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Impact of national policies on the microbial aetiology of surgical site infections in acute NHS hospitals in England: analysis of trends between 2000 and 2013 using multi-centre prospective cohort data

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SUMMARY

Our study aimed to evaluate changes in the epidemiology of pathogens causing surgical site infections (SSIs) in England between 2000 and 2013 in the context of intensified national interventions to reduce healthcare-associated infections introduced since 2006. National prospective surveillance data on target surgical procedures were used for this study. Data on causative organism were available for 72% of inpatient-detected SSIs meeting the standard case definitions for superficial, deep and organ-space infections (9767/13 531) which were analysed for trends. A multivariable logistic linear mixed model with hospital random effects was fitted to evaluate trends by pathogen. *Staphylococcus aureus* was the predominant cause of SSI between 2000 (41%) and 2009 (24%), decreasing from 2006 onwards reaching 16% in 2013. Data for 2005–2013 showed that the odds of SSI caused by *S. aureus* decreased significantly by 14% per year [adjusted odds ratio (aOR) 0·86, 95% confidence interval (CI) 0·83–0·89] driven by significant decreases in methicillin-resistant *S. aureus* (MRSA) (aOR 0·71, 95% CI 0·68–0·75). However a small significant increase in methicillin-sensitive *S. aureus* was identified (aOR 1·06, 95% CI 1·02–1·10). Enterobacteriaceae were stable during 2000–2007 (12% of cases overall), increasing from 2008 (18%) onwards, being present in 25% of cases in 2013; the model supported these increasing trends during 2007–2013 (aOR 1·12, 95% CI 1·07–1·18). The decreasing trends in *S. aureus* SSIs from 2006 and the increases in Enterobacteriaceae SSIs from 2008 may be related to intensified national efforts targeted at reducing MRSA bacteraemia combined with changes in antibiotic use aimed at controlling *C. difficile* infections.

Key words: Enterobacteriaceae, infections, *Staphylococcus aureus*, surgical wound, surgical wound infections.

INTRODUCTION

Surgical site infections (SSIs) are the third most common healthcare-associated infections (HCAIs) and are associated with excess length of stay, hospital costs and mortality [1–3]. The national SSI surveillance system in England operated by Public Health England (PHE) has captured data on microorganisms, but evidence for trends in aetiology, as observed in bacteraemias captured separately by PHE, have not been comprehensively assessed [4–6].

Data captured by PHE's voluntary surveillance of laboratory isolates in England and Wales showed that bacteraemia due to methicillin-resistant *S. aureus* (MRSA) increased sharply from 1990 to 2003 [7].

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Progress in the control of HCAIs was subject to scrutiny by England's National Audit Office in 2004 and the Public Accounts Committee in 2005 highlighting problems with commitment to hospital hygiene. In October 2005 the Department of Health (DoH) expanded an existing policy of mandatory public reporting of MRSA bacteraemia counts (since 2001) by introducing enhanced (patient-level) surveillance. The DoH also introduced targeted infection control policies to standardize and improve practices around the prevention of MRSA which included MRSA screening and decolonization, care of invasive devices and hand hygiene [5, 7, 8].

In addition, all NHS hospitals were required to achieve the target of reducing their rate of MRSA bacteraemia by 50% by 2008 (from a 2004 baseline), supported by visits to hospitals by national improvement teams (from 2008). Considerable reductions in rates of MRSA bacteraemia were noted since 2006 [5, 7, 9].

Concern about *C. difficile* infection (CDI) led to additional initiatives including mandatory public reporting (introduced in 2004), reduction targets for all NHS hospitals and antimicrobial prescribing guidance introduced in 2007 [10, 11]. This guidance recommended the restricted use of broad-spectrum antimicrobials particularly quinolones and cephalosporins. Considerable reductions in CDI cases occurred from 2008 and in subsequent years [9, 12, 13].

The emergence of *Escherichia coli* infections has also caused concern. Using PHE's voluntary laboratory surveillance data, *E. coli* reported as causing bacteraemia in England increased by 33% between 2004 and 2008 [6].

For this study, SSI microorganism data captured by PHE's national SSI surveillance provided an opportunity to ascertain whether similar trends to those observed in bacteraemia were also present in SSIs.

MATERIALS AND METHODS

Case ascertainment and data collection process

The data for this study were captured by the national SSI surveillance system (SSISS). This programme was established in 1997 by the Public Health Laboratory Service (now PHE) to provide a benchmarking service and to enable hospitals to use data to improve practice. Initially participation was voluntary but since 2004, all NHS hospitals have been mandated to undertake a minimum of 3 months' surveillance each year in orthopaedic surgery. An additional 13 categories of surgical procedure are offered for voluntary national surveillance [14, 15]. Thus the surveillance dataset comprises orthopaedic surgical procedures collected annually by most hospitals and other surgical categories collected on an intermittent basis by some hospitals. All participating hospitals are trained by PHE in using the standard case definitions for superficial, deep or organ-space SSIs based on internationally recognized criteria with minor modifications in the English protocol [15]. In England the presence of pus cells is additionally required for microbiological confirmation and for superficial SSIs, a clinician diagnosis must accompany two clinical signs and symptoms. All eligible patients are followed up on a prospective basis to identify SSIs within 30 days of surgery for superficial SSIs or non-implant procedures. For procedures with an implant, an SSI can be reported for up to 1 year. Data validation is undertaken to correct errors and from 2004 has been handled automatically via the web-based application. Participating hospitals can voluntarily report up to three clinically significant isolates using a standard set of codes denoting species, genus, or a generic group, e.g. 'coliforms'. Specific antimicrobial susceptibility data on causative organisms are not collected except for *S. aureus* which is reported as methicillin-sensitive, methicillin-resistant or vancomycin-intermediate (VISA). MRSA is inclusive of VISA. Data on surgical antimicrobial prophylaxis agents are not collected.

Inclusion criteria

Data on causative organism from SSI cases detected during the inpatient stay between 1 January 2000 and 31 December 2013 were included. Data from non-NHS hospitals were excluded. The data covered 13 defined surgical categories. SSIs diagnosed on readmission were excluded as readmission surveillance did not become mandatory until 2008. Given the nature of our study (examining long-term trends in the microbial aetiology of SSIs), it was important to exclude this potential source of bias arising from the mandatory readmission surveillance, introduced part way through our study period. The length of hospital stay was included in the adjusted analysis.

Statistical analysis

This study was based on an analysis of cases of SSI. All pathogens reported as a causative organisms

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were included in the analysis. For analyses at genus or family level, monomicrobial and polymicrobial cases were combined provided the latter included species from the same genera or family.

