Antibiotic-associated suspected adverse drug reactions among hospitalized patients in Uganda: a prospective cohort study

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Abstract

We sought to determine the prevalence at admission and incidence during hospitalization of antibiotic-associated suspected adverse drug reactions (aa-ADRs) among Ugandan inpatients; and to characterize these aa-ADRs. We conducted a prospective cohort study of 762 consented adults admitted on medical and gynecological wards of the 1790-bed Mulago National Referral Hospital. Thirty percent were known HIV-seropositive (232/762). Nineteen percent (148/762; 95% CI: 17–22%) of inpatients experienced at least one aa-ADR. At hospital admission, 6% (45/762; 95% CI: 4–8%) of patients had at least one aa-ADR; and 15% (45/300; 11–20%) of those who had received antibiotics in the 4-weeks preadmission. Twenty-four (53%) of these 45 patients had serious aa-ADRs. The incidence of aa-ADRs was 19% (117/629; 95% CI: 16–22%) of patients who received antibiotics [community-acquired: 9% (27/300; 95% CI: 6–13%); hospital-acquired: 16% (94/603; 95% CI: 13–19%)]: 39 (33%) of 117 patients had serious aa-ADRs. Of 269 aa-ADRs, 115 (43%) were community-acquired, 66 (25%) probable/definite, 171 (64%) preventable, 86 (32%) serious, and 24 (9%) rare. Ceftriaxone was the most frequently implicated for serious hospital-acquired aa-ADRs. Cotrimoxazole, isoniazid, rifampicin, ethambutol, and pyrazinamide were the most frequently linked to serious community-acquired aa-ADRs. Fatal jaundice (isoniazid), life-threatening difficulty in breathing with shortness of breath (rifampicin) and disabling itchy skin rash with numbness of lower swollen legs (ethambutol, isoniazid) were observed. Pharmaceutical quality testing of implicated antibiotics could be worthwhile. Periodic on-ward collection and analysis of antibiotic-safety-data standardized by consumption is an efficient method of tracking antibiotics with 1%-risk for serious aa-ADRs.

Introduction

Antibiotics rank among the most widely prescribed medications globally (WHO, 2004; Shehab et al. 2008; Adriaenssens et al. 2011). Widespread antibiotic use predisposes patients to antibiotic-associated adverse drug reactions (aa-ADRs), including serious aa-ADRs (WHO-UMC, 2000). Antibiotics contributed to 19% of emergency department visits for suspected ADRs in the United States (US) between 2004 and 2006 (Shehab et al. 2008), 8% of...
ADRs linked to hospital admissions in Greece in 2005 (Alexopoulou et al. 2008), 6% in Spain between 2001 and 2006 (Carrasco-Garrido et al. 2010), 5% in The Netherlands in 2003 (van der Hooft et al. 2008), and 11% in India between 2002 and 2009 (Sonal et al. 2011); and are responsible for a considerable proportion of hospital-acquired ADRs in the US (10%) (Weiss et al. 2011) and South Africa (22%) (Mehta et al. 2008). Allergic reactions constitute 79% of aa-ADRs at US emergency departments (Shehab et al. 2008).

Developing countries contributed 76% of the global rise in antibiotic use between 2000 and 2010 (Van Boeckel et al. 2014), which increases their risk of aa-ADRs. Cotrimoxazole use is standard-of-care for prophylaxis against opportunistic infections among HIV/AIDS patients in resource-limited settings (WHO, 2006a). Thus, the high burden of HIV/AIDS in sub-Saharan Africa (SSA) implies increased risk of cotrimoxazole-linked ADRs (Mouton et al. 2015). Little is known about the frequency (Kiguba et al. 2015) and characteristics of aa-ADRs among inpatients in SSA (Mehta et al. 2008), particularly in Uganda. Moreover, it is a challenge to ascertain aa-ADR causality in our hospital setting where a large proportion of inpatients have comorbidities and/or concurrently receive multiple medicines.

Four-fifths of inpatients at a tertiary care public health facility in Uganda consume at least one antibiotic during hospitalization, whereas two-fifths use at least one antibiotic during the 4-weeks preadmission (Kiguba et al. 2016a). Patients can receive parenteral antibiotics at private clinics in the community prior to their subsequent referral to tertiary care public health facilities.

The reported antibiotic prescribing patterns in our hospital setting excluded antituberculous drugs and focused on commonly used antibacterial agents (Kiguba et al. 2016a), whose prescription is not restricted to specialists, to identify key areas for antibiotic stewardship. For the benefit of antituberculous drugs pharmacovigilance in Uganda, this paper includes data on the aa-ADRs of antituberculous drugs. We sought to determine the prevalence at hospital admission and the incidence during hospital stay of aa-ADRs among Ugandan inpatients: their seriousness, rarity, preventability, causality, and severity.

Materials and Methods

Study design and setting

This prospective cohort study (Kiguba et al. 2016a) was conducted among hospitalized adult patients (≥18 years) at the Mulago National Referral Hospital (1790 beds; more than 140,000 inpatients annually). Briefly, three medical wards were studied: Infectious Diseases and Gastrointestinal Illnesses (IDGI); Haematology, Neurology and Endocrinology (HNE); and Cardiovascular, Pulmonology and Nephrology (CPN); and one Gynecology ward (GYN). IDGI and CPN each admitted 10–15 patients/day and HNE received 5–10 patients/day; therefore 25–40 admissions/day on medical wards. However, GYN had 20–25 admissions/day.

Patients gave written informed consent.

Data collection

From October to November 2013, we undertook a pilot study on the four wards to assess practicability and to pretest the study instruments. The main study (reported here) was implemented in December 2013 to April 2014. Four trained ward-teams, each having a medical doctor, pharmacist and degree-nurse, were to recruit and follow-up inpatients using a systematic random sampling procedure: three new admissions daily on long-stay wards (HNE/CPN) and six on short-stay wards (IDGI/GYN). Ward-teams randomly selected the first study patient from the first two (IDGI), three (HNE), and four (CPN/GYN) new admissions; and subsequently aimed at recruiting every second, third, and fourth admission, respectively (Kiguba et al. 2016a).

Baseline patient assessment captured relevant data on demographics, clinical conditions including aa-ADRs, and antibiotic medications used. Subsequently, daily assessments were conducted until discharge, transfer, death, or loss to follow-up. Ward-teams collected data from 8.00 am to 6.00 pm from Monday to Friday and from 10.00 am to 6.00 pm on weekends and public holidays (Kiguba et al. 2016a).

