Extensive antibiotic prescription rate among hospitalized patients in Uganda: but with frequent missed-dose days

Ronald Kiguba1*, Charles Karamagi2 and Sheila M. Bird3

1Department of Pharmacology and Therapeutics, Makerere University College of Health Sciences, Kampala, Uganda; 2Clinical Epidemiology Unit, Makerere University College of Health Sciences, Kampala, Uganda; 3Medical Research Council Biostatistics Unit, Cambridge, UK

*Corresponding author. E-mail: kiguba@gmail.com

Received 3 October 2015; returned 25 November 2015; revised 5 January 2016; accepted 20 January 2016

Objectives: To describe the patterns of systemic antibiotic use and missed-dose days and detail the prescription, dispensing and administration of frequently used hospital-initiated antibiotics among Ugandan inpatients.

Methods: This was a prospective cohort of consented adult inpatients admitted on the medical and gynaecological wards of the 1790 bed Mulago National Referral Hospital.

Results: Overall, 79% (603/762; 95% CI: 76%–82%) of inpatients received at least one antibiotic during hospitalization while 39% (300/762; 95% CI: 36%–43%) had used at least one antibiotic in the 4 weeks pre-admission; 1985 antibiotic DDDs, half administered parenterally, were consumed in 3744 inpatient-days. Two-fifths of inpatients who received at least one of the five frequently used hospital-initiated antibiotics (ceftriaxone, metronidazole, ciprofloxacin, amoxicillin and azithromycin) missed at least one antibiotic dose-day (44%, 243/558). The per-day risk of missed antibiotic administration was greatest on day 1: ceftriaxone (36%, 143/398), metronidazole (27%, 67/245), ciprofloxacin (34%, 39/114) and all inpatients who missed at least one dose-day of prescribed amoxicillin and azithromycin. Most patients received fewer doses than were prescribed: ceftriaxone (74%, 273/371), ciprofloxacin (90%, 94/105) and metronidazole (97%, 222/230). Of prescribed doses, only 62% of ceftriaxone doses (1178/1895), 35% of ciprofloxacin doses (396/1130) and 27% of metronidazole doses (1043/3862) were administered. Seven percent (13/188) of patients on intravenous metronidazole and 6% (5/87) on intravenous ciprofloxacin switched to oral route.

Conclusions: High rates of antibiotic use both pre-admission and during hospitalization were observed, with low parenteral/oral switch of hospital-initiated antibiotics. Underadministration of prescribed antibiotics was common, especially on the day of prescription, risking loss of efficacy and antibiotic resistance.

Introduction

Worldwide use of antibiotics, pharmacologically classified as antibacterial agents, increased by 36% in healthcare in the first decade of the new millennium. Indiscriminate use may have contributed to this upward trend. Inappropriate prescribing, dispensing and administration of systemic antibiotics undermines their utility and cost-effectiveness and increases the risk of suspected adverse drug reactions (ADRs), including serious suspected ADRs and antibiotic resistance.

Resistance to single antibiotic agents may render entire antibiotic classes ineffective. Antibiotic resistance contributes to increased morbidity and mortality: the EU (population: 500 million) estimates up to 25 000 deaths annually and the USA (population: 319 million) estimates up to 23 000 deaths annually. Similar data are lacking in the developing world.

For almost three decades, hardly any new antibiotic classes have been discovered to combat resistance. Thus, healthcare professionals (HCPs) must preserve the effectiveness of currently available antibiotics through rational prescribing, dispensing, administration and monitoring of these medicines and by promoting their proper use by patients.

In sub-Saharan Africa, there is a paucity of published literature on the prescribing, dispensing and administration of systemic antibiotics to inpatients. Recent global estimates for antibiotic consumption did not include data from the East African region. Yet, if made available, such data could enhance future strategies...
for improving antibiotic use and combating resistance in resource-limited settings.\textsuperscript{13}

In Uganda, decisions by HCPs to prescribe systemic antibiotics to inpatients are often based on unconfirmed diagnosis. Evidence-based prescribing and dispensing of antibiotics should be the standard,\textsuperscript{14} but the lack of rapid diagnostic tools is a limitation.\textsuperscript{13} Little is known about the patterns of systemic antibiotic use by hospitalized Ugandan patients. It is not known e.g. whether hospitalized patients receive correct prescriptions of systemic antibiotics or whether patients complete full courses of prescribed antibiotics (e.g. if discharged prior to receipt of all prescribed parenteral doses).

We therefore describe the pattern of systemic antibiotic use by DDDs, antibiotic class, individual antibiotic, missed-dose days and parenteral/oral switch. We also provide an account of the prescription, dispensing and administration of frequently used hospital-initiated systemic antibiotics (ceftriaxone, metronidazole, ciprofloxacin, amoxicillin and azithromycin) among hospitalized Ugandan patients admitted on the medical and gynaecological wards of Mulago National Referral Hospital.

Methods

Study design and setting

We conducted a prospective cohort study among hospitalized patients, \( \geq 18 \) years of age, at the 1790 bed Mulago National Referral Hospital\textsuperscript{15} where the annual turnover exceeds 140000 inpatients. The study setting comprised three medical wards [Infectious Diseases and Gastrointestinal Illnesses (IDGI), Haematology, Neurology and Endocrinology (HNE) and Cardiovascular, Pulmonology and Nephrology (CPN)] and one Gynaecology (GYN) ward. Each of the four wards has an official bed capacity of 54, but can receive 70–80 admissions. Admissions on the medical wards average 10–15 patients per day in each of wards IDGI and CPN and 5–10 patients per day in the HNE ward, thus about 25–40 medical wards admissions per day; and 20–25 admissions per day on the GYN ward.

