.32 to 7.53	0.58	1.11	0.20 to 6.06	0.91	1.29	0.18 to 9.27	0.80

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio; HH, hand hygiene.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.

Table A5: Full model results for the multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced hand hygiene~~Standard Control~~	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Screening and decolonisation~~Active Detection~~	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.12	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced hand hygiene~~Standard Control~~	0.89	0.78 to 1.01	0.06	0.88	0.75 to 1.04	0.13	0.89	0.73 to 1.07	0.21
Screening and decolonisation~~Active Detection~~	0.85	0.74 to 0.97	0.02	0.83	0.69 to 0.99	0.04	0.81	0.66 to 1.00	0.05
Combined	0.82	0.71 to 0.95	0.01	0.84	0.70 to 1.00	0.06	0.84	0.68 to 1.03	0.10
Washout phase									
Change in level	3.01	1.05 to 8.63	0.04	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21
Patient-to-nurse ratio (per 1-unit increment)†	0.99	0.91 to 1.07	0.73	0.99	0.90 to 1.09	0.81	0.99	0.88 to 1.12	0.90
Calendar month									
January	1.00	-	-	1.00	-	-	1.00	-	-
February	1.06	0.54 to 2.07	0.86	1.58	0.66 to 3.81	0.31	1.22	0.45 to 3.28	0.69
March	1.13	0.60 to 2.16	0.70	1.68	0.72 to 3.95	0.23	1.51	0.60 to 3.84	0.38
April	1.32	0.68 to 2.57	0.41	2.12	0.89 to 5.03	0.09	1.52	0.57 to 4.09	0.41
May	2.00	1.06 to 3.76	0.03	3.07	1.34 to 7.04	0.01	2.61	1.04 to 6.52	0.04
June	2.34	1.25 to 4.39	0.01	3.33	1.43 to 7.74	0.01	3.06	1.22 to 7.65	0.02
July	2.19	1.16 to 4.15	0.02	3.20	1.35 to 7.57	0.01	2.94	1.14 to 7.59	0.03
August	2.25	1.18 to 4.26	0.01	2.80	1.18 to 6.65	0.02	2.77	1.08 to 7.10	0.03
September	2.35	1.26 to 4.39	0.01	2.88	1.24 to 6.72	0.01	2.89	1.15 to 7.26	0.02
October	1.49	0.81 to 2.73	0.20	2.66	1.20 to 5.90	0.02	2.39	1.00 to 5.72	0.05
November	1.70	0.93 to 3.09	0.09	2.52	1.12 to 5.67	0.03	1.86	0.75 to 4.62	0.18
December	1.96	1.06 to 3.60	0.03	2.44	1.06 to 5.66	0.04	2.02	0.80 to 5.08	0.14
Surgical subspecialty									
Orthopaedics	1.00	-	-	1.00	-	-	1.00	-	-
Vascular	2.14	1.00 to 4.58	0.05	1.57	0.70 to 3.54	0.27	1.29	0.50 to 3.33	0.60
Cardiothoracic	1.22	0.55 to 2.72	0.62	1.25	0.58 to 2.68	0.57	1.51	0.68 to 3.38	0.31
Neurosurgery	0.72	0.21 to 2.40	0.59	0.87	0.22 to 3.42	0.84	0.78	0.17 to 3.62	0.75
Plastic surgery	0.57	0.11 to 3.03	0.51	0.50	0.07 to 3.88	0.51	0.53	0.07 to 3.83	0.53
Baseline HH compliance rate (per increment from 0 to 100%)	2.07	0.45 to 9.53	0.35	1.37	0.29 to 6.53	0.69	2.15	0.34 to 13.60	0.42

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio; HH, hand hygiene.

*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

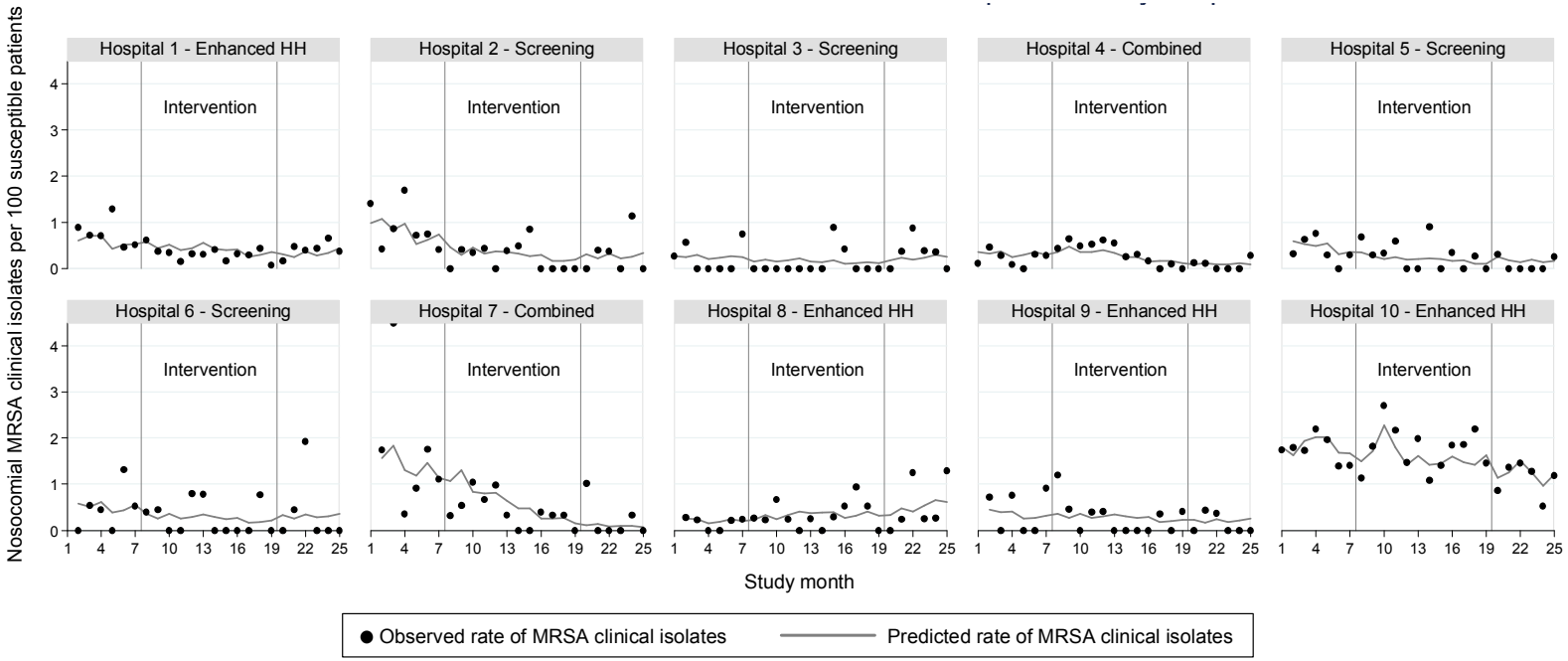
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.

Table A6: Exploratory analysis using multiple segmented multilevel Poisson regression models including interventions implemented by centres as covariates in the model*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase						
Trend	1.00	0.95 to 1.05	0.92	1.00	0.95 to 1.06	0.92
Hand ~~H~~hygiene ~~P~~promotion						
Change in level	1.05	0.87 to 1.27	0.63	1.03	0.83 to 1.28	0.80
Change in trend	0.98	0.92 to 1.04	0.47	0.99	0.92 to 1.06	0.68
MRSA screening						
Change in level	0.71	0.40 to 1.26	0.24	0.95	0.49 to 1.84	0.88
Change in trend†	0.91	0.85 to 0.98	0.01	0.92	0.85 to 0.99	0.03

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*The models used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, though there was no evidence that baseline trends significantly correlated with intercepts.
†Each additional month with x% compliance with admission screening would be associated with a reduction in the MRSA isolation rate by a factor of $aIRR^{x/100}$.

Figure A1 Nosocomial meticillin resistant *Staphylococcus aureus* isolation rates from clinical specimens by hospital



The solid dots represent the observed meticillin resistant *Staphylococcus aureus* (MRSA) rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*; HH, hand hygiene; ~~ESC, Enhanced Standard Control (hospitals using hand hygiene promotion); ACD, Active detection, Contact precautions and Decolonisation (hospitals using MRSA screening); MIX, Combined (hospitals using a combination of hand hygiene promotion and targeted MRSA screening)~~.

ORION Checklist of items to include when reporting an outbreak or intervention study of a nosocomial organism

	Item No.	Descriptor	Reported on page no.
Title & Abstract	1	Description of paper as outbreak report or intervention study. Design of intervention study (eg Randomised Controlled Trial , Cluster Randomised Controlled Trial, Interrupted Time Series, Cohort study etc). Brief description of intervention and main outcomes.	1,2
Introduction Background	2	Scientific and/or local clinical background and rationale. Description of organism as epidemic, endemic or epidemic becoming endemic.	5, 6
Type of paper	3	Description of paper as Intervention study or an Outbreak Report. If an outbreak report, report the number of outbreaks.	5
Dates	4	Start and finish dates of the study or report.	6
Objectives	5	Objectives for outbreak reports. Hypotheses for intervention studies	5, 6
Methods Design	6	Study design. Use of EPOC classification recommended (RCT or CRCT, CBA, or ITS) Whether study was retrospective, prospective or ambidirectional. Whether decision to report or intervene was prompted by any outcome data. Whether study was formally implemented with predefined protocol and endpoints.	6-10
Participants	7	Number of patients admitted in study or outbreak. Summaries of distributions of age and lengths of stays. If possible, proportion admitted from other wards, hospitals, nursing homes or from abroad. Where relevant, potential risk factors for acquiring the organism. Eligibility criteria for study. Case definitions for outbreak report.	6, 7, 11, 27
Setting	8	Description of the unit, ward or hospital and, if a hospital, the units included. Number of beds, the presence and staffing levels of an infection control team.	6, 25, 26
Interventions	9	Definition of phases by major change in specific infection control practice (with start and stop dates). A summary table is strongly recommended with precise details of interventions, how and when administered in each phase.	6, 7
Culturing & Typing	10	Details of culture media, use of selective antibiotics and local and /or reference typing. Where relevant, details of environmental sampling.	8, 9
Infection-related outcomes	11	Clearly defined primary and secondary outcomes (eg incidence of infection, colonisation , bacteraemia) at regular time intervals (eg daily, weekly, monthly) rather than as totals for each phase, with at least three data points per phase and, for many two phase studies, 12 or more monthly data points per phase. Denominators (eg numbers admissions or discharges, patient bed days). If possible, prevalence of organism and incidence of colonisation on admission at same time intervals. Criteria for infection, colonisation on admission and directly attributable mortality. For short studies or outbreak reports, use of charts with duration patient stay & dates organism detected may be useful (see text)	8, 9
Economic outcomes	12	If a formal economic study done, definition of outcomes to be reported, description of resources used in interventions, with costs broken down to basic units, stating important assumptions.	Not applicable
Potential Threats to internal validity	13	Which potential confounders were considered, recorded or adjusted for (eg: changes in length of stay, case mix, bed occupancy, staffing levels, hand-hygiene compliance, antibiotic use, strain type, processing of isolates, seasonality). Description of measures to avoid bias including blinding & standardisation of outcome assessment & provision of care.	9-11
Sample size	14	Details of power calculations, where appropriate	10
Statistical methods	15	Description of statistical methods to compare groups or phases. Methods for any subgroup or adjusted analyses, distinguishing between planned and unplanned (exploratory) analysis. Unless outcomes are independent, statistical approaches able to account for dependencies in the outcome data should be used, adjusting, where necessary, for potential confounders. For outbreak reports statistical analysis may be inappropriate.	10, 11
Results Recruitment	16	For relevant designs the dates defining periods of recruitment and follow-up. A flow diagram is recommended to describe participant flow in each stage of study.	6, 11, 27
Outcomes & estimation	17	For the main outcomes, the estimated effect size and its precision (usually using confidence intervals). A graphical summary of the outcome data is often appropriate for dependent data (such as most time series).	13, 14, 29, Fig 3
Ancillary analyses	18	Any subgroup analyses should be reported and it should be stated whether or not it was planned (specified in the protocol) and possible confounders adjusted for	11,13,14,30
Adverse events	19	Pre-specified categories of adverse events and occurrences of these in each intervention group . This might include drug side effects, crude or disease specific mortality in antibiotic policy studies or opportunity costs in isolation studies.	Not applicable
Discussion Interpretation	20	For intervention studies an assessment of evidence for/against hypotheses, accounting for potential threats to validity of inference including regression to mean effects and reporting bias. For outbreak reports, consider clinical significance of observations and hypotheses generated to explain them.	15-17
Generalisability	21	External validity of the findings of the intervention study i.e. to what degree can results be expected to generalise to different target populations or settings.	15
Overall evidence	22	General interpretation of results in context of current evidence.	17, 18

Abbreviations: RCT: randomised controlled trial CRCT : Cluster Randomised Controlled Trial CBA: controlled before and after study ITS: interrupted time series

TABLES OF STUDY OUTCOMES PRESENTING THE RESULTS OF THE WASHOUT PHASE BY STUDY ARM

Table 4 version 2: Multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.96	0.89 to 1.05	0.41	0.99	0.89 to 1.09	0.81	1.02	0.90 to 1.15	0.80
Intervention phase									
Change in level									
Enhanced Standard Control	1.37	0.90 to 2.07	0.138	1.21	0.74 to 1.98	0.44	1.23	0.68 to 2.23	0.50
Active Detection	1.03	0.42 to 2.48	0.95	0.99	0.36 to 2.74	0.99	0.86	0.26 to 2.90	0.81
Combined	2.29	1.14 to 4.61	0.020	2.10	0.88 to 4.99	0.093	1.57	0.52 to 4.72	0.42
Change in trend									
Enhanced Standard Control	1.01	0.92 to 1.11	0.77	1.01	0.91 to 1.13	0.83	0.99	0.86 to 1.13	0.85
Active Detection	0.94	0.81 to 1.08	0.37	0.95	0.81 to 1.11	0.52	0.89	0.73 to 1.09	0.27
Combined	0.84	0.74 to 0.96	0.008	0.83	0.71 to 0.97	0.020	0.84	0.70 to 1.02	0.081
Washout phase									
Change in level									
Enhanced Standard Control	1.43	0.64 to 3.21	0.39	1.11	0.44 to 2.78	0.82	1.68	0.55 to 5.07	0.36
Active Detection	3.16	0.50 to 19.96	0.22	1.93	0.24 to 15.78	0.54	2.76	0.22 to 34.28	0.43
Combined	8.65	1.20 to 62.29	0.032	13.31	1.38 to 128.72	0.025	4.43	0.19 to 102.38	0.35
Change in trend									
Enhanced Standard Control	1.05	0.92 to 1.21	0.44	1.04	0.90 to 1.21	0.58	0.97	0.80 to 1.16	0.71
Active Detection	0.98	0.73 to 1.32	0.90	0.93	0.64 to 1.34	0.70	0.90	0.58 to 1.40	0.64
Combined	0.89	0.57 to 1.39	0.62	0.90	0.57 to 1.43	0.66	0.86	0.42 to 1.74	0.67

Table 5 version 2: Multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.04	0.92 to 1.17	0.55	1.08	0.93 to 1.26	0.32	1.10	0.91 to 1.32	0.32
Intervention phase									
Change in level									
Enhanced Standard Control	1.22	0.68 to 2.18	0.50	0.98	0.47 to 2.04	0.97	1.04	0.44 to 2.45	0.93
Active Detection	1.19	0.38 to 3.69	0.76	1.21	0.28 to 5.13	0.80	1.14	0.20 to 6.50	0.89
Combined	2.66	0.98 to 7.24	0.056	2.46	0.66 to 9.22	0.180	1.96	0.40 to 9.53	0.40
Change in trend									
Enhanced Standard Control	0.91	0.80 to 1.04	0.186	0.91	0.77 to 1.08	0.28	0.91	0.74 to 1.10	0.33
Active Detection	0.83	0.68 to 1.00	0.046	0.87	0.66 to 1.05	0.125	0.80	0.61 to 1.06	0.13
Combined	0.79	0.66 to 0.93	0.005	0.76	0.61 to 0.95	0.018	0.79	0.61 to 1.02	0.075
Washout phase									
Change in level									
Enhanced Standard Control	2.05	0.64 to 6.57	0.23	1.46	0.36 to 5.85	0.60	2.05	0.42 to 10.05	0.37
Active Detection	8.01	0.78 to 82.15	0.080	4.85	0.28 to 85.02	0.28	3.70	0.10 to 139.96	0.48
Combined	11.10	0.74 to 165.93	0.081	18.46	0.77 to 443.38	0.072	13.88	0.32 to 605.54	0.172
Change in trend									
Enhanced Standard Control	1.00	0.82 to 1.23	0.97	0.95	0.75 to 1.21	0.70	0.87	0.66 to 1.15	0.33
Active Detection	0.91	0.63 to 1.30	0.59	0.79	0.48 to 1.30	0.35	0.88	0.48 to 1.62	0.68
Combined	0.92	0.54 to 1.59	0.77	0.91	0.52 to 1.60	0.75	0.78	0.38 to 1.61	0.50

Comparison of the original models to the models with the washout phase results by study arm

The results of the likelihood ratio tests used to compare the models are shown in the following table:

	Log likelihood of original model (Tables 4 and 5)	Log likelihood of model with washout phase by study arm (version 2 of Tables 4 and 5)	Chi-squared value	p value
All wards				
Clinical isolates	-792.26794	-790.7097	3.11648	0.5385
Total infections	-636.3387	-634.07165	4.5341	0.3385
Surgical site infections	-531.56843	-531.34369	0.44948	0.9782
Clean surgery wards				
Clinical isolates	-478.45898	-477.32009	2.27778	0.6848
Total infections	-377.10528	-375.54585	3.11886	0.5381
Surgical site infections	-315.91438	-315.4368	0.95516	0.9165

The table shows no significant difference in fit of the models including parameters for the washout phase for each study arm compared to the original models in which the washout phase results were combined for all study arms; in other words, there was no evidence to reject the null hypothesis that the effect of the washout phase was the same in each study arm.

Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a controlled multicentre intervention trial

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Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a controlled multicentre intervention trial

Running head: MRSA control strategies in surgical patients

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ABSTRACT

Objective: To compare the effect of two strategies (enhanced hand hygiene versus meticillin resistant *Staphylococcus aureus* [MRSA] screening and decolonisation) alone and in combination on MRSA rates in surgical wards.

Design: Prospective, controlled, interventional cohort study, with 6-month baseline, 12-month intervention, and 6-month washout phases.

Setting: 33 surgical wards in ten hospitals in nine countries in Europe and Israel.

Participants: All patients admitted to the enrolled wards for more than 24 hours.

Interventions: The two strategies compared were: 1) enhanced hand hygiene promotion; and 2) universal MRSA screening with contact precautions and decolonisation (intranasal mupirocin and chlorhexidine bathing) of MRSA carriers. Four hospitals were assigned to each intervention and two hospitals combined both strategies, using targeted MRSA screening.

Outcome measures: Monthly rates of MRSA clinical cultures per 100 susceptible patients (primary outcome) and MRSA infections per 100 admissions (secondary outcome). Planned subgroup analysis for clean surgery wards was performed.

