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Impact of infection control interventions on rates of *Staphylococcus aureus* bacteraemia in National Health Service acute hospitals, East Midlands, UK, using interrupted time-series analysis☆

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SUMMARY

Background: Reducing healthcare-associated infection (HCAI) is a UK national priority. Multiple national and regional interventions aimed at reduction have been implemented in National Health Service acute hospitals, but assessment of their effectiveness is methodologically challenging.

Aim: To assess the effectiveness of national and regional interventions undertaken between 2004 and 2008 on rates of meticillin-resistant *Staphylococcus aureus* (MRSA) and meticillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia within acute hospitals in the East Midlands, using interrupted time-series analysis.

Methods: We used segmented regression to compare rates of MRSA and MSSA bacteraemia in the pre-intervention, implementation, and post-intervention phases for combined intervention packages in eight acute hospitals.

Findings: Most of the change in MSSA and MRSA rates occurred during the implementation phase. During this phase, there were significant downward trends in MRSA rates for seven of eight acute hospital groups; in four, this was a steeper quarter-on-quarter decline compared with the pre-intervention phase, and, in one, an upward trend in the pre-intervention phase was reversed. Regarding MSSA, there was a significant positive effect in four hospital groups: one upward trend during the pre-intervention phase was reversed, two upward trends plateaued, and in one hospital group an indeterminate trend decreased significantly. However, there were significant increasing trends in quarterly MSSA rates in four hospital groups during the implementation or post-intervention periods.

☆ Study carried out whilst affiliated with Public Health England, East Midlands.

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Conclusion: The impact of interventions varied by hospital group but the overall results suggest that national and regional campaigns had a beneficial impact on MRSA and MSSA bacteraemia within the East Midlands.

Introduction

The prevalence of healthcare-associated infections (HCAIs) was 6.4% in English National Health Service (NHS) hospitals during 2011 with estimated treatment costs of approximately £1 billion per year.[1,2] Substantial resources have been devoted towards decreasing the incidence of HCAI in the UK, including, since 2004, the national campaigns: 'Saving Lives', 'Cleanyourhands', 'Clean Safe Care' and 'Deep Clean Programme'; and regional initiatives such as 'Hand in Hand' (2007) in the East Midlands region. These campaigns involved hand hygiene, high-impact patient-level interventions, and improved infection control and awareness (Supplementary Table I).

The evaluation of HCAI interventions has generally been constrained by methodological shortcomings in dealing with multiple, often overlapping interventions and a lack of control sites for national interventions. Nevertheless, it is important that interventions, particularly those that require substantial resources, are evaluated using robust methods. This study used interrupted time-series analysis to assess the impact of national and regional HCAI interventions on rates of meticillin-resistant *Staphylococcus aureus* (MRSA) and meticillin-sensitive *Staphylococcus aureus* (MSSA) bacteraemia in NHS acute hospitals in the East Midlands. NHS acute hospital services are managed by 'acute trusts', organizations that each deliver services to a defined geographical area through one or more acute hospitals. Interrupted time-series analysis is recognized as the strongest quasi-experimental design to evaluate longitudinal effects of an intervention.[3]

Methods

Data sources

Anonymized quarterly counts of MRSA bacteraemia (both hospital- and community-apportioned) from April 2001 to March 2011 for the eight acute NHS trusts (hereafter called 'trusts') in the East Midlands were obtained from mandatory data sets from Public Health England (known during 2004–2013 as the Health Protection Agency, and before 2004 as the Public Health Laboratory Service). Mandatory reporting of MSSA bacteraemia only began in January 2011; therefore numbers of MSSA cases were calculated by subtracting the number of 'blood culture MRSA-positive samples' in quarterly mandatory laboratory returns from total 'blood culture *Staphylococcus aureus*-positive samples'. Bacteraemia counts were converted into time-series of MRSA and MSSA incidence rates per 100,000 bed-days using reported average bed-day activity.[4] Ethical approval was not required as this analysis used only aggregate, anonymized data.