Data management

The data were double-entered into a database using EpiData 3.1 software (Odense, Denmark) with check programs to limit out-of-range data entry errors. Where data discrepancies occurred, the original case report form was cross-checked and corrections were made.

Identification of aa-ADRs

We defined aa-ADRs according to the WHO definition (WHO-UMC, 2011b). Clinical examination was the major approach used to identify aa-ADRs due to limitations in timely availability of laboratory investigation results (Kiguba et al. 2016b). To increase the probability to detect aa-ADRs, patients were screened using an ADR trigger tool (Rozich et al. 2003). To assess causality, a suspected aa-ADR was assigned to a Naranjo ADR probability category based on a total score obtained from 10
weighted questions. These questions assessed the temporal association between suspected drug and adverse reaction, alternative cause(s) of the reaction, plasma drug levels (if available), dose–response relationships and previous patient experience with the drug. Suspected aa-ADRs with Naranjo score of 0 were doubtful, 1–4 possible, 5–8 probable, and ≥9 definite (Naranjo et al. 1981). Thus, coding an adverse event as “aa-ADR” required at least possible grading on the Naranjo scale. Operationally, an aa-ADR was any undesirable medical occurrence that developed after the administration of an antibiotic and for which there was, at least, possible causality between the antibiotic and the medical occurrence. Consensus agreement on aa-ADR causality was reached in a committee headed by the ward-based study physician and senior clinical pharmacist (RK). This team approach reflected the routine on-ward approach whereby nurses, medical doctors, and clinical pharmacists brainstorm on patients’ clinical problems before making clinical decisions (Kiguba et al. 2016a). Community-acquired aa-ADRs were defined as ADRs linked to preadmission use of antibiotics. Some community-acquired aa-ADRs manifested preadmission, whereas others occurred after hospital admission. Hospital-acquired aa-ADRs were those linked to hospital-initiated antibiotics used during the current hospitalization.

Preventability, severity (grade or intensity), and seriousness (incapacitating or life-threatening) of aa-ADRs were also determined by consensus as described above. Preventability was assessed using the modified Schumock and Thornton Preventability Scale (Schumock and Thornton 1992; Lau et al. 2003), whereas severity was evaluated using the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (Division of AIDS (DAIDS), 2004) and seriousness using the WHO Uppsala Monitoring Centre (UMC) criteria (WHO-UMC, 2000). Rarity of an aa-ADR (occurrence in <0.1% of medication users) (WHO-UMC, 2011b), was assessed by RK using the British National Formulary (BNF) (British National Formulary, 2014) as the principal reference.

Statistical analysis

We determined the prevalence of aa-ADRs at hospital admission, and the incidence of aa-ADRs during hospitalization. Numerators for prevalence and incidence were the number of patients who had experienced preadmission aa-ADRs and new cases of in-hospital aa-ADRs, respectively, whereas the denominator was the number of study patients who received antibiotics (both incidence and prevalence) or total number of patients in the cohort (prevalence only).

We also computed the incidence of hospital-acquired aa-ADRs per 100 defined daily doses (DDDs) (Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) Index, 2015; Hamad et al. 2013) of each implicated antibiotic administered during the current hospitalization.

We assessed aa-ADRs as community-acquired or hospital-acquired; and for causality, preventability, severity, seriousness, and rarity.

All statistical analyses were conducted using Stata 12.0 (StataCorp, 2011).

Ethical clearance

Ethical approval for the study was obtained 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

Of 762 inpatients included in the study, 70% (534/762; 191 in gynecology, 343 in the medical wards) were female. Median age of inpatients was 30 years [interquartile range (IQR) of 24–42] and median length of hospital stay was 4 days (IQR: 3–6). Thirty percent were known HIV-seropositive [(232/762): 38% (215/571) being on the medical wards and 9% (17/191) on gynecology], see Table 1.

Extent of aa-ADRs

Overall, 42% (320/762; 95% CI: 38–46%) of patients experienced at least one suspected ADR attributable to any medication class: 46% (148/320; 95% CI: 41–52%) of these patients, or 19% (148/762; 95% CI: 17–22%) of all patients, experienced at least one aa-ADR, see Table 2. Fifty-eight percent (86/148) of the patients with aa-ADRs encountered hospital-acquired aa-ADRs only, 37% (54/148) had community-acquired aa-ADRs only and 5% (8/148) both community-acquired (incident and prevalent) and hospital-acquired aa-ADRs.

Prevalence of community-acquired aa-ADRs

The prevalence of community-acquired aa-ADRs was 6% (45/762; 95% CI: 4–8%) of all patients or 15% (45/300; 95% CI: 11–20%) of those who had received antibiotics in the 4-weeks preadmission. Serious prevalent aa-ADRs were encountered by 8% (24/300; 95% CI: 5–12%) of patients who used antibiotics preadmission or by half
(53%, 24/45; 95% CI: 39–68%) of those with prevalent aa-ADRs, see Table 2.

The prevalence of aa-ADRs among preadmission antibiotic-users was three-fold higher among HIV-positive vs. HIV-negative/unknown serostatus inpatients [21% (38/178) vs. 6% (7/122); \( \chi^2 = 13.8; \ P < 0.001 \)]; and 13-fold higher for serious prevalent aa-ADRs [13% (23/178) vs. 1% (1/122); \( \chi^2 = 14.4; \ P < 0.001 \)], see Table 2.

### Incidence of aa-ADRs during hospitalization

The incidence of aa-ADRs was 19% (117/629; 95% CI: 16–22%) of inpatients who received antibiotics [community-acquired: 9% (27/300; 95% CI: 6–13%); hospital-acquired: 16% (94/603; 95% CI: 13–19%)], four patients having developed incident community-acquired and hospital-acquired aa-ADRs during the current hospitalization, see Tables 1,2. Serious incident aa-ADRs were encountered by 6% (39/629; 95% CI: 4–8%) of patients or by one-third (33%, 39/117; 95% CI: 25–42%) of those with incident aa-ADRs, see Table 2.

The incidence of serious community-acquired/hospital-acquired aa-ADRs was two-fold higher among HIV-positive vs. HIV-negative/unknown serostatus inpatients [10% (23/228) vs. 4% (16/401); \( \chi^2 = 9.3; \ P = 0.002 \)].