The process of medication ordering and administration is a handwritten system whereby doctors prescribe medicines and transcribe medication orders onto patients’ treatment/administration charts. Prescribed injectable antibiotics are dispensed to patients by ward pharmacists/pharmacy technicians in amounts that are sufficient for 1 or 2 days of treatment. Patients/caregivers are expected to refill prescriptions at ward pharmacies sufficiently early to avoid missed medication doses. Controlled dispensing, as described, is to avoid misuse of on-ward prescribed medicines. Key/essential medicines (e.g. injectable ceftriaxone) are stocked in small amounts by ward nurses for emergencies. If in stock, prescribed medicines are provided free of charge to patients; otherwise, patients have to purchase them from private community pharmacies. Nurses urge patients to take their prescribed oral or topical medication, but directly administer parenteral medicines and record this information (drug name, dose, route and time of administration) on patients’ hospital medication administration charts.

Data collection

During October to November 2013, a pilot phase was conducted on all four wards to assess the feasibility of undertaking the cohort study and to refine study instruments. The pilot data, however, are excluded from the final results presented in this paper. The main study commenced in December 2013 to April 2014, when research teams recruited and followed up patients on the study wards according to a systematic random sampling procedure whereby three new admissions per day on long-stay wards (HNE/CPN) and six per day on short-stay wards (IDGI/GYN) were to be recruited. Each ward team purpose to select at random one of the first two (IDGI), three (HNE) and four (CPN/GYN) new admissions and thereafter every second, third and fourth admission, respectively.

In practice, however, it was difficult to implement systematic random sampling because of the following reasons: (i) the sampling frames (ward registers) were not always reliable since registration of new patients into the study wards was not always done immediately on admission (hence, the registers were sometimes not up to date when the research teams needed to use them to identify and approach new study patients); (ii) selected registered patients were sometimes unavailable on their hospital beds at the time of recruitment; (iii) patients were too ill to cooperate; (iv) patients declined to give informed consent when research teams approached them; (v) ward admissions were irregular, ranging from zero to rather high admission rates that would upset systematic random sampling by the research teams; and (vi) routine minor and major ward rounds interrupted recruitment of new study patients since patient engagement was not permitted during ward rounds, which were sometimes rather lengthy. Given these limitations, we modified the sampling approach from just using the registers to also actively looking for newly admitted patients who, although admitted, were not yet recorded in the ward register(s). Delays in patient registration usually occurred immediately after weekends (on Mondays and Tuesdays) when patient admission rates frequently exceeded the capacity/work rate of the ward staff. However, the patients were typically registered within 24 h after admission.

Voluntary participation of patients was sought through provision of written informed consent. Consenting and recruiting a new patient took between 1 and 2 h, sometimes longer, while the daily mean time burden of patient contact with a research team was estimated at 10–30 min.

Research assistants were trained intensively for a 1 week period on the practical pharmacovigilance aspects of the project and thereafter R. K. conducted daily reviews of study procedures to ensure adherence to the study protocol (see the Supplementary Methods, available as Supplementary data at JAC Online).

Four research teams collected the data. Each team comprised a medical doctor (clinician), pharmacist and degree nurse. Ward-based physicians, all staff of Mulago National Referral Hospital (one physician based on the medical wards and another on the GYN ward), served as study physicians to resolve any clinical problems encountered by the data collection teams, while R. K. resolved pharmacological issues.

On recruitment (day 1), each research team conducted baseline assessment of the consented patients to obtain relevant data on demographics, clinical conditions and medications and thereafter conducted daily assessments until discharge, transfer, death or loss to follow-up. A 26 page case report form (CRF) was used to capture both baseline and daily follow-up patient information (see the Supplementary Methods for further details on data collection). For example, medication data were obtained from the patient’s hospital file (clinical notes, treatment sheets and drug administration charts), dispensing records of ward pharmacies, pill count validation of a patient’s oral medication (tablets, capsules) and by viewing of unused injectable medicine vials/ampoules in the possession of the patient/caregiver.

Research teams collected data daily from 8.00am to 6.00pm from Monday to Friday and from 10.00am to 6.00pm on weekends and public holidays.

Data management

Given the large amount of data collected, R. K. and S. M. B. adopted an efficient data entry design that accorded with planned statistical analyses. Key variables for initial capture were identified (demographics, relevant baseline data on medication history and clinical condition). Data for the 762 cases were manually abstracted by R. K. from the CRFs onto data abstraction forms. See the Supplementary Methods for further details on data management.
Antibiotic use among hospitalized patients in Uganda

Antibiotic classification
Using the WHO Anatomical Therapeutic Chemical (ATC) classification system,16 antibiotics are defined as antibacterial agents for systemic use (J01) and include dapsone (J04BA02) and oral nitroimidazole derivatives (P01AB). Dapsone was prescribed mainly for prophylaxis against opportunistic infections in HIV-positive patients who could not tolerate co-trimoxazole. Topical (ophthalmic, otic, dermatologic or vaginal) antibiotics and other antimycobacterial agents (ATC group J04) were excluded.