Fixed and mixed-effects models were fitted using Stata/SE 13.1 (StataCorp, USA). Standard logistic regression was used to analyse binary outcome data under a Bernoulli distribution. The mean annual change in the odds of SSI due to a pathogen was estimated using a linear predictor with seven confounding variables: age (continuous), patient sex, ASA score (pre-operative health status dichotomised into <3 and $\geqslant 3$), wound class (dichotomized into clean/clean-contaminated and contaminated/dirty), duration of operation (dichotomized according to the 75th percentile value rounded to the nearest hour), days of in-patient follow-up (continuous) and surgical category. For the surgical category predictor data from eight surgical categories were compressed into four groups to permit model maximization: gastrointestinal (large, small bowel, gastric), orthopaedic (total hip and knee prosthesis, hip hemiarthroplasty, reduction of long bone fracture), coronary artery bypass graft (CABG) and vascular surgery. The other five categories were excluded from the model because the annual volumes were small and they were unrelated to the four groups. As our dataset comprised inpatient-detected cases, we adjusted for variation in the length of follow-up during the inpatient stay. The logistic linear mixed model added random hospital effects to take into account extra variation not explained by the confounding factors. Akaike's Information Criterion approach was used to determine the relative optimum fit compared to the fixed-effects model. Adjusted ORs (aORs), 95% confidence intervals (CIs) and *P* values are reported.

The time periods 2000–2005 and 2005–2013 were selected for modelling *S. aureus* SSI trends to represent pre- and post-implementation of national guidelines on the prevention and control of HCAIs, particularly MRSA, introduced from 2006. The periods 2000–2007 and 2007–2013 were used for modelling trends in Enterobacteriaceae SSIs as these periods represented pre- and post-implementation of the antimicrobial prescribing guideline introduced in 2007. Enterobacteriaceae merited focus given the recent emergence of antimicrobial resistance in Gram-negative bacilli. Each post-implementation period included the year preceding the national policy of interest.

Changes in microbial aetiology were modelled by surgical category using the same nine modules included in the surgical category predictor in the main analysis. The analysis by surgical category was based on $\geqslant 100$ cases with organism data per pooled period: 2000–2005 (baseline prior to national HCAI policies) and 2008–2013 post-implementation of HCAI policies).

Separate analyses of deep incisional or organ/space for SSIs were undertaken to determine if similar effects were observed in this clinically important subgroup. This analysis included coagulase-negative staphylococci (CoNS) as their presence in these more severe SSIs is not likely to reflect colonization.

RESULTS

Between 2000 and 2013, patient-level data on 968 662 procedures and 13 531 in-hospital SSIs were submitted by 253 acute NHS hospitals in England (Table 1). Orthopaedic procedures accounted for 84% of total volume, followed by CABG (7%) then gastrointestinal surgery (4%). The number of procedures included in the surveillance increased steadily from April 2004 (not shown), reflecting the introduction of the mandatory surveillance of SSI in orthopaedic surgery.

The proportion of SSIs that were deep/organ-space varied by surgical category. Complex SSIs were more likely to be captured in procedures with a longer post-operative hospital spell. The crude SSI incidence was highest in gastrointestinal surgery and lowest in prosthesis surgery (Table 1).

Data on causative microorganism was reported for 72% of SSIs (9767/13 531), although this proportion declined gradually from 82% in 2000 to 58% in 2013 (Table 2). Of 9767 SSIs, 29% ($n = 2838$) were polymicrobial comprising 6419 isolates. *S. aureus* accounted for 33% of SSIs (3250/9767) inclusive of SSI cases where both MRSA and MSSA were isolated in the same patient ($n = 20$). Enterobacteriaceae accounted for 16% of SSIs (1536/9767) of which 8% (149/1536) comprised solely Enterobacteriaceae organisms isolated in the same patient. Overall, the majority of Enterobacteriaceae were reported as 'coliforms'; 47% (654/1387) and 52% (70/149) in the monomicrobial and polymicrobial subsets, respectively. Due to the reporting of 'coliforms', data on Enterobacteriaceae species were aggregated to family level for analysis.

S. aureus was the predominant pathogen between 2000 and 2009, peaking at 45% of SSI cases in 2002 (Table 2, Fig. 1). This predominance persisted despite

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Table 1. *Number of surgical procedures and in-hospital surgical site infection (SSI) cases by surgical category, data from 2000 to 2013, NHS hospitals, England*

Type of procedure	No. of procedures (%)	No. of participating hospitals	Median length of hospital stay (days)	In-hospital SSI cases			Cumulative incidence	
				Total	Superficial* *n* (% of SSI)	Deep/organ-space* *n* (% of SSI)	%	95% CI
Abdominal hysterectomy	15 150 (1·6%)	68	4	181	148 (81·7%)	33 (18·2%)	1·2%	1·0–1·4
Bile duct/liver/pancreatic surgery	3214 (0·3%)	12	9	196	109 (55·6%)	87 (44·1%)	6·1%	5·3–7·0
Cholecystectomy	1162 (0·1%)	14	6	43	11 (25·6%)	32 (74·4%)	3·7%	2·7–5·0
Coronary artery bypass graft	63 065 (6·5%)	30	7	2156	1414 (65·6%)	741 (34·4%)	3·4%	3·3–3·6
Gastric surgery	1818 (0·2%)	16	10	74	23 (31·5%)	50 (68·5%)	4·1%	3·2–5·1
Hip hemiarthroplasty	85 511 (8·8%)	183	13	2072	1280 (62·0%)	783 (38·0%)	2·4%	2·3–2·5
Hip prosthesis	329 688 (34·0%)	235	5	2144	1472 (68·8%)	666 (31·2%)	0·7%	0·6–0·7
Knee prosthesis	336 836 (34·7%)	226	5	1150	824 (71·9%)	322 (28·1%)	0·3%	0·3–0·4
Large bowel surgery	34 777 (3·6%)	93	9	3118	1917 (61·6%)	1,197 (38·4%)	9·0%	8·7–9·3
Limb amputation	5907 (0·6%)	55	14	424	316 (74·7%)	107 (25·3%)	7·2%	6·5–7·9
Open reduction of long bone fracture	65 279 (6·7%)	139	10	797	586 (73·5%)	211 (26·5%)	1·2%	1·1–1·3
Small bowel surgery	6941 (0·7%)	34	9	517	342 (66·7%)	171 (33·3 %)	7·5%	6·8–8·1
Vascular surgery	19 314 (2·0%)	60	7	659	496 (75·7%)	159 (24·3%)	3·4%	3·2–3·7
Total	**968 662**	**253**	–	**13 531**	**8938**	**4559**	–	

CI, Confidence interval.
* Based on SSI cases with SSI type data given.

an initial decline in 2006 and steep decreases from 2007 (38%) to 2009 (24%). By 2013, *S. aureus* accounted for 16% of SSIs. This trend was explained by marked reductions in MRSA from 2006. Enterobacteriaceae were the second most frequent pathogens accounting for 12% of SSIs overall during 2000–2007 (inter-year range 9–14%) increasing to 18% of cases in 2008. They overtook *S. aureus* in 2010 (22%) increasing to 25% in 2013. Similar trends were observed by surgical category (Fig. 1). Similar trends in *S. aureus* and Enterbacteriaceae were observed in deep/organ-space SSIs (Table 2).

