PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Trends in *Staphylococcus aureus* bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time-series intervention analysis**
AUTHORS	Lawes, Timothy; Raigmore Hospital, Paediatrics Edwards, Becky; Aberdeen Royal Infirmary, Medical Microbiology López-Lozano, José-Maria; Hospital Vega Baja, Epidemiology; Hospital Vega Baja, ViResiST project Gould, Ian; Aberdeen Royal Infirmary, Medical Microbiology

VERSION 1 - REVIEW

REVIEWER	**Reviewer 2: Stefania, Stefani** University of Catania, Department of Bio-Medical Sciences
REVIEW RETURNED	26/1/12

THE STUDY	
RESULTS & CONCLUSIONS	
REPORTING & ETHICS	
GENERAL COMMENTS	The reviewer filled out the checklist but didn't make any other comments

REVIEWER	**Reviewer 2: Larsen, Anders** Statens Serum Institut, Microbiological Surveillance & Research
REVIEW RETURNED	6/2/12

THE STUDY	
RESULTS & CONCLUSIONS	
REPORTING & ETHICS	
GENERAL COMMENTS	The manuscript is well written, and the results are very and convincing. The decline in MRSA- SAB due to universal screening may not be surprising. However, since it is not widely implemented, this study is of importance to show the effects. The manuscript needs a brief read through; S. aureus in italics and explanations of all abbreviations (i.e ITU first time used, L. 252). Specific remarks Table 1: Line: Admitting department, comes out significantly, but no values are shown? Line 307 and Line 335: fig, write figure explain white noise

REVIEWER	**Reviewer 3: Harbarth, Stephan** University of Geneva Hospitals and Medical School, Infection Control Program CoI: SH is a member of the speakers' bureau of bioMérieux and Pfizer, a member of the advisory board of Destiny Pharma, DaVolterra, and bioMérieux, and has received financial support for MRSA research activities from B.Braun, Pfizer, and the European Commission under the Life Science Health Priority of the 6th Framework Programme (MOSAR network contract LSHP-CT-2007-037941).
REVIEW RETURNED	22/2/12

THE STUDY	
RESULTS & CONCLUSIONS	
REPORTING & ETHICS	
GENERAL COMMENTS	**HOPITAUX UNIVERSITAIRES DE GENEVE** Service de Prévention et Contrôle de l'Infection (SPCI) Tél. 022/372 98 28, Fax 022/372.3987 *Review BMJ Open 2012. 08/06/2012* • This paper describes the experience of a large hospital in Scotland with endemic MRSA over a 6-year period, and the concurrent evaluation of the impact of universal MRSA admission screening on invasive MRSA infections. It shows that MRSA bacteremia and associated mortality were substantially reduced, whereas the incidence of MSSA bacteremia did not change. The topic is important because it deals with one of the most controversial control measures to contain endemic MRSA. The research question remains original, although it has attracted much scientific attention in the last 20 years. • This manuscript is well-written and presents an interesting and carefully designed retrospective analysis of MRSA control measures. The data were collected and generated in a labor-intensive way, followed by a deluge of various statistical analyses, generating sometimes results with limited novelty (e.g. Tables 1 and 2). The main message is that universal MRSA admission screening seems to be beneficial since it reduced the rates and clinical impact of *S.aureus* bacteremia, through a huge reduction of MRSA bacteremia without affecting MSSA incidence, however. This message is very important and certainly deserves publication in a widely distributed medical journal. It is much likely that some useful lessons and recommendations for clinical microbiologists, hospital epidemiologists and policy makers can be extracted from the results of this experience. • For the present reviewer, there are a few major concerns about the internal and external validity of the results, as listed below: 1) Several effect modifiers and determinants influence the causal pathway between improved identification of MRSA carriers upon admission and decreased incidence of MRSA bloodstream infection. Although screening compliance was high after introduction of the universal MRSA screening policy, no data are provided about other important process indicators such as compliance with decolonization and isolation measures. For instance, readers would like to know