Statistical analysis
Patterns of antibiotic use
The proportion of patients who received any antibiotic prior to admission and/or during their hospital stay was computed before and after excluding: (i) co-trimoxazole use alone; or (ii) co-trimoxazole and dapsone use (both used for prophylaxis against HIV/AIDS-related opportunistic infections). For the former, we computed proportions of patients who were switched from the intravenous to the oral route of antibiotic administration and those who experienced prescription errors and missed antibiotic dose-days. We used the ATC/DDD index14 to convert administered doses (in grams or mega units) of each antibiotic and route of administration into DDDs (see Table S1). We standardized antibiotic use into DDDs per 1000 patient-days for each antibiotic and computed overall antibiotic use in DDDs per 1000 patient-days. Patient-days were calculated by summing the number of days of hospital stay contributed by each studied inpatient. For example, if a patient was admitted on 1 March 2014 and discharged on 3 March 2014, the patient would contribute three patient-days. We also computed antibiotic DDDs per 100 hospital admissions.

Identification of missed antibiotic dose-days
Some patients were prescribed an antibiotic that they did not receive. We account for them separately. For patients who were prescribed each of the five frequently administered hospital-initiated individual antibiotics (ceftriaxone, metronidazole, ciprofloxacin, amoxicillin and azithromycin) and received at least one dose, we determined the number of missed-dose days of the individual antibiotic(s) per patient, as detailed in Figure S1. Detailed analyses of co-trimoxazole prescription, dispensing and administration were excluded since most patients had commenced co-trimoxazole use several weeks, months or years pre-admission.

Ethics clearance
We obtained ethics approval for the study from the School of Medicine Research and Ethics Committee, Makerere University College of Health Sciences (REC REF no. 2011-113), the Mulago Hospital Research and Ethics Committee (MREC 253) and the Uganda National Council for Science and Technology (HS 1151).

Results
Study population
We studied 762 patients, 70% of whom were female (534/762; 95% CI: 67%–73%); all GYN ward patients (n = 191) and 60% otherwise (343/571; 95% CI: 56%–64%). Patients’ mean age was 34.8 years (SD = 14.8). Patients spent 3741 patient-days in hospital with median length of hospital stay of 4 (IQR: 3–6) days. Thirty percent of patients were known to be HIV positive (232/762) and 30% had been hospitalized in the previous 3 months (230/762) (see Table 1), including 32% (75/232) of known HIV-positive patients.

Extent of antibiotic use
Seventy-nine percent (603/762; 95% CI: 76%–82%) of hospitalized patients received at least one antibiotic during their hospital stay while 39% (300/762; 95% CI: 36%–43%) used at least one antibiotic in the 4 weeks pre-admission. Twenty-one percent of patients (162/762; 95% CI: 18%–24%) used co-trimoxazole during hospital stay, 159 of them known to be HIV positive, of whom 81% (131/162) had received co-trimoxazole during the month preceding hospitalization. Excluding this group, 75% (472/631; 95% CI: 71%–78%) of patients who reported that they did not use co-trimoxazole during the month preceding hospitalization received at least one antibiotic initiated during their hospital stay. The proportion of patients who used at least one antibiotic during hospitalization increased with the number of working diagnoses: single diagnosis (61%, 84/138; 95% CI: 52%–69%), two diagnoses (78%, 162/208; 95% CI: 72%–84%), three diagnoses (83%, 155/186; 95% CI: 78%–89%) and four or more diagnoses (88%, 202/230; 95% CI: 83%–92%). Hospital-initiated antibiotic use was 68% (160/237; 95% CI: 62%–74%) for patients with no changes to working diagnoses from admission to discharge and 84% otherwise (443/525; 95% CI: 81%–87%). See Table 1 also for other major working diagnoses for which antibiotics were administered.

Antibiotic use by DDDs and antibiotic class
Overall, 1985 systemic antibiotic DDDs, half administered parenterally (48%, 960/1985), were consumed during 3741 in-hospital patient-days, i.e. 531 DDDs per 1000 patient-days or 261 DDDs per 100 hospital admissions. Commonly used antibiotic classes by percentage DDDs were: cephalosporins (21%), combinations of sulphonamides with trimethoprim (18%), fluoroquinolones (17%), imidazole derivatives (16%), macrolides, lincosamides and streptogramins (13%) and penicillins (11%) (see Table 2 and Table S2).

Frequently used individual antibiotics
The most frequently used individual antibiotics, by percentage of patients using antibiotics, were ceftriaxone (66%, 398/603; 95% CI: 62%–70%), metronidazole (41%, 246/603; 95% CI: 37%–45%), co-trimoxazole (27%, 162/603; 95% CI: 23%–31%), azithromycin (15%, 90/603; 95% CI: 11%–19%), amoxicillin (15%, 90/603; 95% CI: 11%–19%), imipenem (13%, 78/591; 95% CI: 10%–16%), and ciprofloxacin (6%, 36/603; 95% CI: 4%–9%). Ceftriaxone was prescribed only for infections (88%, 202/230; 95% CI: 83%–92%).
### Table 1. Demographic and clinical characteristics of 762 hospitalized patients, Uganda, 2014

#### Characteristics

| Characteristic                                                                 | Mean (SD) | Median (IQR) |
|-------------------------------------------------------------------------------|-----------|--------------|
| Age (years), mean (SD) / median (IQR)                                         | 34.8 (14.8) / 30 (24–42) |
| Length of hospital stay (days), mean (SD) / median (IQR)                      | 4.9 (2.9) / 3 (3–6)      |
| Patient-days of observation, overall                                          | 3741       |

