JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac108

JAC-Antimicrobial Resistance

Evaluating the long-term impact of an antimicrobial stewardship programme in a Central London mixed medical and surgical intensive care unit

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Received 30 March 2022; accepted 16 September 2022

Background: Antimicrobial overuse causes increased antimicrobial resistance in ICUs; antimicrobial stewardship programmes (ASPs) aim to optimize usage. Following an MDR *Acinetobacter baumannii* (MRAb) outbreak in 2008, an ASP was implemented at a London ICU, and then continued as a long-term programme. This study aimed to determine long-term changes in antimicrobial prescribing 9 years on.

Methods: Data were collected from ICU patients in 2008 immediately before ASP implementation, and thereafter for 6 month cohort periods in 2010–2011, 2012 and 2017. Antimicrobial usage in DDD per 1000 occupied bed days (OBD) were compared. Multivariate linear regression models for antimicrobial days were fitted, adjusting for APACHE II score and patient days. Antimicrobial resistance in *Pseudomonas aeruginosa* (as an indicator organism) was compared across cohort periods.

Findings: Across 400 patients over 9 years, antimicrobial use changed significantly ($P<0.011$) and remained lower in all post-ASP cohorts compared with pre-ASP [(2008; 1827 DDD/1000 OBD), (2010; 1264 DDD/1000 OBD), (2012; 1270 DDD/1000 OBD) and (2017; 1566 DDD/1000 OBD)]. There was reduction in usage of all antimicrobial classes except β-lactams (where there was no significant increase nor decrease, $P=0.178$) and aminoglycosides (where there was a significant increase in usage, $P<0.0001$). The latter was temporally associated with restrictions on specific carbapenems. There was an increase in carbapenem-resistant *P. aeruginosa* in 2012 only ($P=0.028$) but not subsequently.

Conclusions: Following ASP implementation after an outbreak of MRAb, reduced antimicrobial prescribing was maintained 9 years on. We identify several factors influencing successful long-term maintenance of ASPs in ICUs.

Introduction

The 2020 WHO Global Antimicrobial Resistance Surveillance System (GLASS) report highlights increasing prevalence of resistant organisms, in particular those resistant to carbapenems[1] and ESBL-producing Enterobacterales.[2] ICUs have the highest antimicrobial concentration of use in secondary care due to the high incidence of infection, multiple and frequent medical interventions, and high-acuity patients.[3] The Extended Prevalence of Infection in Intensive Care study indicated that 51% of patients in ICUs in 76 countries were considered infected and 71% received antimicrobials. Mortality among infected patients was more than twice that of non-infected patients.[4]

Antimicrobial stewardship programmes (ASPs) minimize selection pressure by optimizing therapy.[5] In addition to reducing selection pressure, optimizing therapy reduces side effects and incidence of certain pathogenic organisms such as *Clostridioides difficile*.[6] In October 2009 at a London university

teaching hospital, there was an outbreak of MDR *Acinetobacter baumannii* (MRAb) on the ICU with concerns over increased mortality.[7] A 6 month period of significant disruption to elective and emergency services followed, at substantial cost.

During this phase of the disturbance, a multi-modal ASP was introduced on the ICU, including leadership and accountability, guidelines and access to antimicrobial expertise, prospective audit and feedback, and education & training. In a retrospective cohort study on patients in the ICU at three cohort periods; before, 1 and 3 years after ASP implementation, there was a sustained drop in antimicrobial usage.[8] In the context of an observed increased severity of illness of patients, decreased antimicrobial burden was favourable. Carbapenem usage, however, had increased, while there was an increasing trend in overall DDD 3 years after ASP introduction.[8]

To evaluate the longer-term success of the ASP, using the key metrics of antimicrobial consumption and antimicrobial resistance, we evaluated data over a 9 year period (pre-outbreak to 8 years after the ASP implementation). Using an observational cohort design we measured changes across four cohort periods; 2008 (pre-ASP) and 2010–11, 2012 and 2017.

Methods

Study setting and design

A retrospective observational study of four cohort periods of 6 months duration, from which sequential patients were selected: January to June 2008 (pre-ASP) and October 2010 to March 2011, March to September 2012 and January to June 2017. The first cohort period was before the MRAb outbreak and the latter three were after. Data collected during ASP implementation were reviewed with an addition of a fourth cohort (2017) since our previous publication.[8] Fewer data were collected in the previous three cohorts as these were collected before patient records were electronically retrievable.

