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**Perioperative drug and allergen exposure in United Kingdom practice in 2016. The 6th National Audit Project Allergen Survey.**

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## Perioperative drug and allergen exposure in United Kingdom practice in 2016. The 6th National Audit Project Allergen Survey.

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## Abstract

**Background.** Details of current UK drugs and allergen exposure were needed for interpretation of reports of perioperative anaphylaxis to the Sixth National Audit Project (NAP6).

**Methods.** We surveyed United Kingdom National Health Service hospitals for this purpose. We also surveyed anaesthetic activity, which is reported separately. Results are compared to a similar 2013 survey for NAP5 where relevant.

**Results.** 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 (GAs). Propofol was the dominant induction agent (90.4%) and used more often in Caesarean section than in NAP5. Nitrous oxide use has fallen 30% since NAP5. Neuromuscular blocking agents were used in 47.2% of GAs. Suxamethonium use has fallen. Use of reversal agents is overall unchanged, but sugammadex use increased 4-fold. Analgesics were used in 88% of cases: opioids 82.1%; paracetamol 56.1% and non-steroidal anti-inflammatory drugs 28.3%. Overall antibiotic use was 57.2% of cases and >3 million annual perioperative administrations: gentamicin 19.7%, co-amoxiclav 17.0% and cefuroxime 13.6% were prominent. In 25% of teicoplanin or vancomycin uses allergy history influenced drug choice. Local anaesthetics were used in 74.2% 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%. Blood products were used in ≈3% of cases, synthetic colloids in <2% (starch in only 1 in 600 cases), tranexamic acid in ≈6%. Chlorhexidine and iodine exposure were reported as 73.5% and 40.0% of cases and a latex-free environment in 21.2%. Exposure to bone cement, blue dyes and x-ray contrast were each reported in 2-3% of cases.

**Conclusions.** This extensive national survey of anaesthetic practice provides new insights into drug uses and allergen exposures in perioperative care. It is important for use as denominator in the main NAP6 analysis and the data provide significant insights into many aspects of perioperative practice.

## Keywords

audit; anaesthesia; allergen exposure; drugs

1  
2 The Royal College of Anaesthetists National Audit Projects (NAPs) study major complications of  
3 anaesthesia and concurrently review current practice and use the findings to improve patient care.  
4  
5 The Sixth National Audit Project of the Royal College of Anaesthetists (NAP6), is a large-scale  
6  
7 prospective service evaluation of perioperative anaphylaxis across the hospitals of the United  
8  
9 Kingdom. It has gathered comprehensive quantitative and qualitative information on these events,  
10  
11 enabling the anaesthetic and allergy/immunology communities to collaborate in order to make  
12  
13 recommendations for the improvement of the quality of patient care.<sup>1-3</sup>

14  
15 During the NAP6 project a one-year registry was established to collect reports on all suspected cases  
16  
17 of perioperative anaphylaxis in 2015-16. This provided a numerator, but in order to interpret the  
18  
19 results of the registry and to estimate the incidence of perioperative anaphylaxis overall and of its  
20  
21 causes (drugs/other substances), contemporary information about anaesthetic activity, drug use and  
22  
23 exposure to other relevant substances (such as antiseptics and dyes), was required. This data would  
24  
25 provide a denominator.

26  
27 In 2013, the NAP5 project reported a similar activity and drug survey,<sup>4</sup> providing information on  
28  
29 aspects of anaesthetic activity and some drug uses, but insufficient for the needs of NAP6. Published  
30  
31 Hospital Episode Statistics (HES)<sup>5</sup> show an increase in inpatient and day case procedures since 2013,  
32  
33 but do not give detailed information on anaesthetists' involvement. NHS Maternity Statistics show a  
34  
35 slight decrease in deliveries in NHS hospitals since 2013, of which 60% involved anaesthetic  
36  
37 intervention.<sup>6</sup> Such changes over time mean that figures collected for NAP5 may not necessarily be  
38  
39 applicable for NAP6. In addition, the NAP5 survey did not collect sufficient detailed information on  
40  
41 perioperative administration of drugs and other potential allergens. National data for hospital drug  
42  
43 usage is collected by IQVIA<sup>TM</sup> and recorded in the Hospital Pharmacy Audit Index (HPAI) database.<sup>7</sup>  
44  
45 This records all medication that is issued by pharmacies for use on wards, in operating theatres and  
46  
47 on patient discharge. It does not, however, record what is administered to the patient nor in what  
48  
49 context a certain drug is delivered, so does not provide information on actual perioperative drug use.

46 An 'Activity/Allergen survey' was therefore designed to collect such data and this is reported here.  
47  
48 During the survey, anaesthetic activity data and drug/allergen exposure data was collected. The  
49  
50 'Activity survey' is reported separately<sup>8</sup> and here we report results of the 'Allergen survey'

## 51 52 **Methods**

53  
54 The NAP6 project was defined as a service evaluation by the Health Regulatory Authority  
55  
56 therefore did not require National Research Ethics Service approval. All NHS hospitals, Trusts  
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2 and Boards in the UK believed to undertake surgery were invited to, and did, volunteer a local  
3 co-ordinator (LC) who supervised all aspects of the study at that location.  
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6  
7 Local co-ordinators (LCs) were approached at 356 NHS hospitals and organised data collection  
8 from every perioperative case involving care delivered by an anaesthetist for a period of 48-  
9 hours. This included all adult and paediatric cases requiring general, regional and local  
10 anaesthesia, as well as sedation if involving an anaesthetist. Obstetric cases included epidural  
11 pain relief in labour. Any cases where sedation or local anaesthesia was delivered by a non-  
12 anaesthetist were not included. Routine sedation in intensive care was excluded.  
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18 The majority of data collection took place between 13th and 31st October 2016, during which  
19 time there were no public holidays; seven sites collected data between January and June 2017  
20 for logistical reasons. Data were recorded using a paper proforma (Appendix 1) and each form  
21 was transferred, using optical character recognition, to electronic storage. Each hospital was  
22 randomised to record activity on two consecutive days of the week, with specialist hospitals  
23 (cardiac, neurology or paediatric centres) block-randomised separately to prevent skewed  
24 allocation. Patient characteristics, method of anaesthesia, anaesthetic staffing, induction  
25 location, type of monitoring and drugs/substances used, and the presence of any allergy history  
26 were reported for each case. Local co-ordinators were also asked to record a capture rate at  
27 their site to estimate the proportion of cases for which a completed case report form was  
28 submitted. Data regarding staffing, workload and anaesthetic activity are reported separately.<sup>8</sup>  
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37 Data were analysed using IBM SPSS Statistics for Windows, Version 23 (IBM Corp. Armonk, New  
38 York). An annual caseload was estimated by multiplying the number of cases by a scaling factor.  
39 This factor was calculated by converting the number of cases from two days to one week  
40 (scaling factor of 3.5), and from one week to one year (scaling factor of 50.6, the effective  
41 number of working weeks in 2016 (Appendix 2). This was then divided by the hospital response  
42 rate, the mean reported capture rate at individual sites and the proportion of interpretable  
43 forms, to account for cases that were not reported. Responses marked as 'unknown' and  
44 incomplete fields were combined and reported as 'unknown'.  
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51 Here we report data relevant to allergen exposure in the perioperative period and relating to  
52 anaesthetist practices in using certain drugs. Where relevant this data is compared to that from the  
53 2013 NAP5 study.<sup>4</sup>  
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## 57 **Results**

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2 Out of 356 sites approached, 342 took part in the survey submitting a total of 15 942 forms. Applying  
3 the calculated scaling factor, the estimated annual caseload was 3 126 067. The distribution of  
4 numbers of forms returned from each hospital are shown in Supplementary figure 1. Where relevant,  
5 illogical forms (e.g. patients reported to be awake when neuromuscular blocking agents (NMBAs)  
6 were used), were excluded but these represented <1.0% of any analysis.  
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11 The scaling factor was 196.09. Patient Characteristics are described in the accompanying paper.<sup>8</sup>  
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14 Intended conscious level was reported as general anaesthesia (GA) 76.6% (annual estimate 2 394  
15 847) sedation 8.2% (258 250 cases) and awake 14.2% (442 379 cases) (Supplementary table 1).  
16  
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### 18 **Anaesthetic Drug Use**

#### 19 **Previous Allergy History and Choice of Drugs**

20  
21 Choice of drugs was reported as influenced by previous allergy history in 1 351 cases (8.6% of 15 723  
22 responses); in 64% because of allergy to an antibiotic, 35% allergy to another drug and in 3% to both.  
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#### 25 **Number of Drugs Used per Procedure**

