PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of strategies to reduce meticillin resistant *Staphylococcus aureus* rates in surgical patients: a controlled multicentre intervention trial
AUTHORS	Lee, Andie; Cooper, Ben; Malhotra-Kumar, Surbhi; Chalfine, Annie; Daikos, George; Fankhauser, Carolina; Carevic, Biljana; Lemmen, Sebastian; Martínez, José Antonio; Masuet-Aumatell, Cristina; Pan, Angelo; Phillips, Gabby; Rubinovitch, Bina; Goossens, Herman; Brun-Buisson, Christian; Harbarth, Stephan

VERSION 1 - REVIEW

REVIEWER	Jan Kluytmans Professor of medical microbiology and infection control, VU University Medical Center, Amsterdam and Amphia Hospital Breda, The Netherlands I have no competing interest
REVIEW RETURNED	08-May-2013

THE STUDY	An active screening and decolonization policy for S. aureus in surgical patients was recently described using a double blind placebo controlled design. In the discussion the authors refer to review published in 2005 (ref 21). The more recent data from Bode et al published in the NEJM should be included in the discussion.
GENERAL COMMENTS	This paper deals with an important topic, namely the control of MRSA in surgical wards. The authors have performed a multicenter, European study that is representative for the current state of affairs in hospitals. The design reflects the 'real' situation regarding infection control practices, especially the adherence to recommendations regarding, hand hygiene, screening and subsequent control measures. The low compliance with screening, isolation and decolonization shows the problematic implementation of infection control measures. Even during a study with motivated participants. The design of the study has some intrinsic limitations that are adjusted for using a sophisticated analyses and at the end the limitations are discussed in sufficient detail. I have several remarks and questions. 1) the most critical point in my opinion is the timing of the screening and decolonization in this group of surgical patients. Most patients are admitted the day before surgery.

	This means that the results of screening as performed in this study are only available after surgery, meaning that decolonization is started after surgery as well. This is likely too late to have an optimal effect to preevnet the development of a SSI, if any at all. A recent study by Bode and colleagues (NEJM 2010;362:9-17) used a rapid test, the result of which was available before surgery and a decolonization treatment similar to the one used in this study, was started before surgery. This had a major effect on the S. aureus SSI rate (60% reduction). In the discussion the authors refer to a better effect in clean surgical cases using reference 21. The study by Bode provides further and more recent evidence that decolonization to pevent S. aures SSI is most effective in clean surgical cases. The authors state that they changed from a chromogenic culture based screening to PCR based screening at the end of the study. This was only done in a small subset of the patients. The authors should take the timing of the intervention (decolonization) in relation to the moment of surgery into consideration and provide some information on the effects of this if available. At least a discussion on this item should be part of this manuscript. 2) The adherence to hand hygiene (HH) at baseline may have been higher than in in real life. The higher baseline compliance in the wards were HH was part of the intervention compared to the ACD wards is remarkable. Were the observers known to observe HH-compliance and was the allocation known during the baseline phase? In general a baseline HH compliance of 49% in the study wards is not realistic in my experience. 3) The adherence to screening, isolation and decolonization was low. The lack of single rooms is a plausible explanation for the isolation component. But why was adherence to decolonization so low? Can the authors adjust for differences in adherence to ACD and the effects on the outcome?

REVIEWER	Prof Peter Wilson Consultant Microbiologist University College London Hospitals London UK I have no competing interests.
REVIEW RETURNED	16-May-2013

THE STUDY	I think the supplemental documents are appropriate.
GENERAL COMMENTS	This is a good quality paper from a well established group of researchers. The size is appropriate for these types of intervention. My one criticism is that many of the infection control measures would be being introduced across the hospital anyway and it may be difficult to keep the staus quo adn avoid confounders such as encoraging hand hygiene in campaigns. The relative paucity of response in that arm is not surprising. PCR screening was introduced only later. I was not entirely clear on the HCAI definitions and whether they were used in the same way across all institutions. Hand hygiene was observed overtly so open to Hawthorne effect. Was covert observation made by independent observers?. Please

	spell Gram with a capital G. I was pleased to see the ORION checklist included.

REVIEWER	Sheldon Stone BSc, MD, FRCP Senior Lecturer, Stroke Physician and General Physician for Older People, Department of Medicine, Royal Free Campus, University College London Medical School,
REVIEW RETURNED	22-May-2013