### Suspected aa-ADRs by single antibiotic class, individual antibiotic, and system organ class

At the suspected ADR level of analysis, antibiotics contributed 41% (269/662) of all suspected ADRs (148 patients shared 269 aa-ADRs), 44% (118/269) of which were linked to a single antibiotic class only. Ceftriaxone accounted for 43% (50/117) of aa-ADRs attributable to individual antibiotics only, followed by metronidazole (21%, 24/117) and cotrimoxazole (13%, 15/117). Forty-three percent (115/269) of aa-ADRs were community-

### Table 1. Demographic and clinical characteristics of 762 hospitalized patients, Uganda, 2014.

| Characteristic                        | Number of patients (n = 762) | Patients with community-acquired antibiotic-associated. ADRs at admission | Patients who developed new antibiotic-associated. ADRs while in hospital² |
|---------------------------------------|-------------------------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| **Age, years [median, interquartile range (IQR)]** | 30 (24–42)                   | 33 (27–42)                                                               | 33 (26–40)                                                               |
| **Number of administered medicines (median, IQR)** | 7 (5–10)                      | 10 (8–12)                                                                | 11 (7–14)                                                                |
| **Length of hospital stay, days (median, IQR)** | 4 (3–6)                       | 4 (3–7)                                                                  | 7 (5–9)                                                                  |

| Characteristic                        | Number of patients (n = 762), % col¹ | Patients with community-acquired antibiotic-associated ADRs at admission (% Prevalence) | Patients who developed new antibiotic-associated ADRs while in hospital (% Incidence²) |
|---------------------------------------|-------------------------------------|----------------------------------------------------------------------------------|-----------------------------------------------------------------------------------|
| **Gender**                            |                                     |                                                                                  |                                                                                  |
| Male                                  | 228 [30]                            | 20 (9)                                                                          | 9 (4)                                                                            |
| Female                                | 534 [70]                            | 25 (4)                                                                          | 14 (3)                                                                          |
| **Ward-type**                         |                                     |                                                                                  |                                                                                  |
| Medical wards                         | 571 [75]                            | 40 (7)                                                                          | 22 (4)                                                                          |
| Infectious diseases & gastrointestinal illnesses | 320 [42]                    | 19 (6)                                                                          | 5 (2)                                                                           |
| Hematology, neurology & endocrinology | 117 [15]                            | 0 (0)                                                                          | 2 (2)                                                                           |
| Cardiovascular, pulmonology & nephrology | 134 [18]                     | 21 (16)                                                                         | 19 (14)                                                                         |
| Gynecology ward                       | 191 [25]                            | 5 (3)                                                                           | 1 (1)                                                                           |
| **HIV status by ward-type**           |                                     |                                                                                  |                                                                                  |
| Positive                              | 232 [30]                            | 38 (16)                                                                         | 18 (8)                                                                          |
| Medical wards                         | 215 [38]                            | 37 (17)                                                                         | 18 (8)                                                                          |
| Gynecology ward                       | 17 [9]                              | 1 (6)                                                                           | 0 (0)                                                                           |
| Negative or unknown                   | 530 [70]                            | 7 (1)                                                                           | 9 (2)                                                                           |
| Medical wards                         | 356 [62]                            | 3 (1)                                                                           | 8 (2)                                                                           |
| Gynecology ward                       | 174 [91]                            | 4 (2)                                                                           | 1 (1)                                                                           |

¹Of 762 patients, 300 had received antibiotics preadmission, 603 initiated antibiotics during hospital stay, and 629 received antibiotics either preadmission or during hospital stay; square brackets [ ] represent column percentages; round brackets ( ) represent row percentages.

²Four patients experienced incident community-acquired and hospital-acquired antibiotic-associated ADRs during the current hospitalization.
Hospital-acquired aa-ADRs were more likely than community-acquired aa-ADRs to involve a single antibiotic class only (56% vs. 27%), see Table 3. Individual antibiotics with the highest frequencies of community-acquired/hospital-acquired aa-ADRs were ceftriaxone (110), cotrimoxazole (58), metronidazole (54), isoniazid (35), rifampicin (26), pyrazinamide (23), ethambutol (23), levofloxacin (15), and ciprofloxacin (13), among others. Most cotrimoxazole aa-ADRs were community-acquired (54/58), see Table 4.

The highest incidence-rates of hospital-acquired aa-ADRs, standardized by DDDs, were from ceftriaxone (24 aa-ADRs/100 DDDs), levofloxacin (24 aa-ADRs/100 DDDs), and metronidazole (14 aa-ADRs/100 DDDs); though levofloxacin consumption was quite low ($n = 17$; DDDs = 62), see Table 4. Ceftriaxone showed stronger signals for hospital-acquired aa-ADRs than metronidazole in both HIV-positive [(19 per 100 DDDs) vs. (10 per 100 DDDs); $P = 0.046$] and HIV-negative/unknown status [(26 per 100 DDDs) vs. (17 per 100 DDDs); $P = 0.014$] patients, respectively, see Table S1.

The incidence of serious hospital-acquired aa-ADRs, standardized by DDDs, was highest for ceftriaxone (7 aa-ADRs/100 DDDs) followed by metronidazole (3 aa-ADRs/100 DDDs) and levofloxacin (2 aa-ADRs/100 DDDs).

The system organ classes most frequently affected were the gastrointestinal (50%, 135/269), neurological (24%, 64/269), body-general (10%, 27/269), and skin/appendages (6%, 17/269), among others. Serious aa-ADRs from patients of known HIV-positive status were significantly more frequent in the gastrointestinal [HIV-positive: 35% (20/57) vs. HIV-negative/unknown: 6% (5/89); $\chi^2 = 17.9; P < 0.001$] and neurological [HIV-positive: 52% (15/29) vs. HIV-negative/unknown: 20% (7/35); $\chi^2 = 7.1; P = 0.008$] systems, see Table 5.