Results: After adjusting for clustering and potential confounders, neither strategy when used alone was associated with significant changes in MRSA rates. Combining both strategies was associated with a reduction in the rate of MRSA clinical cultures of 12% per month (aIRR 0.88, 95% CI 0.79 to 0.98). In clean surgery wards, strategy 2 (MRSA screening, contact precautions, and decolonisation) was associated with decreasing rates of MRSA clinical cultures (15% monthly decrease, aIRR 0.85, 95% CI 0.74 to 0.97) and MRSA infections (17% monthly decrease, aIRR 0.83, 95% CI 0.69 to 0.99).

Conclusions: In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard and MRSA-specific infection control approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation was associated with significant reductions in MRSA clinical culture and infection rates.

Trial Registration: clinicaltrials.gov identifier: NCT00685867

ARTICLE SUMMARY

Article focus

- The relative effectiveness of different meticillin resistant *Staphylococcus aureus* (MRSA) control measures is controversial.
- This study directly compared the effect of two strategies (enhanced hand hygiene versus MRSA screening and decolonisation, alone and in combination) on MRSA rates in surgical wards.

Key messages

- Neither enhanced standard infection control measures (emphasising hand hygiene promotion) nor MRSA-specific control interventions (universal MRSA screening coupled with contact precautions and decolonisation therapy) when used alone for 12 months effectively reduced MRSA rates in surgical wards with relatively low MRSA rates.
- A combination of interventions, including targeted screening of high risk patients, did result in reduction in the rate of MRSA isolated from clinical cultures.
- In surgical subspecialties that perform clean surgery, universal MRSA screening coupled with contact precautions and decolonisation therapy effectively reduced both the rates of MRSA isolated from clinical cultures as well as MRSA infections.

Strengths and limitations of this study

- Unlike many previous studies, this was a large, controlled, prospective, multicentre, intervention study. The enrolled wards, from ten hospitals in Europe and Israel, varied in terms of infection control infrastructure and MRSA prevalence, thus the results are likely to be generalisable to other settings.
- Due to the nature of the quality improvement initiatives, investigators were not blinded to the allocated intervention. Interventions were not randomly allocated.

INTRODUCTION

Healthcare associated infections affect hundreds of millions of patients worldwide every year and represent an important cause of patient mortality and a major financial burden to health systems.[1] Meticillin resistant *Staphylococcus aureus* (MRSA), now endemic in many healthcare facilities, is a leading cause of healthcare associated infections,[2] and patients in surgical units are at increased risk due to factors such as invasive procedures, antibiotic exposure, and prolonged healthcare contact. A number of countries mandate implementation of control measures, including MRSA screening.[3,4] Not all mandated interventions, however, are supported by robust evidence.

Studies evaluating MRSA control strategies show conflicting results, particularly with regards to the use of active surveillance cultures.[5-7] It is argued that broader infection control approaches, such as improving hand hygiene (HH) practices, may be as successful as MRSA-specific strategies.[8,9] There are limitations, however, to current evidence with few prospective, controlled studies,[10,11] and many studies have assessed multiple interventions simultaneously.[12] Quantifying the relative benefits of individual approaches is important, particularly as some strategies have significant cost implications, and will allow efficient use of limited resources.

Due to the ongoing debate concerning optimal approaches to MRSA control,[13,14] we performed a prospective, interventional, quality improvement study to compare the effect of an enhanced HH promotion strategy to an MRSA screening, isolation and decolonisation strategy when used alone and in combination on the incidence rates of MRSA clinical cultures and infections in surgical patients admitted to healthcare facilities across Europe and

Israel. We also aimed to specifically assess these interventions in clean surgery wards where their benefits may be expected to be more pronounced.

METHODS

Study design and population

This prospective, controlled, multicentre, interventional cohort study with a three phase interrupted time series design was conducted between March 2008 and July 2010. Thirty-three surgical wards of ten hospitals in nine countries (Serbia, France, Spain [two hospitals], Italy, Greece, Scotland, Israel, Germany, and Switzerland) were enrolled. Wards included orthopaedic (8), vascular (6), cardiothoracic/cardiovascular (5), general (4), abdominal (4), urology (3), neurosurgery (2), and plastic surgery (1) subspecialties. Characteristics of the enrolled wards varied (table 1).

The study consisted of baseline (6 to 7 months), intervention (12 months), and washout (6 months) phases. Initial baseline phase data collection commenced in one centre in March 2008 prior to the implementation of any interventions. All other centres commenced baseline phase data collection after May 2008. The intervention phase did not start for any study site until October 2008. During baseline and washout phases, wards employed their usual infection control practices. During the intervention phase, two strategies were investigated, with hospitals implementing one or both interventions in parallel (figure 1).

Interventions

The first intervention, the enhanced HH strategy, used the WHO multi-modal HH promotion method consisting of: 1) using alcohol-based handrub at the point of care, 2) training and

education of healthcare workers, 3) observation and feedback of HH practices, 4) reminders in the workplace (e.g. posters), and 5) improving the safety climate in the institution with management support for the initiative.[15] Adherence to standard precautions (e.g. gloves for body fluid contact) was encouraged. There was no attempt to change local practices regarding isolation of MRSA patients as part of this intervention.

The second intervention, the screening and decolonisation strategy, used a universal MRSA screening approach. It consisted of screening patients admitted for more than 24 hours for MRSA, on admission (within 48 hours) then weekly. Patients were excluded from screening if they were undergoing ambulatory surgery or had already been screened within 5 days prior to admission to the surgical ward. The nares, perineum, and wounds (if present) were swabbed. Chromogenic agar screening was used with the addition of polymerase chain reaction (PCR) testing during the latter part of the intervention phase for patients who had risk factors for MRSA (e.g. hospitalisation in the last year) whose chromogenic agar results were unlikely to be available before surgery. MRSA carriers were placed on contact precautions (gown and gloves during patient contact), administered decolonisation therapy with twice daily intranasal mupirocin and daily chlorhexidine washes for five days, and perioperative prophylaxis was modified to reflect MRSA carriage. Chlorhexidine bathing was limited to identified MRSA carriers and not used as a unit-wide intervention. Pre-emptive isolation was not used as part of this strategy.

The hospital was the unit for assignment of interventions due to practical reasons and the nature of the strategies. Four hospitals were assigned to each intervention and two hospitals used a combination of both strategies (the combined strategy) due to the introduction of national or local mandatory targeted MRSA screening policies during the study period which

necessitated deviation from the original trial protocol (figure 1). The choice of allocation was influenced by the constraints upon the study centres, such as cost and personnel (n=3), population size (n=1), capacity of the microbiology laboratories (n=3), prior exposure to specific interventions (n=1) and mandatory local or national interventions (n=2). Thus, this pragmatic approach took into account the institutions' preferences, as participation in an entirely cluster-randomised trial would have meant that some of the hospitals could not have participated.

The targeted screening in the two hospitals in the combined strategy arm was based on risk factors for MRSA carriage (including patient characteristics or surgical subspecialty). One hospital using the combined strategy (Hospital 4) introduced targeted screening of patients who were previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. The other hospital in the combined strategy arm (Hospital 7) used targeted screening of patients with the same risk factors as Hospital 4, but also screened nursing home residents, patients admitted to the hospital in the last three months, patients transferred from another ward within the same hospital, and those admitted to vascular or abdominal surgery subspecialties. The assignment of hospitals to each study arm occurred prior to commencement of data collection. A summary of the nature of the interventions for each study arm is presented in table 2. The study protocol was registered with a public registry of clinical studies (available at: http://clinicaltrials.gov/ Identifier: NCT00685867).

Outcomes measures

The primary outcome measure was the monthly nosocomial MRSA isolation rate, defined as the number of MRSA clinical isolates (those from specimens collected other than for

screening purposes, counting one isolate per patient per month), per 100 susceptible patients (not previously known to be MRSA colonised or infected). Isolates from specimens collected more than 48 hours after admission or within 30 days after discharge from study wards were considered nosocomial.

Secondary outcomes were the monthly rate of nosocomial MRSA infections per 100 admissions, and adherence to HH guidelines and contact precautions. Infections were defined using CDC criteria.[16] Adherence to HH guidelines was measured as the percentage of opportunities for HH in which staff used alcohol-based handrub and/or washed their hands according to the WHO method.[15] Adherence to contact precautions was measured as the percentage of randomly audited MRSA patients for whom precautions with gown and gloves during patient contact had been implemented.

Microbiological methods

Standardised laboratory manuals were provided to centres. Samples were processed in local laboratories using standard culture-based identification of MRSA from clinical specimens. In hospitals assigned to the screening and decolonisation arm, nasal and perineal swabs were pooled in the laboratory then plated directly onto chromogenic medium (BBL CHROMagar MRSA II, BD Diagnostics, Belgium) and also incubated overnight in an enrichment medium to increase test sensitivity.[17] Positive results could be reported within 24 to 48 hours.[18] PCR testing directly from pooled screening swabs was performed with the BD GeneOhm MRSA (BD Diagnostics, Belgium) or GeneXpert MRSA (Cepheid, Belgium) tests, which have turnaround times of 2 to 3 hours and 1.5 hours respectively (see online supplementary table A1).[18] All laboratories participated in an external quality assurance program to evaluate their ability to detect, identify and perform antibiotic sensitivity testing on staphylococci from a

variety of different specimens.[19] MRSA isolates were shipped to the central laboratory (University of Antwerp, Belgium) for confirmation of identification.

Data collection

Research personnel from each hospital collected data and implemented the interventions at their study site. These personnel were from departments that supervise infection control activities at the participating hospitals, including Infection Control, Infectious Diseases and Hospital Epidemiology departments. They were trained at the study coordinating centre with regards to the study protocol, the outcome definitions and the use of the data collection tools prior to the commencement of the study to ensure consistency of data collection across the hospitals. Local microbiology laboratory data were reviewed to obtain information regarding MRSA isolated from screening and clinical cultures. Infections were monitored by twice weekly ward visits to review medical records and interview staff. Surgical site infection surveillance occurred up to 30 days post-procedure (or 12 months after prosthetic device insertion).

HH adherence was monitored by the research personnel who had been trained and validated in the WHO method of direct observation at the study coordinating centre.[15] A standardised observation form was used by all centres. All hospitals collected data for 100 HH opportunities per ward during baseline and washout phases.[20] HH observers were specifically instructed not to provide feedback to healthcare workers concerning their HH practices during these study phases, and the observers were independent of surgical ward staff, reducing the likelihood of the Hawthorne effect, in which staff improve their practices when they are aware that they are being observed.[21] During the intervention phase, there was intensive monitoring of HH practices in wards using the enhanced HH and combined

strategies. In these wards, 100 HH opportunities per ward per month were observed as part of the intervention. Implementation of contact precautions, decolonisation therapy, and single room isolation for MRSA carriers was randomly audited each month. Signage of MRSA status and availability of gowns, gloves and alcohol-based handrub for contact with MRSA carriers was also audited.

Data regarding numbers of admissions, patient-days, surgical procedures, and level of staffing were collected. Due to variation in the availability and quality of electronic medical record and pharmacy data between the study sites, individual-level data (such as length of stay) and antibiotic utilisation data for the surgical wards was not collected as part of this study. Ward-level data were submitted monthly to a central data management centre via a password protected secure online database which included range, consistency, and missing data checks. Meetings, site visits, and monthly teleconferences were held to review data, ensure adherence to study protocols, and address queries. Data were reviewed monthly for completeness and 6-monthly for validity by teleconferences with individual study sites. Institutional review boards of all centres approved the study with a waiver of individual informed consent.

Statistical analysis

The study was designed to detect a 30% difference in nosocomial MRSA isolation rate assuming a baseline rate of 1.0 clinical isolate per 100 susceptible patients and an absolute difference of 10% between intervention arms. Sample size calculations assumed a two-sided test, a type I error rate of 0.05 and 80% power, taking the wards as the unit of analysis. A minimum of 15 wards was required per study arm.

Crude MRSA rates were calculated by study arm. Adjusted incidence rate ratios (aIRR) were calculated using multilevel Poisson segmented regression accounting for stepwise changes in MRSA level and changes in log-linear trends associated with the interventions.[22] This analysis allowed for two levels of random-effects: hospital-level variation in intercepts and baseline trends, and nested ward-level variation in intercepts. It adjusted for exposure given by the monthly number of susceptible patients or admissions per ward and allowed for extra-Poisson variation. Surgical subspecialty, baseline HH compliance, seasonal effects (using calendar month), and patient-to-nurse ratios were adjusted for. Autocorrelation was accounted for using a lagged dependent variable. A similar analysis was performed for HH compliance, but used segmented multilevel logistic regression, adjusting for ward-specific baseline levels and trends, professional category, HH indication, patient-to-nurse ratios, and monthly MRSA colonisation pressure (number of days patients known to be MRSA colonised/infected were in the wards each month).

Planned subgroup analyses were performed by hospital and for clean surgery wards (cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery) as studies have shown that intranasal mupirocin, which is active against Gram-positive organisms, may be more effective for surgical site infection prevention in clean compared to clean-contaminated surgery (e.g. general or gastrointestinal surgery) where Gram-negative and anaerobic organisms may play a larger role.[23] As screening intensity varied in the combined arm, a planned exploratory analysis of MRSA outcome data was conducted to better quantify the intervention effects. It accounted for stepwise changes and log-linear trends in outcomes associated with the HH intervention, as well as the monthly proportion of patients screened and monthly cumulative screening rate on wards to account for changes in trends of outcomes associated with screening. Analyses were conducted with STATA 11.0 (STATA Corp, USA).

RESULTS

During the study period, there were a total of 126 750 admissions and 99 638 surgical procedures on the study wards. Baseline admission MRSA prevalence, without systematic screening of all admitted patients, was 0.8% (269 of 33 608), ranging from 0.1% to 2.2% across surgical wards of each hospital. Baseline HH adherence varied between hospitals (39.5% overall, 95% CI 38.1% to 40.9%) as did use of targeted MRSA screening (0 to 30.9% of admissions) (table 1). Study characteristics are shown in table 3 and online supplementary table A2.

Adherence to hand hygiene guidelines

In the enhanced HH and combined arms, HH compliance improved in all centres with overall compliance increasing from 49.3% (95% CI 47.2% to 51.4%) to 63.8% (95% CI 63.2% to 64.4%) from baseline to intervention phases (figure 2a). After multivariable analysis, commencing HH promotion was associated with a significant immediate increase in HH compliance (adjusted odds ratio [aOR] 1.19, 95% CI 1.01 to 1.42) (see online supplementary table A3). However, this benefit was not sustained after cessation of the HH campaign with a significant decreasing trend in HH adherence of 9% per month (aOR for month post-intervention 0.91, 95% CI 0.85 to 0.97) during the washout phase. In wards in the screening and decolonisation arm, where no HH promotion occurred, compliance remained low at 30.5% (95% CI 28.7% to 32.4%) at baseline and 23.9% (95% CI 22.0% to 25.9%) during the washout phase.

Screening, contact precautions and decolonisation of MRSA carriers

During the intervention phase, 9250 (75.3%) of 12 279 patients were screened on admission to wards in the screening and decolonisation arm. Admission MRSA prevalence was 2.1% (259 of 12 279), consisting of 27 patients (10.4%) with MRSA-positive clinical cultures and 232 patients (89.6%) identified by screening alone. PCR screening was used in addition to chromogenic agar cultures in 1047 (11.3%) of 9250 patients. Between baseline and intervention phases in screening and decolonisation wards, the proportion of audited MRSA carriers placed on contact precautions increased (81.1% to 90.7%), as did administration of decolonisation therapy (34.4% to 69.8%) (figure 3). However, the proportion of audited MRSA carriers in single rooms decreased (67.8% to 40.1%), possibly due to a shortage of rooms for the higher number of identified MRSA carriers. Reasons for non-adherence to decolonisation therapy included discharge prior to an MRSA-positive result, discharge prior to commencement of decolonisation therapy or the patient declining the intervention.

Screening occurred to a lesser extent in the other study arms (figure 2b). About 10% of admissions to wards in the enhanced HH arm were screened throughout the study. In wards in the combined arm, screening increased from 9.2% to 22.3%, then 36.9% during baseline, intervention, and washout phases respectively. In this arm, adherence to contact precautions was high throughout the study (93.0% to 99.6%), but only 32.9% of MRSA patients at baseline and 35.9% of patients during the intervention phase received decolonisation therapy (figure 3).

Nosocomial MRSA isolation rate from clinical cultures

Crude MRSA isolation rates from clinical cultures decreased in all study arms during the intervention phase (enhanced HH arm: 0.99 to 0.80; screening and decolonisation arm: 0.47 to 0.23; combined arm: 0.55 to 0.36; p=0.04; per 100 susceptible patients) (table 4). After

adjusting for clustering and potential confounders with multilevel segmented Poisson regression (table 5 and see online supplementary table A4 for full model), commencement of HH promotion in the enhanced HH arm was associated with an immediate non-significant increase in nosocomial MRSA isolation rate (aIRR 1.44, 95% CI 0.96 to 2.15) with no change in the trend in rates over time. In clean surgery wards, HH promotion was associated with a non-significant decreasing monthly MRSA isolation rate (aIRR 0.89, 95% CI 0.78 to 1.01) (table 6 and see online supplementary table A5 for full model).

In the screening and decolonisation arm, there were no significant changes in MRSA isolation rates. However, in clean surgery, this intervention was associated with a reduction in MRSA clinical cultures of 15% per month (aIRR 0.85, 95% CI 0.74 to 0.97).

In the combined arm (wards that used a combination of HH promotion with targeted screening), there was a significant decreasing trend in MRSA isolation rate of 12% per month overall (aIRR 0.88, 95% CI 0.79 to 0.98), and 18% per month in clean surgery (aIRR 0.82, 95% CI 0.71 to 0.95). Observed and model-predicted MRSA isolation rates from clinical cultures are illustrated in figure 4a and online supplementary figure A1.

During the washout phase, MRSA clinical culture isolation rates increased. A post-hoc analysis of the washout phase results by study arm showed that the increase in MRSA rates was due to an abrupt increase in the level of MRSA clinical cultures on cessation of the intervention phase in all study arms, but particularly with the conclusion of the intensive HH promotion campaign in the combined arm (see online supplementary table A6).

Nosocomial MRSA infection rates

There were 470 nosocomial MRSA infections in total (335 [71.3%] surgical site, 41 [8.7%] bloodstream, and 94 [20.0%] other infections). Crude infection rates decreased over time in all study arms (table 4). After multivariable analysis (table 5, figure 4b and see online supplementary table A4), enhanced HH promotion alone was not associated with changes in MRSA infection rates. Both the screening/decolonisation and combined interventions resulted in non-significant decreasing trends in total MRSA infection (screening and decolonisation arm: aIRR 0.93, 95% CI 0.82 to 1.05; combined arm: aIRR 0.90, 95% CI 0.80 to 1.02) and surgical site infection rates (table 5, figure 4c and online supplementary table A4).

In clean surgery, the screening and decolonisation strategy was associated with significant reductions in total MRSA infection rate of 17% per month (aIRR 0.83, 95% CI 0.69 to 0.99) and MRSA surgical site infection rate of 19% per month (aIRR 0.81, 95% CI 0.66 to 1.00) (table 6 and online supplementary table A5).