Chelsea and Westminster NHS Foundation Trust is a London university teaching hospital with a mixed medical-surgical ICU and separate burns centre (this study has excluded burns patients). In addition to the aforementioned ASP components, there was no formal protocol-based stop trigger to de-escalate antimicrobial therapy nor computerized decision support tools. The study was reviewed by the local ethics committee and considered a service evaluation of clinical practice. Patient consent to participate was waived as a result.

Definitions

Patients were stratified by type of admission. Medical emergency (ME) patients were admitted to ICU from the Emergency Department, Acute Medical Assessment Unit or from the medical wards. Surgical Emergency (SE) patients had undergone non-planned surgery within 24 h of admission. Surgical Elective (SEL) patients had undergone planned surgery. APACHE II measured severity of illness of patients when admitted to the ICU; the worst score within 24 h of admission for all patients was recorded. Antimicrobial DDD, as defined by the WHO, was determined.[9] The number of DDD was calculated as follows for each course of antimicrobial therapy. Total dose for each antimicrobial drug over each cohort period was divided by the DDD for that drug, which was listed in the WHO DDD index.[10] The DDD/1000 occupied bed days (OBD) were calculated to compare inpatient antimicrobial drug use across cohorts.[9]

Demographic and admission data

Demographic data were collated using AcuBase Critical IV (v9.6.51, AcuBase Ltd, UK). Age, date of admission, gender, presence of sepsis (2016 criteria) on admission, date of ICU discharge, category of admission, APACHE II score and ICU length of stay were collected. Patients who were admitted more than once during the cohort period or appeared in more than one cohort period were identified as duplicates and only data for the first admission were included for analysis. Patients with a length of stay in ICU of less than 2 days were excluded.

Microbiology data

Antimicrobial resistance rates for specific organisms have previously been used as an indicator of effectiveness of antimicrobial stewardship.[11] One commonly cultured organism in respiratory samples is *Pseudomonas aeruginosa*. Implementation of ASPs has been linked to decreased antimicrobial prescribing and subsequent increased susceptibility of this indicator organism.[10] Microbiology data, including sample descriptors and culture and susceptibility results, were collected from the Sunquest® (v7.3, Sunquest Information Systems Inc., Tuscon, AZ, USA) laboratory information management system used for the hub-and-spoke pathology provider serving the hospital (North West London Pathology).

Antimicrobial data

Antimicrobial data were collected from ICU pharmacy records. These were stored in an Excel spreadsheet (Microsoft Office 2017, Microsoft, Seattle, WA, USA). All antimicrobial data were cross-referenced against the patient's scanned drug charts to confirm accuracy. These were viewed using the software Kainos Evolve (Kainos Group plc., 2013, Belfast, UK). If scanned drug charts were irretrievable, data were excluded.

For each antimicrobial course, drug name, start date, end date, duration and dose were collected. Patient notes contained start and stop dates of antimicrobial courses and were used to cross-check antimicrobial data. Antimicrobials were grouped into classes: β-lactams, carbapenems, glycopeptides, aminoglycosides, quinolones, macrolides, other antibacterials and other anti-infectives.

Statistical methods

Quantitative data were compared across independent group cohorts using a one-way ANOVA test for parametric data while a Kruskal–Wallis test was used for non-parametric data. Categorical data were compared using Fisher's exact test or a chi-squared test. Univariate logistic regression models were used to identify factors associated with mortality. All variables found to be significant in univariate logistic regression models ($P < 0.2$) were used to derive a multivariable logistic regression model that identified significant independent predictors of mortality. These were fitted for each class of antimicrobial drug. All P values presented are two-tailed. A certified medical statistician (S.M.) undertook all analysis, in conjunction with R.A., S.S. and L.S.P.M.

Results

Five hundred and sixty-six ICU patients were identified during the cohort periods selected. Of these, 112 patients with a length of stay in ICU of less than 2 days were excluded. A further 38 patients with missing or incomplete data were excluded, as were 16 patients who had repeat admissions. Four hundred patients were included for final analysis; demographic characteristics are shown in Table 1.

