9 The Allergen Survey: perioperative drug exposure


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Key findings

- Details of current UK drugs and allergen exposure were needed for interpretation of reports of perioperative anaphylaxis to the 6th National Audit Project (NAP6).
- We surveyed United Kingdom NHS hospitals for this purpose. Where relevant we compared results to NAP5.
- From 342 (96%) hospitals we collected 15,942 forms: equating to an annual caseload for anaesthetists of 3,126,067, including 2,394,874 general anaesthetics (GA).
- Propofol was the dominant induction agent (90.4%) and was used more often in caesarean section than in NAP5.
- Nitrous oxide use (17% of cases) has fallen by 30% since NAP5.
- Neuromuscular blocking agents were used in 47.2% of general anaesthetics. Suxamethonium use has fallen.
- Use of reversal agents is overall unchanged, but sugammadex use increased four-fold.
- Analgesics were used in 88% of cases – opioids in 82.1%, paracetamol in 56.1%, and non-steroidal anti-inflammatory drugs in 28.3%. Local anaesthetics were used in 74.2% of all cases and 68.9% of GAs.
- Anti-emetics were used in 73.1% of cases: during GA ondansetron in 78.3% and dexamethasone in 60.4%.
- Overall antibiotic use was 57.2% of cases. Among more than 3 million annual perioperative administrations gentamicin (19.7% of cases), co-amoxiclav (17.0%) and cefuroxime (13.6%) were prominent.
- In 25% of teicoplanin or vancomycin uses, allergy history influenced drug choice.
- Chlorhexidine and iodine exposure were reported in 73.5% and 40.0% of cases respectively, and a latex-free environment in 21.2%.
- Blood products were used in ≈3% of cases, synthetic colloids in less than 2% (starch in only 1 in 600 cases), tranexamic acid in ≈6%.
- Exposure to bone cement, blue dyes and X-ray contrast were each reported in 2–3% of cases.
- This extensive national survey of anaesthetic practice provides detailed data on drug uses and allergen exposures in perioperative care. It is important for use as a denominator in the main NAP6 analysis, and the data provide significant insights into many aspects of perioperative practice.

The Royal College of Anaesthetists National Audit Projects (NAPs) study major complications of anaesthesia, and concurrently review current practice and use the findings to improve patient care. The 6th National Audit Project of the Royal College of Anaesthetists (NAP6), is a large-scale prospective service evaluation of perioperative anaphylaxis across the hospitals of the United Kingdom. It has gathered comprehensive quantitative and qualitative information on these clinical events, enabling the anaesthetic and allergy/immunology communities to collaborate in order to make recommendations for the improvement of the quality of patient care (Chapter 5, Methods; Chapter 6 Main findings; Chapter 14, Investigation).

During the NAP6 project, a one-year registry was established to collect reports on all suspected cases of perioperative anaphylaxis in 2015-16. This provided a numerator, but in order to interpret the results from the registry and to estimate the incidence of perioperative anaphylaxis overall and of its causes (drugs/other substances), contemporary information about anaesthetic activity, drug use, and exposure to other relevant substances (such as antiseptics and dyes), was required. This data would provide a denominator.

In 2013, the NAP5 project undertook a similar activity and drug survey (Sury 2014), providing information on aspects of anaesthetic activity and some drug uses, but these were insufficient for the needs of NAP6. Published Hospital Episode Statistics (NHS digital 2017a) show an increase in inpatient and day-case procedures since 2013, but do not give detailed information on anaesthetists' involvement. NHS Maternity Statistics show a slight decrease in deliveries in NHS hospitals since 2013, of which 60% involved anaesthetic intervention (HSCIC 2013). Such changes over time mean that figures collected for NAP5 may not necessarily be applicable for NAP6. In addition, the NAP5 survey did not collect sufficient detailed information on perioperative administration of drugs and other potential allergens. National data for hospital

drug usage is collected by IQVIA™ and recorded in the Hospital Pharmacy Audit Index database (Prescribing costs 2014). This records all medication that is issued by pharmacies for use on wards, in operating theatres and on patient discharge. It does not, however, record what is administered to the patient nor in what context a certain drug is delivered, and so does not provide information on actual perioperative drug use.

An Activity Survey and Allergen Survey were therefore designed to collect such data, and these are detailed in this report. During the surveys, anaesthetic activity data and drug/allergen exposure data were collected. The Activity Survey is reported separately (Chapter 8), and in this chapter we report results of the Allergen Survey.

Methods

The NAP6 project was defined as a service evaluation by the Health Regulatory Authority, and therefore did not require National Research Ethics Service approval. All NHS hospitals, trusts and boards in the UK believed to undertake surgery were invited to, and did, volunteer a Local Coordinator who supervised all aspects of the study at that location.

Local Coordinators were approached at 356 NHS hospitals, and they organised data collection from every perioperative case during a period of 48 hours in which care was delivered by an anaesthetist. This included all adult and paediatric cases requiring general, regional and local anaesthesia, as well as sedation if involving an anaesthetist. Obstetric cases included epidural pain relief in labour. Any cases where sedation or local anaesthesia was delivered by a non-anaesthetist were not included. Routine sedation in critical care was excluded.

The majority of data collection took place between 13 and 31 October 2016, during which time there were no public holidays. Seven sites collected data between January and June 2017 for logistical reasons. Data were recorded using a paper pro-forma (Appendix 1), and each form was transferred, using optical character recognition, to electronic storage. Each hospital was randomised to record activity on two consecutive days of the week, with specialist hospitals (cardiac, neurology or paediatric centres) block-randomised separately to prevent skewed allocation. Patient characteristics, method of anaesthesia, anaesthetic staffing, induction location, type of monitoring and drugs/substances used, and the presence of any allergy history were reported for each case. Local Coordinators were also asked to record a capture rate at their site to estimate the proportion of cases for which a completed case report form was submitted. Data regarding staffing, workload and anaesthetic activity are reported separately (Chapter 8).

Data were analysed using IBM SPSS Statistics for Windows, Version 23. An annual caseload was estimated by multiplying the number of cases by a scaling factor. This factor was calculated by converting the number of cases from two days to one week (scaling factor of 3.5), and from one week to one year (scaling factor of 50.6, the effective number of working weeks in 2016) (Appendix 2). This was then divided by the hospital response rate, the mean reported capture rate at individual sites and the proportion of interpretable forms, to account for cases that were not reported. Responses marked as 'unknown' and those with incomplete fields were combined and reported as 'unknown'.

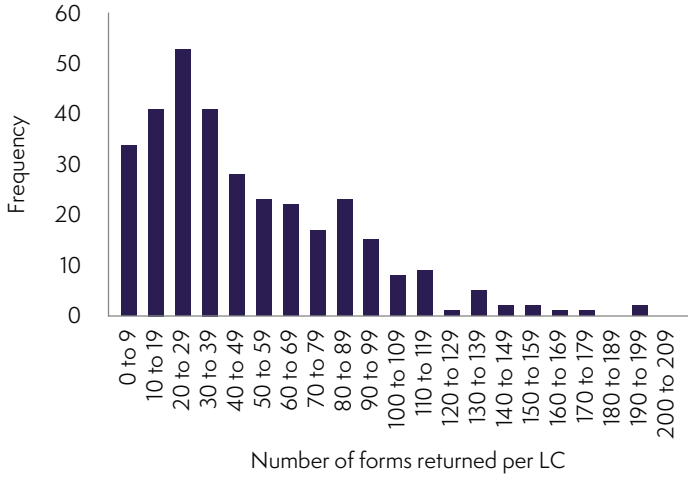
Here we report data relevant to allergen exposure in the perioperative period and relating to anaesthetists' practices in using certain drugs. Where relevant this data is compared to that from the 2013 NAP5 study (Sury 2014).

Results

Out of 356 sites approached, 342 took part in the survey, submitting a total of 15,942 forms. Applying the calculated scaling factor, the estimated annual caseload was 3,126,067. The distribution of numbers of forms returned from each hospital are shown in Figure 1. Where relevant, illogical forms (eg. patients eported to be awake when neuromuscular blocking agents (NMBAs) were used), were excluded but these represented less than 1.0% of any analysis.

The scaling factor was 196.09. Patient Characteristics are described in Chapter 8, Activity Survey.

Figure 1. Distribution of number of forms returned by Local Coordinators



Intended consciousness level was reported as general anaesthesia (GA) 76.6% (annual estimate 2,394,847), sedation 8.2% (258,250 cases) and awake 14.2% (442,379 cases) (Table 1).

Table 1. Intended consciousness level

Intended consciousness level	Number	%
General anaesthesia	12,213	76.6%
Deep sedation	290	1.8%
Moderate sedation	542	3.4%
Minimal sedation	485	3.0%
Awake	2,256	14.2%
Unknown	156	1.0%
Total	15,942	100.0%

Anaesthetic drug use

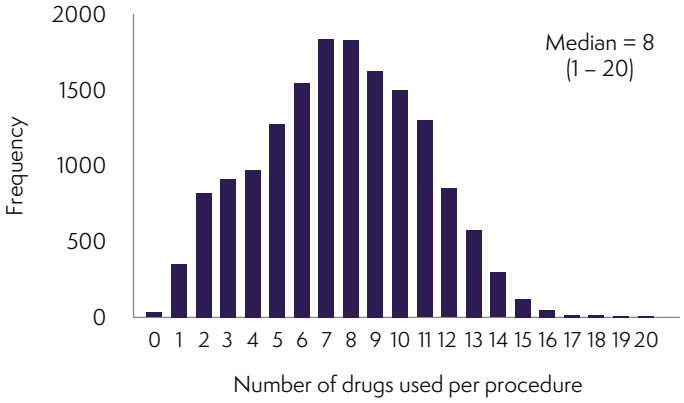
Previous allergy history and choice of drugs

Choice of drugs was reported as having been influenced by previous allergy history in 1,351 cases (8.6% of 15,723 responses). In 64% of these cases this was because of allergy to an antibiotic, in 35% allergy to another drug, and in 3% to both.

Number of drugs used per procedure

The median number of drugs given in each procedure was 8 – minimum 1 and maximum 20 (Figure 2).

Figure 2. Number of drugs used per procedure



Induction agents

Induction agents were used in 13,019 cases including all intended consciousness levels; the estimated annual exposures was 2,552,896 (Table 2).

Table 2a. Use of induction agents and estimated annual exposures for all levels of consciousness

All cases of general anaesthesia and sedation				
Individual drug/ substance	Number exposed in Activity Survey	Estimated annual exposure	% of cases having at least one induction agent	% of total drug group usage (sum of all; total > total no. of cases)
At least one induction agent used	**13,019**	**2,552,896**	**100.0%**	**–**
Propofol	11,682	2,290,723	89.7%	74.7%
Thiopental	215	42,159	1.7%	1.4%
Etomidate	36	7,059	0.3%	0.2%
Midazolam	1,515	297,076	11.6%	9.7%
Ketamine	198	38,826	1.5%	1.3%
Sevoflurane	1,662	325,902	12.8%	10.6%
Other volatile agent	166	32,551	1.3%	1.1%
Other induction agents	156	30,590	1.2%	1.0%

Table 2b. Use of induction agents for general anesthesia

General anaesthesia cases only			
Individual drug/ substance	Number exposed in Activity Survey	Estimated annual exposure	% of cases having at least one induction agent
At least one induction agent used	**12,143**	**2,381,121**	**100.0%**
Propofol	11,145	2,185,423	91.8%
Thiopental	211	41,375	1.7%
Etomidate	36	7,059	0.3%
Midazolam	1,057	207,267	8.7%
Ketamine	154	30,198	1.3%
Sevoflurane	1,656	324,725	13.6%
Other volatile agent	166	32,551	1.4%
Other induction agents	147	28,825	1.2%

For cases performed with general anaesthesia (Table 2b), 15% of returns indicated two induction agents, with a volatile reported as an induction agent in 14.8% of cases and a combined volatile/ IV induction in 9%. Of those with volatile co-induction, 51% were adults. As some respondents had probably included both an intravenous (IV) and a volatile agent as an 'induction agent', to determine the primary induction agent we only analysed a subset of these cases where one agent was used.

