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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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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.

ABSTRACT

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

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

Setting: Teaching hospital in North East Scotland.

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

Intervention: Universal admission screening programme for MRSA introduced in August 2008 (NHS Scotland pathfinder project), incorporating isolation and selective decolonisation.

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

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

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

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.

METHODS

Study design:

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

Setting:

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

Admission Screening Intervention:

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

Outcomes and potential confounders:

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

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

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

Box 1: Definitions of outcomes

- **Prevalence** = $\frac{\text{All episodes of } S.\ aureus \text{ bacteraemia (SAB)}}{\text{All admissions}} \times 1000$
- **Prevalence density** = $\frac{\text{All episodes of } S.aureus \text{ bacteraemia}}{\text{Acute Occupied Bed Days}} \times 1000$
- **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.

Study population

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

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

Data collection

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

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

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

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

Laboratory methods:

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

All *S.aureus* blood isolates were identified initially by agglutination, using the Prolex™ – Blue Staph Latex Kit (Pro-Lab), and subsequently by a Vitek™ instrument, using custom made Staphylococcus sensitivity cards (Biomerieux).

Statistical analysis

Clinical epidemiology and secular trends:

Comparisons between characteristics of MRSA and MSSA and non-bacteraemic inpatient cohorts were made by χ^2, Mann-Whitney U or independent-samples *t*-tests. Univariate linear or logistic regression was used to model associations between risk factors and rates of SAB. An indirect standardised mortality ratio (SMR) was calculated to explore excess mortality in SAB, using all ARI inpatients between 2006 and 2010 as the reference population, and standardising by age, gender and speciality. Attributable mortality, defined as the excess mortality caused by bacteraemia, was calculated using matched controls from this inpatient reference group, as crude mortality rate in controls *minus* crude mortality rate after bacteraemia.

Restricting analysis to the *S.aureus* bacteraemia cohort, determinants of 30-day mortality were explored by multivariate logistic regression. *A priori* determinants of methicillin sensitivity, month and demographics were included in a multivariate model alongside significant variables from univariate analysis (p <0.10). Interaction terms were generated for terms significantly associated by Spearman rank correlation but retained only where contributing to model fit. Competing hazards of inpatient mortality and being discharged alive were further explored with multivariate Cox-regression, with censoring at date of discharge or death respectively. Length of stay was included as a time-dependent determinant of mortality after SAB.[16]

Secular trends in demographics and clinical characteristics of *S. aureus* bacteraemia cohorts, were evaluated by logistic or linear regressions, with month of isolate as the sole explanatory variable. Trends in rates were examined using Poisson regression, with Poisson distribution, log-link function and Ln(AOBDs) as the offset. Monthly count of bacteraemia or death was the dependent variable and month of study the independent variable. Multivariate Poisson regression models assessed secular trends after adjusting for changes in case-mix.

Impacts of universal MRSA admission screening:

We conducted intervention analyses to model the effects of universal screening and dynamic explanatory factors on MRSA bacteraemia using the Linear Transfer Function identification method suggested by Pankratz.[35] After ensuring stationary series , an initial transfer function model was

created, with 6 lags for all explanatory variables and an autoregressive term of order 1. An iterative process of eliminating non-significant terms, and identifying further autoregressive or moving average terms for parts of the model remaining unexplained, determined the most parsimonious LTF model. Model parameters were estimated using unconditional least squares and goodness-of-fit evaluated by R^2. Finally, diagnostic checks were used to determine whether models adequately represented times series data. These included checking; the statistical significance of parameters, AR parameter stationarity and MA parameter invertibility, and ACF and PACF of residuals to ensure remaining variability was random. Analysis of concurrent trends in MSSA bacteraemia controlled for unidentified aspects of care or infection control affecting the clinical epidemiology of SAB.

Intervention analysis was conducted using SCA software (Chicago, IL, USA, 1992) as described by Liu and Hudak.[36] All other analyses were performed using SPSS 19.0 for windows.

RESULTS

Descriptive epidemiology

Cohort and rates of S.aureus bacteraemia:

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

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

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 *S. aureus* bacteraemia	-[α]	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	-[α]	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. [α] 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.

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

Clinical outcomes:

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

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

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 X^2 (df) = 115 (6); P < 0.001

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

* Entered as a time-dependent covariate.

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

Secular trends:

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

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

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

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					
	2006 n = 218	2007 n = 188	2008 n=151	2009 n = 152	2010 n = 158	p value*
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 *S.aureus* 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

Trends in inpatient case mix:

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

Impacts of universal MRSA admission screening

Screening adherence and importation pressures:

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

Patient characteristics by study period:

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

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" Antiobiotic usage (% of all antibiotic DDDs / 1000 AOBDs)*	41%*	29%
Hand-hygiene (Dispensed alcohol gel in Litres / 1000 AOBDs)†	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 *S.aureus* 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

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

Time series intervention analysis:

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

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

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.
[a] Delay necessary to observe the effect (in months).
[b] Size and direction of effect.
[c] AR, autoregressive term representing past values of bacteraemia rates or mortality.
[d] MA, moving average term representing abrupt changes in bacteraemia rates or mortality in immediate future.
[e] Length-of-stay, average inpatient length-of-stay by month,
[f] % Bed occupancy, average bed-occupancy weighted by admitting department, by month.

Discussion

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

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

Strengths and limitations

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

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

Universal MRSA admission screening was introduced as part of an NHS Scotland pathfinder project, precluding the use of cross-over, or controlled, trial designs as elsewhere.[40,41] Data on isolation-days captured – suggested as a measure of surveillance effectiveness,[42] were also not available. We attempted to minimise threats to internal validity common to quasi-experimental studies of infection control measures.[22,34] A definition of bacteraemia based on blood isolates rather than clinical suspicion made the study less vulnerable to detection bias whilst follow-up to a minimum of two weeks post-discharge prevented attrition bias arising for changes in length of stay. An attempt to identify and prevent selection and performance bias was made by identifying and controlling for, changes in case-mix, importation pressure,[40] and other aspects of care,[22] before and after the intervention. Investigation of concurrent trends in MSSA bacteraemia provided some control for impacts of general improvements in infection control or clinical management, and supports an

independent effect of screening on MRSA bacteraemia.[34] ARIMA techniques, account for non-independence of parameters and stochastic elements in time-series. This is convergent with understanding of the spread of resistance and infectious disease within populations,[32,34] and minimises the potential for regression to the mean to account for trends.

Transfer function models including screening, length-of-stay and bed-occupancy accounted for 35-48% of variation in rates of bacteraemia, suggesting unmeasured factors affecting rates. Universal screening was one of several sequentially implemented control measures for MRSA in North East Scotland, including introduction of environmental swabbing and disinfection (2001), alcohol hand gel (2002) and targeted admission screening (2003) [31] Antibiotic use in hospital has been linked to rates of all MRSA infections in the region.[31,33,43] Decline in the use of "4C" antibiotics occurred during implementation of screening. However, this antibiotic stewardship policy started 9 months after universal screening and with typical lags of 4-8 months between changes in antibiotic usage and rates of MRSA infections,[32] any impacts would have occurred late in the study period. Introduction of screening was likely to be associated with improved awareness amongst healthcare workers and the public around MRSA, with potential improvements in adherence to general infection control policy such as hand hygiene. Performance in infection control may also have been influenced by internal audit of MRSA screening. However, non-declining trends in MSSA suggested general infection control measures were an inadequate explanation for MRSA-specific declines.