### Table 2. Extent of antibiotic-associated suspected ADRs at patient-level among 762 inpatients, Uganda, 2014.

| Characteristic at patient-level | Number of suspected ADRs, $n$ |
|---------------------------------|-------------------------------|
|                                 | HIV+  | HIV- or Unknown | Total |
| Suspected ADRs attributed to any medication class | 136   | 184             | 320   |
| Antibiotic-associated suspected ADRs | 75    | 73              | 148   |
| Incident antibiotic-associated suspected ADRs during hospital stay | 51    | 66              | 117   |
| Serious incident in-hospital suspected ADRs | 23    | 16              | 39    |
| Prevalent antibiotic-associated suspected ADRs at admission | 38    | 7               | 45    |
| Serious prevalent suspected ADRs at admission | 23    | 1               | 24    |
| Community-acquired antibiotic-associated suspected ADRs | 47    | 17              | 64    |
| Incident community-acquired suspected ADRs during hospital stay | 18    | 9               | 27    |
| Serious incident community-acquired suspected ADRs | 7     | 2               | 9     |
| Hospital-acquired antibiotic-associated suspected ADRs | 33    | 61              | 94    |
| Serious incident hospital-acquired suspected ADRs | 16    | 16              | 32    |

| Characteristic at patient-level | Proportion with suspected ADRs, % ($n/N$) |
|---------------------------------|------------------------------------------|
|                                 | HIV+  | HIV- or Unknown | Total |
| Overall, suspected ADRs<sup>1</sup> | 59% (136/232) | 35% (184/530) | 42% (320/762) |
| Antibiotic-associated community- or hospital-acquired suspected ADRs | 32% (75/232) | 14% (73/530) | 19% (148/762) |
| Percent of overall sample<sup>2</sup> | 55% (75/136) | 40% (73/184) | 46% (148/320) |
| Percent of patients who experienced at least one ADR<sup>2</sup> | 16% (38/232) | 1% (7/530) | 6% (45/762) |
| Prevalence of antibiotic-associated community-acquired ADRs at hospital admission<sup>2</sup> | 21% (38/178) | 6% (7/122) | 15% (45/300) |
| Among antibiotic-users in the 4-weeks preadmission<sup>2</sup> | 13% (23/178) | 1% (1/122) | 8% (24/300) |
| Incidence of antibiotic-associated suspected ADRs<sup>2</sup> | 22% (51/228) | 16% (66/401) | 19% (117/629) |
| Incidence of community- or hospital-acquired ADRs<sup>1,2</sup> | 10% (18/178) | 7% (9/122) | 9% (27/300) |
| Incidence of community-acquired ADRs during hospital stay | 15% (33/221) | 16% (61/382) | 16% (94/603) |
| Incidence of hospital-acquired ADRs during hospital stay | 10% (23/228) | 4% (16/401) | 6% (39/629) |
| Incidence of serious community/hospital-acquired ADRs<sup>2</sup> | 4% (7/178) | 2% (2/122) | 3% (9/300) |
| Incidence of serious community-acquired ADRs | 7% (16/221) | 4% (16/382) | 5% (32/603) |

<sup>1</sup>Some patients experienced more than one community-acquired or hospital-acquired antibiotic-associated suspected ADR with incidence overlap in four patients.

<sup>2</sup>Statistically significant difference at $P < 0.05$. © 2017 The Authors. Pharmacology Research & Perspectives published by John Wiley & Sons Ltd, British Pharmacological Society and American Society for Pharmacology and Experimental Therapeutics.
Causality, preventability and severity of aa-ADRs

Only 25% (66/269) of aa-ADRs were of probable/definite causality. Vomiting was the commonest aa-ADR in both the possible (17%, 35/203) and probable/definite (20%, 13/66) causality categories. Loss of appetite (12%, 25/203) was the only aa-ADR in the top 10 most frequent possible aa-ADRs that did not feature among the top 10 most frequent probable/definite aa-ADRs, see Table S2.

Most aa-ADRs were preventable (64%, 171/269). However, 65% (43/66) of probable/definite aa-ADRs were nonpreventable. Table 6 shows that one in seven (14%, 38/269) aa-ADRs was severe (grade three intensity).

Seriousness of aa-ADRs

Thirty-two percent (86/269) of aa-ADRs were judged as serious: the majority (56%, 48/86) required intervention to prevent permanent damage, and 29% (25/86) caused or prolonged hospitalization. Fatal jaundice [isoniazid], disabling itchy skin rash with numbness of lower swollen legs [ethambutol, isoniazid] and life-threatening difficulty in breathing with shortness of breath [rifampicin] occurred in known HIV-positive patients; see Table 7.

Ceftriaxone was the most frequently linked to serious hospital-acquired aa-ADRs (70% (26/37); HIV-positive: 83% (15/18) & HIV-negative/unknown status: 58% (11/19); the commonest being fever (6) and vomiting (6), see Tables 7, S3.
Allergic reactions occurred in 22% (32/148, 95% CI: 15–29%) of patients who experienced aa-ADRs [community-acquired: 19% (12/62; 95% CI: 10–31%); hospital-acquired: 26% (24/94; 95% CI: 17–36%)]: 14 (44%) of 32 allergic reactions were serious.

A quarter of the patients who were admitted with at least one ADR related to any medication class had...

Table 4. Individual antibiotics most frequently implicated in causing the 269 antibiotic-associated suspected ADRs (aa-ADRs) among 148 of 762 hospitalized patients, Uganda, 2014.

| Antibiotic class, antibiotic | No. of aa-ADRs | No. of community-acquired aa-ADRs | No. of hospital-acquired aa-ADRs | DDDs used during current hospitalization | No. of Patients who used drug in hospital | No. of hospital-acquired aa-ADRs/100 DDDs | 95% CIs of hospital-acquired ADRs/100 DDDs |
|-----------------------------|----------------|----------------------------------|----------------------------------|-----------------------------------------|----------------------------------------|------------------------------------------|------------------------------------------|
| Cephalosporins              |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Ceftriaxone                 | 110            | 16                               | 94                               | 398.0                                   | 398                                    | 24                                       | 19–28                                     |
| Penicillins                 |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Ampicillin                  | 2              | 0                                | 2                                | 2                                       | 8.8                                    | 11                                       | 14–28                                    |
| Amoxicillin-clavulanate     | 1              | 0                                | 1                                | 19.0                                    | 8                                      | 5                                        | 0–15                                     |
| Amoxicillin                 | 6              | 4                                | 2                                | 169.0                                   | 57                                     | 1                                        | 0–6                                      |
| Ampicillin-cloxacillin      | 1              | 1                                | 1                                | 24.4                                    | 32                                     | 0                                        | 0–4                                      |
| Quinolones                  |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Levofloxacin                | 15             | 0                                | 15                               | 62.0                                    | 17                                     | 24                                       | 14–35                                    |
| Ciprofloxacin               | 13             | 3                                | 10                               | 279.9                                   | 114                                    | 4                                        | 1–6                                      |
| Nitroimidazole derivatives  |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Metronidazole               | 54             | 10                               | 44                               | 309.1                                   | 246                                    | 14                                       | 10–18                                    |
| Sulfonamides and trimethoprim |            |                                  |                                  |                                         |                                        |                                          |                                          |
| Cotrimoxazole               | 58             | 54                               | 4                                | 358.0                                   | 162                                    | 1                                        | 0–6                                      |
| Macrolide antibiotics       |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Erythromycin                | 12             | 6                                | 6                                | 79.5                                    | 19                                     | 8                                        | 2–13                                     |
| Azithromycin                | 8              | 2                                | 6                                | 123.3                                   | 26                                     | 5                                        | 1–9                                      |
| Aminoglycosides             |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Gentamicin                  | 1              | 0                                | 1                                | 15.0                                    | 12                                     | 7                                        | 0–19                                     |
| Antileprotics               |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Dapsone                     | 3              | 3                                | 0                                | 0                                       | 5                                      | 0                                        | 0–4                                      |
| Antituberculous drugs       |                |                                  |                                  |                                         |                                        |                                          |                                          |
| Pyrazinamide                | 23             | 21                               | 2                                | 117.3                                   | 38                                     | 2                                        | 0–7                                      |
| Isoniazid                   | 35             | 33                               | 2                                | 155.8                                   | 49                                     | 1                                        | 0–6                                      |
| Rifampicin                  | 26             | 25                               | 1                                | 113.8                                   | 40                                     | 1                                        | 0–6                                      |
| Ethambutol                  | 23             | 22                               | 1                                | 122.8                                   | 46                                     | 1                                        | 0–6                                      |