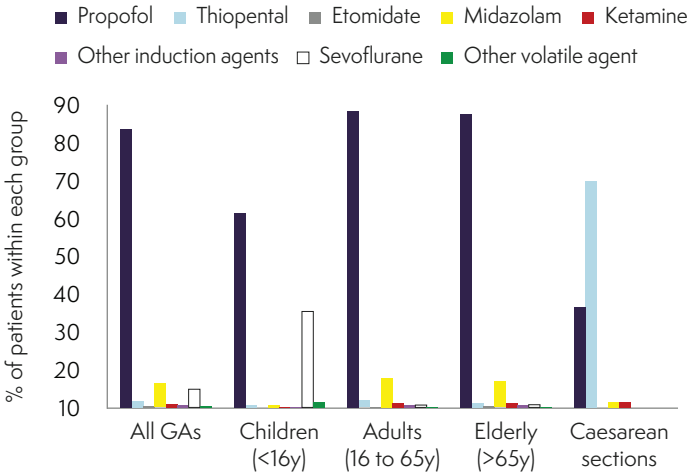
Considering only patients who received general anaesthesia induced with a single agent or a single agent and midazolam (n=10,969), the distribution of drugs used was propofol 90.4%, thiopental 1.6%, ketamine 0.7%, etomidate (0.3%), sevoflurane (6.2%), and other volatile agents (0.1%) (Table 3). Midazolam was used as a sole agent in 0.1% of cases (predominantly urgent/emergency cases in ASA Grades 4–5 patients) and as a co-induction agent in 7.5%. These proportions did not vary significantly whether midazolam was included or not (Table 3). These results suggest that since 2013 there has been a small reduction in use of thiopental (1.6% from 2.9%) and an equivalent increase in the use of propofol (90.4% from 88%) (Sury 2014). Cases involving a volatile agent alone for induction were predominantly children (86%).

Table 3. Use of induction agents when given as single agents (or with midazolam). Case return forms and proportions

GA cases with a single induction agent (or with midazolam)				
Drug	Numbers (only one induction agent)	%	Numbers (only one induction agent and midazolam)	%
Propofol	9,180	90.39%	9,973	90.92%
Thiopental	173	1.70%	179	1.63%
Etomidate	26	0.26%	31	0.28%
Ketamine	79	0.78%	86	0.78%
Midazolam	11	0.11%	11	0.10%
Sevoflurane	677	6.67%	678	6.18%
Other volatile	10	0.10%	11	0.10%
Total	10,156	100.00%	10,969	100.00%

Propofol was the most widely used induction agent in all groups: 57.7% in children (under 16 years), 96.2% in adults and 89.7% in patients aged over 65 years. Distribution of induction agents used by patient's age is shown in Figure 3. Sixty-four patients undergoing caesarean section, received general anaesthesia, and in these cases thiopental was used in 62.7% (97% in NAP5), propofol in 29.7%, and midazolam and ketamine in 1.6% each. Etomidate and sevoflurane were not used (Figure 3).

Figure 3. Use of induction agents by age group and in caesarean sections



Maintenance agents

Among GAs where a maintenance agent was used, an inhalational agent was used in 94.6% – sevoflurane in 69.9% (58.5% in NAP5), nitrous oxide in 17.1% (25% in NAP5) and propofol in 8.7%. In 2.2% of cases, both a volatile agent and propofol were used as maintenance agents (Table 4).

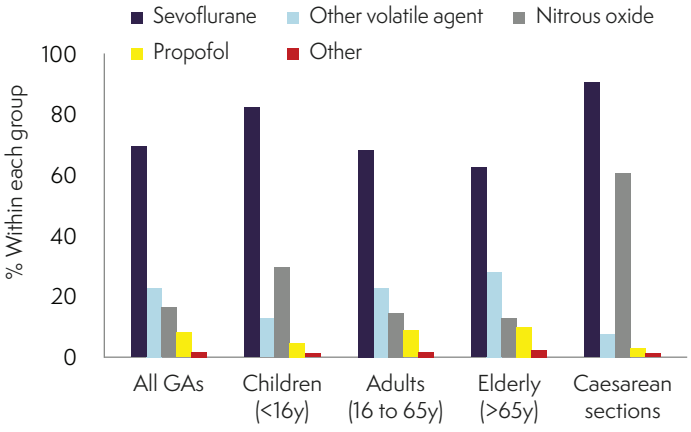
Table 4. Use of maintenance agents during general anaesthesia and estimated annual caseload

Individual drug/ substance	Number exposed in Activity Survey	Estimated annual exposure	% of cases having at least one maintenance agent
At least one maintenance agent used	**11,921**	**2,337,589**	**100.0%**
Sevoflurane	8,499	1,666,569	71.3%
Other volatile agent	2,773	543,758	23.3%
Nitrous oxide	2,041	400,220	17.1%
Propofol	1,032	202,365	8.7%
Other	249	48,826	2.1%

Thus, for a large cohort of children an extremely low-risk technique was used as far as antigen exposure is concerned.

The use of maintenance agents by age and in caesarean sections is illustrated in Figure 4. Sevoflurane was the preferred maintenance agent across all age groups and specialties. Induction and maintenance exclusively with sevoflurane was reported in 2.8% of GAs: 14.5% of paediatric and 0.4% of adult GAs. Sevoflurane was used during general anaesthesia for 90.6% of caesarean sections. Nitrous oxide was reported as being used in 17.1% of cases, in 30.1% of children and 60.9% of caesarean sections: a fall from 2013 (25% overall, 45% in children and 71.4% in caesarean sections). Nitrous oxide was used most frequently during general anaesthesia in orthopaedics/trauma, general surgery and ENT cases, perhaps associated with the increased numbers of paediatric cases in these specialties (Sury 2014).

Figure 4. Maintenance agent use by age group and in caesarean section



Neuromuscular blocking agents (NMBAs)

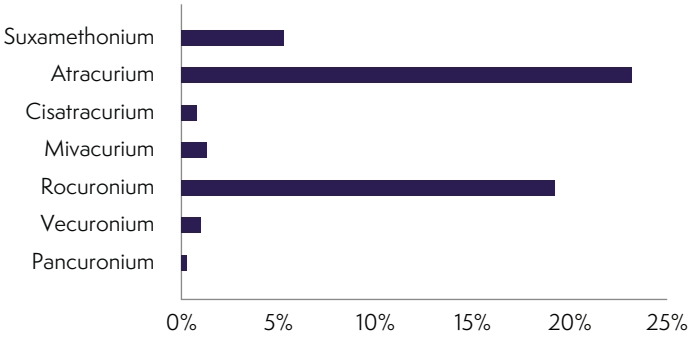
NMBAs were reported to have been used in 5,760 (47.2%) cases receiving GA; the estimated annual caseload was 1,129,478 (Table 5).

Table 5. Use of NMBAs and estimated annual exposures

GA cases					
Individual drug/ substance	Number exposed in Activity Survey	Estimated annual exposure	% of all GAs	% of NMBA use	% of total drug group usage (sum of all; total > total no of cases)
At least 1 NMBA used	**5,760**	**1,129,478**	**47.2%**	**100.0%**	**% of all NMBA use**
Suxamethonium	643	126,086	5.3%	11.2%	10.3%
Atracurium	2,828	554,543	23.2%	49.1%	45.4%
Cisatracurium	95	18,629	0.8%	1.6%	1.5%
Mivacurium	157	30,786	1.3%	2.7%	2.5%
Rocuronium	2,341	459,047	19.2%	40.6%	37.6%
Vecuronium	124	24,315	1.0%	2.2%	2.0%
Pancuronium	36	7,059	0.3%	0.6%	0.6%

Of those receiving NMBAs (12,213), 88.8% received non-depolarising NMBAs only, 4% suxamethonium only and 7.2% both suxamethonium and a non-depolarising NMBA. The distribution of NMBAs was not captured in the NAP5 survey.

Figure 5. Use of all NMBAs during general anaesthesia (whether individually or multiples), as a proportion of all general anaesthetic cases (n=12,213)



Within age groups, NMBAs were used in 23% of children, 49.6% of adults and 58.2% of elderly patients, and in almost all general anaesthetic caesarean sections (98.4%); distribution is shown in Figures 6 and 7. These figures are stable since NAP5.

Figure 6. Use of NMBAs by age group and in caesarean sections

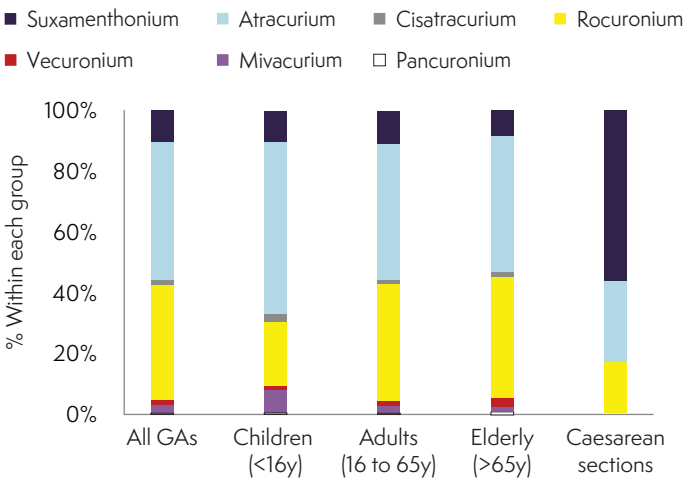
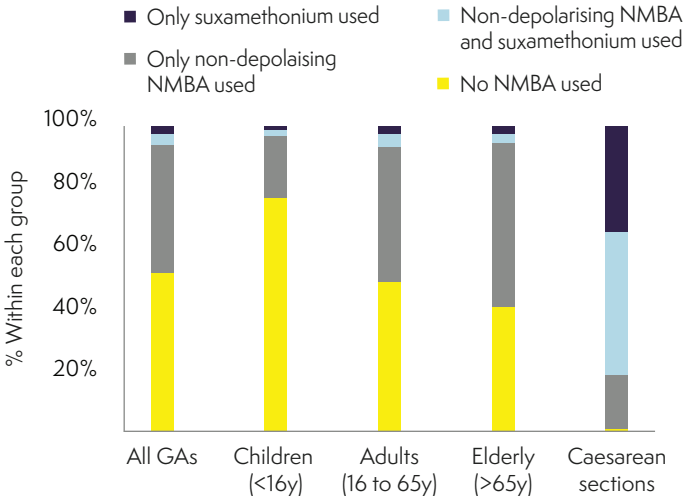


Figure 7. Use of NMBAs (by class) across different age groups and in caesarean sections



In most specialties atracurium and rocuronium were used predominantly, with the main exceptions being cardiac surgery, obstetrics and psychiatry. In cardiac surgery, pancuronium and vecuronium were used in 25.7% and 17.9% of cases respectively. All psychiatry cases received suxamethonium and 1.3% also received atracurium. The distribution of NMBAs in obstetrics was suxamethonium 72.5%, atracurium 35.2% and rocuronium 23.1%; 16.9% received only a non-depolarising NMBA.