Intervention data

Information on the HCAI interventions implemented in each acute trust and their start dates had been collected previously using detailed questionnaires with trust staff (Supplementary Figure 1).[5] These start dates were used in this study rather than official campaign roll-out dates because actual implementation of national campaigns varied within individual trusts due to local practicalities or involvement in pilot studies. Where discrepant dates were identified which could not be resolved, the earliest start date of the campaign was used to ensure that the earliest possible implementation was captured. The five interventions covered in the study are detailed in Supplementary Table I.

Statistical analysis

The various campaigns were implemented simultaneously or very close together in many trusts, making it difficult to isolate and identify the individual effects of specific campaigns. Therefore, campaigns were evaluated together as a composite intervention package. As in previous analyses, we defined an 'implementation phase' spanning the start date of the first intervention to the start date of the last (fifth) intervention.[3,6] Three trusts either did not implement or did not know the start date for the intervention 'Clean Safe Care', hence only four interventions were included in the analysis for these trusts. For the segmented regression analysis, each time-series was split into three segments: a 'pre-intervention phase', an 'implementation phase' and a 'post-intervention phase'. Segmented regression models were applied to each hospital group for MRSA and MSSA bacteraemia separately, assessing changes in the level and the trend of each segment compared with the segment immediately beforehand. We used non-automated backward elimination using the likelihood ratio test at a significance level of $P < 0.05$ to remove non-significant parameters and build a parsimonious model.[3] An example showing the fitted model for trust A is shown in Supplementary Figure 2. Each model was checked for the presence of autocorrelation by visual inspection of the autocorrelation function of the model residuals, and conducting a Portmanteau test using a significance level of $P < 0.05$. There was no evidence of seasonal autocorrelation in the model residuals. Given the relatively short time-series and limited power to detect autocorrelation, a sensitivity analysis was conducted using Prais–Winsten regression for all models to include an 'AR(1)' term in the model *a priori* to account for non-seasonal autocorrelation. This had no appreciable effect on the results, suggesting that any autocorrelation was appropriately accounted for; therefore these data are not presented here (but are available on request). All analyses were carried out using Stata version 11.2 (Stata Corp., College Station, TX, USA).

Table I
Final segmented regression models for MRSA rates in the eight hospital trusts in the East Midlands, UK[a]

Trust	Mean cases per quarter		Pre-intervention phase	Implementation phase			Post-intervention phase			Interpretation
	Pre intervention	Post intervention	Trend in the pre-intervention phase	Immediate change in level compared to pre-intervention phase	Change in trend compared to pre-intervention phase	Trend in the implementation phase	Immediate change in level compared to implementation phase	Change in trend compared to implementation phase	Trend in the post-intervention phase	
Trust A	$N = 4$	$N = 2$		7.81 (2.62 to 13.00) $P = 0.004$	−1.09 (−1.60 to −0.57) $P < 0.001$	−1.09 (−1.60 to −0.57) $P < 0.001$		1.07 (0.19 to 1.95) $P = 0.018$		Immediate increase in level of MRSA rates at start of implementation, but significant decreasing trend during implementation.
Trust B	$N = 10$	$N = 4$			−0.39 (−0.55 to −0.22) $P < 0.001$	−0.39 (−0.55 to −0.22) $P < 0.001$			−0.39 (−0.55 to −0.22) $P < 0.001$	Significant decreasing trend found during implementation and maintained post implementation.
Trust C	$N = 5$	$N = 2$		5.18 (0.4 to 9.96) $P = 0.034$	−0.58 (−0.83 to −0.34) $P < 0.001$	−0.58 (−0.83 to −0.34) $P < 0.001$			−0.58 (−0.83 to −0.34) $P < 0.001$	Increase in level of MRSA rates at start of implementation but significant decreasing trend during and maintained post implementation.
Trust D	$N = 6$	$N = 3$			−0.37 (−0.55 to −0.19) $P < 0.001$	−0.37 (−0.55 to −0.19) $P < 0.001$			−0.37 (−0.55 to −0.19) $P < 0.001$	Significant decreasing trend found during implementation and maintained post implementation.