THE STUDY	This is a considerably better paper than 99% of papers in a field where it is notoriously difficult to carry out studies to examine the efficacy of interventions. The investigators and participants should be congratulated on their completion of such an ambitious study, their use of a study design that provides a template for future studies (especially regarding data collection and statistical techniques) and their transparent reporting. If there were a higher proportion of studies like this, I would have less to read , shorter conferences to attend (more touring time) and I wouldn't get so bored at them! It has sufficient scientific rigor to merit publication and my recommendation would be for acceptance subject to minor revisions. These relate mainly to increasing the clarity and transparency of the paper still further, although there are a few of points that might be more substantive. The first of these concerns the allocation of hospitals to interventions. This clearly was not randomised. Was it by preference? This is an important point because one of the criticisms of RCTs is that disappointment effects could exaggerate the differences between intervention limbs. It is also important because implementing an intervention that calls on healthcare workers to change their behaviour faces potential difficulties unless the HCWs are motivated to try the behaviour. If it is preference that determined allocation, this should be stated, and possibly included in the description of the study design: something along the lines of a "controlled preference trial". Indeed I am not quite sure what the best description of the design might be. It is more than an interrupted time sereis as it is a three phase ITS! In addition there is a non randomised allocation of hospitals to different interventions, where the control is with each hospitals baseline and washout rates. Perhaps the best term if allocation is on the basis of preference is a "controlled three phase Interrupted times series preference trial". The authors will have a view on this I am sure. The second substantive issue is that I am not sure I quite understand what the figures for the washout levels and trends in Table 4 (which is the key outcome table of the paper) and Table 5 are really comparing. Is this an overall comparison with a composite of the intervention phase.....I assume that this is so. However, I would be interested to know what the comparison is between wash out and intervention phase for each of the intervention limbs especially for Table 4. Table 5 clearly shows a signficant rise in level for clinical isolates in the washout phase but I still wonder why they have not presented data for direct comparisons with the individual interventions.

	Similarly I am not quite sure I understand the final column on Table 3 where the IRR with 95% CIs for washout v intervention are given. The crude results seem to imply that there is a siginficant continued fall in the "Combined " limb of the trial (0.35 (0.17 to 0.73)..and this is not commented on in the text nor is there an equivalent comparison in Table 4. Thirdly, the paper states that investigators were not blinded to the intervention. Not quite clear what this means. Does it mean that the independent research staff doing the audits of hand hygiene etc and surveillance were not blinded? If so I am not sure why they could not be blinded and this should be explained. However, I presume that the clinical MRSA isolates data was generated from the lab and the recogntion there that these were non screening positive swabs, so there was some blinding to the intervention for the primary outcome, correct? IF so, should be stated. Fourthly, there is no reference to antibiotic use. Although it is extrememly unlikely that reduction in quinolones and cehalosporins sufficient to generate reductions in MRSA occured at the same time and at the same level/rate of change as MRSA in the two combined hospitals . Did authors colelct data on antibiotic prescription? If they did , were there any importnat trends? If they did, were these incorporated into the model as potential confounders? Points of clarification (in no particular order): 1. Who actually implemented the interventions on each site and co-ordinated them? This should be stated..presumably it was the infection control department and staff? 2. The terminology used differs at various stages in tables, figures (Ilike all the figures by the way!!) and text: Combined v MIX (choose one and stick with it); ACD v Active Detection (by and large avoid capitals?) 3. The analysis of outcomes on clean wards was pre-specified and is important. It should therefore be there in the introduction as an aim of the study. It is there in the abstract results. 4. The article summary is not quite correct in describing this as a comparison of two startegies . It is a comparison of three strategies: Enhanced, Active Detection. contact precautions and Decolonisation and combined. 5. I wonder about the choice of terminology - just for clarity. I think the absense of the term hand hygiene from the enhanced startegy makes it less clear and I wonder if "Enhanced Hand Hygiene and Standard Control" might convey the meaning more clearly. Also the discussion should pint out that the study has extra relevance as the Hand hygien promotion is effectively the WHO SAVE LIVES initiative which is now very widespread across the globe. So a study which demonstrates that you need Active Detection and this intervention is very important and of eeven greater generilislability. The discussion should also make it explicit that the results are biologically plausible (in general and for the clean surgery as well). 5. Is the protocol available as a stand alone document? Whether it is

	or not, there needs to eb an explicit statement that there were or were not any deviations from protocol. If there were some they should be specified and explained. This was a very pragmatic trial of neccessity so it would not be surprising if there were some. 6. Document is delighfully ORION compliant but I wonder if the authors would consider adding ina flow diagram so that the contributing hospitals and wards in each limb are clearly visualised. Table 1 provides that information but if a figure is feasible that might be more immediately easily understood in that a picture is worth a thousand words. Whther table or figure..the country of each hospital should be included. Although the text provides a lot of information about the interventions I think it might be easier for readers to get the gist if there were a summary table as suggested in the ORION. Something along the lines of the example given in the original ORION paper (which was a previous Harbath paper if I remember a right!) should enable readers to get the point quickly. The text could then be given as a web appendix for those wishing to know more details. 7. I think the discussion should mention that the study's strengths include that they ahve tried to separate out the differential effects of active detection (screening) and hand hygiene) and that the study was design and reported using standard reporting guidelines to maximise transparency and scientific rigor (or some such phrase..approriately referenced). 8. "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" ...in addition they should reference the four year national UK cleanyour hands study (Ben Cooper will have the reference) published in the BMJ last year. 9. The discussion should comment briefly on what happens in the washout phase especially in the combined limb..where there is a trend towards increased IRR (Level Table 4) but not a conventionally siginficant one (crosses 1.00).... 10. I am not sure that their results do demonstrate that targeted screening is more effective than universal, so would appreciate some explanantion of this or some reference in the discussion to the results ie the table which shows this. I am sure that it is more cost effective (although that cannot be borne out from this study) but they might like to quote Marc Bonten's modelling study from PLoS ONE last year 2012 around October which makes a case for the superiority targetted screening). 10. I do not understand this sentence: "Our results suggest that selective (clean surgery) or targeted (high risk patient) screening may be more effective than universal screening". Again terminology may need simplifying..although i do not think it a problem that the combined arm just used targetted screening..I wonder whether the paper as a whole should be clear and consistent that the enhanced intervention was "Enhanced Hand Hygiene and routine control", the active detection was "Active Universal MRSA " and that the combined was "Enhanced Handhygiene and Active Targetted MRSA