Distribution of NMBA use by specialty and by clinical setting is shown in Figures 7-10.

Figure 8. Use of each NMBA by main surgical specialty
(*Note:* more than one NMBA may have been used in some procedures.)

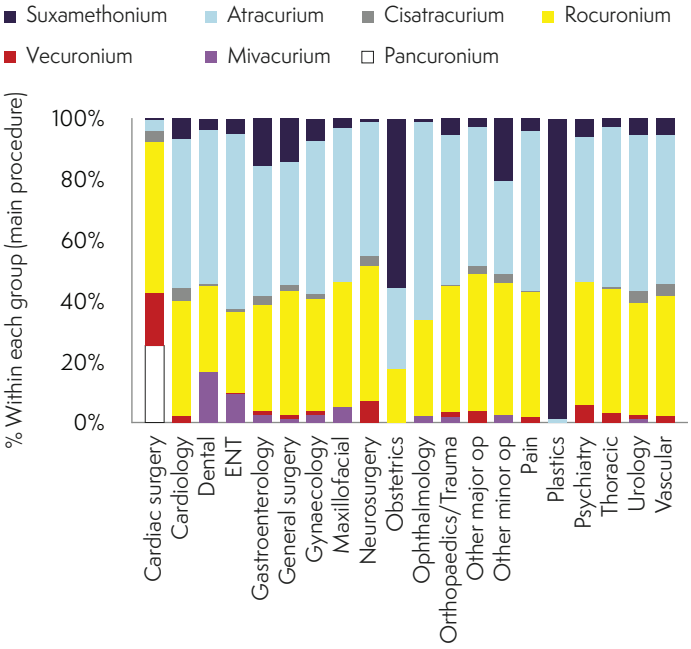
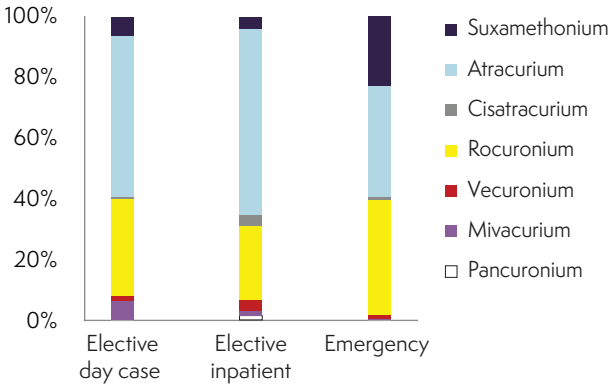
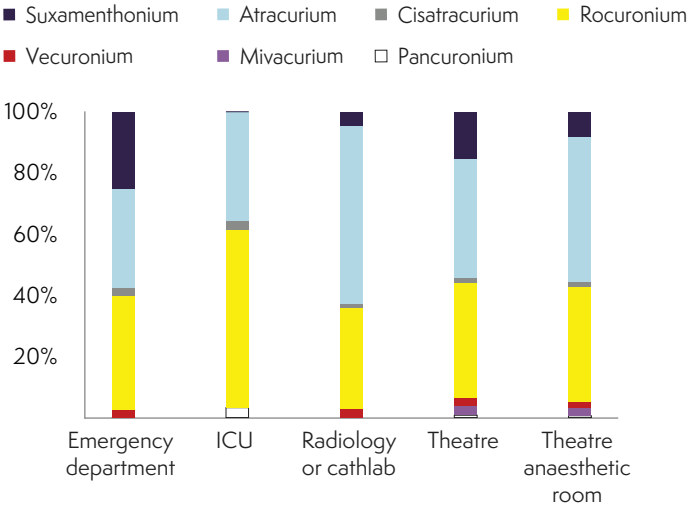


Figure 9. Use of NMBAs by admission type



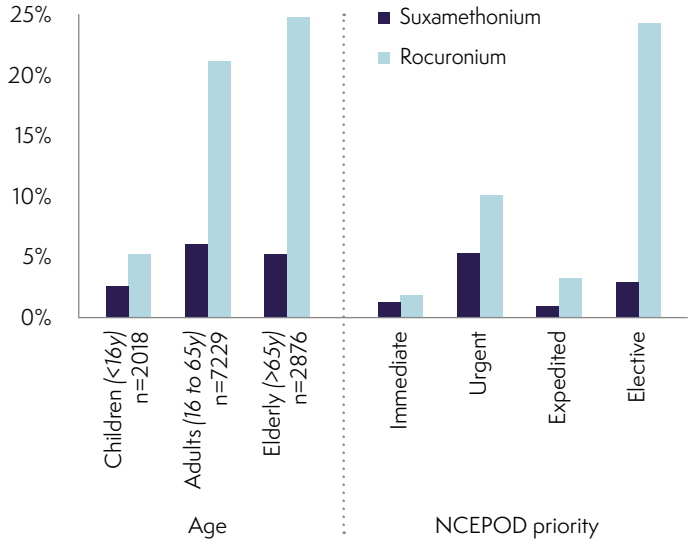
One notable finding is that in ICUs, suxamethonium use was absent and rocuronium was used more often (more than 50%) than in any other location. Conversely, in emergency departments suxamethonium was widely used and rocuronium notably less often (Figure 9).

Figure 10. Use of NMBAs by induction location



When suxamethonium was used, propofol was the induction agent in 73.6% of cases and thiopental in 22.4%, with other agents used rarely. Use of suxamethonium and rocuronium by age and NCEPOD priority is shown in Figure 11.

Figure 11. Use of suxamethonium and rocuronium by age groups (% within each group) and by NCEPOD priority (% within those GA cases receiving an NMBA, n=5,760)



Reversal drugs

The pattern of use of reversal agents is described in Table 6. Sugammadex is now used in almost four times as many cases as in 2013 (2.2% of reversals) (Sury 2014).

Table 6. Use of reversal drugs and estimated annual caseload

GA cases					
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all GAs	% of NMBA use	% of total drug group usage (sum of all; total > total no of cases)
At least one reversal drug used	**3,598**	**705,532**	**29.5%**	**62.5%**	**% of all reversal drug use**
Neostigmine	3,307	648,470	27.1%	57.4%	90.3%
Sugammadex	327	64,121	2.7%	5.7%	8.9%
Other	27	5,294	0.2%	0.5%	0.7%

Analgesics

Analgesics were used in 88.2% of all cases (any intended consciousness level); estimated annual caseload was 2,755,849. Opioids were used in 82.5% of all cases. Paracetamol was administered in 56.1% and a non-steroidal anti-inflammatory drug in 28.3% of cases.

Fentanyl was the most frequently used opioid, administered in 62% of cases, followed by morphine in 26.5% and remifentanil in 8.7% of cases. Diclofenac was the most commonly used NSAID, followed by parecoxib and ibuprofen. Clonidine was administered in 0.9% of cases. Use of each analgesic drug is illustrated in Figure 12 and estimated annual exposures in Table 7.

Figure 12. Use of analgesic agents in all cases
(use of each analgesic drug, whether in isolation or combined, n=15,776)

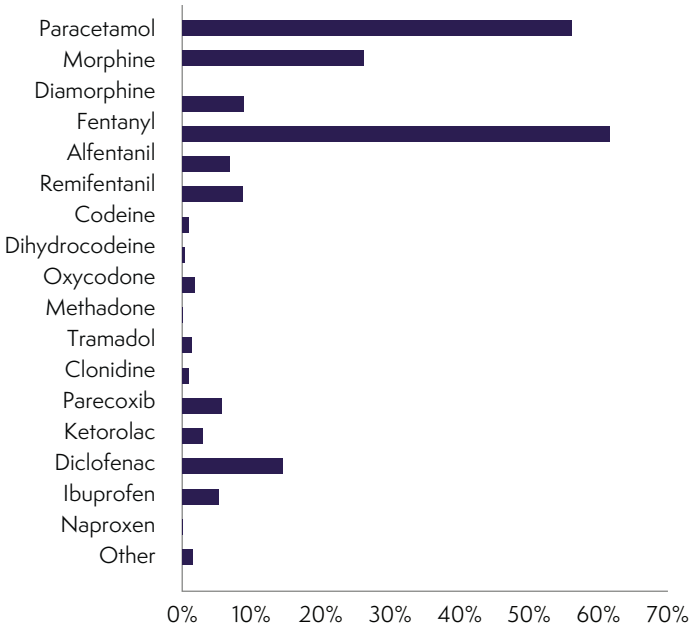


Table 7. Use of analgesic drugs and estimated annual exposures

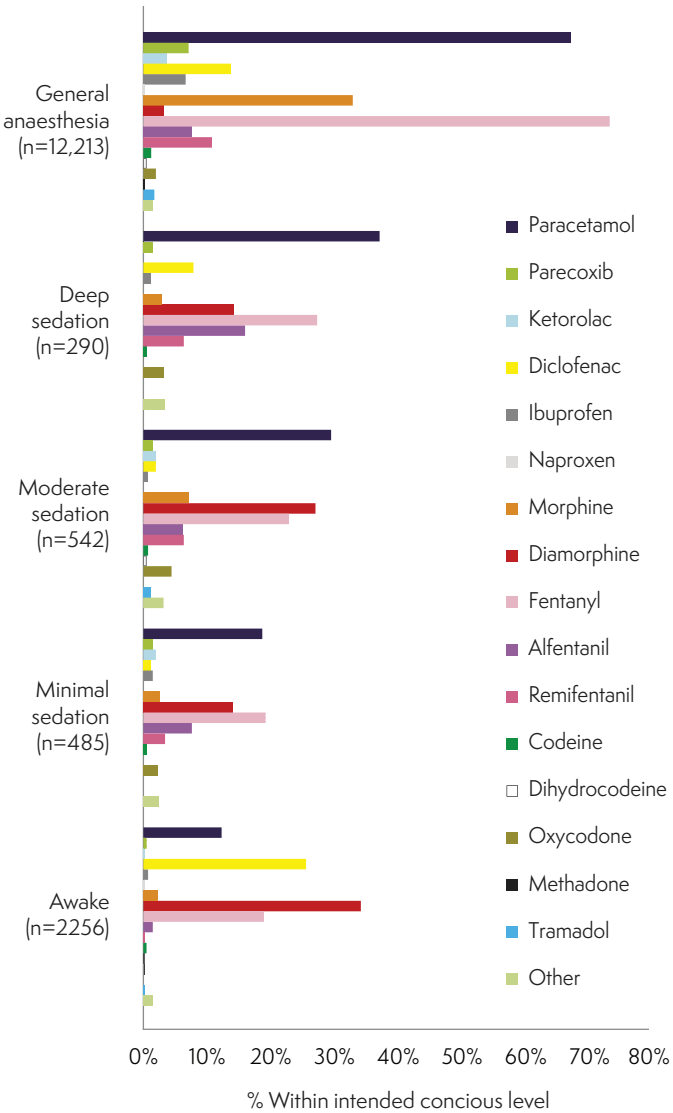
All cases					
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least one analgesic used	**14,054**	**2,755,849**	**88.2%**	**–**	**–**
At least one opioid used	**13,145**	**2,577,603**	**82.5%**	**% of cases receiving opioid**	**% of all opioid use**
Alfentanil	1,095	214,719	6.9%	8.3%	5.9%
Fentanyl	9,822	1,925,996	61.6%	74.7%	52.9%
Remifentanil	1,385	271,585	8.7%	10.5%	7.5%
Diamorphine	1,412	276,879	8.9%	10.7%	7.6%
Morphine	4,162	816,127	26.1%	31.7%	22.4%
Codeine	146	28,629	0.9%	1.1%	0.8%
Dihydrocodeine	40	7,844	0.3%	0.3%	0.2%
Oxycodone	282	55,297	1.8%	2.1%	1.5%
Methadone	7	1,373	0.0%	0.1%	0.0%
Tramadol	215	42,159	1.3%	1.6%	1.2%
Clonidine	149	29,217	0.9%	–	–
Paracetamol	8,939	1,752,849	56.1%	–	–