Exploratory analysis to directly assess implemented interventions

The exploratory analysis did not show any significant effects of HH promotion on nosocomial MRSA isolation rates (see online supplementary table A7). The intensity of admission screening was associated with a decreasing trend in monthly MRSA isolation rate from clinical cultures (aIRR 0.91 per month with 100% compliance with screening, 95% CI 0.85 to 0.98). A similar effect was seen in the trend in MRSA infection rate (aIRR 0.92, 95% CI 0.85 to 0.99).

DISCUSSION

We found that implementation of individual interventions in surgical wards, with either an enhanced HH promotion strategy or universal MRSA screening with contact precautions and decolonisation of MRSA carriers, was not effective in reducing MRSA rates. However, using a combination of both HH promotion and targeted screening was associated with a reduction in MRSA isolation rate from clinical cultures of 12% per month. When the interventions were specifically evaluated in the subgroup of clean surgery wards, the screening and decolonisation strategy was most effective. In these wards, this intervention was associated with significant reductions in both MRSA clinical culture isolation rate of 15% per month and MRSA infection rate of 17% per month.

This study is unique in that it directly compared strategies individually and in combination using a large, prospective, controlled design.[10] In addition, we used a planned exploratory analysis to separate out the individual effects of the HH and MRSA screening strategies. Interventions were implemented and assessed under operational conditions in ten heterogeneous hospitals across Europe and Israel with widely varying infection control practices, staffing, infrastructure, and MRSA epidemiology, increasing the generalisability of our findings. This study has been reported using standard reporting guidelines that are designed to maximise transparency and scientific rigor of intervention studies of healthcare associated infection.[24]

Our analysis, which adjusted for confounders, seasonal effects and baseline MRSA trends, found no evidence that enhanced HH promotion was effective. MRSA rates are declining in many countries.[25] Failing to account for this would overestimate intervention effects. Overall baseline HH compliance was 49% in study wards that used the HH intervention. In settings where compliance is already above about 50%, modelling studies suggest that further

increases in compliance will have rapidly diminishing returns for reducing MRSA transmission.[26] In facilities with lower HH compliance or higher MRSA rates, this intervention may be more effective than we were able to demonstrate. In addition, HH campaigns involve education and behaviour change and are therefore unlikely to have a short term effect. Other studies have shown that they may be beneficial if activity is sustained over years.[27,28] Although we did not detect any intervention effects of the HH promotion strategy, cessation of this intervention was associated with an increase in MRSA rates in our study, suggesting that discontinuing activities to optimise HH practices may be detrimental.

Active MRSA surveillance identifies the reservoir of asymptomatic carriers, enabling early implementation of contact precautions and decolonisation, which can reduce transmission.[29,30] With universal screening, we found that 90% of MRSA-positive patients would have been missed using clinical cultures alone. However, our results suggest that rather than universal screening of all surgical patients admitted for more than 24 hours, selective screening in clean surgery wards or a combination of HH promotion and targeted screening of high risk patients may be more effective strategies. The relative burden of Gram-positive infections is greater in clean compared to clean-contaminated surgery where other pathogens, including bowel flora, may be more important.[23,31] Thus it is biologically plausible that MRSA-specific interventions would potentially have a greater impact in clean surgery. Indeed, intranasal mupirocin has been shown to reduce surgical site infections in cardiothoracic and orthopaedic surgery, but is less effective in general surgery.[23] The commencement of such decolonisation regimens prior to surgical procedures, which can be facilitated by rapid detection of *S. aureus* carriage with molecular tests, is likely a key factor in the success of this approach.[32] The use of molecular tests in the latter part of the intervention phase in our study could have significantly contributed to the reduction in

MRSA rates seen over the period of the intervention phase, particularly in clean surgery wards.

The exploratory analysis suggests that screening intensity, rather than HH promotion, explained the intervention effects. It is curious, then, that universal screening did not perform better than HH promotion combined with targeted screening. A significant reduction in MRSA clinical cultures was seen with the combined strategy despite the enrolment of only two hospitals in this study arm. This suggests that the effect of the combined intervention was robust. It is certainly biologically plausible that using two interventions that aim to control MRSA in different ways would be more effective than use of single interventions. Although the universal screening arm enrolled four hospitals, low baseline MRSA rates in this arm may have reduced our ability to detect significant effects. Shortage of isolation rooms may have also contributed. In addition, targeted screening may have been more effective if it identified "superspreaders",[33] facilitating more efficient use of resources including limited single rooms. Modelling studies also demonstrate that targeted screening has the advantage of increased cost-effectiveness compared to universal screening for reducing healthcare associated MRSA infections.[34,35]

This study adds to the conflicting literature regarding active surveillance cultures. Our results apply to surgical settings. The risk of MRSA infection in other wards, such as intensive care units or general medical wards, would differ due to variation in patient comorbidities and exposure to invasive procedures or antibiotics. It is also important to note that previous studies have used a variety of interventions in combination with screening. In some cases, the use of pre-emptive isolation in both study arms[36] or lack of decolonisation strategies,[6] may have led to effect sizes that studies had insufficient power to detect. Comparison of rapid

screening to conventional rather than no screening,[36] differences in screening methods,[10] variation in MRSA strains,[37] or limitations in study design and analyses[10,11] are other potential explanations for the conflicting results of screening studies.

There are some limitations to this study. Research personnel assessing HH, screening, decolonisation, contact precautions, and isolation practices were not blinded to study assignment as they were responsible for implementing the interventions. Although allocation of interventions was not randomised, we accounted for differences in hospitals by adjusting for potential confounders and comparing outcomes between baseline and intervention phases within the same study arm. Decisions to take culture samples were initiated by treating physicians, not research personnel, and standardised definitions for infections were used, reducing the likelihood of bias in the measurement of the study outcomes by unblinded assessors. We used MRSA-positive clinical cultures as our primary outcome. Although this measure does not distinguish between colonisation and infection, it can be a more sensitive marker for changes in MRSA disease rates.[38] We found the results for MRSA clinical cultures similar to those for infections, suggesting that this measure was clinically relevant. Patient-level data, such as age, comorbidities and length of stay, and antibiotic use were not measured for this study. However, results were similar when each centre was excluded in turn from the analysis (data not shown) so changes in factors in individual centres are unlikely to have had a major effect on study outcomes.

Conclusion

In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard infection control measures emphasising HH promotion and MRSA-specific (targeted screening of high risk patients) approaches was required to reduce MRSA rates.

Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation of identified MRSA carriers was associated with significant reductions in MRSA clinical culture and infection rates. These findings are likely generalisable to other settings with varying infection control practices. In addition, the WHO multimodal HH promotion strategy[15] implemented in this study is already being used in many parts of the world. Therefore our study, which provides evidence that this intervention alone is insufficient to reduce MRSA rates, potentially has widespread implications for best clinical practice recommendations and policy change. Further research regarding the cost-effectiveness of these interventions will allow better utilisation of limited healthcare resources.

REFERENCES

1 WHO. Report on the burden of endemic health care-associated infection worldwide. http://whqlibdoc.who.int/publications/2011/9789241501507_eng.pdf (accessed 24 April 2013).

2 Cosgrove SE, Qi Y, Kaye KS, et al. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 2005;26:166-74.

3 Weber SG, Huang SS, Oriola S, et al. Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: Position statement from the Joint SHEA and APIC Task Force. *Am J Infect Control* 2007;35:73-85.

4 UK Department of Health. MRSA Screening - Operational Guidance 2. http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_092844 (accessed 24 April 2013).

5 Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. *Ann Intern Med* 2008;148:409-18.

6 Huskins WC, Huckabee CM, O'Grady NP, et al. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med* 2011;364:1407-18.

7 Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 2008;299:1149-57.

8 Edmond MB, Ober JF, Bearman G. Active surveillance cultures are not required to control MRSA infections in the critical care setting. *Am J Infect Control* 2008;36:461-3.

9 Wenzel RP, Bearman G, Edmond MB. Screening for MRSA: a flawed hospital infection control intervention. *Infect Control Hosp Epidemiol* 2008;29:1012-8.

10 Tacconelli E, De Angelis G, de Waure C, et al. Rapid screening tests for meticillin-resistant *Staphylococcus aureus* at hospital admission: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:546-54.

11 Loveday HP, Pellowe CM, Jones SR, et al. A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant *Staphylococcus aureus* (1996-2004): report to the Joint MRSA Working Party (Subgroup A). *J Hosp Infect* 2006;63 Suppl 1:S45-70.

12 Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med* 2011;364:1419-30.

13 Farr BM, Jarvis WR. Searching many guidelines for how best to control methicillin-resistant *Staphylococcus aureus* healthcare-associated spread and infection. *Infect Control Hosp Epidemiol* 2009;30:808-9.

14 Nijssen S, Bonten MJ, Weinstein RA. Are active microbiological surveillance and subsequent isolation needed to prevent the spread of methicillin-resistant *Staphylococcus aureus*? *Clin Infect Dis* 2005;40:405-9.

15 WHO. WHO Guidelines on Hand Hygiene in Health Care. World Alliance for Patient Safety. Geneva: WHO Press Geneva, 2009.

16 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32.

17 Van Heirstraeten L, Cortinas Abrahantes J, Lammens C, et al. Impact of a short period of pre-enrichment on detection and bacterial loads of methicillin-resistant *Staphylococcus aureus* from screening specimens. *J Clin Microbiol* 2009;47:3326-8.

18 Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.
19 Gazin M, Lee A, Derde L, et al. Culture-based detection of methicillin-resistant *Staphylococcus aureus* by a network of European laboratories: an external quality assessment study. *Eur J Clin Microbiol Infect Dis* 2012;31:1765-70.
20 Lee A, Chalfine A, Daikos GL, et al. Hand hygiene practices and adherence determinants in surgical wards across Europe and Israel: a multicenter observational study. *Am J Infect Control* 2011;39:517-20.
21 Harbarth S, Pittet D, Grady L, et al. Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. *Pediatr Infect Dis J* 2002;21:489-95.
22 Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis* 2007;45:901-7.
23 Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005;26:916-22.
24 Stone SP, Cooper BS, Kibbler CC, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007;7:282-8.
25 Struelens MJ, Monnet DL. Prevention of methicillin-resistant *Staphylococcus aureus* infection: is Europe winning the fight? *Infect Control Hosp Epidemiol* 2010;31 Suppl 1:S42-4.
26 Cooper BS, Medley GF, Scott GM. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J Hosp Infect* 1999;43:131-47.
27 Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. *Lancet* 2000;356:1307-12.
28 Stone SP, Fuller C, Savage J, et al. Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. *BMJ* 2012;344:e3005.
29 Lee AS, Huttner B, Harbarth S. Control of methicillin-resistant *Staphylococcus aureus*. *Infect Dis Clin North Am* 2011;25:155-79.
30 Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis* 2009;48:922-30.
31 Huttner B, Robicsek AA, Gervaz P, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* carriage and MRSA surgical site infections in patients undergoing colorectal surgery: a cohort study in two centers. *Surg Infect (Larchmt)* 2012;13:401-5.
32 Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med* 2010;362:9-17.
33 Lloyd-Smith JO, Schreiber SJ, Kopp PE, et al. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005;438:355-9.
34 Hubben G, Bootsma M, Luteijn M, et al. Modelling the costs and effects of selective and universal hospital admission screening for methicillin-resistant *Staphylococcus aureus*. *PLoS One* 2011;6:e14783.
35 Infectious Disease Research Network (IDRN). Report on MRSA Screening Audit. http://idrn.org/audit.php (accessed 28 July 2013).

36 Jeyaratnam D, Whitty CJ, Phillips K, et al. Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008;336:927-30.
37 Cooper BS, Kypraios T, Batra R, et al. Quantifying type-specific reproduction numbers for nosocomial pathogens: evidence for heightened transmission of an Asian sequence type 239 MRSA clone. *PLoS Comput Biol* 2012;8:e1002454.
38 Walker S, Peto TE, O'Connor L, et al. Are there better methods of monitoring MRSA control than bacteraemia surveillance? An observational database study. *PLoS One* 2008;3:e2378.

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Competing interests

SH is a member of the speakers' bureau for bioMérieux and Pfizer, and the scientific advisory board of Destiny Pharma, DaVolterra, and bioMérieux. He has received financial support for MRSA research activities from Geneva University Hospitals, B.Braun, and Pfizer. AP is a member of the speakers' bureau for Cubist and has received financial support for MRSA research activities from BD. There were no other financial or non-financial relationships, or interests that may be relevant to the submitted work.

Author contributions

Conceived and designed the experiments: SH CBB. Analysed the data: ASL BSC. Contributed reagents/materials: SMK HG. Wrote the first draft of the manuscript: ASL. Contributed to the writing of the manuscript: ASL SH BSC CBB AC GLD CF BC SL SMK JAM CMA AP GP BR HG. ICMJE criteria for authorship read and met: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Agree with manuscript results and conclusions: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Enrolled patients: ASL AC GLD CF BC SL JAM CMA AP GP BR. Statistical support: BSC.

Data sharing

The dataset is available from the corresponding author at stephan.harbarth@hcuge.ch.

FIGURE LEGENDS

Figure 1 Flow of study wards through each phase of the study

Figure 1 Legend
Ten hospitals in nine countries were enrolled and were allocated to one of three study arms during the intervention phase. The enhanced hand hygiene arm used hand hygiene promotion; the screening and decolonisation arm used universal meticillin resistant *Staphylococcus aureus* (MRSA) screening coupled with contact precautions and decolonisation therapy with intranasal mupirocin and chlorhexidine body washes for identified MRSA carriers; the combined arm used a combination of hand hygiene promotion and targeted MRSA screening.

Figure 2 Implementation of the interventions

Figure 2 Legend
The top panel (A) shows the monthly hand hygiene compliance rates for hospitals in the enhanced hand hygiene and combined arms that used hand hygiene promotion campaigns. The solid dots represent the observed compliance rates while the lines represent the predicted compliance rates based on the regression model. The bottom panel (B) shows the proportion of patients screened on admission to the study wards by study arm. HH, hand hygiene.

Figure 3 Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers

Figure 3 Legend
This figure shows the distribution of monthly adherence to infection control measures for randomly audited patients known to be colonised or infected with meticillin resistant *Staphylococcus aureus* (MRSA) for each study arm. The top panel (A) shows adherence to implementation of contact precautions, decolonisation therapy, and isolation in single rooms. The middle panel (B) shows the presence of signage of MRSA status on the patients' room, bed, or nursing chart. The bottom panel (C) shows the availability of gowns, gloves, and alcohol-based handrub in or at the entrance of the room. The horizontal line in each box represents the median, the box represents the interquartile range and the vertical lines represent the minimum and maximum values. MRSA, meticillin resistant *Staphylococcus aureus*.

Figure 4 Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm

Figure 4 Legend
The top panel (A) shows the nosocomial meticillin resistant *Staphylococcus aureus* (MRSA) isolaton rates from clinical specimens. The middle panel (B) shows the nosocomial MRSA infection rates. The bottom panel (C) shows the nosocomial MRSA surgical site infection rates. The solid dots represent the observed MRSA rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*.

TABLES

Table 1: Baseline phase characteristics of hospitals and wards enrolled in the study

	Hospital characteristics			Study ward characteristics							
Hospital	Total beds (n)	Total number of single rooms (%)	Ratio of infection control nurses to beds	Surgical subspecialties	Total beds (n)	Total admissions during baseline phase (n)	Mean patient-to-nurse ratio (SD)*	Percent hand hygiene compliance (95% CI)	Number of patients screened on admission (%)	Number identified MRSA positive on admission (%)†	Study arm
1	3611	45 (1.2)	1:240	Abdominal Cardiovascular Orthopaedic	588	8018	6.4 (1.2)	18.8 (15.1 to 22.9)	0 (0)	9 (0.1)	Enhanced hand hygiene
2	317	235 (74.1)	1:160	Cardiothoracic Orthopaedic Vascular	72	1613	4.1 (1.8)	75.4 (70.3 to 80.0)	29 (1.8)	20 (1.2)	Screening and decolonisation
3	850	135 (15.9)	1:425	Cardiovascular General Orthopaedic	75	1841	5.6 (0.7)	26.8 (24.4 to 29.4)	14 (0.8)	11 (0.6)	Screening and decolonisation
4	822	0 (0)	1:137	Abdominal Orthopaedic Urology Vascular	230	6574	3.7 (0.9)	39.3 (34.6 to 44.1)	182 (2.8)	21 (0.3)	Combined
5	545	89 (16.3)	1:272	General Neurosurgery Orthopaedic Vascular	121	1938	5.8 (1.5)	14.3 (11.3 to 17.6)	56 (2.9)	4 (0.2)	Screening and decolonisation
6	547	4 (0.7)	1:274	General Orthopaedic Vascular	93	1300	16.8 (2.5)	25.1 (20.7 to 30.1)	0 (0)	5 (0.4)	Screening and decolonisation
7	902	62 (6.9)	1:180	Abdominal General Vascular	84	1963	6.1 (1.5)	76.5 (71.3 to 81.1)	607 (30.9)	41 (2.1)	Combined

8	850	202 (23.8)	1:567	Orthopaedic Urology Vascular	87	2434	5.5 (0.6)	50.2 (44.6 to 55.8)	0 (0)	3 (0.1)	Enhanced hand hygiene
9	1350	150 (11.1)	1:260	Cardiothoracic Neurosurgery Plastic surgery	164	1561	10.0 (2.2)	67.0 (61.4 to 72.3)	17 (1.1)	15 (1.0)	Enhanced hand hygiene
10	2044	402 (19.7)	1:204	Abdominal Cardiovascular Orthopaedic Urology	302	6366	4.8 (0.4)	55.9 (51.2 to 60.5)	1666 (26.2)	140 (2.2)	Enhanced hand hygiene
Overall	11 838	1324 (11.2)			1816	33 608	6.6 (3.8)	39.5 (38.1 to 40.9)	2571 (7.6)	269 (0.8)	

MRSA, meticillin resistant *Staphylococcus aureus*.
*Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
†By screening or clinical culture.

Table 2: Summary of the timing and nature of infection control interventions for each study arm

	Standard precautions	Hand hygiene promotion	MRSA screening	MRSA isolation	MRSA decolonisation
Baseline phase: 6-7 months (1 March 2008 to 31 January 2009)*					
Enhanced hand hygiene arm	-†	-	-	-	-
Screening and decolonisation arm	-	-	-	-	-
Combined arm	-	-	-	-	-
Intervention phase: 12 months (1 October 2008 to 31 January 2010)*					
Enhanced hand hygiene arm	Adherence to standard precautions (e.g. gloves and other barriers as needed for contact with mucous membranes, wounds, and body fluids) during care of all patients encouraged.	HH promotion using the WHO multi-modal HH promotion method.[15] Observation of 100 opportunities for HH per ward per month.	-	-	-
Screening and decolonisation arm	-	-	Universal screening of patients admitted for more than 24 hours, on admission then weekly (see "MRSA screening details" box below).	Patients MRSA colonised/infected placed on contact precautions (gown and gloves during contact). MRSA patients placed in single rooms or cohorted based on local capacity. Pre-emptive isolation of previously unknown MRSA-carriers pending screening results not used.	Patients MRSA colonised/infected given twice-daily intranasal mupirocin and daily chlorhexidine body washes (5 days).
Combined arm	Adherence to standard precautions (e.g. gloves and other barriers as needed for contact with mucous membranes, wounds, and body fluids) during care of all patients encouraged.	HH promotion using the WHO multi-modal HH promotion method.[15] Observation of 100 opportunities for HH per ward per month.	Targeted screening based on risk factors (see "MRSA screening details" box below).	Patients MRSA colonised/infected placed on contact precautions (gown and gloves during contact). MRSA patients placed in single rooms or cohorted based on local capacity. Pre-emptive isolation of previously unknown MRSA-carriers pending screening results not used.	Patients MRSA colonised/infected given topical decolonisation therapy at discretion of treating clinicians.