	screening". Does that seem any clearer..assuming Active implies contact precautions and decolonisation. Musing on paper here... but maybe having the summary table with a row that explains what each intervention is would help and just keep the terms Acive Detection, Combined and Enhanced Hand Hygiene would do it. 10. Although the confidence intervals suggest that there was adequate power in the combined intervention limb for one to be certain about the result..it did only involve two hospitals and one would have been more reassured had there been four hospitals doing this. Am not quite sure how to counter this in the discussion but the authors shoudl address it. 11. Although this is not a definitive randomised controlled trial with say four hospitals in each limb and we have long known that a combination of infection control interventions is more likely to be effective, this study puts recommended practice on a much firmer footing than previously. It represents the best available evidence for the effective reduction of MRSA on surgical wards by a a combined strategy of active hand hygiene promotion, targetted MRSA screening, contact precautions and decolonisation. This has implications for best clinical practice and the discussion should make these points. 11. The discussion makes no future research recommendations. Perhaps the authors would like to address this. It is a moot point as to whether it is really worth a furhter trial in this setting but should this be trialled in other settings such as ITU and general medical wards? or should further studies on surgical wards concentrate on the best ways of implement the combined intervention. I leave this to the authors
GENERAL COMMENTS	I should mention that I have worked for many years with Ben Cooper and we have co-authored papers together. I would also add that I have an informal but collegial relationship with Stephan Harbath. However I do not consider that this represents a conflict of interests as should be evident from my comments above. If BMJ does decide to accept this paper I would be prepared to write a commentary or opinion piece in BMJ alerting readership to the lessons of this study for clinical practice and future research.

REVIEWER	Jean Carlet Consultant Groupe hospitalier Paris St Joseph Paris France. I must mention that I have been in this hospital, which is part of the study for 30 years, but without any involment in the study. Furthermore, I was one of the evaluators of the study, when it was submitted. I do not think that those two points are conflicts of interest
REVIEW RETURNED	27-May-2013

THE STUDY	The patients are representative of actual patients No information provided in the supplement are essential for the main manuscript
GENERAL COMMENTS	The paper is an assessement of two strategies either alone or combined, in the prevention of MRSA colonization and infection: enhanced standart control, with emphasis on hand hygiene, and MRSA screening, and decolonisation. The study compared three periods, a 6 months baseline period, the intervention 12 months

	period, and a washout 6 months period.The study is prospective and controlled. The primary outcome is the the clinical culture per 100 patients. the secondary outcome if the MRSA infection rate.The results are that the measures individually were not efficient, exepted in the subgroup of clean surgery patients. the combination of the two methodes, studied in a small number of hospitals (two hospitals) was efficient to reduce MRSA rates.The study is excellent. The data are straightforward. The paper is clear, well presented. The list of references is perfecly appropriate.The tables and figures are clear.I have no main concern either for the study or the paper. The two small comments are 1) The word " compared" is used several times in the paper. I would rather use "assessed", since it is not a comparision between the different arms, but a comparision of periods 2) I am not sure that the study is easily generalisable to standart units and hospitals.In particular, many hospitals do not use PCR to detect MRSA, due to financial or technical reasons

VERSION 1 – AUTHOR RESPONSE

REVIEWER 1: Jan Kluytmans

The recent publication in the NEJM by Bode et al mentioned by the reviewer in his first paragraph has been included in the discussion. Please see the response 1.1 below for further details.

Response 1.1: We agree that this is an important point. Unfortunately, as we did not collect individual-level data, we do not have information regarding the timing of decolonization in relation to the timing of surgical interventions. However, as the reviewer points out, the surgical wards in the screening, contact precautions and decolonisation arm (ACD arm) introduced PCR-based screening in the latter part of the intervention phase. This test was used specifically in patients who required a rapid result prior to surgery. The reduction in trends of MRSA rates over the intervention phase in these wards, particularly in clean surgery wards, could potentially be explained by earlier detection of carriers and implementation of decolonization regimens prior to surgery, when their benefit is likely to be greatest for prevention of surgical site infections. Indeed, in clean surgery wards, of the three intervention arms, screening, contact precautions and decolonization was the most effective strategy for reducing the rates of total MRSA infections (aIRR 0.83, 95% CI 0.69 to 0.99, p=0.04) as well as MRSA surgical site infections (aIRR 0.81, 95% CI 0.66 to 1.00, p=0.05) over the duration of the intervention phase. We have included this point in the discussion section on page 18, as well as citing the recent reference by Bode et al, NEJM 2010;362:9-17 (Reference 32).

