



Trends in *Staphylococcus aureus* bacteraemia and impacts of universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time-series intervention analysis

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000797
Article Type:	Research
Date Submitted by the Author:	03-Jan-2012
Complete List of Authors:	Lawes, Timothy; Raigmore Hospital, Paediatrics Edwards, Becky; Aberdeen Royal Infirmary, Medical Microbiology López-Lozano, José-Maria; Hospital Vega Baja, Epidemiology Gould, Ian; Aberdeen Royal Infirmary, Medical Microbiology
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Infection control < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, MICROBIOLOGY

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Trends in *Staphylococcus aureus* bacteraemia and impacts of universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time-series intervention analysis

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Keywords: Methicillin Resistance, Staphylococcus aureus, bacteraemia, mass screening, intervention studies, cohort studies, inpatients

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Word Count:

Abstract : 298

Background : 356

Methods : 1398

Results : 1100

Discussion : 1474

Main Manuscript (excluding abstract) : **4328**

ARTILCE SUMMARY**Article focus**

- This study describes the changing epidemiology of MRSA and MSSA bacteraemia in a large inpatient population from Scotland over a five year period
- Secondly, it evaluates the impact of universal MRSA admission screening on hospital-wide rates of MRSA bacteramia.

Key messages:

- Recent declines in clinical burdens from *S.aureus* bacteraemia in North East Scotland were attributable to a reduction in invasive MRSA infections.
- 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.
- Strategies to reduce clinical burdens from MSSA bacteraemia are required if progress towards national targets for all *S.aureus* bacteraemia is to be sustained.

Strengths and limitations

- Without a contemporary control, this study did not prove causality but an association between universal admission screening and rates of MRSA bacteraemia.
- ARIMA modelling accounted for the non-independence of data and stochastic elements in time-series of infections, and the dynamic effects of changes in other aspects of care.
- Findings may be limited to large public hospitals with intensive care units and endemic MRSA but low rates of MRSA infection.

1 ABSTRACT

2
3 **Objectives:** To describe secular trends in *Staphylococcus aureus* bacteraemia in an inpatient
4 population, and to assess the impact of universal MRSA admission screening on MRSA bacteraemia.
5

6 **Design:** Retrospective cohort study linking microbiology, patient management and health
7 intelligence databases and time series intervention analysis using transfer function modelling.
8

9 **Setting:** Teaching hospital in North East Scotland.
10

11 **Population:** All patients admitted to Aberdeen Royal Infirmary between 1st January 2006 and 31st
12 December 2010: N = 420,452 admissions and 1,430,052 acute occupied bed days (AOBDs).
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14 **Intervention:** Universal admission screening programme for MRSA introduced in August 2008 (NHS
15 Scotland pathfinder project), incorporating isolation and selective decolonisation.
16

17 **Main outcome measures:** Hospital-wide prevalence density, hospital-associated incidence density
18 and death within 30 days of MRSA or MSSA bacteraemia.
19

20 **Results:** Prevalence density of all *S. aureus* bacteraemia declined by 41% from 0.73 to 0.50 cases
21 1000 AOBDs⁻¹ ($P=0.002$ for trend) and 30-day mortality from 26% to 14% ($P=0.013$) between 2006
22 and 2010. Significant reductions were observed in MRSA bacteraemia only. The percentage of
23 overnight admissions screened for MRSA rose from 43% at baseline (selective screening) to over
24 90% within four months of universal surveillance, with 3.1% colonised or infected at admission. In
25 transfer function models accounting for changes in other aspects of care, universal screening was
26 associated with a 28% reduction in prevalence density of MRSA bacteraemia (-0.053 cases 1000
27 AOBDs⁻¹; $P<0.001$); a 62% fall in hospital-associated incidence density (-0.062 cases 1000 AOBDs⁻¹; P
28 = 0.014) and a 56% reduction in 30-day mortality (-18.8%; $P=0.021$). Rates of MSSA bacteraemia
29 were unaffected.
30

31 **Conclusions:** Declining clinical burdens from *S. aureus* bacteraemia were attributable to reductions
32 in MRSA infections. Universal MRSA admission screening was associated with a decrease in MRSA
33 bacteraemia and associated early mortality. Control of MSSA bacteraemia remains an important
34 priority in Scotland.
35

INTRODUCTION

Staphylococcus aureus is an important cause of serious, invasive, and health care-associated infections worldwide.[1] In high-income countries it remains a leading cause of community and nosocomial bacteraemia,[2] associated with mortality rates of 20-50%,[3,4] and large economic burdens.[5] In the UK, dramatic increases in *S. aureus* bacteraemia (SAB) during the 1990s were attributed to methicillin resistant *S. aureus* (MRSA)[3,6] and healthcare exposures,[7] engendering aggressive public health responses.[8] A decade of national mandatory surveillance of both methicillin sensitive *Staphylococcus aureus* (MSSA) and MRSA bacteraemia has suggested impacts from infection control measures,[9,10] but there remains over 12,000 cases annually.[11,12]

Despite a steep reduction in MRSA bacteraemia from a peak in 2003/4, rates of MSSA bacteraemia have remained relatively stable.[11,12] Reasons for this MRSA specific decline are not fully understood.[9,10] Meanwhile, studies assessing the importance of methicillin resistance to outcomes after SAB have yielded conflicting results.[3,4,13-18] These uncertainties are reflected in different public health approaches: England and Wales implemented performance targets for reducing MRSA bacteraemia only,[9] while NHS Scotland's strategy aimed to reduce all SAB to 70% of 2005/6 by 2010.[19] Some authors have warned that policy focusing on MRSA alone, may have unintended adverse effects on control of MSSA.[20] It is therefore important to understand the evolving epidemiology of both MRSA and MSSA bacteraemia.[21]

UK policy on reducing burdens from MRSA has advocated admission screening, with subsequent decolonisation and isolation, despite weaknesses in evidence.[22-25] Studies on MRSA screening have generally assessed impacts on bacteraemia by surveillance in high-risk groups,[26,27] while studies of universal surveillance have taken all MRSA infections as the primary outcome.[25,28] In 2008, a universal screening strategy was piloted in three NHS Scotland trusts[29,30] providing an opportunity to assess effects on rates of MRSA bacteraemia, compared to a previous strategy of selective screening in high-risk environments.

This study aimed to describe the changing clinical epidemiology of SAB in a large inpatient population over a five year period, and to evaluate the impact of introducing universal MRSA admission screening on MRSA bacteraemia. Our pre-specified null-hypothesis was that universal screening would not significantly reduce rates of bacteraemia, after accounting for prior trends and changes in other aspects of care.

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3 70 **METHODS**
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72 **Study design:**

73 This retrospective cohort study described secular trends in *S.aureus* bacteraemia in all admissions to
74 Aberdeen Royal Infirmary (ARI) between 2006 and 2010. A quasi-experimental before-and-after
75 design used time series data from the same period to assess the impact of introducing universal
76 admission surveillance on MRSA bacteraemia (fig 1). Controls were historic trends in MRSA
77 bacteraemia and concurrent trends in MSSA bacteraemia.

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79 **Setting:**

80 ARI is a tertiary referral centre and acute teaching hospital (1000 beds, 85,000 annual admissions),
81 serving a population of 500,000 in North East Scotland (*NHS Grampian*). It provides a full range of
82 acute medical and surgical services with a 16-bedded intensive care unit (800 admissions yr⁻¹) and a
83 cardiac intensive care unit (6 beds, 600 admissions yr⁻¹). Microbiology services also serve the on-site
84 185-bedded maternity and 85-bedded children's hospitals.

85

86 **Admission Screening Intervention:**

87 Universal admission screening for MRSA was introduced in NHS Grampian in August 2008 as part of
88 an NHS Scotland pathfinder project detailed elsewhere.[29,30] This one year pilot study tested a
89 strategy suggested as most clinically- and cost-effective by an NHS Scotland Health Technology
90 Assessment (supplemental file 1).[29] This involved, screening of all overnight admissions to acute
91 specialities (excluding obstetrics, paediatrics and psychiatry) by nasal (and wound or device as
92 necessary) swabs; isolation or cohorting of all patients with known or new colonisation or infection
93 with MRSA; and decolonising of MRSA-positive patients admitted to 'high-risk' specialities.
94 Decolonisation therapy included five days of daily bodywash with 4% chlorhexidine gluconate and
95 thrice-daily mupirocin nasal ointment. Patients were re-swabbed a minimum of two-days after
96 decolonisation and could be removed from isolation on receipt of three successive negative swabs,
97 taken ≥48 hours apart. Elective patients were screened at pre-admission assessment or on
98 admission. Compliance with screening and infection control protocols was monitored. Prior to the
99 intervention MRSA screening was performed on selected high-risk patients only, including intensive
100 care and elective surgical admissions, with an identical strategy of isolation and decolonisation.

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104 **Outcomes and potential confounders:**

105 *S.aureus* bacteraemia was defined as the isolation of any *S. aureus* from ≥ 1 blood culture bottle.
 106 Cultures from the same patient within 14 days of the original isolate were considered to represent
 107 the same episode. Patients could be included more than once in analysis for different episodes.
 108 Hospital-associated (HA-) bacteraemia was defined as isolation of *S. aureus* from blood cultures > 48
 109 hours after admission or within 14 days of discharge.

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 111 The primary outcome measure was prevalence density of MRSA and MSSA bacteraemia (all cases of
 112 bacteraemia per 1000 acute occupied bed days, AOBDDs). Secondary outcomes are detailed in box 1.
 113 Secular trends in longer-term outcomes were also investigated with recurrence expressed as
 114 episodes per 1000 patient-months to avoid follow-up bias.

115
 116 In examining secular trends and the impacts of universal MRSA admission screening, we considered
 117 changes in other aspects of care and case-mix including: length-of-stay,[3,13] bed-occupancy,[7]
 118 patient age,[3,4,13] admitting department,[3] hand-hygiene,[9] and antibiotic usage.[31-33]

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Box 1: Definitions of outcomes

- **Prevalence** = $\frac{\text{All episodes of } S. \text{ aureus bacteraemia (SAB)} \times 1000}{\text{All admissions}}$
- **Prevalence density** = $\frac{\text{All episodes of } S. \text{ aureus bacteraemia}}{\text{Acute Occupied Bed Days}} \times 1000$
- **Hospital associated incidence** = $\frac{\text{First ever episode of SAB } > 48 \text{ hrs of admission}}{\text{All admissions } \geq 48 \text{ hours}} \times 1000$
- **Hospital-associated incidence density** = $\frac{\text{First ever episode of SAB } > 48 \text{ hrs of admission}}{\text{Acute Occupied Bed Days}} \times 1000$
- **30-day mortality** - deaths from any cause within 30 days of SAB irrespective of discharge status.
- **Inpatient mortality** - deaths from any cause within the same hospital admission, without intervening discharge. Transfers without discharge were included as a single admission episode.
- **Readmission** – readmission to inpatient care at any hospital within 14 days of discharge from admission in which *S. aureus* bacteraemia occurred.
- **Treatment failure** – any repeat blood culture isolate of *S.aureus* within 6 months of initial isolate.
- **Recurrence** – repeat blood culture isolate of *S.aureus* with the same susceptibility to methicillin after 6 months or more from initial isolate.

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122 **Study population**

123 All patients admitted to medical, surgical, paediatric, and maternity services at ARI between 1st
 124 January 2006 and 31st December 2010 were eligible for inclusion in the study. This period was
 125 chosen as it included the time frame stated in national targets for reducing rates of SAB. A time
 126 series of 60 months with equivalent baseline and intervention periods (31 and 29 months), also
 127 facilitated a robust time-series analysis.[34] Outpatients in all specialities were excluded. Admissions
 128 resulting in death or discharge within 24 hours were retained in the main analysis so as to capture
 129 burdens from community-associated bacteraemia. Patients at risk of incident hospital-associated
 130 bacteraemia were those hospitalised for at least 48 hours without previous documented SAB. Follow

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3 131 up was until in-hospital death, 180 days from bacteraemia or a minimum of two weeks post-
4 132 discharge (whichever was longest), and ended on 15th June 2011.

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8 134 **Data collection**

9 135 Electronic laboratory records were screened to identify admission screening swabs, previous or
10 136 current MRSA colonisation or infection, episodes of *S.aureus* bacteraemia and location of sampling.
11 137 Patient identifiers were used to identify multiple samples from the same patient.

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14 139 Health intelligence databases provided data on demographics, admission details and mortality for all
15 140 admissions between 2006 and 2010. Aggregated data on bed-occupancy were also provided by
16 141 month and department. For episodes of bacteraemia, data were triangulated using the hospital's
17 142 Patient Management System. Numbers of admissions within the last 12 months and age were taken
18 143 as a proxy of patients' baseline health.

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21 145 Details on the percentage of antibiotic defined daily doses (DDDs) involving "4C" antibiotics
22 146 (Ciprofloxacin, Cephalosporins, Clindamycin, Co-amoxiclav) and hand-hygiene (Litres of alcohol gel
23 147 dispensed per 1000 AOBDS) were ascertained from pharmacy and infection control departments.

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26 149 Use of routinely collected data meant an almost complete dataset. Data on outcomes after
27 150 discharge were missing for six patients (0.7%) with SAB and for obstetric or neonatal inpatients.
28 151 Outcomes were explored using a complete-case analysis or departments with complete data. Data
29 152 on antibiotic use and hand-hygiene were only available from April 2007 and April 2008 respectively
30 153 and were therefore not introduced as a dynamic explanatory factor in time-series analysis.

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33 155 **Laboratory methods:**

34 156 Screening swabs were tested by latex slide test after plating on chromogenic agar (Brilliance - Oxoid,
35 157 UK), followed by confirmatory coagulase test. Antibiotic sensitivities were evaluated by disc-
36 158 diffusion test. After confirmation by laboratory staff, results were made immediately available on an
37 159 electronic laboratory reporting system. Positive MRSA screens were verbally reported to nursing
38 160 staff on relevant wards and infection control teams. Turnaround time was typically <24 hours.

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41 162 All *S.aureus* blood isolates were identified initially by agglutination, using the ProlexTM – Blue Staph
42 163 Latex Kit (Pro-Lab), and subsequently by a VitekTM instrument, using custom made Staphylococcus
43 164 sensitivity cards (Biomérieux).

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3 165 **Statistical analysis**

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6 167 Clinical epidemiology and secular trends:

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9 169 Comparisons between characteristics of MRSA and MSSA and non-bacteraemic inpatient cohorts
10 were made by χ^2 , Mann-Whitney U or independent-samples *t*-tests. Univariate linear or logistic
11 regression was used to model associations between risk factors and rates of SAB. An indirect
12 standardised mortality ratio (SMR) was calculated to explore excess mortality in SAB, using all ARI
13 inpatients between 2006 and 2010 as the reference population, and standardising by age, gender
14 and speciality. Attributable mortality, defined as the excess mortality caused by bacteraemia, was
15 calculated using matched controls from this inpatient reference group, as crude mortality rate in
16 controls *minus* crude mortality rate after bacteraemia.
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22 178 Restricting analysis to the *S.aureus* bacteraemia cohort, determinants of 30-day mortality were
23 explored by multivariate logistic regression. *A priori* determinants of methicillin sensitivity, month
24 and demographics were included in a multivariate model alongside significant variables from
25 univariate analysis ($p < 0.10$). Interaction terms were generated for terms significantly associated by
26 Spearman rank correlation but retained only where contributing to model fit. Competing hazards of
27 inpatient mortality and being discharged alive were further explored with multivariate Cox-
28 regression, with censoring at date of discharge or death respectively. Length of stay was included as
29 a time-dependent determinant of mortality after SAB.[16]
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32 187 Secular trends in demographics and clinical characteristics of *S. aureus* bacteraemia cohorts, were
33 evaluated by logistic or linear regressions, with month of isolate as the sole explanatory variable.
34 Trends in rates were examined using Poisson regression, with Poisson distribution, log-link function
35 and Ln(AOBDs) as the offset. Monthly count of bacteraemia or death was the dependent variable
36 and month of study the independent variable. Multivariate Poisson regression models assessed
37 secular trends after adjusting for changes in case-mix.
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40 194 Impacts of universal MRSA admission screening:

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43 196 We conducted intervention analyses to model the effects of universal screening and dynamic
44 explanatory factors on MRSA bacteraemia using the Linear Transfer Function identification method
45 suggested by Pankratz.[35] After ensuring stationary series, an initial transfer function model was
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3 199 created, with 6 lags for all explanatory variables and an autoregressive term of order 1. An iterative
4 200 process of eliminating non-significant terms, and identifying further autoregressive or moving
5 201 average terms for parts of the model remaining unexplained, determined the most parsimonious LTF
6 202 model. Model parameters were estimated using unconditional least squares and goodness-of-fit
7 203 evaluated by R^2 . Finally, diagnostic checks were used to determine whether models adequately
8 204 represented times series data. These included checking; the statistical significance of parameters, AR
9 205 parameter stationarity and MA parameter invertibility, and ACF and PACF of residuals to ensure
10 206 remaining variability was random. Analysis of concurrent trends in MSSA bacteraemia controlled for
11 207 unidentified aspects of care or infection control affecting the clinical epidemiology of SAB.
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13 209 Intervention analysis was conducted using SCA software (Chicago, IL, USA, 1992) as described by Liu
14 210 and Hudak.[36] All other analyses were performed using SPSS 19.0 for windows.
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237 **RESULTS**

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239 **Descriptive epidemiology**

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241 Cohort and rates of *S.aureus* bacteraemia:

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243 There were 430,452 admissions to ARI between 2006 and 2010 representing 1,430,052 acute
 244 occupied bed days (8% in ICU). The total number of days of follow-up was 7,578,805: median, 181
 245 days (range 180 to 355 days) for episodes of SAB, and 16 days (14 to 129 days) for other admissions.

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247 867 episodes of *S. aureus* bacteraemia were identified in 795 patients, including 208 cases of MRSA
 248 bacteraemia (24%). 62% of MRSA and 44% of MSSA bacteraemia were hospital-associated ($P <$
 249 0.001). Overall prevalence density of SAB was 0.61 per 1,000 AOBs and HA-incidence density was
 250 0.29 per 1,000 AOBs. Prevalence and HA-incidence were 2.1 per 1000 admissions and 3.0 per 1000
 251 admissions, respectively. Patients with SAB were more likely to be male, older and admitted to
 252 medical or ITU settings than the remainder inpatient population (table 1).

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Table 1: Characteristics of inpatient cohorts with and without *S.aureus* bacteraemia, 2006-2010

Characteristics	Cohort				P-value*	
	None n = 419,585	All SAB n = 867	MSSA n = 659	MRSA n = 208	MRSA v MSSA	All SAB v None
Overnight admissions	262,412 (63%)	864 (99%)	656 (99%)	206 (99%)	0.801	<0.001
Hospital associated (onset >48hrs)	137,520 (33%)§	416 (48%)	287 (44%)	129 (62%)	<0.001	<0.001
Demographics						
Gender (female)	242,668 (58%)	287 (33%)	227 (34%)	60 (29%)	0.14	<0.001
Mean age in years (SD)	56 (5)	58 (22)	55 (22)	65 (18)	<0.001	<0.001
Clinical background						
Admitting department					<0.001	<0.001
Medical	130,209 (31%)	600 (69%)	471 (72%)	129 (62%)	0.010	<0.001
Surgical	173,851 (41%)	173 (20%)	118 (18%)	55 (26%)	0.007	<0.001
ITU	6206 (1%)	60 (7%)	37 (6%)	23 (11%)	0.007	<0.001
Paediatrics / neonatal	47726 (10%)	27 (4%)	26 (4%)	1 (1%)	0.008	<0.001
Maternity	61593 (15%)	7 (1%)	7 (1%)	0 (0%)	0.136	<0.001
Previous <i>S. aureus</i> bacteraemia	- ^a	73 (9%)	49 (8%)	24 (12%)	0.068	-
MRSA colonisation at admission (%) ^b	8134 (4.3%)	160 (19%)	72 (11%)	88 (43%)	<0.001	<0.001
Admission within past 12 months	- ^a	522 (60%)	366 (56%)	156 (75%)	<0.001	-
Median (IQR) time from admission to bacteraemia, days	-	2 (0 to 9)	1 (0 to 7)	7 (0 to 19)	0.002	-
Outcomes						
30-day mortality	-	173 (20%)	110 (17%)	63 (30%)	<0.001	-
In hospital death	7165 (2%)‡	209 (25%)‡	134 (21%)‡	75 (36%)‡	<0.001	<0.001
Median (IQR) length-of-stay, days	3.8 (3.4 -3.9)	20 (11 to 39)	19 (10 to 37)	27 (14 to 52)	<0.001	<0.001
Readmission (≤ 14 days)†	26,534 (8%)‡	119 (19%)‡	86 (17%)‡	33 (25%)‡	0.036	<0.001
Treatment failure	-	42 (4.8%)	31 (4.7%)	13 (6.3%)	0.732	-
Recurrence rate (100 patient yrs ⁻¹)	-	0.78	0.81	1.26	0.627	-

255 Data are n (%), mean (SD), or median (IQR). § Patients without bacteraemia admitted > 48hrs. * χ^2 , Mann-Whitney U, or independent-
 256 samples t-test. ^a data not available. ^b % eligible admissions. † In those alive at discharge, ‡ Excluding admissions to maternity and neonatal
 257 departments (data not available, n = 65,849) and episodes of SAB with incomplete data (n=6) associated with survival at discharge.

258 There were strong associations between rate of SAB and age, days since admission and length-of-
 259 stay (fig 2). Patients colonised with MRSA at admission were 17 times more likely to develop
 260 hospital-associated MRSA bacteraemia (0.78 cases 1000 AOBDS⁻¹) than those not colonised (0.05
 261 cases 1000 AOBDS⁻¹); crude OR (95% CI) = 17.2 (15 to 20), *P* < 0.001. Methicillin-resistant
 262 bacteraemia occurred more frequently in ITU or surgical settings, older patients, following MRSA
 263 colonisation and after prolonged or recent admission.

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Clinical outcomes:

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268 Inpatient and 30-day all-cause mortality rates after SAB were 25% and 20% respectively, and
 269 outcomes were consistently worse than for patients without bacteraemia (table 1). Inpatient
 270 mortality was over six-times higher than expected in the SAB cohort (SMR, 95% CI 6.4, 5.7 to 7.0).
 271 Attributable inpatient mortality was 20% (31% for MRSA and 17% for MSSA bacteraemia).

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273 Methicillin resistance was associated with longer length-of-stay and increased readmission rates.
 274 The crude odds ratio for mortality within 30 days of isolation of MRSA versus MSSA was 2.15 (95% CI
 275 1.50 to 3.08; *p* < 0.001). A final multivariate logistic regression model confirmed age, month of study
 276 (secular trend) and hospital-associated infection as independent risk-factors for 30-day mortality,
 277 however after adjustment for these covariates methicillin resistance was not a significant
 278 determinant (OR, 95% CI: 1.38 (0.93-2.06); *p* = 0.112) – table 2.