Table 7. Use of analgesic drugs and estimated annual exposures *(continued)*

All cases					
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least 1 NSAID used (excludes paracetamol)	**4,509**	**884,170**	**28.3%**	**% of cases receiving NSAID**	**% of all NSAID use**
Parecoxib	905	177,461	5.7%	20.1%	19.9%
Ketorolac	468	91,770	2.9%	10.4%	10.3%
Diclofenac	2,317	454,341	14.5%	51.4%	50.9%
Ibuprofen	850	166,677	5.3%	18.9%	18.7%
Naproxen	16	3,137	0.1%	0.4%	0.4%
Other	240	47,062	1.5%	–	–

Opioids were used more frequently during general anaesthesia than in other cases. At least one opioid was used in 99.8% of GAs – fentanyl in 73.7%, morphine in 33.0%, remifentanil in 10.7%. Paracetamol was used in 67.5% of GA cases. The distribution of use of different analgesic drugs by intended consciousness level is illustrated in Figure 13.

Figure 13. Use of analgesic drugs by intended consciousness level



Antibiotics

Antibiotics were used in 57.2% of all cases, with an estimated 1,787,360 annual exposures. Gentamicin (19.7%), co-amoxiclav (17.0%) and cefuroxime (13.6%) were the three most commonly used antibiotics (Fig. 14), with estimated annual exposures of around a half a million for the former two and approximately 400,000 for the latter. Table 8 details antibiotics used and estimated annual exposures.

Figure 14. Use of antibiotics in all procedures (of each antibiotic, whether in isolation or combined, n=15,790.)

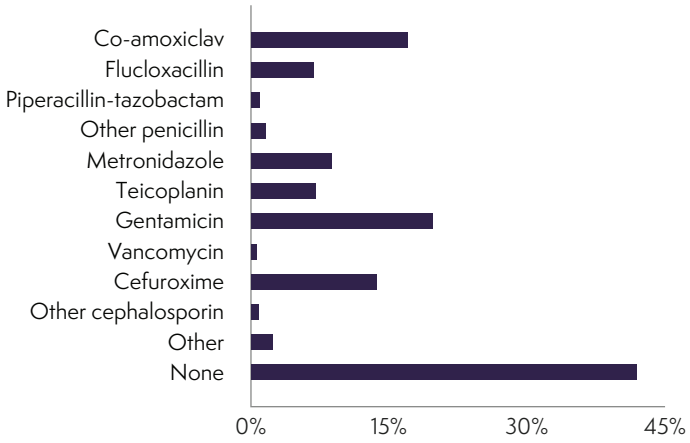
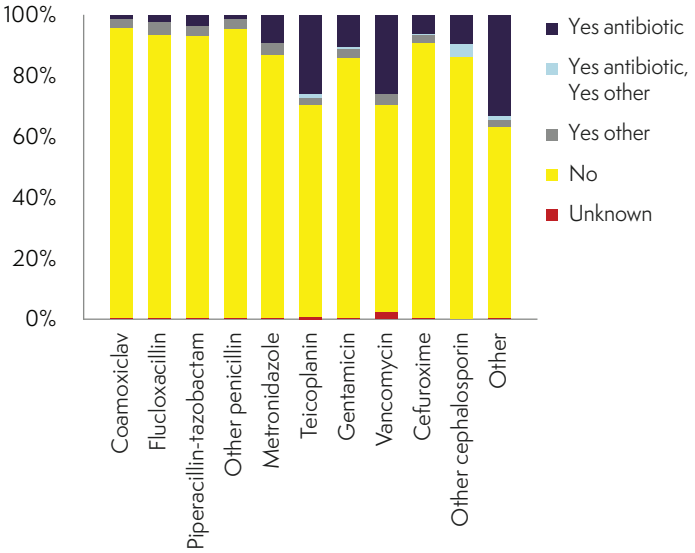


Table 8. Use of antibiotics and estimated annual caseload

All cases					
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least one antibiotic used	**9,115**	**1,787,360**	**57.2%**	**% of cases receiving antibiotic**	**% of all antibiotic use**
Co-amoxiclav	2,716	532,580	17.0%	29.8%	21.6%
Flucloxacillin	1,081	211,973	6.8%	11.9%	8.6%
Piperacillin-tazobactam	144	28,237	0.9%	1.6%	1.1%
Other penicillin	248	48,630	1.6%	2.7%	2.0%
Metronidazole	1,388	272,173	8.7%	15.2%	11.0%
Teicoplanin	1,120	219,621	7.0%	12.3%	8.9%
Gentamicin	3,146	616,899	19.7%	34.5%	25.0%
Vancomycin	90	17,648	0.6%	1.0%	0.7%
Cefuroxime	2,163	424,143	13.6%	23.7%	17.2%
Other cephalosporin	135	26,472	0.8%	1.5%	1.1%
Other	364	71,377	2.3%	4.0%	2.9%

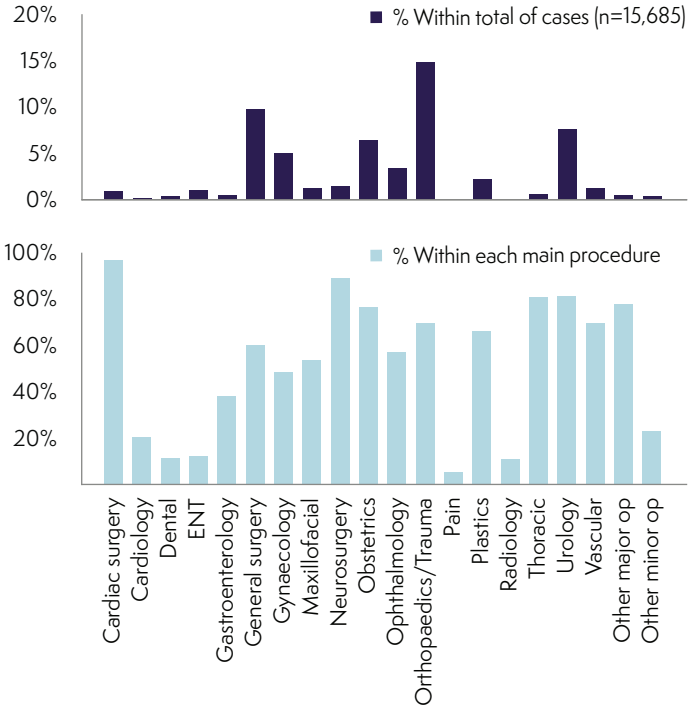
In a quarter of cases where teicoplanin or vancomycin were used (287/1120 and 23/90 cases, respectively), their choice was reported to have been influenced by past allergy history to an antibiotic (Figure 15).

Figure 15. Choice of antibiotics and past allergy history



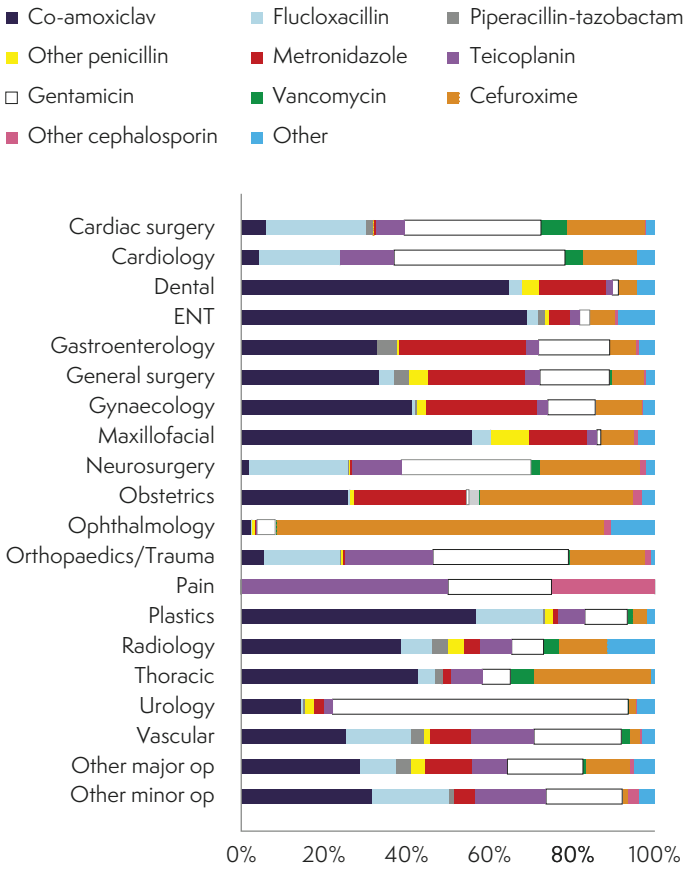
The greatest proportion of all antibiotics use by surgical specialty was in orthopaedics/trauma, accounting for 23.1%, followed by general surgery (14.4%), obstetrics (9.2%), urology (8.9%) and gynaecology (6.5%). The proportion of cases administered antibiotics by specialty was, in descending order, cardiac surgery 97.2%, neurosurgery 89.4%, urology 81.7%, thoracic surgery 80.9%, orthopaedics/trauma 69.9%, and general surgery 60.3% (Figure 16).

Figure 16. Antibiotic use by specialty: (top) percentage of all surgical cases (bottom) percentage of cases in specialty receiving antibiotics



Co-amoxiclav was commonly used across most specialties. In ophthalmology, cefuroxime was the most common antibiotic used. In cardiac surgery and cardiology, the dominant antibiotic was gentamicin, with flucloxacillin, cefuroxime and teicoplanin also being frequently used (Fig. 19). Use of antibiotics in orthopaedics/trauma was almost evenly spread between gentamicin (32.7% of all orthopaedics/trauma procedures), teicoplanin (21.3%), flucloxacillin (18.2%) and cefuroxime (17.9%) (Figure 17).

Figure 17. Distribution of individual antibiotics use, by specialty



Co-amoxiclav

Co-amoxiclav was the most commonly used antibiotic: 21.6% of all antibiotic uses. It was regularly used in general surgery (27.5% of all cases receiving this drug), gynaecology (15.4%) and obstetrics (13.6%). When co-amoxiclav was used the choice of antibiotic was rarely affected by drug allergy (5.8%).

Teicoplanin

Teicoplanin accounted for 8.9% of all antibiotic administrations. It was used mainly in orthopaedics/trauma (17.5% of all cases receiving this drug), general surgery (16.9%) and gynaecology (10.8%). In 25.6% of cases receiving this antibiotic its choice was determined by previous history of antibiotic allergy.