Mortality

Mortality was highest in the 2010–11 post-ASP cohort at 18.5%, decreasing thereafter and lowest in the 2017 cohort at 9.4%. However, this change in survival was not statistically significant

Table 1. Patient demographics during long-term (9 year) follow-up of an ICU ASP, London, UK

	Pre-ASP	Post-ASP			
	2008 ($n=75$)	2010–11 ($n=49$)	2012 ($n=31$)	2017 ($n=245$)	*P* value
Age[a], median (IQR), *n*	58 (40.5–70.5) 75	63 (44–75) 49	55 (45.5–68) 31	62 (46–74) 245	0.197
ME	54 (42–66.5) 31	56 (40–73) 24	54.5 (41.5–68) 20	60 (44–75) 100	0.594
SE	60.5 (40.5–70.5) 24	63 (50–79) 13	54 (46–73.5) 8	68 (49–81.5) 67	0.136
SEL	62.5 (37–72) 20	63.5 (53–75) 12	64 (59.5–71.5) 3	61.5 (49–67) 78	0.687
Female[b], *n* (%)	36 (48)	21 (42.9)	20 (64.5)	127 (51.8)	0.276
Male, *n* (%)	39 (52)	28 (57.1)	11 (35.5)	118 (48.2)	
Median length of stay[a] (IQR)	3 (2–6)	3 (2–4)	4 (2–5)	4 (2–6)	0.428
ME	4 (3–9.5)	4 (4–6.5)	3 (2–6)	5 (3–8.5)	0.292
SE	4.5 (2–12.5)	2 (2–3)	3 (2–4)	4 (2–6)	0.032*
SEL	2(2–2)	2 (2–2)	5 (3.5–5.5)	2 (2–3)	0.016*
Median APACHE II score[a] (IQR)	14 (10–17.25)	17 (11.25–20.75)	14 (10.75–22.25)	11 (8–16)	0.005*
ME	15 (11.5–21)	15 (12–23)	19 (12.0–24.5)	16 (11–21)	0.628
SE	16 (13–25)	13 (8–16)	14 (12.5–17.5)	12 (8–15)	0.040*
SEL	9.5 (5–14)	8 (6–11)	10 (8–12)	8 (6–11)	0.697
Mortality[b], *n* (%)	6 (10.9)	5 (18.5)	3 (13.0)	21 (9.4)	0.536
Sepsis[b], *n* (%)	9 (12)	2 (4.1)	5 (16.1)	40 (16.3)	0.195

Patient characteristics at four cohort periods, 2008–17. Patients were categorized by type of admission: ME, SE and SEL.
*Indicates a *P* value of less than 0.05, which was deemed significant.
[a]Indicates variable analysed by Kruskal–Wallis test.
[b]Indicates categorical variable, where a chi-squared test was used.

in the four cohorts ($P=0.536$).For each 1 year increase in age, risk of survival significantly reduced; OR 0.97 (95% CI: 0.95–0.99) ($P=0.011$). A lower APACHE II score was also a significant predictor of survival; OR 0.76 (95% CI: 0.72–0.84) ($P<0.0001$). Longer length of stay was significantly associated with likelihood of lower survival; OR 0.90 (95% CI: 0.87–0.94). No significant association was observed in likelihood of survival by gender ($P=0.086$).

Adjusted logistic regression models showed there was no significant association between class of admission and survival and no significant association was observed between antimicrobial days and likelihood of survival, with OR 1.02 (95% CI: 0.97–1.07), nor of the number of antimicrobial courses, with OR 0.93 (95% CI: 0.74–1.16).

Antimicrobial prescribing

Total DDD/1000 OBD changed significantly between the pre-ASP (1827 DDD/1000 OBD) and all post-ASP cohort time periods ($P<0.0001$)[(2010; 1267 DDD/1000 OBD—30.8% reduction compared with pre-ASP), (2012; 1270 DDD/1000 OBD—30.5% reduction compared with pre-ASP), (2017; 1566 DDD/1000 OBD—14.3% reduction compared with pre-ASP)] (Table 2). A higher APACHE II score predicted a greater number of antimicrobial days ($P<0.0001$)—1.18 more antimicrobial days were predicted for each point increase in APACHE II score (CI 0.92–1.45). Length of stay was associated with more antimicrobial days ($P<0.0001$); each 1 day increase in length of stay lead to 0.9 more antimicrobial days (CI 0.78–1.02).

There was a decrease in adjusted total antimicrobial days in 2017 to 13.8% of pre-ASP levels (CI 7.8%–58%, $P=0.011$). However, there was no significant difference in adjusted total antimicrobial days between the post-ASP cohorts 2017, 2012 or 2010–11.