Washout phase: 6 months (1 October 2009 to 31 July 2010)*					
Enhanced hand hygiene arm	-	-	-	-	-
Screening and decolonisation arm	-	-	-	-	-
Combined arm	-	-	Targeted screening based on risk factors (see "MRSA screening details" box below).	Patients MRSA colonised/infected placed on contact precautions (gown and gloves during contact). MRSA patients placed in single rooms or cohorted based on local capacity. Pre-emptive isolation of previously unknown MRSA-carriers pending screening results not used.	Patients MRSA colonised/infected given topical decolonisation therapy at discretion of treating clinicians.

MRSA screening details: Screening of nares, perineum, and wounds (if present).
Universal screening (intervention phase) was used in the screening and decolonisation arm. It refers to screening patients admitted for more than 24 hours and excluded patients undergoing ambulatory surgery and those screened within 5 days prior to admission to the surgical ward.
Targeted screening (intervention and washout phase) was used in the two centres in the combined arm due to introduction of local and national mandatory screening policies. One study centre (Hospital 4) screened patients previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. The other centre (Hospital 7) screened patients with the same risk factors as Hospital 4, but also included nursing home residents, patients admitted to the hospital in the last three months, patients transferred from another ward within the same hospital, and those admitted to vascular or abdominal surgery subspecialties.

MRSA, meticillin resistant *Staphylococcus aureus*; HH, hand hygiene.
*Commencement of the study period was staggered for hospitals. For each study phase, the start date is the date on which the first hospital entered the study phase and the end date indicates the date on which the last hospital completed the study phase.
†The dash indicates that there were no specific interventions as part of the study. Hospitals employed their usual infection control practices during these study phases.

Table 3: Study characteristics by study period

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Total patient-days (n)	264 035	496 975	249 119
Total surgical procedures (n)	27 768	49 747	22 123
Procedures in clean surgery wards (n)†	12 916	21 463	8787
Procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Number positive by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Number positive by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the screening and decolonisation arm and one hospital in each of the enhanced hand hygiene and combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table 4: Crude nosocomial meticillin resistant *Staphylococcus aureus* incidence rates and incidence rate ratios by study arm for each study period*

Outcome	Baseline phase	Intervention phase	Washout phase	Crude IRR (95% CI) for intervention vs. baseline phases	Crude IRR (95% CI) for washout vs. intervention phases
MRSA isolation rate from clinical cultures (no. per 100 susceptible patients)					
Enhanced hand hygiene	0.99 (181/183.47)	0.80 (279/349.50)	0.65 (106/163.83)	0.81 (0.67 to 0.98)	0.81 (0.65 to 1.01)
Screening and decolonisation	0.47 (31/66.61)	0.23 (28/122.56)	0.26 (17/66.04)	0.49 (0.29 to 0.82)	1.13 (0.62 to 2.06)
Combined	0.55 (47/85.35)	0.36 (60/165.23)	0.13 (8/63.04)	0.66 (0.45 to 0.97)	0.35 (0.17 to 0.73)
MRSA infection rate (no. per 100 admissions)					
Enhanced hand hygiene	0.58 (106/183.79)	0.50 (175/349.96)	0.45 (74/164.13)	0.87 (0.68 to 1.10)	0.90 (0.69 to 1.18)
Screening and decolonisation	0.24 (16/66.92)	0.19 (23/122.79)	0.17 (11/66.15)	0.78 (0.41 to 1.48)	0.89 (0.43 to 1.82)
Combined	0.29 (25/85.37)	0.19 (32/165.35)	0.13 (8/63.04)	0.66 (0.39 to 1.12)	0.66 (0.30 to 1.42)
MRSA surgical site infection rate (no. per 100 surgical procedures)					
Enhanced hand hygiene	0.60 (79/132.27)	0.49 (123/250.03)	0.42 (54/127.06)	0.82 (0.62 to 1.09)	0.86 (0.63 to 1.19)
Screening and decolonisation	0.26 (14/54.00)	0.15 (15/99.63)	0.16 (8/50.74)	0.58 (0.28 to 1.20)	1.05 (0.44 to 2.47)
Combined	0.20 (18/91.41)	0.14 (21/147.81)	0.07 (3/43.43)	0.72 (0.38 to 1.35)	0.49 (0.15 to 1.63)
MRSA bloodstream infection rate (no. per 10 000 patient-days)					
Enhanced hand hygiene	0.93 (14/15.0757)	0.56 (16/28.6667)	0.44 (6/13.5745)	0.60 (0.29 to 1.23)	0.79 (0.31 to 2.02)
Screening and decolonisation	0.17 (1/5.7754)	0.18 (2/11.2971)	0.17 (1/5.8473)	1.02 (0.09 to 11.28)	0.97 (0.09 to 10.65)
Combined	0.18 (1/5.5524)	0.00 (0/9.7337)	0.00 (0/5.4901)	-	-

IRR, incidence rate ratio; MRSA, meticillin resistant *Staphylococcus aureus*.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward.

Table 5: Multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced hand hygiene	1.44	0.96 to 2.15	0.076	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
Screening and decolonisation	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.070	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced hand hygiene	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Screening and decolonisation	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.162
Combined	0.88	0.79 to 0.98	0.016	0.90	0.80 to 1.02	0.096	0.86	0.74 to 1.01	0.059
Washout phase									
Change in level	1.90	0.91 to 3.95	0.087	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53

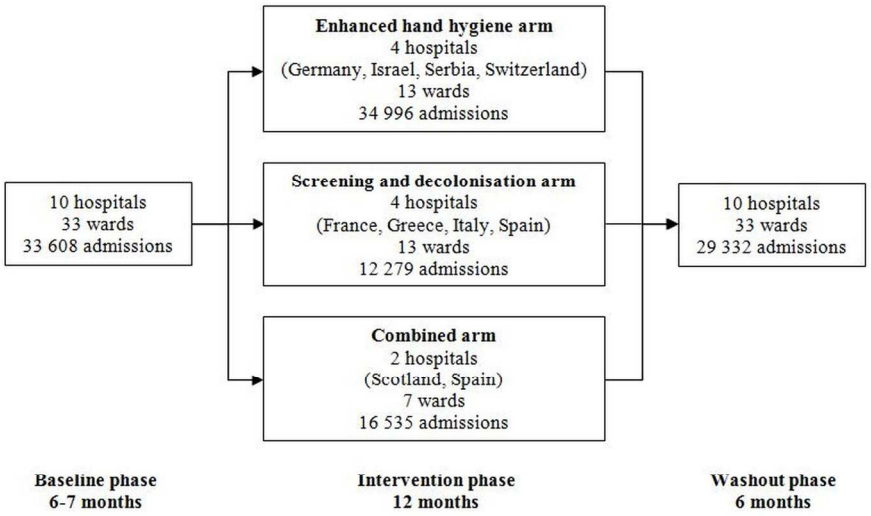
MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.

*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

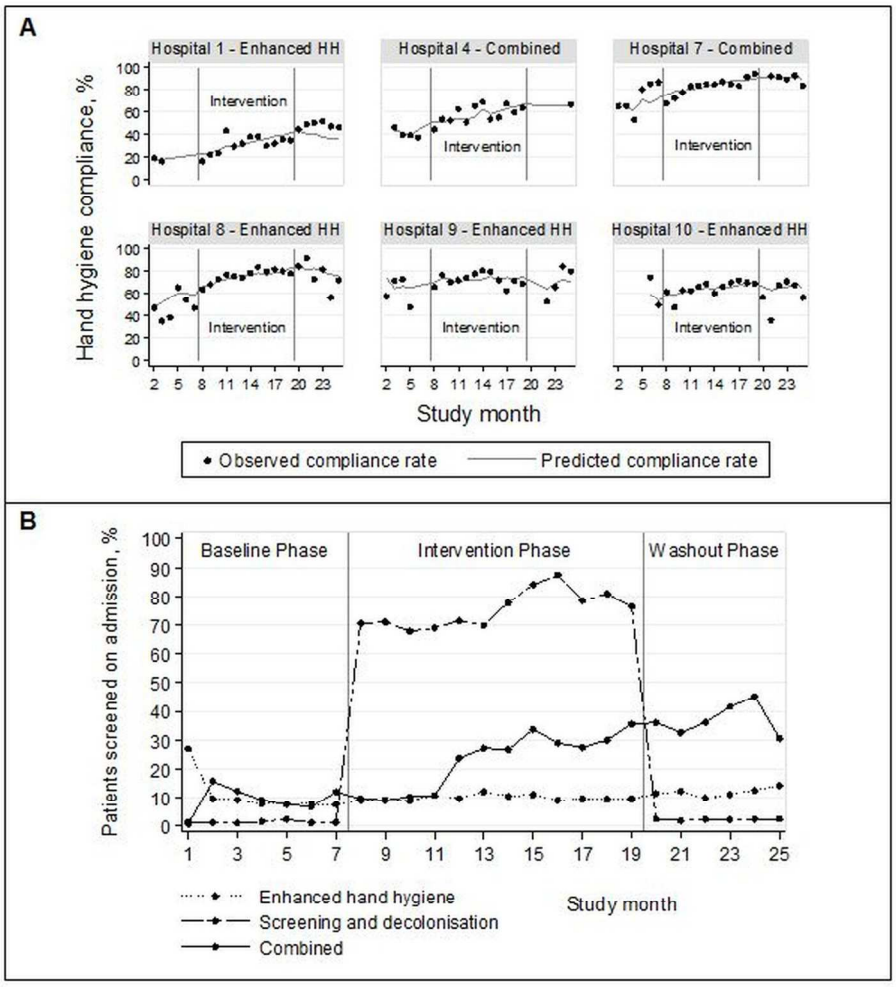
Table 6: Multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced hand hygiene	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Screening and decolonisation	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.121	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced hand hygiene	0.89	0.78 to 1.01	0.063	0.88	0.75 to 1.04	0.127	0.89	0.73 to 1.07	0.21
Screening and decolonisation	0.85	0.74 to 0.97	0.019	0.83	0.69 to 0.99	0.041	0.81	0.66 to 1.00	0.054
Combined	0.82	0.71 to 0.95	0.007	0.84	0.70 to 1.00	0.055	0.84	0.68 to 1.03	0.095
Washout phase									
Change in level	3.01	1.05 to 8.63	0.041	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).



Flow of study wards through each phase of the study
233x137mm (300 x 300 DPI)



Implementation of the interventions
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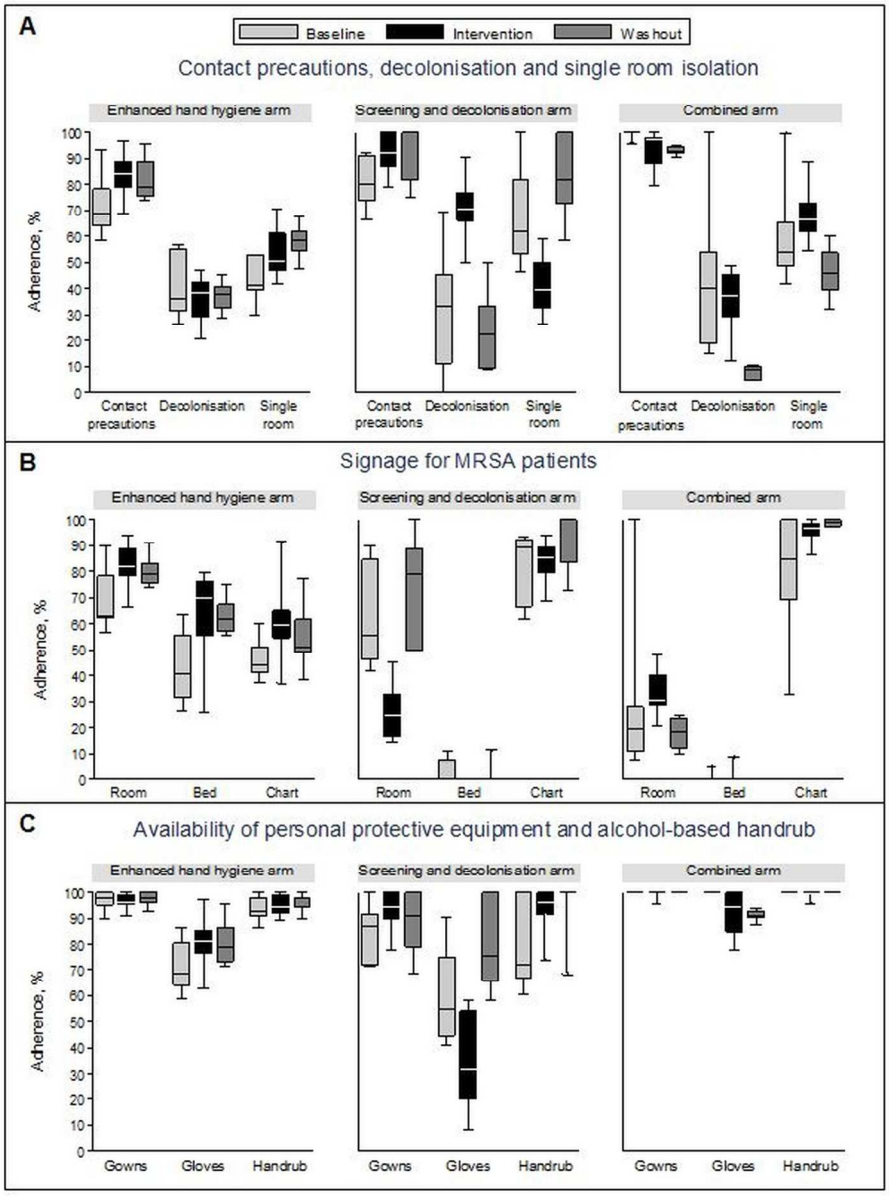
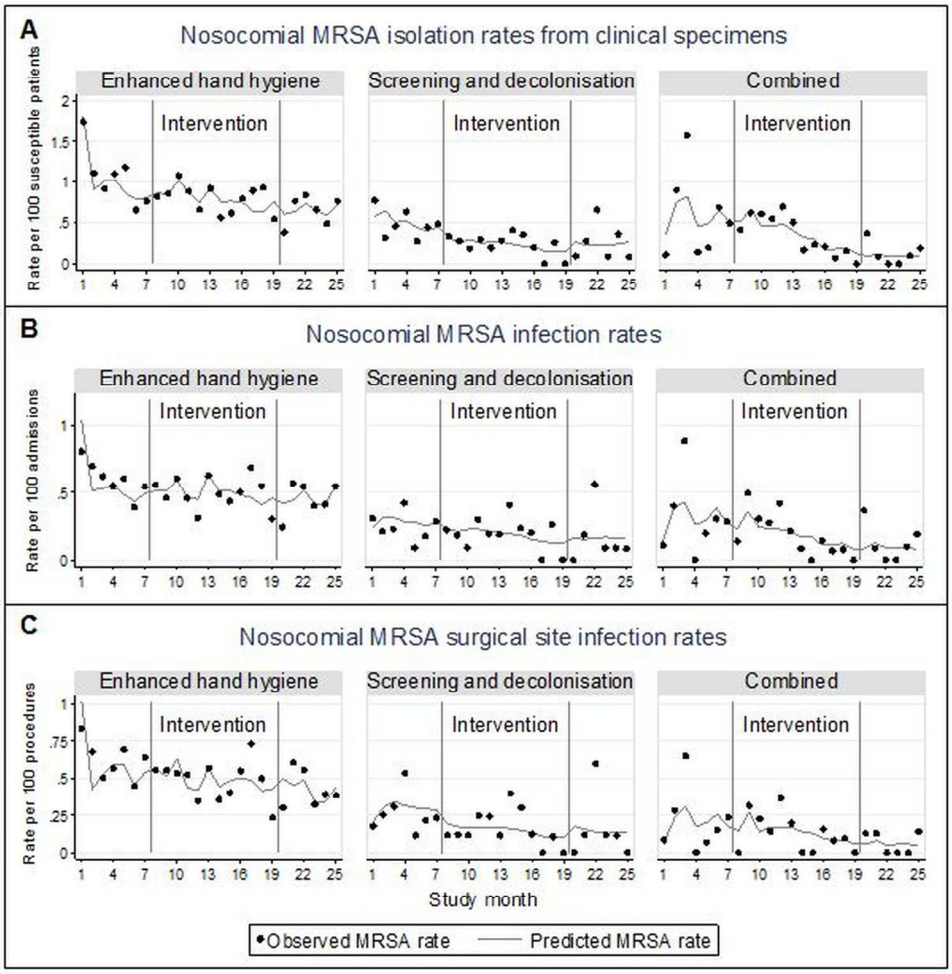


Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers
161x214mm (300 x 300 DPI)



Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm
166x170mm (300 x 300 DPI)

SUPPLEMENTARY DATA FOR MANUSCRIPT:

Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a controlled multicentre intervention trial

Table A1: Meticillin resistant *Staphylococcus aureus* screening methods used in study centres in the screening and decolonisation arm and combined arm

Table A2: Study characteristics by study period and study arm

Table A3: Multiple segmented multilevel logistic regression model showing factors associated with monthly hand hygiene compliance rates

Table A4: Full model results for the multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates

Table A5: Full model results for the multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only

Table A6: Multiple segmented multilevel Poisson regression models showing nosocomial meticillin resistant *Staphylococcus aureus* rates in the washout phase by study arm

Table A7: Exploratory analysis using multiple segmented multilevel Poisson regression models including interventions implemented by centres as covariates in the model

Figure A1: Nosocomial meticillin resistant *Staphylococcus aureus* isolation rates from clinical specimens by hospital

Table A1: Meticillin resistant *Staphylococcus aureus* screening methods used in study centres in the screening and decolonisation arm and combined arm

Study arm	Hospital	Chromogenic medium used	Minimum time to detection (days)*	Months during intervention phase test used†	Molecular assay used	Total assay time (hours)*	Months during intervention phase test used†‡
Screening and decolonisation	2	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	1 to 10
					GeneXpert (Cepheid)	<1.5	7 to 12
	3	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneXpert (Cepheid)	<1.5	6 to 12
	5	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	10 to 12
	6	BBL CHROMagar (BD Diagnostics)	1.72	1 to 12	GeneXpert (Cepheid)	<1.5	8 to 12
Combined	4	MRSA Select (Bio-Rad Laboratories)	1.35	1 to 12	GeneOhm (BD Diagnostics)	2 to 3	1 to 12
	7	ChromID (bioMérieux)	1.65	1 to 12	Not used	-	-

*From Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.
†Screening for meticillin resistant *Staphylococcus aureus* occurred during all study phases for centres in the combined arm using existing local methods.
‡For the screening and decolonisation arm, molecular assays were introduced during the latter part of the intervention phase. In one centre in this arm (Hospital 2) a locally available molecular assay was used from the commencement of the intervention phase.