Local anaesthetics

The pattern of use of local anaesthetics (LAs) is described in Table 9.

Use of LAs by consciousness level is detailed in Figure 18.

Figure 18. Use of local anaesthetics by intended consciousness level

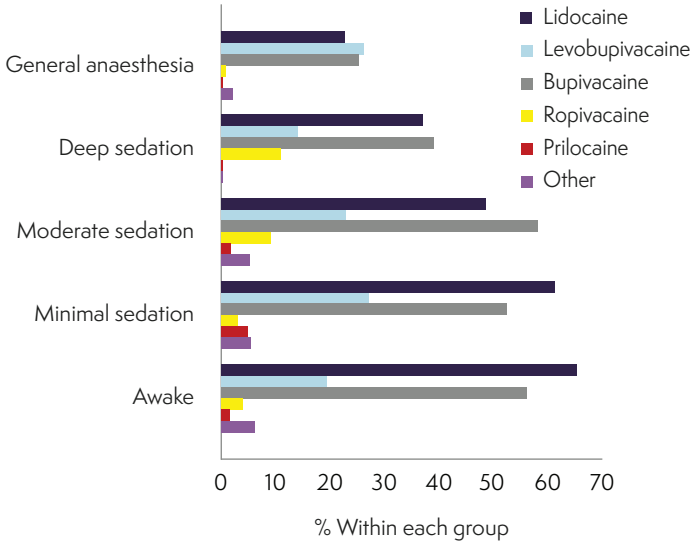


Table 9. Use of local anaesthetics and estimated annual exposures

All cases					
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least one local anaesthetic used	**11,831**	**2,319,941**	**74.2%**	**% of cases receiving LA**	**% of all LA use**
Lidocaine	4,951	970,842	31.1%	41.8%	33.3%
Bupivacaine	5,092	998,490	31.9%	43.0%	34.2%
Levobupivacaine	3,954	775,340	24.8%	33.4%	26.6%
Ropivacaine	302	59,219	1.9%	2.6%	2.0%
Prilocaine	103	20,197	0.6%	0.9%	0.7%
Other	469	91,966	2.9%	4.0%	3.2%

Table 10. Use of anti-emetics and estimated annual exposures

All cases					
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
At least one anti-emetic used	**11,655**	**2,285,429**	**73.1%**	**% of cases receiving anti-emetic**	**% of all anti-emetic use**
Ondansetron	10,456	2,050,317	65.6%	89.7%	52.6%
Dexamethasone	7,739	1,517,541	48.5%	66.4%	38.9%
Cyclizine	901	176,677	5.7%	7.7%	4.5%
Prochlorperazine	99	19,413	0.6%	0.8%	0.5%
Droperidol	267	52,356	1.7%	2.3%	1.3%
Metoclopramide	285	55,886	1.8%	2.4%	1.4%
Other	136	26,668	0.9%	1.2%	0.7%

Anti-emetics

Anti-emetics were used in 73.1% of all cases: ondansetron in 65.6% of all cases, dexamethasone in 48.5%, cyclizine in 5.7%, and all other anti-emetics less than 2% each (Table 10). During general anaesthesia anti-emetic use was higher: ondansetron 78.3% of cases and dexamethasone 60.4%. Ondansetron and dexamethasone were used in combination in 53.1% of all GA cases.

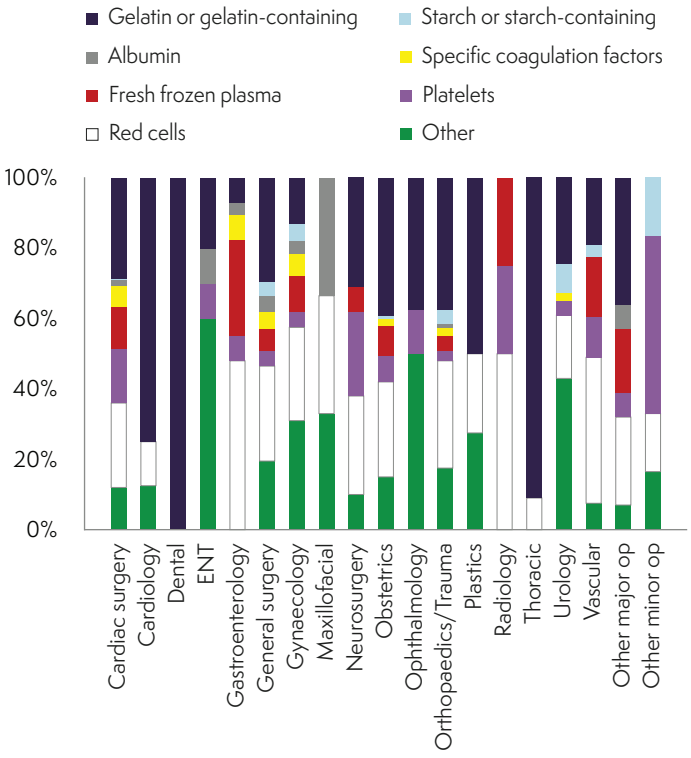
Intravenous colloids and blood products

Intravenous colloids and/or blood products were used in 4.2% of all cases. Gelatin-containing products (1.7%) and red blood cells (1.5%) were the most frequently used products. Starch or starch-containing products (0.2%), albumin (0.1%), platelets (0.4%), fresh frozen plasma (0.5%) and specific coagulation factors (0.2%), were used uncommonly (Table 11) The surgical specialties that used the greatest proportion of IV colloids or blood products were orthopaedics/ trauma, general surgery, cardiac surgery and obstetrics (1.0%, 0.8% and 0.5% each respectively of all cases). The specialties using IV colloids or blood products most frequently were cardiac surgery, other major operations and vascular surgery (56.6%, 16.7% and 13.6% respectively of cases within each specialty). Figure 19 details use of these substances by main procedure. There was no evidence that starch use was concentrated in a particular site or specialty.

Table 11. Use of IV colloids and blood products and estimated annual caseload

All cases			
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases
At least one IV colloid/ blood product used	**668**	**130,988**	**4.2%**
Gelatin or gelatin-containing	266	52,160	1.7%
Starch or starch-containing	26	5,098	0.2%
Albumin (any concentration)	18	3,530	0.1%
Red cells	242	47,454	1.5%
Platelets	68	13,334	0.4%
Fresh frozen plasma	74	14,511	0.5%
Specific coagulation factors	28	5,491	0.2%
Other	156	30,590	1.0%

Figure 19. Use of IV colloids and blood products by main procedure



Drugs affecting coagulation

Drugs affecting coagulation were used in 8.3% of all cases. Tranexamic acid was the drug most commonly used (5.9% of all cases), followed by heparin (2.7%). Protamine, aprotinin, vitamin K and other coagulation drugs (not specified) were each used in less than 1% of all cases (Table 12). Use of these drugs was mostly concentrated in orthopaedics, cardiac and vascular surgery (52.2%, 25.4% and 10.9% respectively of all cases where a coagulation drug was used). Tranexamic acid was administered in 71% of cardiac surgery and 19% of orthopaedic operations.

Table 12. Use of coagulation drugs and estimated annual caseload

	All cases		
Individual drug/ substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases
At least one coagulation drug used	**1,319**	**258,643**	**8.3%**
Heparin – any	435	85,299	2.7%
Tranexamic acid	940	184,325	5.9%
Aprotinin	12	2,353	0.1%
Protamine	139	27,257	0.9%
Vitamin K	27	5,294	0.2%
Other	45	8,824	0.3%
Specific coagulation factors	28	5,491	0.2%
Other	156	30,590	1.0%

Chlorhexidine

Chlorhexidine exposure was reported in 73.5% of all cases (Table 13), mostly via skin preparation by the anaesthetist (51.6% of all cases, accounting for 70.2% of all chlorhexidine-exposed cases) and/or the surgeon (44.7% of all cases, 60.7% of chlorhexidine-exposed cases). Very few cases were reported to be via urethral exposure (3.3% of all cases), coated/impregnated central venous catheter (CVC), surgical irrigation, or other exposure (0.6% of all cases each for the latter three routes). Exposure to this antiseptic was reported to be 'Unknown' in 0.9% of all cases and 23.6% of cases were reported to have no exposure. Chlorhexidine exposure was reported in more than two-thirds of cases for most surgical specialties (Figure 20).

Povidone-iodine

Povidone-iodine exposure was reported in 40.0% of all cases (Table 14), mostly via skin preparation by the surgeon (36.7% of all cases, accounting for 91.7% of all povidone-iodine-exposed cases) or by the anaesthetist (6.6% of all cases, 16.4% of povidone-iodine-exposed cases), with minor contributions by surgical irrigation (0.9% of all cases) or other routes (1.0% of all cases). A total of 54.6% of cases were reported to have had no exposure. Povidone-iodine was used in less than half of cases for all surgical specialties except for ophthalmology (where its use was almost ubiquitous at 95.6%), and neurosurgery, vascular surgery, general surgery and plastics, where it was used in more than half of the cases (Figure 20).

Table 13. Use of chlorhexidine and estimated annual exposures

	All cases				
Chlorhexidine exposure	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
Exposure – at least one route	**11,722**	**2,298,567**	**73.5%**	**% of cases exposed to chlorhexidine**	**% of all chlorhexidine exposure**
Coated/impregnated CVC	93	18,236	0.6%	0.8%	0.6%
Urethral	532	104,320	3.3%	4.5%	3.3%
Skin Prep – anaesthetist	8,232	1,614,213	51.6%	70.2%	50.9%
Skin Prep – surgeon	7,120	1,396,161	44.7%	60.7%	44.0%
Surgical irrigation	95	18,629	0.6%	0.8%	0.6%
Other	101	19,805	0.6%	0.9%	0.6%

Table 14. Use of povidone-iodine and estimated annual exposures

	All cases				
Povidone-iodine exposure	Number exposed in Activity Survey	Estimated annual exposure	% of all cases	% of all cases receiving drug group	% of total drug group usage (sum of all; total > total no of cases)
Exposure – at least one route	**6,382**	**1,251,446**	**40.0%**	**% of cases exposed to povidone-iodine**	**% of all povidone-iodine exposure**
Skin prep anaesthetist	1,047	205,306	6.6%	16.4%	14.6%
Skin prep surgeon	5,852	1,147,519	36.7%	91.7%	81.3%
Surgical irrigation	137	26,864	0.9%	2.1%	1.9%
Other	159	31,178	1.0%	2.5%	2.2%
Surgical irrigation	95	18,629	0.6%	0.8%	0.6%
Other	101	19,805	0.6%	0.9%	0.6%