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27 The median number of drugs given in each procedure was 8, minimum 1 and maximum 20  
28 (Supplementary figure 2).  
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#### 31 **Induction Agents**

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33 In terms of allergen exposure: induction agents were used in 13 019 cases including all intended  
34 conscious levels: estimated annual caseload was 2 552 896 (Supplementary table 2).  
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37  
38 For cases performed with general anaesthesia 15% of returns indicated two induction agents with a  
39 volatile reported as an induction agent in 14.8% of cases and a combined volatile/IV induction in 9%:  
40 of those with volatile co-induction 51% were adults (Supplementary table 2). As some respondents  
41 had likely included both an intravenous and a volatile agent as an 'induction agent' to determine the  
42 primary induction agent we only analysed a subset of these cases where one agent was used.  
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46  
47 Considering only patients who received general anaesthesia induced with a single agent, or a single  
48 agent and midazolam, (n=10 969) the distribution of drugs used was propofol 90.4%, and thiopental  
49 1.6%, ketamine 0.7%, etomidate (0.3%), sevoflurane (6.2%) other volatile agents (0.1%). Midazolam  
50 was used as a sole agent in 0.1% of cases (predominantly urgent/emergency cases in ASA 4 - 5  
51 patients) and as a co-induction agent in 7.5%. These proportions did not vary significantly whether  
52 midazolam was included or not (Supplementary table 3). These results suggest a small reduction in  
53 use of thiopental (1.6% from 2.9%) and an equivalent increase in the use of propofol (90.4% from  
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2 88%) since 2013.<sup>4</sup>Cases involving a volatile agent alone for induction were predominantly children  
3 (86%).  
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7 Propofol was the most widely used induction agent in all groups: 57.7% in children (<16 yrs), 96.2% in  
8 adults and 89.7% in patients aged >65 yrs. Distribution of induction agents used by age is shown in  
9 Supplementary figure 3). Sixty four patients undergoing Caesarean section, received general  
10 anaesthesia; thiopental was used in 62.7% (97% in NAP5), propofol in 29.7%, midazolam and  
11 ketamine in 1.6% each. Etomidate and sevoflurane were not used (Supplementary figure 3).  
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### 14 **Maintenance Agents**

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16 Amongst general anaesthetics where a maintenance agent was used, as inhalational agents was used  
17 in 94.6%; sevoflurane in 69.9% (58.5% in NAP5), nitrous oxide in 17.1% and propofol in 8.7%. In 2.2%  
18 of cases, both a volatile agent and propofol were used as maintenance agents (Supplementary table  
19 4).  
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24 The drug exposure survey showed that 293 (14%) of paediatric cases were administered with  
25 sevoflurane only (both for induction and maintenance) with no other agents. Thus a large cohort of  
26 children had an extremely low risk technique as far as antigen exposure is concerned.  
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31 The use of maintenance agents by age and in Caesarean sections is illustrated in Supplementary  
32 figure 4; sevoflurane was the preferred maintenance agent across all age groups and indications.  
33 Induction and maintenance exclusively with sevoflurane was reported in 2.8% of general  
34 anaesthetics: 14.5% of paediatric and 0.4% of adult general anaesthetics. Sevoflurane was used  
35 during general anaesthesia for 90.6% Caesarean sections. Nitrous oxide was reported to be used in  
36 17.1% of cases, 30.1% in children and 60.9% during Caesarean section: a fall from 2013: 25% overall,  
37 45% in children and 71.4% in Caesarean section. Nitrous oxide was used most frequently during  
38 general anaesthesia in orthopaedics/trauma, general surgery and ENT, perhaps associated with the  
39 increased numbers of paediatric in these specialties.<sup>4</sup>  
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### 46 **Neuromuscular Blocking Agents (NMBAs)**

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48 NMBAs were reported to be used in 5760 (47.2%) cases receiving GA; estimated annual caseload  
49 1 129 478. Use of NMBAs and estimated annual caseload are detailed in Supplementary table 5.  
50 Of those receiving NMBAs, 88.8% received non-depolarising NMBAs only, 4% suxamethonium only  
51 and 7.2% both suxamethonium and a non-depolarising NMBA (Supplementary figure 5). Use of  
52 different NMBAs in all GA cases is illustrated in Figure 1. Atracurium (23.2%) and rocuronium (19.2%)  
53 were the agents most commonly used, followed by suxamethonium (5.3%), with cisatracurium,  
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2 mivacurium, vecuronium and pancuronium being used rarely. The distribution of NMBAs was not  
3 captured in the NAP5 survey.  
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7 (Figure 1 near here)  
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10 Within age groups, NMBAs were used in 23% of children, 49.6% of adults and 58.2% of elderly  
11 patients, and in almost all general anaesthetic Caesarean sections (98.4%); distribution shown in  
12 Figure 2 and Supplementary figure 6. These figures are stable since NAP5.  
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16 (Fig 2 near here)  
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19 In most specialties atracurium and rocuronium were used predominantly, with the main exceptions  
20 being cardiac surgery, obstetrics and psychiatry. In cardiac surgery, pancuronium and vecuronium  
21 were used, in 25.7% and 17.9% of cases, respectively. All psychiatry cases received suxamethonium  
22 and 1.3% also received atracurium. The distribution of NMBAs in obstetrics was suxamethonium  
23 72.5%, atracurium 35.2% and rocuronium 23.1%; 16.9% received only a non-depolarising NMBA.  
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29 Distribution of NMBA use by specialty and by clinical setting is shown in Supplementary figures 6-8.  
30 One notable finding is that in ICU, suxamethonium use was absent and rocuronium was used more  
31 often (>50%) than in any other location. Conversely in the emergency department, suxamethonium  
32 was widely used and rocuronium notably less often (supplementary Figure 9).  
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36  
37 When suxamethonium was used, propofol was the induction agent in 73.6% of cases and thiopental  
38 in 22.4%, with other agents used rarely. Supplementary figure 10 shows use of induction agents by  
39 NMBA. Use of suxamethonium and rocuronium by age and NCEPOD priority is depicted in  
40 Supplementary figure 11.  
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#### 44 **Reversal Drugs**

45 Reversal agents were used in 62.2% of patients undergoing a general anaesthetic with an NMBA. In  
46 cases involving a non-depolarising NMBA, reversal was used in 64.6% (68% in NAP5<sup>1</sup>). Neostigmine  
47 was used in 59.4% (91.9% of all reversed cases) and sugammadex in 5.9% (9.1% of reversed cases).  
48 Sugammadex is now used in almost four-fold more cases than seen in 2013 (2.2% of reversals).<sup>4</sup>  
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Supplementary table 6 details reversal agents used and estimated annual caseloads.

#### 54 **Analgesics**

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2 Analgesics were used in 88.2% of all cases (any intended conscious level); estimated annual caseload  
3 2 755 849. Opioids were used in 82.5% of all cases. Paracetamol was administered in 56.1% and a  
4 non-steroidal anti-inflammatory drug in 28.3% of cases.  
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8 Fentanyl was the most frequently used opioid, administered in 61% of cases, followed by morphine  
9 in 26.5% and remifentanyl in 8.7% of cases. Diclofenac was the most commonly used NSAID, followed  
10 by parecoxib and ibuprofen. Clonidine was administered in 0.9% of cases. Use of each analgesic drug  
11 is illustrated in Figure 3 and estimated annual caseload in Supplementary table 6.  
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16 (Fig 3 near here)  
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19 Opioids were used more frequently during general anaesthesia than in other cases. At least one  
20 opioid was used in 99.8% of general anaesthetics: fentanyl in 73.7%; morphine in 33.0%, remifentanyl  
21 in 10.7%. Paracetamol was used in 67.5%. The distribution of use of different analgesic drugs by  
22 intended conscious level is illustrated in Supplementary figure 12.  
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### 26 **Antibiotics**

27 Antibiotics were used in 57.2% of all cases, with an estimated annual caseload of 1 787 360.  
28 Gentamicin (19.7%), co-amoxiclav (17.0%) and cefuroxime (13.6%) were the three most commonly  
29 used antibiotics (Figure 4), with estimated annual caseloads of around a half a million for the former  
30 two and approximately 400,000 for the latter. Supplementary table 8 details antibiotics used and  
31 estimated annual caseloads.  
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37 (Fig 4 near here)  
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40 In a quarter of cases where teicoplanin or vancomycin were used (287/1120 and 23/90 cases,  
41 respectively), their choice was reported to be influenced by past allergy history to an antibiotic  
42 (Supplementary figure 13).  
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46 The greatest proportion of all antibiotics use by surgical specialty was in orthopaedics/trauma,  
47 accounting for 23.1%, followed by general surgery (14.4%), obstetrics (9.2%), urology (8.9%) and  
48 gynaecology (6.5%; Figure 5). The proportion of cases administered antibiotics by specialty was, in  
49 descending order cardiac surgery 97.2%; neurosurgery 89.4%; urology 81.7%; thoracic surgery 80.9%;  
50 orthopaedics/trauma 69.9% and general surgery 60.3% (Figure 5).  
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4 Co-amoxiclav was commonly used across most specialties. In ophthalmology, cefuroxime was the  
5 most common antibiotic used. In cardiac surgery and cardiology, the dominant antibiotic was  
6 gentamicin, with flucloxacillin, cefuroxime and teicoplanin also being frequently used (Figure 6). Use  
7 of antibiotics in orthopaedics/trauma was almost evenly spread between gentamicin (32.7% of all  
8 orthopaedics/trauma procedures), teicoplanin (21.3%), flucloxacillin (18.2%) and cefuroxime (17.9%,  
9 Figure 6).