Response 1.2: The hand hygiene observers were research personnel who were staff of the enrolled hospital but independent of the surgical ward staff. Hand hygiene observations were performed by direct observation using standardised observations forms. All observers were trained and validated at the central study coordinating centre. We were therefore confident that the baseline hand hygiene compliance rates were comparable between hospitals during the baseline phase. Although the allocation of the interventions was known to research personnel during the baseline phase, research personnel were instructed to observe a predefined number of hand hygiene opportunities and were specifically asked not to give feedback on hand hygiene practices during the baseline phase.

We acknowledge the reviewer's concerns that the baseline HH compliance may be higher than that in real life, and this may have partly been due to the Hawthorne effect where healthcare workers' practices improve when they know they are being observed. However, we believe that this is likely to have been similar across all hospitals and we accounted for differences in baseline HH compliance rates by adjusting for this in the analysis. This has been elaborated on in the manuscript on pages 9-

Response 1.3: Adherence to decolonization was low for a number of reasons including discharge prior to an MRSA-positive result, discharge prior to commencement of the decolonization regimen, or the patient declining the intervention. These reasons have been included in the manuscript text on page 13. We have already explored the effects of compliance with different components of the interventions (i.e. hand hygiene promotion and level of screening) according to a pre-specified analysis plan and would rather not further complicate the manuscript by adding an unplanned analysis. However, if the editors think this additional analysis is appropriate, it could be performed and added to the manuscript.

REVIEWER 2: Prof Peter Wilson

Response 2.1: We share this reviewer's concerns about the introduction of other interventions during the study period which could have potentially had an effect on the study outcomes. We attempted to monitor this by asking centres to provide information about such planned activities and advising that they be deferred until after the study period. With regards to hand hygiene campaigns, the hospitals in the screening, contact precautions and decolonization arm did not report interventions to improve hand hygiene, and their hand hygiene compliance rates remained suboptimal at 23.9% during the washout phase, compared to 30.5% during the baseline phase. At least one hospital in this arm planned to implement a hand hygiene campaign at the conclusion of the study due to ongoing poor hand hygiene compliance. As mentioned in the discussion section on page 19, we accounted for differences between hospitals by adjusting for potential confounders and comparing outcomes between baseline and intervention phases within the same study arm. As outlined in the methods section, there was also use of some targeted screening in the hand hygiene arm and the effect of this was investigated in the exploratory analysis. Although it is possible that there may have been other measures introduced in individuals hospitals, results were similar when each centre was excluded in turn from the analysis so changes in factors in individual centres are unlikely to have had a major effect on outcomes. This point has been included in the discussion section on pages 19-20.

Response 2.2: The reviewer states that PCR screening was introduced only later. This is correct and the effect of this testing on the outcomes has been discussed in the response to Reviewer 1's first comment (see Response 1.1 above).

Response 2.3: The reviewer comments that he was not entirely clear on the HCAI definitions and whether they were used in the same way across all institutions. Healthcare associated infections were defined according to the CDC criteria (see page 8 and reference 16). Personnel from each study site were provided with a study protocol and handbook as well as receiving training regarding the definitions at the study coordinating centre prior to commencement of the study. All study outcomes were reviewed by the staff at the central coordinating centre and discussed with study personnel at the individual study centres during site visits and teleconferences to ensure infection definitions were applied uniformly across the study centres. Further details regarding this point are included in the revised manuscript on pages 9 and 10 under the heading "Data collection".

Response 2.4: The reviewer comments that hand hygiene was observed overtly so open to Hawthorne effect. He asks whether covert observation was made by independent observers. Direct observation was used. Although this method of hand hygiene practice observation has its limitations, including possible overestimation of true hand hygiene compliance due to the Hawthorne effect, it is still considered the gold standard by leading authorities (WHO (2009). WHO Guidelines on Hand Hygiene in Health Care. World Alliance for Patient Safety. Geneva, WHO Press Geneva). Observers were independent of the staff on the surgical wards and did not provide feedback to healthcare workers of hand hygiene practices during the baseline phase. We therefore consider that the

Hawthorne effect was likely minimal for observations made in the baseline phase. This has been elaborated on pages 9-10.

Response 2.5: "Gram" has been capitalised throughout the text.

Response 2.6: We agree with the reviewer that the ORION checklist is highly appropriate for ensuring the optimal reporting of quasi-experimental intervention studies for healthcare associated infections.

REVIEWER 3:

Response 3.1: We thank the reviewer for the helpful and extremely constructive comments and the appreciation of the importance and timeliness of our work. We are also grateful for mentioning the strengths of this real-life intervention study. The reviewer makes important points about allocation of centres in clinical trials. Allocation of hospitals was not by preference but related to practical considerations such as cost constraints with regards to the MRSA screening tests and availability of laboratory personnel and infrastructure for screening implementation. In addition, the introduction of mandatory screening policies at a local or national level also influenced intervention allocation (see page 7 of the Methods section).