Multivariable analysis

For the analysis of trends in aetiology among cases of SSI, a total of 7476 inpatient SSIs with microbiology data were available for the multivariable analysis based on nine surgical categories. The excluded SSIs (2291/9767) were due to the four surgical categories that could not be grouped with any of the nine categories and missing data on required covariates. The majority of the missing data related to ASA score (1480/2291).

After controlling for covariates, there was insufficient evidence to support an association between *S. aureus* and time (year) during 2000–2005 (Table 3). A similar conclusion applied to MRSA and Enterobacteriaceae SSIs. These reflected the unchanging variation in the underlying data. A barely detectable decline in the odds of MSSA was found in this period (aOR 0·94, 95% CI 0·88–1·01, $P = 0·078$).

The decreases in *S. aureus* as a relative cause of SSI during 2005–2013 were strongly supported by the model. The adjusted odds of SSI due to *S. aureus* was 0·86 per unit increase in time (year) (95% CI 0·83–0·89). This trend was due to significant decreases in MRSA (aOR 0·71, 95% CI 0·68–0·75). A small but significant relative increase in MSSA occurred during this time (aOR 1·06, 95% CI 1·02–1·10).

During 2000–2007, the model showed no evidence of change in the contribution of Enterobacteriaceae as reported causes of SSI, reflecting the crude trends. However, during 2007–2013, the observed increase in SSIs due to Enterobacteriaceae were strongly supported by the model; the estimated adjusted odds ratio was 1·12 per unit change in time (year) (95% CI 1·07–1·18).

Trends in the subset of deep/organ-space SSIs were similar to those observed in main analyses except for MSSA during 2005–2013 (Table 3) where the positive

Table 2. *Distribution of organisms reported to cause in-hospital surgical site infection (SSI) cases, NHS hospitals, England, 2000 to 2013*

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
All SSIs														
Enterobacteriaceae*	10·8	9·4	11·8	12·3	13·1	9·9	13·7	12·2	18·0	23·1	22·2	23·1	23·1	24·6
MRSA†	25·4	27·8	30·8	25·9	25·6	29·0	24·8	23·7	15·4	9·1	5·9	4·1	4·5	4·4
MSSA‡	15·3	12·6	13·9	13·5	13·0	12·4	14·5	14·4	15·4	14·9	14·2	13·3	15·1	12·0
S. aureus	40·9	40·6	44·6	39·8	39·0	41·7	39·8	38·0	30·8	24·2	20·2	17·4	19·6	16·4
CoNS§	3·7	5·5	8·0	6·6	8·3	6·0	7·1	8·3	10·7	10·4	10·6	9·6	9·1	12·4
Pseudomonas spp.	6·5	5·0	5·5	5·7	4·3	5·1	5·5	5·4	6·2	6·1	4·6	5·4	6·5	4·7
Enterococcus spp.	2·7	3·3	2·4	4·8	3·6	4·6	3·6	3·9	4·7	2·5	4·0	4·7	5·8	4·2
Other‖	35·7	36·4	27·7	31·1	32·1	33·2	30·8	32·1	29·7	33·9	38·6	40·0	36·0	37·8
SSIs with microbiology data (*n*)	678	818	780	771	816	769	759	613	657	637	677	615	603	574
Total SSI cases (*n*)	**825**	**976**	**937**	**954**	**1000**	**954**	**1052**	**889**	**883**	**969**	**1036**	**1038**	**1034**	**984**
Deep organ space SSIs														
Enterobacteriaceae*	10·7	7·1	10·2	11·9	15·3	6·4	13·1	1·1	19·1	22·5	19·7	19·5	20·7	26·4
MRSA†	27·2	23·7	31·6	24·2	25·1	27·4	24·5	18·9	14·3	9·3	7·2	4·0	5·2	2·9
MSSA‡	8·7	8·9	10·2	15·0	13·1	12·4	11·7	8·3	12·9	9·7	7·2	12·9	12·1	9·4
S. aureus	36·4	33·0	41·8	40·1	38·9	41·0	36·5	27·2	27·2	19·5	14·8	16·9	17·2	12·3
CoNS	1·0	6·3	8·9	4·4	8·4	5·6	8·4	8·8	10·3	12·7	11·7	12·1	9·7	13·0
Enterococcus spp.	3·9	2·7	0·9	4·0	3·3	5·6	4·0	4·1	5·1	2·5	6·1	5·5	7·6	4·7
Pseudomonas spp.	2·9	1·3	3·1	4·0	1·5	3·4	2·9	4·1	3·7	3·8	3·4	5·5	4·8	2·9
Other§	45·6	50·0	35·1	36·6	33·5	39·2	35·4	44·7	34·6	39·4	44·7	40·4	40·0	40·6
SSIs with microbiology data (*n*)	206	224	225	227	275	234	274	217	272	236	264	272	290	276
Total SSI cases (*n*)	**238**	**264**	**263**	**263**	**321**	**280**	**368**	**297**	**334**	**336**	**374**	**390**	**433**	**398**

CoNS, Coagulase-negative staphylococci.

Values given are percentages unless stated otherwise.

* Includes 'coliforms'.

† Methicillin-resistant *S. aureus*.

‡ Methicillin-sensitive *S. aureus*.

§ Other organisms or Gram-positive and Gram-negative combinations.

association between MSSA and time disappeared although this could be due to the effect of a reduced sample size. The increasing trend in CoNS during 2005–2013 missed statistical significance (aOR 1·07, 95% 1·00–1·14, $P = 0·065$).

There was a significant variation between hospitals for all analyses were based on all SSIs. For example, in the analysis for MRSA during 2005–2013, the estimated variance between hospitals was 0·63 (S.E. = 0·08) and in the analysis for Enterobacteriaceae during 2007–2013, this was 0·58 (S.E. = 0·08). However, the effect of hospital difference was minimal in terms of model fit for some of the deep/organ-space pathogens except in 2005–2013 and 2007–2013 where the mixed model was a significant improvement over the logistic model for all pathogens examined.