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15 (Fig 6 near here)

### 16 17 18 **Co-amoxiclav**

19 Co-amoxiclav was the most commonly used antibiotic: 21.6% of all antibiotic uses. It was regularly  
20 used in general surgery (27.5% of all cases receiving this drug), gynaecology (15.4%) and obstetrics  
21 (13.6%). Choice of co-amoxiclav was not influenced by past allergy history (94.2%).

### 22 23 24 **Teicoplanin**

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

### 29 30 31 32 **Local Anaesthetics**

33 Local anaesthetics (LA) administered by any route, were used in 74.2% of all cases and in 68.9% of all  
34 general anaesthetics. The proportion of LA drug use was bupivacaine 33.3%; lidocaine 32.0%;  
35 levobupivacaine 25.6%; ropivacaine, prilocaine and other LAs each <3% each. Supplementary table 9  
36 details LA use and estimated annual caseloads. Use of LAs by conscious level is detailed in Figure 7.

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44 (Fig 7 near here)

### 45 46 **Anti-emetics**

47 Anti-emetics were used in 73.1% of all cases: ondansetron in 65.6% of all cases; dexamethasone in  
48 48.5%; cyclizine in 5.7%; all other anti-emetics <2% (Supplementary table 10 for details of anti-emetic  
49 use and estimated annual caseloads). During general anaesthesia, antiemetic use was higher:  
50 ondansetron 78.3% of cases and dexamethasone 60.4%. Ondansetron and dexamethasone were  
51 used in combination in 53.1% of all GA cases.

### 52 53 54 55 **IV Colloids and Blood Products**

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2 Intravenous colloids and/or blood products were used in 4.2% of all cases. Gelatin-containing  
3 products (1.7% of all cases) and red blood cells (1.5%) were the most frequently used products).  
4 Starch or starch-containing products (0.2% of all cases), albumin (0.1%), platelets (0.4%), fresh frozen  
5 plasma (0.5%) and specific coagulation factors (0.2%), were used uncommonly. Supplementary table  
6 11 details use of IV colloids and blood products and estimated annual caseloads. The surgical  
7 specialties that used the greatest proportion of IV colloids or blood products were orthopaedics/  
8 trauma, general surgery, cardiac surgery and obstetrics (1.0%, 0.8% and 0.5% each, of all cases,  
9 respectively). The specialties that used IV colloids or blood products most frequently were cardiac  
10 surgery, other major operations and vascular surgery (56.6%, 16.7% and 13.6% of cases within each  
11 specialty, respectively). Supplementary figure 14 details use of these substances by main procedure.  
12 There was no evidence that starch use was concentrated in a particular site or specialty.  
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### 20 ***Drugs Affecting Coagulation***

21 Drugs affecting coagulation were used in 8.3% of all cases. Tranexamic acid was the most common  
22 drug used (5.9% of all cases), followed by heparin (2.7%). Protamine, aprotinin, vitamin K and other  
23 coagulation drugs (not specified) were used in less than 1% of all cases. Supplementary table 12  
24 details use of drugs affecting coagulation and estimated annual caseloads. Use of these drugs was  
25 mostly concentrated in orthopaedics, cardiac and vascular surgery (52.2%, 25.4% and 10.9% of all  
26 cases where a coagulation drug was used, respectively). Tranexamic acid was administered in 71% of  
27 cardiac surgery and 19% of orthopaedic operations.  
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### 33 ***Antiseptics***

34 Use of antiseptics and estimated annual caseload is detailed in Supplementary tables 13 and 14.  
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### 37 ***Chlorhexidine***

38 Chlorhexidine exposure was reported in 73.5% of all cases, mostly via skin prep by the anaesthetist  
39 (51.6% of all cases, accounting for 70.2% of all chlorhexidine-exposed cases) and/or the surgeon  
40 (44.7% of all cases, 60.7% of chlorhexidine-exposed cases), with very few cases reported to be via  
41 urethral exposure (3.3% of all cases), coated/impregnated CVC, surgical irrigation, or other (0.6% of  
42 all cases each for the latter three routes). Exposure to this antiseptic was reported to be unknown in  
43 0.9% of all cases and 23.6% of cases were reported to have no exposure. Chlorhexidine exposure was  
44 reported in more than two thirds of cases for most surgical specialties (Supplementary figure 15).  
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### 50 ***Povidone-iodine***

51 Povidone-iodine exposure was reported in 40.0% of all cases, mostly via skin prep by the surgeon  
52 (36.7% of all cases, accounting for 91.7% of all povidone-iodine-exposed cases) or by the anaesthetist  
53 (6.6% of all cases, 16.4% of povidone-iodine-exposed cases), with minor contributions by surgical  
54 irrigation (0.9% of all cases) or other routes (1.0% of all cases). A total of 54.6% of cases were  
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2 reported to have no exposure. Povidone-iodine was used in less than half of cases for all surgical  
3 specialties except for ophthalmology, where its use was almost ubiquitous (95.6%), and  
4 neurosurgery, vascular, general surgery and plastics, where it was used in more than half of the cases  
5 (Supplementary figure 15).  
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### 8 9 **Latex**

10 More than two thirds of cases (69.7%) were reported to be exposed to latex, with the main route  
11 being latex gloves (64.3% of all cases, accounting for 92.1% of all latex-exposed cases). A latex-free  
12 environment was reported for 21.2% of all cases and latex exposure was unknown for 7.1%.

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14 Supplementary table 15 details latex exposure and estimated annual caseload. The specialty with  
15 highest rate of latex exposure was cardiac surgery (94.8% of cases) and the lowest was psychiatry  
16 (30.8%) (Supplementary figure 16).  
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### 20 21 **Miscellaneous Drugs / Substances**

22 Bone cement was used in 2.6% of all cases and in 11.8% of orthopaedics/trauma cases, with an  
23 annual caseload of 78,240.  
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27 Blue dyes were used in 2.8% of all cases: patent blue in 2% and methylene blue in 0.9%. Both patent  
28 blue and methylene blue dyes were mostly used in general surgery: 29.8% and 35.3% of all cases  
29 receiving these dyes, respectively.  
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33 X-ray contrast was used in 1.7% of all cases, mostly in urology, radiology and orthopaedics: 24.5%,  
34 22.3%, and 14.2% of all cases receiving X-ray contrast.  
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38 Supplementary table 16 details use of the above substances and estimated annual caseload.  
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### 41 42 **Discussion**