With regards to the description for the study design, we have included the terms “three phase interrupted time series” in the Methods section on page 6.

Response 3.2: The washout phase results in Tables 4 and 5 were indeed comparing results to a composite of the intervention phase. Comparisons between washout and intervention phases for each of the study arms were not in the original analysis plan but we agree that post-intervention levels and trends may be different in each study arm. We have therefore re-analysed the data to provide washout phase results by study arm. These results are included as a supplementary file with the submission entitled "Tables with models with washout phase by study arm" which contains Table 4 version 2 and Table 5 version 2. These new models do not provide a significantly better fit for the data compared to the original models (in all cases a likelihood ratio test for nested models gives $p>0.3$); in other words, we don’t have evidence to reject the null hypothesis that the effect of the washout phase was the same in each study arm. We also feel that this new unplanned analysis increases the complexity of data interpretation without substantially altering the main study findings and may be better left out of the current manuscript. If, however, you feel they would significantly add to the paper, we suggest that these results could be included in an appendix.

With regards to Table 3, the crude results for the Combined arm do show a reduction in rate of MRSA clinical culture isolation in the washout phase compared to the intervention phase. However, this reduction was not seen after adjustment for confounders, seasonal effects and baseline trends in the multivariate analysis, as demonstrated by the washout phase results for the combined arm in version 2 of Table 4. We have added some text regarding the adjusted washout phase results on page 15.

Response 3.3: These points are correct and the manuscript text has been modified to include further details and clarification about the blinding on page 19.

Response 3.4: The centres did not prospectively collect antibiotic prescribing data as part of this study. We did, however, analyse the data excluding each centre in turn from the analysis to see if changes in factors in individual centres were likely to have had a major effect on outcomes. The results of these analyses were similar to those of the entire dataset which reassured us that even if there had been changes in practices such as antibiotic prescribing in a single hospital, it was unlikely to have appreciably altered the study findings. We have included this point in the discussion section on pages 19-20.

Response 3 point no. 1: The interventions were implemented by trained research personnel at each study site and coordinated through the central study coordinating centre in Geneva, with on-site supervision by the Principal Investigator at each site. Research personnel from each site were trained at the coordinating centre prior to study commencement and had ongoing support in terms of study protocols and implementation through email, monthly telephone conferences and site visits. Staff at each site were predominantly those that supervised infection control activities in each of the hospitals, and included staff of Infection Control, Infectious Diseases and Hospital Epidemiology Departments. This has been clarified in the text in the first paragraph under “Data collection” on page 9.

Response 3 point no. 2: The terminology has been reviewed for clarity and has been made uniform throughout the text, tables and figures. The three study arms have been renamed:
1. enhanced hand hygiene - in place of Enhanced Standard Control [ESC]
2. screening and decolonisation – in place of Active detection, Contact precautions and Decolonisation [ACD]
3. combined – this name has been retained and also replaces the term “MIX”

Response 3 point no. 3: This has been included at the end of the introduction on page 6.

Response 3 point no. 4: This has been corrected on page 4 to state that the study compares the strategies of HH and screening, either alone or in combination.

Response 3 point no. 5a: The terminology has been modified for clarity (see response to point no. 2 above). The discussion points have been included in the discussion on pages 18 and 20.

Response 3 point no. 5b: There was one major deviation from the original protocol due to the introduction of mandatory screening policies during the study in two centres which therefore used a combined strategy (see the last paragraph of the “Interventions” section on page 7. This change in allocations occurred prior to the commencement of data collection. Furthermore, the study protocol and trial synopsis were preregistered on an open clinical trial registration site (clinicaltrials.gov NCT00685867).

Response 3 point no. 6a: A figure (figure 1) has been included but the data linking each country with individual hospital data shown in Table 1 has not been included in order to de-identify the hospitals in the Table.

Response 3 point no. 6b: While we agree that a table would provide readers with a quick summary of the study interventions, we currently already have 5 tables and 4 figures, and the web appendix also contains 6 supplementary tables and 1 figure. We are therefore hesitant to add another table and we hope the information in the text is clear enough for the readers to appreciate the nature of the interventions. Furthermore, to present a detailed ORION table summarising the characteristics and interventions in 10 different hospitals would represent a formidable challenge. If, however, you and the editor would still like us to include this extra table, and the editors permit an increase in the number of tables in the submission, we will gladly do so.

Response 3 point no. 7: We thank the reviewer for this valuable suggestion. This has been included in the discussion on pages 16-17.

Response 3 point no. 8: This reference has been included as reference number 28 on page 17.

Response 3 point no. 9: This has been included in the discussion section on page 17.