Table A2: Study characteristics by study period and study arm

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Enhanced hand hygiene	18 379	34 996	16 413
Screening and decolonisation	6692	12 279	6615
Combined	8537	16 535	6304
Total patient-days (n)	264 035	496 975	249 119
Enhanced hand hygiene	150 757	286 667	135 745
Screening and decolonisation	57 754	112 971	58 473
Combined	55 524	97 337	54 901
Total surgical procedures (n)	27 768	49 747	22 123
Enhanced hand hygiene	13 227	25 003	12 706
Screening and decolonisation	5400	9963	5074
Combined	9141	14 781	4343
Surgical procedures in clean surgery wards (n)†	12 916	21 463	8787
Enhanced hand hygiene	5160	9102	4693
Screening and decolonisation	1310	2551	1185
Combined	6446	9810	2909
Surgical procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Enhanced hand hygiene	8067	15 901	8013
Screening and decolonisation	4090	7412	3889
Combined	2695	4971	1434
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Enhanced hand hygiene	6.46 (2.35)	6.73 (2.11)	6.99 (2.57)
Screening and decolonisation	7.68 (5.11)	7.96 (4.74)	8.31 (5.52)
Combined	4.65 (1.62)	4.14 (1.17)	3.96 (1.30)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Enhanced hand hygiene	167 (0.9)	272 (0.8)	136 (0.8)
Screening and decolonisation	40 (0.6)	259 (2.1)	13 (0.2)
Combined	62 (0.7)	193 (1.2)	79 (1.3)
Number of patients MRSA positive on admission by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Enhanced hand hygiene	32 (0.2)	46 (0.1)	30 (0.2)
Screening and decolonisation	31 (0.5)	27 (0.2)	11 (0.2)
Combined	2 (0.02)	12 (0.1)	0 (0)
Number of patients MRSA positive on admission by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)
Enhanced hand hygiene	135 (0.7)	226 (0.6)	106 (0.6)
Screening and decolonisation	9 (0.1)	232 (1.9)	2 (0.03)
Combined	60 (0.7)	181 (1.1)	79 (1.3)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the screening and decolonisation arm and one hospital in each of the enhanced hand hygiene and combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table A3: Multiple segmented multilevel logistic regression model showing factors associated with monthly hand hygiene compliance rates*

Variable	Adjusted odds ratio	95% CI	p Value
Baseline phase			
Trend	1.04	0.98 to 1.10	0.24
Intervention phase			
Change in level	1.19	1.01 to 1.42	0.04
Change in trend	1.03	0.97 to 1.09	0.30
Washout phase			
Change in level	1.17	0.82 to 1.68	0.39
Change in trend	0.91	0.85 to 0.97	0.004
Professional category			
Physician	1.00	-	-
Nurse	1.37	1.28 to 1.46	<0.001
Auxiliary nurse	1.27	1.16 to 1.39	<0.001
Other	1.11	0.99 to 1.24	0.06
Indication for hand hygiene			
Before touching patient	1.00	-	-
Before clean/aseptic procedure	1.20	1.09 to 1.32	<0.001
After body fluid exposure	4.95	4.47 to 5.48	<0.001
After touching patient	2.79	2.60 to 3.00	<0.001
After touching patient surroundings	1.52	1.41 to 1.65	<0.001
Patient-to-nurse ratio (per 1-unit increment)†	0.91	0.89 to 0.94	<0.001
MRSA colonisation pressure‡			
0 to 0.7%	1.00	-	-
0.8 to 3.2%	0.86	0.79 to 0.94	<0.001
3.3 to 8.2%	0.90	0.81 to 1.01	0.07
>8.2%	0.78	0.68 to 0.90	<0.001

MRSA, meticillin resistant *Staphylococcus aureus*.
*Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all statistically significant, though baseline trends and intercepts showed no evidence of correlation.
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.
‡Calculated by dividing the patient-days of subjects known to be colonised or infected with meticillin resistant *Staphylococcus aureus* by the total number of patient-days in the ward in any given study month. This variable was divided into quartiles for the analysis.

Table A4: Full model results for the multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced hand hygiene	1.44	0.96 to 2.15	0.08	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
Screening and decolonisation	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.07	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced hand hygiene	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Screening and decolonisation	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.16
Combined	0.88	0.79 to 0.98	0.02	0.90	0.80 to 1.02	0.10	0.86	0.74 to 1.01	0.06
Washout phase									
Change in level	1.90	0.91 to 3.95	0.09	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53
Patient-to-nurse ratio (per 1-unit increment)†	1.01	0.94 to 1.08	0.87	1.01	0.93 to 1.09	0.84	1.04	0.96 to 1.14	0.33
Calendar month									
January	1.00	-	-	1.00	-	-	1.00	-	-
February	0.83	0.54 to 1.28	0.41	0.89	0.53 to 1.50	0.67	0.76	0.40 to 1.45	0.41
March	1.16	0.78 to 1.72	0.47	1.49	0.94 to 2.35	0.09	1.34	0.76 to 2.37	0.31
April	0.93	0.61 to 1.43	0.75	1.16	0.70 to 1.90	0.57	0.81	0.42 to 1.55	0.52
May	1.19	0.78 to 1.83	0.42	1.33	0.80 to 2.21	0.27	1.31	0.71 to 2.41	0.39
June	1.40	0.92 to 2.12	0.11	1.40	0.84 to 2.33	0.19	1.45	0.79 to 2.64	0.23
July	1.31	0.86 to 1.99	0.21	1.44	0.88 to 2.38	0.15	1.52	0.83 to 2.77	0.17
August	1.20	0.78 to 1.84	0.40	1.14	0.67 to 1.94	0.63	1.22	0.65 to 2.30	0.54
September	1.40	0.92 to 2.13	0.11	1.39	0.84 to 2.32	0.20	1.41	0.77 to 2.58	0.27
October	0.89	0.59 to 1.34	0.58	1.06	0.65 to 1.72	0.81	1.19	0.67 to 2.10	0.55
November	1.04	0.70 to 1.55	0.85	1.13	0.70 to 1.82	0.63	1.11	0.62 to 1.98	0.72
December	1.29	0.87 to 1.90	0.21	1.34	0.84 to 2.14	0.23	1.33	0.75 to 2.35	0.32
Surgical subspecialty									
Orthopaedics	1.00	-	-	1.00	-	-	1.00	-	-
Vascular	2.91	1.44 to 5.88	0.003	2.07	0.98 to 4.37	0.06	1.90	0.73 to 4.92	0.19
Cardiothoracic	1.10	0.52 to 2.34	0.80	1.16	0.55 to 2.45	0.70	1.35	0.55 to 3.27	0.51
General	1.65	0.70 to 3.89	0.26	1.92	0.81 to 4.55	0.14	2.06	0.72 to 5.88	0.18
Abdominal	1.51	0.69 to 3.29	0.30	1.44	0.67 to 3.13	0.35	1.30	0.52 to 3.27	0.58
Urology	0.82	0.33 to 2.05	0.67	0.63	0.24 to 1.64	0.34	0.90	0.29 to 2.86	0.87
Neurosurgery	0.79	0.22 to 2.78	0.71	0.85	0.23 to 3.07	0.80	0.53	0.10 to 2.71	0.44
Plastic surgery	0.75	0.13 to 4.41	0.75	0.59	0.08 to 4.38	0.60	0.54	0.06 to 4.51	0.57
Baseline HH compliance rate (per increment from 0 to 100%)	1.56	0.32 to 7.53	0.58	1.11	0.20 to 6.06	0.91	1.29	0.18 to 9.27	0.80

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio; HH, hand hygiene.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).
†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.

Table A5: Full model results for the multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced hand hygiene	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Screening and decolonisation	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.12	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced hand hygiene	0.89	0.78 to 1.01	0.06	0.88	0.75 to 1.04	0.13	0.89	0.73 to 1.07	0.21
Screening and decolonisation	0.85	0.74 to 0.97	0.02	0.83	0.69 to 0.99	0.04	0.81	0.66 to 1.00	0.05
Combined	0.82	0.71 to 0.95	0.01	0.84	0.70 to 1.00	0.06	0.84	0.68 to 1.03	0.10
Washout phase									
Change in level	3.01	1.05 to 8.63	0.04	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21
Patient-to-nurse ratio (per 1-unit increment)†	0.99	0.91 to 1.07	0.73	0.99	0.90 to 1.09	0.81	0.99	0.88 to 1.12	0.90
Calendar month									
January	1.00	-	-	1.00	-	-	1.00	-	-
February	1.06	0.54 to 2.07	0.86	1.58	0.66 to 3.81	0.31	1.22	0.45 to 3.28	0.69
March	1.13	0.60 to 2.16	0.70	1.68	0.72 to 3.95	0.23	1.51	0.60 to 3.84	0.38
April	1.32	0.68 to 2.57	0.41	2.12	0.89 to 5.03	0.09	1.52	0.57 to 4.09	0.41
May	2.00	1.06 to 3.76	0.03	3.07	1.34 to 7.04	0.01	2.61	1.04 to 6.52	0.04
June	2.34	1.25 to 4.39	0.01	3.33	1.43 to 7.74	0.01	3.06	1.22 to 7.65	0.02
July	2.19	1.16 to 4.15	0.02	3.20	1.35 to 7.57	0.01	2.94	1.14 to 7.59	0.03
August	2.25	1.18 to 4.26	0.01	2.80	1.18 to 6.65	0.02	2.77	1.08 to 7.10	0.03
September	2.35	1.26 to 4.39	0.01	2.88	1.24 to 6.72	0.01	2.89	1.15 to 7.26	0.02
October	1.49	0.81 to 2.73	0.20	2.66	1.20 to 5.90	0.02	2.39	1.00 to 5.72	0.05
November	1.70	0.93 to 3.09	0.09	2.52	1.12 to 5.67	0.03	1.86	0.75 to 4.62	0.18
December	1.96	1.06 to 3.60	0.03	2.44	1.06 to 5.66	0.04	2.02	0.80 to 5.08	0.14
Surgical subspecialty									
Orthopaedics	1.00	-	-	1.00	-	-	1.00	-	-
Vascular	2.14	1.00 to 4.58	0.05	1.57	0.70 to 3.54	0.27	1.29	0.50 to 3.33	0.60
Cardiothoracic	1.22	0.55 to 2.72	0.62	1.25	0.58 to 2.68	0.57	1.51	0.68 to 3.38	0.31
Neurosurgery	0.72	0.21 to 2.40	0.59	0.87	0.22 to 3.42	0.84	0.78	0.17 to 3.62	0.75
Plastic surgery	0.57	0.11 to 3.03	0.51	0.50	0.07 to 3.88	0.51	0.53	0.07 to 3.83	0.53
Baseline HH compliance rate (per increment from 0 to 100%)	2.07	0.45 to 9.53	0.35	1.37	0.29 to 6.53	0.69	2.15	0.34 to 13.60	0.42

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio; HH, hand hygiene.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular

surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

†Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts) for each month.

Table A6: Multiple segmented multilevel Poisson regression models showing nosocomial meticillin resistant *Staphylococcus aureus* rates in the washout phase by study arm

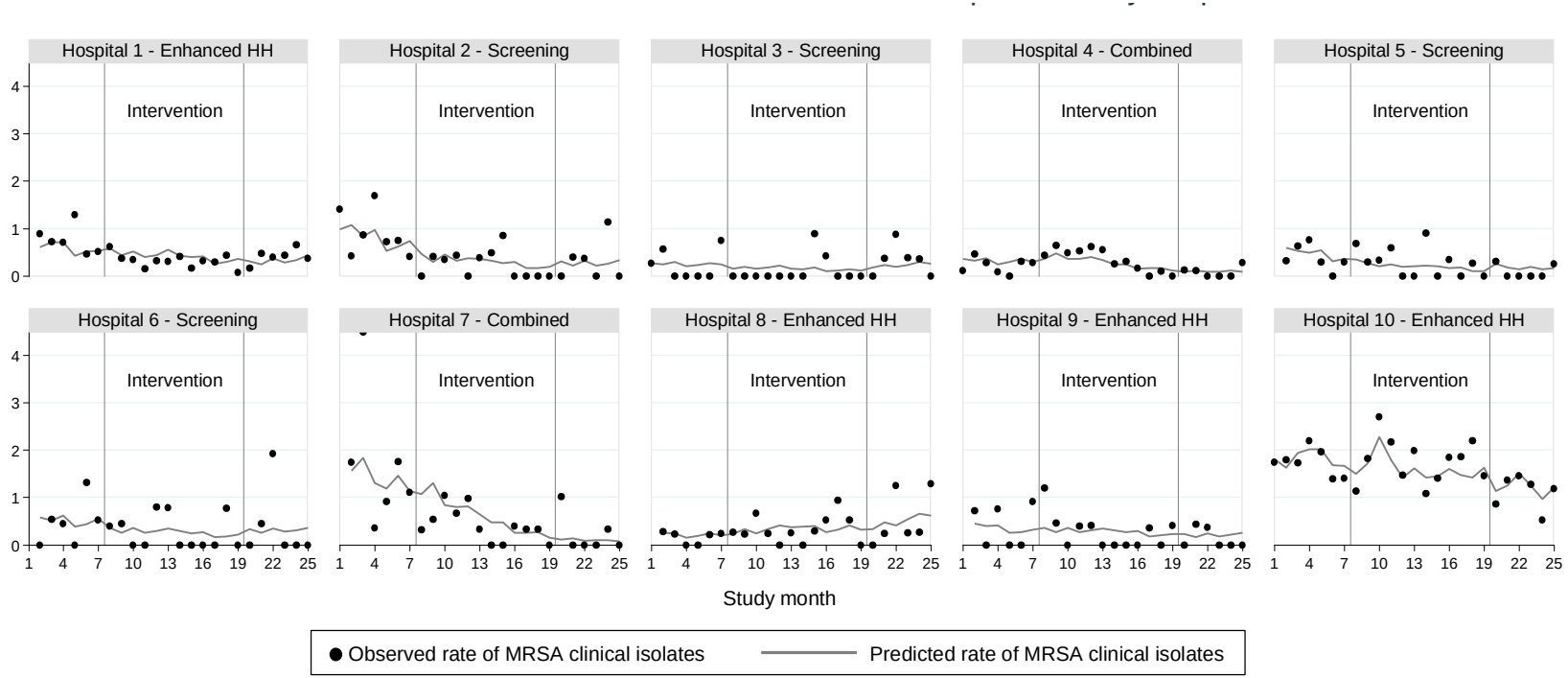
	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.96	0.89 to 1.05	0.41	0.99	0.89 to 1.09	0.81	1.02	0.90 to 1.15	0.80
Intervention phase									
Change in level									
Enhanced hand hygiene	1.37	0.90 to 2.07	0.138	1.21	0.74 to 1.98	0.44	1.23	0.68 to 2.23	0.50
Screening and decolonisation	1.03	0.42 to 2.48	0.95	0.99	0.36 to 2.74	0.99	0.86	0.26 to 2.90	0.81
Combined	2.29	1.14 to 4.61	0.020	2.10	0.88 to 4.99	0.093	1.57	0.52 to 4.72	0.42
Change in trend									
Enhanced hand hygiene	1.01	0.92 to 1.11	0.77	1.01	0.91 to 1.13	0.83	0.99	0.86 to 1.13	0.85
Screening and decolonisation	0.94	0.81 to 1.08	0.37	0.95	0.81 to 1.11	0.52	0.89	0.73 to 1.09	0.27
Combined	0.84	0.74 to 0.96	0.008	0.83	0.71 to 0.97	0.020	0.84	0.70 to 1.02	0.081
Washout phase									
Change in level									
Enhanced hand hygiene	1.43	0.64 to 3.21	0.39	1.11	0.44 to 2.78	0.82	1.68	0.55 to 5.07	0.36
Screening and decolonisation	3.16	0.50 to 19.96	0.22	1.93	0.24 to 15.78	0.54	2.76	0.22 to 34.28	0.43
Combined	8.65	1.20 to 62.29	0.032	13.31	1.38 to 128.72	0.025	4.43	0.19 to 102.38	0.35
Change in trend									
Enhanced hand hygiene	1.05	0.92 to 1.21	0.44	1.04	0.90 to 1.21	0.58	0.97	0.80 to 1.16	0.71
Screening and decolonisation	0.98	0.73 to 1.32	0.90	0.93	0.64 to 1.34	0.70	0.90	0.58 to 1.40	0.64
Combined	0.89	0.57 to 1.39	0.62	0.90	0.57 to 1.43	0.66	0.86	0.42 to 1.74	0.67

Table A7: Exploratory analysis using multiple segmented multilevel Poisson regression models including interventions implemented by centres as covariates in the model*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase						
Trend	1.00	0.95 to 1.05	0.92	1.00	0.95 to 1.06	0.92
Hand hygiene promotion						
Change in level	1.05	0.87 to 1.27	0.63	1.03	0.83 to 1.28	0.80
Change in trend	0.98	0.92 to 1.04	0.47	0.99	0.92 to 1.06	0.68
MRSA screening						
Change in level	0.71	0.40 to 1.26	0.24	0.95	0.49 to 1.84	0.88
Change in trend†	0.91	0.85 to 0.98	0.01	0.92	0.85 to 0.99	0.03

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*The models used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, though there was no evidence that baseline trends significantly correlated with intercepts.
†Each additional month with x% compliance with admission screening would be associated with a reduction in the MRSA isolation rate by a factor of $aIRR^{x/100}$.

Figure A1 Nosocomial meticillin resistant *Staphylococcus aureus* isolation rates from clinical specimens by hospital



The solid dots represent the observed meticillin resistant *Staphylococcus aureus* (MRSA) rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*; HH, hand hygiene.