#### Extent of antibiotic use

| Antibiotic use, n (%) | yes | no | total |
|-----------------------|-----|----|-------|
| Antibiotic use pre-admission  | 300 (39) | 462 (61) | 762 |
| Antibiotic use during hospitalizationa | 603 (79) | 159 (21) | 762 |
| no co-trimoxazole use pre-admission | 472 (75) | 159 (25) | 631 |
| no in-hospital co-trimoxazole and dapsone use | 436 (73) | 159 (27) | 595 |
| Antibiotic use either pre-admission or during hospitalization | 629 (83) | 133 (17) | 762 |

#### Subgroup analyses on key variables

| Antibiotic use, n (%) | yes | no | total (column) | OR  | 95% CI for OR | P   |
|-----------------------|-----|----|----------------|-----|---------------|-----|
| Gender                |     |    |                |     |               |     |
| male                  | 190 (83) | 38 (17) | 228 (30) | 1.0 |               |     |
| female                | 413 (77) | 121 (23) | 534 (70) | 0.7 | 0.46–1.02     | 0.063 |
| Ward                  |     |    |                |     |               |     |
| GYN                   | 129 (68) | 62 (32) | 191 (25) | 1.0 |               |     |
| IDGI                  | 273 (85) | 47 (15) | 320 (42) | 2.8 | 1.81–4.30     | <0.001 |
| HNE                   | 88 (75) | 29 (25) | 117 (15) | 1.5 | 0.87–2.45     | 0.153 |
| CPN                   | 113 (84) | 21 (16) | 134 (18) | 2.6 | 1.48–4.51     | 0.001 |
| Number of working diagnoses |     |    |                |     |               |     |
| 1                     | 84 (61) | 54 (39) | 138 (18) | 1.0 |               |     |
| 2                     | 162 (78) | 46 (22) | 208 (27) | 2.3 | 1.41–3.63     | 0.001 |
| 3                     | 155 (83) | 31 (17) | 186 (24) | 3.2 | 1.92–5.38     | <0.001 |
| ≥4                    | 202 (88) | 28 (12) | 230 (30) | 4.6 | 2.75–7.82     | <0.001 |
| Changes to working diagnoses versus discharge diagnoses |     |    |                |     |               |     |
| 0                     | 160 (68) | 77 (32) | 237 (31) | 1.0 |               |     |
| 1                     | 291 (84) | 57 (16) | 348 (46) | 2.5 | 1.66–3.64     | <0.001 |
| ≥2                    | 152 (86) | 25 (14) | 177 (23) | 2.9 | 1.77–4.84     | <0.001 |
| Length of hospital stay |     |    |                |     |               |     |
| <5 days               | 308 (71) | 124 (29) | 432 (57) | 1.0 |               |     |
| ≥5 days               | 295 (89) | 35 (11) | 330 (43) | 3.4 | 2.26–5.10     | <0.001 |
| HIV serostatus        |     |    |                |     |               |     |
| negative              | 242 (71) | 98 (29) | 340 (45) | 1.0 |               |     |
| positive              | 221 (95) | 11 (5) | 232 (30) | 8.1 | 4.25–15.6     | <0.001 |
| unknown               | 140 (74) | 50 (26) | 190 (25) | 1.1 | 0.76–1.69     | 0.537 |
| Hospitalization in previous 3 months |     |    |                |     |               |     |
| no                    | 419 (79) | 113 (21) | 532 (70) | 1.0 |               |     |
| yes                   | 184 (80) | 46 (20) | 230 (30) | 1.1 | 0.73–1.58     | 0.699 |

Continued
ciprofloxacin (19%, 114/603; 95% CI: 16%–22%) and amoxicillin (10%, 57/603; 95% CI: 7%–12%) (see Table 3). When standardized by percentage DDDs, the most commonly used individual antibiotics were ceftriaxone (20%), co-trimoxazole (18%), metronidazole (16%) and ciprofloxacin (14%), followed by amoxicillin (9%) and azithromycin (6%) (see Table S2).

Missed-dose days of five frequently used hospital-initiated antibiotics

Ceftriaxone

Forty-three percent (171/398; 95% CI: 38%–48%) of patients who received intravenous ceftriaxone missed at least one dose-day of ceftriaxone. The per-day risk of missed ceftriaxone administration was greatest on day 1 of prescribed treatment (36%, 143/398; 95% CI: 31%–41%) (see Table S3). Moreover, 26% (105/398; 95% CI: 22%–31%) received only one dose-day of ceftriaxone treatment; or 21% (42/200; 95% CI: 16%–27%) of the patients prescribed a 5 day course of ceftriaxone.

Metronidazole

Thirty-one percent (77/245; 95% CI: 25%–37%) of patients who received oral or intravenous metronidazole missed at least one dose-day of metronidazole. The per-day risk of missed metronidazole administration was greatest on day 1 of prescribed treatment (27%, 67/245; 95% CI: 21%–33%) (see Table S3); 26% (63/245; 95% CI: 20%–32%) received only one dose-day of metronidazole administration.