Figure 20. Exposure to chlorhexidine and povidone-iodine, by main procedure

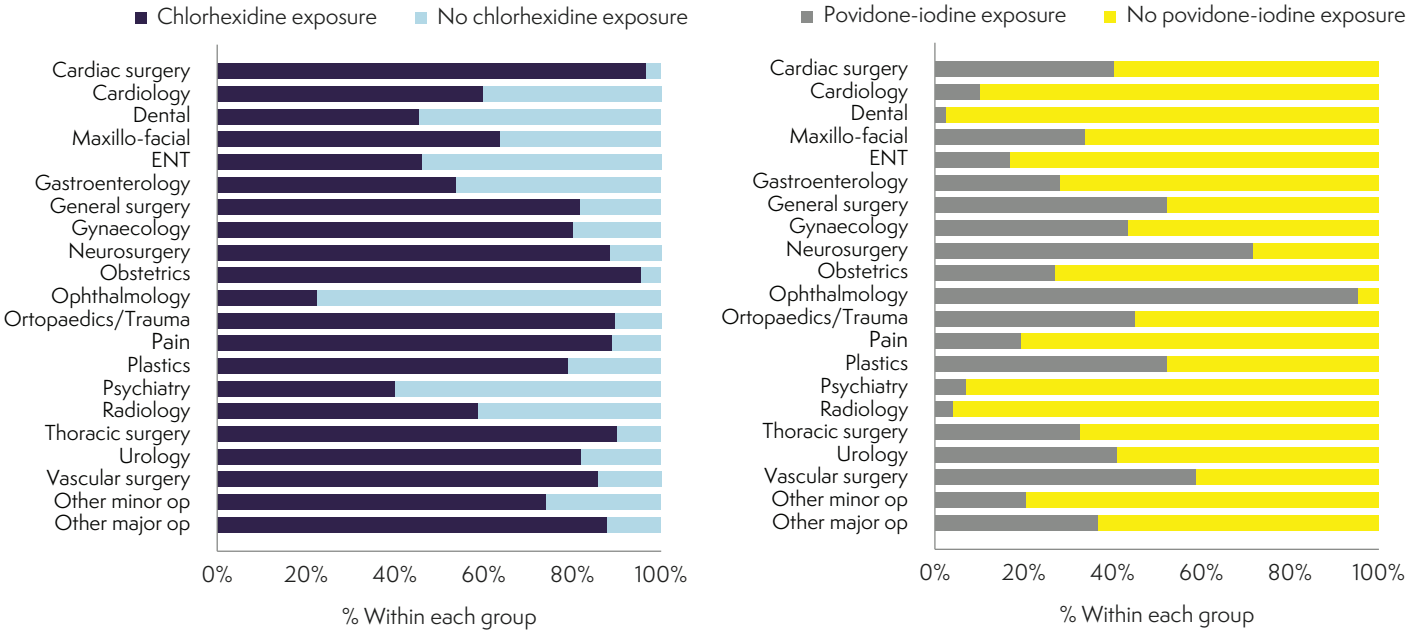
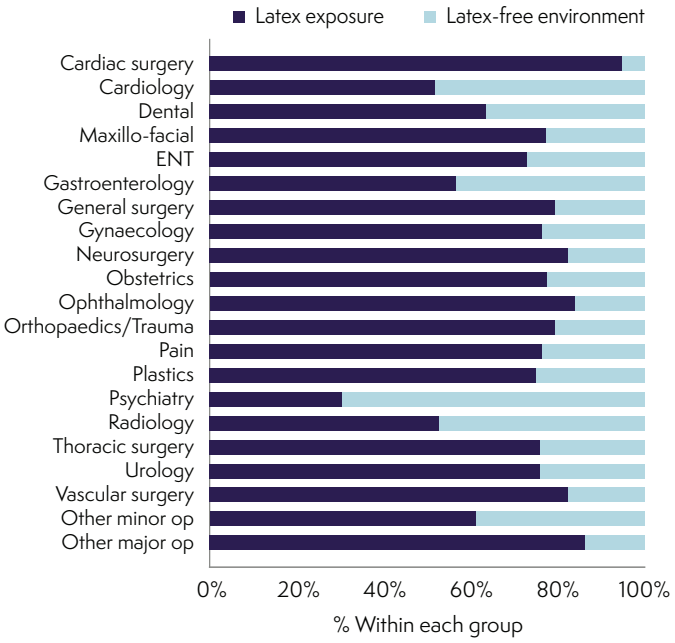


Table 15. Latex exposure and estimated annual caseload

All cases					
Latex exposure	**Number exposed in Activity Survey**	**Estimated annual exposure**	**% of all cases**	**% of all cases receiving drug group**	**% of total drug group usage (sum of all; total > total no of cases)**
Exposure – at least one route	**11,119**	**2,180,325**	**69.7%**	**% of cases exposed to latex**	**% of all latex exposure**
Gloves	10,244	2,008,746	64.3%	92.1%	88.0%
Other	1,397	273,938	8.8%	12.6%	12.0%

Figure 21. Latex exposure, by main procedure



Latex

More than two-thirds of cases (69.7%) were reported to have been exposed to latex (Table 15), with the main route being latex gloves (64.3% of all cases, accounting for 92.1% of all latex-exposed cases). A latex-free environment was reported for 21.2% of all cases; latex exposure was 'Unknown' for 7.1%.

The specialty with the highest rate of latex exposure was cardiac surgery (94.8% of cases), and the lowest was psychiatry (30.8%) (Figure 21).

Miscellaneous drugs/substances

Bone cement was used in 2.6% of all cases and in 11.8% of orthopaedics/trauma cases, with an annual caseload of 78,240.

Blue dyes were used in 2.8% of all cases: Patent Blue in 2% and Methylene Blue in 0.9%. Both Patent Blue and Methylene Blue dyes were mostly used in general surgery: 29.8% and 35.3% respectively of all cases receiving these dyes, X-ray contrast was used in 1.7% of all cases, mostly in urology, radiology and orthopaedics: 24.5%, 22.3%, and 14.2% respectively of all cases receiving X-ray contrast.

Table 16 details use of the above substances and estimated annual exposures.

Table 16. Use of miscellaneous drugs/substances and estimated annual exposures

All cases			
Individual drug/substance	Number exposed in Activity Survey	Estimated annual exposure	% of all cases
Patent Blue dye	315	61,768	2.0%
Methylene Blue dye	139	27,257	0.9%
Bone cement	407	79,809	2.6%
X-ray contrast	274	53,729	1.7%

Discussion

This survey represents the most recent, comprehensive snapshot of anaesthetic activity and drug use in the United Kingdom. It provides unique, detailed insight into drug/substance exposure during anaesthetic activity in the perioperative period. In particular, compared with the equivalent Activity Survey performed in 2013 (Sury 2014), it provides considerably greater detail on use of analgesics, antibiotics, local anaesthetics, anti-emetics, intravenous colloids and blood products, as well as providing more information on all drugs assessed in that survey, enabling an examination of trends in practice. This survey also provides information on reported exposure to other substances, such as latex, antiseptics (chlorhexidine and povidone-iodine), radiocontrast media, dyes, and bone cement.

As not all drug use was studied in NAP5 we can only comment on changes in choice of induction and maintenance agents, and NMBAs and their reversal agents. We observed a substantial increase in the use of propofol for induction of anaesthesia for caesarean section and a reduction in the use of thiopental. NAP5 identified such surgery as particularly high risk for accidental awareness during general anaesthesia (AAGA) and thiopental was highlighted as a particular contributor to that (Pandit 2014, Cook 2014). We also saw a reduction (by about a third) of use of nitrous oxide in all age groups. We are aware that nitrous oxide may have become less popular after the publication of the ENIGMA (Myles 2007) study, and that some new hospital builds stopped including piped nitrous oxide to theatres. However the publication of ENIGMA-II has dispelled concerns about the safety of nitrous oxide, including safety in the elderly population (Myles 2014). A recent Canadian publication noted that ENIGMA had reduced use of nitrous oxide among anaesthesiologists, but that ENIGMA-II had not led to any recovery in usage (Jain 2018). Use of NMBAs has remained stable since the 2013 survey (Sury 2014), with almost half of patients undergoing general anaesthesia receiving NMBAs, and with stable distribution across age groups. Regarding choice of NMBA, use of suxamethonium appears to have declined slightly since 2013, both overall (5.3% vs 13% of cases in which an NMBA was used), and during caesarean section (81% vs 92%). Use of NMBA reversal agents has not increased overall, but the proportion of uses of sugammadex has increased four-fold. With the drug soon to come off patent a further increase might be anticipated. Overall, the static nature of NMBA use, the persistent underuse of reversal agents, and the underwhelming use of neuromuscular monitoring reported in Chapter 8, Activity Survey, indicates no evidence of improvement in practice since increased vigilance in this area was recommended in NAP5 (Pandit 2014) and described as mandatory in the AAGBI minimum standards for monitoring document in 2015 (Checketts 2016).

This survey provides comprehensive and, to the best of our knowledge, previously unavailable data on the use of multiple drug classes, including analgesics, antibiotics, local anaesthetics, anti-emetics, drugs affecting coagulation, intravenous colloids and blood products. These data will be useful primarily in acting as a denominator for the wider NAP6 project, but we believe they will also have other uses.

Our data show that analgesics are used in ≈90% of all procedures involving an anaesthetist, and that opioids are used in virtually all general anaesthesia cases – a modest increase from NAP5 (92%). With increasing concerns about the use of opioids for reasons of both immune function and dependence potential (Brat 2018), the knowledge provided by this survey on proportional drug usage and allergenic potential, is useful, not only directly to inform practice, but also for the purpose of tracking usage changes over time. In total an estimated 3.6 million opioid drugs were administered in 3.1 million procedures, with fentanyl and morphine the dominant drugs, and oxycodone (about which some commentators have particular concerns) (Haffajee 2017) accounting for less than 2% of all opioid use and ranking as the fifth most frequently used opioid.

The widespread use of local anaesthetics, which were administered in three quarters of all cases, and the distribution of drugs used indicates that local and regional anaesthetic techniques were used in three quarters of cases, and with the previous results of NAP5, which indicated that neuraxial anaesthesia was being used for ≈30% of cases, suggests that most suitable cases are receiving neuraxial, peripheral nerve block or local anaesthesia infiltration, the first two of which are associated with improved patient reported satisfaction (Walker 2016). These data also provide numerator data – 2.3 million perioperative administrations of local anaesthetics – which may be of value when measuring the safety impact of non-Luer connectors on avoidance of wrong route errors (Cook 2012, NHS England 2016).

We have documented the use of anti-emetics in approximately three quarters of all cases, with dexamethasone now administered routinely (60%) during general anaesthesia. With concerns about the impact of dexamethasone on cancer recurrence (Singh 2014) and the relatively modest impact of this drug on postoperative nausea and vomiting (DREAMS trials collaborators 2017) this is also a notable finding.

Drugs affecting coagulation were used in ≈8% of all cases, with tranexamic acid used in ≈6% of all cases, in the majority of cardiac surgery cases, and in one in five orthopaedics/trauma operations. This is probably a relatively new phenomenon, but, with tranexamic acid now recommended for all patients undergoing surgery with anticipated blood loss greater than 500 mls (NICE 2016), our findings not only act as a benchmark, but also suggest that this recommendation may not be being widely applied.

The use of IV colloids is also of interest in relation both to blood-product use (one administration in every 37 cases) and to the use of synthetic colloids (less than 2% of cases). Among the synthetic colloids, the gelatins accounted for 90% of use, mostly during cardiac and vascular surgery. Starch-containing fluids are used in approximately 1 in 600 cases, and while there was no particular pattern to their use (surgical specialty, patient age, or ASA grade), it did include emergency cases and patients of ASA Grades 3–4. The 26 administrations of starch-containing fluids were reported from only 17 locations suggesting that perhaps the use is clustered in certain hospitals. The use of starch-containing fluid remains highly controversial, and the European Medicines Agency recently recommended their suspension from sale (EMA 2018). Based on our data this will have little impact on UK anaesthetic practice.