Median antimicrobial days did not change significantly in patients admitted as ME or SEL. However, median antimicrobial days changed significantly in SE patients ($P<0.001$), decreasing from 12 to 4 days after ASP implementation with a subsequent peak at 7 days in 2012. This significant post-ASP reduction was maintained in subsequent cohort time periods up to and including 2017 where it was 4 days.

Antimicrobial variation by class

For β-lactams, the most commonly used class of antibiotic, DDD/1000 OBD did not change ($P=0.178$) across cohorts (Table 2).

Carbapenem usage in DDD/1000 OBD changed across cohorts ($P<0.0001$), decreasing from 164 DDD/1000 OBD pre-ASP to 67 DDD/1000 OBD in 2010, but then subsequently oscillated, with a peak in 2012 of 224 DDD/1000 OBD, which decreased to 160 DDD/1000 OBD in 2017.

Quinolone DDD/1000 OBD was lower in all post-ASP cohorts ($P<0.0001$), decreasing from 122 DDD/1000 OBD pre-ASP to 0 DDD/1000 OBD in 2010, 22 DDD/1000 OBD in 2012 and 65 DDD/1000 OBD in 2017.

For aminoglycosides, DDD/1000 OBD changed across cohorts ($P<0.0001$) when compared with pre-ASP levels (2008; 54.8 DDD/1000 OBD). There was a decrease post-ASP in 2010–11 (14.93 DDD/1000 OBD—72.9% reduction compared with pre-ASP). However, a numerical rise to levels higher than 2008 pre-ASP in 2012 (94.82 DDD/1000 OBD—73% increase compared with pre-ASP) and 2017 (93.17 DDD/1000 OBD—70% increase compared with pre-ASP) was apparent. In particular, there was

Table 2. Antimicrobial consumption during long-term (9 year) follow-up of an ICU ASP, London, UK

	Pre-ASP	Post-ASP			
	2008 ($n=75$)	2010–11 ($n=49$)	2012 ($n=31$)	2017 ($n=245$)	*P* value
Total DDD/1000 OBD	1827.05	1263.61	1270.14	1565.99	<0.0001
Aminoglycoside DDD/1000 OBD	54.8	14.93	94.82	93.17	<0.0001
Amikacin	0	9.95	33.52	41.15	
Gentamicin	47.95	4.98	61.3	47.36	
β-Lactam DDD/1000 OBD	547.94	491.81	409.71	472.05	0.178
Amoxicillin	3.42	11.17	0	6.99	
Benzylpenicillin	37.67	50.28	7.46	0	
Ceftazidime	0	0	0	48.91	
Ceftriaxone	18.84	104.48	39.11	18.63	
Cefuroxime	178.08	44.78	67.04	17.86	
Co-amoxiclav	80.48	126.87	67.04	246.12	
Flucloxacillin	37.67	9.95	22.35	12.42	
Tazobactam/piperacillin	188.36	144.28	201.12	107.92	
Temocillin	0	0	0	11.65	
Carbapenem DDD/1000 OBD	164.38	67.16	224.2	159.94	<0.0001
Imipenem	102.74	0	0	0	
Meropenem	61.64	67.16	224.2	159.94	
Glycopeptide DDD/1000 OBD	126.71	52.2	30.42	37.27	<0.0001
Teicoplanin	39.38	29.85	27.93	19.41	
Vancomycin	87.33	22.35	2.49	17.86	
Macrolide DDD/1000 OBD	128.42	64.68	61.45	72.99	<0.0001
Azithromycin	1.71	0	0	20.19	
Clarithromycin	126.71	64.68	50.28	50.47	
Quinolone DDD/1000 OBD	121.58	0	22.35	65.22	<0.0001
Ciprofloxacin	113.01	0	22.35	48.14	
Levofloxacin	0	0	0	6.99	
Moxifloxacin	8.56	0	0	10.09	
Other antibacterial DDD/1000 OBD	328.77	402.05	223.48	358.68	0.021
Chloramphenicol	13.7	0	39.11	21.74	
Clindamycin	30.82	173.18	12.44	10.09	
Colistin	18.84	94.53	0	19.41	
Co-trimoxazole	0	14.93	38.5	91.61	
Doxycycline	0	4.98	0	16.3	
Linezolid	23.97	0	21.7	58.23	
Metronidazole	195.21	114.43	94.97	79.19	
Tigecycline	0	0	0	20.96	
Antiviral DDD/1000 OBD	56.51	92.61	55.87	62.11	0.166
Aciclovir	56.51	34.83	33.52	46.58	
Oseltamivir	0	17.41	22.35	15.53	
Zanamivir	0	12.44	0	0	
Ganciclovir	0	27.93	0	0	
Antifungal DDD/1000 OBD	297.94	44.77	147.84	210.4	<0.0001
Liposomal amphotericin	5.14	0	72.63	36.49	
Anidulafungin	0	0	0	1.55	
Caspofungin	54.79	7.46	5.59	70.65	
Fluconazole	82.19	37.31	33.52	61.34	
Nystatin	155.82	0	36.1	32.61	
Posaconazole	0	0	0	6.21	
Voriconazole	0	0	0	1.55	