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Table 2: Multivariate logistic and Cox regression models of risk factors for 30-day mortality, inpatient mortality and discharge alive

	30 day mortality ^a		Inpatient mortality ^b		Discharge alive ^c	
	OR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
MRSA	1.38 (0.93 to 2.06)	0.112	1.47 (1.09 – 1.98)	0.012	1.09 (0.89 - 1.33)	0.416
Gender (female)	1.41 (0.96 to 2.04)	0.075	1.18 (0.89-1.58)	0.244	1.06 (0.89-1.25)	0.536
Age (10 yrs ⁻¹)	1.79 (1.58 to 1.97)	<0.001	1.42 (1.29 - 1.57)	<0.001	0.86 (0.83-0.90)	<0.001
Hospital associated SAB	1.56 (1.08 to 2.26)	0.018	0.44 (0.33-0.60)	<0.001	1.50 (1.26-1.80)	<0.001
Secular trend per 3 months	0.87 (0.77 to 0.99)	0.028	0.92 (0.83-1.02)	0.094	-	-
Length of stay (7 days ⁻¹)*	-	-	1.02 (1.01 to 1.03)	<0.001	0.98 (0.97-0.98)	<0.001
ITU admission	-	-	-	-	0.70 (0.59-1.00)	0.052

OR = odds ratio, HR = Hazards Ratio, CI = confidence interval.

a Logistic regression for 30-day mortality. This model had good calibration (Hosmer-Lemeshow goodness of fit *p* = 0.93) and discrimination (area under receiver operator characteristic curve = 0.77).

b Cox (proportional hazards) regression. Model χ^2 (df) = 115 (6); *P* < 0.001

c Cox (proportional hazards) regression. Model χ^2 (df) = 265 (6); *P* < 0.001

* Entered as a time-dependent covariate.

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 288 In a multivariate Cox-regression model, methicillin resistance was associated with increased hazard
 289 of inpatient death (adjusted HR = 1.47, 95% CI 1.1 to 2.0; *P*=0.012) – table 2, but there was no
 290 significant difference in discharge rate in survivors. Age, duration of hospitalisation and hospital-
 291 associated infection were independent predictors of hazard of inpatient death.

292 **Secular trends:**

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294 Trends in *S.aureus* bacteraemia and clinical outcomes:

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296 Prevalence density of all SAB declined from 0.73 1000 AOBDS⁻¹ to 0.50 1000 AOBDS⁻¹ between
 297 January 2006 and December 2010, (-0.07 year⁻¹, 95% CI -0.11 to -0.02); a decrease of 41% ($P=0.002$
 298 for trend). Prevalence density of MRSA bacteraemia fell 73% from 0.26 to 0.07 1000 AOBDS⁻¹ ($P <$
 299 0.001) and HA-incidence density 82%, from 0.16 to 0.03 1000 AOBDS⁻¹ ($P <0.001$), however rates of
 300 MSSA bacteraemia were unchanged (Fig 3). An increasing proportion of MRSA bacteraemia was
 301 associated with previous colonisation or infection (table 3). Case-mix within the SAB cohort was
 302 otherwise stable.

303

304 Over the five year period, 30-day mortality declined from 26% to 14% (-46%; $P=0.013$ for trend) and
 305 inpatient mortality from 29% to 18% (-38%; $P = 0.045$). 30-day mortality after MRSA bacteraemia
 306 declined from 37% to 13% ($P = 0.027$) but no significant change was observed in mortality after
 307 MSSA bacteraemia (fig 3). By 2010, 90% of episodes of bacteraemia and 86% of associated inpatient
 308 deaths were attributable to MSSA.

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Table 3: *S. aureus* bacteraemia by methicillin sensitivity, demographic and clinical characteristics and outcomes by year of study: N (%), Mean (SD) or median (IQR).

	Year					p value*
	2006 n = 218	2007 n = 188	2008 n=151	2009 n = 152	2010 n = 158	
Frequencies						
% of bacteraemia involving:						<0.001
MSSA (%)	156 (72%)	140 (74%)	100 (66%)	121 (80%)	142 (90%)	
MRSA (%)	62 (28%)	48 (26%)	51 (34%)	31 (20%)	16 (10%)	
Demographics						
Gender (female)	66 (30%)	62 (33%)	55 (36%)	55 (36%)	49 (30%)	0.603
Age (years)	57 (22)	56 (21)	58 (22)	56 (22)	57 (20)	0.744
Clinical characteristics						
Admitting department ITU (%)	17 (8%)	11 (6%)	12 (9%)	12 (8%)	8 (5%)	0.501
Hospital Associated (%)	112 (51%)	108 (60%)	69 (46%)	75 (50%)	92 (58%)	0.750
Previous <i>S.aureus</i> bacteraemia, any (%)	10 (5%)	18 (10%)	19 (13%)	14 (10%)	12 (8%)	0.787
Previous MRSA colonisation or infection (%)†	24 (39%)	24 (50%)	29 (57%)	16 (52%)	10 (63%)	0.056
Admission within past 12 months (%)	134 (62%)	101 (54%)	92 (61%)	96 (63%)	99 (62%)	0.503
Outcomes						
30-day mortality	52 (24%)	39 (22%)	31 (21%)	27 (18%)	24 (15%)	0.013
In hospital death	63 (29%)	45 (25%)	34 (23%)	34 (23%)	33 (21%)	0.045
Length-of-stay (days)	19 (10-41)	17 (7-36)	27 (12-36)	22 (12-44)	19 (12-42)	0.508
Readmission (≤ 14 days)	25 (17%)	19 (14%)	25 (22%)	31 (27%)	19 (16%)	0.291

* Linear and logistic regressions with month of study as sole explanatory variable. † Data presented for MRSA bacteraemia only.
 CI = Confidence Intervals, MRSA = methicillin-resistant *Staphylococcus aureus*, AOBDS = acute occupied bed days

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3 313 Trends in inpatient case mix:

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6 315 There were no significant trends in admitting speciality, or gender among inpatients over the five
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8 316 year period. Mean age of adult and all patients increased between 2006 and 2010 (+1.7, 95% CI: +1.3
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10 317 to +2.2 years, for all patients; $P < 0.001$), while mean length-of-stay (-1.3, -1.6 to -1.11 days; $P <$
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12 318 0.001) and weighted average bed occupancy (-2.6%, -4.8% to -0.4%; $P = 0.021$) declined
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14 319 (supplemental file 2). Consideration the associations noted earlier, these changes represented
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16 320 opposing upward (increasing age), and downward (reduced length-of-stay, bed occupancy)
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18 321 pressures on rates of bacteraemia. Secular trend in MRSA prevalence density ($P = 0.03$ for trend) and
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20 322 HA-incidence density ($P = 0.01$) remained significant after adjusting for these changes in case-mix in
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22 323 a multivariate Poisson regression model.

23 324

24 325 **Impacts of universal MRSA admission screening**

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27 328 Screening adherence and importation pressures:

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29 330 43% of all adult, non-obstetric overnight admissions and 84% of eligible patients in high-risk
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31 331 environments were screened prior to routine surveillance. During universal surveillance 87% of
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33 332 eligible patients were screened ($n = 86,890$). A target of 90% adherence was achieved within four
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35 333 months of initiation and sustained thereafter, excluding a special study period in which trial of
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37 334 additional throat, perineum and axillae swabs and discharge screening reduced patient participation
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39 335 (fig 4). MRSA prevalence at admission (importation pressure) steadily declined during the period of
40
41 336 universal surveillance, averaging 3.1%, with 1.7% known to be previously colonised or infected with
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43 337 MRSA. There was an increase in episodes of MRSA bacteraemia preceded by screening at admission
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45 338 (95% vs. 81%; $P = 0.008$) and identified as being colonised at admission (56% vs. 38% of all
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47 339 admissions; $P = 0.013$) after introduction of universal surveillance.

48 340

49 341 Patient characteristics by study period:

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51 343 Case-mix remained stable between periods of selective screening and universal admission screening
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53 344 – table 4. However, there were significant reductions in bed occupancy, length-of-stay and use of
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55 345 “4C” antibiotics ($P < 0.03$ for all comparisons). Alcohol-gel was introduced in 2002 with no significant
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57 346 change in usage noted after introduction of screening, although baseline data were limited. A
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59 347 significant decline in “4C” usage was only observed after 10 months of universal screening, with a
60
348 reduction from 38% to 20% within 4 months.

349 **Table 4: Characteristics pre and post-intervention**

Characteristics	Selective screening only	Universal admission screening
Admission data		
No. of all admissions	210,745	209,707
No. of Acute Occupied bed days (at risk)	748,569	681,483
Case-mix		
Mean (SD) age all patients, years	45.9 (0.45)	47.3 (0.57)
Mean (SD) age, ITU, medical and surgical adult services, years	55.3 (0.41)	56.4 (0.56)
Gender: n (%) of all admissions		
Female,	122,538 (58%)	120,417 (57%)
Male	88,207 (42%)	89,290 (43%)
Speciality, n (%) of all admissions		
Surgical	84,216 (40%)	89,808 (43%)
Medical	65,711 (31%)	65,098 (31%)
ITU	3312 (2%)	2954 (1%)
Maternity	31,862 (15%)	29,738 (14%)
Paediatric / neonatal	24606 (12%)	23,147 (12%)
Other aspects of care		
Mean (SD) length of stay in hospital, days	3.96 (0.23)	3.33 (0.51)
Bed-occupancy (% all available beds occupied)	79%	77%
"4C" Antibiotic usage (% of all antibiotic DDDs / 1000 AOBDDs)*	41%*	29%
Hand-hygiene (Dispensed alcohol gel in Litres / 1000 AOBDDs)†	38.1†	37.2
MRSA Screening, colonisation and infections		
Number (%) of overnight admissions‡ screened for MRSA	43,158 (43%)	86,890 (87%)
Number (%) of overnight admissions‡ screen positive for MRSA	2909 (3.5%)	2694 (3.1%)
Number (‰) of admissions with any MRSA infection	1891 (9 ‰)	798 (4‰)
Clinical burdens from <i>S.aureus</i> bacteraemia		
Prevalent MSSA bacteraemia (n)	353	306
Prevalent MRSA bacteraemia (n)	144	64
Hospital-associated incident MRSA bacteraemia (n)	89	29
Deaths within 30 days MSSA(n)	62	48
Deaths within 30 days MRSA(n)	51	12

350 DDDs = Daily Defined Doses; AOBDDs = Acute Occupied Bed Days; ARI = Aberdeen Royal Infirmary; "4Cs" are Ciprofloxacin, Cephalosporins,
351 Clindamycin, Co-amoxiclav.*Data available from April 2007 only (44 months). ‡ Adult, non-obstetric patients only. † Data available from
352 Apr 2008 only (35 months).
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356 Time series intervention analysis:

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358 In multivariate transfer function models, adjusting for changes in other aspects of care and prior
359 trends (table 5 and fig 5), universal screening was associated with a 28% reduction in prevalence
360 density (absolute change, 0.189 to 0.136 (-0.053) cases 1000 AOBDDs⁻¹; P <0.001), a 62% reduction in
361 hospital-associated incidence density (0.100 to 0.048 (-0.062) cases 1000 AOBDDs⁻¹; P = 0.014) and a
362 56% fall in 30-day mortality (34% to 15.2% (-18.8%); P =0.021). Final models explained 19-48% of
363 variance but in all models residuals corresponded to white-noise. Using targeted screening as the
364 comparison, during universal screening the number needed to screen (NNS) to avoid one episode of
365 MRSA bacteraemia was 1863.

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367 No significant associations were found between universal screening and rates of MSSA bacteraemia
368 and %SAB involving MRSA fell by 38% (from 28.6% to 17.6% (-11.0%); P = 0.014).

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374**Table 5: Multivariate transfer function models[†] for MRSA bacteraemia taking into account introduction of universal admission screening and changes in other aspects of care (January 2006 to December 2010)**

Term	Order ^a	Parameter ^b (SE)	T-ratio	P-value
(a) Prevalence density of MRSA bacteraemia (cases per 1000 AOBDS) , R2 = 0.48				
AR ^c	6	-0.315 (0.116)	-2.71	0.007
Length-of-stay ^e	1	0.044 (0.003)	16.55	<0.001
Universal MRSA screening intervention	0	-0.053 (0.014)	-3.83	<0.001
(b) Hospital-associated incidence density of MRSA bacteraemia (cases per 1000 AOBDS) R2 = 0.35				
Constant	0	0.100 (0.019)	5.43	<0.001
AR ^c	1	0.476 (0.115)	4.13	<0.001
Universal MRSA screening intervention	0	-0.062 (0.025)	-2.46	0.014
(c) % SABs involving MRSA (%), , R2= 0.35				
AR ^c	1	0.293 (0.129)	2.27	0.023
MA ^d	9	-0.457 (0.132)	-3.47	<0.001
Bed-occupancy (%) ^f	4	0.36 (0.046)	7.89	<0.001
Universal MRSA screening intervention	0	-11.0 (4.53)	-2.44	0.014
(d) 30-day mortality (%) after MRSA bacteraemia, R2 = 0.19				
AR ^c	6	0.349 (0.150)	2.33	0.02
Bed-occupancy (%) ^f	2	0.454 (0.090)	5.05	<0.001
Universal MRSA screening intervention	0	-18.8 (8.16)	-2.3	0.021

[†]All series stationary before model identification. Residuals in all models corresponded to white-noise.^aDelay necessary to observe the effect (in months).^bSize and direction of effect.^cAR, autoregressive term representing past values of bacteraemia rates or mortality.^dMA, moving average term representing abrupt changes in bacteraemia rates or mortality in immediate future.^eLength-of-stay, average inpatient length-of-stay by month,^f% Bed occupancy, average bed-occupancy weighted by admitting department, by month.375
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402 Discussion

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405 This retrospective cohort study identified a 41% decrease in prevalence density of all *S.aureus*
406 bacteraemia in an inpatient population from Scotland between 2006 and 2010. Secular trends were
407 attributable to steep reductions in MRSA bacteraemia.

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409 Introduction of a universal MRSA admission screening programme was associated with significant
410 reductions in rates of MRSA bacteraemia and associated early mortality, whilst having no
411 discernable impact on burdens from MSSA bacteraemia.

412

413 Strengths and limitations

414 Analyses of risk-factors for SAB acquisition and outcomes were limited by a lack of information on
415 comorbidities, severity of sepsis, source control and clinical management.[4,13,37] However, age has
416 been shown to be an appropriate proxy for co-morbidity and risk of death,[13] and our estimates of
417 attributable mortality approximate those in more detailed analyses.[4]

418

419 Changes in strain distribution have been linked to secular trends in invasive *S.aureus*
420 infections,[6,21] although declines in epidemic strains predated decreases in MRSA in the UK.[10]
421 Reflecting national data,[10] regional studies of MRSA infections from the same period identified
422 significant increase in EMRSA-15, with a reciprocal decline in EMRSA-16.[38,39] Trends in strain may
423 have confounded, or mediated, the associations between infection control measures and SAB
424 epidemiology. [10]

425

426 Universal MRSA admission screening was introduced as part of an NHS Scotland pathfinder project,
427 precluding the use of cross-over, or controlled, trial designs as elsewhere.[40,41] Data on isolation-
428 days captured – suggested as a measure of surveillance effectiveness,[42] were also not available.

429 We attempted to minimise threats to internal validity common to quasi-experimental studies of
430 infection control measures.[22,34] A definition of bacteraemia based on blood isolates rather than
431 clinical suspicion made the study less vulnerable to detection bias whilst follow-up to a minimum of
432 two weeks post-discharge prevented attrition bias arising for changes in length of stay. An attempt
433 to identify and prevent selection and performance bias was made by identifying and controlling for,
434 changes in case-mix, importation pressure,[40] and other aspects of care,[22] before and after the
435 intervention. Investigation of concurrent trends in MSSA bacteraemia provided some control for
436 impacts of general improvements in infection control or clinical management, and supports an

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3 437 independent effect of screening on MRSA bacteraemia.[34] ARIMA techniques, account for non-
4 438 independence of parameters and stochastic elements in time-series. This is convergent with
5 439 understanding of the spread of resistance and infectious disease within populations,[32,34] and
6 440 minimises the potential for regression to the mean to account for trends.
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10 442 Transfer function models including screening, length-of-stay and bed-occupancy accounted for 35-
11 443 48% of variation in rates of bacteraemia, suggesting unmeasured factors affecting rates. Universal
12 444 screening was one of several sequentially implemented control measures for MRSA in North East
13 445 Scotland, including introduction of environmental swabbing and disinfection (2001), alcohol hand gel
14 446 (2002) and targeted admission screening (2003) [31] Antibiotic use in hospital has been linked to
15 447 rates of all MRSA infections in the region.[31,33,43] Decline in the use of "4C" antibiotics occurred
16 448 during implementation of screening. However, this antibiotic stewardship policy started 9 months
17 449 after universal screening and with typical lags of 4-8 months between changes in antibiotic usage
18 450 and rates of MRSA infections,[32] any impacts would have occurred late in the study period.
19 451 Introduction of screening was likely to be associated with improved awareness amongst healthcare
20 452 workers and the public around MRSA, with potential improvements in adherence to general
21 453 infection control policy such as hand hygiene. Performance in infection control may also have been
22 454 influenced by internal audit of MRSA screening. However, non-declining trends in MSSA suggested
23 455 general infection control measures were an inadequate explanation for MRSA-specific declines.
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27 457 Rates of MRSA colonisation, infection and bacteraemia, and effect sizes from intervention in the
28 458 present study are comparable to those described in previous investigations of universal
29 459 surveillance.[26,41] Findings may be generalisable to other large public hospitals with intensive
30 460 care units in high-income countries, with endemic MRSA and relatively low rates of MRSA infection.
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34 462 **Comparison to literature:**

35 463 We identified a number of risk-factors for developing *S.aureus* bacteraemia and associated early
36 464 mortality consistent with previous findings, including; older age,[3,4,13] recent or prolonged
37 465 hospitalisation,[3,37,44] prior history of colonisation or infection,[45] colonisation on
38 466 admission,[45,46] and ITU admission.[9] Associations were significantly stronger for MRSA
39 467 bacteraemia.[46] Despite two meta-analyses suggesting an excess mortality in MRSA, compared to
40 468 MSSA bacteraemia,[15,17] there remains considerable debate about the importance of methicillin
41 469 resistance to outcomes.[4,13,18] Our findings suggest that much of the increase in mortality
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3 470 associated with methicillin resistance may be explained by infection of more vulnerable patients,[13-
4 471 18,37] often in the context of extended contact with healthcare.[15,37]
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8 473 Reflecting the findings of an earlier study from Oxfordshire, which found that MRSA-related disease
9 474 was responsible for increasing rates of SAB between 1997 and 2003,[3] our findings suggest that
10 475 subsequent declines have occurred, almost exclusively in MRSA-related disease. An equivalent
11 476 upward pressure on MSSA rates has not been observed, consistent with observations that MRSA
12 477 appears to add to, rather than displace MSSA infection.[21] These findings match experience across
13 478 the UK.[8]
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19 480 Evidence on the role of universal screening in reducing all MRSA infections, is
20 481 conflicting.[28,30,41,42,47-50] and benefits may depend on target population, screening technology
21 482 and subsequent control interventions.[47] A recent US study of routine surveillance for MRSA noted
22 483 a significant downward trend in MRSA bacteraemia in ICU but not in other hospital settings.[30] A
23 484 second US study found a decrease in hospital-wide MRSA, but not MSSA bacteraemia during
24 485 universal screening.[42] Hospital-wide reductions in bacteraemia, of similar magnitude to that seen
25 486 in our study, were reported following introduction of screening in intensive care[29] or high-risk
26 487 patients only.[28] In agreement with these studies, we found that rates of MRSA bacteraemia
27 488 declined in parallel with all MRSA infections,[51] and there was no reciprocal rise in hospital-wide
28 489 MSSA bacteraemia or infections.[48]
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37 491 Our findings suggest additional considerations in assessing utility of universal surveillance. Patients
38 492 colonised at admission were at high risk of developing hospital-associated MRSA bacteraemia and
39 493 early identification of colonised patients provides opportunities to reduce invasive infection by
40 494 decolonisation.[27] As elsewhere,[29] declines in hospital-associated infection were steeper than
41 495 those in rates including community-associated infection, coherent with reductions in transmission.
42 496 Similarly, decline in importation pressure during universal surveillance suggested interruption of
43 497 connections between prevalence of MRSA in hospital and community populations, focused in
44 498 frequently admitted patients.[43,52,53] However, approximately 50% of hospital-associated MRSA
45 499 bacteraemia occurred in patients not colonised at admission highlighting the limitations in admission
46 500 surveillance and the persistence of cross-transmission.[54]
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504 Implications for practice, policy and research

505 Our study suggests that universal admission screening for MRSA may have an important effect on
506 rates of MRSA bacteraemia, and associated mortality, beyond selective screening of high-risk
507 patients. However, there remains debate around the cost-effectiveness of universal surveillance in
508 comparison to alternative control measures,[49,55-58] risks of chlorhexidine resistance with
509 widespread decolonisation,[11] and opportunity costs or unintended harms associated with
510 isolation.[59] Subsequent to the pathfinder study, NHS Scotland has suggested hospital-wide
511 targeted surveillance based on clinical risk-assessment as a minimum standard.[60] This is
512 convergent with an emerging consensus that admission screening based on clinical prediction rules
513 may offer a more efficient and pragmatic approach outside of populations with high-prevalence of
514 MRSA.[47,58,61] Irrespective of the chosen strategy, experience suggests benefits of admission
515 screening will only be realised where integrated with a broader package of infection prevention and
516 control measures.[28,47,54]

517

518 The concentration of both MRSA and MSSA blood stream infections in susceptible patient groups
519 with higher levels of healthcare contact suggests some measures successfully limiting invasive MRSA
520 infections may be generalizable to control of all SAB. A more rigorous approach to identify and limit
521 iatrogenic sources of bacteraemia, including peripheral or central catheters,[37,40,62] is required.
522 Screening for MSSA with isolation and decolonisation has been suggested for selected, high-risk
523 patients.[63]

524

525 Equally, strategies are required that account for the distinct epidemiology of MSSA and MRSA
526 bacteraemia. In contrast to MRSA, the majority of MSSA bacteraemia in this study were community
527 associated and occurred in younger patients. Targeted measures are required to prevent invasive
528 infection in at-risk groups including IV drug users,[37,64] surgical, diabetic and renal patients.[63,65]
529 Given the role of social and risk-networks in sustaining *S.aureus* transmission,[64] broadening
530 control of SAB to the community is likely to require the commitment of multiple agencies and
531 healthcare providers.

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533 Changes in virulence of MSSA and MRSA may account for divergence in trends in outcomes.[13]
534 Genetic sequencing or typing could be used to quantify the contribution of clonal expansions to
535 recent trends in SAB epidemiology. A recent multicentre study found large variation in management
536 of SAB in the UK and called for high-level evidence to define optimal care.[37] Future research and
537 guidelines should consider both MSSA and MRSA bacteraemia.

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In summary, this study described decreasing trends in *S. aureus* bacteraemia following a decade of infection control policies focusing on MRSA. Expansion from targeted to universal MRSA admission screening was associated with important reductions in MRSA bacteraemia, when combined with isolation and selective decolonisation. However, findings also highlighted the need for strategies to reduce clinical burdens from invasive MSSA infection if progress towards national targets for SAB is to be sustained.[21,44]

For peer review only

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2
3 573 **Acknowledgements:** The authors would like to thank all the staff in the routine microbiology
4 574 diagnostic lab and all the clinical staff at Aberdeen Royal Infirmary, whose work made this possible.
5
6 575 We are grateful to Richard Slessor and the health intelligence services, Aberdeen for providing data
7
8 576 on admissions. We would also like to thank Health Protection Scotland for help in the
9
10 577 implementation of the pathfinder project.
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578

12 579 **Contributors:** BE and IMG conceived this study. The statistical analysis was performed by TL and
13
14 580 JMLL. All authors assisted in drafting the manuscript. Ian M Gould is the guarantor for this study.
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16
17 582 **Funding:** The NHS pathfinder study on universal admission screening was funded by the Scottish
18
19 583 Government Health Directorate. This research received no specific grant from any funding agency in
20
21 584 the public, commercial or not-for-profit sectors
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24 586 **Competing Interests:** All authors have completed the Unified Competing Interest form at
25
26 587 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare
27
28 588 no support from any organisation for the submitted work. IM Gould has received personal and grant
29
30 589 financial support from companies manufacturing diagnostics and therapeutics for MRSA. B Edwards
31
32 590 has received grant financial support from Novartis. T Lawes and JM López-Lozano have no conflicts
33
34 591 to declare. TL BE JMLL IMG know of no other relationships or activities that could appear to have
35
36 592 influenced the submitted work.
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38 594 **Ethical approval:** Ethics approval was not required.