The unadjusted analysis yielded similar results in terms of the direction of effect as the adjusted analysis except for MSSA and CoNS (data not shown). For MSSA, the annual decrease was much more distant from the null in 2000–2005, and in 2005–2013 the annual increase was strongly non-significant. For deep/organ-space SSIs, the unadjusted increase in CoNs was significant in 2000–2005 ($P = 0·022$) and in 2005–2013 ($P = 0·030$).

For the multivariable analysis by surgical category, two pooled time periods were used; 2008–2013 compared to 2000–2005 (baseline). Of 8395 SSI cases with microorganism data for the two combined periods, 23% ($n = 1898$) were excluded as described earlier leaving 6497 cases available for analysis. The majority of missing records were due to missing ASA score data (1212/1898). Changes in microbial aetiology in gastric surgery were not evaluated due to sparse data (<25 SSI cases per time period). The adjusted odds of SSIs due to MRSA decreased significantly between these two periods in all eight categories examined with the largest decrease observed in CABG surgery (Table 4). The adjusted odds of Enterobacteriaceae increased significantly in all categories except in CABG and knee prosthesis surgery, where no evidence of change was identified. The largest increases

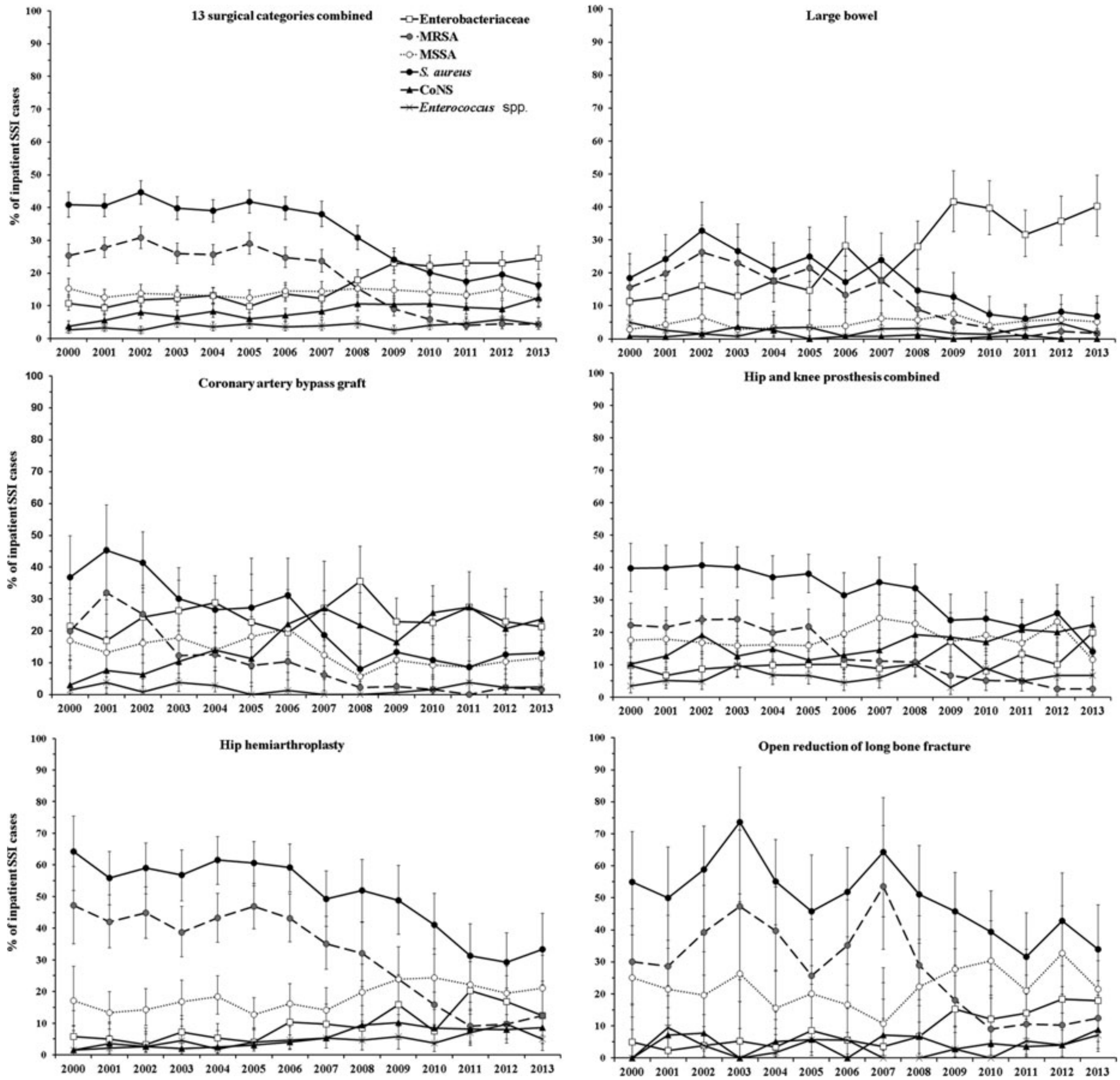

Fig. 1. Trends in key pathogens reported as causes of in-hospital (SSIs) for selected surgical categories, NHS hospitals, England.

were in open reduction of long bone fracture and large bowel surgery. The odds of SSI due to CoNS (not shown) increased significantly in hip prosthesis (aOR 1·62, 95% CI 1·10–2·40, $P = 0{\cdot}016$), knee prosthesis (aOR 2·22, 95% CI 1·43–3·44, $P < 0{\cdot}001$), hip hemiarthroplasty (aOR 3·85, 95% CI 2·07–7·15, $P < 0{\cdot}001$) and CABG surgery (aOR 2·63, 95% CI 1·64–4·22, $P < 0{\cdot}001$). The unadjusted analysis yielded similar results in terms of direction of effect and significance except for CoNS in hip prosthesis as this showed a non-significant increase (data not shown).

We also examined the background trends in the odds of all-cause SSI based on all exposure data for each of the eight surgical categories also using the mixed model (not shown). The data comprised 810 763 procedures and 10 350 in-hospital SSIs. All covariates were included except surgical category. The adjusted annual odds of in-hospital SSI decreased significantly in each category except in large bowel surgery where the odds increased significantly by 2% annually over the study period (95% CI 1·01–1·03).

