

## Omitted doses as an unintended consequence of a hospital restricted antibacterial system: a retrospective observational study

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**Objectives:** The objective of this study was to determine the frequency of omitted doses of antibacterial agents and explore a number of risk factors, including the effect of a restricted antibacterial system.

**Methods:** Antibacterial data were extracted from a hospital electronic prescribing and medication administration system for the period 1 January to 30 April 2014. Percentage dose omission rates were calculated. Omission rates for the first dose of antibacterial courses were analysed using logistic regression to identify any correlation between first dose omission rates and potential risk factors, including the antibacterials' restriction status and whether or not they were ward stock.

**Results:** The study included 90 761 antibacterial doses. Of these, 6535 (7.2%) were documented as having been omitted; omission of 847 (0.9% of 90 761) was due to medication being unavailable. Non-restricted, ward stock antibacterials had the lowest frequency of omission, with 6.2% (271 of 4391) first doses omitted. The prevalence was 10.4% (27 of 260) for restricted, ward-stock antibacterials (OR=1.6, 95% CI=1.0–2.4,  $P=0.027$ ) and 15.5% (53 of 341) for non-restricted, non-ward stock antibacterials (OR=2.7, 95% CI=2.0–3.7,  $P<0.001$ ). Restricted, non-ward stock antibacterials had the highest frequency (30.7%, 71 of 231; OR=6.2, 95% CI=4.5–8.4,  $P<0.001$ ).

**Conclusions:** Antibacterials not stocked in clinical areas were significantly more likely to be omitted. The prevalence of omitted doses increased further if the antibiotic was also restricted. To achieve safe, effective antimicrobial use, a balance is needed between promoting antimicrobial stewardship and preventing unintended omitted doses.

### Introduction

It is widely recognized that many advances in modern medicine have been made possible by the availability of effective antibacterials. However, antibacterial resistance is a growing worldwide public health issue and a significant public health concern in the UK<sup>1</sup> and elsewhere.<sup>2</sup>

*Clostridium difficile*-associated diarrhoea is often associated with antibacterial prescribing and deemed largely avoidable;<sup>3–6</sup> it increases mortality and morbidity, hospital length of stay and healthcare costs.<sup>7,8</sup> It is imperative that available antibacterials are conserved and utilized in a way that treats infections effectively but at the same time reduces the risk of *C. difficile*-associated diarrhoea and antibacterial resistance. The term 'antimicrobial stewardship' captures these desired practices and outcomes.<sup>9</sup>

A Cochrane review of antimicrobial stewardship interventions to improve inpatient antibacterial prescribing practices concluded that restrictive interventions work faster than persuasive interventions in bringing about a change in antibacterial prescribing practice. However, the review goes on to suggest more reassurance is needed that restrictive interventions do not have unintended consequences.<sup>9</sup> The effect of such restriction systems on omitted antibacterial doses has not been studied. Omitted or delayed doses have the potential for patient harm<sup>10</sup> through (i) increased risk of treatment failure, thus hampering the goals of the Surviving Sepsis Campaign,<sup>11</sup> and (ii) selection for more resistant strains of bacteria.<sup>12</sup>

In response to escalating *C. difficile* rates, the study hospital introduced a more robust, restricted antibacterial system for adult inpatients in May 2013.

The objectives of the present study were to determine the frequency of omitted doses of antibacterial agents and to explore a number of risk factors for omitted doses. The primary risk factors of interest were whether antibacterials were classified as restricted and/or removed from ward stock; we also explored the time doses were scheduled to be administered, day of the week, route of administration and clinical specialty.

## Methods

### Setting

The study was conducted at a 650 bed teaching hospital in England. The hospital used a typical UK drug distribution system in which commonly used medications were kept in clinical areas as ward stock; non-stock medications were dispensed to individual patients from the pharmacy department. However, unlike most English hospitals,<sup>13</sup> an electronic prescribing and medication administration (EPMA; JAC Computer Services Ltd) system was in use in all inpatient areas except for the emergency department and critical care unit.