Trust E	$N = 31$	$N = 7$	−0.62 (−0.71 to −0.53) $P < 0.001$			−0.62 (−0.71 to −0.53) $P < 0.001$			−0.62 (−0.71 to −0.53) $P < 0.001$	Stable long-term downward trend with no significant changes.
Trust F	$N = 15$	$N = 5$		−4.95 (−7.01 to −2.90) $P < 0.001$				−1.26 (−1.51 to −1.01) $P < 0.001$	−1.26 (−1.51 to −1.01) $P < 0.001$	Immediate decrease in level of MRSA rates at start of implementation and a significant decreasing trend found post implementation.
Trust G	$N = 19$	$N = 6$	0.76 (0.31 to 1.49) $P = 0.041$		−1.36 (−2.26 to −0.46) $P = 0.004$	−0.60 (−0.85 to −0.34) $P < 0.001$			−0.60 (−0.85 to −0.34) $P < 0.001$	Significant reversal of upward trend during implementation, decreasing trend maintained post implementation.
Trust H	$N = 34$	$N = 6$	−0.59 (−0.67 to −0.51) $P < 0.001$			−0.59 (−0.67 to −0.51) $P < 0.001$			−0.59 (−0.67 to −0.51) $P < 0.001$	Stable long-term downward trend with no significant changes.

MRSA, meticillin-resistant *Staphylococcus aureus*.

[a] Values in parentheses are 95% confidence intervals. Only parameters significant in the most parsimonious models have been presented, as non-significant components were removed from the final models. All statistics relate to MRSA cases per 100,000 bed-days. The models for trusts A, F, and G were estimated using Prais–Winsten regression to include a term for AR(1) autocorrelation.

Table II

Results of the final segmented regression models for MSSA rates in the eight trusts in the East Midlands[a]

Trust	Mean cases per quarter		Pre-intervention phase	Implementation phase			Post-intervention phase			Interpretation
	Pre intervention	Post intervention	Trend in the pre-intervention phase	Immediate change in level compared to pre-intervention phase	Change in trend compared to pre-intervention phase	Trend in the implementation phase	Immediate change in level compared to implementation phase	Change in trend compared to implementation phase	Trend in the post-intervention phase	
Trust A	$N = 18$	$N = 13$			−0.65 (−1.04 to −0.25) $P = 0.002$	−0.65 (−1.04 to −0.25) $P = 0.002$			−0.65 (−1.04 to −0.25) $P = 0.002$	Significant decreasing trend found during implementation and maintained post implementation.
Trust B	$N = 27$	$N = 30$	−1.68 (−2.81 to −0.54) $P = 0.005$		3.40 (1.60 to 5.20) $P < 0.001$	1.73 (0.85 to 2.6) $P < 0.001$		−4.77 (−7.37 to −2.17) $P = 0.001$	−3.04 (−5.03 to −1.06) $P = 0.004$	Significant increasing trend during implementation but significant decreasing trend post implementation.
Trust C	$N = 8$	$N = 11$	2.05 (0.41 to 3.70) $P = 0.016$		−2.12 (−3.96 to −0.28) $P = 0.003$					Significant upward trend in pre-implementation phase reduced during implementation phase.
Trust D	$N = 11$	$N = 14$	1.04 (0.39 to 1.70) $P < 0.003$			1.04 (0.39 to 1.70) $P < 0.003$	−23.1 (−37.0 to −9.14) $P = 0.002$		1.04 (0.39 to 1.70) $P < 0.003$	Immediate decrease in level of MSSA post implementation but no change to trend.
Trust E	$N = 50$	$N = 47$								Stable long-term flat trend with no significant changes.