ORION Checklist of items to include when reporting an outbreak or intervention study of a nosocomial organism

	Item No.	Descriptor	Reported on page no.
Title & Abstract	1	Description of paper as outbreak report or intervention study. Design of intervention study (eg Randomised Controlled Trial , Cluster Randomised Controlled Trial, Interrupted Time Series, Cohort study etc). Brief description of intervention and main outcomes.	1,2
Introduction Background	2	Scientific and/or local clinical background and rationale. Description of organism as epidemic, endemic or epidemic becoming endemic.	5, 6
Type of paper	3	Description of paper as Intervention study or an Outbreak Report. If an outbreak report, report the number of outbreaks.	5
Dates	4	Start and finish dates of the study or report.	6
Objectives	5	Objectives for outbreak reports. Hypotheses for intervention studies	5, 6
Methods Design	6	Study design. Use of EPOC classification recommended (RCT or CRCT, CBA, or ITS) Whether study was retrospective, prospective or ambidirectional. Whether decision to report or intervene was prompted by any outcome data. Whether study was formally implemented with predefined protocol and endpoints.	6-10
Participants	7	Number of patients admitted in study or outbreak. Summaries of distributions of age and lengths of stays. If possible, proportion admitted from other wards, hospitals, nursing homes or from abroad. Where relevant, potential risk factors for acquiring the organism. Eligibility criteria for study. Case definitions for outbreak report.	6, 7, 11, 27
Setting	8	Description of the unit, ward or hospital and, if a hospital, the units included. Number of beds, the presence and staffing levels of an infection control team.	6, 25, 26
Interventions	9	Definition of phases by major change in specific infection control practice (with start and stop dates). A summary table is strongly recommended with precise details of interventions, how and when administered in each phase.	6, 7
Culturing & Typing	10	Details of culture media, use of selective antibiotics and local and /or reference typing. Where relevant, details of environmental sampling.	8, 9
Infection-related outcomes	11	Clearly defined primary and secondary outcomes (eg incidence of infection, colonisation , bacteraemia) at regular time intervals (eg daily, weekly, monthly) rather than as totals for each phase, with at least three data points per phase and, for many two phase studies, 12 or more monthly data points per phase. Denominators (eg numbers admissions or discharges, patient bed days). If possible, prevalence of organism and incidence of colonisation on admission at same time intervals. Criteria for infection, colonisation on admission and directly attributable mortality. For short studies or outbreak reports, use of charts with duration patient stay & dates organism detected may be useful (see text)	8, 9
Economic outcomes	12	If a formal economic study done, definition of outcomes to be reported, description of resources used in interventions, with costs broken down to basic units, stating important assumptions.	Not applicable
Potential Threats to internal validity	13	Which potential confounders were considered, recorded or adjusted for (eg: changes in length of stay, case mix, bed occupancy, staffing levels, hand-hygiene compliance, antibiotic use, strain type, processing of isolates, seasonality). Description of measures to avoid bias including blinding & standardisation of outcome assessment & provision of care.	9-11
Sample size	14	Details of power calculations, where appropriate	10
Statistical methods	15	Description of statistical methods to compare groups or phases. Methods for any subgroup or adjusted analyses, distinguishing between planned and unplanned (exploratory) analysis. Unless outcomes are independent, statistical approaches able to account for dependencies in the outcome data should be used, adjusting, where necessary, for potential confounders. For outbreak reports statistical analysis may be inappropriate.	10, 11
Results Recruitment	16	For relevant designs the dates defining periods of recruitment and follow-up. A flow diagram is recommended to describe participant flow in each stage of study.	6, 11, 27
Outcomes & estimation	17	For the main outcomes, the estimated effect size and its precision (usually using confidence intervals). A graphical summary of the outcome data is often appropriate for dependent data (such as most time series).	13, 14, 29, Fig 3
Ancillary analyses	18	Any subgroup analyses should be reported and it should be stated whether or not it was planned (specified in the protocol) and possible confounders adjusted for	11,13,14,30
Adverse events	19	Pre-specified categories of adverse events and occurrences of these in each intervention group . This might include drug side effects, crude or disease specific mortality in antibiotic policy studies or opportunity costs in isolation studies.	Not applicable
Discussion Interpretation	20	For intervention studies an assessment of evidence for/against hypotheses, accounting for potential threats to validity of inference including regression to mean effects and reporting bias. For outbreak reports, consider clinical significance of observations and hypotheses generated to explain them.	15-17
Generalisability	21	External validity of the findings of the intervention study i.e. to what degree can results be expected to generalise to different target populations or settings.	15
Overall evidence	22	General interpretation of results in context of current evidence.	17, 18

Abbreviations: RCT: randomised controlled trial CRCT : Cluster Randomised Controlled Trial CBA: controlled before and after study ITS: interrupted time series

Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a controlled multicentre intervention ~~study~~trial

Running head: MRSA control strategies in surgical patients

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Key words: meticillin resistant *Staphylococcus aureus*; methicillin resistant *Staphylococcus aureus*; screening; active surveillance cultures; hand hygiene; healthcare-associated infection

ABSTRACT

Objective: To compare the effect of two strategies (enhanced hand hygiene versus meticillin resistant *Staphylococcus aureus* [MRSA] screening and decolonisation) alone and in combination on MRSA rates in surgical wards.

Design: Prospective, controlled, interventional cohort study, with 6-month baseline, 12-month intervention, and 6-month washout phases.

Setting: 33 surgical wards in ten hospitals in nine countries in Europe and Israel.

Participants: All patients admitted to the enrolled wards for more than 24 hours.

Interventions: The two strategies compared were: 1) enhanced hand hygiene promotion; and 2) universal MRSA screening with contact precautions and decolonisation (intranasal mupirocin and chlorhexidine bathing) of MRSA carriers. Four hospitals were assigned to each intervention and two hospitals combined both strategies, using targeted MRSA screening.

Outcome measures: Monthly rates of MRSA clinical cultures per 100 susceptible patients (primary outcome) and MRSA infections per 100 admissions (secondary outcome). Planned subgroup analysis for clean surgery wards was performed.

Results: After adjusting for clustering and potential confounders, neither strategy when used alone was associated with significant changes in MRSA rates. Combining both strategies was associated with a reduction in the rate of MRSA clinical cultures of 12% per month (aIRR 0.88, 95% CI 0.79 to 0.98). In clean surgery wards, strategy 2 (MRSA screening, contact precautions, and decolonisation) was associated with decreasing rates of MRSA clinical cultures (15% monthly decrease, aIRR 0.85, 95% CI 0.74 to 0.97) and MRSA infections (17% monthly decrease, aIRR 0.83, 95% CI 0.69 to 0.99).

Conclusions: In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard and MRSA-specific infection control approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation was associated with significant reductions in MRSA clinical culture and infection rates.

Trial Registration: clinicaltrials.gov identifier: NCT00685867

ARTICLE SUMMARY

Article focus

- The relative effectiveness of different meticillin resistant *Staphylococcus aureus* (MRSA) control measures is controversial.
- This study directly compared the effect of two strategies (enhanced hand hygiene versus MRSA screening and decolonisation, alone and in combination) on MRSA rates in surgical wards.

Key messages

- Neither enhanced standard infection control measures (emphasising hand hygiene promotion) nor MRSA-specific control interventions (universal MRSA screening coupled with contact precautions and decolonisation therapy) when used alone for 12 months effectively reduced MRSA rates in surgical wards with relatively low MRSA rates.
- A combination of interventions, including targeted screening of high risk patients, did result in reduction in the rate of MRSA isolated from clinical cultures.
- In surgical subspecialties that perform clean surgery, universal MRSA screening coupled with contact precautions and decolonisation therapy effectively reduced both the rates of MRSA isolated from clinical cultures as well as MRSA infections.

Strengths and limitations of this study

- Unlike many previous studies, this was a large, controlled, prospective, multicentre, intervention study. The enrolled wards, from ten hospitals in Europe and Israel, varied in terms of infection control infrastructure and MRSA prevalence, thus the results are likely to be generalisable to other settings.
- Due to the nature of the quality improvement initiatives, investigators were not blinded to the allocated intervention. Interventions were not randomly allocated.

INTRODUCTION

Healthcare associated infections affect hundreds of millions of patients worldwide every year and represent an important cause of patient mortality and a major financial burden to health systems.[1] Meticillin resistant *Staphylococcus aureus* (MRSA), now endemic in many healthcare facilities, is a leading cause of healthcare associated infections,[2] and patients in surgical units are at increased risk due to factors such as invasive procedures, antibiotic exposure, and prolonged healthcare contact. A number of countries mandate implementation of control measures, including MRSA screening.[3,4] Not all mandated interventions, however, are supported by robust evidence.

Studies evaluating MRSA control strategies show conflicting results, particularly with regards to the use of active surveillance cultures.[5-7] It is argued that broader infection control approaches, such as improving hand hygiene (HH) practices, may be as successful as MRSA-specific strategies.[8,9] There are limitations, however, to current evidence with few prospective, controlled studies,[10,11] and many studies have assessed multiple interventions simultaneously.[12] Quantifying the relative benefits of individual approaches is important, particularly as some strategies have significant cost implications, and will allow efficient use of limited resources.

Due to the ongoing debate concerning optimal approaches to MRSA control,[13,14] we performed a prospective, interventional, quality improvement study to compare the effect of an enhanced HH promotion strategy to an MRSA screening, isolation and decolonisation strategy when used alone and in combination on the incidence rates of MRSA clinical cultures and infections in surgical patients admitted to healthcare facilities across Europe and

Israel. We also aimed to specifically assess these interventions in clean surgery wards where their benefits may be expected to be more pronounced.

METHODS

Study design and population

This prospective, controlled, multicentre, interventional cohort study with a three phase interrupted time series design was conducted between March 2008 and July 2010. Thirty-three surgical wards of ten hospitals in nine countries (Serbia, France, Spain [two hospitals], Italy, Greece, Scotland, Israel, Germany, and Switzerland) were enrolled. Wards included orthopaedic (8), vascular (6), cardiothoracic/cardiovascular (5), general (4), abdominal (4), urology (3), neurosurgery (2), and plastic surgery (1) subspecialties. Characteristics of the enrolled wards varied (table 1).

The study consisted of baseline (6 to 7 months), intervention (12 months), and washout (6 months) phases. Initial baseline phase data collection commenced in one centre in March 2008 prior to the implementation of any interventions. All other centres commenced baseline phase data collection after May 2008. The intervention phase did not start for any study site until October 2008. During baseline and washout phases, wards employed their usual infection control practices. During the intervention phase, two strategies were investigated, with hospitals implementing one or both interventions in parallel (figure 1).

Interventions

The first intervention, the enhanced HH strategy, used the WHO multi-modal HH promotion method consisting of: 1) using alcohol-based handrub at the point of care, 2) training and

education of healthcare workers, 3) observation and feedback of HH practices, 4) reminders in the workplace (e.g. posters), and 5) improving the safety climate in the institution with management support for the initiative.[15] Adherence to standard precautions (e.g. gloves for body fluid contact) ~~and isolation of MRSA patients according to local policies were~~was encouraged. There was no attempt to change local practices regarding isolation of MRSA patients as part of this intervention.

The second intervention, the screening and decolonisation strategy, used a universal MRSA screening approach. It consisted of screening patients admitted for more than 24 hours for MRSA, on admission (within 48 hours) then weekly. Patients were excluded from screening if they were undergoing ambulatory surgery or had already been screened within 5 days prior to admission to the surgical ward. The nares, perineum, and wounds (if present) were swabbed. Chromogenic agar screening was used with the addition of polymerase chain reaction (PCR) testing during the latter part of the intervention phase for patients who had risk factors for MRSA (e.g. hospitalisation in the last year) whose chromogenic agar results were unlikely to be available before surgery. MRSA carriers were placed on contact precautions (gown and gloves during patient contact), administered decolonisation therapy with twice daily intranasal mupirocin and daily chlorhexidine washes for five days, and perioperative prophylaxis was modified to reflect MRSA carriage. Chlorhexidine bathing was limited to identified MRSA carriers and not used as a unit-wide intervention. Pre-emptive isolation was not used as part of this strategy.

The hospital was the unit for assignment of interventions due to practical reasons and the nature of the strategies. Four hospitals were assigned to each intervention and two hospitals used a combination of both strategies (the combined strategy) due to the introduction of

national or local mandatory targeted MRSA screening policies during the study period which necessitated deviation from the original trial protocol (~~table 1~~figure 1). The choice of allocation was influenced by the constraints upon the study centres, such as cost and personnel (n=3), population size (n=1), capacity of the microbiology laboratories (n=3), prior exposure to specific interventions (n=1) and mandatory local or national interventions (n=2). Thus, this pragmatic approach took into account the institutions' preferences, as participation in an entirely cluster-randomised trial would have meant that some of the hospitals could not have participated.

The targeted screening in the two hospitals in the combined strategy arm was based on risk factors for MRSA carriage (including patient characteristics or surgical subspecialty). One hospital using the combined strategy (Hospital 4) introduced targeted screening of patients who were previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. The other hospital in the combined strategy arm (Hospital 7) used targeted screening of patients with the same risk factors as Hospital 4, but also screened nursing home residents, patients admitted to the hospital in the last three months, patients transferred from another ward within the same hospital, and those admitted to vascular or abdominal surgery subspecialties.

The~~se~~ assignment~~s~~ of hospitals to each study arm occurred prior to commencement of data collection. A summary of the nature of the interventions for each study arm is presented in table 2. The study protocol was registered with a public registry of clinical studies (available at: http://clinicaltrials.gov/ Identifier: NCT00685867).

Outcomes measures

The primary outcome measure was the monthly nosocomial MRSA isolation rate, defined as the number of MRSA clinical isolates (those from specimens collected other than for screening purposes, counting one isolate per patient per month), per 100 susceptible patients (not previously known to be MRSA colonised or infected). Isolates from specimens collected more than 48 hours after admission or within 30 days after discharge from study wards were considered nosocomial.

Secondary outcomes were the monthly rate of nosocomial MRSA infections per 100 admissions, and adherence to HH guidelines and contact precautions. Infections were defined using CDC criteria.[16] Adherence to HH guidelines was measured as the percentage of opportunities for HH in which staff used alcohol-based handrub and/or washed their hands according to the WHO method.[15] Adherence to contact precautions was measured as the percentage of randomly audited MRSA patients for whom precautions with gown and gloves during patient contact had been implemented.

Microbiological methods

Standardised laboratory manuals were provided to centres. Samples were processed in local laboratories using standard culture-based identification of MRSA from clinical specimens. In hospitals assigned to the screening and decolonisation arm, nasal and perineal swabs were pooled in the laboratory then plated directly onto chromogenic medium (BBL CHROMagar MRSA II, BD Diagnostics, Belgium) and also incubated overnight in an enrichment medium to increase test sensitivity.[17] Positive results could be reported within 24 to 48 hours.[18] PCR testing directly from pooled screening swabs was performed with the BD GeneOhm MRSA (BD Diagnostics, Belgium) or GeneXpert MRSA (Cepheid, Belgium) tests, which have turnaround times of 2 to 3 hours and 1.5 hours respectively (see online supplementary table

A1).[18] All laboratories participated in an external quality assurance program to evaluate their ability to detect, identify and perform antibiotic sensitivity testing on staphylococci from a variety of different specimens.[19] MRSA isolates were shipped to the central laboratory (University of Antwerp, Belgium) for confirmation of identification.

Data collection

Research personnel from each hospital collected data and implemented the interventions at their study site. These personnel were from departments that supervise infection control activities at the participating hospitals, including Infection Control, Infectious Diseases and Hospital Epidemiology departments. They were trained at the study coordinating centre with regards to the study protocol, the outcome definitions and the use of the data collection tools prior to the commencement of the study to ensure consistency of data collection across the hospitals. Local microbiology laboratory data were reviewed to obtain information regarding MRSA isolated from screening and clinical cultures. Infections were monitored by twice weekly ward visits to review medical records and interview staff. Surgical site infection surveillance occurred up to 30 days post-procedure (or 12 months after prosthetic device insertion).

HH adherence was monitored by the research personnel who had been trained and validated in the WHO method of direct observation at the study coordinating centre.[15] A standardised observation form was used by all centres. All hospitals collected data for 100 HH opportunities per ward during baseline and washout phases.[20] HH observers were specifically instructed not to provide feedback to healthcare workers concerning their HH practices during these study phases, and the observers were independent of surgical ward staff, reducing the likelihood of the Hawthorne effect, in which staff improve their practices when

they are aware that they are being observed.[21] During the intervention phase, there was intensive monitoring of HH practices in wards using the enhanced HH and combined strategies. In these wards, 100 HH opportunities per ward per month were observed as part of the intervention. Implementation of contact precautions, decolonisation therapy, and single room isolation for MRSA carriers was randomly audited each month. Signage of MRSA status and availability of gowns, gloves and alcohol-based handrub for contact with MRSA carriers was also audited.

Data regarding numbers of admissions, patient-days, surgical procedures, and level of staffing were collected. Due to variation in the availability and quality of electronic medical record and pharmacy data between the study sites, individual-level data (such as length of stay) and antibiotic utilisation data for the surgical wards was not collected as part of this study. Ward-level data were submitted monthly to a central data management centre via a password protected secure online database which included range, consistency, and missing data checks. Meetings, site visits, and monthly teleconferences were held to review data, ensure adherence to study protocols, and address queries. Data were reviewed monthly for completeness and 6-monthly for validity by teleconferences with individual study sites. Institutional review boards of all centres approved the study with a waiver of individual informed consent.

Statistical analysis

The study was designed to detect a 30% difference in nosocomial MRSA isolation rate assuming a baseline rate of 1.0 clinical isolate per 100 susceptible patients and an absolute difference of 10% between intervention arms. Sample size calculations assumed a two-sided

test, a type I error rate of 0.05 and 80% power, taking the wards as the unit of analysis. A minimum of 15 wards was required per study arm.

Crude MRSA rates were calculated by study arm. Adjusted incidence rate ratios (aIRR) were calculated using multilevel Poisson segmented regression accounting for stepwise changes in MRSA level and changes in log-linear trends associated with the interventions.[22] This analysis allowed for two levels of random-effects: hospital-level variation in intercepts and baseline trends, and nested ward-level variation in intercepts. It adjusted for exposure given by the monthly number of susceptible patients or admissions per ward and allowed for extra-Poisson variation. Surgical subspecialty, baseline HH compliance, seasonal effects (using calendar month), and patient-to-nurse ratios were adjusted for. Autocorrelation was accounted for using a lagged dependent variable. A similar analysis was performed for HH compliance, but used segmented multilevel logistic regression, adjusting for ward-specific baseline levels and trends, professional category, HH indication, patient-to-nurse ratios, and monthly MRSA colonisation pressure (number of days patients known to be MRSA colonised/infected were in the wards each month).

Planned subgroup analyses were performed by hospital and for clean surgery wards (cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery) as studies have shown that intranasal mupirocin, which is active against Gram-positive organisms, may be more effective for surgical site infection prevention in clean compared to clean-contaminated surgery (e.g. general or gastrointestinal surgery) where Gram-negative and anaerobic organisms may play a larger role.[23] As screening intensity varied in the combined arm, a planned exploratory analysis of MRSA outcome data was conducted to better quantify the intervention effects. It accounted for stepwise changes and log-linear trends in outcomes

associated with the HH intervention, as well as the monthly proportion of patients screened and monthly cumulative screening rate on wards to account for changes in trends of outcomes associated with screening. Analyses were conducted with STATA 11.0 (STATA Corp, USA).

RESULTS

During the study period, there were a total of 126 750 admissions and 99 638 surgical procedures on the study wards. Baseline admission MRSA prevalence, without systematic screening of all admitted patients, was 0.8% (269 of 33 608), ranging from 0.1% to 2.2% across surgical wards of each hospital. Baseline HH adherence varied between hospitals (39.5% overall, 95% CI 38.1% to 40.9%) as did use of targeted MRSA screening (0 to 30.9% of admissions) (table 1). Study characteristics are shown in table ~~2~~3 and online supplementary table A2.