Response 3 point no. 10a: This has been clarified in the discussion on page 17. We refer to a combination of HH promotion and targeted screening (combined arm) being superior to universal screening (active detection arm). In the results of the exploratory analysis, however, hand hygiene promotion was not associated with reduction in MRSA rates so we postulate that it was likely the targeted screening component of the combined intervention that explained the reduction in MRSA rates in this study arm. We have also cited Marc Bonten's PLoS One study about cost-effectiveness of a targeted MRSA screening approach on page 18.

Response 3 point no. 10b: This sentence has been clarified on page 17 (see response to previous comment). The names of the study arms have been modified as mentioned under point no. 2 and the interventions are also explained in the legend for the newly added Figure 1.

Response 3 point no. 10c: This point has been discussed further on page 18.

Response 3 point no. 11a: We thank the reviewer for this constructive comment. This is an important point which has been included in the discussion on page 20.

Response 3 point no. 11b: A suggestion for further research has been included in the discussion on page 20. We believe that the evaluation of the cost-effectiveness of these interventions in the surgical setting is an important next step.

REVIEWER 4: Jean Carlet

Response 4.1: We would like to thank the reviewer for highlighting the strengths of the study and the manuscript. We agree with the reviewer that in order to determine the effect of the interventions in the three study arms, we analysed the data using intra-group comparisons, i.e. compared the intervention period results to baseline period results within the same study arm. Although the analysis of direct between-group comparisons of study arms was not presented, we nevertheless were able to make an evaluation of the differential effects of each intervention strategy over the same time periods and adjusting for similar variables across the study arms. We are therefore confident that we can compare the results between each study arm using its own baseline as the most appropriate control.

Response 4.2: This study was a pragmatic study which was carried out in settings with varying infection control infrastructures. The hand hygiene intervention is an initiative which could be implemented in most hospitals as demonstrated in our study where each centre adapted the WHO method of hand hygiene promotion to their local circumstances and the materials for this intervention are readily available on the WHO website. Indeed many countries throughout the world have already implemented such an initiative.

With regards to MRSA screening methods, hospitals in the screening, contact precautions and decolonisation arm used culture-based screening to begin with. In this study, we do not know the relative contribution of PCR-based screening over culture-based methods on the study outcomes. However, one of the hospitals in the arm that used a combination of screening and standard measures (with associated reductions in MRSA rates) used solely culture-based methods for MRSA screening. Therefore PCR screening may not be necessary to achieve the MRSA reductions seen in the study. In addition, previous studies comparing culture and PCR-based screening methods have not found that the latter method was superior to culture in controlling MRSA (Jeyaratnam et al. (2008). "Impact of rapid screening tests on acquisition of meticillin resistant Staphylococcus aureus: cluster randomised crossover trial." BMJ 336(7650): 927-930; and Tacconelli et al. (2009). "Rapid screening tests for meticillin-resistant Staphylococcus aureus at hospital admission: systematic review and meta-analysis." Lancet Infect Dis 9(9): 546-554).

We therefore believe that our results would be generalisable to other hospitals which implement either culture- or PCR-based screening techniques. Of note this was a pragmatic study which was able to be implemented in centres with widely varying hospital and infection control infrastructures as shown in Table 1. We therefore consider the implementation of the study strategies and findings highly generalisable to other settings. This has been outlined in the discussion on page 16.

VERSION 2 – REVIEW

REVIEWER	Stone, Sheldon University College London
REVIEW RETURNED	05-Jul-2013

THE STUDY	Those points that aren't absolutely yes (although I have ticked them as yes) are dealt with in the repeat review. I think the two main issues are the trial design description, the exact descritpion of allocation and making the screening policy clear.
GENERAL COMMENTS	They have done a very good job and I am largely in agreemtn with their changes. However two important points remain. The first is the description of the design which I think would be better described as a partially randomised controlled preference trial. The second is that it is now apparent to me that I do not understand the screening policy at all. I therefore deal with these two points first in this document. Response to 3.1 I still think they should go for “Preference trial”. The choice or allocation was influenced by the constraints upon the various institutions, such as cost, personnel, national interventions. This amounts to taking account of the institution’s preferences, as participation in an entirely randomised allocation would have meant that some of the hospitals could not have participated. ie “we would prefer not to be in the hand hygiene only intervention because we have to do screening”..or “we would prefer not to be in the screening limb because we haven’t the manpower or financial resources”. The correct term is “Partially randomised controlled preference trial” (I shall upload the original reference paper for this design). Although this concept was initially introduced in the setting of patients’ preference to participate in interventions, especially psychological interventions, it was also to be applied to doctors’ or clinicians’ preference and beliefs, and therefore by extension, to those of institutions. It makes it much more feasible to do international or even national multicentre studies in infection control and reflect the realities and changing contexts of the infection control world which make trials so difficult. The conclusions can be generalised according to the settings which expressed preference, and to the reasons for those preferences. Therefore: a flow diagram of recruitment and allocation might have several branches (see original paper on this study design) with lines for those who were genuinely randomised and those who were not. Also: Text could explain in more detail the reason for preferences for each centre…along the lines of their response. So these details