Table 1. Continued

| Subgroup analyses on key variables | Antibiotic use, n (%) | Single factor analysis |
|-----------------------------------|-----------------------|-----------------------|
|                                   | yes  | no  | total (%) column | OR  | 95% CI for OR | P     |
| Major working diagnoses           |      |     |                 |     |              |       |
| respiratory tract conditions      |      |     |                 | 632 | 1.0           |       |
| no                                | 479  | 153 | (83)            | 1.0 | 6.6           | <0.001|
| yes                               | 124  | 6   | (17)            | 6.6 | 2.85–15.3     |       |
| gastrointestinal tract conditions |      |     |                 | 569 | 1.0           |       |
| no                                | 431  | 138 | (75)            | 1.0 | 2.6           | <0.001|
| yes                               | 172  | 21  | (25)            | 2.6 | 1.60–4.29     |       |
| genitourinary tract conditions    |      |     |                 | 193 | 1.0           |       |
| no                                | 518  | 140 | (86)            | 1.0 | 1.2           | 0.484 |
| yes                               | 85   | 18  | (14)            | 1.2 | 0.71–2.06     |       |
| skin conditions                   |      |     |                 | 746 | 1.0           |       |
| no                                | 587  | 159 | (98)            | 1.0 | infinite      |       |
| yes                               | 16   | 2  | (2)             | infinite |       |       |
| malaria                           |      |     |                 | 621 | 1.0           |       |
| no                                | 502  | 119 | (81)            | 1.0 | 0.6           | 0.016 |
| yes                               | 101  | 40  | (28)            | 0.6 | 0.39–0.91     |       |
| ISS or HIV/AIDS<sup>b</sup>       |      |     |                 | 610 | 1.0           |       |
| no                                | 456  | 154 | (80)            | 1.0 | 9.9           | <0.001|
| yes                               | 147  | 5   | (20)            | 9.9 | 3.99–24.7     |       |
| TB                                |      |     |                 | 640 | 1.0           |       |
| no                                | 485  | 155 | (84)            | 1.0 | 9.4           | <0.001|
| yes                               | 118  | 4   | (16)            | 9.4 | 3.42–26.0     |       |
| chronic/comorbid conditions       |      |     |                 | 384 | 1.0           |       |
| no                                | 302  | 82  | (50)            | 1.0 | 1.1           | 0.738 |
| yes                               | 301  | 77  | (50)            | 1.1 | 0.75–1.51     |       |
| miscellaneous infections          |      |     |                 | 648 | 1.0           |       |
| no                                | 498  | 150 | (85)            | 1.0 | 3.5           | <0.001|
| yes                               | 105  | 9   | (15)            | 3.5 | 1.74–7.11     |       |
| other conditions                  |      |     |                 | 676 | 1.0           |       |
| no                                | 533  | 143 | (89)            | 1.0 | 1.2           | 0.584 |
| yes                               | 70   | 16  | (11)            | 1.2 | 0.66–2.08     |       |

<sup>a</sup>Eighty-one percent (131/162) of patients who received co-trimoxazole during hospital stay had received it during the month preceding hospitalization. Overall, 167 patients used either co-trimoxazole (162) or dapsone (5) for prophylaxis against opportunistic infections.

<sup>b</sup>Not all HIV-positive patients had ISS.
treatment; or 24% (31/131; 95% CI: 17%–32%) of the patients prescribed a 5 day course of metronidazole.

Ciprofloxacin
Thirty-eight percent (43/114; 95% CI: 29%–47%) of patients who received oral or intravenous ciprofloxacin missed at least one dose-day. The per-day risk of missed ciprofloxacin administration was greatest on day 1 (34%, 39/114; 95% CI: 25%–43%) (see Table S3); 29% (33/114; 95% CI: 21%–38%) received only one dose-day of ciprofloxacin treatment; or 26% (25/98; 95% CI: 17%–35%) of the patients prescribed a 5 day course of ciprofloxacin.

Amoxicillin
Eleven percent (6/57; 95% CI: 3%–18%) of patients who received oral amoxicillin missed one dose-day of treatment, all of whom missed day 1 (see Table S3). Most patients (93%, 53/57) received the amoxicillin towards discharge from the ward and 26% (15/57; 95% CI: 15%–43%) received only one dose-day of amoxicillin.

Azithromycin
Thirty-one percent (8/26; 95% CI: 13%–61%) of patients who received oral azithromycin missed at least one dose-day of treatment, all of whom missed day 1 (see Table S3), and 27% (7/26; 95% CI: 11%–55%) received only one dose-day of azithromycin.

**Summary of missed antibiotic dose-days**
Overall, 73% (558/762; 95% CI: 70%–76%) of patients in the cohort used at least one of the five frequently administered hospital-initiated antibiotics (ceftriaxone, metronidazole, ciprofloxacin, amoxicillin and azithromycin), 44% (243/558; 95% CI: 39%–48%) of whom missed at least one dose-day of antibiotic treatment.
Table 4. Prescribed, dispensed and administered doses of the three most frequently used hospital-initiated antibiotics among inpatients, Uganda, 2014

| Individual antibiotic | Number of patients | Patient-days (mean) | Overall number of antibiotic doses (median, IQR) |
|-----------------------|--------------------|---------------------|-------------------------------------------------|
|                       |                    |                     | prescribed           | dispensed          | administered       |
| Ceftriaxone*          | 398                | 2174 (5.5)          | 1895 (5, 5–5)       | 783 (2, 1–3)       | 1178 (3, 1–3)     |
| Metronidazole*        | 245                | 1240 (5.1)          | 3862 (15, 9–18)     | 1642 (4, 2–12)     | 1043 (3, 2–6)     |
| Ciprofloxacin*        | 114                | 666 (5.8)           | 1130 (10, 10–11)    | 728 (6, 3–10)      | 396 (3, 1–4)      |

*Administered doses as a percentage of prescribed doses: ceftriaxone (62%, 1178/1895), metronidazole (27%, 1043/3862) and ciprofloxacin (35%, 94/266).