Rates of MRSA colonisation, infection and bacteraemia, and effect sizes from intervention in the present study are comparable to those described in previous investigations of universal surveillance.[26,41] Findings may be generalisable to other large public hospitals with intensive care units in high-income countries, with endemic MRSA and relatively low rates of MRSA infection.

Comparison to literature:

We identified a number of risk-factors for developing *S.aureus* bacteraemia and associated early mortality consistent with previous findings, including; older age,[3,4,13] recent or prolonged hospitalisation,[3,37,44] prior history of colonisation or infection,[45] colonisation on admission,[45,46] and ITU admission.[9] Associations were significantly stronger for MRSA bacteraemia.[46] Despite two meta-analyses suggesting an excess mortality in MRSA, compared to MSSA bacteraemia,[15,17] there remains considerable debate about the importance of methicillin resistance to outcomes.[4,13,18] Our findings suggest that much of the increase in mortality

associated with methicillin resistance may be explained by infection of more vulnerable patients,[13-18,37] often in the context of extended contact with healthcare.[15,37]

Reflecting the findings of an earlier study from Oxfordshire, which found that MRSA-related disease was responsible for increasing rates of SAB between 1997 and 2003,[3] our findings suggest that subsequent declines have occurred, almost exclusively in MRSA-related disease. An equivalent upward pressure on MSSA rates has not been observed, consistent with observations that MRSA appears to add to, rather than displace MSSA infection.[21] These findings match experience across the UK.[8]

Evidence on the role of universal screening in reducing all MRSA infections, is conflicting.[28,30,41,42,47-50] and benefits may depend on target population, screening technology and subsequent control interventions.[47] A recent US study of routine surveillance for MRSA noted a significant downward trend in MRSA bacteraemia in ICU but not in other hospital settings.[30] A second US study found a decrease in hospital-wide MRSA, but not MSSA bacteraemia during universal screening.[42] Hospital-wide reductions in bacteraemia, of similar magnitude to that seen in our study, were reported following introduction of screening in intensive care[29] or high-risk patients only.[28] In agreement with these studies, we found that rates of MRSA bacteraemia declined in parallel with all MRSA infections,[51] and there was no reciprocal rise in hospital-wide MSSA bacteraemia or infections.[48]

Our findings suggest additional considerations in assessing utility of universal surveillance. Patients colonised at admission were at high risk of developing hospital-associated MRSA bacteraemia and early identification of colonised patients provides opportunities to reduce invasive infection by decolonisation.[27] As elsewhere,[29] declines in hospital-associated infection were steeper than those in rates including community-associated infection, coherent with reductions in transmission. Similarly, decline in importation pressure during universal surveillance suggested interruption of connections between prevalence of MRSA in hospital and community populations, focused in frequently admitted patients.[43,52,53] However, approximately 50% of hospital-associated MRSA bacteraemia occurred in patients not colonised at admission highlighting the limitations in admission surveillance and the persistence of cross-transmission.[54]

Implications for practice, policy and research

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

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

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

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

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]

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Authors' note: This study used anonymised and routinely collected data from laboratory systems, infection control, pharmacy, and health intelligence departments. Patient-orientated information on MRSA screening, and NHS Grampian's participation in a national pathfinder project, was made widely available in Aberdeen Royal Infirmary. This information included a statement that patient information would be held in the strictest confidence and used only for stated purposes of informing the NHS about the value of a national screening programme, in accordance with the Data Protection Act 1998. The authors hold that extraction of data for the purposes of this study did not impose any predictable additional burdens on patients at ARI and its use was justified by foreseeable benefits to the patient populations in the NHS and the general public. The authors believe that the present study was conducted in accordance with the Declaration of Helsinki 1964.

Data sharing: Technical appendix available on request from the corresponding author.

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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[§]

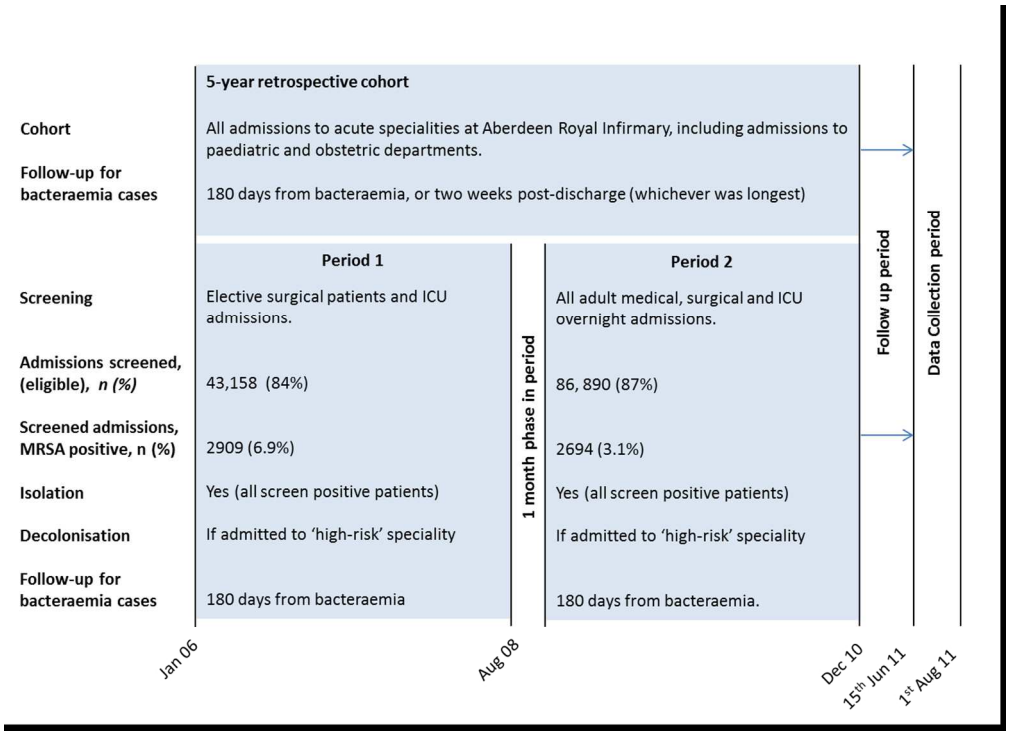
***** Prevalence density (t) = 0.189 + 0.044*Length-of-stay(t-1) – 0.315*prevalence-density(t-6) – 0.053* U(t).

[†] HA-associated incidence density (t) = 0.100 + 0.476*HA incidence-density(t-1) – 0.062* U(t).

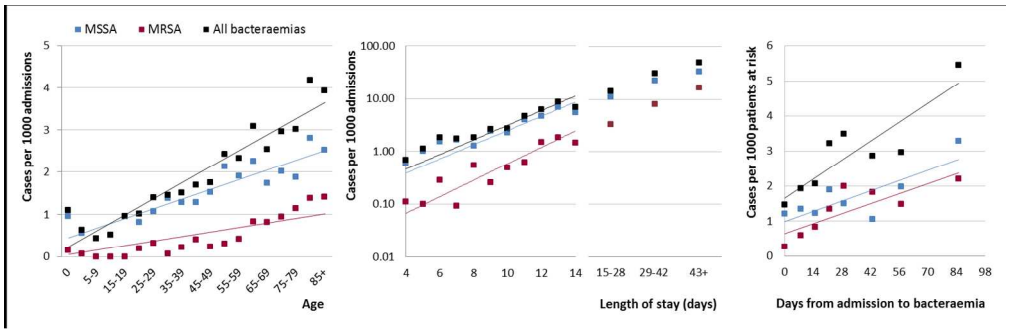
[‡] 30-day mortality (t) = 0.189 + 0.454*%BedOcc (t-2) – 0.349*30-day mortality(t-6) – 11.0* U(t).