	whether patients were housed in single rooms or just flagged and equipped with contact precautions in multi-bed rooms? Most importantly, a recent article by the same group of authors had reported a very low success rate of MRSA decolonization attempts (Reilly JS et al. J Hosp Infect 2010). Thus, more data are needed to better understand the real-life effect and practical implications of early identification of previously unknown MRSA carriers upon admission. 2) The data on MRSA surveillance are incomplete. Information on other MRSA infections should be reported, if available (as done in a recent article from Scotland: Reilly JS et al. J Hosp Infect 2012). Did the incidence of MRSA surgical site infections also decrease? Was discharge screening performed during certain periods in selected hospital units (as reported from Scotland by van Velzen EV, ICHE 2011)? Furthermore, which hospital units were most affected by the reduction of MRSA bacteremia? Finally, are data available about the incidence density of nosocomial MRSA transmission (e.g. expressed as number of new nosocomial MRSA cases / 1000 patient-days)? 3) The ITS analysis is methodologically sound but lacks information on important confounders and therefore yields a poor predictive value with R-values ≤ 0.35 for the 3 most important analyses (nosocomial incidence, proportion and mortality) – some experts in the field would not accept that >75% of the model variance remains unexplained, especially in an article submitted to BMJ. Therefore, the authors should improve their current ITS analysis by attempting to include important explanatory determinants (hand hygiene compliance, antibiotic use, MRSA colonization pressure, environmental cleaning) in a complementary statistical approach, using, for instance, segmented regression analysis. 4) Huge efforts have been made in Scotland to improve HH compliance over the last 10 years. In a similar multicenter evaluation of decreasing MRSA rates in England (S Stone, ECCMID 2010), increased usage of HH rubs was the most important driver of decreased MRSA bacteremia rates. Thus, without providing more accurate data and analyses on HH consumption this analysis remains deficient and of lower quality compared to similar studies (e.g. Aldeyab MA, JAC 2008: *Modelling the impact of antibiotic use and infection control practices on the incidence of hospital-acquired methicillin-resistant Staphylococcus aureus: a time-series analysis*). Furthermore, most experts would agree that incorporating only the volume of ABHR usage does not necessarily reflect the true HH compliance during patient contacts. In summary, I would suggest making every possible effort to improve the explanatory power of this analysis and include ABRH use or true HH compliance into the multivariate models (see above). 5) The policy implications of this study should be presented in more detail, considering the questionable value to screen all admissions for MRSA carriage in a period of budget cuts and low prevalence of MRSA carriage. Should the national guidelines be modified or enhanced? Please also comment in more detail on the obvious contradictions between the present study and the conclusions of 2 Scottish HPA reports that recently stated: (a) "*There was a temporal association between the initiation of universal screening and a decline in*

MRSA infections, as defined by the number of first clinical isolates from hospital-based laboratory-confirmed cases during the study. The reduction reached statistical significance within the combined study board data, a finding in line with other studies, although of course this does not necessarily show that the screening caused the reduction. Indeed comparator hospital data, although limited, indicated that whereas the rate of reduction in those hospitals which had implemented universal screening was greater than those that had not, there was no statistically significant difference." (Reilly JS et al. J Hosp Infect 2012); (b) "*Universal screening for MRSA on admission will in itself not be sufficient to reduce the number of MRSA colonizations and subsequent MRSA infections*." (van Velzen EV, ICHE 2011)

- Discussion:
  - The authors should highlight and better discuss the discrepancies and contradictions between this study and previous work by the same group, in particular considering their published work about the added value of antibiotic stewardship interventions, enhanced environmental cleaning and improved hand hygiene compliance (Monnet DL, Emerg Infect Dis 2004; Mahamat, Int J Antimicrob Agents 2007; Mahamat, J Hosp Infect 2011).
  - A few key references could be added and discussed:
    - Spiegelhalter DJ, BMJ 2005
    - Aldeyab MA, JAC 2008
    - Robotham JV, BMJ 2011 (universal MRSA screening with isolation alone did not appear cost-effective for most scenarios)
    - Wyllie DH, Walker AS, Miller R, et al. Decline of MRSA in Oxfordshire hospitals is strain-specific and preceded infection-control intensification. BMJ Open 2011;1:e000160
  - The power of the mortality analysis may have been too low to demonstrate a significant impact of MRSA BSI on 30-day mortality. However, the generated non-significant effect estimate (OR=1.38) is similar to previously published results (e.g. Cosgrove SE, ICHE 2005; Ammerlaan H, Clin Infect Dis 2009). This could be briefly mentioned.

Minor comments:

- L160: Was the microbiology laboratory opened 24/7 for processing screening specimens and notification of positive results?
- L248: The high proportion (38%) of community-associated MRSA bacteremia deserves further comments (see also Ref 53, Wyllie DH, BMJ 2005).
- Table 2: Hospital-associated SAB increases the risk of 30-d mortality (OR=1.56) but is protective against inpatient mortality (HR=0.44). This surprising observation should be checked for accuracy and plausibility and (if true) deserves a careful explanation.

Geneva, 2012-02-22
Prof. Stephan Harbarth

VERSION 1 – AUTHOR RESPONSE

Dear Editors and peer-reviewers,

We are grateful for the comments provided by the three reviewers. Please note that we have uploaded a word-document of our responses as below for ease of reading. In this word-document:
• Our responses to specific comments (in order of appearance in the manuscript decision letter) are provided in plain blue type.
• Changed content is highlighted in red (italics) with line numbers where appropriate (these line number correspond to the revised manuscript as uploaded)
• Tables / figure references are underlined and in red.
• Supporting references are in square brackets.