Table 5. Proportion of inpatients who received the full course, fewer doses or more doses of the three most frequently used hospital-initiated antibiotics, Uganda, 2014

| Individual antibiotic | Number of patients* | Number of patients receiving antibiotics (%) |                       |
|-----------------------|--------------------|---------------------------------------------|------------------------|
|                       |                    | full course       | fewer doses          | more doses          |
| Ceftriaxone           | 371                | 60 (16)           | 273 (74)            | 38 (10)             |
| Metronidazole         | 230                | 6 (3)             | 222 (97)           | 2 (1)               |
| Ciprofloxacin         | 105                | 7 (7)            | 94 (90)            | 4 (4)               |

*Variables have missing data.

Administration of frequently prescribed hospital-initiated antibiotics

Of prescribed doses, only 62% of ceftriaxone doses (1178/1895), 35% of ciprofloxacin doses (396/1130) and 27% of metronidazole doses (1043/3862) were administered (see Table 4). Most patients received fewer doses than were prescribed: ceftriaxone (74%, 273/371), ciprofloxacin (90%, 94/105) and metronidazole (97%, 222/230) (see Table 5). Medication errors were observed in half (13/26) of the patients who received oral azithromycin. Seven of the 26 (27%) patients purchased the azithromycin from a private community pharmacy. Six medication administration errors were committed by patients, one medication dispensing error by a ward pharmacist and one prescription error by a medical doctor. See Tables S3 and S4 and the Supplementary Results for details on prescription, dispensing and administration.

Switching from parenteral to oral antibiotics

Eighty-one percent (491/603; 95% CI: 78%–85%) of patients who used antibiotics during their hospital stay received at least one parenteral formulation of the antibiotic(s). In particular, 77% (188/245; 95% CI: 73%–80%) of patients on metronidazole and 76% (87/114; 95% CI: 73%–80%) on ciprofloxacin received at least one intravenous dose of their prescribed drug (see Table 2 and Table S2). Only 7% (13/188; 95% Poisson CI: 4%–12%) of patients on intravenous metronidazole and 6% (5/87; 95% Poisson CI: 2%–13%) on intravenous ciprofloxacin switched from intravenous to oral antibiotic medication.

Parenteral/oral antibiotic administration and missed-dose days

Missing at least one dose-day of any of the five frequently used hospital-initiated antibiotics occurred in 46% (222/485; 95% CI: 41%–50%) of inpatients who received at least one parenteral form of antibiotic, but in 29% (21/73; 95% CI: 19%–41%) of those who used the oral route only ($\chi^2$ (1 df) = 7.46; $P=0.006$).

Prescription errors of the three most frequently used hospital-initiated antibiotics

Overall, treatment duration was omitted by the prescriber in 9% (47/536; 95% CI: 7%–11%) of patients who received the oral/intravenous form of ceftriaxone, metronidazole or ciprofloxacin. Treatment duration was omitted by the prescriber in 7% (27/398; 95% CI: 4%–9%) of patients for whom intravenous ceftriaxone was prescribed; 7% (16/245; 95% CI: 3%–10%) for oral/intravenous metronidazole; and 8% (9/114; 95% Poisson CI: 4%–15%) for oral/intravenous ciprofloxacin.

Discussion

Antibiotic prescription and consumption

A high proportion of inpatients used antibiotics in the month preceding hospitalization (39%), predominantly co-trimoxazole and dapson (31%, 136/762), for prophylaxis against opportunistic infections in HIV-positive patients.\textsuperscript{17,20} A household survey of 2914 cases from five African countries (Gambia, Ghana, Kenya, Nigeria and Uganda) reported a similar proportion (36%) of antibiotic use in the community.\textsuperscript{21} A comparable prevalence of antibiotic use (30%), as measured by the antibacterial activity of the urine samples of 450 outpatients at two regional referral hospitals in northern Uganda, was recently reported.\textsuperscript{22} Antibiotic use may increase during influenza seasons.\textsuperscript{23} Influenza infections occur all year round in Uganda but peak during October—November, which coincides with the second, heavier rainy season of the year that spans September—November,\textsuperscript{24} at the tail-end of which we commenced data collection.

Three-quarters of inpatients received at least one antibiotic during their hospital stay whether co-trimoxazole and dapson users were included or excluded from the analysis. High rates of hospital-initiated antibiotic use among inpatients are consistently reported in other resource-limited settings: 83% among 435 medical and surgical inpatients in a 60 bed...
hospital located in a small Indian community; and 79% (n = 5381) and 82% (n = 2463) among inpatients at 350 bed and 570 bed tertiary health facilities, respectively, in a large Indian community.25,26

Although antibiotics were extensively used, our inpatients were frequently underdosed on the prescribed/dispensed antibiotics. The measured extent of antibiotic use in our setting, as quantified by DDDs per 1000 patient-days (531), was similar to Dutch hospitals (523 in 2003 and 698 in 2009), yet Dutch hospitals are known to have the lowest levels of total antibiotic consumption in Europe.27 Also, a South African study reported similar DDDs per 1000 patient-days (592) in the pre-intervention arm of a ward-based antibiotic stewardship programme.28 If all prescribed doses were administered to inpatients, clearly antibiotic consumption in Uganda, as measured by DDDs per 1000 inpatient-days, would be automatically higher than the Dutch estimates of antibiotic use. Prescribers might be more certain of the treatment needs of inpatients with single working diagnoses and those with unchanged diagnoses from admission to discharge, which might partly explain why both inpatient groups had the lowest proportions of antibiotic use. The extensive antibiotic prescription/use rates during hospitalization could, in part, be driven by uncertainties in working diagnoses due to the lack of rapid point-of-care tests in our setting.13 As reported elsewhere,3,21,29 respiratory conditions ranked among the most frequent diagnoses linked to antibiotic prescribing.