[§] %SABsMRSA (t) = 0.189 + 0.360*%BedOcc (t-4) – 0.457*%SABsMRSA(t-9)– 0.293*%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).

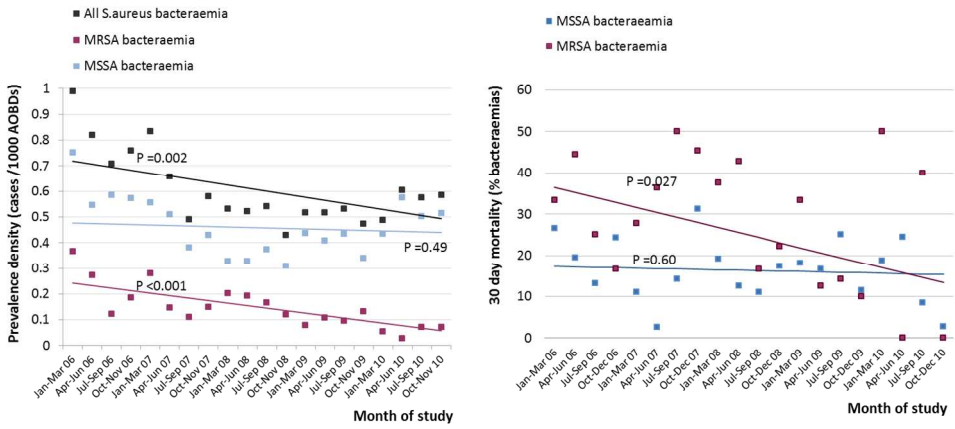


Study timeline



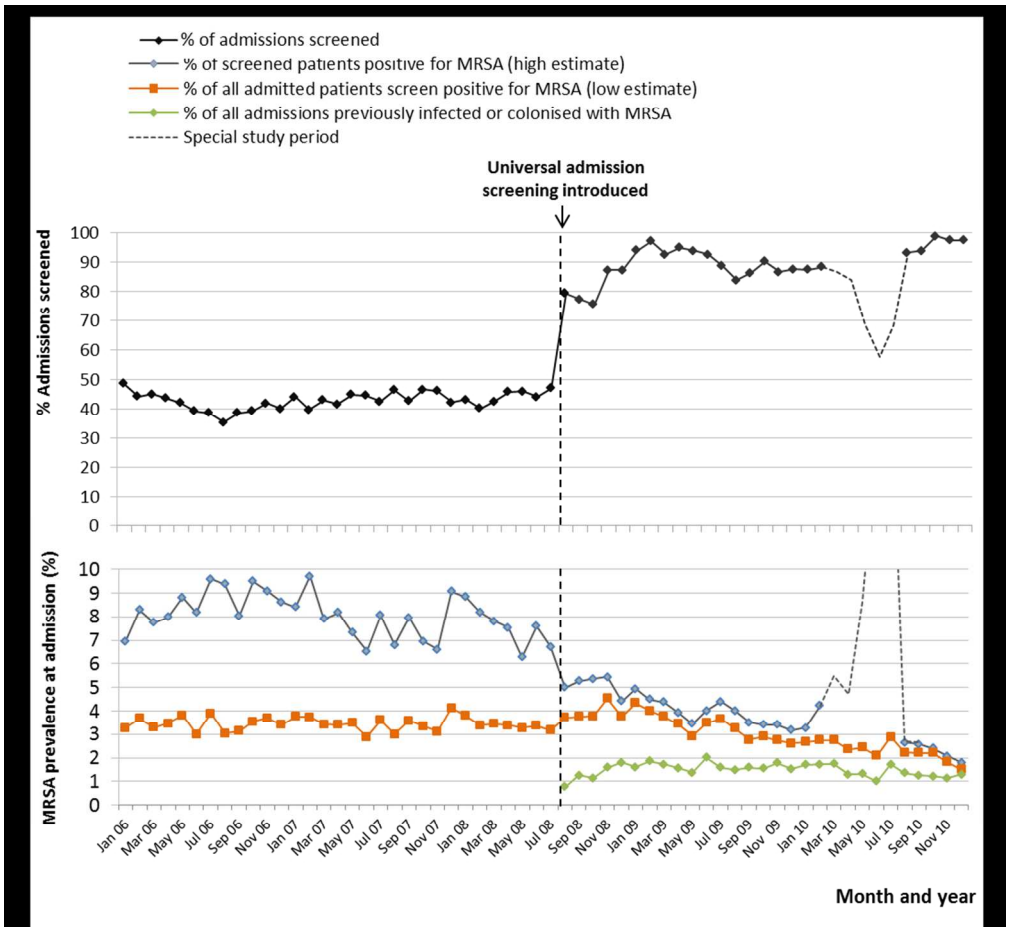
Rates of S.aureus bacteraemia by age-group, length of stay and days from admission

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



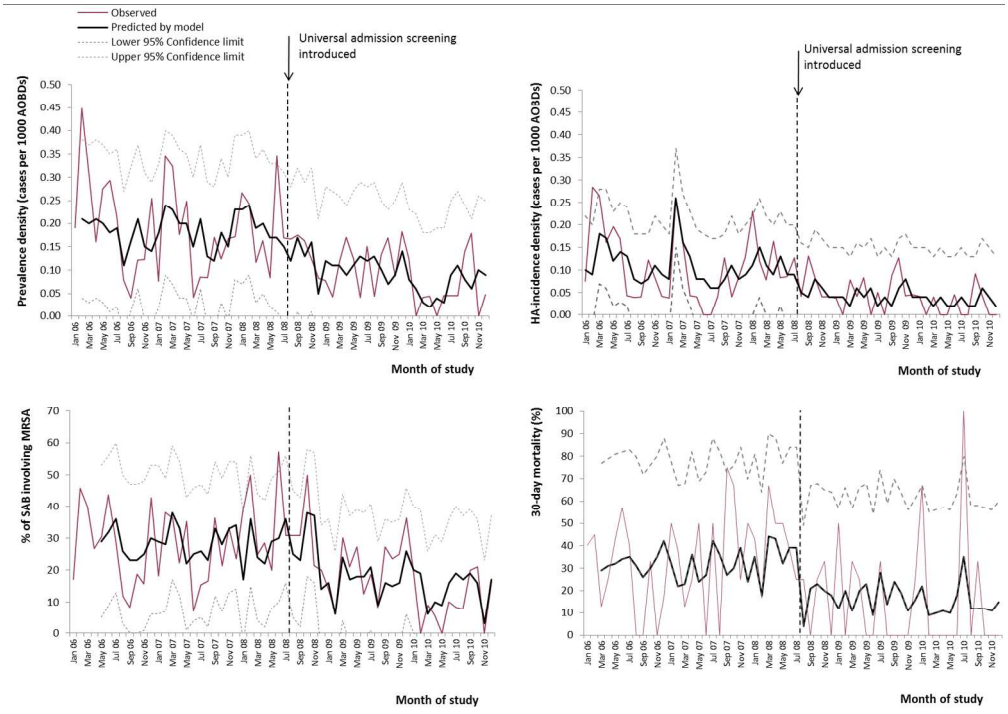
Secular trends in prevalence density and all-cause 30-day mortality after S. aureus bacteraemia by methicillin resistance