Reviewer 1: Anders Rhod Larson

The manuscript needs a brief read through; S. aureus in italics and explanations of all abbreviations (i.e ITU first time used, L. 252).

- Italicised where required (lines 241, Footnote table 3, References)
- Explanations and standardisation of abbreviations:
"ICU" used as standard abbreviation for intensive care unit (explained in line 282 and ITU changed to ICU in line 291,301 and 532 table 1,2,3,4)
"SMR" explained as Standardised Mortality Ratio (line 211)
"Ln(AOBDs)" expanded to natural logarithm of AOBDs (line 229)

Specific remarks

Table 1: Line: Admitting department, comes out significantly, but no values are shown?

REPLY: This line refers to the X2 test applied to the distribution of admissions across all departments detailed in indented lines below -(i.e. Medical, surgical, ITU, paed/neonatal ,and maternity). P-values against each department represent results of X2 tests applied (post-hoc) to establish in which specific departments differences arose (comparison is admissions to specified department vs. admissions to all other departments by cohort)
- To clarify this point this line in table 1 now reads: "Admitting department (all)"

Line 307 and Line 335: fig, write figure.

REPLY: Corrected as requested (lines 298,343, 350, 382)

Explain white noise:

REPLY: Revised to read: "residuals were randomly distributed." (line 435-6)

Reviewer 2: Professor Stephan Harbarth

Initial comment: This manuscript is well-written and presents an interesting and carefully designed retrospective analysis of MRSA control measures. The data were collected and generated in a labor-intensive way, followed by a deluge of various statistical analyses, generating sometimes results with limited novelty (e.g. Tables 1 and 2). The main message is that universal MRSA admission screening seems to be beneficial since it reduced the rates and clinical impact of S.aureus bacteremia, through a huge reduction of MRSA bacteremia without affecting MSSA incidence, however. This message is very important and certainly deserves publication in a widely distributed medical journal. It is much likely that some useful lessons and recommendations for clinical microbiologists, hospital epidemiologists and policy makers can be extracted from the results of this experience.

REPLY: Responding particularly to the comments highlighted in bold:

(1) Content:
We accept findings reported in the sections on descriptive epidemiology and secular trends closely reflect those found in previous studies with comparable study populations and bacteraemia cohorts. However, we feel that the detailed epidemiological survey of SAB in Aberdeen may contain several points of interest to the groups acknowledged by the reviewer:

i) We detail longer-term outcomes including length-of-stay, readmission, treatment failure and recurrence rates which have been noted previously as infrequently reported upon for SAB. [Wyllie, Crook and Peto; BMJ 2006; 333:281-6].
ii) Regional data can add detail to understandings gathered from national surveillance particularly in regard to risk-factors. Johnson et al [J Antimicrob Chemother. 2005;56(3):455-62] notes that geographic variation in SAB rates in the UK may reflect differences in admitting specialities and case-mix but that is inadequately captured by national (especially mandatory) surveillance.
iii) From a policy perspective the high proportion of community-associated MRSA bacteraemias (38% vs. 24% reported in Oxfordshire between 1997 and 2003 by Wyllie et al [BMJ 2005;331(7523):992-7]) may suggest both real-effects of control measures in hospitals and the need to broaden control to community settings.
iv) Finally, the most important implication of our epidemiological survey is the need to address invasive infections from MSSA if national targets for all SAB are to be met. The lack of progress in reducing mortality rates after MSSA bacteraemia should be of particular concern. We emphasis that commonalities and differences in epidemiologies of MRSA and MSSA bacteraemia should inform strategies to tackle all SAB.

(2) Style:
Nevertheless, we appreciate the need to balance description of useful data with readability. To accommodate both we have retained detail in tables while reducing, where possible the amount of statistics reported in the text. See Lines 319,331,340,347

Major concerns:

Major concern (1): no data are provided about other important process indicators such as compliance with decolonization and isolation measures. For instance, readers would like to know whether patients were housed in single rooms or just flagged and equipped with contact precautions in multi-bed rooms? Most importantly, a recent article by the same group of authors had reported a very low success rate of MRSA decolonization attempts (Reilly JS et al. J Hosp Infect 2010). Thus, more data are needed to better understand the real-life effect and practical implications of early identification of previously unknown MRSA carriers upon admission.