DISCUSSION

Using 14 years of national surveillance data, this study identifies, for the first time, important changes in the microbial aetiology of SSIs in English NHS hospitals. A significant decrease in *S. aureus* was identified with

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Table 3. *Annual change in the adjusted odds of in-hospital SSIs due to a causative pathogen, pre and post implementation of targeted national policies on healthcare associated infections, NHS hospitals, England*

	Trends between 2000 and 2005*			Trends between 2005 and 2013*†‡			Trends between 2000 and 2007*†			Trends between 2007 and 2013†‡		
	aOR	95% CI	*P*	aOR	95% CI	*P*	aOR	95% CI	*P*	aOR	95% CI	*P*
All SSIs												
S. aureus	0·98	0·93–1·02	0·319	0·86	0·83–0·89	<0·001	–	–	–	0·82	0·78–0·86	<0·001
MRSA	1·01	0·95–1·06	0·814	0·71	0·68–0·75	<0·001	–	–	–	0·66	0·62–0·72	<0·001
MSSA	0·94	0·88–1·01	0·078	1·06	1·02–1·10	0·001	–	–	–	1·00	0·94–1·05	0·930
Enterobacteriaceae	1·05	0·97–1·13	0·214	–	–	–	1·04	0·99–1·09	0·132	1·12	1·07–1·18	<0·001
Total isolates§	***n* = 3371**			***n* = 4691**			***n* = 4350**			***n* = 3592**		
Deep organ space SSIs												
S. aureus	1·02	0·94–1·11	0·642	0·83	0·79–0·88	<0·001	–	–	–	0·83	0·77–0·90	<0·001
MRSA	0·99‖	0·91–1·08	0·894	0·70	0·65–0·75	<0·001	–	–	–	0·66	0·59–0·75	<0·001
MSSA	1·03‖	0·91–1·16	0·668	1·04	0·98–1·11	0·173	–	–	–	1·02	0·93–1·12	0·647
CoNS	1·16‖	0·98–1·38	0·093	1·07	1·00–1·14	0·065	–	–	–	1·04	0·94–1·14	0·455
Enterobacteriaceae	1·03‖	0·91–1·18	0·603	–	–	–	1·04‖	0·96–1·13	0·293	1·14	1·06–1·23	0·001
Total isolates§	***n* = 1005**			***n* = 1854**			***n* = 1348**			***n* = 1502**		

CI, Confidence interval; aOR, adjusted odds ratio based on a mixed model adjusting for age, sex, ASA score, duration of operation, wound class, patient days of follow-up, surgical category and variation between hospitals; CoNS, coagulase-negative staphylococci.

* This period included the 'Cleanyourhands' campaign funded by Department of Health rolled out from December 2004 to June 2005.

† Antimicrobial prescribing guidance introduced in late 2007.

‡ This period included inspection of hygiene standards in hospitals by the Healthcare Commission (now the Care Quality Commission) from 2008.

§ Final sample available for analysis inclusive of all pathogens in the dataset including those under study.

‖ Results from the fixed effects model due to better fit (lower AIC than the mixed model).

Table 4. *Changes in the adjusted odds of in-hospital SSI due to S. aureus, MRSA or Enterobacteriaceae by surgical category: pooled data 2008–2013 compared to 2000–2005 (baseline), NHS hospitals, England*

	No. SSIs with microbiology data		*S. aureus* No. (%)					Methicillin-resistant *S. aureus* (MRSA) No. (%)					Enterobacteriaceae No. (%)				
	2000–2005	2008–2013	2000–2005	2008–2013	aOR	95% CI	*P*	2000–2005	2008–2013	aOR	95% CI	*P*	2000–2005	2008–2013	aOR	95% CI	*P*
CABG*	355	562	98 (27·6%)	67 (11·9%)	0·28	0·17–0·44	<0·001	63 (17·8%)	10 (1·8%)	0·08	0·04–0·19	<0·001	87 (24·5%)	144 (25·6%)	1·01	0·69–1·48	0·949
Hip hemiarthroplasty*†	703	521	420 (59·7%)	199 (38·2%)	0·41	0·31–0·55	<0·001	304 (43·2%)	84 (16·1%)	0·23	0·16–0·32	<0·001	40 (5·7%)	69 (13·2%)	2·45	1·61–3·73	<0·001
Hip prosthesis	749	497	319 (42·6%)	131 (26·4%)	0·48	0·36–0·64	<0·001	188 (25·1%)	29 (5·8%)	0·15	0·09–0·24	<0·001	62 (8·3%)	73 (14·7%)	1·67	1·12–2·50	0·012
Knee prosthesis*‡	304	211	106 (34·9%)	46 (21·8%)	0·53	0·35–0·79	0·002	50 (16·5%)	13 (6·2%)	0·34	0·18–0·64	0·001	26 (8·6%)	12 (5·7%)	0·67	0·32–1·43	0·301
Large bowel	676	792	163 (24·1%)	72 (9·1%)	0·26	0·18–0·38	<0·001	133 (19·7%)	27 (3·4%)	0·14	0·08–0·22	<0·001	104 (15·4%)	276 (34·8%)	3·13	2·28–4·31	<0·001
Open reduction of long bone fracture*†	194	302	113 (58·3%)	118 (39·1%)	0·43	0·26–0·69	<0·001	71 (36·6%)	42 (13·9%)	0·22	0·13–0·39	<0·001	8 (4·1%)	44 (14·6 %)	3·89	1·76–8·59	0·001
Small bowel§	106	109	28 (26·4%)	10 (9·2%)	0·28	0·13–0·62	0·002	23 (21·7%)	5 (4·6%)	0·19	0·07–0·52	0·001	19 (17·9%)	36 (33·0%	2·28	1·19–4·35	0·013
Vascular*	292	116	128 (43·8%)	30 (25·9%)	0·37	0·19–0·71	0·003	91 (31·2%)	13 (11·2%)	0·24	0·11- 0·52	<0·001	31 (10·6%)	21 (18·1%)	2·43	1·10–5·39	0·028
Combined nine categories (including gastric surgery)‖¶	3,371	3,126	1,370 (40·6%)	675 (21·6%)	0·41	0·36–0·47	<0·001	918 (27·2%)	224 (7·2%)	0·20	0·17–0·24	<0·001	374 (11·1%)	682 (21·8%)	2·02	1·72 –2·37	<0·001

CI, Confidence interval; aOR, adjusted odds ratio based on a mixed model adjusting for age, sex, ASA score duration of operation, wound class, patient days of follow-up, surgical category (forcombined analysis only) and variation between hospitals; CABG, coronary artery bypass graft.

* Model excludes wound class from all three analyses due to underlying sparse data;

† Results from the fixed effects model presented for Enterobacteriaceae only due to better model fit [lower Akaike's Information Criterion (AIC)].

‡ Results from the fixed effects model presented for MRSA and *S. aureus* due to better model fit (lower AIC).

§ Results from the fixed effects model presented for all three analyses due to better model fit (lower AIC).