39 595 Authors' note: This study used anonymised and routinely collected data from laboratory systems,
40
41 596 infection control, pharmacy, and health intelligence departments. Patient-orientated information on
42
43 597 MRSA screening, and NHS Grampian's participation in a national pathfinder project, was made
44
45 598 widely available in Aberdeen Royal Infirmary. This information included a statement that patient
46
47 599 information would be held in the strictest confidence and used only for stated purposes of informing
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49 600 the NHS about the value of a national screening programme, in accordance with the Data Protection
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51 601 Act 1998. The authors hold that extraction of data for the purposes of this study did not impose any
52
53 602 predictable additional burdens on patients at ARI and its use was justified by foreseeable benefits to
54
55 603 the patient populations in the NHS and the general public. The authors believe that the present
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57 604 study was conducted in accordance with the Declaration of Helsinki 1964.
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59 606 **Data sharing:** Technical appendix available on request from the corresponding author.
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References:

1. Allegranzi B, Bagheri Nejad S, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011;377(9761):228-41.
2. Wilson J, Elgohari S, Livermore DM, et al. Trends among pathogens reported as causing bacteraemia in England, 2004-2008. *Clin Microbiol Infect* 2011;17(3):451-8.
3. Wyllie DH, Crook DW, Peto TEA. Mortality after *Staphylococcus aureus* bacteraemia in two hospitals in Oxfordshire, 1997-2003: cohort study. *BMJ* 2006; 333: 281-6.
4. Blot SI, Vandewoude KH, Hoste EA, et al. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. *Arch Intern Med* 2002;162(19):2229-35.
5. de Kraker MEA, Davey PG, Grundmann H; on behalf of the BURDEN study group. Mortality and Hospital Stay Associated with Resistant *Staphylococcus aureus* and *Escherichia coli* Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe. *PLoS Med*, 2011; 8(10): e1001104.
6. Johnson AP, Pearson A, Duckworth G. Surveillance and epidemiology of MRSA bacteraemia in the UK. *J Antimicrob Chemother*. 2005;56(3):455-62.
7. Clements A, Halton K, Graves N, et al. Overcrowding and understaffing in modern health-care systems: key determinants in methicillin-resistant *Staphylococcus aureus* transmission. *Lancet Infect Dis* 2008;8(7):427-34.
8. Pearson A, Chronias A, Murray M: Voluntary and mandatory surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteraemia in England. *J Antimicrob Chemother*. 2009; 64 Suppl 1:i11-7.
9. Edgeworth JD. Has decolonization played a central role in the decline in UK methicillin-resistant *Staphylococcus aureus* transmission? A focus on evidence from intensive care. *J Antimicrob Chemother*. 2011;66 Suppl 2:ii41-7.
10. Wyllie D, Paul J, Crook D. Waves of trouble: MRSA strain dynamics and assessment of the impact of infection control. *J Antimicrob Chemother* 2011;66(12):2685-8
11. Health Protection Agency. Voluntary reporting of *Staphylococcus aureus* bacteraemia in England, Wales and Northern Ireland, 2010. London: Health Protection Agency; 2011.
12. Health Protection Scotland. SNBTS Annual Infection Control Report: April 2010 to March 2011. Edinburgh: Health Protection Scotland; 2011.

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2
3 662 13. Shurland S, Zhan M, Bradham DD, et al. Comparison of Mortality Risk Associated With Bacteremia Due to
4 663 Methicillin-Resistant and Methicillin-Susceptible *Staphylococcus aureus*. *Infection Control and Hospital*
5 664 *Epidemiology* 2007; 28 (3): 273-9.
6 665
7 666
8 667 14. Wang JL, Chen SY, Wang JT, et al. Comparison of both clinical features and mortality risk associated with
9 668 bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible
10 669 *S. aureus*. *Clin Infect Dis* 2008;46(6):799-806.
11 670
12 671
13 672 15. Whitby M, McLaws M-L, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus*
14 673 bacteraemia: a meta-analysis. *Med J Aust* 2001;175:264-7.
15 674
16 675
17 676 16. Wolkewitz M, Frank U, Philips G, et al: Mortality associated with in-hospital bacteraemia caused by
18 677 *Staphylococcus aureus*: a multistate analysis with follow-up beyond hospital discharge; *J antimicrob*
19 678 *chemother*, 2011; 66: 381-386.
20 679
21 680
22 681 17. Cosgrove SE, Sakoulas G, Perencevich EN, et al. Comparison of mortality associated with methicillin-
23 682 resistant and methicillin-susceptible *Staphylococcus aureus* bacteraemia: a meta-analysis. *Clin Infect Dis* 2003;
24 683 36: 53–9.
25 684
26 685
27 686 18. Cosgrove SE, Qi Y, Kaye KS, et al. The Impact of Methicillin Resistance in *Staphylococcus aureus*
28 687 Bacteraemia on Patient Outcomes: Mortality, Length of Stay, and Hospital Charges. *Infection Control and*
29 688 *Hospital Epidemiology*; 26(2): 166-174.
30 689
31 690
32 691 19. NHS Scotland. HEAT Targets due for delivery in 2009/10: Summary of performance. Edinburgh: NHS
33 692 Scotland Performance and Business Management;2011.
34 693
35 694
36 695 20. Paul J. Surveillance and management of all types of *Staphylococcus aureus* bacteraemia [editorial]. *BMJ*
37 696 2006; 333: 269.
38 697
39 698
40 699 21. Mostofsky E, Lipsitch M and Regev-Yochay G. Is methicillin-resistant *Staphylococcus aureus* replacing
41 700 methicillin-susceptible *S.aureus*? *J Antimicrob Chemother* 2011; 66: 2199-2214.
42 701
43 702
44 703 22. Cooper BS, Stone SP, Kibbler CC, et al. Systematic review of isolation measures in the hospital management
45 704 of methicillin resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic
46 705 modelling. *Health Technol Assess*. 2003;7(39):191-4
47 706
48 707
49 708 23. Wilcox MH. Screening for MRSA. *BMJ* 2008;336(7650):899-900.
50 709
51 710
52 711 24. Loeb M, Main C, Walker-Dilks C, et al. Antimicrobial drugs for treating methicillin-resistant *Staphylococcus*
53 712 *aureus* colonization. *Cochrane Database Syst Rev* 2003;(4): CD003340.
54 713
55 714
56 715 25. McGinagle KL, Gourlay ML, Buchanan IB. The use of active surveillance cultures in adult intensive care units
57 716 to reduce methicillin-resistant *Staphylococcus aureus*-related morbidity, mortality, and costs: a systematic
58 717 review. *Clin Infect Dis* 2008;46(11):1717-25.
59 718
60

- 1
2
3 719 26. Chowers MY, Paitan Y, Gottesman BS, et al. Hospital-wide Methicillin Resistant *Staphylococcus aureus*
4 720 control program: A 5-year follow-up. *Inf control and hospital epidem* 2009;30(8):777-781.
5 721
6 722
7 723 27. Huang SS, Yokoe DS, Hinrichsen VL, et al. Impact of routine intensive care unit surveillance cultures and
8 724 resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin*
9 725 *Infect Dis*, 2006;43(8):971-8.
10 726
11 727
12 728 28. Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant
13 729 *Staphylococcus aureus* infections. *N Engl J Med*. 2011; 364(15):1419-30.
14 730
15 731
16 732 29. Reilly JS, Stewart S, Christie P, et al. Universal screening for methicillin resistant *Staphylococcus aureus*:
17 733 interim results from the NHS Scotland pathfinder project. *J of hospital Infection* 2010;74:35-41.
18 734
19 735
20 736 30. Health Protection Scotland; National Services Scotland. NHS Scotland MRSA Screening Pathfinder
21 737 Programme Final Report Volume 1: An investigation of the Clinical Effectiveness of MRSA Screening [Report].
22 738 Glasgow: Health Protection Scotland; Feb 2011.
23 739
24 740
25 741 31. Mahamat A, MacKenzie FM, Brooker K, et al. Impact of infection control interventions and antibiotic use on
26 742 hospital MRSA: a multivariate interrupted time-series analysis. *Int J Antimicrob Agents* 2007;30(2):169-76.
27 743
28 744
29 745 32. Monnet DL, Mackenzie FJ, Lopez-Lozano J-M, et al. Antimicrobial drug use and methicillin-resistant
30 746 *Staphylococcus aureus*, Aberdeen, 1996-2000. *Emerg Infect Dis*. 2004;10:1432-41.
31 747
32 748
33 749 33. Tacconelli E, De Angelis G, Cataldo MA, et al. Does antibiotic exposure increase the risk of methicillin-
34 750 resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *Journal of*
35 751 *Antimicrobial Chemotherapy*, 2008; 61: 26-38.
36 752
37 753
38 754 34. Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to
39 755 antimicrobial resistance intervention studies. *Clin Infect Dis*. 2007;45(7):901-7.
40 756
41 757
42 758 35. Pakratz A. Forecasting with Dynamic regression Models. New York (NY): Wiley; 1991.
43 759
44 760
45 761 36. Liu L-M, Hudak GB: Forecasting and time series analysis using the SCA statistical system. Chicago (IL):
46 762 Scientific Computing Associates; 1994.
47 763
48 764
49 765 37. Thwaites GE; United Kingdom Clinical Infection Research Group (UKCIRG). The management of
50 766 *Staphylococcus aureus* bacteraemia in the United Kingdom and Vietnam: A multi-centre evaluation. *PLoS ONE*
51 767 2010;5(12):e14170.
52 768
53 769
54 770 38. Edwards B, Milne K, Lawes T, et al. Is Vancomycin MIC 'creep' method dependent? Analysis of methicillin-
55 771 resistant *S. aureus* (MRSA) susceptibility trends in blood isolates from North East Scotland, 2006-10. *J Clin*
56 772 *Microbiol*. Forthcoming 2011.
57 773
58 774

- 1
2
3 775 39. Hunt AC, Edwards B, Girvan EK, et al. Methicillin-resistant *Staphylococcus aureus* in northeastern Scotland
4 776 in 2003 to 2007: evolving strain distribution and resistance patterns. *J Clin Microbiol* 2011; 49: 1975–8.
5 777
6 778
7 779 40. Jeyaratnam D, Whitty CJM, Phillips K, et al. Impact of rapid screening tests on acquisition of methicillin
8 780 resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008;336: 927-30.
9 781
10 782
11 783 41. Harbarth S, Fankhauser C, Schrenzel J, et al: Universal screening for methicillin resistant *Staphylococcus*
12 784 *aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 2008; 299:1149-57.
13 785
14 786
15 787 42. Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus*
16 788 *aureus* in 3 affiliated hospitals. *Ann Intern Med.* 2008;148(6):409-18.
17 789
18 790
19 791 43. MacKenzie FM, Lopez-Lozano JM, Monnet DL, et al. Temporal relationship between prevalence of
20 792 methicillin-resistant *Staphylococcus aureus* (MRSA) in one hospital and prevalence of MRSA in the surrounding
21 793 community: a time-series analysis. *J Hosp Infect* 2007;67(3):225-31.
22 794
23 795
24 796 44. Graham PL, Morel AS, Zhou J, et al. Epidemiology of methicillin-susceptible *Staphylococcus aureus* in the
25 797 neonatal intensive care unit. *Infect Control Hosp Epidemiol* 2002;23(11):677-82.
26 798
27 799
28 800 45. Seybold U, Schubert S, Bogner JR, et al. *Staphylococcus aureus* infection following nasal colonisation: an
29 801 approach to rapid risk stratification in a university healthcare system. *J Hosp Infect* 2011; 79(4): 297-301.
30 802
31 803
32 804 46. Honda H, Krauss MJ, Coopersmith CM, et al: *Staphylococcus aureus* nasal colonization and subsequent
33 805 infection in intensive care unit patients: does methicillin resistance matter? *Infect Control Hosp Epidemiol*
34 806 2010;31(6):584-91.
35 807
36 808
37 809 47. Harbarth S, Hawkey PM, Tenover F, et al. Update on screening and clinical diagnosis of methicillin-resistant
38 810 *Staphylococcus aureus* (MRSA). *Int J Antimicrob Agents.* 2011;37(2):110-7
39 811
40 812
41 813 48. Hacek DM, Paule SM, Thomson RB, et al. Implementation of a Universal Admission Surveillance and
42 814 Decolonisation Program for Methicillin-Resistant *Staphylococcus aureus* (MRSA) reduces the number of MRSA
43 815 and total number of *S. aureus* isolates reported by the clinical laboratory. *J Clin Microbiol* 2009;47(11):3749-52.
44 816
45 817
46 818 49. Leonhardt KK, Yakusheva O, Phelan D, et al. Clinical effectiveness and cost benefit of universal versus
47 819 targeted methicillin-resistant *Staphylococcus aureus* screening upon admission in hospitals. *Infect Control*
48 820 *Hosp Epidemiol* 2011;32(8):797-803.
49 821
50 822
51 823 50. Hardy K, Price C, Szczepura A, et al. Reduction in the rate of methicillin-resistant *Staphylococcus aureus*
52 824 acquisition in surgical wards by rapid screening for colonization: a prospective, cross-over study. *Clin Microbiol*
53 825 *Infect* 2009; 16:333-339.
54 826
55 827
56 828 51. Walker S, Peto TEA, O'Conner L, et al. Are there better methods of monitoring MRSA control than
57 829 bacteraemia surveillance? An observational database study. *PLoS ONE* 2008;3:e2378.
58 830
59 831
60

- 1
2
3 832 52. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-
4 833 analysis of prevalence and risk factors. *Clin Infect Dis* 2003;36: 131-139.
5 834
6 835
7 836 53. Wyllie DH, Peto TEA, Crook D. MRSA bacteraemia in patients on arrival in hospital: a cohort study in
8 837 Oxfordshire 1997-2003. *BMJ* 2005;331(7523):992-7.
9 838
10 839
11 840 54. van Velzen EV, Reilly JS, Kavanagh K, et al. A retrospective cohort study into acquisition of MRSA and
12 841 associated risk factors after implementation of universal screening in Scottish hospitals. *Infect Control Hosp*
13 842 *Epidemiol.* 2011;32(9):889-96.
14 843
15 844
16 845 55. Murthy A, De Angelis G, Pittet D, et al. Cost-effectiveness of universal MRSA screening on admission to
17 846 surgery. *Clin Microbiol Infect.* 2010;16(12):1747-53.
18 847
19 848
20 849 56. Hubben G, Bootsma M, Luteijn M, et al. Modelling the costs and effects of selective and universal hospital
21 850 admission screening for Methicillin resistant *Staphylococcus aureus*. *PLoS ONE* 2011;6(3):e14783.
22 851
23 852
24 853 57. Lee BY, Bailey RR, Smith KJ, et al. Universal methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance
25 854 for adults at hospital admission: an economic model and analysis. *Infect Control Hosp Epidemiol*
26 855 2010;31(6):598-606.
27 856
28 857
29 858 58. Collins J, Raza M, Ford M, et al. Review of a three-year methicillin-resistant *Staphylococcus aureus* screening
30 859 programme. *J Hosp Infect.* 2011;78(2):81-5.
31 860
32 861
33 862 59. Kirkland KB. Taking off the gloves: Towards a less dogmatic approach to the use of contact isolation.
34 863 *Clinical Infectious Diseases* 2009;48:766-771.
35 864
36 865
37 866 60. Health Protection Scotland: Protocol for CRA MRSA Screening National Rollout in Scotland. Glasgow: Health
38 867 Protection Scotland; 2nd September 2011.
39 868
40 869
41 870 61. Morgan DJ, Day HR, Furuno JP, et al. Improving efficiency in active surveillance for methicillin-resistant
42 871 *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* at hospital admission. *Infect Control Hosp*
43 872 *Epidemiol* 2010; 31(12):1230-5.
44 873
45 874
46 875 62. Hetem DJ, de Ruiter SC, Buiting AG, et al. Preventing *Staphylococcus aureus* bacteremia and sepsis in
47 876 patients with *Staphylococcus aureus* colonization of intravascular catheters: a retrospective multicenter study
48 877 and meta-analysis. *Medicine* 2011;90(4):284-8.
49 878
50 879
51 880 63. Lucet JC, Regnier B. Screening and decolonization: does methicillin-susceptible *Staphylococcus aureus* hold
52 881 lessons for methicillin-resistant *S. aureus*? *Clin Infect Dis* 2010;51(5):585-90.
53 882
54 883
55 884 64. Gwizdala RA, Miller M, Bhat M, et al. *Staphylococcus aureus* colonization and infection among drug users:
56 885 identification of hidden networks. *Am J Public Health.* 2011;101(7):1268-76.
57 886
58 887
59
60

65. Saxena AK, Panhotra BR, Venkateshappa CK, et al. The impact of nasal carriage of methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* (MRSA & MSSA) on vascular access-related septicemia among patients with type-II diabetes on dialysis. *Ren Fail*. 2002;24(6):763-777.

FIGURE LEGENDS

Footnotes in small plain script.

Figure 1: Study timeline

Figure 2: Rates of *S.aureus* bacteraemia by age-group, length of stay and days from admission

$P < 0.01$ for all linear regression lines. Note logarithmic scale for Length-of-stay. Linear trend fitted after logarithmic transformation.

Figure 3: Secular trends in prevalence density and all-cause 30-day mortality after *S. aureus* bacteraemia by methicillin resistance

Data aggregated in 3 month blocks. Lines represent results of trend analysis, using Poisson regression with time (month) as sole explanatory variable.

Figure 4: Adherence to MRSA admission testing during universal surveillance (August 2008 to December 2010)

* Special study period (February 2010 to August 2010) involved a trial of axillae and groin swabs.

Figure 5: Observed trends and multivariate transfer model predictions for prevalence density,* hospital associated incidence density[†] and 30-day mortality in MRSA bacteraemia[‡] and % of *S.aureus* bacteraemia involving MRSA[§]

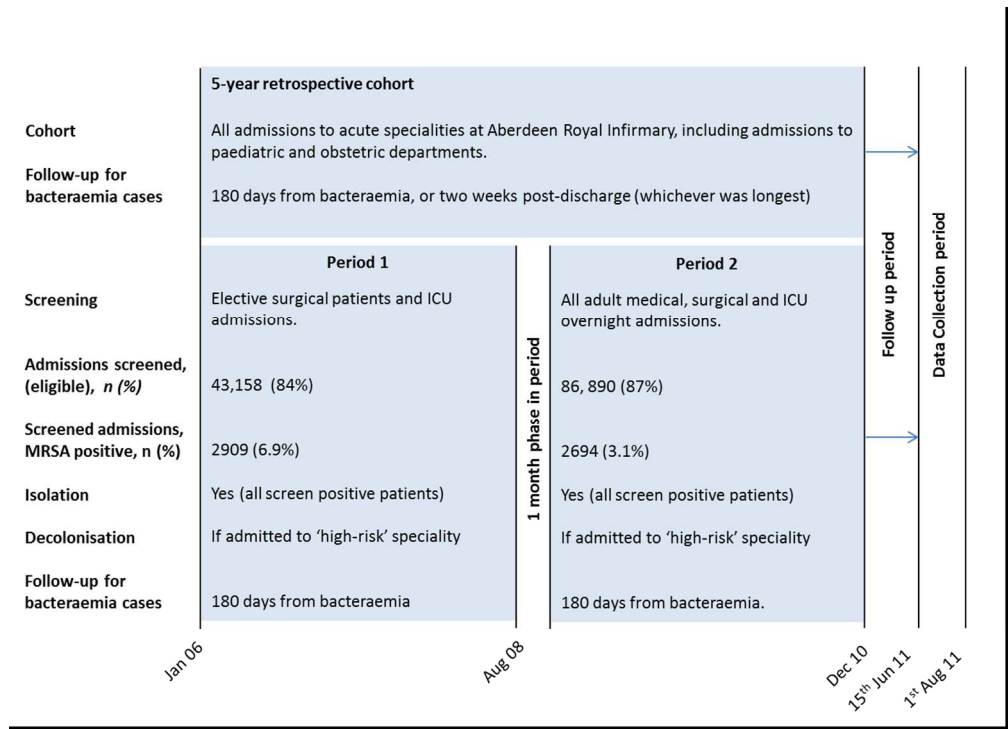
* Prevalence density (t) = $0.189 + 0.044 * \text{Length-of-stay}(t-1) - 0.315 * \text{prevalence-density}(t-6) - 0.053 * U(t)$.

[†] HA-associated incidence density (t) = $0.100 + 0.476 * \text{HA incidence-density}(t-1) - 0.062 * U(t)$.

[‡] 30-day mortality (t) = $0.189 + 0.454 * \% \text{BedOcc}(t-2) - 0.349 * 30\text{-day mortality}(t-6) - 11.0 * U(t)$.

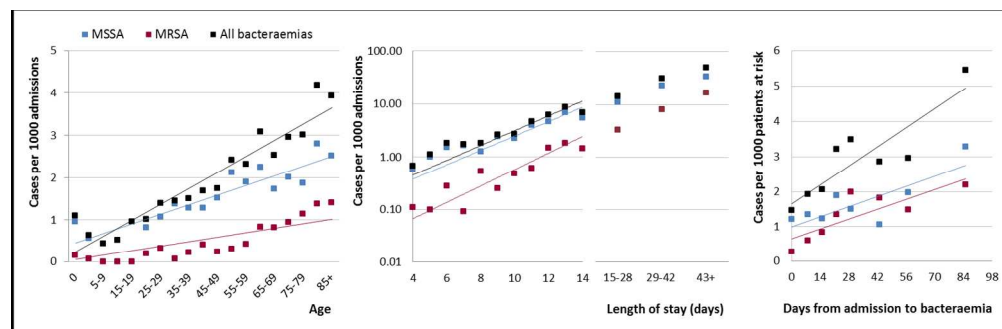
[§] %SABsMRSA (t) = $0.189 + 0.360 * \% \text{BedOcc}(t-4) - 0.457 * \% \text{SABsMRSA}(t-9) - 0.293 * \% \text{SABsMRSA}(t-1) - 18.8 * U(t)$.

Where; LoS = length-of-stay; %BedOcc = Monthly average bed-occupancy (%) weighted by admitting department; %SABsMRSA = proportion of *S.aureus* bacteraemia involving MRSA; U = Universal Admission Screening intervention (=0 before introduction, = 1 after introduction); t = present time(month); and j ($t - n$) is value of parameter (j) at n months prior to the present time (t).



Study timeline

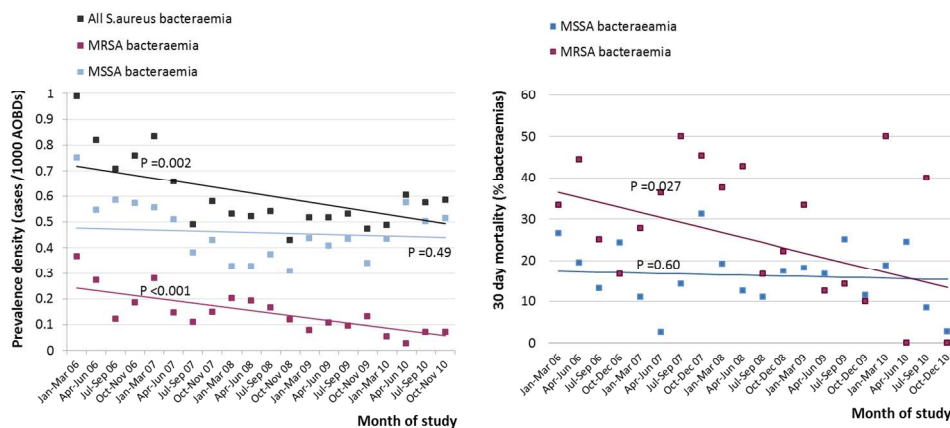
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Rates of *S.aureus* bacteraemia by age-group, length of stay and days from admission

$P < 0.01$ for all linear regression lines. Note logarithmic scale for Length-of-stay. Linear trend fitted after logarithmic transformation.