Amidst the current threat of increasing antibiotic resistance (WHO 2014 and 2017), our data provide detailed information on antibiotic usage, which was reported for more than half of the procedures and accounted for almost two million administrations annually. Gentamicin, co-amoxiclav and cefuroxime were the most commonly used drugs – each used for approximately 500,000 uses. Orthopaedics/trauma and general surgery are the main specialties using antibiotics, but cardiac and neurosurgery, urology and thoracic surgery are the specialties with the greatest proportion of cases receiving an antibiotic. The wide distribution of antibiotics used within specialties might perhaps hint at a lack of consistent application of best practice, but this would require further investigation.

The choice of drugs administered was reported to be influenced by allergy history in almost 10% of cases, and a history of antibiotic allergy influenced choice of teicoplanin or vancomycin in more than a quarter of cases when either of these antibiotics were used. We did not collect information on the specific antibiotic(s) that patients reported allergy to, but it is likely that a history of penicillin allergy was dominant, as these drugs are common substitutes for penicillins and penicillin allergy is reported in up to 10% of the general population and 20% of hospital in-patients (Weiss 2010, Lee 2000, Macy 2014a). Importantly more than 90% of patients with a history of penicillin allergy are deemed not allergic when investigated via skin and drug provocation tests (Macy 2015). The NAP6 baseline survey on anaesthetists' perspectives and experiences of perioperative anaphylaxis reported that penicillins were the drugs anaesthetists were most concerned about and avoided most often. Notably, teicoplanin, although it was prominent among suspected causative agents, was not frequently avoided (Kemp 2017). There is emerging evidence of teicoplanin as an important trigger of anaphylaxis events (Savic 2015), and it accounted for 28% of antibiotic-related anaphylaxis in one series (Chapter 8). A growing body of evidence has shown that use of second-line (often more expensive) antibiotics has significant public health implications and increased healthcare costs with increased duration of treatment and hospital stay. They also, lead to higher rates of antibiotic resistance and infections, including methicillin-resistant Staphylococcus aureus (MRSA), Clostridium difficile (C. diff) and vancomycin-resistant enterococcus (VRE) (Macy 2014b, Sade 2003, Solensky 2014). Our data provide additional evidence of use of second-line antibiotics, namely teicoplanin, driven by drug allergy history, adding further strength to calls from the international allergy community for robust programmes to tackle the problem of inaccurate labels of antibiotic allergy, thus improving antibiotic stewardship (Macy 2014b, Sade 2003, Solensky 2014, Krishna 2017).

Chlorhexidine is a widely used antiseptic (Opstrup 2015) that has been increasingly reported as an emerging cause of allergy and of perioperative anaphylaxis in particular (Garvey 2007, Rutowski 2015, Nakonecha 2014, Mertes 2016, Egner 2017, Sharp 2016), although its use still appears to be under-recognised in the healthcare sector, especially in the perioperative setting, and its potential to cause allergic reactions seems to be underestimated by healthcare professionals (Totty 2017, Wittczak 2013, Faber 2012). Despite its known ubiquitous use in the hospital in accordance with infection prevention guidelines, our data reported chlorhexidine exposure in only ≈75% of all cases, mostly via skin preparation by the anaesthetist and/or the surgeon. Very few cases of exposure were reported via urethral exposure and coated/impregnated CVCs. National guidelines, such as NICE CG74 (NICE 2008), recommend use of chlorhexidine to prevent surgical site infections, and many local hospital guidelines advocate the use of chlorhexidine prior to venous cannulation. We suspect that our data may reflect under-reporting due to under-recognition of chlorhexidine exposure, for example, due to lack of awareness of chlorhexidine being present in many antiseptic alcohol wipes, urethral lubricants and CVCs. Conversely, it was unsurprising to find that povidone-iodine is used in about two fifths of cases and that exposure is mostly via skin prep by the surgeon.

Finally, our survey data suggest a latex-free environment was in place for only one fifth of cases.

This survey adopted similar methodology to that used for the NAP5 Activity Survey (Sury 2014). Discussion and details of the methodology used, in particular, the duration of the census over two days instead of a longer sampling time, the randomisation of specialist hospitals, and the extrapolation of sample data to estimate the annual workload, is already considered in Chapter 8. As also noted there, the large size of our sample data set means we can be confident that we have a true representation of the overall anaesthetic activity and allergen exposure in the UK, and that it is reasonable to scale-up the two-day sample data to estimate the annual data. However, where the sample size is small, variations in data captured or missed would have proportionately larger impacts on annual estimates, so these data should be treated more circumspectly.

This survey suggests an annual anaesthetic caseload of 3,126,067, which is a 15% reduction compared to that reported in NAP5 (3,685,800). We are not aware of any comparable data against which to benchmark. It should be noted that the NAP6 annual estimate of caesarean section caseload (171,579) is within 2% of that reported in NHS maternity data (174,720) (NHS Digital 2017b). We attempted to control for limitations in data collection by incorporating an estimated capture rate per hospital, by accounting for uninterpretable forms, and by calculating a scaling factor to allow for bank holidays. There are many factors that may have contributed to a fall in activity between 2013 and 2016,

and these are discussed in Chapter 8. However, the possibility also exists that we have missed a proportion of cases. If this is the case, we would have underestimated caseload, drug and allergen exposure, and activity by up to 15%. However, it would not impact on relative proportions and patterns of use/exposure within the dataset.

Overall this extensive national survey of anaesthetic practice in the United Kingdom provides new insights into drug uses and allergen exposures in UK perioperative care. It is important for use as the denominator in the main NAP6 analysis, and the data provide significant insights into many aspects of perioperative practice.

References

Brat 2018: Brat GA, Agniel D, Beam A, *et al.* Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. BMJ. 2018; 360: j5790.

Checketts 2016: Checketts MR, Alladi R, Ferguson K, *et al.* Recommendations for standards of monitoring during anaesthesia and recovery 2015: Association of Anaesthetists of Great Britain and Ireland. Anaesthesia. 2016; 71: 85-93.

Cook 2012: Cook TM. Non-Luer connectors: are we nearly there yet? Anaesthesia 2012; 67: 784-92.

Cook 2014: Cook TM, Andrade J, Bogod DG, *et al.* 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: patient experiences, human factors, sedation, consent, and medicolegal issues. Br J Anaesth. 2014; 113: 560-74.

DREAMS trial collaborators 2017: DREAMS Trial Collaborators and West Midlands Research Collaborative. Dexamethasone versus standard treatment for post-operative nausea and vomiting in gastrointestinal surgery: randomised controlled trial (DREAMS Trial). BMJ. 2017; 357: j1455.

EMA 2018: Hydroxyethyl-starch solutions for infusion to be suspended – CMDh endorses PRAC recommendation. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002892.jsp&mid=WC0b01ac058004d5c1 (Accessed 8 Feb 2018).

Egner 2017: Egner W, Helbert M, Sargur R, *et al.* Chlorhexidine allergy in four specialist allergy centres in the United Kingdom, 2009–13: clinical features and diagnostic tests. Clin Exp Immunol 2017; 188: 380–6.

Faber 2012: Faber M, Leysen J, Bridts C, Sabato V, De Clerck LS, Ebo DG. Allergy to chlorhexidine: beware of the central venous catheter. Acta Anaesthesiol Belg 2012; 63: 191–4.

Garvey 2007: Garvey LH, Krøigaard M, Poulsen LK, *et al.* IgE-mediated allergy to chlorhexidine. J Allergy Clin Immunol 2007; 120: 409–15.

Haffajee 2017: Haffajee RL, Mello MM. Drug Companies' Liability for the Opioid Epidemic. N Engl J Med. 2017; 377: 2301-05.

HSCIC 2013: Health and Social Care information Centre. NHS Maternity Statistics 2012-13. Hosp Epis Stat. 2013;(November). http://www.hscic.gov.uk/catalogue/PUB12744/nhs-mate-eng-2012-13-summ-repo-rep.pdf Accessed 8 Feb 2018.

Jain 2018: Jain D, Ma HK, Buckley N. Impact of ENIGMA trials on nitrous oxide: a survey of Canadian anesthesiologists and residents. Can J Anaesth. 2018 Jan 11. doi: 10.1007/s12630-018-1060-z. [Epub ahead of print].

Kemp 2017: Kemp HI, Cook TM, Thomas M, Harper NJN. UK anaesthetists' perspectives and experiences of severe perioperative anaphylaxis: NAP6 baseline survey. Br J Anaesth 2017; 119: 132–9.

Krishna 2017: Krishna MT, Huissoon AP, Li M, *et al.* Enhancing antibiotic stewardship by tackling 'spurious' penicillin allergy. Clin Exp Allergy 2017; 47: 1362-73.

Lee 2000: Lee CE, Zembower TR, Fotis MA, *et al.* The incidence of antimicrobial allergies in hospitalized patients: implications regarding prescribing patterns and emerging bacterial resistance. Arch Intern Med 2000; 160: 2819–22.

Macy 2014a: Macy E. Penicillin and Beta-Lactam Allergy: Epidemiology and Diagnosis. Curr Allergy Asthma Rep. 2014; 14: 476.

Macy 2014b: Macy E, Contreras R. Health care use and serious infection prevalence associated with penicillin 'allergy' in hospitalized patients: A cohort study. J Allergy Clin Immunol 2014; 133: 790–6.

Macy 2015: Macy E. Penicillin allergy: Optimizing diagnostic protocols, public health implications, and future research needs. Curr. Opin. Allergy Clin. Immunol. 2015; 15: 308–13.

Mertes 2016: Mertes PM, Volcheck GW, Garvey LH, *et al.* Epidemiology of perioperative anaphylaxis. Press Med 2016; 45: 758-67.

Myles 2007: Myles PS, Leslie K, Chan MT, *et al.* Avoidance of nitrous oxide for patients undergoing major surgery: a randomized controlled trial. Anesthesiology 2007; 107: 221-31.

Myles 2014: Myles PS, Leslie K, Chan MT, *et al.* The safety of addition of nitrous oxide to general anaesthesia in at-risk patients having major non-cardiac surgery (ENIGMA-II): a randomised, single-blind trial. Lancet 2014; 384: 1446-54.

Nakonechna 2014: Nakonechna A, Dore P, Dixon T, *et al.* Immediate hypersensitivity to chlorhexidine is increasingly recognised in the United Kingdom. Allergol 2014; 42: 44–9.

NICE 2016: NICE QS138 Blood transfusion. National Institute for Health and Care Excellence. December 2016. https://www.nice.org.uk/guidance/qs138 (Accessed 8 Feb 2018).

NHS England 2016: Never Events List 2015/16. NHS England Patient Safety Domain https://www.england.nhs.uk/wp-content/uploads/2015/03/never-evnts-list-15-16.pdf (Accessed 8 Feb 2018).

NHS Digital 2017a: NHS Digital. Provisional Monthly HES for Admitted Patient Care, Outpatient and Accident and Emergency Data - April 2017 to September 2017: Admitted Patient Care Dat. 2017

NHS Digital 2017b: NHS Digital. NHS Maternity Statistics 2016-2017. http://digital.nhs.uk/catalogue/PUB30137 (Accessed 8 Feb 2018).

NICE 2008. NICE. Surgical site infections: prevention and treatment Guidance and guidelines NICE; https://www.nice.org.uk/guidance/cg74 (accessed 8 Feb 2018).

Opstrup 2015: Opstrup MS, Johansen JD, Garvey LH. Chlorhexidine allergy: sources of exposure in the health-care setting. Br J Anaesth. 2015; 114: 704-5.