	should be in the end of the intervention section on page 7). Overall: I think this would increase the novelty value of this paper, and act as an exemplar for trials of this type in this field. I would strongly suggest they consider this as the design seems theoretically coherent to me…and is a whole lot better than saying "it was a pragmatic trial". If they are going to use the phrase "three phase interrupted time series" in the methods it should be there in the title BUT I think it makes a much stronger point, and will be a more influential paper, if it has the courage to state what it is and call it a "partially randomised controlled preference trial". Break new ground…why not?! I think the current title is really weak and does the study a disservice…and they should have the word trial in it really as well as controlled. 3. point 11a: Fine. Glad to have helped. HOWEVER on page 19 the authors state "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." I think the use of the term "targeted screening" is misleading as it would usually be taken to mean screening patients in a particular specialty group (such as orthopaedic, vascular, neurosurgery etc) . Indeed I now realise that I do not understand the screening policy at all. They call it high risk screening but it is really screening all those "admitted for more than 24 hours" (page 7) (with exclusions for ambulatory patients or those screened within 5 days for MRSA). On page 17 they state that their 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." However, there seems to be little targeting going on here, it is all admissions to these wards that are going to stay for more than 24 hours. However, this does not match up with the small proportions of those screened in the screening arms! So I just don't get it (even though many of the patients are in traditional high risk specialty groups).. Or is it that most admssions were out in 24hours...in which case the conclusion is that patients expected to be in for more than 24 hours should be screened. This is not what is known as high risk screening, so should be called something else like "screening of patients staying longer than 24 hours" THIS IS AN IMPORTANT POINT AND NEEDS RESOLVING. Sorry I should have picked this point up previously from Table 1. Am probably being dense but they will have to help me out here. Other comments 3.2. I appreciate them doing a reanalysis and take their point that it does not alter the results. However, I think we should take up their offer to include this additional analysis in the supplemental tables as I am sure there will be others who will ask the same questions and just a line in the text to indicate they looked at this would suffice. 3.2 part 2: Excellent

	3.3: They have now clearly acknowledged this but I think they need to be even more explicit on page 19 where they currently state : “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.”. I would suggest making it clear in this section, as they do on page 9 that these investigators were in fact the “ Research personnel” from each hospital who actually implemented the interventions. So I suggest revise to say, instead of “investigators” they should say ““research personnel assessing hand hygiene, contact precautions, decolonisation, screening and isolation practices were not blinded to study assigment as they were responsible for implementing the interventions” 3. 4 OK fair point but I think they should specify why they could not collect antibiotic data or LOS data in the methods section. I can well imagine that the antibiotic data may not have been collectable at ward level as DDDor tonnage /1000 bed days or number of admissions for many of the hospitals. 3. point 1 Fine! 3. point 2. Good. So does this mean that the interventions were: A. enhanced hand hygiene + standard (do they mean universal? precautions) with isolation of MRSA patients B. screening, decolonisation + contact precautions (with isolation of MRSA patients). C. combined However, it is mentioned that pre-emptive isolation was not used in intervention B, so was it used in intervention C?) This is where a summary table would be so useful to identify the exact contact, isolation and other policies in place in the different phases…… I take their point that providing patient details or setting details may not be feasible in an ORION table but this information could be retained as in the current paper and the other bits of a standard ORION table presented. As it is, one is currently going forth and back to the text to remind yourself exactly what the differences in policies and interventions was so to have that tabulated would be very helpful, especially as the table could be explicit as to the exact definition of contact and standard (universal) in this study (as you know these terms can be interpreted in different ways by different people). Saves using a glossary as well. 3. point 3 Fine 3. point 4. OK 3. point 5a. OK..the biologically plausible is actually on page 17 with respect to clean surgery but the general result of combined interventions being most effective seems biologically plausible to me, but I leave it to the authors to state this.

	On page 20 I would suggest they are more specific and state: “the WHO multi-modal HH promotion” with the relevant reference, so that it reads: “In addition, the WHO multimodal HH promotion strategy15 implemented in this study is already being used in many…..” 3. point 5 b: The existence of a trial protocol should be stated in the methods, the website given, and the deviation reported as a deviation. I am a little confused now as the reason for deviation from protocol given at end of intervention section on page 7, seems to apply solely to those centers that had a national screening policy imposed on them. However, there were other reasons given in their response “cost constraints with regards to the MRSA screening tests and availability of laboratory personnel and infrastructure for screening implementation”. These should be mentioned too on page 7 (see my first comments above in this document) 3.point 6a: Great..this could be adapted to show how allocation took palce (see my first comment above) 3.point 6b: I still think an additional table would be helpful (see my comments above 3. point 2) 3. point 7 : Good 3. point 8 Thank you kindly! 3. point 9: Thanks 3.point 10a: OK. Absolutely fine. In addition to Marc Bonten’s study, now that the English national NOW cost effectiveness study has been extensively peer reviewed and the department of health has allowed its release on www.idrn.org/audit.php you might like to consider a reference to that as it is a very extensive modelling study utilising national audit data from 90% of acute hospitals, and making a very strong case for targeted screening. 3. point 10b and c: Fine. 3. point 11b. Fine.