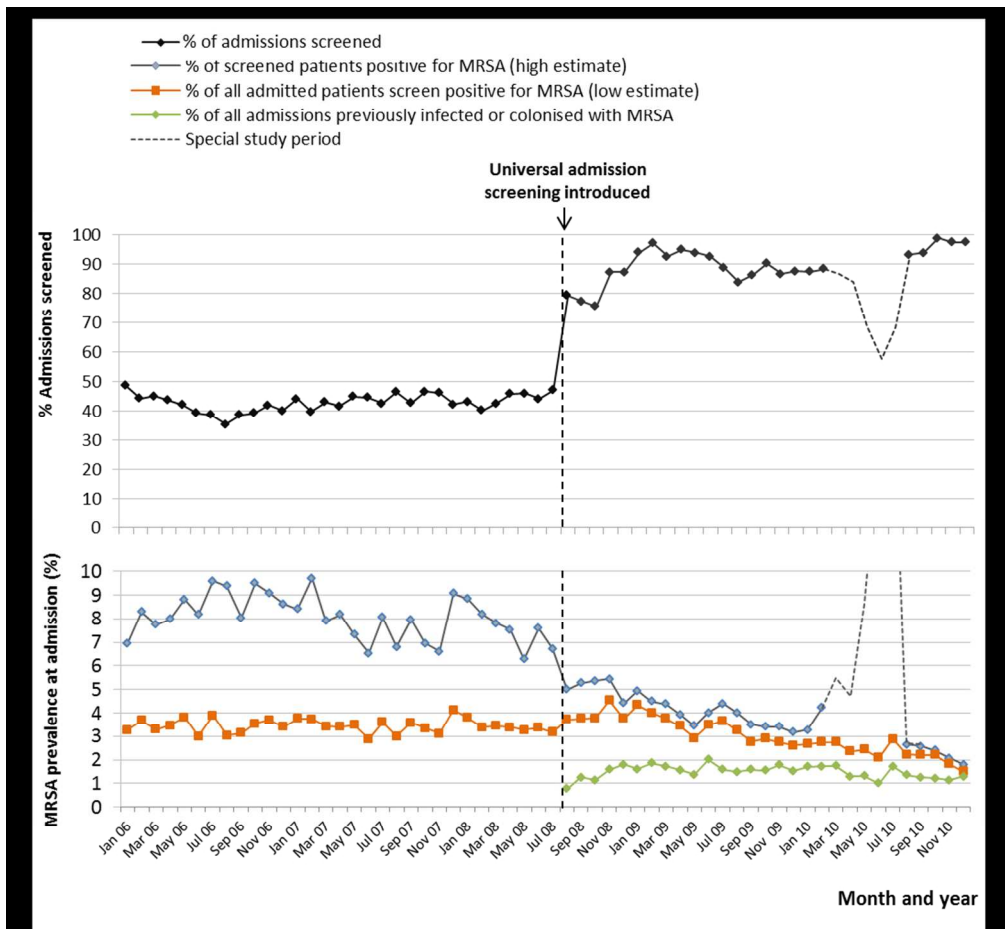
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Secular trends in prevalence density and all-cause 30-day mortality after *S. aureus* bacteraemia by methicillin resistance

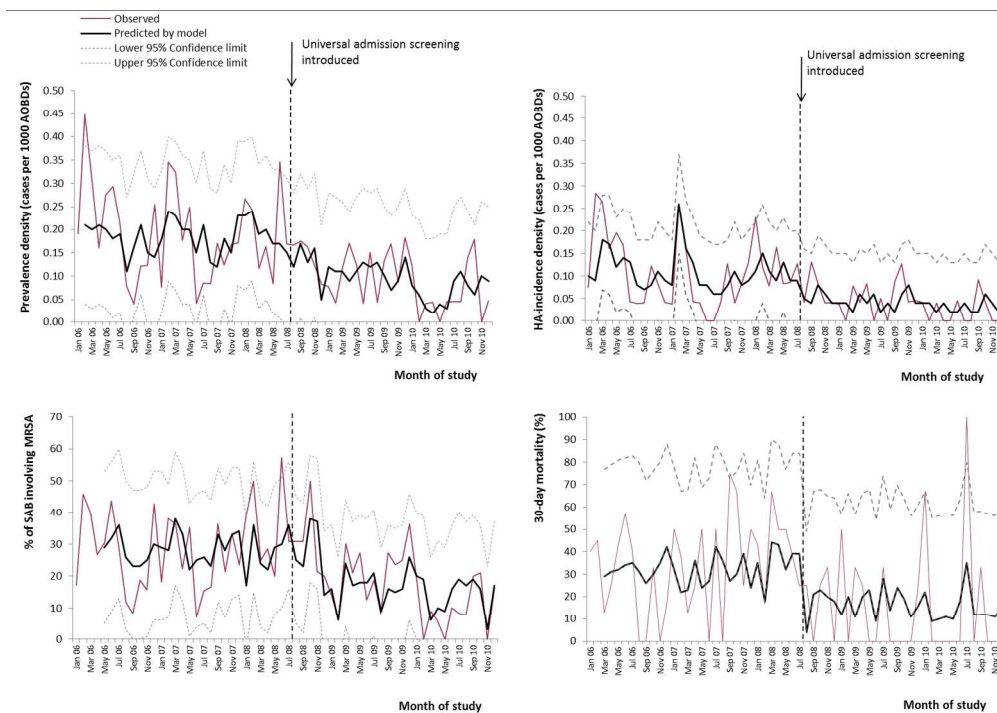
Data aggregated in 3 month blocks. Lines represent results of trend analysis, using Poisson regression with time (month) as sole explanatory variable.

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Adherence to MRSA admission testing during universal surveillance (August 2008 to December 2010)

* Special study period (February 2010 to August 2010) involved a trial of axillae and groin swabs.



Observed trends and multivariate transfer model predictions for prevalence density, hospital associated incidence density and 30-day mortality in MRSA bacteraemia and % of *S.aureus* bacteraemia involving MRSA

Review only

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STROBE Statement—Checklist of items that should be included in reports of cohort studies

Study: Trends in *Staphylococcus aureus* bacteraemia and impacts of universal MRSA admission screening in a hospital in Scotland, 2006-2010: retrospective cohort study and time series intervention analysis

Authors: Timothy Lawes, Becky Edwards, José-Maria López-Lozano, Ian M Gould

Submitted: 03/01/2012

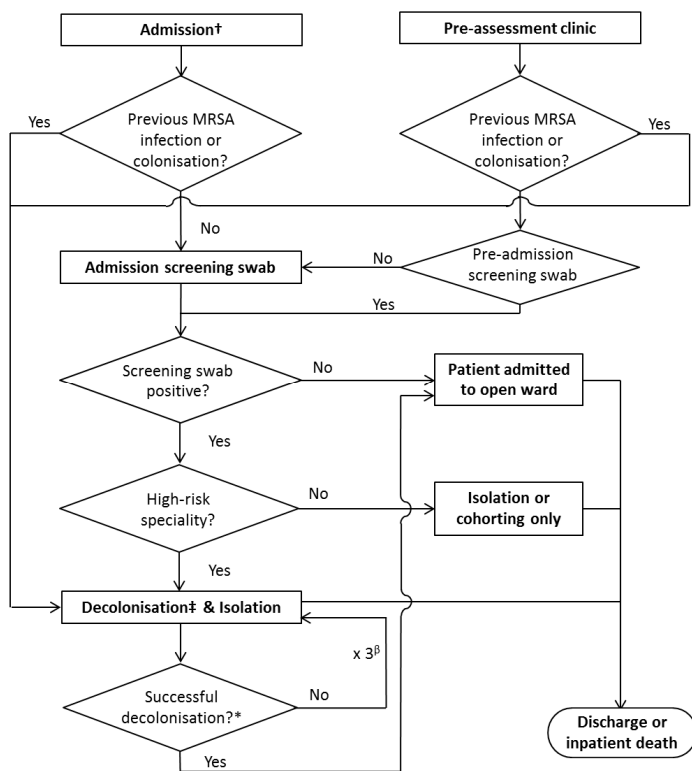
	Item No	Recommendation	Identification in manuscript		Notes
			Page	Line	
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2	Title, 6-7	See Title and Abstract: Retrospective cohort study and time series intervention analysis Brief explanation of key methods
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	3	1-34	See Abstract: Structured abstract. Main results given as absolute changes.
Introduction					
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4	36-63	See Background
Objectives	3	State specific objectives, including any prespecified hypotheses	4	65-69	See Background Pre-specified null hypothesis of no impact of screening above other infection control measured.
Methods					
Study design	4	Present key elements of study design early in the paper	5	72-77	See Methods: Study design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5	123-124, 87, 79-84, Fig 1.	See Methods: Setting, Study design and Admission screening intervention; and fig 1. Dates of study Date of intervention Setting Periods of recruitment, exposure, f/u and data collection.
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6&7	123-132	See Methods: Study Population
		(b) For matched studies, give matching criteria and number of exposed and unexposed	NA	NA	(No. exposed to screening in each time period provided in fig 1.)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6 & Box	104-118	See Methods: Outcomes and potential confounders
Data sources/	8*	For each variable of interest, give	7	135 -157	See Methods: Data collection

measurement		sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group			
Bias	9	Describe any efforts to address potential sources of bias	6	105-118	Methods: Outcomes and potential confounders and Study population
Study size	10	Explain how the study size was arrived at	7	124-127	See Study population: 60 month time series with 32 months of follow up allowed robust analysis.
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6 & 8 Box 1		Methods: Outcomes and potential confounders; Statistical analysis.
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	8-9	165-210	See Statistical analysis
		(b) Describe any methods used to examine subgroups and interactions	8-10	218-274	See Statistical analysis
		(c) Explain how missing data were addressed	7	149-153	See Data collection
		(d) If applicable, explain how loss to follow-up was addressed	7	149-153	See Data collection
		(e) Describe any sensitivity analyses	-	-	None described or used.
Results					
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10	243-245	See Descriptive epidemiology, Cohort and rates of S.aureus bacteraemia:
		(b) Give reasons for non-participation at each stage	10	243-245	See Descriptive epidemiology, Cohort and rates of S.aureus bacteraemia and fig 1.
		(c) Consider use of a flow diagram			Not used.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10 & 13-14 Tables 1 & 4	251-263 Table 1 315-353 343-348 Table 4	See a) Descriptive epidemiology, b) Impacts of universal MRSA admission screening
		(b) Indicate number of participants with missing data for each variable of interest	10 & 14	-	Table 1 Table 4
		(c) Summarise follow-up time (eg, average and total amount)	10	243-245	See Descriptive epidemiology Cohort and rates of S.aureus bacteraemia:

Outcome data	15*	Report numbers of outcome events or summary measures over time	10, 11, 12, 12, 14, 15	247-251 Table 1 268-271 296-308 Table 3 Table 4 Table 5	See Results: a) Descriptive epidemiology b) Secular trends c) Impacts of universal MRSA admission screening.
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	15 & 17	Table 5 358-368 476-482 503-516	See results: a) Secular trends b) Impacts of universal MRSA admission screening c) Table 2,3,5 and 6
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-	-	See results: Trends and time series analysis Not disaggregation by methicillin sensitivity throughout.
Discussion					
Key results	18	Summarise key results with reference to study objectives	16	405-411	See Discussion (first section)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17	413-455	See Discussion, Strengths & Limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	17-18	462-500	See Discussion, Comparison to literature
Generalisability	21	Discuss the generalisability (external validity) of the study results	17	457-460	See Discussion, Strengths & Limitations
Other information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21	582-584	See Funding. No funding involved in this study. Data includes outcomes from NHS pathfinder study commissioned by NHS Scotland.

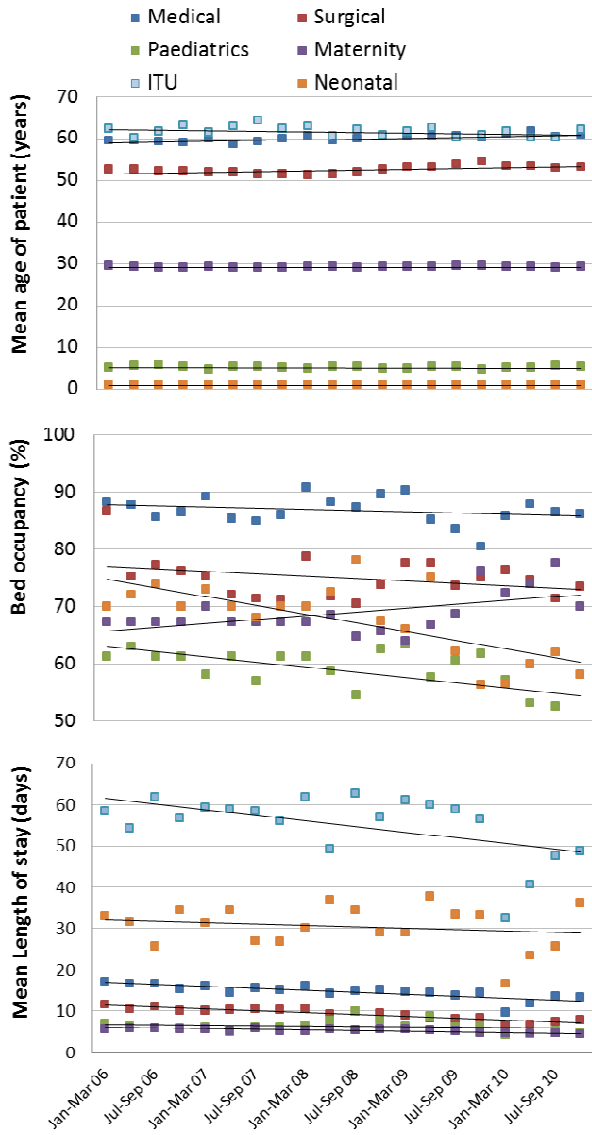
*Give information separately for exposed and unexposed groups.

Supplemental file 1: Admission screening strategy during universal surveillance



† Overnight admissions to acute specialities excluding paediatrics, obstetrics and psychiatry. ‡ Decolonisation involved 5-days of once-daily antiseptic body wash and thrice-daily mupirocin nasal ointment. * Successful decolonisation assessed as three successive negative swabs ≥ 2 days post-decolonisation period. β If failure to decolonise after three attempts, referral to clinical microbiologist advised. Adapted from reference (27).

Supplemental file 2: Secular trends in mean patient age, length-of-stay and % bed occupancy by department and month



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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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000797.R1
Article Type:	Research
Date Submitted by the Author:	20-Mar-2012
Complete List of 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
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Public health
Keywords:	Infection control < INFECTIOUS DISEASES, Epidemiology < INFECTIOUS DISEASES, MICROBIOLOGY

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3 **Trends in *Staphylococcus aureus* bacteraemia and impacts of infection**
4 **control practices including universal MRSA admission screening in a hospital**
5 **in Scotland, 2006-2010: retrospective cohort study and time-series**
6 **intervention analysis**
7
8

9
10 Timothy Lawes, Becky Edwards, José-Maria López-Lozano, Ian M Gould

11 **Keywords:** Methicillin Resistance, Staphylococcus aureus, bacteraemia, mass screening, intervention
12 studies, cohort studies, inpatients
13

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44 **Word Count:**

45 *Abstract* : 299

46 *Introduction* : 361

47 *Methods* : 1499

48 *Results* : 1304

49 *Discussion* : 1939

50 *Main Manuscript (excluding abstract)* : 5083
51

ARTILCE SUMMARY**Article focus**

- This study describes the changing epidemiology of MRSA and MSSA bacteraemia in a large inpatient population from Scotland over a five year period
- Secondly, it evaluates the impact of universal MRSA admission screening, and other infection control practices, on hospital-wide rates of MRSA bacteremia.

Key messages:

- Recent declines in clinical burdens from *S.aureus* bacteraemia in North East Scotland were attributable to a reduction in invasive MRSA infections.
- 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.
- Strategies to reduce clinical burdens from MSSA bacteraemia are required if progress towards national targets for all *S.aureus* bacteraemia is to be sustained.

Strengths and limitations

- Without a contemporary control, this study did not prove causality but a temporal association between universal admission screening and rates of MRSA bacteraemia.
- ARIMA modelling accounted for the non-independence of data and stochastic elements in time-series of infections, and the dynamic effects of changes in other aspects of care.
- Findings may be limited to large public hospitals with intensive care units and endemic MRSA but low rates of MRSA infection.

1 ABSTRACT

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3 **Objectives:** To describe secular trends in *Staphylococcus aureus* bacteraemia, and assess the impacts
4 of infection control practices including universal MRSA admission screening on associated clinical
5 burdens.

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7 **Design:** Retrospective cohort study and multivariate time-series analysis linking microbiology,
8 patient management and health intelligence databases.

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10 **Setting:** Teaching hospital in North East Scotland.

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12 **Participants:** All patients admitted to Aberdeen Royal Infirmary between 1st January 2006 and 31st
13 December 2010: n= 420,452 admissions and 1,430,052 acute occupied bed days (AOBDs).

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15 **Intervention:** Universal admission screening programme for MRSA (August 2008) incorporating
16 isolation and decolonisation

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18 **Primary and secondary measures:** Hospital-wide prevalence density, hospital-associated (HA-
19)incidence density, and death within 30 days of MRSA or MSSA bacteraemia.

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21 **Results:** Between 2006 and 2010, prevalence density of all *S.aureus* bacteraemia declined by 41%,
22 from 0.73 to 0.50 cases/1000 AOBDs ($P = 0.002$ for trend), and 30-day mortality from 26% to 14% (P
23 = 0.013). Significant reductions were observed in MRSA bacteraemia only. Overnight admissions
24 screened for MRSA rose from 43% during selective screening to >90% within four months of
25 universal screening. In multivariate time-series analysis (R^2 0.45 to 0.68) universal screening was
26 associated with a 19% reduction in prevalence density of MRSA bacteraemia (-0.035, 95% CI: -0.049
27 to -0.021/1000 AOBDs; $P < 0.001$); a 29% fall in HA-incidence density (-0.029, -0.035 to -0.023/1000
28 AOBDs; $P < 0.001$) and a 46% reduction in 30-day mortality (-15.6, -24.1 to -7.1%; $P < 0.001$). Positive
29 associations with fluoroquinolone and cephalosporin use suggested that antibiotic stewardship
30 reduced prevalence density of MRSA bacteraemia by 0.027 (0.015 to 0.039)/1000 AOBDs. Rates of
31 MSSA bacteraemia were not significantly affected by screening or antibiotic use.

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33 **Conclusions:** Declining clinical burdens from *S.aureus* bacteraemia were attributable to reductions in
34 MRSA infections. Universal admission screening and antibiotic stewardship were associated with

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35 decreases in MRSA bacteraemia and associated early mortality. Control of MSSA bacteraemia
36 remains a priority.

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INTRODUCTION

Staphylococcus aureus is an important cause of serious, invasive, and health care-associated infections worldwide.[1] In high-income countries it remains a leading cause of community and nosocomial bacteraemia,[2] associated with mortality rates of 20-50%,[3,4] and large economic burdens.[5] In the UK, dramatic increases in *S. aureus* bacteraemia (SAB) during the 1990s were attributed to methicillin resistant *S. aureus* (MRSA)[3,6] and healthcare exposures,[7] engendering aggressive public health responses.[8] A decade of national mandatory surveillance of both methicillin sensitive *Staphylococcus aureus* (MSSA) and MRSA bacteraemia has suggested impacts from infection control measures,[9,10] but there remain over 12,000 cases annually.[11,12]

Despite a steep reduction in MRSA bacteraemia from a peak in 2003/4, rates of MSSA bacteraemia have remained relatively stable.[11,12] Reasons for this MRSA specific decline are not fully understood.[9,10] Meanwhile, studies assessing the importance of methicillin resistance to outcomes after SAB have yielded conflicting results.[3,4,13-18] These uncertainties are reflected in different public health approaches: England and Wales implemented performance targets for reducing MRSA bacteraemia only,[9] while NHS Scotland's strategy aimed to reduce all SAB to 70% of 2005/6 by 2010.[19] Some authors have warned that policy focusing on MRSA alone, may have unintended adverse effects on control of MSSA.[20] It is therefore important to understand the evolving epidemiology of both MRSA and MSSA bacteraemia.[21]

UK policy on reducing burdens from MRSA has advocated admission screening, with subsequent decolonisation and isolation, despite weaknesses in evidence.[22-25] Studies on MRSA screening have generally assessed impacts on bacteraemia by surveillance in high-risk groups,[26,27] while studies of universal surveillance have taken all MRSA infections as the primary outcome.[25,28] In 2008, a universal screening strategy was piloted in three NHS Scotland trusts[29,30] providing an opportunity to assess effects on rates of MRSA bacteraemia, compared to a previous strategy of selective screening in high-risk environments.

This study aimed to describe the changing clinical epidemiology of SAB in a large inpatient population over a five year period, and to evaluate the impact of infection control measures including universal MRSA admission screening. Our pre-specified null-hypothesis was that universal screening would not significantly reduce rates of MRSA bacteraemia, after accounting for prior trends and changes in other aspects of care in time-series intervention analysis.

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3 103 **METHODS**

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7 105 **Study design:**

8 106 This retrospective cohort study described secular trends in *S.aureus* bacteraemia in all admissions to
9 107 Aberdeen Royal Infirmary (ARI) between 2006 and 2010. A quasi-experimental before-and-after
10 108 design used time series data from the same period to assess the impact of introducing universal
11 109 admission surveillance on MRSA bacteraemia alongside other infection control practices (figure 1).
12 110 Controls were historic trends in MRSA bacteraemia and concurrent trends in MSSA bacteraemia.
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18 112 **Setting:**

19 113 ARI is a tertiary referral centre and acute teaching hospital (1000 beds, 85,000 annual admissions),
20 114 serving a population of 500,000 in North East Scotland (*NHS Grampian*). It provides a full range of
21 115 acute medical and surgical services with a 16-bedded intensive care unit (800 admissions yr⁻¹) and a
22 116 cardiac intensive care unit (6 beds, 600 admissions yr⁻¹). Microbiology services also serve the on-site
23 117 185-bedded maternity and 85-bedded children's hospitals.
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30 119 **Admission Screening Intervention:**

31 120 Universal admission screening for MRSA was introduced in NHS Grampian in August 2008 as part of
32 121 an NHS Scotland pathfinder project detailed elsewhere.[29,30] This 32 month pilot study (ending
33 122 March 2011) tested a strategy suggested as most clinically- and cost-effective by an NHS Scotland
34 123 Health Technology Assessment (supplemental file 1).[29] This involved, screening of all overnight
35 124 admissions to acute specialities (excluding obstetrics, paediatrics and psychiatry) by nasal (and
36 125 wound or device as necessary) swabs; isolation or cohorting of all patients with known or new
37 126 colonisation or infection with MRSA; and decolonising of all MRSA-positive patients admitted to any
38 127 speciality. Decolonisation therapy included five days of daily body wash with 4% chlorhexidine
39 128 gluconate and thrice-daily mupirocin nasal ointment. Patients were re-swabbed a minimum of two-
40 129 days after decolonisation and could be removed from isolation on receipt of three successive
41 130 negative swabs, taken ≥48 hours apart. Elective patients were screened at pre-admission assessment
42 131 or on admission. Compliance with screening and infection control protocols was monitored. Prior to
43 132 the intervention MRSA screening was performed on selected high-risk patients only, including
44 133 intensive care and elective surgical admissions, with an identical strategy of isolation and
45 134 decolonisation.
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3 137 **Outcomes and potential confounders:**

4 138 *S.aureus* bacteraemia was defined as the isolation of any *S. aureus* from ≥ 1 blood culture bottle.