Prescribing costs 2014: Prescribing & Medicines Team Health and Social Care Information Centre. Prescribing Costs in Hospitals and the Community: England 2014-15. 2015; 29.

Pandit 2014: Pandit JJ, Andrade J, Bogod DG, *et al.* 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors. Br J Anaesth. 2014; 113: 549-59.

Rutkowski 2015: Rutkowski K, Wagner A. Chlorhexidine: a new latex? Eur Urol. 2015; 68: 345-7.

Sade 2003: Sade K, Holtzer I, Levo Y, Kivity S. The economic burden of antibiotic treatment of penicillin-allergic patients in internal medicine wards of a general tertiary care hospital. Clin Exp Allergy 2003; 33: 501–6.

Savic 2015: Savic LC, Garcez T, Hopkins PM, Harper NJN, Savic S. Teicoplanin allergy - An emerging problem in the anaesthetic allergy clinic. Br J Anaesth 2015; 115: 595-600.

Sharp 2016: Sharp G, Green S, Rose M. Chlorhexidine-induced anaphylaxis in surgical patients: a review of the literature. ANZ J Surg 2016; 86: 237–43.

Singh 2014: Singh PP, Lemanu DP, Taylor MH, Hill AG. Association between preoperative glucocorticoids and long-term survival and cancer recurrence after colectomy: follow-up analysis of a previous randomized controlled trial. Br J Anaesth 2014; 113 Suppl 1: i68-73.

Solensky 2014: Solensky R. Penicillin allergy as a public health measure. J Allergy Clin Immunol 2014; 133: 797–8.

Sury 2014: Sury MJR, Palmer JHMacG, Cook TM, Pandit JJ. The state of UK anaesthesia: a survey of National Health Service Activity in 2013. Br J Anaesth 2014; 113: 575-84.

Totty 2017: Totty J, Forsyth J, Mekako A, Chetter I. Life-threatening intraoperative anaphylaxis as a result of chlorhexidine present in Instillagel. BMJ Case Rep 2017; 2017 pii: bcr-2017-221443.

Walker 2016: Walker EMK, Bell M, Cook TM, Grocott MPW, Moonesinghe SR, for the SNAP-1 investigator group. Patient reported outcome after anaesthesia in the UK: a 2-day National cohort study. Br J Anaesth 2016: 117: 758-66.

Weiss 2010: Weiss ME, Bernstein DI, Blessing-Moore J, *et al.* Drug allergy: an updated practice parameter. Ann Allergy Asthma Immunol 2010; 105: 259–73.

WHO 2014: World Health Organization. Antimicrobial resistance : global report on surveillance 2014 http://www.who.int/drugresistance/documents/surveillancereport/en/ (Accessed 8 Feb 2018).

WHO 2017: World Health Organization. Antibiotic resistance. WHO. World Health Organization; 2017 http://www.who.int/mediacentre/factsheets/antibiotic-resistance/en/ (Accessed 8 Feb 2018).

Wittczak 2013: Wittczak T, Dudek W, Walusiak-Skorupa J, Swierczynska-Machura D, Palczynski C. Chlorhexidine--still an underestimated allergic hazard for health care professionals. Occup Med (Lond) 2013; 63: 301–5.

NAP6 Anaesthetic Activity/Allergen Exposure Survey

NAP6 Hospital Code: ☐☐☐ **Date:** ☐☐/☐☐/☐☐ (dd/mm/yy)

PLEASE INDICATE ALL SPECIFIED DRUGS/SUBSTANCES THE PATIENT WAS EXPOSED TO DURING THE PERIOPERATIVE PERIOD (until patient discharged to the ward or HDU/ICU) *PLEASE SELECT ALL BOXES THAT APPLY IN EACH CATEGORY*

Theatre Number/Location: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐ **Actual List Order** (first patient is 01): ☐☐

Please complete this form for all patients where anaesthesia care is provided by an Anaesthetist during the two day survey period

Day of the Week
☐ Mon ☐ Tues ☐ Wed
☐ Thurs ☐ Fri ☐ Sat
☐ Sun

Admission Type
☐ Elective Day Case
☐ Elective Inpatient
☐ Emergency
☐ Other
☐ Unknown

Main Procedure
☐ Cardiac surgery
☐ Cardiology
☐ Dental
☐ Maxillo-facial
☐ ENT
☐ Gastroenterology
☐ General surgery
☐ Gynaecology
☐ Neurosurgery
☐ Obstetrics
☐ Ophthalmology
☐ Orthopaedics/Trauma
☐ Pain
☐ Plastics
☐ Psychiatry
☐ Radiology
☐ Thoracic
☐ Urology
☐ Vascular
☐ Other minor op
☐ Other major op

Either
NCEPOD Priority
☐ Immediate ☐ Urgent
☐ Expedited ☐ Elective
☐ Unknown

Or
Caesarean Category
☐ 1 ☐ 2
☐ 3 ☐ 4
☐ Unknown

Age of Patient (yrs)
☐ <1 ☐ 1-5
☐ 6-15 ☐ 16-25
☐ 26-35 ☐ 36-45
☐ 46-55 ☐ 56-65
☐ 66-75 ☐ 76-85
☐ >86 ☐ Unknown

Sex of Patient
☐ Male ☐ Female
☐ Unknown

ASA Grade
☐ 1 ☐ 2 ☐ 3
☐ 4 ☐ 5 ☐ 6
☐ Unknown

Body Habitus (BMI)
☐ Underweight (<18.5)
☐ Normal weight (18.5-24.9)
☐ Overweight (25-29.9)
☐ Obese (30-34.9)
☐ Morbidly obese (>35)
☐ Unknown

Ethnicity
☐ British (White)
☐ Irish (White)
☐ Any other White Background
☐ White and Black Caribbean (Mixed)
☐ White and Black African (Mixed)
☐ White and Asian (Mixed)
☐ Any other Mixed Background
☐ Indian (Asian or Asian British)
☐ Pakistani (Asian or Asian British)
☐ Bangladeshi (Asian or Asian British)
☐ Any Other Asian Background
☐ Caribbean (Black or Black British)
☐ African (Black or Black British)
☐ Any other Black Background
☐ Chinese
☐ Any Other Ethnic Group
☐ Unknown

Premed Given on the Ward
☐ Yes ☐ No ☐ Unknown

Induction Location
☐ Theatre anaesthetic room
☐ Theatre
☐ Radiology or Cath-lab
☐ ICU
☐ Emergency Department
☐ Other
☐ Unknown

Intended Conscious Level
☐ General anaesthesia
☐ Deep sedation
☐ Moderate sedation
☐ Minimal sedation
☐ Awake

Was Your Choice of Drugs Influenced By Previous Allergy History?
☐ No ☐ Yes - antibiotic
☐ Yes - other ☐ Unknown

Latex Exposure During This Case
☐ Yes (gloves)
☐ Yes (other latex)
☐ Latex-free environment
☐ Unknown

Povidone Iodine Exposure During This Case
☐ None
☐ Skin prep (anaesthetist)
☐ Skin prep (surgeon)
☐ Surgical irrigation
☐ Other
☐ Unknown

Chlorhexidine Exposure During This Case
☐ None
☐ Coated/impregnated CVC
☐ Urethral
☐ Skin prep (anaesthetist)
☐ Skin prep (surgeon)
☐ Surgical irrigation
☐ Other
☐ Unknown

Induction Agents
☐ None
☐ Propofol
☐ Thiopental
☐ Etomidate
☐ Midazolam
☐ Ketamine
☐ Sevoflurane
☐ Other volatile agent
☐ Other

Maintenance Agents
☐ None
☐ Sevoflurane
☐ Other volatile agent
☐ Nitrous oxide
☐ Propofol
☐ Other

Analgesics (any route)
☐ None
☐ Paracetamol
☐ Morphine
☐ Diamorphine
☐ Fentanyl
☐ Alfentanil
☐ Remifentanil
☐ Codeine
☐ Dihydrocodeine
☐ Oxycodone
☐ Methadone
☐ Tramadol
☐ Clonidine
☐ Parecoxib
☐ Ketorolac
☐ Diclofenac
☐ Ibuprofen
☐ Naproxen
☐ Other

Neuromuscular Blockers
☐ None
☐ Suxamethonium
☐ Atracurium
☐ Cisatracurium
☐ Mivacurium
☐ Rocuronium
☐ Vecuronium
☐ Pancuronium

Reversal Drugs
☐ None
☐ Neostigmine
☐ Sugammadex
☐ Other

Local Anaesthetics (any route)
☐ None
☐ Lidocaine
☐ Bupivacaine
☐ Levobupivacaine
☐ Ropivacaine
☐ Prilocaine
☐ Other

Was anaphylaxis (requiring urgent treatment) suspected during this case?
☐ Yes ☐ No

Antibiotics
☐ None
☐ Co-amoxiclav
☐ Flucloxacillin
☐ Tazocin
☐ Other penicillin
☐ Metronidazole
☐ Teicoplanin
☐ Gentamicin
☐ Vancomycin
☐ Cefuroxime
☐ Other Cephalosporin
☐ Other

IV Colloids/Blood Products
☐ None
☐ Gelatin or gelatin-containing
☐ Starch or starch-containing
☐ Albumin (any concentration)
☐ Red cells
☐ Platelets
☐ Fresh Frozen Plasma
☐ Specific coagulation factors
☐ Other

Anti-Emetics (any route)
☐ None
☐ Ondansetron
☐ Dexamethasone
☐ Cyclizine
☐ Prochlorperazine
☐ Metoclopramide
☐ Droperidol
☐ Other

Coagulation Drugs
☐ None
☐ Heparin (any)
☐ Tranexamic acid
☐ Aprotinin
☐ Protamine
☐ Vitamin K
☐ Other

Miscellaneous Exposure
☐ Patent blue dye
☐ Methylene blue dye
☐ Bone cement
☐ X-Ray contrast

Monitoring
☐ Depth of Anaesthesia
☐ Peripheral nerve stimulator
☐ Quantitative neuromuscular monitoring
☐ Cardiac output

Most Senior Anaesthetist Present
☐ Consultant
☐ Other career grade doctor
☐ ST4-7
☐ ST3/CT3
☐ CT2
☐ CT1
☐ Other (e.g. research fellow)
☐ Unknown

Appendix 2:

Calculation of Scaling Factor

Number of weeks in the year

It is not possible to multiply the weekly caseload by 52 due to bank holidays where activity will be reduced. Assuming activity on a bank holiday is similar to a weekend day the 'effective' number of weeks can be calculated. For 2016 the number of weeks used as a scaling factor to estimate annual activity was 50.6:

There were 366 days in 2016 (leap year), and 52.28 weeks (366/7 = 52.29).

Using the number of weekdays, a scaling a factor x, and y as the number of 'effective' weeks in 2016:

5/7 * x = 52.29 and 253/366 * x = y

Therefore x = 7 * 52.29/5 = y * 366/253

And y = (7 * 52.28 * 253) / (5 * 366) = 50.6

Multiplication factor

Number of returns in a week = number of returned forms *3.5

Number of returns in a year (2016) = returned forms * 3.5 * 50.6

Estimated annual caseload = (returned forms * 3.5 * 50.6) / (proportion of interpretable forms * proportion of hospitals responding * individual site capture rate).

Multiplication factor = (3.5 * 50.6) / (0.98 * 0.96 * 0.96) = 196.09