43 This survey represents the most recent, comprehensive snapshot of anaesthetic activity and drug use  
44 in the United Kingdom. It provides unique detailed insight into drug/substance exposure during  
45 anaesthetic activity in the perioperative period. In particular compared to the equivalent Activity  
46 survey performed in 2013.<sup>1</sup> it provides considerably greater detail on use of analgesics, antibiotics,  
47 local anaesthetics, anti-emetics, intravenous colloids and blood products, as well as providing more  
48 information on all drugs assessed in that survey, enabling an examination of trends in practice. This  
49 survey also provides information on reported exposure to other substances, such as latex, antiseptics  
50 (chlorhexidine and povidone-iodine), radiocontrast media, dyes and bone cement.  
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2 As not all drug use was studied in NAP5 we can only comment on changes in choice of induction and  
3 maintenance agents, NMBAs and their reversal agents. We observed a substantial increase in the use  
4 of propofol for induction of anaesthesia for Caesarean section and a reduction in the use of  
5 thiopental. NAP5 identified such surgery as particularly high risk for Accidental Awareness during  
6 General Anaesthesia (AAGA) and thiopental was highlighted as a particular contributor to that.<sup>9,10</sup> We  
7 also saw a reduction (by about a third) of use of nitrous oxide in all age groups. We are aware that  
8 nitrous oxide may have become less popular after the publication of the ENIGMA<sup>11</sup> study and some  
9 new hospital builds stopped including piped nitrous oxide to theatres. However the publication of  
10 ENIGMA-II has dispelled concerns about the safety of nitrous oxide, including in the elderly  
11 population.<sup>12</sup> A recent Canadian publication noted that ENIGMA had reduced use of nitrous oxide  
12 amongst anaesthesiologists, but that ENIGMA-II had not led to any recovery in usage.<sup>13</sup> Use of  
13 NMBAs has remained stable since the 2013 survey<sup>1</sup>, with almost half of patients undergoing general  
14 anaesthesia receiving NMBAs and with stable distribution across age groups. Regarding choice of  
15 NMBA, use of suxamethonium appears to have declined slightly, both overall (5.3% vs. 13% of cases  
16 in which an NMBA was used) and during Caesarean section (81% vs. 92%). Use of NMBA reversal  
17 agents has not increased overall but the proportion of uses of sugammadex has increased four-fold.  
18 With the drug soon to come off patent a further increase might be anticipated. Overall the static  
19 nature of NMBA use, the persistent under-use of reversal agents and the underwhelming use of  
20 neuromuscular monitoring reported in our accompanying paper<sup>8</sup> indicates no evidence of  
21 improvement in practice since increased vigilance in this area was recommended in NAP5<sup>9</sup> and  
22 described as mandatory in the AAGBI minimum standards for monitoring document in 2015.<sup>14</sup>

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37 This survey provides comprehensive and, to the best of our knowledge, previously unavailable data  
38 on the use of multiple drug classes including analgesics, antibiotics, local anaesthetics, anti-emetics,  
39 drugs affecting coagulation, intravenous colloids and blood products. These data will be useful  
40 primarily in acting as a denominator for the wider NAP6 project<sup>1,2</sup> but we believe these data also  
41 have other uses.  
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46 Our data show that analgesics are used in ≈90% of all procedures involving an anaesthetist and that  
47 opioids are used in virtually all general anaesthesia cases, a modest increase from NAP5 (92%). With  
48 increasing concerns about use of opioids for reasons of both immune function and dependence  
49 potential,<sup>15</sup> this knowledge and the distribution of drugs used is useful of itself and for tracking  
50 changes. In total an estimated 3.6 million opioid drugs were administered in 3.1 million procedures,  
51 with fentanyl and morphine the dominant drugs, and oxycodone (about which some commentators  
52 have particular concerns)<sup>16</sup> accounting for <2% of all opioid use and ranking as 5<sup>th</sup> most frequently  
53 used opioid.  
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4 The widespread use of local anaesthetics, which were administered in three quarters of all cases,  
5 and the distribution of drugs used indicates local and regional anaesthetic techniques were used in  
6 three quarters of cases, and with the previous results of NAP5, which indicated neuraxial anaesthesia  
7 being used for ≈30% of cases, suggests most suitable cases are receiving neuraxial, peripheral nerve  
8 block or local anaesthesia infiltration, the first two of which are associated with improved patient  
9 reported satisfaction.<sup>17</sup> These data also provide numerator data – 2.3 million perioperative  
10 administration of local anaesthetics – which may be of value when measuring the safety impact of  
11 non-Luer connectors on avoidance of wrong route errors.<sup>18,19</sup>  
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18 We have documented the use of anti-emetics in approximately three quarters of all cases with  
19 dexamethasone now administered routinely (60%) during general anaesthesia. With concerns about  
20 the impact of dexamethasone on cancer recurrence<sup>20</sup> and the relatively modest impact of this drug  
21 on post-operative nausea and vomiting<sup>21</sup> this is also a notable finding.  
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26 Drugs affecting coagulation were used in ≈8% of all cases, with tranexamic acid used in ≈6% of all  
27 cases, in the majority of cardiac surgery cases and in one in five orthopaedics/trauma operations.  
28 This is likely a relatively new phenomenon, but with tranexamic acid now recommended to be  
29 offered to all patients undergoing surgery with anticipated blood loss >500 mls<sup>22</sup> our findings act  
30 both as a benchmark, but also suggest that this recommendation may not be being widely applied.  
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35 The use of IV colloids, is also of interest in relation both to blood product use (one administration in  
36 every 37 cases) and in the use of synthetic colloids (<2% of cases). Amongst the synthetic colloids the  
37 gelatins accounted for 90% of use, mostly during cardiac and vascular surgery. Starch-containing  
38 fluids are used in approximately 1 in 600 cases and while there was no particular pattern to their use  
39 (surgical specialty, patient age, ASA) it did include emergency cases and patients of ASA 3-4. The 26  
40 administrations of starch-containing fluids were reported from only 17 locations suggesting perhaps  
41 the use is clustered in certain hospitals. The use of starch containing fluid remains highly  
42 controversial and the European Medicines Agency recently recommended their suspension from  
43 sale.<sup>23</sup> Based on our data this will have little impact on UK anaesthetic practice.  
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51 Amidst the current threat of increasing antibiotic resistance,<sup>24,25</sup> our data provide detailed  
52 information on antibiotic usage, which was reported for over half of the procedures and accounted  
53 for almost 2 million administrations annually. Gentamicin, co-amoxiclav and cefuroxime being the  
54 most commonly used drugs – each used for approximately 500,000 uses. Orthopaedics/trauma and  
55 general surgery are the main specialties using antibiotics, but cardiac and neurosurgery, urology and  
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2 thoracic surgery are the specialties with the greatest proportion of cases receiving an antibiotic. The  
3 wide distribution of antibiotics used within specialties might perhaps hint at a lack of consistent  
4 application of best practice, but this would require further investigation.  
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8 The choice of drugs administered was reported to be influenced by allergy history in almost 10% of  
9 cases and a history of antibiotic allergy influenced choice of teicoplanin or vancomycin in over a  
10 quarter of cases when either of these antibiotics were used. We did not collect information on the  
11 specific antibiotic(s) that patients reported allergy to, but it is likely that a history of penicillin allergy  
12 was dominant, as these drugs are common substitutes for penicillins and penicillin allergy is reported  
13 in up to 10% of the general population and 20% of in patients.<sup>26-28</sup> Importantly more than 90% of  
14 patients with a history of penicillin allergy are deemed not allergic when investigated via skin and  
15 drug provocation tests.<sup>29</sup> The NAP6 baseline survey on anaesthetists' perspectives and experiences of  
16 perioperative anaphylaxis reported that penicillins were the drugs anaesthetists were most  
17 concerned about and avoided most often. Notably teicoplanin, although prominent among  
18 suspected causative agents, was not frequently avoided.<sup>30</sup> There is emerging evidence of teicoplanin  
19 as an important trigger of anaphylaxis events<sup>31</sup> and it accounted for 28% of antibiotic-related  
20 anaphylaxis in one series.<sup>8</sup> A growing body of evidence has shown that use of second-line (often  
21 more expensive) antibiotics has significant public health implications and increased healthcare costs  
22 with increased duration of treatment and hospital stay, and leads to higher rates of antibiotic  
23 resistance and infections including methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium*  
24 *difficile* (C. diff) and vancomycin-resistant enterococcus (VRE).<sup>32-34</sup> Our data provide additional  
25 evidence of use of second-line antibiotics, namely teicoplanin, driven by drug allergy history, adding  
26 further strength to calls from the international allergy community for robust programmes to tackle  
27 inaccurate labels of antibiotic allergy, improving antibiotic stewardship.<sup>32-35</sup>  
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41 Chlorhexidine is a widely used antiseptic<sup>36</sup> that has been increasingly reported as an emerging cause  
42 of allergy and perioperative anaphylaxis in particular,<sup>37-42</sup> although its use still appears to be under-  
43 recognised in the healthcare and especially in the perioperative setting and its potential to cause  
44 allergic reactions under-estimated by healthcare professionals.<sup>43-45</sup> Despite its known ubiquitous use  
45 in the hospital, following infection prevention guidelines, our data evidenced reported chlorhexidine  
46 exposure in only ≈75% of all cases, mostly via skin prep by the anaesthetist and/or the surgeon. Very  
47 few cases of exposure were reported via urethral exposure and coated/impregnated central venous  
48 catheters (CVCs). National guidelines such as NICE CG74<sup>46</sup>, recommend use of chlorhexidine to  
49 prevent surgical site infections and many local hospital guidelines advocate the use of chlorhexidine  
50 prior to venous cannulation. We suspect our data likely reflects under-reporting due to under-  
51 recognition of chlorhexidine exposure, for example due to lack of awareness of chlorhexidine being  
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2 present in many antiseptic alcohol wipes, urethral lubricants and CVCs. Conversely, it was  
3  
4 unsurprising to find that povidone-iodine is used in ≈two fifths of cases and mostly via skin prep by  
5  
6 the surgeon.  
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8 Finally, our survey data suggest a latex-free environment was in place for only one fifth of cases.  
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11 This survey adopted similar methodology to that used for the NAP5 activity survey.<sup>4</sup> Discussion and  
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13 details on the methodology used, in particular, the duration of the census over two days instead of a  
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15 longer sampling time, the randomisation of specialist hospitals, and extrapolation of sample data to  
16  
17 estimate the annual workload is already considered in the relevant paper.<sup>8</sup> As also noted then, the  
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19 large size of our sample data set means we can be confident that we have a true representation of  
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21 the overall anaesthetic activity and allergen exposure in the UK and that it is reasonable to scale-up  
22  
23 the 2-day sample data to estimate the annual data. However, where the sample size is small,  
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25 variations in data captured or missed would have proportionately larger impacts on annual  
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27 estimates, so these data should be treated more circumspectly.