1One or more antibiotics or other drug class(es) may have been implicated in the causation of an aa-ADR.
2CIs is confidence intervals.
395% CIs are wide and include null value.

Table 5. System Organ Class distribution of the 269 antibiotic-associated suspected ADRs experienced by 148 hospitalized patients, Uganda, 2014.

| System Organ Class (SOC) name | No. of aa-ADRs (% column) | No. of serious aa-ADRs (% row) | Serious aa-ADRs by HIV-status, % (n/N) |
|-------------------------------|---------------------------|-------------------------------|---------------------------------------|
| Gastrointestinal disorders1   | 135 [50]                  | 25 (19)                       | 35% (20/57)                          |
| Neurological disorders1       | 64 [24]                   | 22 (34)                       | 52% (15/29)                          |
| Body – General disorders      | 27 [10]                   | 13 (48)                       | 60% (9/15)                           |
| Skin and appendages disorders | 17 [6]                    | 5 (29)                        | 33% (4/12)                           |
| Others                        | 26 [10]                   | 21 (81)                       | 83% (15/18)                          |

1Statistically significant difference in proportions of serious ADRs by HIV-status at P < 0.05 (gastrointestinal: \( \chi^2 = 17.9; P < 0.001 \) & neurological: \( \chi^2 = 7.1; P = 0.008 \)).
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Table 6. Severity, seriousness, and rarity of 269 antibiotic-associated suspected ADRs in hospitalized patients, Uganda, 2014.

| Assessment | Category                          | Frequency of suspected aa-ADRs (n, %)1 |
|------------|-----------------------------------|----------------------------------------|
| Severity   | Mild                              | 110 (41)                               |
|            | Moderate                          | 120 (45)                               |
|            | Severe                            | 38 (14)                                |
|            | Life-threatening                   | 1 (0)                                  |
| Serious    | Yes1                              | 86 (32)                                |
|            | Required intervention to prevent damage2 | 48 (56)                              |
|            | Caused or prolonged hospitalization2 | 25 (29)                                |
|            | Other medically significant condition2 | 10 (12)                               |
|            | Caused death2                     | 1 (1)                                  |
|            | Life-threatening2                 | 1 (1)                                  |
|            | Caused disability2                | 1 (1)                                  |
| Rare       | Yes1                              | 24 (9)                                 |
|            | No1                               | 183 (68)                               |
|            | Incidence unknown                 | 3 (1)                                  |

1Denominator used was the total number of antibiotic-associated suspected ADRs, n = 269.
2Denominator used was the number of serious antibiotic-associated suspected ADRs, n = 86.

Discussion

Suspected aa-ADRs were common both at admission and during hospital stay. The incidence of aa-ADRs in our study was threefold higher than that observed in a French cohort of 3963 hospitalized patients (Courjon et al. 2013) which could, in part, be linked to the higher consumption of antibiotics by our inpatients for HIV-associated comorbidities. Most of our inpatients received antibiotics whose use was significantly higher among HIV-infected patients (Kiguba et al. 2016a). The medical wards showed a higher HIV-seroprevalence (38%) than gynecology where HIV-seroprevalence (9%) was similar to the national estimate (7.3%) (Uganda AIDS Commission, 2015). The fact that most patients received antibiotics makes our study epidemiologically efficient. Few aa-ADRs would be observed in a hospitalized-population in which antibiotic prescribing was infrequent. Of all suspected ADRs attributed to any medication class, a large proportion (one in three) was linked to antibiotics, which corroborates findings from South Africa, a setting with a similarly high HIV/AIDS burden, where one in five ADRs (11/51) was antibiotic-associated (Mehta et al. 2008).