Antimicrobial usage, stratified by antimicrobial class, in DDD/1000 OBD) was compared between a pre-ASP cohort in 2008 and three post-ASP cohorts in 2010–11, 2012 and 2017. Chi-squared test was used to compare DDD/1000 OBD across the four cohorts. A *P* value less than 0.05 was deemed significant.

Table 3. Resistance patterns in *P. aeruginosa* samples during long-term (9 year) follow-up of an ICU ASP, London, UK

		Pre-ASP	Post-ASP				
Antimicrobial drug	Susceptibility	2008 ($n=75$)	2010–11 ($n=49$)	2012 ($n=31$)	2017 ($n=245$)	Total	*P* value
Aztreonam	Resistant	0	1	7	0	8	0.1515
	Susceptible	0	2	1	0	3	
Ceftazidime	Resistant	0	0	3	0	3	0.4185
	Susceptible	3	9	11	1	23	
Ciprofloxacin	Resistant	2	0	2	0	4	0.06575
	Susceptible	1	9	11	1	21	
Gentamicin	Resistant	0	0	1	1	1	0.08
	Susceptible	2	9	13	0	24	
Imipenem*	Resistant	0	0	5	0	5	0.02769
	Susceptible	2	8	4	0	14	
Meropenem	Resistant	0	0	4	0	4	0.1625
	Susceptible	2	9	8	0	19	
Tazocin	Resistant	0	0	2	0	2	0.6667
	Susceptible	3	9	12	2	24	
Tobramycin	Resistant	0	0	2	0	2	1
	Susceptible	0	4	10	0	14	

Antimicrobial resistance in *P. aeruginosa,* (as an indicator organism) was compared across cohort periods using Fisher's exact test.
*Indicates a *P* value less than 0.05, which was deemed significant.

a shift from gentamicin towards amikacin, reflecting changes in aminoglycoside resistance across the wider geographical area.

For glycopeptides, usage decreased post-ASP implementation and remained lower than 2008 pre-ASP levels (127 DDD/1000 OBD) in the 2010–11 (52 DDD/1000 OBD), 2012 (30 DDD/1000 OBD) and 2017 (37 DDD/1000 OBD) post-ASP cohorts ($P<0.0001$). This perhaps reflected greater emphasis on central line care and minimization of MRSA colonization through routine use of bundled line care for the former and chlorhexidine use for the latter.

Macrolide usage changed across cohorts ($P<0.0001$) when compared with pre-ASP (128.42 DDD/1000 OBD). Levels of macrolide usage decreased after ASP implementation in 2010–11 to 64.68 DDD/1000 OBD and remained lower than pre-ASP levels in 2012 (61.45 DDD/1000 OBD) and 2017 (72.99 DDD/1000 OBD).

Use of other antibacterials changed across cohorts ($P=0.021$), increasing after ASP implementation in 2010–11, reflecting purposeful attempts at antimicrobial mixing.

Prescribing of other antimicrobials in DDD/1000 OBD changed across cohorts ($P<0.001$). There was a trough in 2010–11 after ASP implementation followed by a steady increase; however, not to pre-ASP levels.

Microbiological resistance data

P. aeruginosa samples showed no significant difference in resistance patterns across cohorts to aztreonam ($P=0.152$), ciprofloxacin ($P=0.066$), gentamicin ($P=0.08$), meropenem ($P=0.163$), piperacillin/tazobactam ($P=0.667$) or tobramycin ($P=0.999$) (Table 3).

There was a significant increase in imipenem-resistant organisms in 2012 ($P=0.028$) compared with the pre- and other post-ASP groups.