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29 This survey suggests an annual caseload of 3 126 067, which is a 15% reduction compared to that  
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31 reported in NAP5 (3 685 800). We are not aware of any comparable data against which to  
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33 benchmark. Of note, the NAP6 annual estimate of Caesarean section caseload (171 579) is within  
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35 <2% of that reported in NHS maternity data (174 720).<sup>47</sup> We attempted to control for limitations in  
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37 data collection by incorporating an estimated capture rate per hospital, accounting for  
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39 uninterpretable forms, and calculating a scaling factor to include bank holidays. There are many  
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41 factors that may have contributed to a fall in activity between 2013 and 2016, and these are  
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43 discussed in the accompanying paper.<sup>8</sup> However, the possibility also exists that we have missed a  
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45 proportion of cases. If this is the case, we would have underestimated caseload, drug and allergen  
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47 exposure, and activity by up to 15%. However, it would not impact on relative proportions and  
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49 patterns of use/exposure within the dataset.  
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52 Overall this extensive national survey of anaesthetic practice in the United Kingdom provides new  
53  
54 insights into drug uses and allergen exposures in UK perioperative care. It is important for use as  
55  
56 denominator in the main NAP6 analysis, and the data provide significant insights into many aspects  
57  
58 of perioperative practice.  
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**Declaration of interest**

1  
2 TMC: is an associate editor of the British Journal of Anaesthesia. He is not aware of any financial  
3 conflicts.  
4

5 SM, HK, NH LF, SF, DNL, TG, KFI, HT, MT, AW JH, KFe, WE, SN, SK, K-LK, NMcG and MB all declare they  
6 have no conflicts of interest.  
7  
8  
9

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12  
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15

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25 and Harefield NHS Foundation Trust, London. Dr Thirumala Krishna, Consultant Immunologist, Heart  
26 of England NHS Foundation Trust, Birmingham. Ms Ruth Collins, Staff Nurse, Hillsborough Private  
27 Clinic (The Association for Perioperative Practice), Ms Mandy East, Former National Coordinator of  
28 the Anaphylaxis Campaign (Anaphylaxis Campaign).  
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### 34 **Authors' contributions and authorship**

35  
36 SM - Contributed to design and methodology or the study. Analysed results. Wrote all drafts of the  
37 paper and the final draft.  
38

39 HK – Contributed to design and methodology or the study. Analysed results. Reviewed and revised  
40 early drafts of the paper and the final draft  
41

42 TC - Contributed to design and methodology or the study. Analysed results. Reviewed and revised  
43 early drafts of the paper and the final draft.  
44

45 NH - Contributed to design and methodology or the study. Analysed results. Reviewed and revised  
46 early drafts of the paper and the final draft.  
47  
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49 LF - Contributed to design and methodology or the study. Administered study. Took part in review of  
50 draft manuscript leading to finalisation.  
51

52 All other panel members contributed to the design and methodology of the study, reviewed the  
53 results and took part in review of draft manuscript leading to finalisation.  
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55

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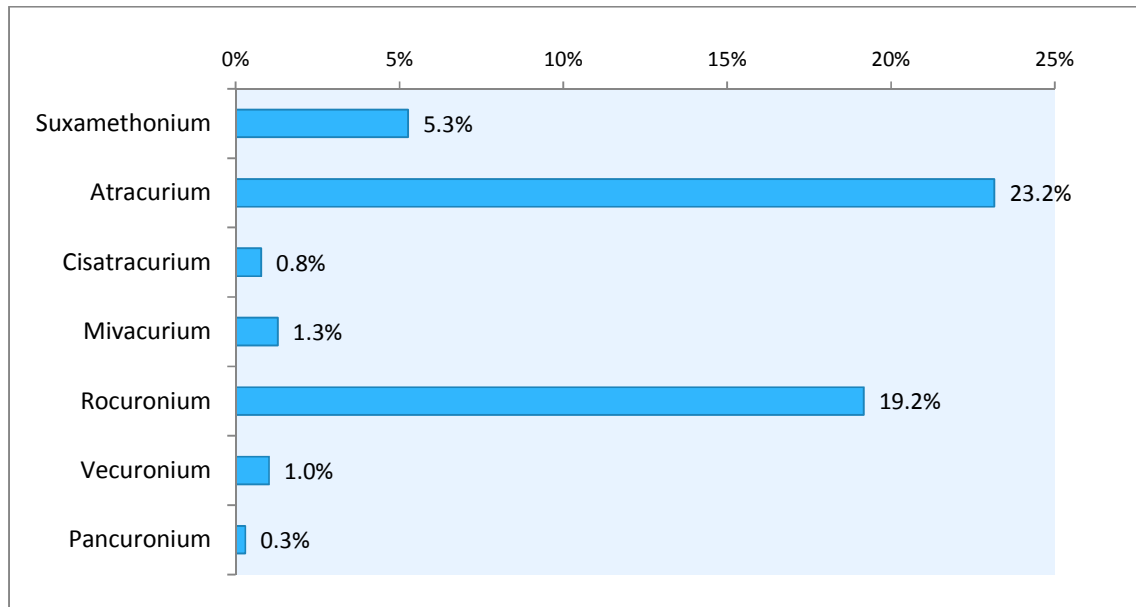
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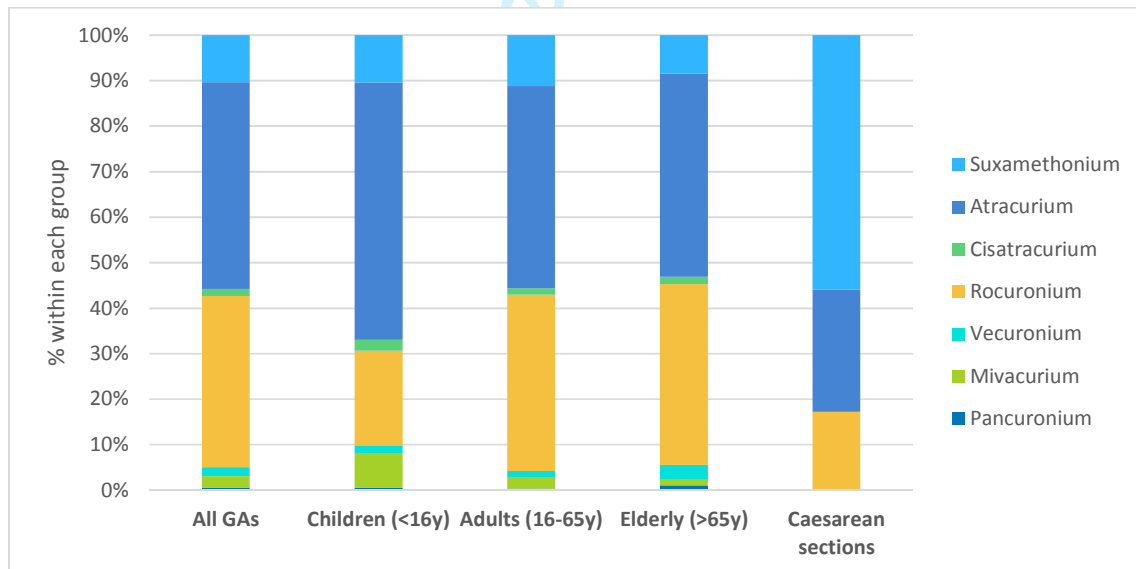
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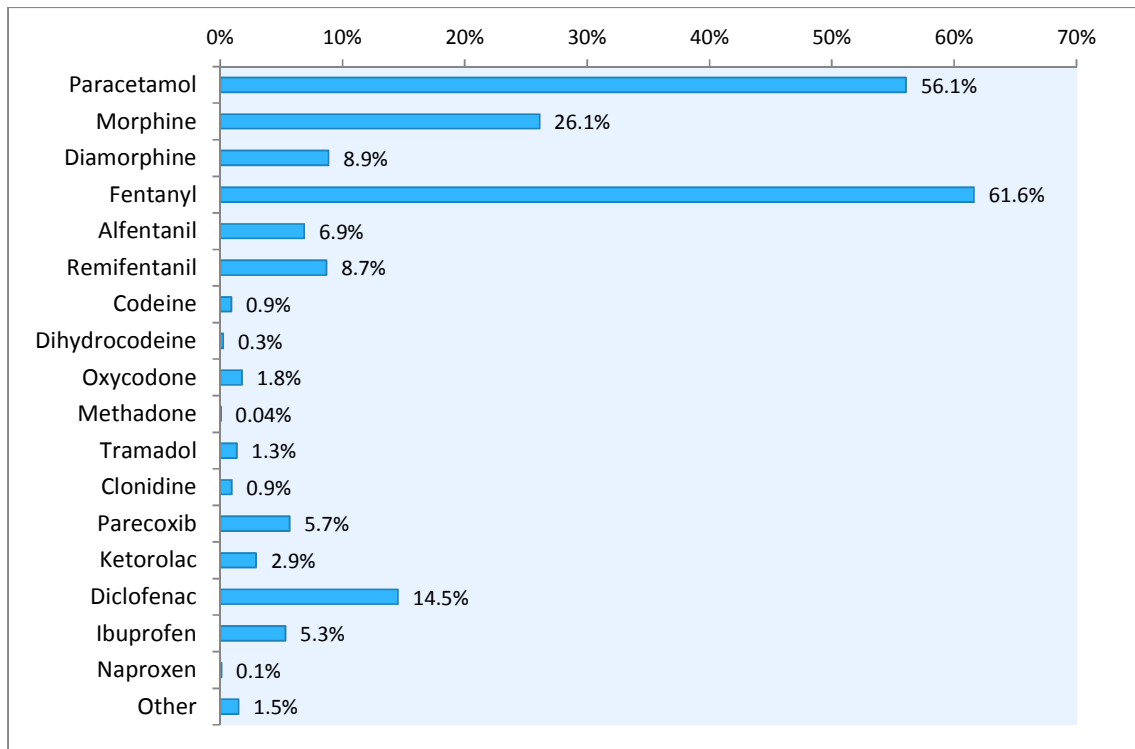
## Figures