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6 139 Cultures from the same patient within 14 days of the original isolate were considered to represent
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8 140 the same episode. Patients could be included more than once in analysis for different episodes.

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10 141 Hospital-associated (HA-) bacteraemia was defined as isolation of *S. aureus* from blood cultures > 48
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12 142 hours after admission or within 14 days of discharge, without previous history of bacteraemia or
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14 143 MRSA colonisation or infection.

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16 145 The primary outcome measure was prevalence density of MRSA and MSSA bacteraemia. Secondary
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18 146 outcomes are detailed in box 1. Secular trends in longer-term outcomes were also investigated with
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20 147 recurrence expressed as episodes per 1000 patient-months to avoid follow-up bias.

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22 149 In examining secular trends and the impacts of universal MRSA admission screening, we considered
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24 150 changes in other aspects of care and case-mix including: MRSA importation pressure (No. of patients
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26 151 MRSA-positive or with a history of MRSA at admission/1000 AOBs) length-of-stay,[3,13] bed-
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28 152 occupancy,[7] patient age,[3,4,13] admitting department,[3] hand-hygiene,[9,32-35] and antibiotic
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30 153 usage.[34-37] We considered the effects of other hospital-wide infection control measures with
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32 154 potential to affect MRSA including a national hand-hygiene campaign (January 2007) and a mixed
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34 155 persuasive and restrictive antibiotic stewardship intervention (May 2009) limiting use of antibiotics
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36 156 associated with *C.difficile* and resistant gram-positive or gram-negative infections - figure 1 and
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38 157 supplemental file 2.

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39 159 **Study population**

39 160 All patients admitted to medical, surgical, paediatric, and maternity services at ARI between 1st
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41 161 January 2006 and 31st December 2010 were eligible for inclusion in the study. This period was
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43 162 chosen as it included the time frame stated in national targets for reducing rates of SAB. A time
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45 163 series of 60 months with equivalent baseline and intervention periods (31 and 29 months), also
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47 164 facilitated a robust time-series analysis.[38] Outpatients in all specialities were excluded. Admissions
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49 165 resulting in death or discharge within 24 hours were retained in the main analysis so as to capture
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51 166 burdens from community-associated bacteraemia. Patients at risk of incident hospital-associated
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53 167 bacteraemia were those hospitalised for at least 48 hours without previous documented SAB. Follow
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55 168 up was until in-hospital death, 180 days from bacteraemia or a minimum of two weeks post-
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57 169 discharge (whichever was longest), and ended on 15th June 2011.

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3 170 **Data collection**

4 171 Electronic laboratory records were screened to identify admission screening swabs, previous or
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6 172 current MRSA colonisation or infection, episodes of *S.aureus* bacteraemia and location of sampling.
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8 173 Patient identifiers were used to identify multiple samples from the same patient.
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11 175 Health intelligence databases provided data on demographics, admission details and mortality for all
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13 176 admissions between 2006 and 2010. Aggregated data on bed-occupancy were also provided by
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15 177 month and department. For episodes of bacteraemia, data were triangulated using the hospital's
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17 178 Patient Management System. Numbers of admissions within the last 12 months and age were taken
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19 179 as a proxy of patients' baseline health.
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22 181 Details on use of '4C' (Ciprofloxacin, Cephalosporins, Clindamycin, Co-amoxiclav) and macrolide
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24 182 antibiotics (defined daily doses (DDDs)/1000 AOBs) and hand-hygiene (Litres of alcohol gel
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26 183 used/1000 AOBs; monthly average hand-hygiene compliance assessed by nationally standardised
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28 184 audit of opportunity and technique) were ascertained from pharmacy and infection control
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30 185 departments.
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33 187 Use of routinely collected data meant an almost complete dataset. Data on outcomes after
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35 188 discharge were missing for six patients (0.7%) with SAB and for obstetric or neonatal inpatients
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37 189 without bacteraemia. Outcomes were explored using a complete-case analysis or departments with
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39 190 complete data.
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42 192 **Laboratory methods:**

43 193 Screening swabs were tested by latex slide test after plating on chromogenic agar (Brilliance - Oxoid,
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45 194 UK), followed by confirmatory coagulase test. Antibiotic sensitivities were evaluated by disc-
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47 195 diffusion test. Processing of screening and clinical samples was carried out 24 hours a day, 7 days a
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49 196 week. After confirmation by laboratory staff, results were made immediately available on an
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51 197 electronic laboratory reporting system. Between 9am and 5pm daily, positive MRSA screens were
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53 198 verbally reported to nursing staff on relevant wards and infection control teams. Turnaround time
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55 199 was typically <24 hours. All *S.aureus* blood isolates were identified initially by agglutination, using
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57 200 the Prolex™ – Blue Staph Latex Kit (Pro-Lab), and subsequently by a Vitek™ instrument, using
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59 201 custom made Staphylococcus sensitivity cards (Biomerieux).
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3 204 **Statistical analysis**
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6 206 Clinical epidemiology and secular trends:
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9 208 Comparisons between characteristics of MRSA and MSSA and non-bacteraemic inpatient cohorts
10 209 were made by χ^2 , Mann-Whitney U or independent-samples *t*-tests. Univariate linear or logistic
11 210 regression was used to model associations between risk factors and rates of SAB. An indirect
12 211 standardised mortality ratio (SMR) was calculated to explore excess mortality in SAB, using all ARI
13 212 inpatients between 2006 and 2010 as the reference population, and standardising by age, gender
14 213 and speciality. Attributable mortality, defined as the excess mortality caused by bacteraemia, was
15 214 calculated using matched controls from this inpatient reference group, as crude mortality rate in
16 215 controls *minus* crude mortality rate after bacteraemia.
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19 217 Restricting analysis to the *S.aureus* bacteraemia cohort, determinants of 30-day mortality were
20 218 explored by multivariate logistic regression. *A priori* determinants of methicillin sensitivity, month
21 219 and demographics were included in a multivariate model alongside significant variables from
22 220 univariate analysis ($p < 0.10$). Interaction terms were generated for terms significantly associated by
23 221 Spearman rank correlation but retained only where contributing to model fit. Competing hazards of
24 222 inpatient mortality and being discharged alive were further explored with multivariate Cox-
25 223 regression, with censoring at date of discharge or death respectively. Length of stay was included as
26 224 a time-dependent determinant of mortality.[16]
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29 226 Secular trends in demographics, clinical characteristics, and outcomes in *S. aureus* bacteraemia
30 227 cohorts, were evaluated by logistic or linear regressions, with month of isolate as the sole
31 228 explanatory variable. Trends in rates were examined using Poisson regression, with Poisson
32 229 distribution, log-link function and the natural logarithm of AOBs as the offset. Difference in trends
33 230 by admitting department were assessed by an interaction term (department x month of study).
34 231 Multivariate Poisson regression models assessed secular trends after adjusting for changes in case-
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3 238 Impacts of universal MRSA admission screening:
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6 240 We conducted intervention analyses to model the effects of universal screening on SAB while
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8 241 controlling for hand-hygiene, antibiotic use and other dynamic explanatory factors using the Linear
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10 242 Transfer MRSA bacteraemia using the Linear Transfer Function identification method suggested by
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12 243 Pankratz[39] After ensuring stationary series , an initial transfer function model was created, with 6
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14 244 lags for all explanatory variables and an autoregressive term of order 1. An iterative process of
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16 245 eliminating non-significant terms, and identifying further autoregressive or moving average terms
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18 246 for parts of the model remaining unexplained, determined the most parsimonious LTF model. Model
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20 247 parameters were estimated using unconditional least squares and goodness-of-fit evaluated by R^2 .
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22 248 Finally, diagnostic checks were used to determine whether models adequately represented times
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24 249 series data. These included checking; the statistical significance of parameters, AR parameter
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26 250 stationarity and MA parameter invertibility, and ACF and PACF of residuals to ensure remaining
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28 251 variability was random. Analysis of concurrent trends in MSSA bacteraemia controlled for
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30 252 unidentified aspects of care or infection control affecting the clinical epidemiology of SAB.
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34 254 Intervention analysis was conducted using SCA software (Chicago, IL, USA, 1992) as described by Liu
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36 255 and Hudak.[40] All other analyses were performed using SPSS 19.0 for windows.
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275 **RESULTS**

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277 **Descriptive epidemiology**

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279 Cohort and rates of *S.aureus* bacteraemia:

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281 There were 430,452 admissions to ARI between 2006 and 2010, representing 1,430,052 acute
 282 occupied bed days (8% Intensive Care Unit, ICU). The total number of days of follow-up was
 283 7,578,805: median, 181 days (range 180 to 355 days) for episodes of SAB, and 16 days (14 to 129
 284 days) for other admissions.

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286 867 episodes of *S. aureus* bacteraemia were identified in 795 patients, including 208 cases of MRSA
 287 bacteraemia (24%). 62% of MRSA and 44% of MSSA bacteraemia were hospital-associated ($P <$
 288 0.001). Overall prevalence density of SAB was 0.61/1,000 AOBs and HA-incidence density was
 289 0.29/1,000 AOBs. Prevalence and HA-incidence were 2.1/1000 admissions and 3.0/1000
 290 admissions, respectively. Patients with SAB were more likely to be male, older and admitted to
 291 medical or ICU settings than the remainder inpatient population (table 1).

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Table 1: Characteristics of inpatient cohorts with and without *S.aureus* bacteraemia, 2006-2010

Characteristics	Cohort				P-value*	
	None <i>n</i> = 419,585	All SAB <i>n</i> = 867	MSSA <i>n</i> = 659	MRSA <i>n</i> = 208	MRSA v MSSA	All SAB v None
Overnight admissions	262,412 (63%)	864 (99%)	656 (99%)	206 (99%)	0.801	<0.001
Hospital associated (onset >48hrs)	137,520 (33%)§	416 (48%)	287 (44%)	129 (62%)	<0.001	<0.001
Demographics						
Gender (female)	242,668 (58%)	287 (33%)	227 (34%)	60 (29%)	0.14	<0.001
Mean age in years (SD)	56 (5)	58 (22)	55 (22)	65 (18)	<0.001	<0.001
Clinical background						
Admitting department (all)					<0.001	<0.001
Medical	130,209 (31%)	600 (69%)	471 (72%)	129 (62%)	0.010	<0.001
Surgical	173,851 (41%)	173 (20%)	118 (18%)	55 (26%)	0.007	<0.001
ICU	6206 (1%)	60 (7%)	37 (6%)	23 (11%)	0.007	<0.001
Paediatrics / neonatal	47726 (10%)	27 (4%)	26 (4%)	1 (1%)	0.008	<0.001
Maternity	61593 (15%)	7 (1%)	7 (1%)	0 (0%)	0.136	<0.001
Previous <i>S. aureus</i> bacteraemia	- ^a	73 (9%)	49 (8%)	24 (12%)	0.068	-
MRSA colonisation at admission (%) ^β	8134 (4.3%)	160 (19%)	72 (11%)	88 (43%)	<0.001	<0.001
Admission within past 12 months	- ^a	522 (60%)	366 (56%)	156 (75%)	<0.001	-
Median (IQR) time from admission to bacteraemia, days	-	2 (0 to 9)	1 (0 to 7)	7 (0 to 19)	0.002	-
Outcomes						
30-day mortality	-	173 (20%)	110 (17%)	63 (30%)	<0.001	-
In hospital death	7165 (2%)‡	209 (25%)‡	134 (21%)‡	75 (36%)‡	<0.001	<0.001
Median (IQR) length-of-stay, days	3.8 (3.4 -3.9)	20 (11 to 39)	19 (10 to 37)	27 (14 to 52)	<0.001	<0.001
Readmission (≤ 14 days)†	26,534 (8%)‡	119 (19%)‡	86 (17%)‡	33 (25%)‡	0.036	<0.001
Treatment failure	-	42 (4.8%)	31 (4.7%)	13 (6.3%)	0.732	-
Recurrence rate (100 patient yrs ⁻¹)	-	0.78	0.81	1.26	0.627	-

Data are n (%), mean (SD), or median (IQR). § Patients without bacteraemia admitted > 48hrs. * χ^2 , Mann-Whitney *U*, or independent-samples *t*-test. ^a data not available. ^β % eligible admissions. † In those alive at discharge, ‡ Excluding admissions to maternity and neonatal departments (data not available, n = 65,849) and episodes of SAB with incomplete data (n=6) associated with survival at discharge.

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297 There were strong associations between rate of SAB and age, days since admission and length-of-
 298 stay (figure 2). Patients colonised with MRSA at admission were 17 times more likely to develop
 299 hospital-associated MRSA bacteraemia (0.78 cases 1000 AOBDS⁻¹) than those not colonised (0.05
 300 cases 1000 AOBDS⁻¹); crude OR (95% CI) = 17.2 (15 to 20), *P* < 0.001. Methicillin-resistant
 301 bacteraemia occurred more frequently in ICU or surgical settings, older patients, following MRSA
 302 colonisation and after prolonged or recent admission. Comparing community with hospital-
 303 associated bacteraemia there were no significant differences in demographics or rates of previous
 304 admission in the last 12 months (41% vs. 37%; *P* = 0.10).

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 307 Clinical outcomes:
 308 Inpatient and 30-day all-cause mortality rates after SAB were 25% and 20% respectively, and
 309 outcomes were consistently worse than for patients without bacteraemia (table 1). Inpatient
 310 mortality was over six-times higher than expected in the SAB cohort (SMR, 95% CI 6.4, 5.7 to 7.0).
 311 Attributable inpatient mortality was 20% (MRSA 31%, MSSA 17%).

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 313 Methicillin resistance was associated with longer length-of-stay and increased readmission rates.
 314 The crude odds ratio for mortality within 30 days of isolation of MRSA versus MSSA was 2.15 (95% CI
 315 1.50 to 3.08; *p* < 0.001). A final multivariate logistic regression model confirmed age, month of study
 316 (secular trend) and hospital-associated infection as independent risk-factors for 30-day mortality,
 317 however after adjustment for these covariates methicillin resistance was not a significant
 318 determinant – table 2.

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 320 **Table 2: Multivariate logistic and Cox regression models of risk factors for 30-day mortality, inpatient mortality and**
 321 **discharge alive**

	30 day mortality ^a		Inpatient mortality ^b		Discharge alive ^c	
	OR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
MRSA	1.38 (0.93 to 2.06)	0.112	1.47 (1.09 – 1.98)	0.012	1.09 (0.89 - 1.33)	0.416
Gender (female)	1.41 (0.96 to 2.04)	0.075	1.18 (0.89-1.58)	0.244	1.06 (0.89-1.25)	0.536
Age (10 yrs ⁻¹)	1.79 (1.58 to 1.97)	<0.001	1.42 (1.29 - 1.57)	<0.001	0.86 (0.83-0.90)	<0.001
Hospital associated SAB	1.56 (1.08 to 2.26)	0.018	2.27 (1.67 to 2.27)	<0.001	1.50 (1.26-1.80)	<0.001
Secular trend per 3 months	0.87 (0.77 to 0.99)	0.028	0.92 (0.83-1.02)	0.094	-	-
Length of stay (7 days ⁻¹)*	-	-	1.02 (1.01 to 1.03)	<0.001	0.98 (0.97-0.98)	<0.001
ICU admission	-	-	-	-	0.70 (0.59-1.00)	0.052

322 OR = odds ratio, HR = Hazards Ratio, CI = confidence interval.

323 a Logistic regression for 30-day mortality. This model had good calibration (Hosmer-Lemeshow goodness of fit *p* = 0.93) and
 324 discrimination (area under receiver operator characteristic curve = 0.77).

325 b Cox (proportional hazards) regression. Model χ^2 (df) = 115 (6); *P* < 0.001

326 c Cox (proportional hazards) regression. Model χ^2 (df) = 265 (6); *P* < 0.001

327 * Entered as a time-dependent covariate.

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 329 In a multivariate Cox-regression model, methicillin resistance was associated with a nearly 50%
 330 increased hazard of inpatient death (table 2), but there was no significant difference in discharge

331 rate in survivors. Age, duration of hospitalisation and hospital-associated infection were
332 independent predictors of hazard of inpatient death.

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334 **Secular trends:**

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336 Trends in *S.aureus* bacteraemia and clinical outcomes:

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338 Prevalence density of all SAB declined from 0.73/1000 AOBs to 0.50/1000 AOBs (-41%; $P = 0.002$
339 for trend) between January 2006 and December 2010, Prevalence density of MRSA bacteraemia fell
340 73% from 0.26 to 0.07/1000 AOBs ($P < 0.001$) and HA-incidence density 82%, from 0.16 to
341 0.03/1000 AOBs ($P < 0.001$), however rates of MSSA bacteraemia were unchanged (Figure 3). An
342 increasing proportion of MRSA bacteraemia was associated with previous colonisation or infection
343 (table 3). Case-mix within the SAB cohort was otherwise stable.

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345 30-day mortality after MRSA bacteraemia declined from 37% to 13% ($P = 0.027$) but no significant
346 change was observed in mortality after MSSA bacteraemia (figure 3). By 2010, 90% of episodes of
347 bacteraemia and 86% of associated inpatient deaths were attributable to MSSA. These MRSA-
348 specific declines closely correlated with changes in rates of *all* MRSA or MSSA infection or
349 colonisation. By admitting department, declines in MRSA prevalence density, HA-incidence density
350 and mortality were significantly steeper in ICU than medical or surgical departments ($P < 0.05$ for
351 interaction term) – figure 3.

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353 **Table 3: Characteristics of *S. aureus* bacteraemia, associated outcomes and frequencies of all *S.aureus* isolates by year**
354 **of study: N (%), Mean (SD) or median (IQR).**

	Year					p value*
	2006 n = 218	2007 n = 188	2008 n=151	2009 n = 152	2010 n = 158	
<i>S.aureus</i> bacteraemia						
No (%) involving:						<0.001
MSSA	156 (72%)	140 (74%)	100 (66%)	121 (80%)	142 (90%)	
MRSA	62 (28%)	48 (26%)	51 (34%)	31 (20%)	16 (10%)	
Demographics						
Gender (female)	66 (30%)	62 (33%)	55 (36%)	55 (36%)	49 (30%)	0.603
Age (years)	57 (22)	56 (21)	58 (22)	56 (22)	57 (20)	0.744
Clinical characteristics						
Hospital Associated (%)	112 (51%)	108 (60%)	69 (46%)	75 (50%)	92 (58%)	0.750
Previous <i>S.aureus</i> bacteraemia, any (%)	10 (5%)	18 (10%)	19 (13%)	14 (10%)	12 (8%)	0.787
Previous MRSA colonisation or infection (%) [†]	24 (39%)	24 (50%)	29 (57%)	16 (52%)	10 (63%)	0.056
Admission within past 12 months (%)	134 (62%)	101 (54%)	92 (61%)	96 (63%)	99 (62%)	0.503
Outcomes						
30-day mortality	52 (24%)	39 (22%)	31 (21%)	27 (18%)	24 (15%)	0.013
In hospital death	63 (29%)	45 (25%)	34 (23%)	34 (23%)	33 (21%)	0.045
Length-of-stay (days)	19 (10-41)	17 (7-36)	27 (12-36)	22 (12-44)	19 (12-42)	0.508
Readmission (≤ 14 days)	25 (17%)	19 (14%)	25 (22%)	31 (27%)	19 (16%)	0.291
All <i>S.aureus</i> infection/colonisations						

No.(%) involving: •	<0.001				
MSSA	1682 (72%)	1532 (75%)	1250 (74%)	1416 (83%)	1351 (90%)
MRSA	638 (28%)	510 (25%)	448 (26%)	289 (17%)	151 (10%)

* Linear and logistic regressions with month of study as sole explanatory variable. † Data presented for MRSA bacteraemia only. CI = Confidence Intervals, MRSA = methicillin-resistant *Staphylococcus aureus*, AOBs = acute occupied bed days • Data available for adult, non-obstetric patients 2006 to 2010. Counts represent non-duplicate isolates (1 per patient per year).

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356

357 Trends in inpatient case mix:

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359 There were no significant trends in admitting speciality, or gender among inpatients over the five
 360 year period. Mean age of adult and all patients increased between 2006 and 2010 (+1.7, 95% CI: +1.3
 361 to +2.2 years, for all patients; $P < 0.001$), while mean length-of-stay (-1.3, -1.6 to -1.11 days; $P <$
 362 0.001) and weighted average bed occupancy (-2.6%, -4.8% to -0.4%; $P = 0.021$) declined
 363 (supplemental file 3). Considering the associations noted earlier, these changes represented
 364 opposing upward (increasing age), and downward (reduced length-of-stay, bed occupancy)
 365 pressures on rates of bacteraemia. Secular trend in MRSA prevalence density ($P = 0.03$ for trend) and
 366 HA-incidence density ($P = 0.01$) remained significant after adjusting for these changes in case-mix in
 367 a multivariate Poisson regression model.

368

369 Impacts of universal MRSA admission screening

370

371

372 Screening adherence and importation pressures:

373

374 43% of all adult, non-obstetric overnight admissions and 84% of eligible patients in high-risk
 375 environments were screened prior to routine surveillance. During universal surveillance 87% of
 376 eligible patients were screened ($n = 86,890$). A target of 90% adherence was achieved within four
 377 months of initiation and sustained thereafter, excluding a special study period in which trial of
 378 additional throat, perineum and axillae swabs and discharge screening reduced patient participation
 379 (figure 4).

380

381 MRSA prevalence at admission (importation pressure) steadily declined during the period of
 382 universal surveillance, averaging 3.1%, with 1.7% known to be previously colonised or infected with
 383 MRSA. There was an increase in episodes of MRSA bacteraemia preceded by screening at admission
 384 (95% vs. 81%; $P = 0.008$) and identified as being colonised at admission (56% vs. 38% of all
 385 bacteraemia; $P = 0.013$; 30% vs. 11% without history of MRSA; $P = 0.011$) after introduction of

386 universal surveillance. Data from all hospitals involved in the pathfinder study demonstrated that
 387 78% of MRSA positive patients were successfully isolated or cohorted, and 41% received at least 1
 388 day of decolonisation therapy.[29] Given that less than 11% of admissions to ARI stayed for more
 389 than the minimum 10 days required to identify MRSA from screening, complete a full course of
 390 decolonisation and obtain confirmatory swabs, only 4.1% of MRSA positive patient were identified
 391 as being successfully decolonised during the index admission – table 4.[29]

392

393 Patient characteristics by study period:

394

395 Case-mix remained stable between periods of selective screening and universal admission screening
 396 – table 4. However, there were significant reductions in bed occupancy, length-of-stay. There was an
 397 abrupt and permanent decline in use of '4C' and macrolide antibiotics within 3 months of the
 398 antibiotic stewardship intervention (month 11 of universal screening). Improvements in hand-
 399 hygiene were suggested by audited compliance but not by consumption of alcohol-based hand-rub.