Discussion

In this 9 year observational study of antimicrobial use at sequential time periods on a medicosurgical university hospital ICU, following implementation of an ASP due to a prior outbreak of MRAb, the key finding was a sustained significant reduction in total antimicrobial usage with no detrimental impact on either length of stay or mortality. Since usage defined by DDD/1000 OBD was significantly lower in all post-ASP cohorts, presence of the ASP would seem associated with, if not definite proof of, the maintenance of reduced antimicrobial consumption over 9 years. Furthermore, this has been observed across separate cohort time periods, in different seasons. This could have been because of increased scrutiny of drugs so fewer were prescribed unnecessarily. It could also have been caused by signposting the opportunities for de-escalation, or cessation of therapy because of daily microbiologist input at ward rounds and multidisciplinary team meetings. Qualitative details of which aspects of the ASP contributed to its success have not been elucidated. However, we speculate the educational component of the ASP, and the presence of consultant microbiologists on ward rounds may have influenced intensivist behaviour change by increased joint discussion regarding prescribing decisions. ASPs have been observed to positively influence prescribing behaviour by providing personalized feedback and updates to clinicians.[12] This study does not prove that the change in antimicrobial prescribing is due to the ASP. However, it is consistent with other studies that the presence of an ASP causes a reduction in prescribing.[13,14]

We do however note that following a fall in early post-ASP total antimicrobial usage in 2010–11 and 2012, there was a numerical rise by 2017 (although not to pre-ASP levels). The reduction in the first two time periods could justifiably be attributed to the ASP effect given the relative temporal proximity to the intervention.

ASP fatigue by 2017 is an important point that cannot be ruled out. It is also possible that there was a difference in the case mix in 2017 with increased infections compared with the previous cohorts.

We find reduced prescribing without a significant change in patient survival to discharge. That said, mortality rates are historically low on this unit. There was a peak in mortality in 2010–11 and a trough in 2017; this could have been linked to severity of illness on admission, which followed a similar trend and may have been caused by normal variation in patients admitted to ICU across cohort periods.

In general, antimicrobial prescribing in DDD/1000 OBD was lower across classes of antimicrobials in 2017 than in 2008 pre-ASP. However, there was an increase in aminoglycoside prescription and in prescription of other antibacterials. This could have been due to an incentive from NHS England Commissioning for Quality and Innovation (CQUIN) in 2016 and 2017. This may have been a confounding factor in the persistently lower antimicrobial prescribing. However, implementation of this strategy may not have been effective without the provenance and role of consultant microbiologists and specialist pharmacists responsible for its implementation; as such it can be considered part of the ASP.[15] To avoid prescribing these broad-spectrum antimicrobials, single doses of aminoglycoside were prescribed in their place. We did not see a rise in gentamicin-resistant *P. aeruginosa* during the time period studied. However, we note the potential for increases in aminoglycoside resistance and indeed toxicity risk associated with extensive, sustained aminoglycoside use. This effect has been observed in other hospitals with restriction focused on one type of antimicrobial, leading to a compensatory increase in prescribing of others with associated development of resistance.[16]

Whilst the prevalence of many drug-resistant bacteria are prone to fluctuation with outbreaks and wider geographical area issues (including MRSA, ESBL-producing Enterobacterales, carbapenem-resistant Enterobacterales), in ICU, real-time generation of drug-resistant *P. aeruginosa* is often reflective of local unit antimicrobial pressures. Our data provide supporting evidence that the suppressed antimicrobial consumption associated with our prolonged ASP was also associated with no rise in drug-resistant strains of *P. aeruginosa*.

Limitations

This retrospective observational study, where the baseline cohort was in a different decade to the subsequent cohorts, is subject to the possibility that changes in practice over time, not related to the introduction of the ASP, influenced the success in sustaining reduced antibiotic usage. That said, we could not ethically conduct a randomized controlled trial of ASP versus standard care, when the presumed health improvement benefits of consultant microbiologist-directed ASP were necessary following the highly disruptive outbreak of MRAb.[8] Cluster randomized controlled trials could feasibly assess the value of an ASP by introducing it sequentially across multiple ICUs and differing cohort periods, so long as the case mix and practices across hospitals are similar.[17] The study may have been subject to selection bias as admissions shorter than 2 days were excluded, because APACHE II score was not calculated for these patients. However, those patients tended to be less sick, without ICU requirements and short antibiotic courses. So inclusion may have contaminated the ICU case mix and arguably lowered the DDD/1000 days inappropriately. Another possibility of bias is the smaller numbers in the time periods before 2017, although consistent within those cohorts.