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



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

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

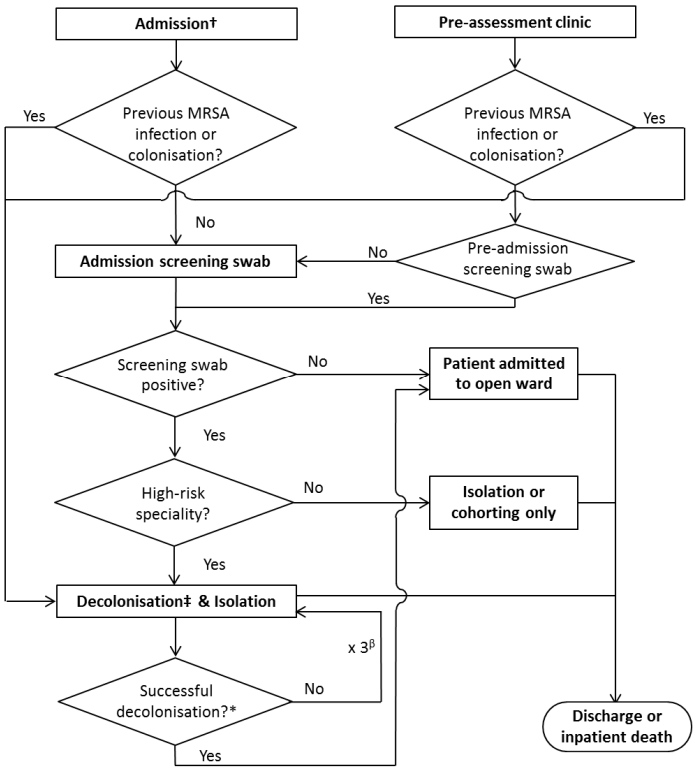
	Item No	Recommendation	Identification in manuscript		Notes
			Page	Line	
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2	Title, 6-7	**See Title and Abstract:** Retrospective cohort study and time series intervention analysis Brief explanation 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	15	Table 5 358-368	**See results: a) Secular trends b) Impacts of universal MRSA admission screening c) Table 2,3,5 and 6**
		(*b*) Report category boundaries when continuous variables were categorized	-	-	Not used.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	16 & 17	476-482 503-516	See results: a) Impacts of universal MRSA admission screening. b) Tables 5 and 6 Absolute and relative change in outcomes reported
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.

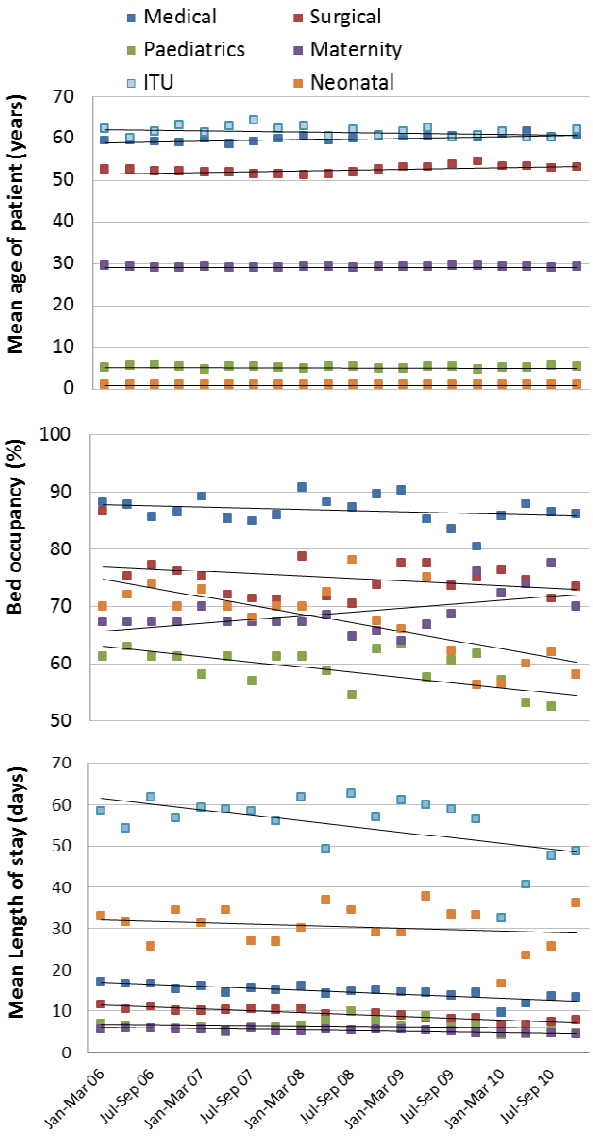
*Give information separately for exposed and unexposed groups.

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



BMJ open

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

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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

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

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

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Results : 1304
Discussion : 1939
Main Manuscript (excluding abstract) : 5083

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 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 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.

ABSTRACT

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

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

Setting: Teaching hospital in North East Scotland.

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

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

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

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

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

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

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.

METHODS

Study design:

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

Setting:

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

Admission Screening Intervention:

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

Outcomes and potential confounders:

S.aureus bacteraemia was defined as the isolation of any *S. aureus* from ≥ 1 blood culture bottle. Cultures from the same patient within 14 days of the original isolate were considered to represent the same episode. Patients could be included more than once in analysis for different episodes. Hospital-associated (HA-) bacteraemia was defined as isolation of *S. aureus* from blood cultures > 48 hours after admission or within 14 days of discharge, without previous history of bacteraemia or MRSA colonisation or infection.

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

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

Study population

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

Data collection

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

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

Details on use of '4C' (Ciprofloxacin, Cephalosporins, Clindamycin, Co-amoxiclav) and macrolide antibiotics (defined daily doses (DDDs)/1000 AOBDs) and hand-hygiene (Litres of alcohol gel used/1000 AOBDs; monthly average hand-hygiene compliance assessed by nationally standardised audit of opportunity and technique) were ascertained from pharmacy and infection control departments.

Use of routinely collected data meant an almost complete dataset. Data on outcomes after discharge were missing for six patients (0.7%) with SAB and for obstetric or neonatal inpatients without bacteraemia. Outcomes were explored using a complete-case analysis or departments with complete data.

Laboratory methods:

Screening swabs were tested by latex slide test after plating on chromogenic agar (Brilliance - Oxoid, UK), followed by confirmatory coagulase test. Antibiotic sensitivities were evaluated by disc-diffusion test. Processing of screening and clinical samples was carried out 24 hours a day, 7 days a week. After confirmation by laboratory staff, results were made immediately available on an electronic laboratory reporting system. Between 9am and 5pm daily, positive MRSA screens were verbally reported to nursing staff on relevant wards and infection control teams. Turnaround time was typically <24 hours. All *S.aureus* blood isolates were identified initially by agglutination, using the Prolex™ – Blue Staph Latex Kit (Pro-Lab), and subsequently by a Vitek™ instrument, using custom made Staphylococcus sensitivity cards (Biomerieux).

Statistical analysis

Clinical epidemiology and secular trends:

Comparisons between characteristics of MRSA and MSSA and non-bacteraemic inpatient cohorts were made by χ^2, Mann-Whitney U or independent-samples *t*-tests. Univariate linear or logistic regression was used to model associations between risk factors and rates of SAB. An indirect standardised mortality ratio (SMR) was calculated to explore excess mortality in SAB, using all ARI inpatients between 2006 and 2010 as the reference population, and standardising by age, gender and speciality. Attributable mortality, defined as the excess mortality caused by bacteraemia, was calculated using matched controls from this inpatient reference group, as crude mortality rate in controls *minus* crude mortality rate after bacteraemia.