400

401

Table 4: Characteristics pre and post-intervention

Characteristics	Selective screening only	Universal admission screening
Admission data		
No. of all admissions	210,745	209,707
No. of Acute Occupied bed days (at risk)	748,569	681,483
Mean (SD) length of stay in hospital, days	3.96 (0.23)	3.33 (0.51)
Bed-occupancy (% all available beds occupied)	79%	77%
Case-mix		
Mean (SD) age all patients, years	45.9 (0.45)	47.3 (0.57)
Mean (SD) age, ICU, medical and surgical adult services, years	55.3 (0.41)	56.4 (0.56)
Gender: n (%) of all admissions		
Female,	122,538 (58%)	120,417 (57%)
Male	88,207 (42%)	89,290 (43%)
Speciality, n (%) of all admissions		
Surgical	84,216 (40%)	89,808 (43%)
Medical	65,711 (31%)	65,098 (31%)
ICU	3312 (2%)	2954 (1%)
Maternity	31,862 (15%)	29,738 (14%)
Paediatric / neonatal	24606 (12%)	23,147 (12%)
MRSA Screening, colonisation and all <i>S.aureus</i> infections		
Number (%) of overnight admissions‡ screened for MRSA	43,158 (43%)	86,890 (87%)
Number of overnight admission screened per 1000 AOBDS	58	128
Number (%) of overnight admissions‡ positive for MRSA	2909 (3.5%)	2694 (3.1%)
Estimated number (%) of MRSA-positive patients isolated/cohorted	No data	2101 (78%)
Estimated number (%) of MRSA-positive patients receiving decolonisation	No data	1105 (41%)
Estimated (%) of MRSA-positive patients with confirmed eradication	No data	110 (4.1%)
Other infection control measures		
Hand-hygiene (Dispensed alcohol gel in Litres / 1000 AOBDS)†	38.1†	37.2
Mean (SD) monthly hand-hygiene compliance, % §	60.5% (12.3%)	92.9% (3.7%)
Mean (SD) monthly use of '4C' and macrolide antibiotics (DDD/1000 AOBDS)	698 (79.4)	416 (107.7)
Monthly use of '4C' and macrolide antibiotics as % of all antibiotic DDDs, %	66%	37%
Clinical burdens from <i>S.aureus</i> bacteraemia		
Prevalent MSSA bacteraemia (n)	353	306
Prevalent MRSA bacteraemia (n)	144	64

Hospital-associated incident MRSA bacteraemia (n)	89	29
Deaths within 30 days MSSA(n)	62	48
Deaths within 30 days MRSA(n)	51	12
Clinical burdens from other <i>S.aureus</i> infections / colonisations		
Prevalent MRSA infection (any) or colonisation (% admissions)•	1457 (1.0%)	579 (0.4%)
Prevalence density of any MRSA infection (cases/1000 AOBDS) •	2.25 (0.53)	0.96 (0.44)
Prevalent MSSA infection (any) or colonisation (% admissions)•	3932 (2.6%)	3299 (2.1%)
Prevalence density of any MSSA infection (cases/1000 AOBDS) •	5.86 (1.15)	5.49 (0.89)

DDD = Daily Defined Doses; AOBDS = Acute Occupied Bed Days; ARI = Aberdeen Royal Infirmary; "4C" antibiotics are Ciprofloxacin (all fluoroquinolones), Cephalosporins, Clindamycin, Co-amoxiclav. † Data available from Apr 2008 only (35 months). *Data available from January 2007 only (48 months). ‡ Adult, non-obstetric patients only. § Average ward compliance weighted by admissions as assessed by standardised audit methods integrating opportunity and technique from January 2007. • Data available for adult, non-obstetric patients 2006 to 2010. Counts represent non-duplicate isolates (1 per patient per year).

Time series intervention analysis:

In multivariate transfer function models, adjusting for changes in other aspects of care and prior trends (table 5 and figure 5), universal screening was associated with a 19% reduction in prevalence density (absolute change, 0.189 to 0.154 (-0.035, 95% CI: -0.049 to -0.021)/ 1000 AOBDS; $P < 0.001$), a 29% reduction in hospital-associated incidence density (0.100 to 0.071 (-0.029, -0.035 to -0.023)/1000 AOBDS; $P < 0.001$) and a 46% fall in 30-day mortality (34% to 18.4% (-15.6%, -24.1 to -7.1%); $P < 0.001$). Using targeted screening as the comparison, during universal screening the number needed to screen (NNS) to avoid one additional episode of MRSA bacteraemia was 1978. Rates of bacteraemia and 30-day mortality were also positively associated with hospital-wide consumption of fluoroquinolone and cephalosporin antibiotics 1-6 months earlier. Assuming an average regimen of 7 DDDs, the number needed to treat (NNT) to cause one additional case of MRSA bacteraemia was 179 for cephalosporins and 204 for fluoroquinolones. Compared to forecasted consumption, reduction in the use of these antibiotics following the '4C' antibiotic stewardship intervention was projected to have reduced prevalence density of MRSA bacteraemia by 0.027 (0.15 to 0.039)/1000 AOBDS. No significant relationships were identified with % Hand-hygiene compliance and effect sizes for screening were comparable across all departments. Final models explained 45-68% of variance and in all models residuals were randomly distributed.

No significant associations were found between universal screening, hand-hygiene, or antibiotic use, and rates of MSSA bacteraemia. The %SAB involving MRSA fell by 52% (from 28.6% to 15.1% (-13.5%, -20% to -7%); $P = 0.014$).

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441**Table 5: Multivariate transfer function models[†] for MRSA bacteraemia taking into account introduction of universal admission screening and changes in other aspects of care (January 2006 to December 2010)-**

Term	Order ^a	Parameter ^b (SE)	T-ratio	P-value
(a) Prevalence density of MRSA bacteraemia (cases per 1000 AOBs), R² = 0.678				
Universal MRSA admission screening intervention	3	-0.0346 (0.0071)	-4.89	<0.001
Cephalosporin use (DDDs/1000 AOBs)	6	+0.0008 (0.0004)	2.03	0.046
Fluoroquinolone use (DDDs/1000 AOBs)	5	+0.0007 (0.0002)	+3.53	<0.001
MA ^c	4	+0.7602 (0.0932)	+8.15	<0.001
AR ^d	6	-0.3100 (0.1309)	-2.37	0.019
(b) Hospital-associated incidence density of MRSA bacteraemia (cases per 1000 AOBs), R² = 0.648				
Universal MRSA admission screening intervention	3	-0.0290 (0.0032)	-8.92	<0.001
Fluoroquinolone use (DDDs/1000 AOBs)	5	+0.0006 (0.0001)	63.93	<0.001
MA1 ^c	2	+0.5801 (0.1273)	4.56	<0.001
MA2 ^c	3	+0.2960 (0.1384)	2.14	0.032
MA3 ^c	5	+0.3028 (0.1298)	2.33	0.014
(c) % SABs involving MRSA (%), R² = 0.504				
Universal MRSA admission screening intervention	3	-13.490 (3.322)	-4.06	<0.001
Fluoroquinolone use (DDDs/1000 AOBs)	5	+0.097 (0.047)	2.06	0.042
Bed-occupancy, % ^e	2	+0.201 (0.094)	2.14	0.032
MA ^c	9	-0.519 (0.115)	-4.51	<0.001
(d) 30-day mortality (%) after MRSA bacteraemia, R² = 0.448				
Universal MRSA admission screening intervention	0	-15.615 (4.349)	-3.59	<0.001
Fluoroquinolone use (DDDs/1000 AOBs)	1	+0.222 (0.023)	9.54	<0.001
MA ^c	8	-0.306 (0.108)	-2.85	0.005

[†]All series stationary before model identification.^a Delay necessary to observe the effect (in months).^b Size and direction of effect.^c MA, moving average term representing abrupt changes in bacteraemia rates or mortality in immediate future.^d AR, autoregressive term representing past values of bacteraemia rates or mortality.^e % Bed occupancy, average bed-occupancy weighted by admitting department, by month.442
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469 Discussion

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471 This retrospective cohort study identified a 41% decrease in prevalence density of all *S.aureus*
472 bacteraemia in an inpatient population from Scotland between 2006 and 2010. Secular trends were
473 attributable to steep reductions in MRSA bacteraemia. Introduction of a universal MRSA admission
474 screening programme was associated with significant reductions in rates of MRSA bacteraemia and
475 associated early mortality, whilst having no discernible impact on burdens from MSSA bacteraemia.
476 Ecological and temporal associations between MRSA bacteraemia and use of fluoroquinolones and
477 cephalosporins suggested that a subsequent antibiotic stewardship programme limiting use of these
478 agents also contributed to control of MRSA blood-stream infections.

479

480 Strengths and limitations

481 Analyses of risk-factors for SAB acquisition and outcomes were limited by a lack of information on
482 comorbidities, severity of sepsis, source control and clinical management.[4,13,41] However, age has
483 been shown to be an appropriate proxy for co-morbidity and risk of death,[13] and our estimates of
484 attributable mortality approximate those in more detailed analyses.[4] The effect of MRSA on risk of
485 30-day mortality approximated estimates from a previous meta-analysis [17] and non-significance
486 may be explained by a limited sample size.

487

488 Changes in strain distribution have been linked to secular trends in invasive *S.aureus*
489 infections,[6,10,21] with declines in epidemic strains predating decreases in MRSA in the UK.[10]
490 Reflecting national data,[10] regional studies of MRSA infections from the same period identified
491 significant increase in EMRSA-15, with a reciprocal decline in EMRSA-16.[42,43] Trends in strain may
492 have confounded, or mediated, the associations between infection control measures and SAB
493 epidemiology. [10]

494

495 Universal MRSA admission screening was introduced as part of an NHS Scotland pathfinder project,
496 precluding the use of cross-over, or controlled, trial designs as elsewhere.[40,41] Data on isolation-
497 days captured – suggested as a measure of surveillance effectiveness,[42] were also not available.
498 We attempted to minimise threats to internal validity common to quasi-experimental studies of
499 infection control measures.[22,38] A definition of bacteraemia based on blood isolates rather than
500 clinical suspicion made the study less vulnerable to detection bias whilst follow-up to a minimum of
501 two weeks post-discharge prevented attrition bias arising for changes in length of stay. An attempt
502 to identify and prevent selection and performance bias was made by identifying and controlling for,
503 changes in case-mix, importation pressure,[44] and other aspects of care,[22] before and after the

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3 504 intervention. Investigation of concurrent trends in MSSA bacteraemia provided some control for
4 505 impacts of general improvements in infection control or clinical management, and supports an
5 506 independent effect of screening on MRSA bacteraemia.[34 38] ARIMA techniques, account for non-
6 507 independence of parameters and stochastic elements in time-series. This is convergent with
7 508 understanding of the spread of resistance and infectious disease within populations,[38] and
8 509 minimises the potential for regression to the mean to account for trends.

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10 511 Transfer function models including screening, antibiotic use and bed-occupancy accounted for 45-
11 512 68% of variation in rates of bacteraemia, suggesting unmeasured factors affecting rates. Universal
12 513 screening was one of several sequentially implemented control measures for MRSA in North East
13 514 Scotland, including introduction of environmental swabbing and disinfection (2001), alcohol hand gel
14 515 (2002) and targeted admission screening (2003). The lack of accurate data on alcohol-based hand-gel
15 516 consumption, and limited baseline data before the national hand-hygiene campaign may explain a
16 517 failure to identify significant effects of hand-improving hand-hygiene [33] as described in other time-
17 518 series analysis [34,35]. Introduction of screening was likely to be associated with improved
18 519 awareness amongst healthcare workers and the public around MRSA, with potential improvements
19 520 in adherence to general infection control policy. Performance in infection control may also have
20 521 been influenced by internal audit of MRSA screening. However, non-declining trends in MSSA
21 522 suggested general infection control measures were an inadequate explanation for MRSA-specific
22 523 declines.

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24 525 Rates of MRSA colonisation, infection and bacteraemia, and effect sizes from intervention in the
25 526 present study are comparable to those described in previous investigations of universal surveillance.
26 527 [28,44-46] Findings may be generalisable to other large public hospitals with intensive care units in
27 528 high-income countries, with endemic MRSA and relatively low rates of MRSA infection.

28 529

29 530 **Comparison to literature:**

30 531 We identified a number of risk-factors for developing *S.aureus* bacteraemia and associated early
31 532 mortality consistent with previous findings, including; older age,[3,4,13] recent or prolonged
32 533 hospitalisation,[3,41] prior history of colonisation or infection,[45 47] colonisation on
33 534 admission,[47,48] and ICU admission.[9] Associations were significantly stronger for MRSA
34 535 bacteraemia.[48] Despite two meta-analyses suggesting an excess mortality in MRSA, compared to
35 536 MSSA bacteraemia,[15,17] there remains considerable debate about the importance of methicillin
36 537 resistance to outcomes.[4,13,18] Our findings suggest that much of the increase in mortality

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3 538 associated with methicillin resistance may be explained by infection of more vulnerable patients,[13-
4 539 18] often in the context of extended contact with healthcare.[15,41]
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8 541 Reflecting the findings of an earlier study from Oxfordshire, which found that MRSA-related disease
9 542 was responsible for increasing rates of SAB between 1997 and 2003,[3] our findings suggest that
10 543 subsequent declines have occurred, almost exclusively in MRSA-related disease. An equivalent
11 544 upward pressure on MSSA rates has not been observed, consistent with observations that MRSA
12 545 appears to add to, rather than displace MSSA infection.[21] These findings match experience across
13 546 the UK.[8]
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19 548 Evidence on the role of universal screening in reducing all MRSA infections, is conflicting.[28,30,44-
20 549 50] and benefits may depend on target population, screening technology and subsequent control
21 550 interventions.[47] A recent US study of routine surveillance for MRSA noted a significant downward
22 551 trend in MRSA bacteraemia in ICU but not in other hospital settings.[28] A second US study found a
23 552 decrease in hospital-wide MRSA but not MSSA bacteraemia during universal screening.[46] In
24 553 agreement with these studies, we found that rates of MRSA bacteraemia declined in parallel with all
25 554 MRSA infections,[51] and there was no reciprocal rise in hospital-wide MSSA bacteraemia or
26 555 infections.[48] Hospital-wide reductions in bacteraemia, of similar magnitude to that seen in our
27 556 study, were reported following introduction of screening in intensive care[27] or high-risk patients
28 557 only.[26] However, we identified additional declines in both general and intensive care settings,
29 558 despite a baseline scenario involving routine screening in high-risk patients. These findings also
30 559 contrast with those from a one-year review of the pathfinder study which found that although
31 560 declines in all MRSA infections/colonisations were greater in intervention than control hospitals
32 561 during universal screening the difference was non-significant.[52] We note this comparison was
33 562 limited by low numbers in control hospitals, risks of contamination where control hospitals were in
34 563 the same NHS board, a short baseline and follow-up period, and methods not accounting for non-
35 564 independence of observations in time-series and lagged effects.
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48 566 We are not aware of a previous time-series analysis describing significant impacts of universal
49 567 screening on % mortality following SAB. A lack of improvement in mortality after MSSA bacteraemia
50 568 did not suggest general improvements in care. The increased proportion of bacteraemia in those
51 569 without history of MRSA identified as positive for MRSA at admission during universal screening may
52 570 have facilitated prompt initiation of appropriate therapy. Other potential explanations include
53 571 increased awareness of invasive MRSA infection in clinical staff with routine screening, greater
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3 572 marginal benefits of universal admission screening in ICU settings,[27,28] and changes in strain
4 573 distribution.[42,43]

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7 575 Our findings suggest additional considerations in assessing utility of universal surveillance. Patients
8 576 colonised at admission were at high risk of developing hospital-associated MRSA bacteraemia and
9 577 early identification of colonised patients provides opportunities to reduce invasive infection by
10 578 decolonisation.[27] As elsewhere,[27] declines in hospital-associated infection were steeper than
11 579 those in rates including community-associated infection, coherent with reductions in transmission.
12 580 Similarly, decline in importation pressure during universal surveillance suggested interruption of
13 581 connections between prevalence of MRSA in hospital and community populations, focused in
14 582 frequently admitted patients.[53-55] However, approximately 50% of hospital-associated MRSA
15 583 bacteraemia occurred in patients not colonised at admission highlighting the limitations in admission
16 584 surveillance and the persistence of cross-transmission . [56] Other lost opportunities to prevent
17 585 transmission may arise in practice given the respective 22% and 59% of MRSA positive patients not
18 586 isolated or receiving any decolonisation therapy during the pathfinder study. The latter is particularly
19 587 concerning as effective decolonisation may be a pre-requisite for cost-effectiveness of universal
20 588 screening.[57]

21 589

22 590 As in previous studies from the region, [31,33,43] we noted the importance of antibiotic use in
23 591 hospital in determining rates of all MRSA infections in the region. Although both patient-level [37]
24 592 and ecological associations [35] between fluoroquinolone and cephalosporin use and MRSA
25 593 infection have been identified, we are not aware of an experimental or quasi-experimental study
26 594 investigating impacts of limiting their use in the control of MRSA bacteraemia specifically.
27 595 Independent effects of screening and antibiotic stewardship were of comparable magnitude
28 596 suggesting complementary roles in the control of both invasive and other MRSA infections.[36]

29 597

30 598 **Implications for practice, policy and research**

31 599 Our study suggests that universal admission screening for MRSA may have an important effect on
32 600 rates of MRSA bacteraemia, and associated mortality, beyond selective screening of high-risk
33 601 patients. However, there remains debate around the cost-effectiveness of universal surveillance in
34 602 comparison to alternative control measures,[49,57-61] risks of chlorhexidine resistance with
35 603 widespread decolonisation,[11] and opportunity costs or unintended harms associated with
36 604 isolation.[61] Subsequent to the pathfinder study, NHS Scotland has suggested hospital-wide
37 605 targeted surveillance based on clinical risk-assessment as a minimum standard.[63] This is

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3 606 convergent with an emerging consensus that admission screening based on clinical prediction rules
4 607 may offer a more efficient and pragmatic approach outside of populations with high-prevalence of
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6 608 MRSA.[47,61,64] Our findings suggest the need to consider the greater marginal benefits in
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8 609 preventing bacteraemia and associated mortality which impose disproportional healthcare and
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10 610 wider societal costs.[65] Considered alongside subsequent experience of low adherence to clinical
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12 611 risk assessment based screening in *NHS Grampian* we suggest the need to re-evaluate the benefits
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14 612 of universal screening in Scotland. Irrespective of the chosen strategy, as the additional effects of
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16 613 antibiotic stewardship in this study and effects of bed-occupancy suggest, benefits of admission
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18 614 screening will be optimised where integrated with a broader package of infection prevention and
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20 615 control measures.[28,47,56]

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24 617 The concentration of both MRSA and MSSA blood stream infections in susceptible patient groups
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26 618 with higher levels of healthcare contact suggests some measures successfully limiting invasive MRSA
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28 619 infections may be generalizable to control of all SAB. A more rigorous approach to identify and limit
29
30 620 iatrogenic sources of bacteraemia, including peripheral or central catheters,[41,44,65] is required.
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32 621 Screening for MSSA with isolation and decolonisation has been suggested for selected, high-risk
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34 622 patients.[67]

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38 624 Equally, strategies are required that account for the distinct epidemiology of MSSA and MRSA
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40 625 bacteraemia. In contrast to MRSA, the majority of MSSA bacteraemia in this study were community
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42 626 associated and occurred in younger patients. Targeted measures are required to prevent invasive
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44 627 infection in at-risk groups including IV drug users,[41,68] surgical, diabetic and renal patients.[67,69]

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48 629 Given the role of social and risk-networks in sustaining *S.aureus* transmission,[64 67] broadening
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50 630 control of SAB to the community is likely to require the commitment of multiple agencies and
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52 631 healthcare providers.

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56 633 Changes in virulence of MSSA and MRSA may account for divergence in trends in outcomes.[13]
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58 634 Genetic sequencing or typing could be used to quantify the contribution of clonal expansion to
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60 635 recent trends in SAB epidemiology. A recent multicentre study found large variation in management
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62 636 of SAB in the UK and called for high-level evidence to define optimal care.[41] Future research and
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64 637 guidelines should consider both MSSA and MRSA bacteraemia.

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3 639 In summary, this study described decreasing trends in *S. aureus* bacteraemia following a decade of
4 640 infection control policies focusing on MRSA. Expansion from targeted to universal MRSA admission
5 641 screening was associated with important reductions in MRSA bacteraemia, when combined with
6 642 isolation and decolonisation. However, findings also highlighted the need for strategies to reduce
7 643 clinical burdens from invasive MSSA infection if progress towards national targets for SAB is to be
8 644 sustained.[21]
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3 672 **Acknowledgements:** The authors would like to thank all the staff in the routine microbiology
4 673 diagnostic lab and all the clinical staff at Aberdeen Royal Infirmary, whose work made this possible.
5
6 674 We are grateful to Richard Slessor and the health intelligence services, Aberdeen for providing data
7
8 675 on admissions. We would also like to thank Health Protection Scotland for help in the
9
10 676 implementation of the pathfinder project.
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13 677
14 678 **Contributors:** BE and IMG conceived this study. The statistical analysis was performed by TL and
15 679 JMLL. All authors assisted in drafting the manuscript. Ian M Gould is the guarantor for this study.
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17 680
18 681 **Funding:** The NHS pathfinder study on universal admission screening was funded by the Scottish
19 682 Government Health Directorate. This research received no specific grant from any funding agency in
20 683 the public, commercial or not-for-profit sectors
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23
24 685 **Competing Interests:** All authors have completed the Unified Competing Interest form at
25 686 www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare
26 687 no support from any organisation for the submitted work. IM Gould has received personal and grant
27 688 financial support from companies manufacturing diagnostics and therapeutics for MRSA. B Edwards
28 689 has received grant financial support from Novartis. T Lawes and JM López-Lozano have no conflicts
29 690 to declare. TL BE JMLL IMG know of no other relationships or activities that could appear to have
30 691 influenced the submitted work.
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35 693 **Ethical approval:** Ethics approval was not required.
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37 694 Authors' note: This study used anonymised and routinely collected data from laboratory systems,
38 695 infection control, pharmacy, and health intelligence departments. Patient-orientated information on
39 696 MRSA screening, and NHS Grampian's participation in a national pathfinder project, was made
40 697 widely available in Aberdeen Royal Infirmary. This information included a statement that patient
41 698 information would be held in the strictest confidence and used only for stated purposes of informing
42 699 the NHS about the value of a national screening programme, in accordance with the Data Protection
43 700 Act 1998. The authors hold that extraction of data for the purposes of this study did not impose any
44 701 predictable additional burdens on patients at ARI and its use was justified by foreseeable benefits to
45 702 the patient populations in the NHS and the general public. The authors believe that the present
46 703 study was conducted in accordance with the Declaration of Helsinki 1964.
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48 704
49 705 **Data sharing:** Technical appendix and data available on request from the corresponding author.
50 706

References:

1. Allegranzi B, Bagheri Nejad S, et al. Burden of endemic health-care-associated infection in developing countries: systematic review and meta-analysis. *Lancet* 2011;377(9761):228-41.
2. Wilson J, Elgohari S, Livermore DM, et al. Trends among pathogens reported as causing bacteraemia in England, 2004-2008. *Clin Microbiol Infect* 2011;17(3):451-8.
3. Wyllie DH, Crook DW, Peto TEA. Mortality after *Staphylococcus aureus* bacteraemia in two hospitals in Oxfordshire, 1997-2003: cohort study. *BMJ* 2006; 333: 281-6.
4. Blot SI, Vandewoude KH, Hoste EA, et al. Outcome and attributable mortality in critically ill patients with bacteremia involving methicillin-susceptible and methicillin-resistant *Staphylococcus aureus*. *Arch Intern Med* 2002;162(19):2229-35.
5. de Kraker MEA, Davey PG, Grundmann H; on behalf of the BURDEN study group. Mortality and Hospital Stay Associated with Resistant *Staphylococcus aureus* and *Escherichia coli* Bacteremia: Estimating the Burden of Antibiotic Resistance in Europe. *PLoS Med*, 2011; 8(10): e1001104.
6. Johnson AP, Pearson A, Duckworth G. Surveillance and epidemiology of MRSA bacteraemia in the UK. *J Antimicrob Chemother*. 2005;56(3):455-62.
7. Clements A, Halton K, Graves N, et al. Overcrowding and understaffing in modern health-care systems: key determinants in methicillin-resistant *Staphylococcus aureus* transmission. *Lancet Infect Dis* 2008;8(7):427-34.
8. Pearson A, Chronias A, Murray M: Voluntary and mandatory surveillance for methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-susceptible *S. aureus* (MSSA) bacteraemia in England. *J Antimicrob Chemother*. 2009; 64 Suppl 1:i11-7.
9. Edgeworth JD. Has decolonization played a central role in the decline in UK methicillin-resistant *Staphylococcus aureus* transmission? A focus on evidence from intensive care. *J Antimicrob Chemother*. 2011;66 Suppl 2:ii41-7.
10. Wyllie D, Paul J, Crook D. Waves of trouble: MRSA strain dynamics and assessment of the impact of infection control. *J Antimicrob Chemother* 2011;66(12):2685-8
11. Health Protection Agency. Voluntary reporting of *Staphylococcus aureus* bacteraemia in England, Wales and Northern Ireland, 2010. London: Health Protection Agency; 2011.
12. Health Protection Scotland. SNBTS Annual Infection Control Report: April 2010 to March 2011. Edinburgh: Health Protection Scotland; 2011.