Collecting data retrospectively, often from paper notes, is subject to missing data. An automated system to collect antimicrobial data came in after the 2012 cohort only. However, all previous cohorts were carefully checked for accuracy and corrected or discarded as necessary. Fortunately, this was rare. The time periods studied were only representative of <6 month periods of each selected year. In 2017, the time range was chosen to overlap with the first cohort period, which was before the ASP implementation. Thus, the first and fourth cohort periods were aligned, whilst the second and third cohort periods were at different timepoints of the year. Infection rates differ throughout the year so could have influenced antimicrobial prescribing. Indeed, seasonality has been shown to affect infection rates and could affect antimicrobial prescribing.[18] Nevertheless, the reduction in antimicrobial prescribing across three separate time periods compared with the pre-ASP cohort period despite seasonality is reassuring.

DDD was used because it did not vary depending on the type of patient, so was an accurate measure of prescribing practices. However, it does not necessarily represent the true doses given. Some studies like this one measure WHO DDD/1000 patient days. Others use days of therapy per 1000 patient days. This metric would have not relied on as many assumptions about the dose given each day.[19] However, we wished to maintain consistency of methodology with our previous study.[8]

We did not display the infections or infective sources linked to antimicrobial usage. That said, sepsis and mortality, key patient-related outcomes were. The cohorts sampled at four different time periods were not the complete microbiological data from all patients, and so comparisons in this regard would have been subject to variability without any likely meaningful differences or indeed inferences being possible. Further, the antibiotic prescribing practice was overseen consistently by the microbiology department, conforming to local and national guidance. As such, antibiotic prescribing related to the type of infection did not change notably, given that the case mix remained similar throughout the time periods.

Finally, there were a limited number of microbiology samples in these patients with susceptibility testing of the same organism, meaning this data may have been underpowered to detect some changes in resistance patterns.

Conclusions

This four-cohort time-period observational study demonstrated the maintenance of reduced antimicrobial usage 9 years after implementation of an ASP, following a disruptive outbreak of MRAb on a university medicosurgical ICU. Although a causative association was not the aim of this study, this success is considered in major part to be the result of a joint microbiologist–intensivist–pharmacy driven initiative. Individual variations in usage of different antibiotic classes between the cohort periods was apparent, with no change in β-lactam usage, but an increase in

aminoglycoside usage. Encouragingly, resistance patterns in *P.aeruginosa* did not increase. Further work should determine the aspects of the ASP that enabled its success.

Acknowledgements

We wish to thank patients and staff of the ICU, Chelsea and Westminster Hospital, who have contributed to the data involved in this study. L.S.P.M. acknowledges support from the National Institute of Health Research (NIHR) Imperial Biomedical Research Centre (BRC) and the National Institute for Health Research Health Protection Research Unit (HPRU) in Healthcare Associated Infection and Antimicrobial Resistance at Imperial College London in partnership with Public Health England (UK Health Security Agency). S.S. acknowledges previous support from the Westminster Medical School Charity Trust, The National Institute of Academic Anaesthesia, and Educational grants from Ambu A/S, Olympus UK and Fisher & Paykel.

Funding

This study was carried out as part of our routine work.

Transparency declarations

L.S.P.M. has consulted for/received speaker fees from bioMérieux (2013–21), Pfizer (2018–21), Eumedica (2016–21), Umovis Lab (2020–21), Shionogi (2021), Pulmocide (2021), DNA Electronics (2015–18), Sumitovant (2021) and Dairy Crest (2017–18), and received research grants from the National Institute for Health Research (2013–19), LifeArc (2020–21), and CW+ Charity (2018–21). S.S. has received speaker fees from Ambu A/S and Fisher & Paykel. All other authors have no conflicts of interest to declare.

Author contributions

R.A., S.S., L.S.P.M. and N.M. designed the study methodology. R.A. and J.T. collected the data. R.A., S.M. and S.S. analysed the data. R.A. and S.S. (Suveer Singh) drafted the initial manuscript with all authors contributing significantly to revising this for submission. All authors reviewed the results and data analysis and contributed comments. All authors agreed on the final version for submission to the journal.

Availability of data and materials

The data analysed during the current study and further details on the assays are available from the corresponding author (S.S.; suveer.singh@imperial.ac.uk) on reasonable request, as long as this meets local ethical and research governance criteria.

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