REPLY: The authors did not intend this study as offering a detailed analysis of the universal screening programme trial but rather as a focus on its effects on SAB epidemiology specifically. As the reviewer acknowledges detailed information on process indicators such as compliance with decolonization and isolation have been previously reported in reports on the whole pathfinder study [HPS, National Services Scotland. NHS Scotland MRSA Screening Pathfinder Programme Final Report Volume 1: An investigation of the Clinical Effectiveness of MRSA Screening. 2011, Health Protection Scotland [Report]; Reilly JS, et al. J of Hosp Infec 2010;74:35-41].
Although specific data on decolonisation and isolation from Aberdeen Royal Infirmary are not currently available from Health Protection Scotland, we expect similar values for process indicators of compliance with decolonization and isolation measures as reported in the references above. We have reflected this now in:
Results: Lines 389-394 and table 4 (projected numbers decolonised and isolated based on pathfinder figures).
Discussion: Lines 580-584

We highlight the following points of interest in response to the reviewer's concern:

• Compliance with elements of intervention in pathfinder were similar to those previously reported by Robicsek et al. [Ann Intern Med. 2008;148(6):409-18] in their US study of universal surveillance:

	Robicsek et al (2008)	Current study
% of admissions ITU	5% of bed-capacity.	2% of bed-capacity.
Adherence to surveillance	84.4%	87%
MRSA+ at admission	6.3%	3.1%
Received decolonisation	55% commenced. 4.1%decolonised*	41% commenced
Isolated / cohorted	Unclear.	78%

* Defined as three successive negative swabs >48 hours apart

• The 4.1% of screen positive patients 'successfully decolonised' [Reilly JS et al J Hosp Infect 2010;74:35-41] must be interpreted with due caution. This figure is defined as 3* negative swabs >48 hours apart. Considering a 24-48 hour turnaround from screening swab to initiation of decolonisation, a 5 day decolonisation course and a minimum of 4 days required to obtain 3 negative swabs the minimum total days required to meet this criteria of decolonisation was 10-11 days. In ARI only 10.6% of all admissions have a length-of-stay of ≥ 10-11 days and only 6% > 14 days. Even allowing for longer lengths of stay in those most likely to be colonised, it is apparent that proving decolonisation during admission by this strict criteria will be difficult.

• More importantly, declonisation therapy in the context of universal screening was used for its short-term suppressive effect and not necessarily long-term eradication. The 41% initiating decolonisation therapy may be of more relevance. The pathfinder report on clinical effectiveness states:"Those who commenced decolonisation treatment had an HAI infection incidence of 2.7 per 1,000 patient days which was a significantly lower rate of infection than those who did not receive decolonisation (4.2 per 1,000 patient days). This indicates that even a day of decolonisation may have a protective effect….The probability of infection were significantly lower in those who had commenced decolonisation treatment as a result of admission screening compared with those who had not (OR 0.69 95% CI 0.524 – 0.899)".

• We believe our findings point to potential values in knowledge of MRSA status extending beyond isolation and decolonisation. We note that for MRSA bacteraemia occurring in patients without prior history of MRSA (n=105, 50% of all), there was a significant increase in the proportion identified as being colonised with MRSA at admission during universal screening (30% vs. 11% during targeted screening; P = 0.012 - lines 386-8). Such knowledge may offer one explanation for the falling % of deaths in MRSA (but not MSSA) bacteraemia if prompting earlier initiation of appropriate therapeutics and specialist involvement at an earlier stage, or initiation of decolonisation suppresses MRSA during admission even without eradication. We are not aware of other observational studies using time-series analysis which have demonstrated this effect on mortality and if confirmed this benefit should be considered in debates around cost-effectiveness of universal screening.

Major concern (2): The data on MRSA surveillance are incomplete. Information on other MRSA infections should be reported, if available (as done in a recent article from Scotland: Reilly JS et al. J Hosp Infect 2012). Did the incidence of MRSA surgical site infections also decrease? Was discharge screening performed during certain periods in selected hospital units (as reported from Scotland by van Velzen EV, ICHE 2011)? Furthermore, which hospital units were most affected by the reduction of MRSA bacteremia? Finally, are data available about the incidence density of nosocomial MRSA. transmission (e.g. expressed as number of new nosocomial MRSA cases / 1000 patient-days)?

REPLY: Again, we intended the focus of our paper to be S.aureus bacteraemia. We will be addressing the contribution of universal admission screening to control of all S.aureus infections (and colonisations) in a forthcoming paper using time-series analysis methods. This said we appreciate the relevance of providing descriptive data on other MRSA infections and departmental impacts:

(a) Other MRSA infections:
- We had provided summary figures for number of all MRSA infections/colonisations in tables 3 and 4. Please note these data were only available in adult services but constitute the vast majority of these infections during the period. We note very similar patterns as observed for bacteraemia only with large reductions in MRSA not observed in MSSA infection/colonisation.

(b) Surgical site infections:
- We were unable to obtain data on surgical site infections during this period but since declines in all MRSA infection/colonisation and MRSA bacteraemia were similar in medical and surgical departments our local experience suggests parallel (diminishing) secular trends in SSIs.