Adherence to hand hygiene guidelines

In the enhanced HH and combined arms, HH compliance improved in all centres with overall compliance increasing from 49.3% (95% CI 47.2% to 51.4%) to 63.8% (95% CI 63.2% to 64.4%) from baseline to intervention phases (figure 2a). After multivariable analysis, commencing HH promotion was associated with a significant immediate increase in HH compliance (adjusted odds ratio [aOR] 1.19, 95% CI 1.01 to 1.42) (see online supplementary table A3). However, this benefit was not sustained after cessation of the HH campaign with a significant decreasing trend in HH adherence of 9% per month (aOR for month post-intervention 0.91, 95% CI 0.85 to 0.97) during the washout phase. In wards in the screening and decolonisation arm, where no HH promotion occurred, compliance remained low at

30.5% (95% CI 28.7% to 32.4%) at baseline and 23.9% (95% CI 22.0% to 25.9%) during the washout phase.

Screening, contact precautions and decolonisation of MRSA carriers

During the intervention phase, 9250 (75.3%) of 12 279 patients were screened on admission to wards in the screening and decolonisation arm. Admission MRSA prevalence was 2.1% (259 of 12 279), consisting of 27 patients (10.4%) with MRSA-positive clinical cultures and 232 patients (89.6%) identified by screening alone. PCR screening was used in addition to chromogenic agar cultures in 1047 (11.3%) of 9250 patients. Between baseline and intervention phases in screening and decolonisation wards, the proportion of audited MRSA carriers placed on contact precautions increased (81.1% to 90.7%), as did administration of decolonisation therapy (34.4% to 69.8%) (figure 3). However, the proportion of audited MRSA carriers in single rooms decreased (67.8% to 40.1%), possibly due to a shortage of rooms for the higher number of identified MRSA carriers. Reasons for non-adherence to decolonisation therapy included discharge prior to an MRSA-positive result, discharge prior to commencement of decolonisation therapy or the patient declining the intervention.

Screening occurred to a lesser extent in the other study arms (figure 2b). About 10% of admissions to wards in the enhanced HH arm were screened throughout the study. In wards in the combined arm, screening increased from 9.2% to 22.3%, then 36.9% during baseline, intervention, and washout phases respectively. In this arm, adherence to contact precautions was high throughout the study (93.0% to 99.6%), but only 32.9% of MRSA patients at baseline and 35.9% of patients during the intervention phase received decolonisation therapy (figure 3).

Nosocomial MRSA isolation rate from clinical cultures

Crude MRSA isolation rates from clinical cultures decreased in all study arms during the intervention phase (enhanced HH arm: 0.99 to 0.80; screening and decolonisation arm: 0.47 to 0.23; combined arm: 0.55 to 0.36; p=0.04; per 100 susceptible patients) (table ~~3~~4). After adjusting for clustering and potential confounders with multilevel segmented Poisson regression (table ~~4~~5 and see online supplementary table A4 for full model), commencement of HH promotion in the enhanced HH arm was associated with an immediate non-significant increase in nosocomial MRSA isolation rate (aIRR 1.44, 95% CI 0.96 to 2.15) with no change in the trend in rates over time. In clean surgery wards, HH promotion was associated with a non-significant decreasing monthly MRSA isolation rate (aIRR 0.89, 95% CI 0.78 to 1.01) (table ~~5~~6 and see online supplementary table A5 for full model).

In the screening and decolonisation arm, there were no significant changes in MRSA isolation rates. However, in clean surgery, this intervention was associated with a reduction in MRSA clinical cultures of 15% per month (aIRR 0.85, 95% CI 0.74 to 0.97).

In the combined arm (wards that used a combination of HH promotion with targeted screening), there was a significant decreasing trend in MRSA isolation rate of 12% per month overall (aIRR 0.88, 95% CI 0.79 to 0.98), and 18% per month in clean surgery (aIRR 0.82, 95% CI 0.71 to 0.95). Observed and model-predicted MRSA isolation rates from clinical cultures are illustrated in figure 4a and online supplementary figure A1.

During the washout phase, MRSA clinical culture isolation rates increased. A post-hoc analysis of the washout phase results by study arm showed that the increase in MRSA rates was~~, particularly in clean surgery wards. This was~~ due to an abrupt increase in the level of

MRSA clinical cultures on cessation of the intervention phase in all study arms, but particularly with the conclusion of the intensive HH promotion campaign in the combined arm (see online supplementary table A6~~data not shown~~).

Nosocomial MRSA infection rates

There were 470 nosocomial MRSA infections in total (335 [71.3%] surgical site, 41 [8.7%] bloodstream, and 94 [20.0%] other infections). Crude infection rates decreased over time in all study arms (table ~~3~~4). After multivariable analysis (table ~~4~~5, figure 4b and see online supplementary table A4), enhanced HH promotion alone was not associated with changes in MRSA infection rates. Both the screening/decolonisation and combined interventions resulted in non-significant decreasing trends in total MRSA infection (screening and decolonisation arm: aIRR 0.93, 95% CI 0.82 to 1.05; combined arm: aIRR 0.90, 95% CI 0.80 to 1.02) and surgical site infection rates (table ~~4~~5, figure 4c and online supplementary table A4).

In clean surgery, the screening and decolonisation strategy was associated with significant reductions in total MRSA infection rate of 17% per month (aIRR 0.83, 95% CI 0.69 to 0.99) and MRSA surgical site infection rate of 19% per month (aIRR 0.81, 95% CI 0.66 to 1.00) (table ~~5~~6 and online supplementary table A5).

Exploratory analysis to directly assess implemented interventions

The exploratory analysis did not show any significant effects of HH promotion on nosocomial MRSA isolation rates (see online supplementary table A7~~6~~). The intensity of admission screening was associated with a decreasing trend in monthly MRSA isolation rate from clinical cultures (aIRR 0.91 per month with 100% compliance with screening, 95% CI

0.85 to 0.98). A similar effect was seen in the trend in MRSA infection rate (aIRR 0.92, 95% CI 0.85 to 0.99).

DISCUSSION

We found that implementation of ~~as~~ individual interventions in surgical wards, with ~~n~~either an enhanced HH promotion strategy ~~n~~or universal MRSA screening with contact precautions and decolonisation of MRSA carriers, ~~were~~was ~~-~~ not effective in reducing MRSA rates ~~in surgical patients~~. However, using a combination of both HH promotion and targeted screening was associated with a reduction in MRSA isolation rate from clinical cultures of 12% per month. When the interventions were specifically evaluated in the subgroup of clean surgery wards, the screening and decolonisation strategy was most effective. In these wards, this intervention was associated with significant reductions in both MRSA clinical culture isolation rate of 15% per month and MRSA infection rate of 17% per month.

This study is unique in that it directly compared strategies individually and in combination using a large, prospective, controlled design.[10] In addition, we used a planned exploratory analysis to separate out the individual effects of the HH and MRSA screening strategies. Interventions were implemented and assessed under operational conditions in ten heterogeneous hospitals across Europe and Israel with widely varying infection control practices, staffing, infrastructure, and MRSA epidemiology, increasing the generalisability of our findings. This study has been reported using standard reporting guidelines that are designed to maximise transparency and scientific rigor of intervention studies of healthcare associated infection.[24]

Our analysis, which adjusted for confounders, seasonal effects and baseline MRSA trends, found no evidence that enhanced HH promotion was effective. MRSA rates are declining in many countries.[25] Failing to account for this would overestimate intervention effects. Overall baseline HH compliance was 49% in study wards that used the HH intervention. In settings where compliance is already above about 50%, modelling studies suggest that further increases in compliance will have rapidly diminishing returns for reducing MRSA transmission.[26] In facilities with lower HH compliance or higher MRSA rates, this intervention may be more effective than we were able to demonstrate. In addition, HH campaigns involve education and behaviour change and are therefore unlikely to have a short term effect. Other studies have shown that they may be beneficial if activity is sustained over years.[27,28] Although we did not detect any intervention effects of the HH promotion strategy, cessation of this intervention was associated with an increase in MRSA rates in our study, suggesting that discontinuing activities to optimise HH practices may be detrimental.

Active MRSA surveillance identifies the reservoir of asymptomatic carriers, enabling early implementation of contact precautions and decolonisation, which can reduce transmission.[29,30] With universal screening, we found that 90% of MRSA-positive patients would have been missed using clinical cultures alone. However, our results suggest that rather than universal screening of all surgical patients admitted for more than 24 hours, selective screening in clean surgery wards or a combination of HH promotion and targeted screening of high risk patients may be more effective strategies. The relative burden of Gram-positive infections is greater in clean compared to clean-contaminated surgery where other pathogens, including bowel flora, may be more important.[23,31] Thus it is biologically plausible that MRSA-specific interventions would potentially have a greater impact in clean surgery. Indeed, intranasal mupirocin has been shown to reduce surgical site infections in

cardiothoracic and orthopaedic surgery, but is less effective in general surgery.[23] The commencement of such decolonisation regimens prior to surgical procedures, which can be facilitated by rapid detection of *S. aureus* carriage with molecular tests, is likely a key factor in the success of this approach.[32] The use of molecular tests in the latter part of the intervention phase in our study could have significantly contributed to the reduction in MRSA rates seen over the period of the intervention phase, particularly in clean surgery wards.

The exploratory analysis suggests that screening intensity, rather than HH promotion, explained the intervention effects. It is curious, then, that universal screening did not perform better than HH promotion combined with targeted screening. A significant reduction in MRSA clinical cultures was seen with the combined strategy despite the enrolment of only two hospitals in this study arm. This suggests that the effect of the combined intervention was robust. It is certainly biologically plausible that using two interventions that aim to control MRSA in different ways would be more effective than use of single interventions. Although the universal screening arm enrolled four hospitals, low baseline MRSA rates in this arm may have reduced our ability to detect significant effects. Shortage of isolation rooms may have also contributed. In addition, targeted screening may have been more effective if it identified "superspreaders",[33] facilitating more efficient use of resources including limited single rooms. Modelling studies also demonstrate that targeted screening has the advantage of increased cost-effectiveness compared to universal screening for reducing healthcare associated MRSA infections.[34,35]

This study adds to the conflicting literature regarding active surveillance cultures. Our results apply to surgical settings. The risk of MRSA infection in other wards, such as intensive care

units or general medical wards, would differ due to variation in patient comorbidities and exposure to invasive procedures or antibiotics. It is also important to note that previous studies have used a variety of interventions in combination with screening. In some cases, the use of pre-emptive isolation in both study arms[36] or lack of decolonisation strategies,[6] may have led to effect sizes that studies had insufficient power to detect. Comparison of rapid screening to conventional rather than no screening,[36] differences in screening methods,[10] variation in MRSA strains,[37] or limitations in study design and analyses[10,11] are other potential explanations for the conflicting results of screening studies.

There are some limitations to this study. ~~Due to the nature of the interventions, which involved HH audits, promotion and feedback and/or implementation of MRSA screening, investigators were not blinded to study assignment.~~ Research personnel assessing HH, screening, decolonisation, contact precautions, and isolation practices were not blinded to study assignment as they were responsible for implementing the interventions. Although allocation of interventions was not randomised, we accounted for differences in hospitals by adjusting for potential confounders and comparing outcomes between baseline and intervention phases within the same study arm. Decisions to take culture samples were initiated by treating physicians, not research personnel, and standardised definitions for infections were used, reducing the likelihood of bias in the measurement of the study outcomes by unblinded assessors. We used MRSA-positive clinical cultures as our primary outcome. Although this measure does not distinguish between colonisation and infection, it can be a more sensitive marker for changes in MRSA disease rates.[38] We found the results for MRSA clinical cultures similar to those for infections, suggesting that this measure was clinically relevant. Patient-level data, such as age, comorbidities and length of stay, and antibiotic use were not measured for this study. However, results were similar when each

centre was excluded in turn from the analysis (data not shown) so changes in factors in individual centres are unlikely to have had a major effect on study outcomes.

Conclusion

In surgical wards with relatively low MRSA prevalence, a combination of enhanced standard infection control measures emphasising HH promotion and MRSA-specific (targeted screening of high risk patients) approaches was required to reduce MRSA rates. Implementation of single interventions was not effective, except in clean surgery wards where MRSA screening coupled with contact precautions and decolonisation of identified MRSA carriers was associated with significant reductions in MRSA clinical culture and infection rates. These findings are likely generalisable to other settings with varying infection control practices. In addition, the WHO multimodal HH promotion strategy[15] implemented in this study is already being used in many parts of the world. Therefore our study, which provides evidence that this intervention alone is ~~not~~ insufficient to reduce MRSA rates, potentially has widespread implications for best clinical practice recommendations and policy change. Further research regarding the cost-effectiveness of these interventions will allow better utilisation of limited healthcare resources.

REFERENCES

1 WHO. Report on the burden of endemic health care-associated infection worldwide. http://whqlibdoc.who.int/publications/2011/9789241501507_eng.pdf (accessed 24 April 2013).

2 Cosgrove SE, Qi Y, Kaye KS, et al. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 2005;26:166-74.

3 Weber SG, Huang SS, Oriola S, et al. Legislative mandates for use of active surveillance cultures to screen for methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci: Position statement from the Joint SHEA and APIC Task Force. *Am J Infect Control* 2007;35:73-85.

4 UK Department of Health. MRSA Screening - Operational Guidance 2. http://www.dh.gov.uk/en/Publicationsandstatistics/Lettersandcirculars/Dearcolleagueletters/DH_092844 (accessed 24 April 2013).

5 Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus aureus* in 3 affiliated hospitals. *Ann Intern Med* 2008;148:409-18.

6 Huskins WC, Huckabee CM, O'Grady NP, et al. Intervention to reduce transmission of resistant bacteria in intensive care. *N Engl J Med* 2011;364:1407-18.

7 Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 2008;299:1149-57.

8 Edmond MB, Ober JF, Bearman G. Active surveillance cultures are not required to control MRSA infections in the critical care setting. *Am J Infect Control* 2008;36:461-3.

9 Wenzel RP, Bearman G, Edmond MB. Screening for MRSA: a flawed hospital infection control intervention. *Infect Control Hosp Epidemiol* 2008;29:1012-8.

10 Tacconelli E, De Angelis G, de Waure C, et al. Rapid screening tests for meticillin-resistant *Staphylococcus aureus* at hospital admission: systematic review and meta-analysis. *Lancet Infect Dis* 2009;9:546-54.

11 Loveday HP, Pellowe CM, Jones SR, et al. A systematic review of the evidence for interventions for the prevention and control of meticillin-resistant *Staphylococcus aureus* (1996-2004): report to the Joint MRSA Working Party (Subgroup A). *J Hosp Infect* 2006;63 Suppl 1:S45-70.

12 Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant *Staphylococcus aureus* infections. *N Engl J Med* 2011;364:1419-30.

13 Farr BM, Jarvis WR. Searching many guidelines for how best to control methicillin-resistant *Staphylococcus aureus* healthcare-associated spread and infection. *Infect Control Hosp Epidemiol* 2009;30:808-9.

14 Nijssen S, Bonten MJ, Weinstein RA. Are active microbiological surveillance and subsequent isolation needed to prevent the spread of methicillin-resistant *Staphylococcus aureus*? *Clin Infect Dis* 2005;40:405-9.

15 WHO. WHO Guidelines on Hand Hygiene in Health Care. World Alliance for Patient Safety. Geneva: WHO Press Geneva, 2009.

16 Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. *Am J Infect Control* 2008;36:309-32.

17 Van Heirstraeten L, Cortinas Abrahantes J, Lammens C, et al. Impact of a short period of pre-enrichment on detection and bacterial loads of methicillin-resistant *Staphylococcus aureus* from screening specimens. *J Clin Microbiol* 2009;47:3326-8.

18 Malhotra-Kumar S, Haccuria K, Michiels M, et al. Current trends in rapid diagnostics for methicillin-resistant *Staphylococcus aureus* and glycopeptide-resistant enterococcus species. *J Clin Microbiol* 2008;46:1577-87.
19 Gazin M, Lee A, Derde L, et al. Culture-based detection of methicillin-resistant *Staphylococcus aureus* by a network of European laboratories: an external quality assessment study. *Eur J Clin Microbiol Infect Dis* 2012;31:1765-70.
20 Lee A, Chalfine A, Daikos GL, et al. Hand hygiene practices and adherence determinants in surgical wards across Europe and Israel: a multicenter observational study. *Am J Infect Control* 2011;39:517-20.
21 Harbarth S, Pittet D, Grady L, et al. Interventional study to evaluate the impact of an alcohol-based hand gel in improving hand hygiene compliance. *Pediatr Infect Dis J* 2002;21:489-95.
22 Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to antimicrobial resistance intervention studies. *Clin Infect Dis* 2007;45:901-7.
23 Kallen AJ, Wilson CT, Larson RJ. Perioperative intranasal mupirocin for the prevention of surgical-site infections: systematic review of the literature and meta-analysis. *Infect Control Hosp Epidemiol* 2005;26:916-22.
24 Stone SP, Cooper BS, Kibbler CC, et al. The ORION statement: guidelines for transparent reporting of outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007;7:282-8.
25 Struelens MJ, Monnet DL. Prevention of methicillin-resistant *Staphylococcus aureus* infection: is Europe winning the fight? *Infect Control Hosp Epidemiol* 2010;31 Suppl 1:S42-4.
26 Cooper BS, Medley GF, Scott GM. Preliminary analysis of the transmission dynamics of nosocomial infections: stochastic and management effects. *J Hosp Infect* 1999;43:131-47.
27 Pittet D, Hugonnet S, Harbarth S, et al. Effectiveness of a hospital-wide programme to improve compliance with hand hygiene. Infection Control Programme. *Lancet* 2000;356:1307-12.
28 Stone SP, Fuller C, Savage J, et al. Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and Clostridium difficile infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. *BMJ* 2012;344:e3005.
29 Lee AS, Huttner B, Harbarth S. Control of methicillin-resistant *Staphylococcus aureus*. *Infect Dis Clin North Am* 2011;25:155-79.
30 Ammerlaan HS, Kluytmans JA, Wertheim HF, et al. Eradication of methicillin-resistant *Staphylococcus aureus* carriage: a systematic review. *Clin Infect Dis* 2009;48:922-30.
31 Huttner B, Robicsek AA, Gervaz P, et al. Epidemiology of methicillin-resistant *Staphylococcus aureus* carriage and MRSA surgical site infections in patients undergoing colorectal surgery: a cohort study in two centers. *Surg Infect (Larchmt)* 2012;13:401-5.
32 Bode LG, Kluytmans JA, Wertheim HF, et al. Preventing surgical-site infections in nasal carriers of *Staphylococcus aureus*. *N Engl J Med* 2010;362:9-17.
33 Lloyd-Smith JO, Schreiber SJ, Kopp PE, et al. Superspreading and the effect of individual variation on disease emergence. *Nature* 2005;438:355-9.
34 Hubben G, Bootsma M, Luteijn M, et al. Modelling the costs and effects of selective and universal hospital admission screening for methicillin-resistant *Staphylococcus aureus*. *PLoS One* 2011;6:e14783.
35 Infectious Disease Research Network (IDRN). Report on MRSA Screening Audit. http://idrn.org/audit.php (accessed 28 July 2013).

36 Jeyaratnam D, Whitty CJ, Phillips K, et al. Impact of rapid screening tests on acquisition of meticillin resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008;336:927-30.
37 Cooper BS, Kypraios T, Batra R, et al. Quantifying type-specific reproduction numbers for nosocomial pathogens: evidence for heightened transmission of an Asian sequence type 239 MRSA clone. *PLoS Comput Biol* 2012;8:e1002454.
38 Walker S, Peto TE, O'Connor L, et al. Are there better methods of monitoring MRSA control than bacteraemia surveillance? An observational database study. *PLoS One* 2008;3:e2378.