Ceftriaxone showed the strongest signal for hospital-acquired aa-ADRs, even among HIV-negative/unknown serostatus patients, which could be a reflection of ceftriaxone’s high prescription rate in our hospital setting. Strong signals were also shown by metronidazole and levofloxacin (based on small numbers of patients for levofloxacin). Unmasking of the signal from the infrequently used levofloxacin demonstrates the utility of standardizing absolute aa-ADRs by DDDs administered (Hamad et al. 2013). However, much larger well-designed epidemiological studies in Uganda and other similar resource-limited settings could provide more clues on the aa-ADR profiles of ceftriaxone and levofloxacin, which are otherwise generally known to be safe. We did not test the quality of the antibiotics used and hence how this impacted on the incidence of hospital-acquired aa-ADRs by individual antibiotics. Nonetheless, this study has identified individual antibiotics (ceftriaxone, metronidazole, levofloxacin) with potentially higher risk for hospital-acquired aa-ADRs. The...
| Adverse Drug Reaction | Drug | Severity | Causality | Rarity | HIV-status | Community or Hospital-acquired | System Organ Class | Grade of Seriousness |
|-----------------------|------|----------|-----------|--------|------------|--------------------------------|-------------------|---------------------|
| FEVER                 | INH, RIFAMPICIN, PYRAZINAMIDE | Moderate | Possible | No | Negative | Community-acquired | Body - General | Required intervention to prevent damage |
| ANEMIA                | UNKNOWN HERBAL, CEFTRIAXONE, CAPTOPRIL | Moderate | Possible | No | Negative | Community-acquired | Blood | Required intervention to prevent damage |
| FEVER                 | CEFTRIAXONE | Severe | Possible | No | Negative | Hospital-acquired | Body - General | Required intervention to prevent damage |
| DIZZINESS             | CEFTRIAXONE | Severe | Possible | No | Negative | Hospital-acquired | Neurological | Required intervention to prevent damage |
| VOMITING              | CEFTRIAXONE, TRAMADOL | Severe | Possible | No | Negative | Hospital-acquired | Gastrointestinal | Required intervention to prevent damage |
| FEVER                 | CEFTRIAXONE | Severe | Possible | No | Negative | Hospital-acquired | Body - General | Required intervention to prevent damage |
| DIZZINESS             | CEFTRIAXONE, METRONIDAZOLE | Moderate | Possible | No | Negative | Hospital-acquired | Neurological | Required intervention to prevent damage |
| PERIPHERAL NEUROPATHY | LEVOFLOXACIN | Moderate | Possible | No | Negative | Hospital-acquired | Neurological | Caused or prolonged Hosp |
| TACHYCARDIA           | CIPROFLOXACIN | Moderate | Possible | No | Negative | Hospital-acquired | Cardiovascular | Required intervention to prevent damage |
| DIZZINESS             | METRONIDAZOLE, AMOXICILLIN | Severe | Possible | NK | Negative | Hospital-acquired | Neurological | Caused or prolonged Hosp |
| WORSENED JAUNDICE     | CIPROFLOXACIN, CEFTRIAXONE, METRONIDAZOLE | Moderate | Possible | No | Negative | Hospital-acquired | Liver and biliary | Other medically significant condition |
| CONVULSIONS - GTC (2 EPISODES) | METRONIDAZOLE | Severe | Possible | No | Negative | Hospital-acquired | Neurological | Required intervention to prevent damage |
| VOMITING              | CEFTRIAXONE | Severe | Possible | No | Negative | Hospital-acquired | Gastrointestinal | Other medically significant condition |
| ORAL SORES            | CEFTRIAXONE | Moderate | Possible | No | Negative | Hospital-acquired | Gastrointestinal | Other medically significant condition |
| HYPERTENSION          | CIPROFLOXACIN | Severe | Probable | No | Negative | Hospital-acquired | Cardiovascular | Required intervention to prevent damage |
| PARESTHESIA           | CEFTRIAXONE | Moderate | Probable | NK | Negative | Hospital-acquired | Neurological | Other medically significant condition |
| ITCHING SKIN - MULTIFORME RASH | DICLOFENAC, METRONIDAZOLE | Moderate | Probable | No | Negative | Hospital-acquired | Skin and appendages | Required intervention to prevent damage |
| PARESTHESIAS (PERIPHERAL NEUROPATHY) | METRONIDAZOLE | Severe | Possible | No | Unknown | Community-acquired | Neurological | Required intervention to prevent damage |
| HIGH GRADE FEVER WITH CHILLS AND RIGOR | HRZE | Severe | Possible | No | Unknown | Community-acquired | Body - General | Caused or prolonged Hosp |

(Continued)
| Adverse Drug Reaction                  | Drug                                      | Severity | Causality | Rarity | HIV-status | Community or Hospital-acquired | System Organ Class | Grade of Seriousness |
|----------------------------------------|-------------------------------------------|----------|-----------|--------|------------|---------------------------------|--------------------|----------------------|
| BLURRED VISION                         | METRONIDAZOLE                             | Mild     | Possible  | No      | Unknown    | Hospital-acquired Vision        | Vision             | Other medically significant condition |
| VOMITING (3 EPISODES)                  | CEFTRIAXONE, TRAMADOL                     | Mild     | Possible  | No      | Unknown    | Hospital-acquired Gastrointestinal | Gastrointestinal   | Other medically significant condition |
| LOSS OF APPETITE                       | METRONIDAZOLE                             | Moderate | Possible  | No      | Unknown    | Hospital-acquired Gastrointestinal | Gastrointestinal   | Caused or prolonged Hosp |
| DECREASED URINE OUTPUT                 | CEFTRIAXONE                              | Severe   | Possible  | No      | Unknown    | Hospital-acquired Urinary tract | Urinary tract      | Other medically significant condition |
| LOSS OF APPETITE                       | CTX, METRONIDAZOLE                        | Moderate | Possible  | No      | Positive   | Community-acquired Gastrointestinal | Gastrointestinal   | Required intervention to prevent damage |
| PARESTHESIAS                           | 3TC, CTX                                 | Moderate | Possible  | No      | Positive   | Community-acquired Neurological  | Neurological        | Other medically significant condition |
| FEVER                                  | AZT/3TC/EFV, CTX                         | Severe   | Possible  | No      | Positive   | Community-acquired Body - General | Body - General     | Required intervention to prevent damage |
| SEVERE PALLOR OF MUCUS MEMBRANES       | HRZE, TDF/3TC/NVP, CTX                   | Severe   | Possible  | No      | Positive   | Community-acquired Blood        | Blood              | Required intervention to prevent damage |
| DIZZINESS                              | HRZE, TDF/3TC, CTX                       | Severe   | Possible  | No      | Positive   | Community-acquired Neurological  | Neurological        | Caused or prolonged Hosp |
| PRODUCTIVE COUGH                       | CTX, TDF/3TC                             | Severe   | Possible  | No      | Positive   | Community-acquired Respiratory   | Respiratory         | Required intervention to prevent damage |
| JAUNDICE                               | HRZE, TDF/3TC, CTX                       | Moderate | Possible  | No      | Positive   | Community-acquired Liver and biliary | Liver and biliary   | Required intervention to prevent damage |
| DIFFICULTY IN BREATHING               | RIFAMPICIN, TDF/3TC, CTX                 | Severe   | Possible  | No      | Positive   | Community-acquired Respiratory   | Respiratory         | Required intervention to prevent damage |
| NUMBNESS OF BOTH LOWER LIMBS          | HE, 3TC, CTX                             | Moderate | Possible  | No      | Positive   | Community-acquired Neurological  | Neurological        | Required intervention to prevent damage |
| DIZZINESS                              | COARTEM, DAPSONE, FLUCONAZOLE            | Moderate | Possible  | No      | Positive   | Community-acquired Neurological  | Neurological        | Caused or prolonged Hosp |
| PAREAPARESIS                           | INH                                       | Moderate | Possible  | No      | Positive   | Community-acquired Neurological  | Neurological        | Caused death |
| JAUNDICE                               | INH                                       | Life-threatening | Possible | No      | Positive   | Community-acquired Liver and biliary | Liver and biliary   | Caused or prolonged Hosp |
| GENERALIZED MACULO-PAPULAR RASH        | CTX, ARVS (TDF/3TC/EFV)                  | Moderate | Possible  | No      | Positive   | Community-acquired Skin and appendages | Skin and appendages | Caused or prolonged Hosp |
| VOMITING                               | FLUCONAZOLE, ACICLOVIR, CEFTRIAXONE      | Moderate | Possible  | Yes     | Positive   | Community-acquired Gastrointestinal | Gastrointestinal   | Caused or prolonged Hosp |
| SEVERE ANEMIA 3.4G/DL                  | TDF/3TC, CTX                             | Severe   | Possible  | No      | Positive   | Community-acquired Blood        | Blood              | Caused or prolonged Hosp |
| WORSENED PALLOR                       | TDF/3TC, CTX                             | Severe   | Possible  | No      | Positive   | Community-acquired Skin and appendages | Skin and appendages | Required intervention to prevent damage |
| DIARRHEA                               | TDF/3TC/EFV, CTX                         | Moderate | Possible  | No      | Positive   | Community-acquired Gastrointestinal | Gastrointestinal   | Caused or prolonged Hosp |
| HEADACHE                               | CTX                                       | Moderate | Possible  | No      | Positive   | Community-acquired Neurological  | Neurological        | Caused or prolonged Hosp |
| VOMITING                               | HRZE                                     | Severe   | Possible  | No      | Positive   | Community-acquired Gastrointestinal | Gastrointestinal   | Caused or prolonged Hosp |
| ANEMIA                                 | CTX                                       | Moderate | Possible  | No      | Positive   | Community-acquired Blood        | Blood              | Caused or prolonged Hosp |