Trust F	$N = 25$	$N = 17$	1.19 (0.21 to 2.17) $P = 0.019$	−1.99 (−3.23 to −0.76) $P = 0.002$	−0.80 (−1.18 to −0.42) $P < 0.001$			−0.80 (−1.18 to −0.42) $P < 0.001$	Significant reversal of upward trend during implementation, decreasing trend maintained post implementation.
Trust G	$N = 27$	$N = 30$	1.06 (0.51 to 1.60) $P < 0.001$	−1.30 (−2.04 to −0.55) $P = 0.001$			0.98 (0.17 to 1.79) $P = 0.019$	0.74 (0.13 to 1.36) $P = 0.019$	Significant decrease in the trend during implementation, but actual trend not significant or maintained.
Trust H	$N = 47$	$N = 31$		0.39 (0.07 to 0.71) $P = 0.020$	0.39 (0.07 to 0.71) $P = 0.020$	−13.31 (−19.44 to −7.17) $P < 0.001$		0.39 (0.07 to 0.71) $P = 0.020$	Immediate decrease in level of MSSA post implementation. Significant increasing trend during implementation and maintained post implementation.

MSSA, meticillin-susceptible *Staphylococcus aureus*.

[a] Values in parentheses are 95% confidence intervals. Only parameters significant in the most parsimonious models have been presented, as non-significant components were removed from the final models. All statistics relate to MSSA cases per 100,000 bed-days.