**Figure 1 – Use of all NMBA during general anaesthesia (whether individually or multiples), as a proportion of all general anaesthetic cases, N=12,213.**

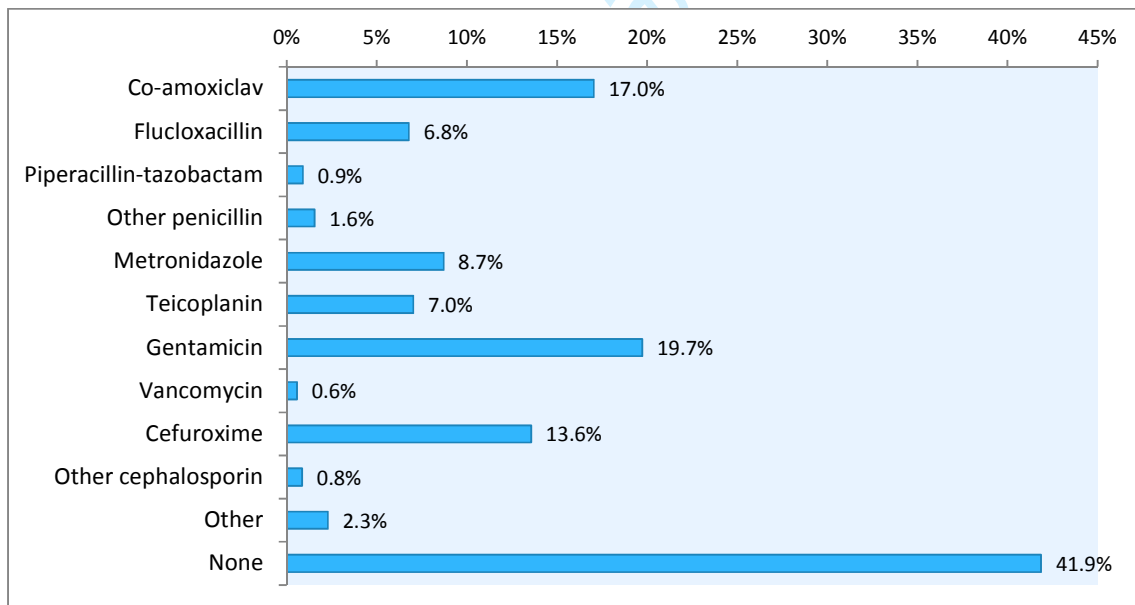


**Figure 2 - Use of NMBA by age group and in Caesarean sections**



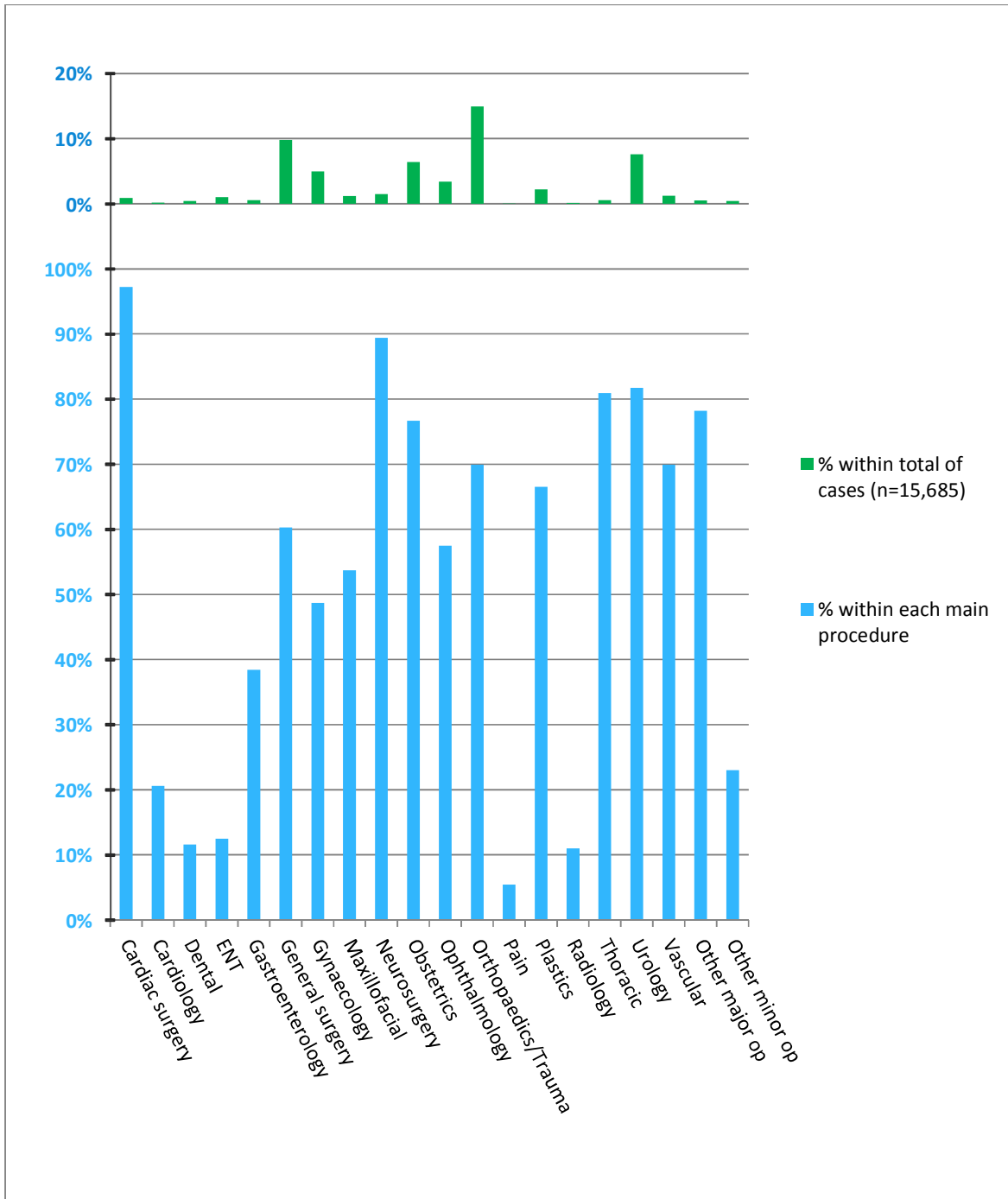
**Figure 3 – Use of analgesic agents in all cases**

This depicts use of each analgesic drug, whether in isolation or combined, n= 15,776.