Following the introduction of the restriction policy in May 2013, individual antibacterial agents were classified by the antibacterial committee as either restricted or non-restricted. The restricted antibacterials were only to be prescribed for pre-authorized indications as listed in local antimicrobial guidelines, or following discussion with a consultant microbiologist. Such approval was evidenced by documentation of a unique alphanumeric code issued by the consultant microbiologist and documented on the medication order.

Restricted antibacterials that appeared in the antibacterial guidelines for common infections were stocked on wards where these infections were commonly treated.

### Data collection

Data on individual adult inpatient doses of prescribed antibacterials (as defined by British National Formulary 66 Section 5.1)<sup>14</sup> were extracted from the EPMA system relating to a 4 month period between 1 January and 30 April 2014. Paediatric wards, critical care and the emergency department were excluded. Data were extracted using a bespoke Crystal Report (Crystal Reporting Application; SAP England 2014) and exported to Excel (Microsoft Office 2010).

The following data were extracted for each prescribed dose: ward name; a unique patient identifier; drug name; form; strength; route of administration; scheduled date and time; administered date and time; administration status (administered or omitted); the reason given for any non-administration (as selected by the administering nurse from a drop-down menu); whether or not the dose was the first dose of that antibacterial course; whether or not the antibacterial prescribed was ward stock; and whether or not the antibacterial was categorized as restricted.

### Data analysis

Regularly prescribed and 'stat' (once only) doses were included in the analysis. Doses were removed from the dataset if an intentional dose omission was evident (Table 1). Doses documented as being omitted for the remaining reasons (Table 1) were assumed to represent doses intended to be given and therefore included in analysis.

The overall prevalence of omitted doses was calculated together with the prevalence of doses documented specifically as being omitted due to unavailability. Multivariable binary logistic regression analysis was performed using SPSS (version 21; IBM 2012) to explore the impact of potential risk factors on the likelihood of the first dose of each antibacterial course being omitted. To meet the independence assumption of logistic regression, for patients prescribed more than one course of antibacterials

**Table 1.** Reasons documented for the antibacterial doses omitted; percentages shown are percentages of intended doses that were documented as having been omitted due to the reason stated

Reason given for omitted dose	All antibacterial doses, n=90761
Administration unknown	1085 (1.2%)
Contra-indicated due to patient factors	1077 (1.2%)
Deferred administration	1 (<0.1%)
Drug awaiting medical review	1172 (1.3%)
Medication unavailable	847 (0.9%)
Other reason	608 (0.7%)
Patient asleep	77 (0.1%)
Patient declined dose	566 (0.6%)
Nil by mouth	226 (0.2%)
Route unavailable	679 (0.7%)
Allergy	6 (<0.1%)
Xxxx	191 (0.2%)
Total missed doses	6535 (7.2%)

The following reasons for an omitted dose were taken to be intentional and removed from the dataset: 'alternative route used'; 'alternative administered'; 'drug discontinued'; 'not charted prior to discharge'; 'order suspended'; 'patient absent'; 'patient on short-term leave'; 'transferred patient'; 'administration lapsed'; 'administration discontinued'; 'zero mg dose prescribed'; and 'not required in recovery'.

in the same patient episode we randomly selected one of these for analysis. We calculated ORs and their CIs for the risk of an omitted first dose. Our primary analysis focused on restriction and ward-stock status; as these were not independent of each other, each drug was classified as: (i) not restricted and ward stock; (ii) restricted and ward stock; (iii) non-ward stock and not restricted; or (iv) non-ward stock and restricted. The model included the following categorical independent variables: (i) or (ii) or (iii) or (iv); weekday or weekend; scheduled in or outside standard working hours; clinical specialty (medicine, surgery and theatres, obstetrics and gynaecology, or oncology); and route of administration (intravenous, oral or other). The dependent variable was first dose omitted versus not omitted.

Ethics approval was not required as this study was deemed a service evaluation; no patient-identifiable data were extracted.