**Prescription adherence/missed doses**

The per-day risk of missed-dose days was greatest on day 1 of prescribed antibiotic. Also, the receipt of only a single dose/day of antibiotic treatment was common even where a 5 day course was prescribed. Clearly, it is more serious to miss the one daily dose of ceftriaxone, used presumably for severe infections such as meningitis, than a dose of thrice-daily metronidazole. Also, to be effective, ceftriaxone relies on its long t1/2 and the T >MIC, while e.g. ciprofloxacin has a concentration-dependent bactericidal effect (AUC/MIC ratio).30,31 A multicentre audit of administered antimicrobials in England found that 13% (802/6062) of patients had missed at least one prescribed dose, which is 3-fold less than the proportion reported in our cohort (44%); the main reasons for omitted doses were ‘drugs were not available’, ‘patient refused’, ‘prescribed route was not available’ or ‘patient was away from ward’.32 The UK’s National Patient Safety Agency has observed that patient harm from omitted doses is mainly by antimicrobials.33 Delayed initiation of prescribed antibiotic medication coupled with frequent missed-dose days and the failure to complete full courses of prescribed antibiotic treatment might result in temporary or permanent patient harm from lack of adequate treatment effect.34,35 Excess morbidity/mortality for undertreated patients could not be reliably measured in our study. However, missed antibiotic doses can promote the occurrence of life-threatening conditions, such as sepsis, and critically ill patients in septic shock cannot afford to miss their antibiotic treatment.36 Exposure of microorganisms to non-lethal subtherapeutic drug concentrations also increases the risk of antibiotic resistance.37

**Parenteral/oral switch**

A low proportion of patients who received hospital-initiated metronidazole (7%) or ciprofloxacin (6%) switched from intravenous to oral antibiotic medication, suggesting heavy inclination towards parenteral antibiotic administration. The use of parenteral antibiotic formulations was associated with a higher risk of missing at least one antibiotic dose-day, typically the first, which merits further investigation. Patients relied entirely on the nurses to administer parenteral antibiotics. Ward nurses administered parenteral medicines at scheduled times implying that a patient had a higher risk of missing his/her dose(s) if not in bed or did not readily have the prescribed parenteral medication during the nurse’s scheduled visit. Oral medications can, however, be self-administered by the patient whenever available without reliance on the ward nurse, thus, possibly lowering the risk of missing a dose-day. See the Supplementary Discussion for further details on drug administration issues. The relationship between missing the first dose-day of antibiotic and route of administration could have been confounded by the higher proportion of parenteral medications usually prescribed at the beginning of hospital stay compared with oral medications largely prescribed towards hospital discharge. Patients should switch from parenteral to oral medication at the earliest opportunity to reduce the risk of patient harm associated with parenteral medications, such as use of the wrong diluent or wrong rate of intravenous medication administration.38 The parenteral/oral switch also facilitates discharge from hospital if patients have recovered well, further reducing associated healthcare costs of longer hospital stay.39 Multiple interventions, ranging from written guidelines and educational programmes to antimicrobial stewardship,3,37,40 may be needed to regulate the use of parenteral antibiotics (and other drug classes) in our resource-limited setting.

**Prescription errors**

Treatment duration was omitted by the prescriber in 7%–8% of prescriptions of the frequently administered antibiotics. These prescription errors, mainly by junior doctors, were usually corrected by senior house officers and consultants within 12 h during subsequent ward round(s). Thus, the system has already built a solution to correct staff prescription errors. Prescription errors will often be committed, but a system that checks for and corrects those errors is more robust.

**Organizational issues**

Missed/delayed doses in our setting might be attributed to drug stock-outs, understaffing and inadequate communication between HCPs and with the patients, all of which are system-related problems that should be addressed at the organizational level. Elsewhere, first doses compared with subsequent doses are twice as likely to be missed due to unavailability of the drug.34 One in four of our patients on azithromycin purchased the medicine from a private community pharmacy, thus underpinning the need for stable stocks of free-of-charge essential antibiotics and other critical medicines that many patients cannot afford to buy. To avoid disruptive drug stock-outs, our hospital and possibly other health facilities in similar resource-poor settings could provide mechanisms for urgent supply of crucial medicines whenever needed.35 Encouraging proper ward-level documentation of patients’ clinical and medication data promotes clearer communication among staff within shift and at shift changes and is essential for ensuring that patients promptly receive their prescribed medication, especially if the patient/caregiver needs to fill prescriptions.
Antibiotic use among hospitalized patients in Uganda

at the pharmacy. Adequate record-keeping also provides audit-
able primary documents that can generate valuable medication
safety data. Medication errors occurred at an unacceptably high
rate in patients who received oral azithromycin, most of which
were medication administration errors by patients. Errors by
patients, particularly those with oral medications, are harder
to correct due to the absence, in our hospital setting, of a formal
mechanism to verify and rectify them. To reduce the pressure
on understaffed wards, it may be necessary to provide training
and practical assistance (e.g. buzzers, alarms on mobile phones
or chimes as reminders of scheduled dosing) to caregivers on
e.g. how to monitor and adhere to a patient’s oral medication dos-
ing intervals. Involving patients and caregivers in safer healthcare
has been encouraged by Ugandan HCPs who endorsed patient
participation in the reporting of medication errors.42