**Figure 4 – Use of antibiotics in all procedures.**

This depicts use of each antibiotic, whether in isolation or combined, n= 15,790.



**Figure 5 - Antibiotic use by specialty.** Top panel indicates the proportion of all cases with antibiotics administered that fell in that surgical specialty. The lower panel indicates the proportion of cases in each surgical specialty receiving antibiotics.

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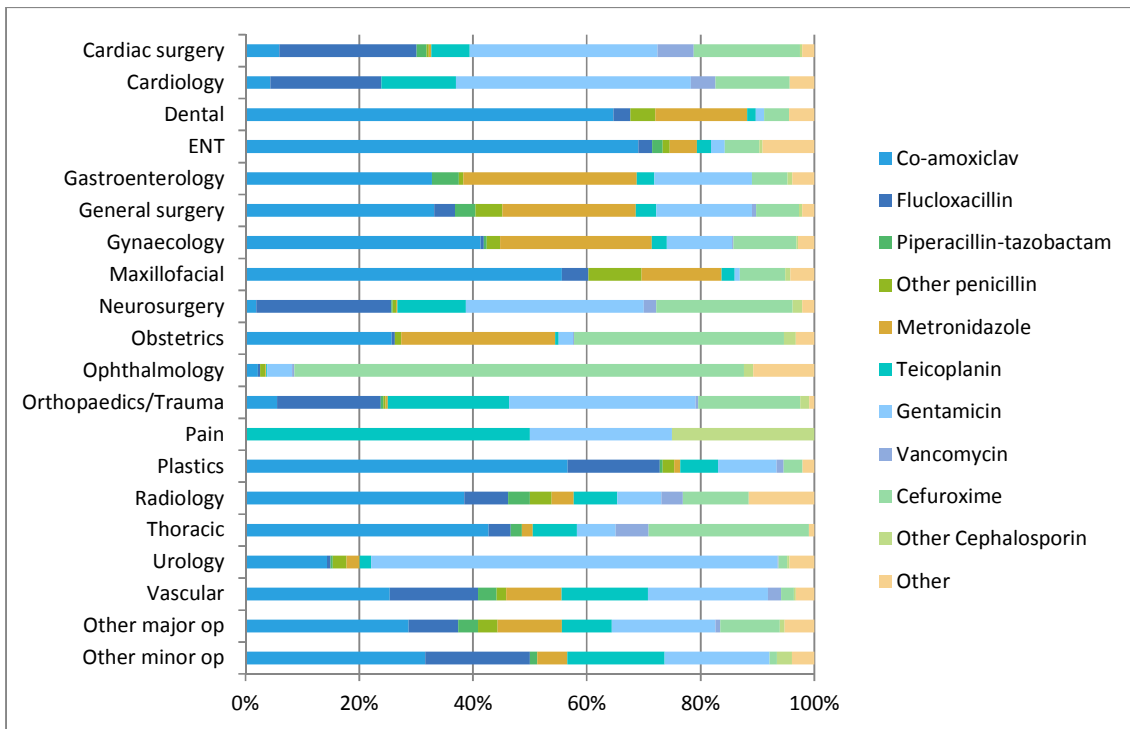


Figure 6 – Distribution of individual antibiotics use by specialty

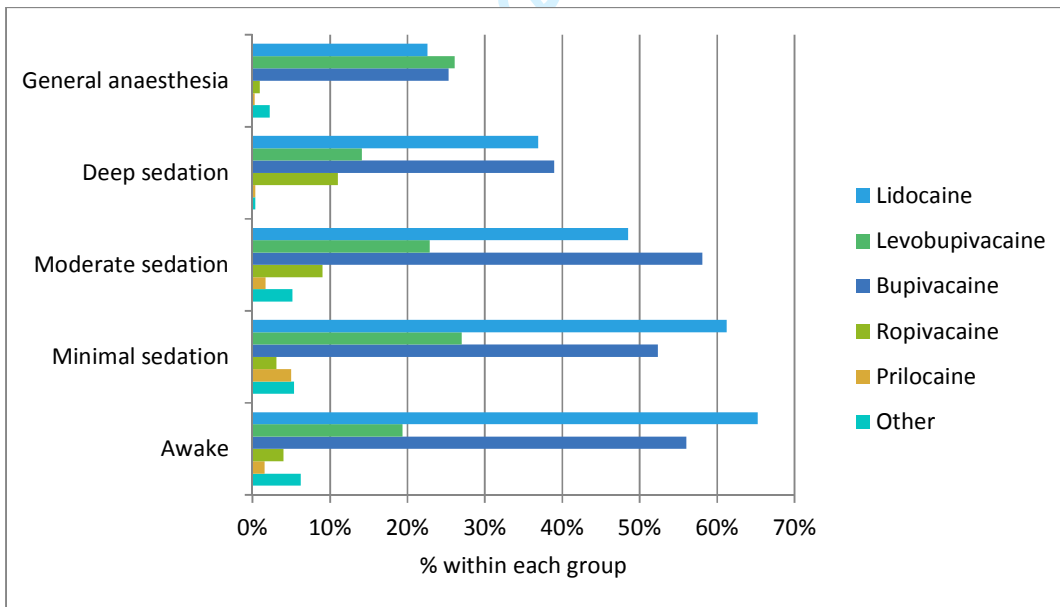


Figure 7 - Use of local anaesthetics by intended conscious level

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## Appendix 1. Survey questionnaire

## NAP6 Anaesthetic Activity/Allergen Exposure Survey

NAP6 Hospital Code: Date: 