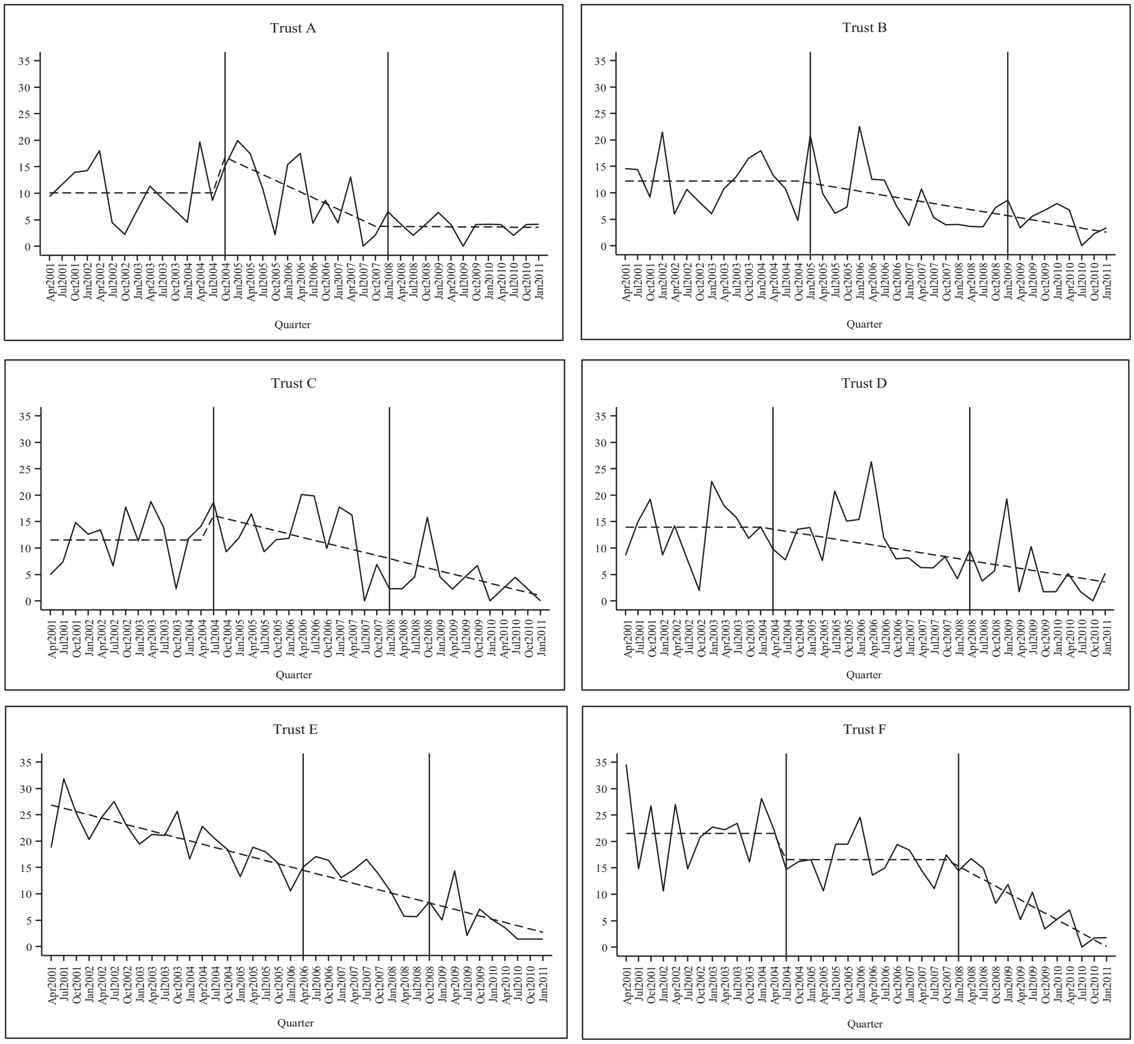

Figure 1. Meticillin-resistant *Staphylococcus aureus* (MRSA) rates per 100,000 bed-days for each trust in the East Midlands (solid line) with the fitted final segmented regression model (dashed line).

Results

The results of the final segmented regression models for each trust can be seen in Tables I and II, and in Figures 1 and 2.

MRSA

In the pre-intervention phase, quarterly rates of MRSA significantly decreased over time in two trusts (E and H), significantly increased in one (G), and there was no significant trend in the remainder ($N = 5$).

During the implementation phase, there was a significant downward trend in MRSA rates in seven trusts (A–E, G, H). In four trusts (A–C, D) the rate of decline of MRSA infection during the implementation phase was significantly steeper than the rate of decline in the pre-intervention phase. Additionally, in trust G the significant upward trend observed in the pre-intervention phase was reversed, giving a significant decreasing trend of 0.60 fewer cases per 100,000 bed-days per quarter [95% confidence interval (CI): −0.85 to −0.34]. Two trusts (A, C) saw an immediate significant increase in the level of the quarterly incidence rate of MRSA between the last quarter in the pre-intervention phase and the first quarter in the implementation phase, and trust F had a significant immediate decrease of 4.95 cases per 100,000 bed-days (95% CI: −7.01 to −2.90).

For six trusts (B–E, G, H) the downward trend in MRSA rates in the implementation phase continued at the same rate during the post-intervention phase, but in trust F there was a significantly steeper rate of decline during this phase of 1.26 cases per 100,000 bed-days per quarter (95% CI: −1.51 to −1.01). In trust A, the declining trend during the implementation phase levelled off post-intervention (significant change in trend 1.07 cases per 100,000 bed-days per quarter; 95% CI: 0.19 – 1.95).

MSSA

In the pre-intervention phase, quarterly rates of MSSA significantly increased over time in four trusts (C, D, F, G), significantly decreased in one (B), and there was no significant trend in the remaining three.

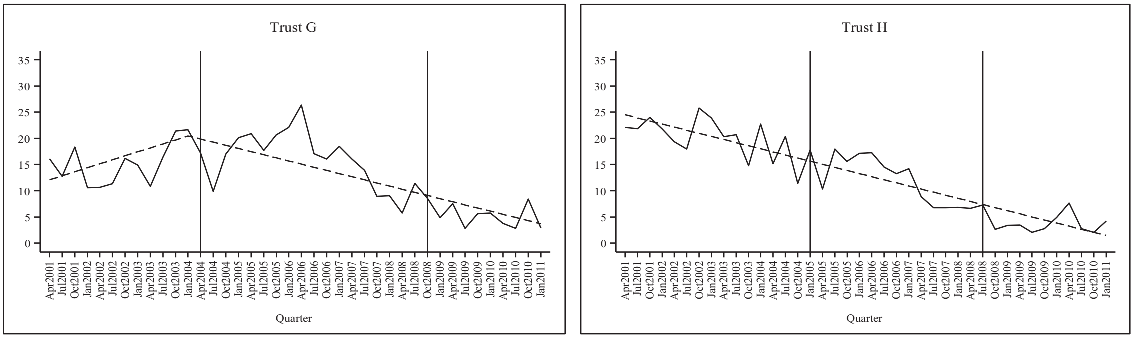

Figure 1. (*continued*).