- 1
2
3 761 13. Shurland S, Zhan M, Bradham DD, et al. Comparison of Mortality Risk Associated With Bacteremia Due to
4 762 Methicillin-Resistant and Methicillin-Susceptible *Staphylococcus aureus*. *Infection Control and Hospital*
5 763 *Epidemiology* 2007; 28 (3): 273-9.
6 764
7 765
8 766 14. Wang JL, Chen SY, Wang JT, et al. Comparison of both clinical features and mortality risk associated with
9 767 bacteremia due to community-acquired methicillin-resistant *Staphylococcus aureus* and methicillin-susceptible
10 768 *S. aureus*. *Clin Infect Dis* 2008;46(6):799-806.
11 769
12 770
13 771 15. Whitby M, McLaws M-L, Berry G. Risk of death from methicillin-resistant *Staphylococcus aureus*
14 772 bacteraemia: a meta-analysis. *Med J Aust* 2001;175:264-7.
15 773
16 774
17 775 16. Wolkewitz M, Frank U, Philips G, et al: Mortality associated with in-hospital bacteraemia caused by
18 776 *Staphylococcus aureus*: a multistate analysis with follow-up beyond hospital discharge; *J antimicrob*
19 777 *chemother*, 2011; 66: 381-386.
20 778
21 779
22 780 17. Cosgrove SE, Sakoulas G, Perencevich EN, et al. Comparison of mortality associated with methicillin-
23 781 resistant and methicillin-susceptible *Staphylococcus aureus* bacteraemia: a meta-analysis. *Clin Infect Dis* 2003;
24 782 36: 53–9.
25 783
26 784
27 785 18. Cosgrove SE, Qi Y, Kaye KS, et al. The Impact of Methicillin Resistance in *Staphylococcus aureus*
28 786 Bacteraemia on Patient Outcomes: Mortality, Length of Stay, and Hospital Charges. *Infection Control and*
29 787 *Hospital Epidemiology*; 26(2): 166-174.
30 788
31 789
32 790 19. NHS Scotland. HEAT Targets due for delivery in 2009/10: Summary of performance. Edinburgh: NHS
33 791 Scotland Performance and Business Management;2011.
34 792
35 793
36 794 20. Paul J. Surveillance and management of all types of *Staphylococcus aureus* bacteraemia [editorial]. *BMJ*
37 795 2006; 333: 269.
38 796
39 797
40 798 21. Mostofsky E, Lipsitch M and Regev-Yochay G. Is methicillin-resistant *Staphylococcus aureus* replacing
41 799 methicillin-susceptible *S.aureus*? *J Antimicrob Chemother* 2011; 66: 2199-2214.
42 800
43 801
44 802 22. Cooper BS, Stone SP, Kibbler CC, et al. Systematic review of isolation measures in the hospital management
45 803 of methicillin resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic
46 804 modelling. *Health Technol Assess*. 2003;7(39):191-4
47 805
48 806
49 807 23. Wilcox MH. Screening for MRSA. *BMJ* 2008;336(7650):899-900.
50 808
51 809
52 810 24. Loeb M, Main C, Walker-Dilks C, et al. Antimicrobial drugs for treating methicillin-resistant *Staphylococcus*
53 811 *aureus* colonization. *Cochrane Database Syst Rev* 2003;(4): CD003340.
54 812
55 813
56 814 25. McGinagle KL, Gourlay ML, Buchanan IB. The use of active surveillance cultures in adult intensive care units
57 815 to reduce methicillin-resistant *Staphylococcus aureus*-related morbidity, mortality, and costs: a systematic
58 816 review. *Clin Infect Dis* 2008;46(11):1717-25.
59 817
60

- 1
2
3 818 26. Clancy M, Graepler A, Wilson M, Douglas I, Johnson J, Price CS. Active screening in high-risk units is an
4 819 effective and cost-avoidant method to reduce the rate of methicillin-resistant *Staphylococcus aureus* infection
5 820 in the hospital. *Infect Control Hosp Epidemiol*. 2006;27(10):1009-17.
6 821
7 822
8 823 27. Huang SS, Yokoe DS, Hinrichsen VL, et al. Impact of routine intensive care unit surveillance cultures and
9 824 resultant barrier precautions on hospital-wide methicillin-resistant *Staphylococcus aureus* bacteremia. *Clin*
10 825 *Infect Dis*, 2006;43(8):971-8.
11 826
12 827
13 828 28. Jain R, Kralovic SM, Evans ME, et al. Veterans Affairs initiative to prevent methicillin-resistant
14 829 *Staphylococcus aureus* infections. *N Engl J Med*. 2011; 364(15):1419-30.
15 830
16 831
17 832 29. Reilly JS, Stewart S, Christie P, et al. Universal screening for methicillin resistant *Staphylococcus aureus*:
18 833 interim results from the NHS Scotland pathfinder project. *J of hospital Infection* 2010;74:35-41.
19 834
20 835
21 836 30. Health Protection Scotland; National Services Scotland. NHS Scotland MRSA Screening Pathfinder
22 837 Programme Final Report Volume 1: An investigation of the Clinical Effectiveness of MRSA Screening [Report].
23 838 Glasgow: Health Protection Scotland; Feb 2011.
24 839
25 840
26 841 31. Stone SP, Cooper BS, Kibbler, CC, et al. The ORION statement: guidelines for transparent reporting of
27 842 outbreak reports and intervention studies of nosocomial infection. *Lancet Infect Dis* 2007; 7: 282-288.
28 843
29 844
30 845 32. Chen YC, Sheng WH, Wang JT, et al. Effectiveness and limitations of hand hygiene promotion on decreasing
31 846 healthcare-associated infections. *PLoS One*. 2011;6(11):e27163.
32 847
33 848
34 849 33. Sroka S, Gastmeier P, Meyer E. Impact of alcohol hand-rub use on methicillin-resistant *Staphylococcus*
35 850 *aureus*: an analysis of the literature. *J Hosp Infect*. 2010;74(3):204-11.
36 851
37 852
38 853 34. Kaier K, Hagist C, Frank U, et al. Two time-series analyses of the impact of antibiotic consumption and
39 854 alcohol-based hand disinfection on the incidences of nosocomial methicillin-resistant *Staphylococcus aureus*
40 855 infection and *Clostridium difficile* infection. *Infect Control Hosp Epidemiol*. 2009;30(4):346-53.
41 856
42 857
43 858 35. Aldeyab MA, Monnet DL, López-Lozano JM et al. Modelling the impact of antibiotic use and infection
44 859 control practices on the incidence of hospital-acquired methicillin-resistant *Staphylococcus aureus*: a time-
45 860 series analysis. *J Antimicrob Chemother*. 2008;62(3):593-600.
46 861
47 862
48 863 36. Monnet DL, Mackenzie FJ, Lopez-Lozano J-M, et al. Antimicrobial drug use and methicillin-resistant
49 864 *Staphylococcus aureus*, Aberdeen, 1996-2000. *Emerg Infect Dis*. 2004;10:1432-41.
50 865
51 866
52 867 37. Tacconelli E, De Angelis G, Cataldo MA, et al. Does antibiotic exposure increase the risk of methicillin-
53 868 resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *Journal of*
54 869 *Antimicrobial Chemotherapy*, 2008; 61: 26-38.
55 870
56 871
57 872 38. Shardell M, Harris AD, El-Kamary SS, et al. Statistical analysis and application of quasi experiments to
58 873 antimicrobial resistance intervention studies. *Clin Infect Dis*. 2007;45(7):901-7.
59 874
60

- 1
2
3 875
4 876 39. Pakratz A. Forecasting with Dynamic regression Models. New York (NY): Wiley; 1991.
5 877
6 878
7 879 40. Liu L-M, Hudak GB: Forecasting and time series analysis using the SCA statistical system. Chicago (IL):
8 880 Scientific Computing Associates; 1994.
9 881
10 882
11 883 41. Thwaites GE; United Kingdom Clinical Infection Research Group (UKCIRG). The management of
12 884 *Staphylococcus aureus* bacteraemia in the United Kingdom and Vietnam: A multi-centre evaluation. *PLoS ONE*
13 885 2010;5(12):e14170.
14 886
15 887
16 888 42. Edwards B, Milne K, Lawes T, et al. Is Vancomycin MIC 'creep' method dependent? Analysis of methicillin-
17 889 resistant *S. aureus* (MRSA) susceptibility trends in blood isolates from North East Scotland, 2006-10. *J Clin*
18 890 *Microbiol.* 2012;50(2):318-25
19 891
20 892
21 893 43. Hunt AC, Edwards B, Girvan EK, et al. Methicillin-resistant *Staphylococcus aureus* in northeastern Scotland
22 894 in 2003 to 2007: evolving strain distribution and resistance patterns. *J Clin Microbiol* 2011; 49: 1975–8.
23 895
24 896
25 897 44. Jeyaratnam D, Whitty CJM, Phillips K, et al. Impact of rapid screening tests on acquisition of methicillin
26 898 resistant *Staphylococcus aureus*: cluster randomised crossover trial. *BMJ* 2008;336: 927-30.
27 899
28 900
29 901 45. Harbarth S, Fankhauser C, Schrenzel J, et al: Universal screening for methicillin resistant *Staphylococcus*
30 902 *aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA* 2008; 299:1149-57.
31 903
32 904
33 905 46. Robicsek A, Beaumont JL, Paule SM, et al. Universal surveillance for methicillin-resistant *Staphylococcus*
34 906 *aureus* in 3 affiliated hospitals. *Ann Intern Med.* 2008;148(6):409-18.
35 907
36 908 47. Seybold U, Schubert S, Bogner JR, et al. *Staphylococcus aureus* infection following nasal colonisation: an
37 909 approach to rapid risk stratification in a university healthcare system. *J Hosp Infect* 2011; 79(4): 297-301.
38 910
39 911
40 912 46. Honda H, Krauss MJ, Coopersmith CM, et al: *Staphylococcus aureus* nasal colonization and subsequent
41 913 infection in intensive care unit patients: does methicillin resistance matter? *Infect Control Hosp Epidemiol*
42 914 2010;31(6):584-91.
43 915
44 916
45 917 47. Harbarth S, Hawkey PM, Tenover F, et al. Update on screening and clinical diagnosis of methicillin-resistant
46 918 *Staphylococcus aureus* (MRSA). *Int J Antimicrob Agents.* 2011;37(2):110-7
47 919
48 920
49 921 48. Hacek DM, Paule SM, Thomson RB, et al. Implementation of a Universal Admission Surveillance and
50 922 Decolonisation Program for Methicillin-Resistant *Staphylococcus aureus* (MRSA) reduces the number of MRSA
51 923 and total number of *S. aureus* isolates reported by the clinical laboratory. *J Clin Microbiol* 2009;47(11):3749-52.
52 924
53 925
54 926 49. Leonhardt KK, Yakusheva O, Phelan D, et al. Clinical effectiveness and cost benefit of universal versus
55 927 targeted methicillin-resistant *Staphylococcus aureus* screening upon admission in hospitals. *Infect Control Hosp*
56 928 *Epidemiol* 2011;32(8):797-803.
57 929
58 930
59
60

- 1
2
3 931 50. Hardy K, Price C, Szczepura A, et al. Reduction in the rate of methicillin-resistant *Staphylococcus aureus*
4 932 acquisition in surgical wards by rapid screening for colonization: a prospective, cross-over study. *Clin Microbiol*
5 933 *Infect* 2009; 16:333-339.
6 934
7 935
8 936 51. Walker S, Peto TEA, O'Conner L, et al. Are there better methods of monitoring MRSA control than
9 937 bacteraemia surveillance? An observational database study. *PLoS ONE* 2008;3:e2378.
10 938
11 939
12 940 52. Reilly JS, Stewart S, Christie P et al. Universal screening for methicillin-resistant *Staphylococcus aureus* in
13 941 acute care: risk factors and outcome from a multicentre study. *J Hosp Infect.* 2012;80(1):31-5.
14 942
15 943
16 944 53. MacKenzie FM, Lopez-Lozano JM, Monnet DL, et al. Temporal relationship between prevalence of
17 945 methicillin-resistant *Staphylococcus aureus* (MRSA) in one hospital and prevalence of MRSA in the surrounding
18 946 community: a time-series analysis. *J Hosp Infect* 2007;67(3):225-31.
19 947
20 948
21 949 54. Salgado CD, Farr BM, Calfee DP. Community-acquired methicillin-resistant *Staphylococcus aureus*: a meta-
22 950 analysis of prevalence and risk factors. *Clin Infect Dis* 2003;36: 131-139.
23 951
24 952
25 953 55. Wyllie DH, Peto TEA, Crook D. MRSA bacteraemia in patients on arrival in hospital: a cohort study in
26 954 Oxfordshire 1997-2003. *BMJ* 2005;331(7523):992-7.
27 955
28 956
29 957 56. van Velzen EV, Reilly JS, Kavanagh K, et al. A retrospective cohort study into acquisition of MRSA and
30 958 associated risk factors after implementation of universal screening in Scottish hospitals. *Infect Control Hosp*
31 959 *Epidemiol.* 2011;32(9):889-96.
32 960
33 961
34 962 57. Robotham JV, Graves N, Cookson BD, et al. Screening, isolation, and decolonisation strategies in the control
35 963 of methicillin resistant *Staphylococcus aureus* in intensive care units: cost effectiveness evaluation. *BMJ*
36 964 2011;343:d5694.
37 965
38 966 58. Murthy A, De Angelis G, Pittet D, et al. Cost-effectiveness of universal MRSA screening on admission to
39 967 surgery. *Clin Microbiol Infect.* 2010;16(12):1747-53.
40 968
41 969
42 970 59. Hubben G, Bootsma M, Luteijn M, et al. Modelling the costs and effects of selective and universal hospital
43 971 admission screening for Methicillin resistant *Staphylococcus aureus*. *PLoS ONE* 2011;6(3):e14783.
44 972
45 973
46 974 60. Lee BY, Bailey RR, Smith KJ, et al. Universal methicillin-resistant *Staphylococcus aureus* (MRSA) surveillance
47 975 for adults at hospital admission: an economic model and analysis. *Infect Control Hosp Epidemiol*
48 976 2010;31(6):598-606.
49 977
50 978
51 979 61. Collins J, Raza M, Ford M, et al. Review of a three-year methicillin-resistant *Staphylococcus aureus* screening
52 980 programme. *J Hosp Infect.* 2011;78(2):81-5.
53 981
54 982
55 983 62. Kirkland KB. Taking off the gloves: Towards a less dogmatic approach to the use of contact isolation.
56 984 *Clinical Infectious Diseases* 2009;48:766-771.
57 985
58 986

- 1
2
3 987 63. Health Protection Scotland: Protocol for CRA MRSA Screening National Rollout in Scotland. Glasgow: Health
4 988 Protection Scotland; 2nd September 2011.
5 989
6 990
7 991 64. Morgan DJ, Day HR, Furuno JP, et al. Improving efficiency in active surveillance for methicillin-resistant
8 992 *Staphylococcus aureus* or vancomycin-resistant *Enterococcus* at hospital admission. *Infect Control Hosp*
9 993 *Epidemiol* 2010; 31(12):1230-5.
10 994
11 995
12 996 65. Gould IM, Reilly J, Bunyan D, et al. Costs of healthcare-associated methicillin-resistant *Staphylococcus*
13 997 *aureus* and its control. *Clin Microbiol Infect*. 2010;16(12):1721-8.
14 998
15 999
16 1000 66. Hetem DJ, de Ruyter SC, Buiting AG, et al. Preventing *Staphylococcus aureus* bacteremia and sepsis in
17 1001 patients with *Staphylococcus aureus* colonization of intravascular catheters: a retrospective multicenter study
18 1002 and meta-analysis. *Medicine* 2011;90(4):284-8.
19 1003
20 1004
21 1005 67. Lucet JC, Regnier B. Screening and decolonization: does methicillin-susceptible *Staphylococcus aureus* hold
22 1006 lessons for methicillin-resistant *S. aureus*? *Clin Infect Dis* 2010;51(5):585-90.
23 1007
24 1008
25 1009 68. Gwizdala RA, Miller M, Bhat M, et al. *Staphylococcus aureus* colonization and infection among drug users:
26 1010 identification of hidden networks. *Am J Public Health*. 2011;101(7):1268-76.
27 1011
28 1012
29 1013 69. Saxena AK, Panhotra BR, Venkateshappa CK, et al. The impact of nasal carriage of methicillin-resistant and
30 1014 methicillin-susceptible *Staphylococcus aureus* (MRSA & MSSA) on vascular access-related septicemia among
31 1015 patients with type-II diabetes on dialysis. *Ren Fail*. 2002;24(6):763-777.
32 1016
33 1017
34 1018
35 1019
36 1020
37 1021
38 1022
39 1023
40 1024
41 1025
42 1026
43 1027
44 1028
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3 1044 **FIGURE LEGENDS**

4 1045 Footnotes in small plain script.
5 1046

6 1047 **Figure 1: Study overview in accordance with the ORION statement†**

7 1048 † Recommended by the Outbreak Reports and Intervention Studies Of Nosocomial infection (ORION) statement. [31]

8 1049 * '4C' antibiotics are clindamycin, ciprofloxacin (all fluoroquinolones), cephalosporins (all generations), co-amoxiclav.

9 1050 MRSA = Methicillin resistant *Staphylococcus aureus*; SAB = *Staphylococcus aureus* bacteraemia, AOBs = Acute occupied bed days; WTE =
10 1051 Whole time equivalents calculated as 37.5 hours/week*52 weeks = 1950 hours year⁻¹. ICN = Infection control nurse; ICD = Infection control
11 1052 doctor. ICU = Intensive Care Unit.
12 1053

13 1054 **Figure 2: Rates of *S.aureus* bacteraemia by age-group, length of stay and days from admission**

14 1055 P < 0.01 for all linear regression lines. Note logarithmic scale for Length-of-stay. Linear trend fitted after logarithmic transformation.
15 1056

16 1057 **Figure 3: Secular trends in prevalence density and all-cause 30-day mortality after *S. aureus* bacteraemia by
17 1058 methicillin resistance and admitting department (MRSA only)**

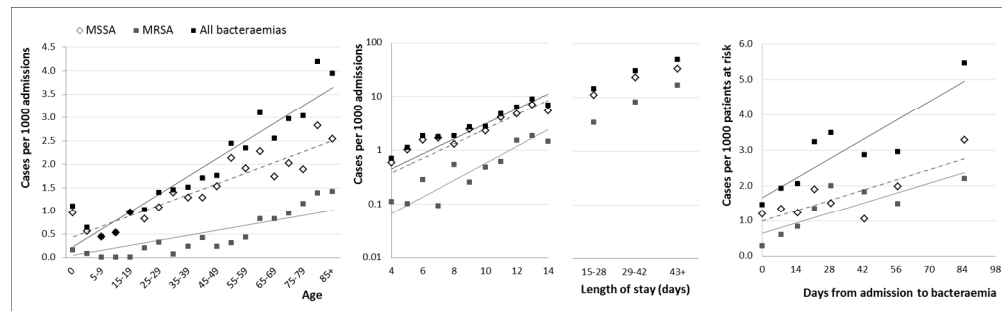
18 1059 Data aggregated in 3 month blocks. Lines represent results of trend analysis, using Poisson regression with time (month) as sole
19 1060 explanatory variable.
20 1061

21 1062 **Figure 4: Adherence to MRSA admission testing during universal surveillance (August 2008 to December
22 1063 2010)**

23 1064 * Special study period (February 2010 to August 2010) involved a trial of axillae and groin swabs.
24 1065

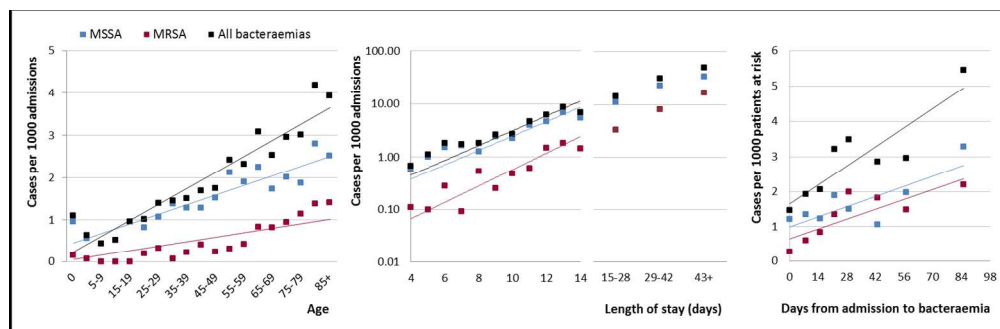
25 1066 **Figure 5: Observed trends and multivariate transfer model predictions (sum of lagged explanatory variables)
26 1067 for prevalence density, hospital associated incidence density, 30-day mortality in MRSA bacteraemia and %
27 1068 *S.aureus* bacteraemia involving MRSA
28 1069**