Study limitations

There are several limitations to this study. First, the intensity of
data collection and associated staff costs coupled with the
need to collect high-quality data limited the number of patients
studied to the range 600–800 rather than 1200–1500 as origin-
ally envisaged. Our initial intention was to recruit almost 250
patients per ward in five wards (four wards in the national referral
and one ward in a regional referral hospital), but the achievement
of ~100 patients per ward has had to suffice. Second, we did not
have a measure of antibiotic resistance engendered by curtailed
antibiotic courses for patients admitted into the four study
wards. Third, we encountered deviations from the random sam-
ping schedule for patients to join the study cohort. However, the
deviations from planned recruitment are unlikely to undermine
the major finding on under-administration of prescribed antibiotics.
Fourth, refusal rates by those omitted were not formally recorded,
but were generally low. Fifth, we observed an excess of adminis-
tered intravenous ceftriaxone doses over dispensed ceftriaxone
doses (see Table S5 for possible explanations). Sixth, the study
was conducted at a national referral and teaching hospital,
which may not be representative of antibiotic prescribing practices
at lower-level, particularly peripheral, health facilities in Uganda.

Conclusions

High rates of antibiotic use both pre-admission and during hospital-
ization were observed, with low parenteral/oral switch of intraven-
ous metronidazole/ciprofloxacin. Antibiotic underdosage was
common and resulted mostly from delayed/missed doses of pre-
scribed/dispensed antibiotics and ultimately from failure to com-
plete full courses of prescribed antibiotic medication. Extensive
exposure of patients to antibiotics coupled with underdosing risks
loss of efficacy and drug resistance, which could wipe out the limited
affordable antibiotic treatment options available in our low-resource
setting.

Funding

R. K. gratefully acknowledges funding support provided by the Training
Health Researchers into Vocational Excellence (THrIVE) in East Africa
grant number 087540, funded by the Wellcome Trust and an African
Doctoral Dissertation Research Fellowship (ADDRF) award 2013-2015
ADF 006 offered by the African Population and Health Research Centre
(APHRC) in partnership with the International Development Research Centre (IDRC). In the UK, S. M. B. is funded by Medical Research Council pro-
gramme number MC_U105260794. The funders had no role in the deci-
sions on what and where to publish.

Transparency declarations

S. M. B. holds GSK shares. Both other authors: none to declare.

Author contributions

R. K. conceived of the study and drafted the manuscript and, in conjunc-
tion with S. M. B., participated in its design, implementation, statistical
analysis and drawing of inferences. C. K. participated in the study design
and, together with S. M. B., took part in the manuscript writing process.
All authors approved the final manuscript.

Disclaimer

The work here reported is solely the responsibility of the authors and does
not necessarily represent the official views of the supporting offices.

Supplementary data

Supplementary Methods, Tables S1 to S5, Figure S1, Supplementary
Results and Supplementary Discussion are available as Supplementary
data at JAC Online (http://jac.oxfordjournals.org/).

References

1 British Medical Association and the Royal Pharmaceutical Society
of Great Britain. British National Formulary. London: BMJ Group and
Pharmaceutical Press, 2014.
2 Van Boeckel TP, Gandra S, Ashok A et al. Global antibiotic consump-
tion 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet
Infect Dis 2014; 14: 742–50.
3 Akkerman AE, Kuyvenhoven MM, van der Wouden JC et al. Determinants
of antibiotic overprescribing in respiratory tract infections in general prac-
tice. J Antimicrob Chemother 2005; 56: 930–6.
4 Dekker ARJ, Verheij TJM, van der Velden AW. Inappropriate antibiotic pre-
scription for respiratory tract indications: most prominent in adult patients.
Fam Pract 2015; 32: 401-7.
5 WHO. Draft Global Action Plan on Antimicrobial Resistance. 2014. http://
apps.who.int/ebwha/pdf_files/EB136/B136_20-en.pdf.
6 Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic
overuse and initiatives to reduce the problem. Ther Adv Drug Saf 2014; 5:
229–41.
7 Chang CY, Schiano TD. Review article: drug hepatotoxicity. Aliment
Pharmacol Ther 2007; 25: 1135–51.
8 Mick P, Westerberg BD. Sensorineural hearing loss as a probable serious
adverse drug reaction associated with low-dose oral azithromycin. J Otolaryngol
2007; 36: 257–63.
9 United States Census Bureau. Population Estimates. 2015. http://www.
census.gov/popest/data/national/totals/2014/index.html.
10 CDC. Antibiotic Resistance Threats in the United States. 2013. http://
www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf.
11 Boucher HW, Talbot GH, Bradley JS et al. Bad bugs, no drugs: no
ESKAPE! An update from the Infectious Diseases Society of America. Clin
 Infect Dis 2009; 48: 1–12.