During the implementation phase there was a significant downward trend in MSSA rates in only two trusts; in trust F, the significant upward trend in the pre-intervention phase was reversed, giving a decreasing quarterly trend of –0.8 cases per 100,000 bed-days, per quarter (95% CI: –1.18 to –0.42) and for trust A there was a rate of decrease of –0.65 cases per 100,000 bed-days, per quarter (95% CI: –1.04 to –0.25). In two trusts (C and G), significant changes in the trend meant that the upward trend in the pre-intervention phase reverted to a constant level during the implementation phase. There was a significant increasing quarterly trend in MSSA cases for three trusts (B, D, H) during the implementation phase. In trust E there were no significant trends or immediate changes in MSSA rates across the three phases. There was an immediate significant decrease in the quarterly rates of MSSA infection, between the last quarter of the implementation phase and the first quarter of the post-intervention phase in trusts D and H, of 23.1 cases (95% CI: –37.0 to –9.14) and 13.31 cases (95% CI: –19.44 to –7.17) per 100,000 bed-days, respectively.

During the post-intervention phase there was a significant downward trend in MSSA cases for three trusts (A, B, F) with the significant increasing trend in quarterly MSSA rates in trust B reversing to a decreasing trend of 3.04 cases per 100,000 bed-days, per quarter (95% CI: –5.03 to –1.06). There was a significant increasing trend in MSSA cases for three trusts (D, G, H) but there was no significant change in the trend from the implementation phase for trusts C and E.

Discussion

During the implementation phase there was a downward trend in MRSA rates for seven trusts; in four trusts this was a steeper quarter-on-quarter decline compared to the pre-intervention phase, and in one other the upward trend in the pre-intervention phase was reversed. In the post-intervention phase, the downward trend in rates continued for six trusts, with one trust experiencing a steeper quarterly decline in MRSA rates compared with the implementation phase. These findings suggest that the intervention package was effective in reducing MRSA bacteraemia in most trusts. The results for MSSA rates were more variable. There was a change in the trend of MSSA rates in six trusts during the implementation phase compared to the pre-intervention phase. For four trusts this was a positive effect with the upward trend in MSSA rates during the pre-intervention phase either reverting to constant or starting to decline. However, for some trusts the trend in quarterly MSSA rates increased during the implementation and post-intervention phase.

Due to the interventions being analysed as a composite intervention package, we cannot disentangle the effects of individual components. Existing literature suggests that a decrease in infection rates would be expected due to hand hygiene interventions and this is consistent with the national evaluation of the 'Cleanyourhands' campaign.[6] In addition to the major national interventions, the targets set by government during the study period may also be relevant: in 2004 trusts were set a target of a 50% reduction in MRSA bacteraemia by 2008; and in 2006 Trust Chief Executives were required to take personal responsibility for their MRSA data.[7] Both requirements undoubtedly had an effect on MRSA rates, with many interventions implemented or intensified in response. Therefore, other interventions may have contributed to our findings, such as universal MRSA screening, hydrogen peroxide decontamination, and the introduction of chlorhexidine decolonization.[8] Although we are not aware of any specific issues, we acknowledge that changes in case mix, laboratory testing methodology or antimicrobial prescribing practices such as the use of quinolones, which are independently associated with changes in MRSA rates, could have been confounding factors. It has been suggested that the reduction in MRSA rates nationally is due to changes in strain types with rates already decreasing before the introduction of interventions.[9,10] However, a reducing trend in MRSA rates in the pre-implementation phase was only observed in two trusts in the East Midlands, making it easier to infer that the observed changes were attributable to interventions during this time period. Both of these trusts also had a high initial rate of MRSA bacteraemia (>20 per 100,000 population) suggesting that the starting rate may impact the rate of reduction. As expected, we observed variation in the effect of interventions by trust. These may be due to differences in compliance and the enthusiasm with which they were introduced locally. Two trusts saw an immediate significant increase in the MRSA rate at the beginning of the implementation phase, which is difficult to explain and may be due to unmeasured confounding.