VERSION 2 – AUTHOR RESPONSE

Response 3.1: We appreciate the thoughtful comments from the reviewer related to the design of the study. Indeed, the trial used a mixed design that included different components and therefore the study can be described in several ways. Please see our comments below in reply to the issues raised:

- We respectfully disagree that the correct term is: “partially randomised controlled preference trial”. First, there was no partial randomisation at the initial stage; we fear that this term may be misleading. Second, it reflects a concept and terminology that has never been used in infection control and hospital epidemiology. Third, we do not want to modify a posteriori central descriptions of the study design and introduce jargon used more frequently in the psychological sciences.

- However, we agree that it was a controlled trial and have modified the title accordingly. Furthermore, we have added a short paragraph to the Interventions section on page 8 describing the reasons for allocation preferences for each centre in more detail.

Response 3 point 11a: We agree that this is a very important point as knowing the details of the interventions is crucial to understanding the differences in outcomes in the study arms and application of the study findings to clinical practice.

To clarify the terms used in the text in the discussion section:

“Universal screening” essentially refers to the intervention applied by hospitals using the “screening and decolonisation” strategy as outlined in the Methods section on page 7: “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 term “universal screening” has been added to the Article Summary on page 4 and the Methods section on page 7 prior to the description of this intervention in order to clarify this.

“Targeted screening” refers to the screening method used by the two hospitals in the “combined” strategy arm. The “targeted screening” in this arm was based on the local screening policies implemented in these hospitals which used risk factors for MRSA carriage (including patient characteristics or surgical specialty such as vascular surgery). One hospital using the combined strategy 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 used targeted screening of patients with the risk factors listed above, as well as 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. We agree with the reviewer that this was unclear so this information has been added to the last paragraph of the “Interventions” section on page 8.

“Selective screening” refers to screening in the subgroup of clean surgery wards, rather than individual patient risk factor-based screening.

The sentences on pages 17 (now 18 in latest revised version) and 19 (now 20) have also been modified to clarify the terminology. We have also added a modified ORION table (the new Table 2, as discussed in the response to 3. Point 2, below). We hope this resolves any confusion about the interventions.

Response 3.2: We have made this data available to interested readers by including the post-hoc analysis in the supplementary material as Table A6 and referring to it on page 15 of the Results section.

Response 3.3: Thank you for this useful suggestion which increases the clarity of the manuscript. We have modified the sentence on page 19 (now page 20 in the new version) accordingly.

Response 3.4: Hospitals varied widely in terms of the availability and quality of electronic medical record and pharmacy data. Accurate antibiotic utilisation data was difficult to obtain. Even if it were available for the whole hospital, it was not necessarily available for individual wards or departments. In addition, available antibiotic data were often for amounts dispensed to the wards rather than prescribed for patients admitted to the wards of interest. Although it would have been ideal to include patient-level data and antibiotic use data, individual chart reviews of all patients admitted to the study wards was not feasible. The variation in the quality of this data from the different centres made it of

questionable utility for inclusion in the analysis thus a decision was made not to make collection of these data a requirement for this study. This point has been included in the “Data collection” section of the Methods on page 11.

Response 3 point 2: We agree with the reviewer that the details of the components of the interventions for each arm may be difficult to remember. We have therefore included a modified ORION table (excluding the population and setting information) as suggested (see the new table 2 referred to on page 8) in order to clearly document the precise nature of the interventions.

The term standard (universal) precautions has been described in the table. The isolation of MRSA patients was not a component of this intervention. Study sites were asked to adhere to their usual practices based on local policies with regards to isolation of MRSA carriers. We have therefore modified the first paragraph of the “Interventions” section of the Methods on page 7 to reflect this.

Pre-emptive isolation was not used in Interventions B or C. This has been detailed in the new table.

Response 3 point 5a: We have included a statement regarding the biological plausibility of the combined intervention in the Discussion section on page 19.

Thank you for this suggestion to specify that the HH campaign employed was the WHO multi-modal HH promotion strategy. The sentence in the manuscript to which the comment refers has been modified accordingly.

Response 3 point 5b: The study protocol registration details are provided at the end of the “Interventions” section of the Methods on page 8 and the allocation of the two hospitals to the combined arm as a deviation from the protocol is also noted on page 8.

The “cost constraints with regards to the MRSA screening tests and availability of laboratory personnel and infrastructure for screening implementation” were reasons for the non-random allocation of the interventions in the original protocol and did not result in deviation from the protocol. The protocol deviation applied solely to the two hospitals in which national or local mandatory screening was introduced. We apologise if this was not clear.

Response 3 point 6a: We thank the reviewer for the suggestion. As stated in the response to the first comment, we have included the details regarding the allocation of the centres in the text in the Intervention section of the Methods. We believe that adding individual hospital allocation preferences in the Figure would reduce its clarity without adding to the newly added information in the text.

Response 3 point 6b: This additional table has been added as the new table 2 as requested. We agree that it significantly improves the clarity of the manuscript.

Response 3 point 10a: This additional reference has been included on page 19 as reference 35.