‖ Includes SSI cases from gastric surgery although a separate analysis for this category was not performed due to low number of SSI cases (n = 10 in 2000–05 and n = 21 in 2008–13);

¶ The data used for the mixed model analysis yields slightly different total SSI cases per pooled period compared to the sum of cases derived from the eight individual categories investigated – this is because wound class was not included as a covariate in five of eight categories investigated on the basis of sparse data.

a subsequent significant rise in Enterobacteriaceae. Despite a background of decreasing odds in all-cause SSI at surgical category level, this masked changes in the underlying microbial aetiology. The subgroup of deep-organ space SSIs exhibited similar trends. The multivariable analysis showed that our results were not explained by case-mix, surgical category, variation between hospitals or length of hospital stay.

We postulate that the changing trends in SSI aetiology coincided temporally with a series of national HCAI policies introduced in England since 2006. Given the ecological nature of this analysis, it is not possible to disentangle the impact of each specific intervention. However, the multi-modal strategy involving vertical (targeting a single pathogen) and horizontal (broad-based) activities may have had a cumulative impact on the trends in pathogens causing SSI that we have identified.

The national MRSA screening and decolonization strategy, introduced in England in November 2006, was targeted at elective patients in high risk specialties [8]. This was expanded in July 2008 to cover all NHS elective (by March 2009) and emergency admissions (by December 2010) [8, 16, 17]. Despite the initial targeted screening strategy, our study identified moderate decreases in MRSA as an aetiological cause of SSI in 2006 and 2007. The steep decreases in 2008 and in subsequent years appeared to coincide with the expanded screening policy. However a prevalence study in 2011 found that 61% of emergency and 81% of elective admissions in NHS Trusts used universal screening [18]. If uptake of universal screening was low from the start, this suggests other drivers may have influenced the marked reduction MRSA SSIs in 2007 and 2008. Our study also identified significant reductions in MRSA SSIs in all eight surgical categories examined. The MRSA SSIs trends were similar to those observed for MRSA bacteraemia, captured separately by the English mandatory programme where moderate decreases from 2004 to 2006 occurred declining steeply from 2007 [7]. This marked decrease coincided with the national guidance on infection prevention for a range of clinical procedures. The national 50% reduction target for MRSA bacteraemia was achieved by 2008.

The effects of antimicrobial prescribing guidance introduced in August 2007 aimed at controlling CDIs may have also indirectly contributed to the steep MRSA reductions. Exposure to broad-spectrum antimicrobials, particularly cephalosporins and quinolones has been shown to be a risk factor for the acquisition of MRSA [19–22]. Restricting the use of these antibiotic classes would be expected to reduce the selection pressure on MRSA. Thus a collective effort across NHS Trusts in reducing the use of several broad-spectrum antibiotics aimed at reducing the burden of CDIs may have had a favourable ecological impact on MRSA. The impact of restricted cephalosporin use on the decreases in MRSA and CDIs has been reported in single-centre studies [23, 24].

The decreasing prevalence of EMRSA-16, one of two dominant MRSA epidemic strains is of interest although these predate the national MRSA control measures [25].The changing ecology of this strain however may have also had some influence in the reduction of MRSA SSIs and mandatory MRSA bacteraemia cases captured by PHE.

The increase in deep/organ-space SSIs caused by CoNS between 2005 and 2013, although in this analysis missed statistical significance, was based on a small sample. CoNS are however indolent pathogens and infections frequently present too late to be captured by inpatient-based surveillance so are likely to be under-reported, hence the small sample size. It should be noted that our analysis by surgical category, though based on all SSI types indicated an increase in CoNS in orthopaedic and CABG surgery both of which include prosthetic material. Potential explanations for the increase include emerging resistance to agents used for prophylaxis such as glycopeptides and aminoglycosides both of which are used as surgical prophylaxis in orthopaedic surgery in some English NHS Trusts [26–28] or sub-optimal skin decontamination due to reduced susceptibility of staphylococci to chlorhexidine [29]. In the UK, there is, as yet, no specific evidence of any reduced susceptibility to chlorhexidine.

An earlier study based on PHE's voluntary laboratory-based surveillance data indicated that bacteraemia episodes due to *E. coli* and *Klebsiella* spp. increased by 33% and 14%, respectively from 2004 to 2008 [6]. This is an important context for the SSI aetiology trends we observed in our study.

The steep decrease in MRSA in 2008 and 2009 we identified were concurrent with steep increases in Enterobacteriaceae as a cause of SSI. A compensatory replacement may be argued although MSSA would have perhaps been a more likely organism for this effect. Nevertheless the marked increase observed for Enterobacteriaceae coincided temporally with the new antimicrobial prescribing guidance introduced in 2007 to address the emerging problem of CDI. This guidance focused on reducing the use of broad-spectrum agents, in particular cephalosporins and fluoroquinolones. The CDI reduction target and associated financial penalties, both introduced in 2007, would have compelled hospitals to adopt the new prescribing guidance thus initiating changes in hospital formulary. Substantial decreases in the number of CDI cases occurred in England between financial year 2007/2008 and 2008/2009 (decreasing by 35% from 55 500 to 36 100 cases, respectively) coinciding with reductions in CDI epidemic ribotype 027. Further reductions in CDI cases (and ribotype 027) were observed in subsequent years [12, 13]. In terms of antibiotic usage, substantial reductions in the use of fluoroquinolones, second- and third-generation cephalosporins from 2005 to 2009 in English NHS Trusts were observed (>40%, >50% and >22%, respectively), while the use of carbapenems and combination β-lactamase inhibitors increased [30]. Consumption of the quinolone and cephalosporin classes in England is currently the lowest in the European Union [31].

Thus, one explanation for the increase in Enterobacteriaceae as a cause of SSI is this antimicrobial stewardship-based (horizontal) approach to reducing CDIs. The impact of the antimicrobial prescribing guidance extended beyond CDIs, changing the antibiotics used for surgical prophylaxis and potentially increasing the opportunity for Enterobacteriaceae to cause SSI. Amended hospital formularies may include agents with less favourable pharmacokinetic properties or narrower antimicrobial spectra, increasing the risk of Gram-negative SSIs. Aminoglycosides or β-lactam/β-lactam inhibitor combinations are the new mainstay for Gram-negative cover. However it is possible that the existing surgical antimicrobial prophylaxis regimens are not always achieving above-minimum inhibitory concentration levels at the surgical site. Conditions of physiological stress such as significant blood loss and fluid replacement may further decrease tissue concentrations [32, 33]. Potentially lower levels might also occur in obese patients [34] than for agents used in the earlier part of our study period. In addition, antibiotic-resistant Enterobacteriaceae may be refractory to the effects of some of the current prophylaxis regimens [35] due to the emergence of extended-spectrum β-lactamases and carbapenamase-producing Enterobacteriaceae reported internationally [36, 37]. As we did not capture antibiotic susceptibility data on Gram-negative SSIs, we could not determine how much of the increase in Enterobacteriaceae SSIs was fuelled by antibiotic resistance.