Restricting analysis to the *S.aureus* bacteraemia cohort, determinants of 30-day mortality were explored by multivariate logistic regression. *A priori* determinants of methicillin sensitivity, month and demographics were included in a multivariate model alongside significant variables from univariate analysis (p <0.10). Interaction terms were generated for terms significantly associated by Spearman rank correlation but retained only where contributing to model fit. Competing hazards of inpatient mortality and being discharged alive were further explored with multivariate Cox-regression, with censoring at date of discharge or death respectively. Length of stay was included as a time-dependent determinant of mortality.[16]

Secular trends in demographics, clinical characteristics, and outcomes in *S. aureus* bacteraemia cohorts, were evaluated by logistic or linear regressions, with month of isolate as the sole explanatory variable. Trends in rates were examined using Poisson regression, with Poisson distribution, log-link function and the natural logarithm of AOBDs as the offset. Difference in trends by admitting department were assessed by an interaction term (department x month of study). Multivariate Poisson regression models assessed secular trends after adjusting for changes in case-mix.

Impacts of universal MRSA admission screening:

We conducted intervention analyses to model the effects of universal screening on SAB while controlling for hand-hygiene, antibiotic use and other dynamic explanatory factors using the Linear Transfer MRSA bacteraemia using the Linear Transfer Function identification method suggested by Pankratz[39] After ensuring stationary series , an initial transfer function model was created, with 6 lags for all explanatory variables and an autoregressive term of order 1. An iterative process of eliminating non-significant terms, and identifying further autoregressive or moving average terms for parts of the model remaining unexplained, determined the most parsimonious LTF model. Model parameters were estimated using unconditional least squares and goodness-of-fit evaluated by R^2. Finally, diagnostic checks were used to determine whether models adequately represented times series data. These included checking; the statistical significance of parameters, AR parameter stationarity and MA parameter invertibility, and ACF and PACF of residuals to ensure remaining variability was random. Analysis of concurrent trends in MSSA bacteraemia controlled for unidentified aspects of care or infection control affecting the clinical epidemiology of SAB.

Intervention analysis was conducted using SCA software (Chicago, IL, USA, 1992) as described by Liu and Hudak.[40] All other analyses were performed using SPSS 19.0 for windows.

RESULTS

Descriptive epidemiology

Cohort and rates of *S.aureus* bacteraemia:

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

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

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 (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 *S. aureus* bacteraemia	-[α]	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	-[α]	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. [α] 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.

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

Clinical outcomes:

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

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

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	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

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 X^2 (df) = 115 (6); P < 0.001

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

* Entered as a time-dependent covariate.

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

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

Secular trends:

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

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

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

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

	Year					
	2006 n = 218	2007 n = 188	2008 n=151	2009 n = 152	2010 n = 158	p value*
***S.aureus* 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 *S.aureus* 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 *S.aureus* 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*, AOBDs = acute occupied bed days • Data available for adult, non-obstetric patients 2006 to 2010. Counts represent non-duplicate isolates (1 per patient per year).

Trends in inpatient case mix:

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

Impacts of universal MRSA admission screening

Screening adherence and importation pressures:

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

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

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

Patient characteristics by study period:

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

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 *S.aureus* 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 *S.aureus* 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 *S.aureus* 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)

DDDs = 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).

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 = 0.678				
Universal MRSA admission screening intervention	3	-0.0346 (0.0071)	-4.89	<0.001
Cephalosporin use (DDDs/1000 AOBDs)	6	+0.0008 (0.0004)	2.03	0.046
Fluoroquinolone use (DDDs/1000 AOBDs)	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 AOBDs), R2 = 0.648				
Universal MRSA admission screening intervention	3	-0.0290 (0.0032)	-8.92	<0.001
Fluoroquinolone use (DDDs/1000 AOBDs)	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 AOBDs)	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 AOBDs)	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.

Discussion

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

Strengths and limitations

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

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

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

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

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

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

Comparison to literature:

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

associated with methicillin resistance may be explained by infection of more vulnerable patients,[13-18] often in the context of extended contact with healthcare.[15,41]

Reflecting the findings of an earlier study from Oxfordshire, which found that MRSA-related disease was responsible for increasing rates of SAB between 1997 and 2003,[3] our findings suggest that subsequent declines have occurred, almost exclusively in MRSA-related disease. An equivalent upward pressure on MSSA rates has not been observed, consistent with observations that MRSA appears to add to, rather than displace MSSA infection.[21] These findings match experience across the UK.[8]

Evidence on the role of universal screening in reducing all MRSA infections, is conflicting.[28,30,44-50] and benefits may depend on target population, screening technology and subsequent control interventions.[47] A recent US study of routine surveillance for MRSA noted a significant downward trend in MRSA bacteraemia in ICU but not in other hospital settings.[28] A second US study found a decrease in hospital-wide MRSA but not MSSA bacteraemia during universal screening.[46] In agreement with these studies, we found that rates of MRSA bacteraemia declined in parallel with all MRSA infections,[51] and there was no reciprocal rise in hospital-wide MSSA bacteraemia or infections.[48] Hospital-wide reductions in bacteraemia, of similar magnitude to that seen in our study, were reported following introduction of screening in intensive care[27] or high-risk patients only.[26] However, we identified additional declines in both general and intensive care settings, despite a baseline scenario involving routine screening in high-risk patients. These findings also contrast with those from a one-year review of the pathfinder study which found that although declines in all MRSA infections/colonisations were greater in intervention than control hospitals during universal screening the difference was non-significant.[52] We note this comparison was limited by low numbers in control hospitals, risks of contamination where control hospitals were in the same NHS board, a short baseline and follow-up period, and methods not accounting for non-independence of observations in time-series and lagged effects.

We are not aware of a previous time-series analysis describing significant impacts of universal screening on % mortality following SAB. A lack of improvement in mortality after MSSA bacteraemia did not suggest general improvements in care. The increased proportion of bacteraemia in those without history of MRSA identified as positive for MRSA at admission during universal screening may have facilitated prompt initiation of appropriate therapy. Other potential explanations include increased awareness of invasive MRSA infection in clinical staff with routine screening, greater

marginal benefits of universal admission screening in ICU settings,[27,28] and changes in strain distribution.[42,43]

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

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

Implications for practice, policy and research

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

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

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

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

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

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

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 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]

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Contributors: BE and IMG conceived this study. The statistical analysis was performed by TL and JMLL. All authors assisted in drafting the manuscript. Ian M Gould is the guarantor for this study.

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Ethical approval: Ethics approval was not required.

Authors' note: This study used anonymised and routinely collected data from laboratory systems, infection control, pharmacy, and health intelligence departments. Patient-orientated information on MRSA screening, and NHS Grampian's participation in a national pathfinder project, was made widely available in Aberdeen Royal Infirmary. This information included a statement that patient information would be held in the strictest confidence and used only for stated purposes of informing the NHS about the value of a national screening programme, in accordance with the Data Protection Act 1998. The authors hold that extraction of data for the purposes of this study did not impose any predictable additional burdens on patients at ARI and its use was justified by foreseeable benefits to the patient populations in the NHS and the general public. The authors believe that the present study was conducted in accordance with the Declaration of Helsinki 1964.

Data sharing: Technical appendix and data available on request from the corresponding author.

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FIGURE LEGENDS

Footnotes in small plain script.

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

† Recommended by the Outbreak Reports and Intervention Studies Of Nosocomial infection (ORION) statement. [31]
* '4C' antibiotics are clindamycin, ciprofloxacin (all fluoroquinolones), cephalosporins (all generations), co-amoxiclav.
MRSA = Methicillin resistant *Staphylococcus aureus; SAB = Staphylococcus aureus* bacteraemia, AOBDs = Acute occupied bed days; WTE = Whole time equivalents calculated as 37.5 hours/week*52 weeks = 1950 hours year^{-1}. ICN = Infection control nurse; ICD = Infection control doctor. ICU = Intensive Care Unit.