The interventions might be expected to have similar effects on both MRSA and MSSA, but national MSSA rates have not decreased at the same rate as MRSA.[11] The limited literature on the effect of interventions on MSSA rates has shown little or no impact, which is in keeping with our findings.[6,12,13] No distinction was made between trust- and community-

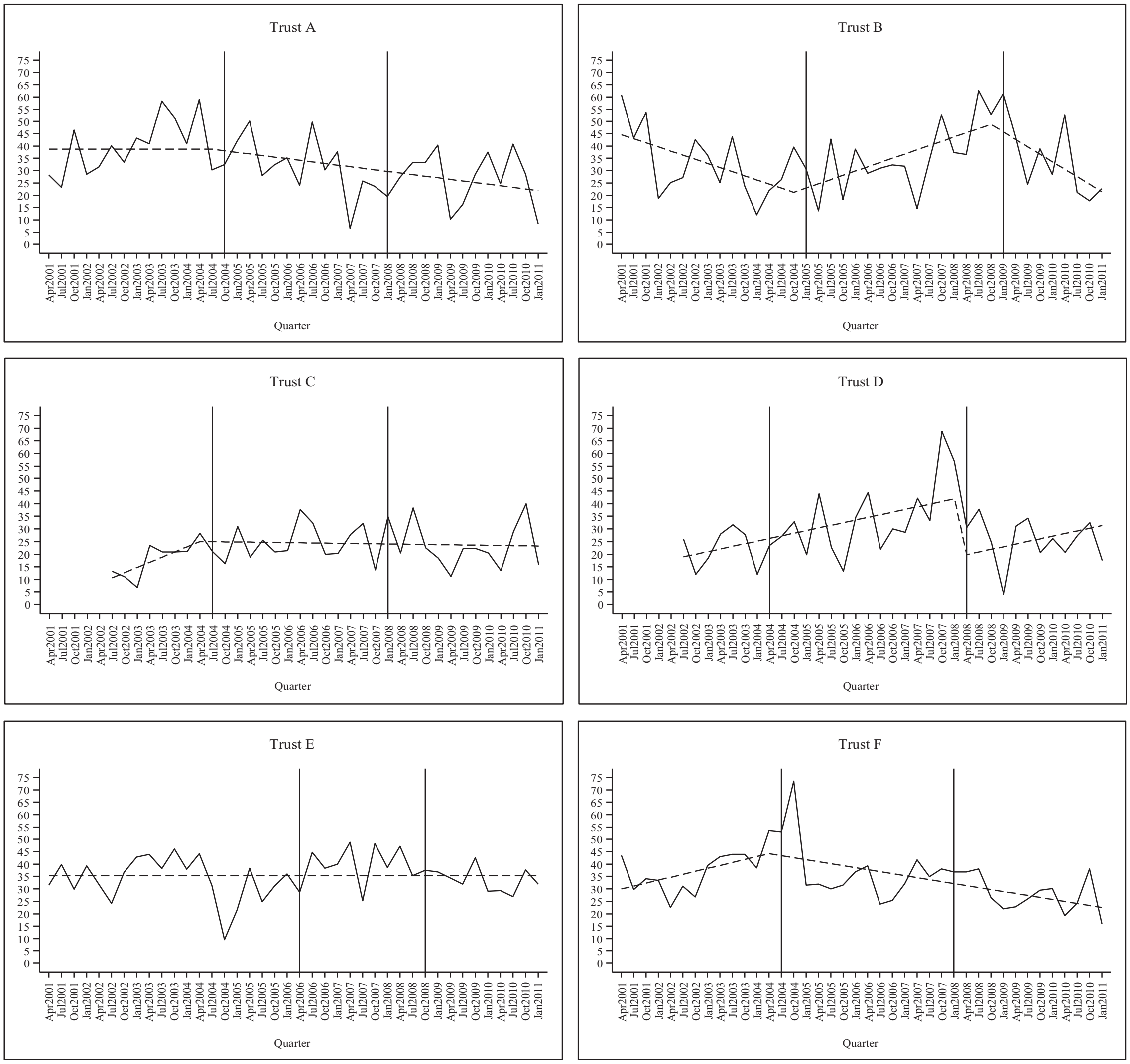

Figure 2. Meticillin-susceptible *Staphylococcus aureus* (MSSA) rates per 100,000 bed-days for each trust in the East Midlands (solid lines) with the fitted final segmented regression model (dashed lines).