## Results

Over the 4 month study period, 90761 antibacterial doses were extracted from the EPMA system and included in the analysis. Of these, 7.2% (6535 of 90761) were documented as having been omitted, and omission of 0.9% (847 of 90761) was due to medication being unavailable (Table 1).

Logistic regression analysis indicated that first doses of non-restricted, ward-stock antibacterials had the lowest risk of being omitted (271 of 4391 first doses; 6.2%; Table 2). The ORs for an omitted first dose in the other categories were 1.6 (95% CI=1.0–2.4,  $P=0.027$ ) for restricted, ward-stock antibacterials, 2.7 (95% CI=2.0–3.7,  $P<0.001$ ) for non-restricted, non-stock antibacterials and 6.2 (95% CI=4.5–8.4,  $P<0.001$ ) for restricted, non-ward-stock antibacterials. Day of the week, route of administration and clinical specialty were non-significant ( $P>0.05$ ) and removed from the model. Antibacterials scheduled to be

**Table 2.** Logistic regression model output and percentage of omitted doses due to any reason and the percentage of omitted doses due to medication unavailability in the sampled first dose data in the antibacterial groups

Antibacterial group	Number of intended first doses	Number of first doses omitted for any reason (% of intended doses)	Number of first doses omitted due to medication unavailability (% of intended doses)	OR, omitted doses for any reason (95% CI)	P value, doses omitted for any reason
All sampled first antibacterial doses	5223	423 (8.1)	102 (1.9)		
Not restricted and ward stock	4391	271 (6.2)	13 (0.3)	control	
Restricted and ward stock	260	27 (10.4)	6 (2.3)	1.6 (1.0–2.4)	0.027
Not restricted and not ward stock	341	53 (15.5)	30 (8.8)	2.7 (2.0–3.7)	<0.001
Restricted and not ward stock	231	71 (30.7)	53 (22.9)	6.2 (4.5–8.4)	<0.001
In standard working hours (0830–1700)	2577	149 (5.8)	27 (1.0)	control	
Outside standard working hours (1701–0829)	2646	273 (10.3)	73 (2.8)	1.7 (1.3–2.0)	<0.001

Logistic regression model:  $\chi^2=167.653$ , d.f.=4,  $P<0.001$ ; Cox and Snell  $R^2=0.032$ ; Nagelkerke  $R^2=0.074$ ; Hosmer and Lemeshow test,  $P>0.05$ . Interaction between ward stock/restriction status and in/outside standard working hours was not significant ( $P=0.315$ ) and the interaction was removed from the model.

administered within standard working hours had a lower frequency of omitted first doses (149 of 2577; 5.8%) compared with those scheduled outside standard working hours (273 of 2646; 10.3%) (OR=1.7, 95% CI=1.3–2.0,  $P<0.001$ ; Table 2).

The antibacterials more commonly associated with omitted doses due to medication unavailability were: nitrofurantoin tablets (100 of 847 doses documented as being omitted due to unavailability), which were not restricted but not widely stocked in ward areas; and ciprofloxacin (84 of 847) and levofloxacin tablets (44 of 847), both of which were restricted and not widely stocked in ward areas.

## Discussion

### Key findings

Of 90761 antibacterial doses prescribed for adult inpatients, 6535 (7.2%) were omitted. We found that 0.9% of all doses were documented as having been omitted due to medication unavailability, a potentially avoidable reason and therefore a particular cause for concern. We found that the non-stock antibacterials were significantly more likely to be omitted than those that were ward stock. If those non-stock antibacterials were also restricted the risk of an omitted dose increased further. Being restricted also increased the risk of omission for ward-stock antibacterials, which may be because stock holding is intentionally low to prompt pharmacy review before further supplies are made. These data suggest that a restricted antibacterial system may have an unintended negative consequence in contributing to dose omissions. Antibacterial doses scheduled outside normal standard working hours were also more likely to be omitted than those scheduled during standard working hours.