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 and admitting department (MRSA only)

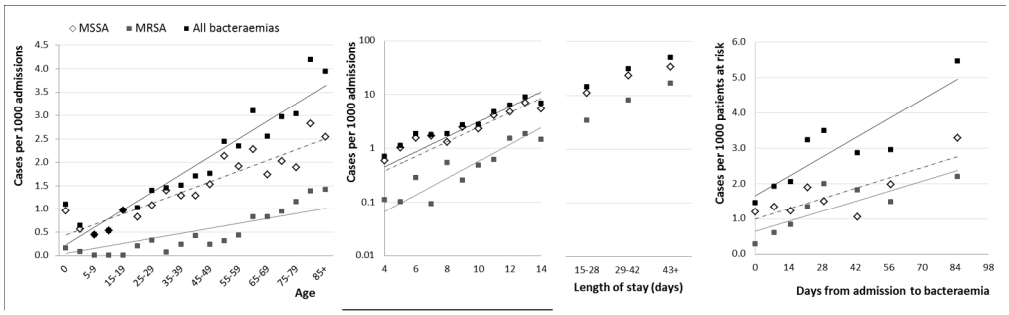
Data aggregated in 3 month blocks. Lines represent results of trend analysis, using Poisson regression with time (month) as sole explanatory variable.

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

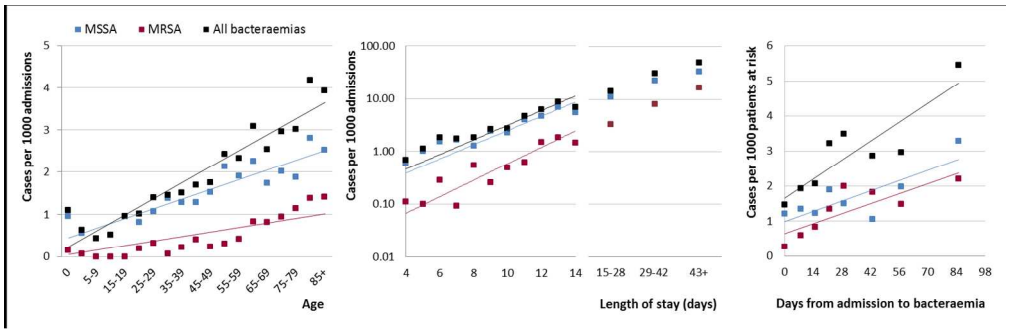
***** Special study period (February 2010 to August 2010) involved a trial of axillae and groin swabs.

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

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:** 1st January 2006 to 31st 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 15th June 2011. Data collection period: 15th June 201 to 1st August 2011.		
	Period 1: 31 months (Jan 2006 - July 2008)		**Period 2: 29 months (August 2009- December 2011)**
MRSA screening policy	Selective screening for elective surgery and ICU admissions. 43,158 (43%) admissions screened 2909 (6.9% of screened) MRSA screen positive		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 *any* 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).
	Antibiotic groups during antibiotic stewardship intervention: *Macrolides and '4C' antibiotics:* Co-amoxiclav, cephalosporins, ciprofloxacin/fluoroquinolones, clindamycin *Targeted for increase* : Amoxicillin, aminoglycosides, co-trimoxazole, piperacillin/tazobactam, flucloxacillin, *Non-target (control):* Tetracyclines, trimethoprim, nitrafurantoin, β-lactamase sensitive penicillins, other. *Therapeutics for MRSA:* Teicoplanin, vancomycin , daptomycin.		
Definitions and outcomes	**Case of *S.aureus* bacteraemia**	Non-duplicate isolate of any *S.aureus* 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 *S.aureus* 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 S.aureus bacteraemia / Monthly total AOBDs (x 1000)	
	Hospital-associated (HA)-incidence	Monthly episodes of HA-*S.aureus* bacteraemia / Monthly total admissions (x 1000)	
	HA-incidence density	Monthly episodes of HA-*S.aureus* bacteraemia / Monthly total AOBDs (x 1000)	
	%SAB involving MRSA	Monthly episodes of MRSA bacteraemia/Monthly episodes of *S.aureus* bacteraemia (x 100)	
	30-day mortality, %	Deaths from any cause ≤ 30 days of SAB/ No. of episodes of *S.aureus* bacteraemia (x 100)	
	Inpatient mortality, %	Deaths from any cause in index admissions / No. of episodes of *S.aureus* 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 *S.aureus* ≤ 6 months of initial isolate.	
	Recurrence	Repeat blood isolate of *S.aureus* with the same susceptibility >6 months from initial isolate.	



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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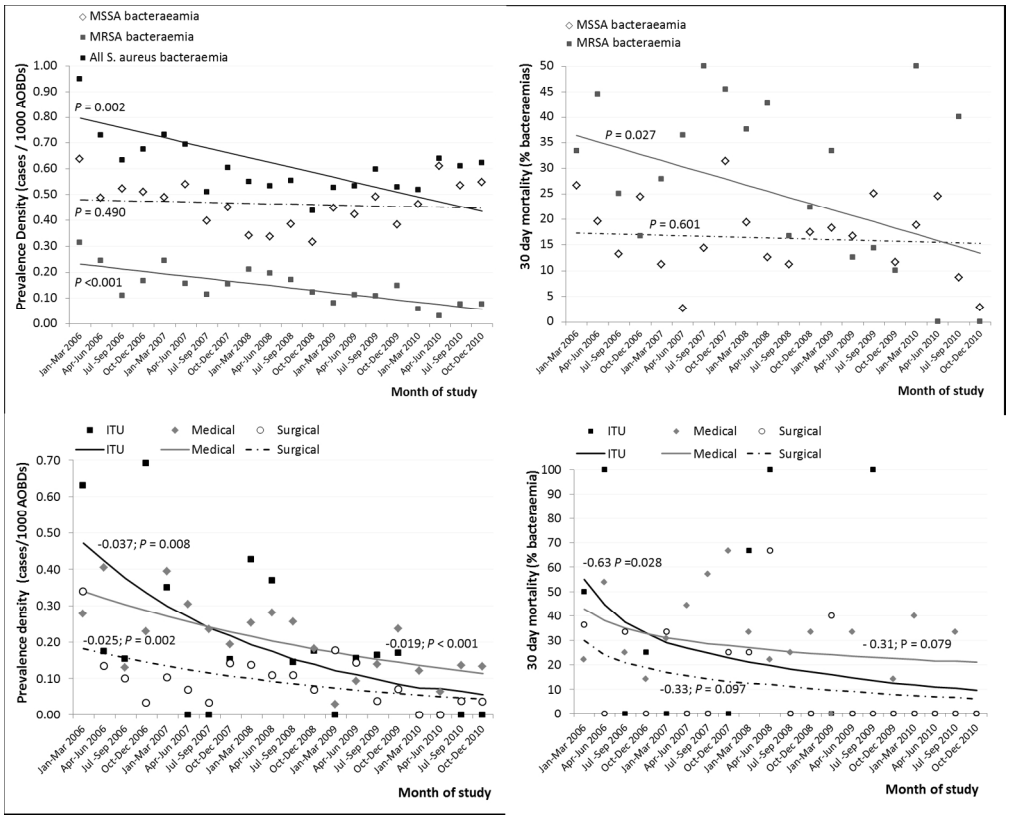
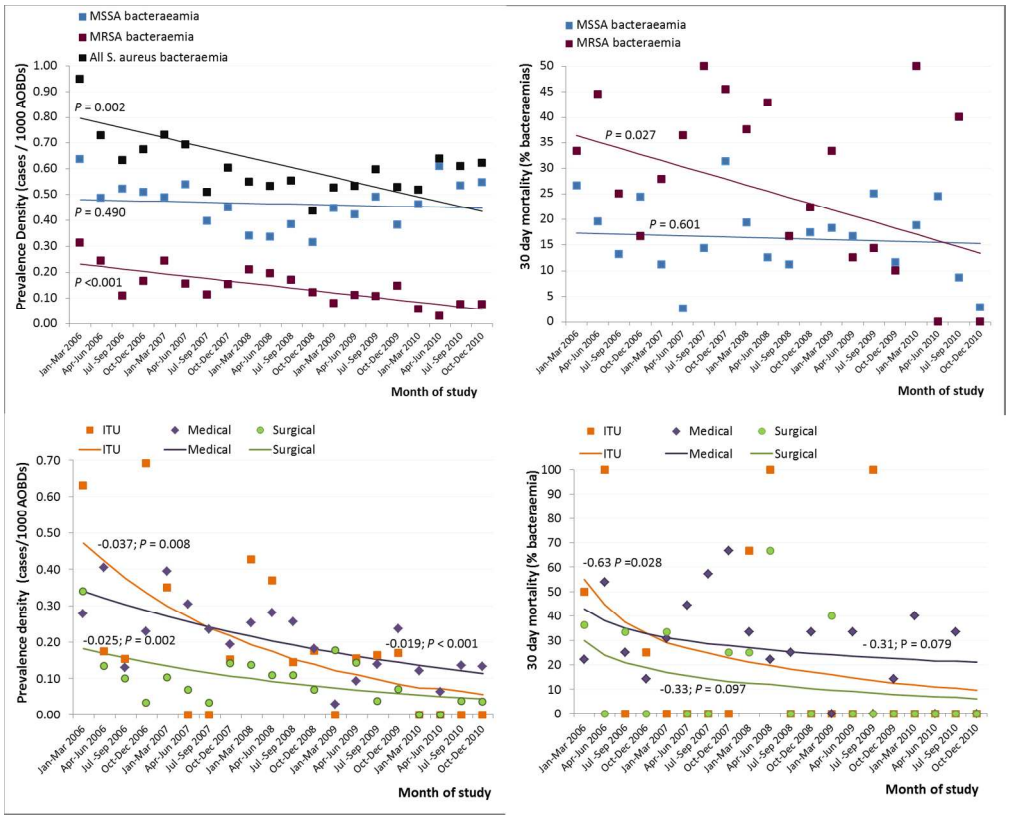