Setting: 1000 bed tertiary referral centre and acute teaching hospital in North East Scotland. 16-bed ICU. 1 WTE ICD and 8 WTE ICNs, 2 Surveillance nurses, 1.84 WTE antibiotic pharmacists, 0.6 WTE prescribing data analyst.	Dates: 1 st January 2006 to 31 st December 2010.	Population: 420,452 consecutive, unselected admissions with average monthly AOBDS of 23,834 (range 19,847 to 26,351). Average length-of-stay 3.8 days, bed-occupancy 78%. Endemic MRSA (E15 and E16), mean prevalence density 1.63 cases/1000 AOBDS																								
Study period	5- year retrospective cohort: January 2006 to December 2010 Cohort: All admission to acute specialities at Aberdeen Royal Infirmary, including Follow-up: 180 days from bacteraemia, or 2 wks post-discharge (whichever is longest). Ended 15 th June 2011. Data collection period: 15 th June 2011 to 1 st August 2011.																									
MRSA screening policy	Period 1: 31 months (Jan 2006 - July 2008) Selective screening for elective surgery and ICU admissions. 43,158 (43%) admissions screened 2909 (6.9% of screened) MRSA screen positive	Period 2: 29 months (August 2009- December 2011) All adult medical, surgical and ICU overnight admissions. 86,890 (87%) admissions screened. 2694 (3.1% of screened) MRSA screen positive																								
Isolation	Isolation (single-room) or cohorting (without dedicated staff) of all patients MRSA positive at admission.	As period 1.																								
Decolonisation	Decolonisation of MRSA-positive patients admitted to high-risk specialities with 5 days chlorhexidine body washes and intra-nasal mupirocin. Clearance defined by three consecutive negative swabs > 48hrs apart.	Decolonisation with same regimen as period 1 of all MRSA-positive patients admitted to <i>any</i> speciality. (see supplemental file 1)																								
General Infection control	Alcohol-based hand-rub for hand-disinfection, and standardised ward-based auditing of compliance. Improvements in compliance after national hand-hygiene campaign (January 2007).	As period 1. Hand-hygiene compliance high and stable.																								
Antibiotic policy	Annual reviews of hospital empirical antibiotic therapy guidelines (revisions April 2007 and April 2008). Revision of empirical antibiotic therapy guidelines (May 2009) recommending regimens avoiding '4C'* antibiotics and restricted supply of these antibiotics requiring permissions from medical microbiology and pharmacy (see supplemental file 2). <u>Antibiotic groups during antibiotic stewardship intervention:</u> <i>Macrolides and '4C' antibiotics:</i> Co-amoxiclav, cephalosporins, ciprofloxacin/fluoroquinolones, clindamycin <i>Targeted for increase :</i> Amoxicillin, aminoglycosides, co-trimoxazole, piperacillin/tazobactam, flucloxacillin, <i>Non-target (control):</i> Tetracyclines, trimethoprim, nitrofurantoin, β -lactamase sensitive penicillins, other. <i>Therapeutics for MRSA:</i> Teicoplanin, vancomycin, daptomycin.																									
Definitions and outcomes	<table border="1"> <tr> <td data-bbox="355 1115 571 1171">Case of <i>S.aureus</i> bacteraemia</td> <td data-bbox="571 1115 1444 1171">Non-duplicate isolate of any <i>S.aureus</i> from ≥ 1 blood culture bottle at any point during admission. Cultures from the same patient ≤ 14 days considered as same episode.</td> </tr> <tr> <td data-bbox="355 1171 571 1227">Hospital-associated (HA)-bacteraemia</td> <td data-bbox="571 1171 1444 1227">Isolation of <i>S.aureus</i> from blood-cultures > 48 hours after admission or ≤ 14 days of discharge in any patient without a history of bacteraemia or MRSA/MSSA infection or colonisation.</td> </tr> <tr> <td data-bbox="355 1227 571 1261">Prevalence</td> <td data-bbox="571 1227 1444 1261">Monthly episodes of SAB / Monthly total admissions (x 1000)</td> </tr> <tr> <td data-bbox="355 1261 571 1294">Prevalence density</td> <td data-bbox="571 1261 1444 1294">Monthly episodes of <i>S.aureus</i> bacteraemia / Monthly total AOBDS (x 1000)</td> </tr> <tr> <td data-bbox="355 1294 571 1328">Hospital-associated (HA)-incidence</td> <td data-bbox="571 1294 1444 1328">Monthly episodes of HA-<i>S.aureus</i> bacteraemia / Monthly total admissions (x 1000)</td> </tr> <tr> <td data-bbox="355 1328 571 1361">HA-incidence density</td> <td data-bbox="571 1328 1444 1361">Monthly episodes of HA-<i>S.aureus</i> bacteraemia / Monthly total AOBDS (x 1000)</td> </tr> <tr> <td data-bbox="355 1361 571 1395">%SAB involving MRSA</td> <td data-bbox="571 1361 1444 1395">Monthly episodes of MRSA bacteraemia/Monthly episodes of <i>S.aureus</i> bacteraemia (x 100)</td> </tr> <tr> <td data-bbox="355 1395 571 1429">30-day mortality, %</td> <td data-bbox="571 1395 1444 1429">Deaths from any cause ≤ 30 days of SAB/ No. of episodes of <i>S.aureus</i> bacteraemia (x 100)</td> </tr> <tr> <td data-bbox="355 1429 571 1462">Inpatient mortality, %</td> <td data-bbox="571 1429 1444 1462">Deaths from any cause in index admissions / No. of episodes of <i>S.aureus</i> bacteraemia (x 100)</td> </tr> <tr> <td data-bbox="355 1462 571 1496">Readmission</td> <td data-bbox="571 1462 1444 1496">Readmission to inpatient care at any hospital ≤ 14 days of discharge of index admission.</td> </tr> <tr> <td data-bbox="355 1496 571 1529">Treatment failure</td> <td data-bbox="571 1496 1444 1529">Any repeat blood culture isolate of <i>S.aureus</i> ≤ 6 months of initial isolate.</td> </tr> <tr> <td data-bbox="355 1529 571 1563">Recurrence</td> <td data-bbox="571 1529 1444 1563">Repeat blood isolate of <i>S.aureus</i> with the same susceptibility >6 months from initial isolate.</td> </tr> </table>		Case of <i>S.aureus</i> bacteraemia	Non-duplicate isolate of any <i>S.aureus</i> from ≥ 1 blood culture bottle at any point during admission. Cultures from the same patient ≤ 14 days considered as same episode.	Hospital-associated (HA)-bacteraemia	Isolation of <i>S.aureus</i> from blood-cultures > 48 hours after admission or ≤ 14 days of discharge in any patient without a history of bacteraemia or MRSA/MSSA infection or colonisation.	Prevalence	Monthly episodes of SAB / Monthly total admissions (x 1000)	Prevalence density	Monthly episodes of <i>S.aureus</i> bacteraemia / Monthly total AOBDS (x 1000)	Hospital-associated (HA)-incidence	Monthly episodes of HA- <i>S.aureus</i> bacteraemia / Monthly total admissions (x 1000)	HA-incidence density	Monthly episodes of HA- <i>S.aureus</i> bacteraemia / Monthly total AOBDS (x 1000)	%SAB involving MRSA	Monthly episodes of MRSA bacteraemia/Monthly episodes of <i>S.aureus</i> bacteraemia (x 100)	30-day mortality, %	Deaths from any cause ≤ 30 days of SAB/ No. of episodes of <i>S.aureus</i> bacteraemia (x 100)	Inpatient mortality, %	Deaths from any cause in index admissions / No. of episodes of <i>S.aureus</i> bacteraemia (x 100)	Readmission	Readmission to inpatient care at any hospital ≤ 14 days of discharge of index admission.	Treatment failure	Any repeat blood culture isolate of <i>S.aureus</i> ≤ 6 months of initial isolate.	Recurrence	Repeat blood isolate of <i>S.aureus</i> with the same susceptibility >6 months from initial isolate.
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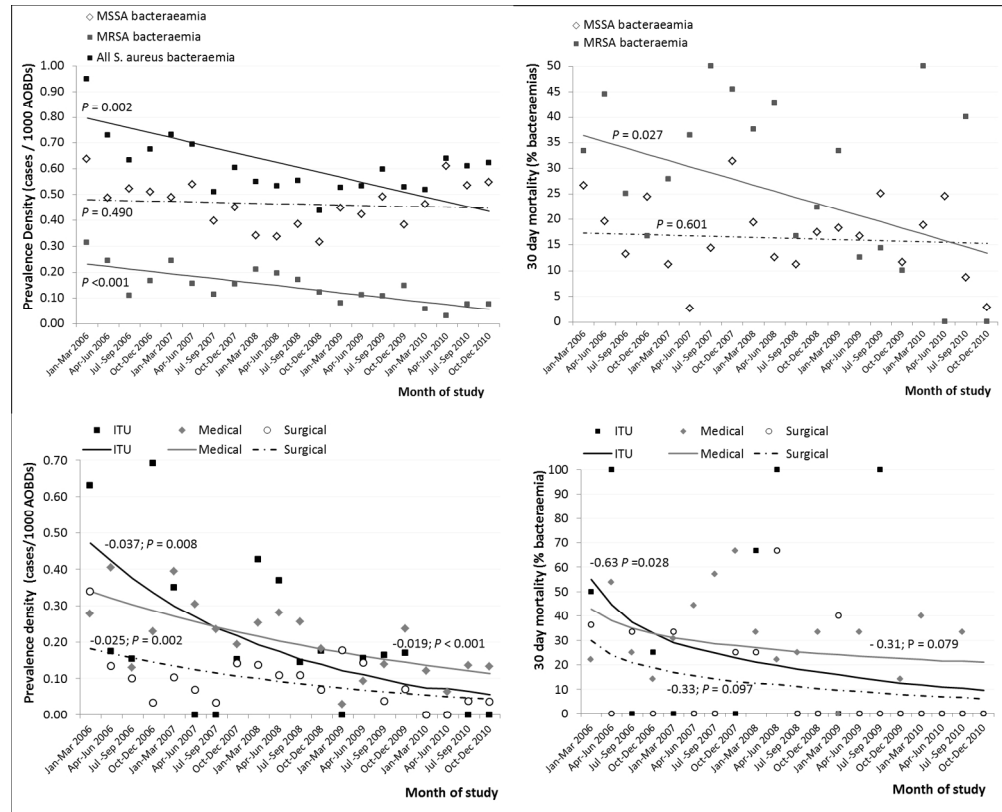
Rates of *S.aureus* bacteraemia by age-group, length of stay and days from admission
 $P < 0.01$ for all linear regression lines. Note logarithmic scale for Length-of-stay. Linear trend fitted after logarithmic transformation.

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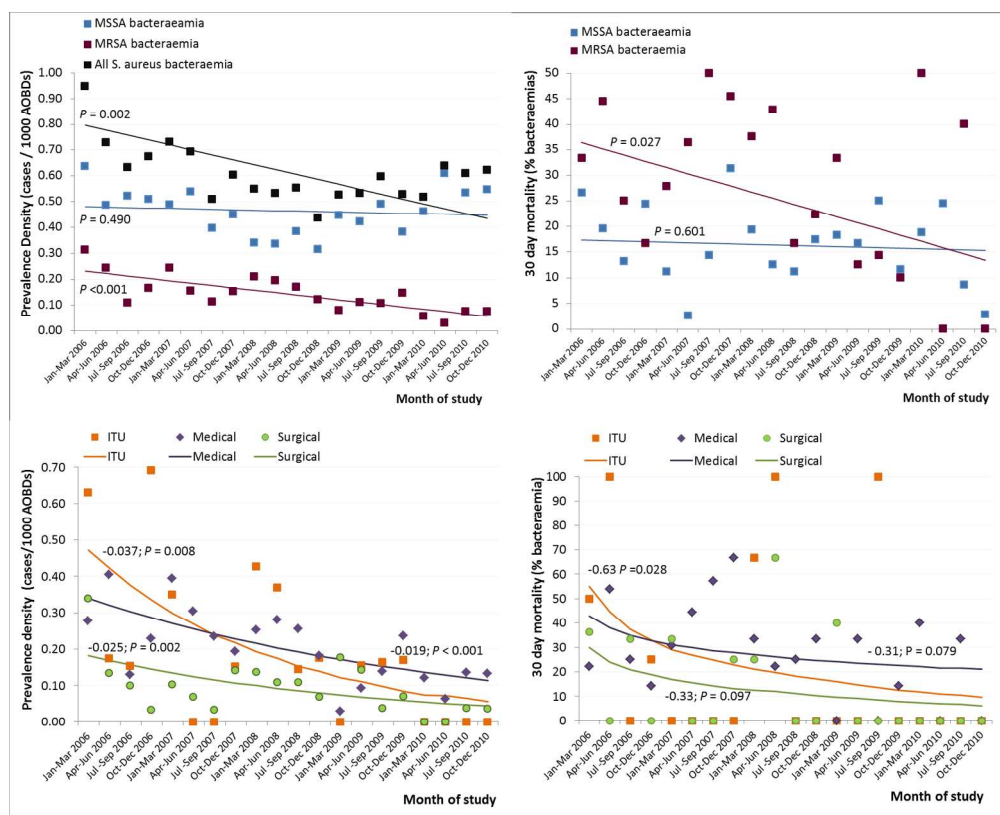


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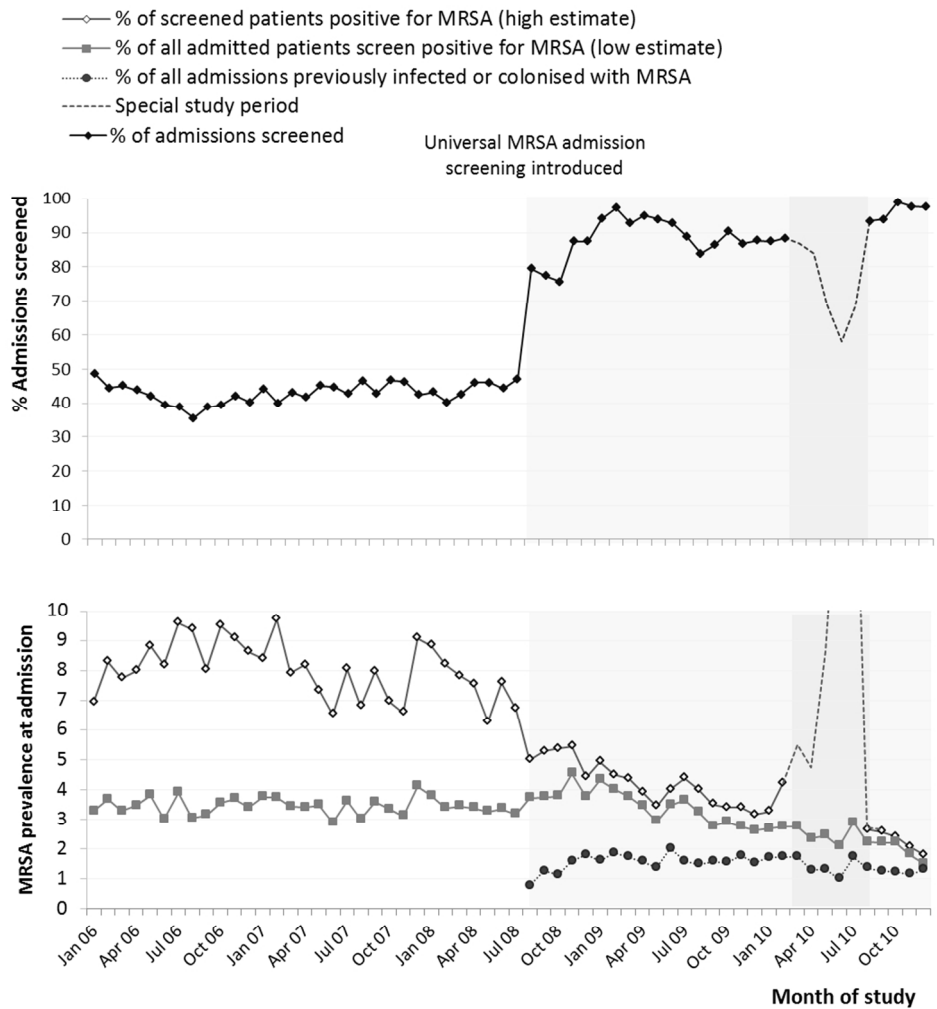
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Secular trends in prevalence density and all-cause 30-day mortality after *S. aureus* bacteraemia by methicillin resistance and admitting department (MRSA only)
Data aggregated in 3 month blocks. Lines represent results of trend analysis, using Poisson regression with time (month) as sole explanatory variable.

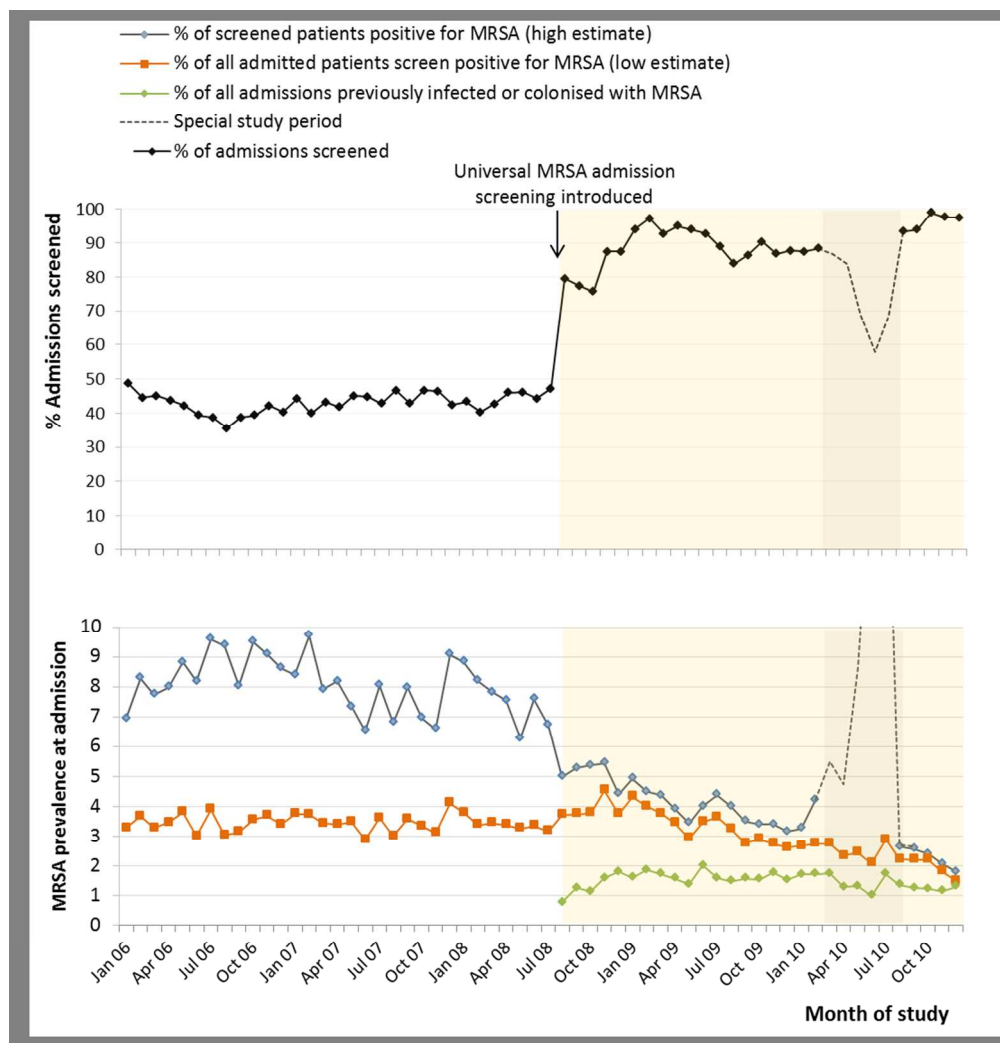


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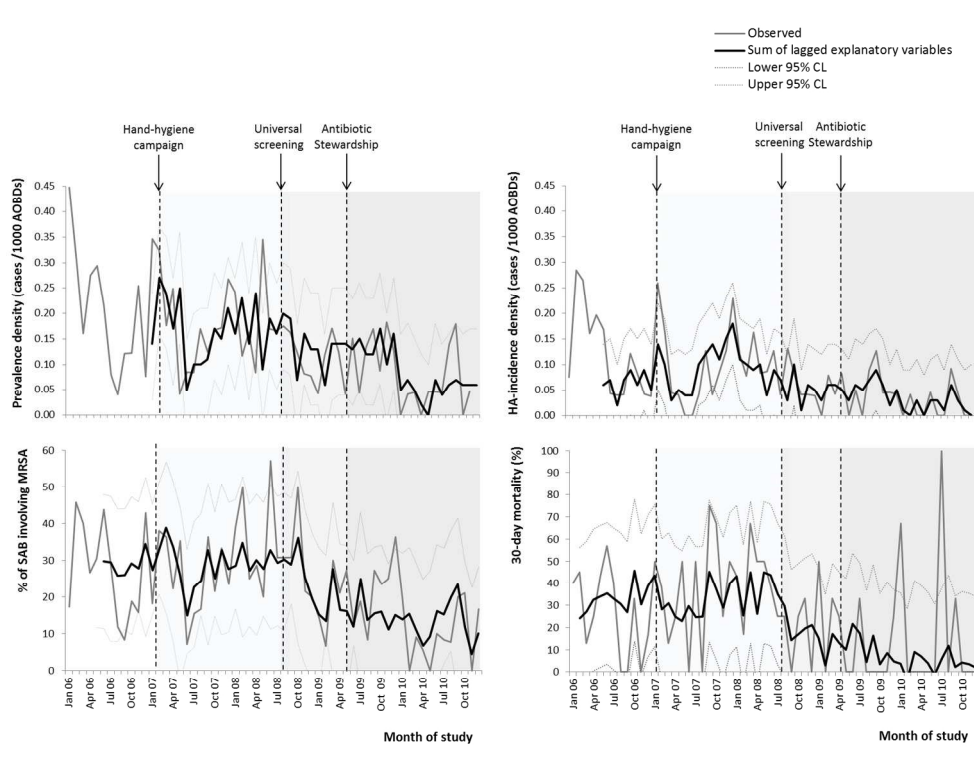
Adherence to MRSA admission testing during universal surveillance (August 2008 to December 2010) *A special study period (February 2010 to August 2010) involved a trial of axillae and groin swabs.

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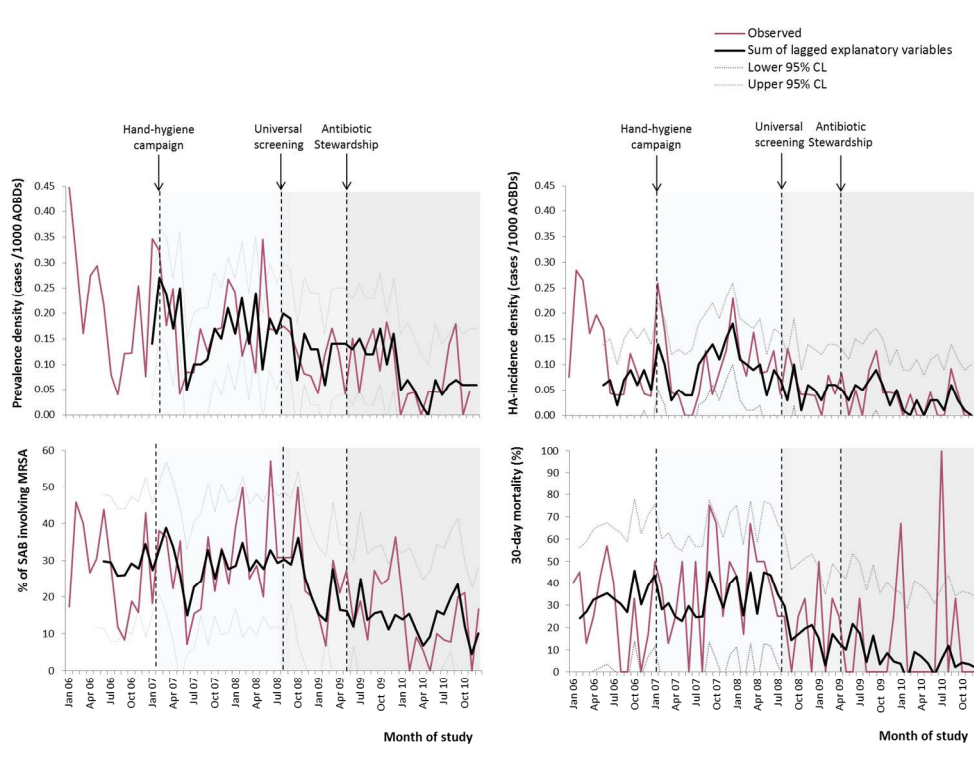
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Observed trends and multivariate transfer model predictions (sum of lagged explanatory variables) for prevalence density, hospital associated incidence density, 30-day mortality in MRSA bacteraemia, and % *S.aureus* bacteraemia involving MRSA.

View only



Observed trends and multivariate transfer model predictions (sum of lagged explanatory variables) for prevalence density, hospital associated incidence density, 30-day mortality in MRSA bacteraemia, and % *S.aureus* bacteraemia involving MRSA.

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