Our study identified increases in SSIs due to Enterobacteriaceae affecting six of eight surgical categories in a range of clean and clean-contaminated procedures. The largest effects were observed in open reduction of long bone fracture and large bowel surgery. No evidence of an increasing trend was found for knee prosthesis perhaps due to small sample sizes or for CABG surgery which may be due to lower limb donor site SSIs being seeded postoperatively by patient flora therefore less influenced by changes in antibiotic prophylaxis. The increase in SSIs in bowel surgery with enteric organisms does raise concern that inadequate prophylaxis may be the main driver here.

Trends in the microbial aetiology of SSIs reported internationally show similarities with the English results. For example, a significant decrease in MRSA SSIs and a significant increase in SSIs due to ceftriaxone-resistant *E. coli* have been reported in Australia between 2002 and 2013 based on data from hospitals in Victoria state [38]. Data from the USA derived from two separate summaries for 2006/2007 and 2009/2010 showed that *S. aureus* remained stable at 30% of SSI isolates in both periods although MRSA decreased from 49% to 44%, respectively. Although the proportion of SSI isolates due to *E. coli* or *K. pneumoniae/K. oxytoca* remained unchanged, an increase in cephalosporin resistance was noted in *E. coli* isolates from 5% to 11% over these two periods [39, 40]. Data from sentinel laboratories in the USA participating in CDC's bacterial surveillance network also showed reductions in MRSA; the modelled incidence of hospital-onset invasive MRSA significantly decreased 9·4% annually from 2005 to 2008. The authors believed this reflected the dissemination of MRSA prevention practices in US hospitals [41]. However, as of 2011, CDIs remain high in the USA as well as the use of broad-spectrum antibiotics in acute hospitals [42, 43].

In England the decrease in MRSA as a reported cause of SSI may reflect the success of intensified MRSA control strategies and the impact of changes in antimicrobial prescribing, the latter reducing the propensity for MRSA selection. The increase in Enterobacteriaceae as reported causes of SSI however demands further study given the increasing antimicrobial resistance in these pathogens and the need to inform the selection of appropriate and effective antimicrobial prophylaxis.

Limitations

Since neither patient- nor hospital-level data on hospital infection control interventions or surgical prophylaxis are collected, an inference is made between the timing of large-scale national policies and the trends in reported SSI pathogens Although ecological analyses are useful at population-level it is not possible to establish direct cause and effect.

An analysis of trends in the leading species of Enterobacteriaceae (*E. coli* and *K. pneumoniae*) could not be undertaken due to the high proportion of organisms reported as 'coliforms'.

Although there was a gradual decline in the proportion of SSIs with causative organism data reported, there was no temporal relationship between tis decline and the observed microbial aetiology trends.

Some of the organisms reported for superficial SSIs and included in the main analysis may represent colonisation with regional flora. However, similar trends in aetiology were observed for deep/organ-space SSIs where such contamination is much less likely.

Participation in the non-orthopaedic categories is voluntary resulting in lower hospital coverage compared to the mandatory orthopaedic categories, intermittent or no surveillance in any given year.

CONCLUSION

S. aureus reported as causing SSIs decreased significantly in England during 2005–2013 and was attributable to significant decreases in MRSA SSIs. These trends coincided with intensified efforts to control MRSA in acute NHS hospitals particularly the screening and decolonization of MRSA carriers. The impact of the national antimicrobial prescribing guidance directed at reducing CDIs may have also contributed to these trends. A small but significant increase in MSSA occurred concurrently.

Enterobacteriaceae reported as causing SSIs increased significantly after 2007, an effect that was present across the majority of surgical categories studied. This trend may be temporally linked with the national antimicrobial guidance. Changes to hospital formulary to control CDIs may have led to the selection of surgical antibiotic prophylaxis with a reduced spectrum of cover against Gram-negative bacilli either due to the effects of antibiotic resistance or inadequate tissue concentrations of prophylaxis at the surgical site.

Our study identified important changes in the aetiology of SSI in England and we postulate that interventions targeted at one HCAI may have indirect consequences for other HCAIs. The true impact of antimicrobial stewardship programmes needs to be evaluated in terms of benefits and harms [44]. Further study is needed to better understand these effects and to ensure that antimicrobial surgical prophylaxis is optimized.

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DECLARATION OF INTEREST

None.

REFERENCES

1. **Health Protection Agency.** English National Point Prevalence Survey on Healthcare-associated infections and Antimicrobial Use, 2011: preliminary data, May 2012 (http://webarchive.nationalarchives.gov.uk/20160210151033/https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/331871/English_National_Point_Prevalence_Survey_on_Healthcare_associated_Infections_and_Antimicrobial_Use_2011.pdf).
2. **Plowman R,** ***et al.*** The rate and cost of hospital-acquired infections occurring in patients admitted to selected specialties of a district general hospital in England and the national burden imposed. *Journal of Hospital Infection* 2001; **47**: 198–209.
3. **Coello R,** ***et al.*** Adverse impact of surgical site infections in English hospitals. *Journal of Hospital Infection* 2005; **60**: 93–103.
4. **Health Protection Agency.** Surveillance of surgical site infection in NHS hospitals in England 2011/12, December 2012 (http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317137334452).
5. **Johnson AP,** ***et al.*** Mandatory surveillance of methicillin-resistant Staphylococcus aureus (MRSA) bacteraemia in England: the first 10 years. *Journal of Antimicrobial Chemotherapy* 2012; **67**: 802–809.
6. **Wilson J,** ***et al.*** Trends among pathogens reported as causing bacteraemia in England, 2004–2008. *Clinical Microbiology and Infection* 2011; **17**: 451–458.
7. **Duerden B,** ***et al.*** The Control of methicillin-resistant Staphylococcus aureus blood stream infections in England. *Open Forum Infectious Diseases* 2015; **2**: ofv035.