Secular trends in prevalence density and all-cause 30-day mortality after *S. aureus* bacteraemia by methicillin resistance and admitting department (MRSA only)
Data aggregated in 3 month blocks. Lines represent results of trend analysis, using Poisson regression with time (month) as sole explanatory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



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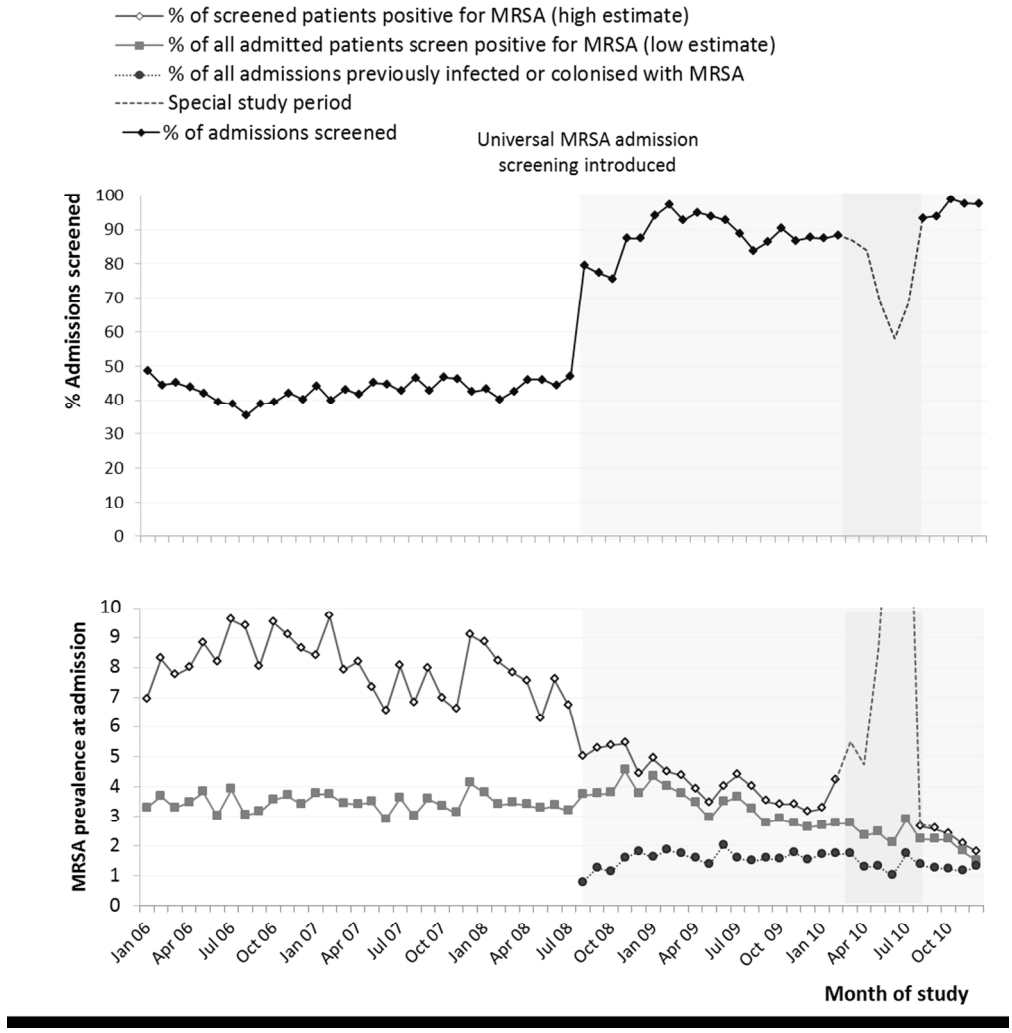
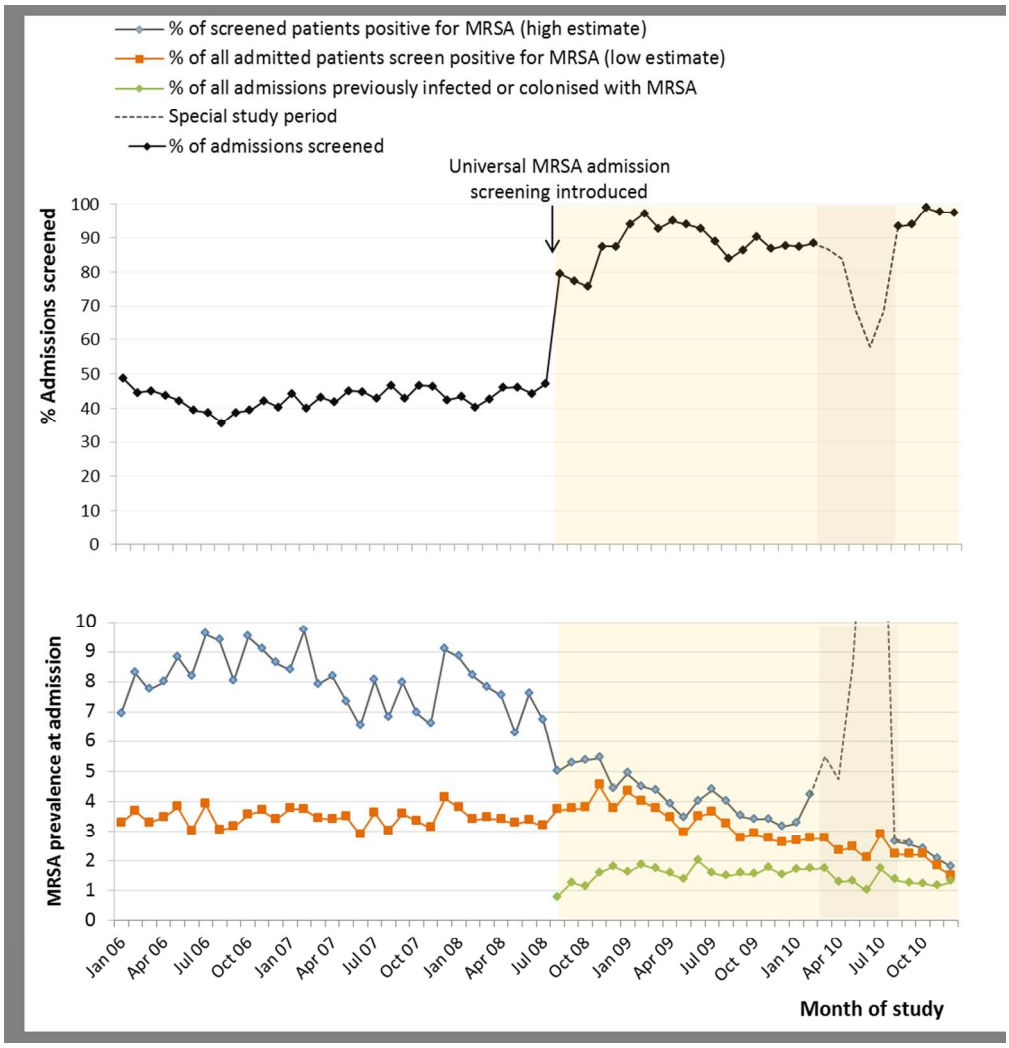