### Interpretation and implications

If we removed the restriction system and ensured all antibacterials were adequately stocked in ward areas, then we could

expect the frequency of omitted first doses to reduce from the current rate of 8.1% to 6.2% of intended first doses. Likewise, doses documented as being omitted due to medication being unavailable might be expected to decrease from 1.9% of first doses to 0.3%.

We have also identified antibacterials commonly associated with omitted doses. Modifications to ward-stock holdings can now be considered to reduce the risks associated with omitted doses while retaining the benefits of a restricted system.

### Comparison with previous literature

This study confirms previous research into the frequency and reasons for omitted antibacterial doses. Carruthers *et al.*<sup>15</sup> set out to determine a minimal acceptable range for omitted antibacterial doses and suggested an acceptable level to be ~5% of the total number of intended doses. In their 1 year study of 1 157 576 antibacterial doses prescribed using EPMA, the frequency of missed doses ranged from 5.90% to 10.26% across three UK hospital organizations. The frequency of missed doses due to medication being unavailable ranged from 0.64% to 0.98% across the three organizations. Our study identified similar findings of 7.2% of all doses omitted, with 0.9% omitted due to unavailability.

### Strengths and limitations

We were able to analyse a large sample across a whole organization, drawing on one of the benefits of EPMA in allowing large datasets for secondary analysis. With the exception of Carruthers *et al.*,<sup>15</sup> previous studies of medication omissions have been based on either point prevalence methods<sup>16</sup> or direct observation of medication administration,<sup>17</sup> both of which are more labour intensive and thus provide smaller sample sizes.<sup>18</sup> Both the Hawthorne effect and observer bias are further potential limitations of direct observation, a limitation avoided through analysing electronic datasets.

Although the EPMA system in the study hospital mandated a reason to be documented for any omitted dose, there were limitations in this regard. First, there were two options for recording reasons for omitted doses that resulted in incomplete data: 'xxxx' and 'administration unknown'. Of the 90 761 intended antibacterial doses, 1.2% were documented as 'administration unknown' and a further 0.2% as 'xxxx'. These limitations may conceal the true nature of omitted doses. Second, the reasons selected from the drop-down menu may not accurately reflect the actual reason for the omitted dose.

The study was observational and can therefore identify correlations but not causality. The EPMA system was not fully deployed in the study hospital prior to the implementation of the restricted antibacterial system. We were therefore unable to obtain omitted dose data prior to the introduction of the restricted antibacterial system for comparison. A further limitation was the exclusion of Critical Care and the Emergency Department, where patients may be more likely to be affected by omitted doses, as well as the paediatric wards.

### Implications for future research

Kumar et al.<sup>19</sup> previously studied the consequences of delayed antibacterial doses in patients with septic shock and found it to have a negative impact on survival in these patients. Our study does not distinguish between those patients with septic shock and those with less severe infections. We do not know whether any doses omitted as a consequence of the restricted policy increased morbidity or mortality and further work is needed to determine whether restricted policies have any detrimental effect on patient outcomes.

One of the aims of the restricted policy studied was to reduce rates of *C. difficile*-associated diarrhoea. Rates of *C. difficile*-associated diarrhoea at the study hospital are at their lowest levels since mandatory recording began in 2007 but the reasons for this may be multifactorial and not due solely to the restricted policy. The effect of the studied restricted policy on resistance of key bacteria to key antibacterials has not been determined.

### Conclusions

Doses of non-stock antibacterials were more likely to be omitted than those that were stock; stock status was the single most important risk factor for an omitted first dose. The likelihood of an omitted dose was increased further if the antibacterial was restricted. Doses scheduled at a time outside standard working hours were more likely to be omitted when compared with doses scheduled within standard working hours. This study demonstrates the potential for restricted antibacterial policies to increase the prevalence of omitted antibacterial doses. When developing a restriction system, a balance is needed in terms of facilitating antimicrobial stewardship versus ensuring patients receive the doses needed.

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### Transparency declarations

None to declare.

### Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, the Department of Health or Public Health England.

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