(c) Discharge screening:
Discharge screening was performed on selected admissions as was reported in previous pathfinder reports but we feel this would add little to the present study. We acknowledge in our discussion, that "50% of hospital-associated MRSA bacteraemia occurred in patients not colonised at admission highlighting the limitations in admission surveillance and the persistence of cross-transmission" while referencing the van-Velsen et al 2011 study. As noted previously we understand that decolonisation therapy may have a role in short-term suppression during admission without eradicating MRSA.

(d) Hospital units/ departments affected by reductions:
We agree that this is of importance to readers. In response we have amended:
Methods: (Line 231)
Results:
i) We have graphed MRSA prevalence density and 30-day mortality by department (Medical, surgical, ITU) with Poisson regression analysis describing and comparing secular trends by use of an interaction term (see revised figure 3 and lines 352-354: "By admitting department, declines in MRSA prevalence density, HA-incidence density and mortality were significantly steeper in ITU than medical or surgical departments ($P < 0.05$ for interaction term)".
ii) It was not possible to perform multivariate time-series analysis on departmental data but we ran segmented regressions which suggested comparable effect sizes (decreases) in ITU, medical and surgical settings. This is reflected in the results (line 434-435): "effect sizes for screening were comparable across all departments".
Discussion: (Lines 555-557): (Lines 269-270)

(e) Nosocomial transmissions of MRSA:
We do not have access to this data for the study period specifically but acknowledge in our discussion our groups earlier findings that 50% of MRSA infections occur in those not colonised or infected at admission suggesting limitations to universal admission screening and the need for other measures to limit nosocomial transmissions. (lines 581-3)

Major concern (3) The ITS analysis is methodologically sound but lacks information on important confounders and therefore yields a poor predictive value with R-values ≤ 0.35 for the 3 most important analyses (nosocomial incidence, proportion and mortality) – some experts in the field would not accept that >75% of the model variance remains unexplained, especially in an article submitted to BMJ. Therefore, the authors should improve their current ITS analysis by attempting to include important explanatory determinants (hand hygiene compliance, antibiotic use, MRSA colonization pressure, environmental cleaning) in a complementary statistical approach, using, for instance, segmented regression analysis.

REPLY:
(a) Improving the ITS analysis by integration of other explanatory variables:
We agree that hand-hygiene and environmental cleaning compliance, antibiotic use and MRSA importation pressure are ecological variables expected to affect rates of MRSA infection and their inclusion could improve our multivariate analyses. We have therefore been able to obtain accurate detailed data for most of these factors (excluding environmental cleaning) and repeated our time-series analysis. To reflect the fact that we formally integrated other infection control measures into

our final multivariate TSA we have amended
Title: Now reads – “Trends in Staphylococcus aureus bacteraemia and impacts of infection control practices including universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time-series intervention analysis
Article summary: Now reads – “Compared to a strategy of targeted screening in high-risk environments, universal admission screening may significantly reduce rates of MRSA bacteraemia and associated early mortality alongside improvements in antibiotic stewardship and infection control”
Abstract: (lines 1-39) revised.
- Objectives: Now reads – “To describe secular trends in Staphylococcus aureus bacteraemia in an inpatient population, and assess the impacts of infection control practices including universal MRSA admission screening on MRSA bacteraemia associated clinical burdens”.
- Results: Amended to reflect revised TSA (see results below). Now reads – “Positive associations with fluoroquinolone and cephalosporin use suggested that subsequent antibiotic stewardship reduced prevalence density of MRSA bacteraemia by 0.027/1000 AOBDs”.
- Conclusion: Now reads- “Universal MRSA admission screening and antibiotic stewardship were was associated with decreases in MRSA bacteraemia and associated early mortality”
Background (aims): (lines 97-98) Now reads – “…to evaluate the impact of introducing infection control measures including universal MRSA admission screening”
Methods: Now reads – “Details on the percentage of antibiotic use use of involving ‘4C’ antibiotics (Ciprofloxacin, Cephalosporins, Clindamycin, Co-amoxiclav) and macrolide antibiotics (defined daily doses (DDDs)/1000 AOBDs) and hand-hygiene (Litres of alcohol gel used/1000 AOBDs; monthly average hand-hygiene compliance assessed by nationally standardised audit of opportunity and technique) were ascertained …”(Lines 181-185)
To clarify other infection control interventions have summarised changes in hand-hygiene, infection control and antibiotic policies in figure 1 in accordance with the ORION (Outbreak Reports and Intervention Studies Of Nosocomial infection) statement.
Results: Amended section on multivariate analysis and revised table 5.
We note now:
(a) significant effects from antibiotic stewardship
(b) With the exception of % SABs MRSA+, more modest reductions attributable to universal screening:
Original TSA F Final (revised) TSA
Prevalence density -0.053 cases/1000 AOBDs - 0.035 cases/1000 AOBDs
HA-incidence density -0.062 cases/1000 AOBDs -0.029 cases/1000 AOBDs
% SAB involving MRSA -11.0% -13.5%
% 30-day mortality -18.8% -15.6%
(c) Improved R2 suggesting a greater % of variance explained (45-68% vs.19-48% previously)
(d) No significant associations with hand-hygiene compliance (data on ABHG was limited).
Discussion: Detailed comments on Hand-hygiene – (lines 507-510) Antibiotic use (lines 587-593, 612-3)