Adherence to MRSA admission testing during universal surveillance (August 2008 to December 2010) *A special study period (February 2010 to August 2010) involved a trial of axillae and groin swabs.



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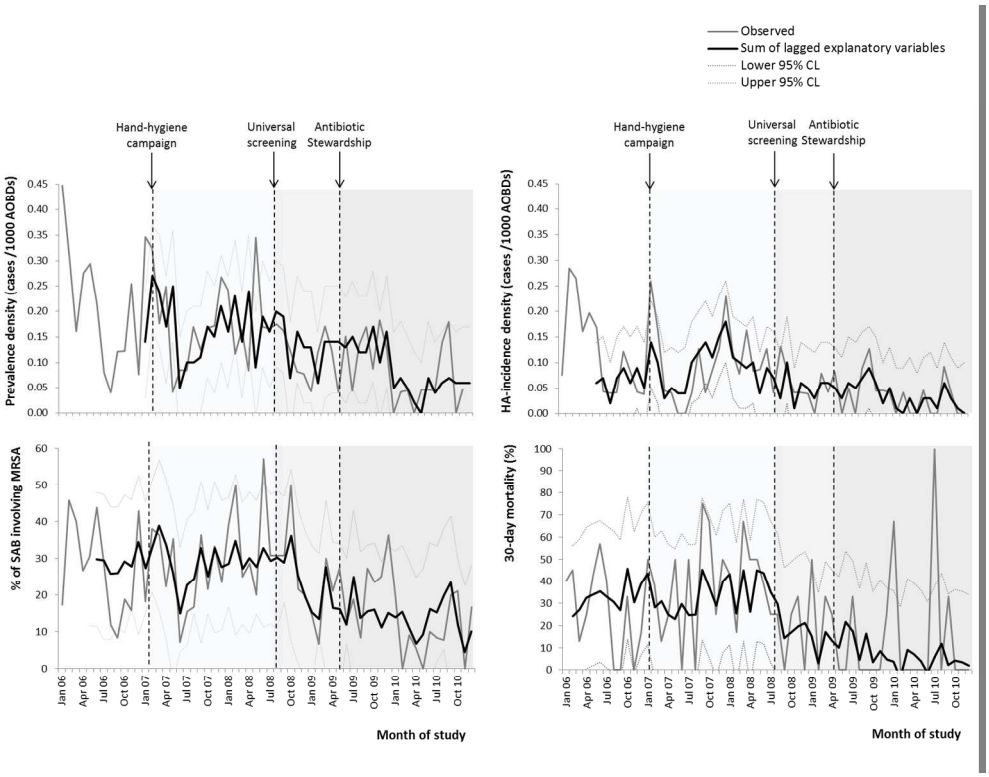
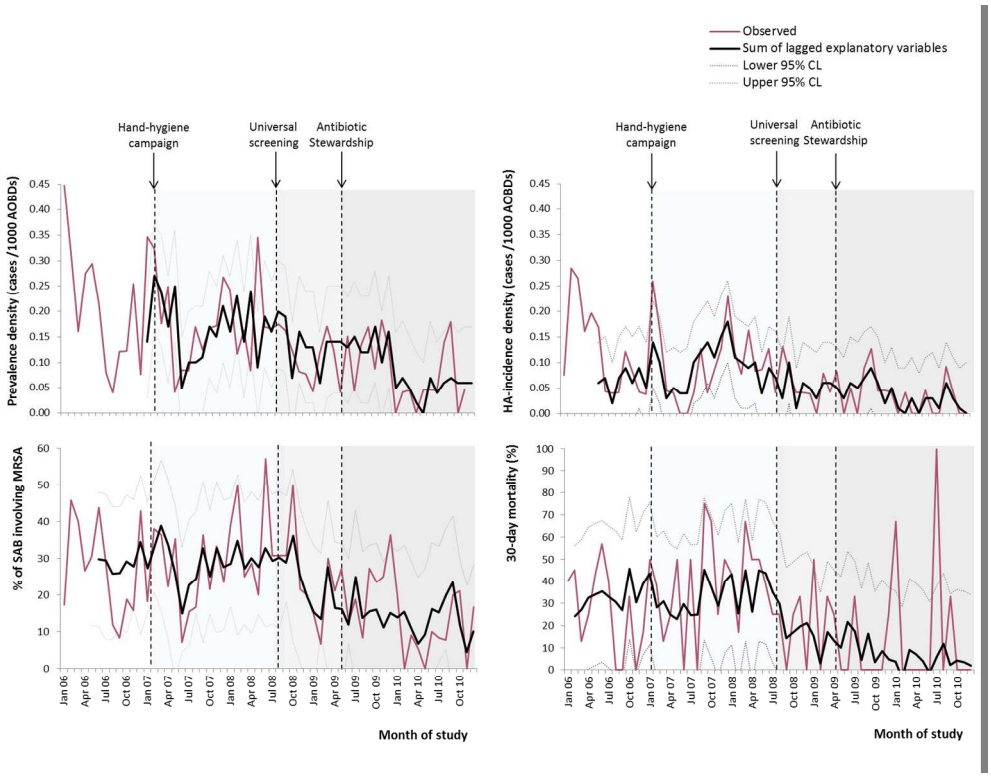


Observed trends and multivariate transfer model predictions (sum of lagged explanatory variables) for prevalence density, hospital associated incidence density, 30-day mortality in MRSA bacteraemia, and % *S.aureus* bacteraemia involving MRSA.



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.