(Continued)
| Adverse Drug Reaction             | Drug                                      | Severity | Causality | Rarity | HIV-status | Community or Hospital-acquired | System Organ Class | Grade of Seriousness                                                                 |
|----------------------------------|-------------------------------------------|----------|-----------|--------|------------|---------------------------------|--------------------|-------------------------------------------------------------------------------------|
| Abdominal discomfort/distention  | HRZE, AZT                                 | Moderate | Possible  | No     | Positive   | Community-acquired              | Gastrointestinal   | Other medically significant condition                                                 |
| Paresthesia                      | CTX, TDF/3TC/LPV/RTV                      | Moderate | Possible  | No     | Positive   | Community-acquired              | Neurological        | Required intervention to prevent damage                                             |
| Persistent diarrhoea             | 3TC/TDF/EFV, CTX                          | Severe   | Possible  | No     | Positive   | Community-acquired              | Gastrointestinal   | Required intervention to prevent damage                                             |
| Vomiting                         | 3TC/TDF/EFV, CTX                          | Severe   | Possible  | No     | Positive   | Community-acquired              | Gastrointestinal   | Required intervention to prevent damage                                             |
| Anorexia                         | 3TC/TDF, CTX                              | Moderate | Possible  | No     | Positive   | Community-acquired              | Gastrointestinal   | Required intervention to prevent damage                                             |
| Joint pain                       | 3TC/TDF, CTX                              | Severe   | Possible  | No     | Positive   | Community-acquired              | Musculoskeletal     | Required intervention to prevent damage                                             |
| Deep jaundice                    | RHZ, AZT/3TC                              | Severe   | Possible  | No     | Positive   | Community-acquired              | Liver and biliary  | Required intervention to prevent damage                                             |
| Peripheral neuropathy            | AZT, 3TC, INH                             | Moderate | Possible  | No     | Positive   | Community-acquired              | Neurological        | Required intervention to prevent damage                                             |
| Cough                            | TDF/3TC, CTX                              | Severe   | Possible  | No     | Positive   | Community-acquired              | Respiratory         | Required intervention to prevent damage                                             |
| Dry cough with shortness of breath | CTX                                       | Severe   | Possible  | Yes    | Positive   | Community-acquired              | Respiratory         | Required intervention to prevent damage                                             |
| Dizziness                        | METRONIDAZOLE                              | Severe   | Possible  | No     | Positive   | Community-acquired              | Neurological        | Required intervention to prevent damage                                             |
| Dizziness                        | TDF/3TC, RHZE                              | Moderate | Probable  | No     | Positive   | Community-acquired              | Neurological        | Required intervention to prevent damage                                             |
| Loss of appetite                 | 3TC, TDF, RIFAMPICIN, PYRAZINAMIDE        | Moderate | Probable  | No     | Positive   | Community-acquired              | Gastrointestinal   | Required intervention to prevent damage                                             |
| Vomiting                         | HRZE                                      | Moderate | Probable  | No     | Positive   | Community-acquired              | Gastrointestinal   | Required intervention to prevent damage                                             |
| Generalized body weakness        | TDF/3TC, RIFAMPICIN                       | Moderate | Probable  | No     | Positive   | Community-acquired              | Body - General      | Caused or prolonged Hosp                                                             |
| Headache                         | INH, RIFAMPICIN                           | Moderate | Probable  | No     | Positive   | Community-acquired              | Neurological        | Required intervention to prevent damage                                             |
| Constipation                     | INH                                        | Moderate | Probable  | No     | Positive   | Community-acquired              | Gastrointestinal   | Required intervention to prevent damage                                             |
| Pruritus                         | TDF/EPV, METRONIDAZOLE, INH, ETHAMBUTOL   | Severe   | Probable  | No     | Positive   | Community-acquired              | Skin and appendages | Caused disability                                                                   |
| Itchy rash with numbness of lower swollen legs | HE, CARVEDILOL                           | Moderate | Probable  | No     | Positive   | Community-acquired              | Skin and appendages | Caused disability                                                                   |
| Jaundice                         | CTX                                       | Moderate | Probable  | No     | Positive   | Community-acquired              | Liver and biliary  | Required intervention to prevent damage                                             |
| Peripheral neuropathy            | 3TC, METRONIDAZOLE                        | Moderate | Probable  | Yes    | Positive   | Community-acquired              | Neurological        | Caused or prolonged Hosp                                                             |

(Continued)
## Table 7. Continued.