8. **Coia JE, *et al.*** Guidelines for the control and prevention of meticillin-resistant Staphylococcus aureus (MRSA) in healthcare facilities. *Journal of Hospital Infection* 2006; **63** (Suppl. 1): S1–44.
9. **Stone SP, *et al.*** Evaluation of the national Cleanyourhands campaign to reduce *Staphylococcus aureus* bacteraemia and *Clostridium difficile* infection in hospitals in England and Wales by improved hand hygiene: four year, prospective, ecological, interrupted time series study. *British Medical Journal* 2012; **344**: e3005.
10. **HM Treasury.** PSA Delivery agreement 19: ensure better care for all. October 2007.
11. **Department of Health.** Saving Lives: reducing infection, delivering clean and safe care. Antimicrobial prescribing – a summary of best practice, August 2007 (http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_078117.pdf).
12. **Public Health England.** Annual epidemiological commentary. Mandatory MRSA, MSSA and *E. coli* bacteraemia and *C. difficile* infection data to 2015/16. July 2016 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/535635/AEC_final.pdf).
13. **Wilcox MH, *et al.*** Changing epidemiology of *Clostridium difficile* infection following the introduction of a national ribotyping-based surveillance scheme in England. *Clinical Infectious Diseases* 2012; **55**: 1056–1063.
14. **Chief Medical Officer.** Surveillance of Healthcare Associated Infections PL/CMO/ 2003, Depatrment of Health, June 2003 (http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4013410.pdf).
15. **Public Health England.** Protocol for the surveillance of surgical site infection. Version 6, June 2013 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/364412/Protocol_for_surveillance_of_surgical_site_infection_June_2013.pdf).
16. **Department of Health.** Screening for meticillin-resistant *Staphylococcus aureus* (MRSA) colonisation. A strategy for NHS Trusts: a summary of best practice, November 2006 (http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_063187.pdf).
17. **Department of Health.** MRSA screening - operational guidance, December 2008 (http://webarchive.nationalarchives.gov.uk/20130107105354/http://:/www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_092845.pdf).
18. **Fuller C, *et al.*** The national one week prevalence audit of universal meticillin-resistant Staphylococcus aureus (MRSA) admission screening 2012. *PLoS ONE* 2013; **8**: e74219.
19. **Monnet DL, Frimodt-Moller N.** Antimicrobial-drug use and methicillin-resistant *Staphylococcus aureus*. *Emerging Infectious Diseases* 2001; **7**: 161–163.
20. **Monnet DL, *et al.*** Antimicrobial drug use and methicillin-resistant *Staphylococcus aureus*, Aberdeen, 1996–2000. *Emerging Infectious Diseases* 2004; **10**: 1432–1441.
21. **MacKenzie FM, *et al.*** Antimicrobial drug use and infection control practices associated with the prevalence of methicillin-resistant *Staphylococcus aureus* in European hospitals. *Clinical Microbiology and Infection* 2007; **13**: 269–269.
22. **Tacconelli E, *et al.*** Does antibiotic exposure increase the risk methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *Journal of Antimicrobial Chemotherapy* 2008; **61**: 26–26.
23. **Stone SP, *et al.*** The effect of an enhanced infection-control policy on the incidence of Clostridium difficile infection and methicillin-resistant Staphyloccocus aureus colonization in acute elderly medical patients. *Age and Ageing* 1998; **27**: 561–568.
24. **Nicastri E, *et al.*** Decrease of methicillin resistant Staphylococcus aureus prevalence after introduction of a surgical antibiotic prophylaxis protocol in an Italian hospital. *New Microbiologica* 2008; **31**: 519–525.
25. **Ellington MJ, *et al.*** Decline of EMRSA-16 amongst methicillin-resistant *Staphylococcus aureus* causing bacteraemias in the UK between 2001 and 2007. *Journal of Antimicrobial Chemotherapy* 2010; **65**: 446–448.
26. **Cremniter J, *et al.*** Decreased susceptibility to teicoplanin and vancomycin in coagulase-negative staphylococci isolated from orthopedic-device-associated infections. *Journal of Clinical Microbiology* 2010; **48**: 1428–1431.
27. **Hope R, *et al.*** Non-susceptibility trends among staphylococci from bacteraemias in the UK and Ireland, 2001–06. *Journal of Antimicrobial Chemotherapy* 2008; **62** (Suppl. 2): ii65–ii74.
28. **Hickson CJ, *et al.*** Prophylactic antibiotics in elective hip and knee arthroplasty: an analysis of organisms reported to cause infections and National survey of clinical practice. *Bone and Joint Research* 2015; **4**: 181–189.
29. **Horner C, Mawer D, Wilcox M.** Reduced susceptibility to chlorhexidine in staphylococci: is it increasing and does it matter? *Journal of Antimicrobial Chemotherapy* 2012; **67**: 2547–2559.
30. **Ashiru-Oredope D, *et al.*** Improving the quality of antibiotic prescribing in the NHS by developing a new antimicrobial stewardship programme: Start Smart – Then Focus. *Journal of Antimicrobial Chemotherapy* 2012; **67** (Suppl. 1): i51–i63.
31. **Public Health England.** English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) 2010 to 2014: Report 2015, November 2015 (https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/477962/ESPAUR_Report_2015.pdf).
32. **Brunner M, *et al.*** Surgery and intensive care procedures affect the target site distribution of piperacillin. *Critical Care Medicine* 2000; **28**: 1754–1759.
33. **Markantonis SL, *et al.*** Effects of blood loss and fluid volume replacement on serum and tissue gentamicin concentrations during colorectal surgery. *Clinical Therapeutics* 2004; **26**: 271–281.
34. **Velissaris D, *et al.*** Pharmacokinetic changes and dosing modification of aminoglycosides in critically ill obese

patients: a literature review. *Journal of Clinical Medicine Research* 2014; **6**: 227–233.
35. **Livermore DM, *et al*.** Non-susceptibility trends among Enterobacteriaceae from bacteraemias in the UK and Ireland, 2001–06. *Journal of Antimicrobial Chemotherapy* 2008; **62** (Suppl. 2): ii41–ii54.
36. **Pitout JD, Laupland KB.** Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infectious Diseases* 2008; **8**: 159–166.
37. **Nordmann P, Naas T, Poirel L.** Global spread of carbapenemase-producing Enterobacteriaceae. *Emerging Infectious Diseases* 2011; **17**: 1791–1798.
38. **Worth LJ, *et al*.** Diminishing surgical site infections in Australia: time trends in infection rates, pathogens and antimicrobial resistance using a comprehensive Victorian surveillance program, 2002–2013. *Infection Control & Hospital Epidemiology* 2015; **36**: 409–416.
39. **Hidron AI, *et al*.** NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infection Control & Hospital Epidemiology* 2008; **29**: 996–1011.
40. **Sievert DM, *et al*.** Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infection Control & Hospital Epidemiology* 2013; **34**: 1–14.
41. **Kallen AJ, *et al*.** Health care-associated invasive MRSA infections, 2005–2008. *Journal of the American Medical Association* 2010; **304**: 641–648.
42. **Lessa FC, *et al*.** Burden of Clostridium difficile infection in the United States. *New England Journal of Medicine* 2015; **372**: 825–834.
43. **Magill S, *et al*.** Point prevalence survey of antimicrobial use in U.S. acute care hospitals. ID Week 2012, October 2012; San Diego, USA.
44. **Evans SR, *et al*.** Desirability of outcome ranking (DOOR) and response adjusted for days of antibiotic risk (RADAR). *Clinical Infectious Diseases* 2015; **61**: 800–806.