(b) Comment on complementary statistical approach and R2 values:
The co-authors wish to emphasise that the ARIMA family of time-series analysis modelling offers substantial benefits over the use of segmented regression. Although widely used and recommended the latter approach is substantially weaker than ARIMA / transfer modelling as:
(i) Segmented regression (linear / Poisson) does not account for the non-independence of observations in time-series which is strongly suggested when considering the transmission of infections or spread of resistance. Some authors ‘test’ for auto-regression but we believe that presumption of autoregression has better construct validity.
(ii) Delayed effects may be missed. This is particularly important since previous TSA’s using ARIMA methods have demonstrated substantial lags (upto 6 months) between determinants such as antibiotic use and rates of infection/resistance.
(ii) Seasonality is not accounted for with the result that erroneous conclusions may be arrived at.
(iii) Outliers are not usually identified and accounted for. (iv) Intervention Analysis represents a unique approach accounting for the overall behaviour of the series and focuses on the impact of the intervention, whether contemporaneous or delayed, while controlling at the same time for other covariates influencing the series itself (trends, other explaining variables, stochastic terms,

seasonality etc).
(v) The relationship between intervention and outcome series (infections /resistance) is typically pre-specified in segmented regression (and in most cases only step functions used). This may miss other relationships including temporary or increasing effects which can be explored more readily in transfer-function models.
Of note intervention analysis using ARIMA methods expands upon segmented regression by integrating terms for the disturbance series (stochastic elements of variation, autoregression, seaonality) alongside those for change in level and trend. In building our multivariate transfer-function models we examined effects of interventions both by terms defining step functions (e.g. introduction of hand-hygiene in Jan 2007) and terms for monthly data on related parameters (e.g. %Compliance with hand-hygiene). Significant effects from either were retained as in final models. The R2 from our revised TSA suggests models explained 65-68% of variation in absolute rates and 45-50% of variation in %MRSA and %30-day mortality. This performance is comparable to the 60-70% of variation explained in similar models for all MRSA infections/colonisations. Modelling may have been improved by more accurate data on alcohol-based hand-gel consumption for the whole time period, but otherwise we integrated most of the factors proposed as important confounders (e.g in ORION statement for infection control intervention studies). We would add that surveillance of all MRSA and MSSA infection/colonisations has been suggested as a more sensitive indicator of effects of interventions than surveillance of S.aureus bacteraemia. [Walker S, Peto TEA, O'Conner L, et al. PLoS ONE 2008;3:e2378] This suggests that ecological analyses may less precisely model for variation in invasive infection (and particularly associated mortality) which requires not only exposure to cases but convergence of individual risk-factors and patient-specific case management.

Major concern (4): Huge efforts have been made in Scotland to improve HH compliance over the last 10 years. In a similar multicenter evaluation of decreasing MRSA rates in England (S Stone, ECCMID 2010), increased usage of HH rubs was the most important driver of decreased MRSA bacteremia rates. Thus, without providing more accurate data and analyses on HH consumption this analysis remains deficient and of lower quality compared to similar studies (e.g. Aldeyab MA, JAC 2008: Modelling the impact of antibiotic use and infection control practices on the incidence of hospital-acquired methicillin-resistant Staphylococcus aureus: a time-series analysis).
Furthermore, most experts would agree that incorporating only the volume of ABHR usage does not necessarily reflect the true HH compliance during patient contacts. In summary, I would suggest making every possible effort to improve the explanatory power of this analysis and include ABRH use or true HH compliance into the multivariate models (see above).