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

<p><b>Day of the Week</b></p> <input type="checkbox"/> Mon <input type="checkbox"/> Tues <input type="checkbox"/> Wed <input type="checkbox"/> Thurs <input type="checkbox"/> Fri <input type="checkbox"/> Sat <input type="checkbox"/> Sun <p><b>Admission Type</b></p> <input type="checkbox"/> Elective Day Case <input type="checkbox"/> Elective Inpatient <input type="checkbox"/> Emergency <input type="checkbox"/> Other <input type="checkbox"/> Unknown <p><b>Main Procedure</b></p> <input type="checkbox"/> Cardiac surgery <input type="checkbox"/> Cardiology <input type="checkbox"/> Dental <input type="checkbox"/> Maxillo-facial <input type="checkbox"/> ENT <input type="checkbox"/> Gastroenterology <input type="checkbox"/> General surgery <input type="checkbox"/> Gynaecology <input type="checkbox"/> Neurosurgery <input type="checkbox"/> Obstetrics <input type="checkbox"/> Ophthalmology <input type="checkbox"/> Orthopaedics/Trauma <input type="checkbox"/> Pain <input type="checkbox"/> Plastics <input type="checkbox"/> Psychiatry <input type="checkbox"/> Radiology <input type="checkbox"/> Thoracic <input type="checkbox"/> Urology <input type="checkbox"/> Vascular <input type="checkbox"/> Other minor op <input type="checkbox"/> Other major op <p>Either</p> <p><b>NCEPOD Priority</b></p> <input type="checkbox"/> Immediate <input type="checkbox"/> Urgent <input type="checkbox"/> Expedited <input type="checkbox"/> Elective <input type="checkbox"/> Unknown <p>Or</p> <p><b>Caesarean Category</b></p> <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> Unknown <p><b>Age of Patient (yrs)</b></p> <input type="checkbox"/> <1 <input type="checkbox"/> 1-5 <input type="checkbox"/> 6-15 <input type="checkbox"/> 16-25 <input type="checkbox"/> 26-35 <input type="checkbox"/> 36-45 <input type="checkbox"/> 46-55 <input type="checkbox"/> 56-65 <input type="checkbox"/> 66-75 <input type="checkbox"/> 76-85 <input type="checkbox"/> >86 <input type="checkbox"/> Unknown <p><b>Sex of Patient</b></p> <input type="checkbox"/> Male <input type="checkbox"/> Female <input type="checkbox"/> Unknown <p><b>ASA Grade</b></p> <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5 <input type="checkbox"/> 6 <input type="checkbox"/> Unknown <p><b>Body Habitus (BMI)</b></p> <input type="checkbox"/> Underweight (<18.5) <input type="checkbox"/> Healthy weight (18.5-24.9) <input type="checkbox"/> Overweight (25-29.9) <input type="checkbox"/> Obese 1 (30-34.9) <input type="checkbox"/> Obese 2 (35-39.9) <input type="checkbox"/> Obese 3 (>40) <input type="checkbox"/> Unknown	<p><b>Ethnicity</b></p> <input type="checkbox"/> British (White) <input type="checkbox"/> Irish (White) <input type="checkbox"/> Any other White Background <input type="checkbox"/> White and Black Caribbean (Mixed) <input type="checkbox"/> White and Black African (Mixed) <input type="checkbox"/> White and Asian (Mixed) <input type="checkbox"/> Any other Mixed Background <input type="checkbox"/> Indian (Asian or Asian British) <input type="checkbox"/> Pakistani (Asian or Asian British) <input type="checkbox"/> Bangladeshi (Asian or Asian British) <input type="checkbox"/> Any Other Asian Background <input type="checkbox"/> Caribbean (Black or Black British) <input type="checkbox"/> African (Black or Black British) <input type="checkbox"/> Any other Black Background <input type="checkbox"/> Chinese (Other Ethnic Group) <input type="checkbox"/> Any Other Ethnic Group <input type="checkbox"/> Not Known <p><b>Premed Given on the Ward</b></p> <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Unknown <p><b>Induction Location</b></p> <input type="checkbox"/> Theatre anaesthetic room <input type="checkbox"/> Theatre <input type="checkbox"/> Radiology or Cath-lab <input type="checkbox"/> ICU <input type="checkbox"/> Emergency Department <input type="checkbox"/> Other <input type="checkbox"/> Unknown <p><b>Intended Conscious Level</b></p> <input type="checkbox"/> General anaesthesia <input type="checkbox"/> Deep sedation <input type="checkbox"/> Moderate sedation <input type="checkbox"/> Minimal sedation <input type="checkbox"/> Managed anaesthesia care <p><b>Was Your Choice of Drugs Influenced By Previous Allergy History?</b></p> <input type="checkbox"/> No <input type="checkbox"/> Yes - antibiotic <input type="checkbox"/> Yes - other <input type="checkbox"/> Unknown <p><b>Latex Exposure During This Case</b></p> <input type="checkbox"/> Yes (gloves) <input type="checkbox"/> Yes (other latex) <input type="checkbox"/> Latex-free environment <input type="checkbox"/> Unknown <p><b>Povidone Iodine Exposure During This Case</b></p> <input type="checkbox"/> Skin prep (anaesthetist) <input type="checkbox"/> Skin prep (surgeon) <input type="checkbox"/> Surgical irrigation <input type="checkbox"/> Other <input type="checkbox"/> None <input type="checkbox"/> Unknown <p><b>Chlorhexidine Exposure During This Case</b></p> <input type="checkbox"/> Coated/impregnated CVC <input type="checkbox"/> Urethral <input type="checkbox"/> Skin prep (anaesthetist) <input type="checkbox"/> Skin prep (surgeon) <input type="checkbox"/> Surgical irrigation <input type="checkbox"/> Other <input type="checkbox"/> None <input type="checkbox"/> Unknown	<p><b>Induction Agents</b></p> <input type="checkbox"/> Propofol <input type="checkbox"/> Thiopental <input type="checkbox"/> Etomidate <input type="checkbox"/> Midazolam <input type="checkbox"/> Ketamine <input type="checkbox"/> Sevoflurane <input type="checkbox"/> Other volatile agent <input type="checkbox"/> Not applicable <input type="checkbox"/> Other <input type="checkbox"/> Unknown <p><b>Maintenance Agents</b></p> <input type="checkbox"/> Volatile agent <input type="checkbox"/> Nitrous oxide <input type="checkbox"/> Propofol infusion (not TCI) <input type="checkbox"/> Propofol infusion (TCI) <input type="checkbox"/> Intermittent bolus Propofol <input type="checkbox"/> Other <input type="checkbox"/> Unknown <p><b>Analgesics (any route)</b></p> <input type="checkbox"/> None <input type="checkbox"/> Paracetamol <input type="checkbox"/> Morphine <input type="checkbox"/> Diamorphine <input type="checkbox"/> Fentanyl <input type="checkbox"/> Alfentanil <input type="checkbox"/> Remifentanil bolus(es) <input type="checkbox"/> Remifentanil infusion <input type="checkbox"/> Codeine <input type="checkbox"/> Dihydrocodeine <input type="checkbox"/> Oxycodone <input type="checkbox"/> Methadone <input type="checkbox"/> Tramadol <input type="checkbox"/> Parecoxib <input type="checkbox"/> Ketorolac <input type="checkbox"/> Diclofenac <input type="checkbox"/> Clonidine <input type="checkbox"/> Unknown <p><b>Neuromuscular Blockers</b></p> <input type="checkbox"/> None <input type="checkbox"/> Suxamethonium <input type="checkbox"/> Atracurium <input type="checkbox"/> Cisatracurium <input type="checkbox"/> Mivacurium <input type="checkbox"/> Rocuronium <input type="checkbox"/> Vecuronium <input type="checkbox"/> Pancuronium <input type="checkbox"/> Unknown <p><b>Reversal Drugs</b></p> <input type="checkbox"/> None <input type="checkbox"/> Neostigmine <input type="checkbox"/> Sugammadex <input type="checkbox"/> Unknown <p><b>Local Anaesthetics (any route)</b></p> <input type="checkbox"/> None <input type="checkbox"/> Lidocaine <input type="checkbox"/> Bupivacaine <input type="checkbox"/> Levobupivacaine <input type="checkbox"/> Ropivacaine <input type="checkbox"/> Prilocaine <input type="checkbox"/> Other <input type="checkbox"/> Unknown	<p><b>Antibiotics</b></p> <input type="checkbox"/> None <input type="checkbox"/> Co-amoxiclav <input type="checkbox"/> Flucloxacillin <input type="checkbox"/> Other penicillin <input type="checkbox"/> Teicoplanin <input type="checkbox"/> Gentamicin <input type="checkbox"/> Vancomycin <input type="checkbox"/> Cefuroxime <input type="checkbox"/> Ceftriaxone <input type="checkbox"/> Other Cephalosporin <input type="checkbox"/> Other <input type="checkbox"/> Unknown <p><b>IV Colloids/Blood Products</b></p> <input type="checkbox"/> Gelatin or gelatin-containing <input type="checkbox"/> Starch or starch-containing <input type="checkbox"/> Albumin <input type="checkbox"/> Red cells <input type="checkbox"/> Platelets <input type="checkbox"/> Fresh Frozen Plasma <input type="checkbox"/> Specific coagulation factors <input type="checkbox"/> Other <input type="checkbox"/> Unknown <p><b>Anti-Emetics</b></p> <input type="checkbox"/> None <input type="checkbox"/> Ondansetron <input type="checkbox"/> Dexamethasone <input type="checkbox"/> Cyclizine <input type="checkbox"/> Metoclopramide <input type="checkbox"/> Droperidol <input type="checkbox"/> Other <p><b>Coagulation Drugs</b></p> <input type="checkbox"/> Heparin (any) <input type="checkbox"/> Tranexamic acid <input type="checkbox"/> Aprotinin <input type="checkbox"/> Protamine <input type="checkbox"/> Other <p><b>Miscellaneous Exposure</b></p> <input type="checkbox"/> Patent blue dye <input type="checkbox"/> Methylene blue dye <input type="checkbox"/> X-Ray contrast <p><b>Monitoring</b></p> <input type="checkbox"/> Depth of Anaesthesia <input type="checkbox"/> Peripheral nerve stimulator <input type="checkbox"/> Quantitative neuromuscular monitoring <input type="checkbox"/> Cardiac output <p><b>Most Senior Anaesthetist Present</b></p> <input type="checkbox"/> Consultant <input type="checkbox"/> Other career grade doctor <input type="checkbox"/> ST4-7 <input type="checkbox"/> ST3/CT3 <input type="checkbox"/> CT2 <input type="checkbox"/> CT1 <input type="checkbox"/> Other (e.g. research fellow) <input type="checkbox"/> Unknown
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**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 50.74:

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

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

$$5/7 * x = 52.29 \text{ and } 253/366 * x = y$$

$$\text{Therefore } x = 7 * 52.29 / 5 = y * 366 / 253$$

$$\text{And } y = (7 * 52.28 * 253) / (5 * 366) = 50.6$$

**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 =  $(3.5 * 50.6) / (0.98 * 0.96 * 0.96) = 196.09$