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Competing interests

SH is a member of the speakers' bureau for bioMérieux and Pfizer, and the scientific advisory board of Destiny Pharma, DaVolterra, and bioMérieux. He has received financial support for MRSA research activities from Geneva University Hospitals, B.Braun, and Pfizer. AP is a member of the speakers' bureau for Cubist and has received financial support for MRSA research activities from BD. There were no other financial or non-financial relationships, or interests that may be relevant to the submitted work.

Author contributions

Conceived and designed the experiments: SH CBB. Analysed the data: ASL BSC. Contributed reagents/materials: SMK HG. Wrote the first draft of the manuscript: ASL. Contributed to the writing of the manuscript: ASL SH BSC CBB AC GLD CF BC SL SMK JAM CMA AP GP BR HG. ICMJE criteria for authorship read and met: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Agree with manuscript results and conclusions: ASL BSC SMK AC GLD CF BC SL JAM CMA AP GP BR HG CBB SH. Enrolled patients: ASL AC GLD CF BC SL JAM CMA AP GP BR. Statistical support: BSC.

Data sharing

The dataset is available from the corresponding author at stephan.harbarth@hcuge.ch.

FIGURE LEGENDS

Figure 1 Flow of study wards through each phase of the study

Figure 1 Legend
Ten hospitals in nine countries were enrolled and were allocated to one of three study arms during the intervention phase. The enhanced hand hygiene arm used hand hygiene promotion; the screening and decolonisation arm used universal meticillin resistant *Staphylococcus aureus* (MRSA) screening coupled with contact precautions and decolonisation therapy with intranasal mupirocin and chlorhexidine body washes for identified MRSA carriers; the combined arm used a combination of hand hygiene promotion and targeted MRSA screening.

Figure 2 Implementation of the interventions

Figure 2 Legend
The top panel (A) shows the monthly hand hygiene compliance rates for hospitals in the enhanced hand hygiene and combined arms that used hand hygiene promotion campaigns. The solid dots represent the observed compliance rates while the lines represent the predicted compliance rates based on the regression model. The bottom panel (B) shows the proportion of patients screened on admission to the study wards by study arm. HH, hand hygiene.

Figure 3 Adherence to contact precautions, decolonisation and isolation measures for meticillin resistant *Staphylococcus aureus* carriers

Figure 3 Legend
This figure shows the distribution of monthly adherence to infection control measures for randomly audited patients known to be colonised or infected with meticillin resistant *Staphylococcus aureus* (MRSA) for each study arm. The top panel (A) shows adherence to implementation of contact precautions, decolonisation therapy, and isolation in single rooms. The middle panel (B) shows the presence of signage of MRSA status on the patients' room, bed, or nursing chart. The bottom panel (C) shows the availability of gowns, gloves, and alcohol-based handrub in or at the entrance of the room. The horizontal line in each box represents the median, the box represents the interquartile range and the vertical lines represent the minimum and maximum values. MRSA, meticillin resistant *Staphylococcus aureus*.

Figure 4 Nosocomial meticillin resistant *Staphylococcus aureus* rates by study arm

Figure 4 Legend
The top panel (A) shows the nosocomial meticillin resistant *Staphylococcus aureus* (MRSA) isolaton rates from clinical specimens. The middle panel (B) shows the nosocomial MRSA infection rates. The bottom panel (C) shows the nosocomial MRSA surgical site infection rates. The solid dots represent the observed MRSA rates while the lines represent the predicted MRSA rates based on the regression models. MRSA, meticillin resistant *Staphylococcus aureus*.

TABLES

Table 1: Baseline phase characteristics of hospitals and wards enrolled in the study

	Hospital characteristics			Study ward characteristics							
Hospital	Total beds (n)	Total number of single rooms (%)	Ratio of infection control nurses to beds	Surgical subspecialties	Total beds (n)	Total admissions during baseline phase (n)	Mean patient-to-nurse ratio (SD)*	Percent hand hygiene compliance (95% CI)	Number of patients screened on admission (%)	Number identified MRSA positive on admission (%)†	Study arm
1	3611	45 (1.2)	1:240	Abdominal Cardiovascular Orthopaedic	588	8018	6.4 (1.2)	18.8 (15.1 to 22.9)	0 (0)	9 (0.1)	Enhanced hand hygiene
2	317	235 (74.1)	1:160	Cardiothoracic Orthopaedic Vascular	72	1613	4.1 (1.8)	75.4 (70.3 to 80.0)	29 (1.8)	20 (1.2)	Screening and decolonisation
3	850	135 (15.9)	1:425	Cardiovascular	75	1841	5.6 (0.7)	26.8 (24.4 to 29.4)	14 (0.8)	11 (0.6)	Screening and decolonisation
4	822	0 (0)	1:137	General Orthopaedic Abdominal Orthopaedic Urology Vascular	230	6574	3.7 (0.9)	39.3 (34.6 to 44.1)	182 (2.8)	21 (0.3)	Combined‡
5	545	89 (16.3)	1:272	General Neurosurgery Orthopaedic Vascular	121	1938	5.8 (1.5)	14.3 (11.3 to 17.6)	56 (2.9)	4 (0.2)	Screening and decolonisation
6	547	4 (0.7)	1:274	General Orthopaedic Vascular	93	1300	16.8 (2.5)	25.1 (20.7 to 30.1)	0 (0)	5 (0.4)	Screening and decolonisation
7	902	62 (6.9)	1:180	Abdominal General Vascular	84	1963	6.1 (1.5)	76.5 (71.3 to 81.1)	607 (30.9)	41 (2.1)	Combined‡

8	850	202 (23.8)	1:567	Orthopaedic Urology	87	2434	5.5 (0.6)	50.2 (44.6 to 55.8)	0 (0)	3 (0.1)	Enhanced hand hygiene
9	1350	150 (11.1)	1:260	Vascular Cardiothoracic Neurosurgery Plastic surgery	164	1561	10.0 (2.2)	67.0 (61.4 to 72.3)	17 (1.1)	15 (1.0)	Enhanced hand hygiene
10	2044	402 (19.7)	1:204	Abdominal Cardiovascular Orthopaedic Urology	302	6366	4.8 (0.4)	55.9 (51.2 to 60.5)	1666 (26.2)	140 (2.2)	Enhanced hand hygiene
Overall	11 838	1324 (11.2)			1816	33 608	6.6 (3.8)	39.5 (38.1 to 40.9)	2571 (7.6)	269 (0.8)	

MRSA, meticillin resistant *Staphylococcus aureus*.
*Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
†By screening or clinical culture.
~~‡Screening in hospitals in the combined arm was performed according to locally introduced policies. Hospital 4 used targeted screening of patients who were previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. Hospital 7 introduced universal screening in two of three study wards and targeted screening in the third ward. In this ward, patients who were previously known to be MRSA-positive, nursing home residents, patients admitted to the hospital in the last three months, contacts of MRSA-positive patients, and patients transferred from another ward or healthcare facility were screened.~~

Table 2: Summary of the timing and nature of infection control interventions for each study arm

	Standard precautions	Hand hygiene promotion	MRSA screening	MRSA isolation	MRSA decolonisation
Baseline phase: 6-7 months (1 March 2008 to 31 January 2009)*					
Enhanced hand hygiene arm	-†	-	-	-	-
Screening and decolonisation arm	-	-	-	-	-
Combined arm	-	-	-	-	-
Intervention phase: 12 months (1 October 2008 to 31 January 2010)*					
Enhanced hand hygiene arm	Adherence to standard precautions (e.g. gloves and other barriers as needed for contact with mucous membranes, wounds, and body fluids) during care of all patients encouraged.	HH promotion using the WHO multi-modal HH promotion method.[15] Observation of 100 opportunities for HH per ward per month.	-	-	-
Screening and decolonisation arm	-	-	Universal screening of patients admitted for more than 24 hours, on admission then weekly (see "MRSA screening details" box below).	Patients MRSA colonised/infected placed on contact precautions (gown and gloves during contact). MRSA patients placed in single rooms or cohorted based on local capacity. Pre-emptive isolation of previously unknown MRSA-carriers pending screening results not used.	Patients MRSA colonised/infected given twice-daily intranasal mupirocin and daily chlorhexidine body washes (5 days).
Combined arm	Adherence to standard precautions (e.g. gloves and other barriers as needed for contact with mucous membranes, wounds, and body fluids) during care of all patients encouraged.	HH promotion using the WHO multi-modal HH promotion method.[15] Observation of 100 opportunities for HH per ward per month.	Targeted screening based on risk factors (see "MRSA screening details" box below).	Patients MRSA colonised/infected placed on contact precautions (gown and gloves during contact). MRSA patients placed in single rooms or cohorted based on local capacity. Pre-emptive isolation of previously unknown MRSA-carriers pending screening results not used.	Patients MRSA colonised/infected given topical decolonisation therapy at discretion of treating clinicians.

Washout phase: 6 months (1 October 2009 to 31 July 2010)*					
Enhanced hand hygiene arm	-	-	-	-	-
Screening and decolonisation arm	-	-	-	-	-
Combined arm	-	-	Targeted screening based on risk factors (see "MRSA screening details" box below).	Patients MRSA colonised/infected placed on contact precautions (gown and gloves during contact). MRSA patients placed in single rooms or cohorted based on local capacity. Pre-emptive isolation of previously unknown MRSA-carriers pending screening results not used.	Patients MRSA colonised/infected given topical decolonisation therapy at discretion of treating clinicians.

MRSA screening details: Screening of nares, perineum, and wounds (if present).
Universal screening (intervention phase) was used in the screening and decolonisation arm. It refers to screening patients admitted for more than 24 hours and excluded patients undergoing ambulatory surgery and those screened within 5 days prior to admission to the surgical ward.
Targeted screening (intervention and washout phase) was used in the two centres in the combined arm due to introduction of local and national mandatory screening policies. One study centre (Hospital 4) screened patients previously known to be MRSA-positive, contacts of MRSA-positive patients, and patients transferred from the Intensive Care Unit or other healthcare facilities. The other centre (Hospital 7) screened patients with the same risk factors as Hospital 4, but also included nursing home residents, patients admitted to the hospital in the last three months, patients transferred from another ward within the same hospital, and those admitted to vascular or abdominal surgery subspecialties.

MRSA, meticillin resistant *Staphylococcus aureus*; HH, hand hygiene.
*Commencement of the study period was staggered for hospitals. For each study phase, the start date is the date on which the first hospital entered the study phase and the end date indicates the date on which the last hospital completed the study phase.
†The dash indicates that there were no specific interventions as part of the study. Hospitals employed their usual infection control practices during these study phases.

Table ~~23~~: Study characteristics by study period

Characteristic	Baseline phase	Intervention phase	Washout phase
Duration (months)	6 to 7*	12	6
Total admissions (n)	33 608	63 810	29 332
Total patient-days (n)	264 035	496 975	249 119
Total surgical procedures (n)	27 768	49 747	22 123
Procedures in clean surgery wards (n)†	12 916	21 463	8787
Procedures in other types of surgery wards (n)†	14 852	28 284	13 336
Mean patient-to-nurse ratio (SD)‡	6.55 (3.78)	6.67 (3.59)	6.87 (4.18)
Total number of patients MRSA positive on admission (%)§	269 (0.8)	724 (1.1)	228 (0.8)
Number positive by clinical culture (%)	65 (0.2)	85 (0.1)	41 (0.1)
Number positive by screening swab (%)	204 (0.6)	639 (1.0)	187 (0.6)

MRSA, meticillin resistant *Staphylococcus aureus*.
*Baseline phase was 6 months in six hospitals and 7 months in four hospitals (two in the screening and decolonisation arm and one hospital in each of the enhanced hand hygiene and combined arms).
†Clean surgery wards included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery. Other types of surgery wards included abdominal, general, and urological surgery.
‡Calculated by dividing the mean patient load by mean number of nurses working on the ward at a given time (averaged over day, evening, and night shifts).
§By screening or clinical culture.

Table ~~3~~4: Crude nosocomial meticillin resistant *Staphylococcus aureus* incidence rates and incidence rate ratios by study arm for each study period*

Outcome	Baseline phase	Intervention phase	Washout phase	Crude IRR (95% CI) for intervention vs. baseline phases	Crude IRR (95% CI) for washout vs. intervention phases
MRSA isolation rate from clinical cultures (no. per 100 susceptible patients)					
Enhanced hand hygiene	0.99 (181/183.47)	0.80 (279/349.50)	0.65 (106/163.83)	0.81 (0.67 to 0.98)	0.81 (0.65 to 1.01)
Screening and decolonisation	0.47 (31/66.61)	0.23 (28/122.56)	0.26 (17/66.04)	0.49 (0.29 to 0.82)	1.13 (0.62 to 2.06)
Combined	0.55 (47/85.35)	0.36 (60/165.23)	0.13 (8/63.04)	0.66 (0.45 to 0.97)	0.35 (0.17 to 0.73)
MRSA infection rate (no. per 100 admissions)					
Enhanced hand hygiene	0.58 (106/183.79)	0.50 (175/349.96)	0.45 (74/164.13)	0.87 (0.68 to 1.10)	0.90 (0.69 to 1.18)
Screening and decolonisation	0.24 (16/66.92)	0.19 (23/122.79)	0.17 (11/66.15)	0.78 (0.41 to 1.48)	0.89 (0.43 to 1.82)
Combined	0.29 (25/85.37)	0.19 (32/165.35)	0.13 (8/63.04)	0.66 (0.39 to 1.12)	0.66 (0.30 to 1.42)
MRSA surgical site infection rate (no. per 100 surgical procedures)					
Enhanced hand hygiene	0.60 (79/132.27)	0.49 (123/250.03)	0.42 (54/127.06)	0.82 (0.62 to 1.09)	0.86 (0.63 to 1.19)
Screening and decolonisation	0.26 (14/54.00)	0.15 (15/99.63)	0.16 (8/50.74)	0.58 (0.28 to 1.20)	1.05 (0.44 to 2.47)
Combined	0.20 (18/91.41)	0.14 (21/147.81)	0.07 (3/43.43)	0.72 (0.38 to 1.35)	0.49 (0.15 to 1.63)
MRSA bloodstream infection rate (no. per 10 000 patient-days)					
Enhanced hand hygiene	0.93 (14/15.0757)	0.56 (16/28.6667)	0.44 (6/13.5745)	0.60 (0.29 to 1.23)	0.79 (0.31 to 2.02)
Screening and decolonisation	0.17 (1/5.7754)	0.18 (2/11.2971)	0.17 (1/5.8473)	1.02 (0.09 to 11.28)	0.97 (0.09 to 10.65)
Combined	0.18 (1/5.5524)	0.00 (0/9.7337)	0.00 (0/5.4901)	-	-

IRR, incidence rate ratio; MRSA, meticillin resistant *Staphylococcus aureus*.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward.

Table 45: Multiple segmented multilevel Poisson regression models showing adjusted incidence rate ratios for changes in level and trend of nosocomial meticillin resistant *Staphylococcus aureus* rates*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	0.97	0.89 to 1.06	0.55	1.00	0.90 to 1.11	0.98	1.02	0.90 to 1.16	0.75
Intervention phase									
Change in level									
Enhanced hand hygiene	1.44	0.96 to 2.15	0.076	1.28	0.79 to 2.06	0.31	1.25	0.70 to 2.23	0.45
Screening and decolonisation	0.87	0.49 to 1.57	0.65	0.97	0.49 to 1.92	0.94	0.79	0.35 to 1.79	0.58
Combined	1.63	0.96 to 2.75	0.070	1.17	0.62 to 2.20	0.63	1.33	0.59 to 3.00	0.49
Change in trend									
Enhanced hand hygiene	0.99	0.91 to 1.09	0.88	0.99	0.89 to 1.10	0.84	0.98	0.86 to 1.12	0.75
Screening and decolonisation	0.94	0.85 to 1.05	0.26	0.93	0.82 to 1.05	0.27	0.90	0.78 to 1.04	0.162
Combined	0.88	0.79 to 0.98	0.016	0.90	0.80 to 1.02	0.096	0.86	0.74 to 1.01	0.059
Washout phase									
Change in level	1.90	0.91 to 3.95	0.087	1.52	0.66 to 3.51	0.32	1.90	0.69 to 5.27	0.21
Change in trend	1.02	0.91 to 1.15	0.74	1.00	0.88 to 1.15	0.95	0.95	0.80 to 1.12	0.53

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).

Table ~~5~~6: Multiple segmented multilevel Poisson regression models showing changes in nosocomial meticillin resistant *Staphylococcus aureus* rates for the subgroup analysis of clean surgery only*

	MRSA clinical isolates (per 100 susceptible patients)			Total MRSA infections (per 100 admissions)			MRSA surgical site infections (per 100 procedures)		
Variable	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**	**aIRR**	**95% CI**	**p Value**
Baseline phase									
Trend	1.05	0.93 to 1.18	0.41	1.10	0.94 to 1.28	0.23	1.11	0.93 to 1.33	0.26
Intervention phase									
Change in level									
Enhanced hand hygiene	1.31	0.75 to 2.30	0.34	1.06	0.52 to 2.16	0.88	1.09	0.47 to 2.53	0.83
Screening and decolonisation	0.87	0.41 to 1.85	0.71	1.03	0.39 to 2.69	0.96	0.92	0.29 to 2.92	0.89
Combined	1.79	0.86 to 3.74	0.121	1.15	0.44 to 2.96	0.78	1.21	0.39 to 3.73	0.75
Change in trend									
Enhanced hand hygiene	0.89	0.78 to 1.01	0.063	0.88	0.75 to 1.04	0.127	0.89	0.73 to 1.07	0.21
Screening and decolonisation	0.85	0.74 to 0.97	0.019	0.83	0.69 to 0.99	0.041	0.81	0.66 to 1.00	0.054
Combined	0.82	0.71 to 0.95	0.007	0.84	0.70 to 1.00	0.055	0.84	0.68 to 1.03	0.095
Washout phase									
Change in level	3.01	1.05 to 8.63	0.041	2.21	0.61 to 8.04	0.23	2.59	0.59 to 11.46	0.21
Change in trend	0.96	0.81 to 1.15	0.67	0.91	0.73 to 1.12	0.37	0.86	0.67 to 1.09	0.21

MRSA, meticillin resistant *Staphylococcus aureus*; aIRR, adjusted incidence rate ratio.
*Meticillin resistant *Staphylococcus aureus* was defined as nosocomial if it was isolated from specimens collected more than 48 hours after admission or within 30 days (or 12 months for infections of prosthetic devices) after discharge from the surgical ward. Clean surgery included cardiothoracic, neuro-, orthopaedic, plastic, and vascular surgery subspecialties. The model used a lagged dependent variable to account for autocorrelation and adjusted for staffing (patient-to-nurse ratios), seasonal effects, type of surgical ward, and baseline hand hygiene compliance rates. The model also accounted for overdispersion. Random effects for intercepts at the hospital and ward levels and random baseline trends at the hospital level were all significant, and baseline trends were negatively correlated with intercepts (i.e. hospitals with higher baseline MRSA rates tended to have larger decreases in baseline rates).