REPLY: (See also reply to major concern 3, above).
We acknowledge the likely importance of Scotland's hand-hygiene campaign in the control of MRSA. We attempted to incorporate hand-hygiene data into the time-series analysis as three variables (i) audited hand-hygiene compliance (by nationally standardised methods) (ii) procurement of Alcohol-based hand-gel (unlikely to be an accurate reflection of use) and (iii) a step-function with various lags from introduction of Scotland's national hand-hygiene campaign (Jan 2007).
Unexpectantly we identified no association with hand-hygiene compliance in our revised time-series analyses. Given our own study of all MRSA infections /colonisation during this period (paper in progress) and previous literature we expected hand-hygiene to have a significant effect on MRSA bacteraemia (and perhaps MSSA bacteraemia). There may be three reasons for the discrepancy:
(i) Applications of TSA to bacteraemia specifically has been limited and it may be that while hand-hygiene improves rates of MRSA colonisation / superficial infection, the combination of pre-disposing factors required for blood-stream infection and subsequent death are more complex
(ii) While we were able to obtain data on audited hand-hygiene compliance for 2006-2010 this was only standardised from 2007 as part of NHS Scotland's hand-hygiene campaign. Previous studies have noted a lack of association with reported compliance despite simultaneous association with ABHR use. [Sroka S, et al. J Hosp Infect. 2010;74(3):204-11]

(iii) Only 12 months of baseline data were available before the national hand-hygiene campaign (Jan 2007) which reduces the power of TSA to identify significant effects.
We have noted the discrepancy between data on ABHR and audited hand-hygiene compliance in our results: (lines 405-6) “Improvements in hand-hygiene were suggested by audited compliance but not by consumption of alcohol-based hand-rub”
We have reflected on this in our discussion (lines 507-510) “The lack of accurate data on alcohol-based hand-gel consumption, and limited baseline data before the national hand-hygiene campaign may explain a failure to identify significant effects of hand-improving hand-hygiene [33] as described in other time-series analysis [34,35]”

Major concern(5) The policy implications of this study should be presented in more detail, considering the questionable value to screen all admissions for MRSA carriage in a period of budget cuts and low prevalence of MRSA carriage. Should the national guidelines be modified or enhanced? Please also comment in more detail on the obvious contradictions between the present study and the conclusions of 2 Scottish HPA reports that recently stated: (a) “There was a temporal association between the initiation of universal screening and a decline in MRSA infections, as defined by the number of first clinical isolates from hospital-based laboratory-confirmed cases during the study. The reduction reached statistical significance within the combined study board data, a finding in line with other studies, although of course this does not necessarily show that the screening caused the reduction. Indeed comparator hospital data, although limited, indicated that whereas the rate of reduction in those hospitals which had implemented universal screening was greater than those that had not, there was no statistically significant difference.” (Reilly JS et al. J Hosp Infect 2012); (b) “Universal screening for MRSA on admission will in itself not be sufficient to reduce the number of MRSA colonizations and subsequent MRSA infections.” (van Velzen EV, ICHE 2011)

REPLY:
We acknowledge the discrepancy between nationally agreed policy following the universal admission screening programme and the evidence we present of gains in terms of control of MRSA bacteraemia even compared to a baseline of targeted screening. It must be emphasised that clinical-risk-assessment based screening is seen as a minimum standard in Scotland, although widely accepted most likely on the basis of cost (rather than pure cost-effectiveness) considerations. The co-authors feel that evidence including that from the present study suggesting significant gains in terms of severe invasive infections and (particularly) mortality mean that universal screening should be revisited as a strategy. We also note that the 1 year review on which the conclusions from Reilly et al 2012 were based was limited in its capacity to identify significant differences between control and intervention hospitals. The power-calculations were not clearly based on use of time-series analysis accounting for non-independent observations and may not have accounted for the time-lag (typically 3 months) required to see effects in our study. Contamination was also possible with control situated in the same NHS board, while baseline and follow-up periods were very limited. The latter may be particularly relevant as we identified declines in importation pressure suggesting cumulative impacts of breaking cycles of transmission between hospital and community.
We have acknowledged these points in our discussion (lines 556-563 and lines 606-610)

Concerns on Discussion:
1) The authors should highlight and better discuss the discrepancies and contradictions between this study and previous work by the same group, in particular considering their published work about the added value of antibiotic stewardship interventions, enhanced environmental cleaning and improved hand hygiene compliance (Monnet DL, Emerg Infect Dis 2004; Mahamat, Int J Antimicrob Agents 2007; Mahamat, J Hosp Infect 2011).
(see also responses to concerns 3 and 4).

REPLY:
Following revision of our TSA our findings are highly convergent with those from previous studies

using similar methodology in the region and beyond. We emphasise again that modelling determinants of bacteraemia may require further integration of patient-specific risk-factors.