apportioned infection within this study, as these data were only available from 2005, by which time, interventions had already been implemented. Although national data show that most MRSA bacteraemia was designated as hospital-acquired during the time period, ~70% of MSSA bacteraemia was thought to be community-acquired.[11] Trust-based interventions would therefore have limited effect on community-apportioned infection and may explain the variable success seen against MSSA. This study did not collect strain typing information, so it is unknown whether changes in or the prominence of certain strains may have played a part in the limited reduction of MSSA.

The national and international importance of HCAI and the resources invested in its prevention mean that evaluation of interventions is essential. This has been problematic, because standard research methodologies such as cluster-randomized trials of specific interventions have seldom been attempted. Reviews of previous local evaluations have highlighted methodological weaknesses in study design, making it difficult to draw conclusions and make comparisons across studies.[14,15] To ensure robust and comparable research into HCAI interventions, we used interrupted time-series analysis, which has been recognized as an appropriate study design for hospital epidemiology.[16] When used appropriately, this methodology can help to make sense of complex data, where multiple interventions have been applied near-simultaneously and where randomization cannot be applied for ethical or logistical reasons. This is the first time to our knowledge that this methodology has been used to assess national and regional campaigns as a composite 'intervention package' on the effect of HCAI rates in multiple acute trusts. In some trusts it appeared that infection rates started to decline only partway through the intervention period rather than at the start. However, the methodology used here adheres to quality criteria for interrupted time-series studies and all intervention points were specified *a priori* to limit the number of statistical tests undertaken.[17]

The strengths of this study include the use of a mandatory data set, where data have been recorded consistently over time and acute trusts were analysed individually rather than for the region as a whole, avoiding ecological fallacy. However, inclusion of a specific regional campaign challenges generalizability of the findings to other trusts or regions in England;

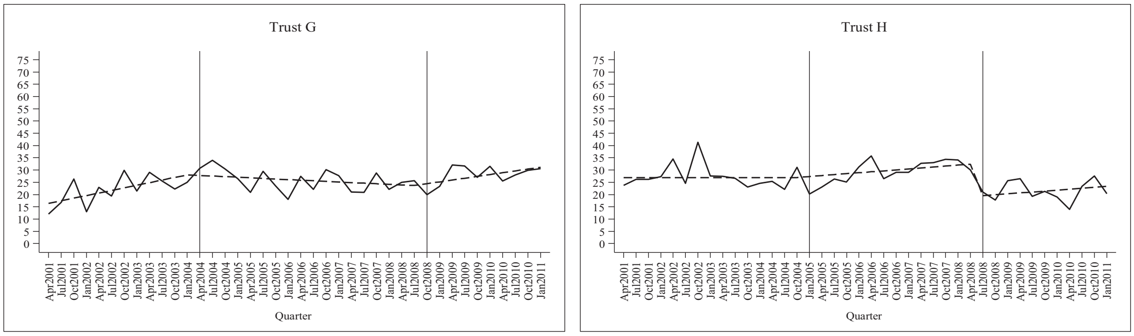

Figure 2. (*continued*).

and the intervention start dates provided from staff may be subject to recall bias. The impact of the interventions we studied varied by trust, but the overall results suggest that national and regional campaigns have played an important role in reducing MRSA bacteraemia rates within East Midlands acute hospitals. The data are somewhat less convincing for MSSA, where other community-related factors may have complicated the epidemiological situation.

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Conflict of interest statement
None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jhin.2014.12.016.

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