2) A few key references could be added and discussed:
• Spiegelhalter DJ, BMJ 2005
• Aldeyab MA, JAC 2008
• Robotham JV, BMJ 2011 (universal MRSA screening with isolation alone did not appear cost-effective for most scenarios)

REPLY:
We discuss the results of the Adleyab et al (2008) paper with respect to our findings on hand-hygiene and antibiotic use (included as Reference 35)
We feel that extensive discussion of the economic evaluation by Robothom (2011) is less appropriate to the current study given its focus on (a) ITU/high-risk patients (b) all MRSA infections. Although we agree that decolonisation is likely to be an important element of universal screening there are problems in interpreting this study's findings in general hospital contexts. In ITU settings the marginal benefits from decolonisation (preventing invasive infection) far outweigh the benefits of reducing transmission, against which precautions are typically rigorous. Of note the authors question long-term cost-effectiveness if widespread decolonisation leads to increasing resistance. In a follow-up study to long-term implementation of decolonisation in ICU at Aberdeen Royal Infirmary (Paper in peer-review) we identified no evidence of declining effectiveness or resistance in MRSA isolates. We have commented that limited adherence to decolonisation may undermine the cost-effectiveness of universal screening (line 585-587, Reference 57)

• Wyllie DH, Walker AS, Miller R, et al. Decline of MRSA in Oxfordshire hospitals is strain-specific and preceded infection-control intensification. BMJ Open 2011;1:e000160

REPLY:
Reference 10 summarises the findings of this study and other similar studies. We do emphasise the potential for changing strain distribution to confound the associations we found (lines 480-5)

• The power of the mortality analysis may have been too low to demonstrate a significant impact of MRSA BSI on 30-day mortality. However, the generated non-significant effect estimate (OR=1.38) is similar to previously published results

REPLY:
We have amended the discussion (strengths and limitations) to include this observation: (Lines 476-8)

Minor comments

Minor comment (1): L160: Was the microbiology laboratory opened 24/7 for processing screening specimens and notification of positive results?

REPLY:
Processing of screening and clinical specimens was carried out 24hrs a day, 7 days a week but reports of positive samples were only made between 9am and 5pm daily
Laboratory methods amended to reflect this information (lines 197 and 199).

Minor comment (2): L248: The high proportion (38%) of community-associated MRSA bacteremia deserves further comments (see also Ref 53, Wyllie DH, BMJ 2005).

REPLY:
We acknowledge the high-proportion of community-associated MRSA bacteraemia in our study (38%), exceeding the 24% reported previously by Wyllie et al with similar definitions. [BMJ 2005; 331(7523):992-7]. As with this study we note the importance of prior healthcare contact in those bacteraemias currently defined as "community-associated", and note in our discussion that the "decline in importation pressure during universal surveillance suggested interruption of

connections between prevalence of MRSA in hospital and community populations, focused in frequently admitted patients." (line 578-580).
We have previously described the importance of strains isolated in hospitals in driving community epidemiology [MacKenzie et al. J Hosp Infect 2007;67(3):225-31]. To this extent separation of community and healthcare associated infections may be somewhat arbitrary. Nevertheless in our discussion we note that: "given the role of social and risk-networks in sustaining S.aureus transmission, broadening control of SAB to the community is likely to require the commitment of multiple agencies and healthcare providers" (line 629-631)
We have amended results to support the relevance of prior healthcare contact in "community-associated" bacteraemias:
(Lines 302-304) "Comparing community with hospital-associated bacteraemia there were no significant differences in demographics or rates of previous admission in the last 12 months (41% vs. 37%; P = 0.10)"

Minor comment (3): Table 2: Hospital-associated SAB increases the risk of 30-d mortality (OR=1.56) but is protective against inpatient mortality (HR=0.44). This surprising observation should be checked for accuracy and plausibility and (if true) deserves a careful explanation.

REPLY:
Apologies, incorrect coding meant that this Hazard ratio represents risk of inpatient death for COMMUNITY vs. hospital acquired SAB. Therefore the corrected hazard ratio (HR) for HOSPITAL vs. community associated is the inverse of this and now reads as: "2.27 (1.67 to 2.27)" (table 2)

With many thanks for this opportunity to respond to the peer-review.
Yours sincerely,
Dr. Tim Lawes
on behalf of the co-authors.

Other corrections identified by the co-authors:
We draw attention to some errors made in the original manuscript:
1. The duration of the pathfinder study was 32 months (August 2008 – March 2011) not 1 year (line 119)
2. The universal screening strategy intended decolonisation of ALL patients found to be MRSA positive not those admitted to high-risk specialities only. (lines 17,124-5, 643)

VERSION 2 - REVIEW

REVIEWER	**Reviewer 3: Harbarth, Stephan**
REVIEW RETURNED	29/3/12

THE STUDY	
RESULTS & CONCLUSIONS	
REPORTING & ETHICS	
GENERAL COMMENTS	This MS has now been much improved and the authors have adequately addressed most of my comments and suggestions. They have performed additional data collection and analysis that increases the strength of this paper. Could be a good reason to ask for an editorial, since the results of this study have important policy implications for MRSA control in the UK.