| Adverse Drug Reaction | Drug | Severity | Causality  | Rarity   | HIV-status | Community or Hospital-acquired | System Organ Class | Grade of Seriousness |
|-----------------------|------|----------|------------|----------|------------|--------------------------------|-------------------|---------------------|
| DIB WITH SHORTNES OF BREATH | RIFAMPICIN | Severe | Probable | No | Positive | Community-acquired | Respiratory | Life-threatening |
| ANEMIA | CTX, TDF/3TC/LPV/RTV | Moderate | Probable | No | Positive | Community-acquired | Blood | Caused or prolonged Hosp |
| PEDAL EDEMA | RIFAMPICIN | Severe | Probable | No | Positive | Community-acquired | Cardiovascular | Required intervention to prevent damage |
| PARESTHESIA | HRZ | Mild | Probable | No | Positive | Community-acquired | Neurological | Caused or prolonged Hosp |
| VOMITING | CEFTRIAXONE, METRONIDAZOLE, BLOOD, DICLOFENAC | Severe | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Required intervention to prevent damage |
| DIZZINESS | CEFTRIAXONE, METRONIDAZOLE, DICLOFENAC | Moderate | Possible | No | Positive | Hospital-acquired | Neurological | Required intervention to prevent damage |
| FEVER | CTX, TDF/3TC/EFV | Moderate | Possible | No | Positive | Hospital-acquired | Body - General | Required intervention to prevent damage |
| FEVER | CEFTRIAXONE | Moderate | Possible | No | Positive | Hospital-acquired | Body - General | Required intervention to prevent damage |
| VOMITING | CEFTRIAXONE, TDF/3TC/EFV | Severe | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Caused or prolonged Hosp |
| DIZZINESS | CEFTRIAXONE, METOCLOPRAMIDE | Moderate | Possible | No | Positive | Hospital-acquired | Neurological | Caused or prolonged Hosp |
| VOMITING | CEFTRIAXONE | Severe | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Caused or prolonged Hosp |
| FEVER 39.6C | CEFTRIAXONE | Severe | Possible | No | Positive | Hospital-acquired | Body - General | Caused or prolonged Hosp |
| FEVER 38.3C | ACICLOVIR, CEFTRIAXONE | Severe | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Caused or prolonged Hosp |
| ANOREXIA | CTX | Moderate | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Required intervention to prevent damage |
| DIARRHEA | CEFTRIAXONE | Moderate | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Caused or prolonged Hosp |
| SEVERE ABDOMINAL PAIN | CIPROFLOXACIN | Severe | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Required intervention to prevent damage |
| VOMITING | CEFTRIAXONE | Severe | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Caused or prolonged Hosp |
| HIGH GRADE FEVER 39.2C | CEFTRIAXONE | Severe | Possible | No | Positive | Hospital-acquired | Body - General | Required intervention to prevent damage |
| VOMITING | ERYTHROMYCIN, CEFTRIAXONE | Severe | Probable | No | Positive | Hospital-acquired | Gastrointestinal | Required intervention to prevent damage |
| FEVER 38.5C | CEFTRIAXONE | Moderate | Possible | No | Positive | Hospital-acquired | Body - General | Required intervention to prevent damage |
| FEVER 38 C | CEFTRIAXONE, DUOVIR-N, INH, PYRAZINAMIDE | Mild | Probable | No | Positive | Hospital-acquired | Body - General | Required intervention to prevent damage |
| VOMITING | CEFTRIAXONE | Moderate | Possible | No | Positive | Hospital-acquired | Gastrointestinal | Required intervention to prevent damage |

CTX, Cotrimoxazole; GTC, General Tonic-Clonic; INH, Isoniazid; HE, Isoniazid/Ethambutol; Hosp, Hospital; RHZ, Rifampicin/Isoniazid/Pyrazinamide; HRZE, Isoniazid/Rifampicin/Pyrazinamide/Ethambutol; AZT, Zidovudine; TDF, Tenofovir; 3TC, lamivudine; NVP, nevirapine; EFV, Efavirenz; LPV, Lopinavir; RTV, Ritonavir; ARVS, Antiretrovirals; DUOVIR-N, Zidovudine/lamivudine/nevirapine; NK, Incidence unknown; DIB, Difficulty in Breathing.
identified antibiotics can be prioritized for routine pharmaceutical quality assessment in resource-limited settings where the challenge of counterfeit and substandard drugs prevails (Almuzaini et al. 2013).

Community-acquired aa-ADRs were mostly linked to the preadmission use of cotrimoxazole for prevention of, and antituberculous drugs for treatment of, HIV-associated opportunistic infections. The cotrimoxazole link to community-acquired aa-ADRs is in accordance with previous research in the US (Shehab et al. 2008) though cotrimoxazole is also a common cause of hospital-acquired aa-ADRs in France (Courjon et al. 2013). Similarly, antituberculous drugs are a major cause of hospital-acquired aa-ADRs in South Africa (Mehta et al. 2008), though most in our study were community-acquired.

We document a many-fold higher risk for serious prevalent aa-ADRs at the time of hospital admission in known HIV-positive patients. Our study also corroborates findings from the United Kingdom, South Africa, and Rwanda which reported that the incidence of serious community-acquired-/hospital-acquired aa-ADRs in HIV-infected patients is at least twice that in HIV-uninfected patients (Breen et al. 2006; Marks et al. 2009; Lorent et al. 2011), probably due to drug-drug interactions from concomitant antiretroviral medications (Breen et al. 2006). Moreover, Marks et al. (2009) have argued that the higher incidence of serious aa-ADRs in South African patients on antituberculous treatment could have been predominated by their HIV-infection rather than by co-administered antiretroviral therapy.

One in four ADRs related to hospital admission was linked to antibiotic use, which is similar to what is reported in the US (Shehab et al. 2008), but higher than as observed in Spain (Carrasco-Garrido et al. 2010), The Netherlands (van der Hooft et al. 2008), and India (Sonal et al. 2011). The fatal, disabling or life-threatening serious community-acquired aa-ADRs linked to individual antituberculous drugs highlight the need for vibrant pharmacovigilance of antituberculous drugs to safeguard patients in our setting where treatment discontinuation or modification may be warranted. The proportion of allergic aa-ADRs in our cohort (22%), two-fifths of them serious, was much lower than is reported in the US (79%) (Shehab et al. 2008), probably by reason of differences in study methodology. Our estimate is based on representatively sampled patients as the unit of analysis, whereas the US study used hospital visits for a drug-related ADR.

The majority of rare and serious aa-ADRs were accounted to cotrimoxazole and metronidazole use, yet the number of inpatients who received ceftriaxone during hospital stay was twofold higher than for metronidazole and cotrimoxazole. The aa-ADRs linked to cotrimoxazole use were probably as a result of long-term exposure to cotrimoxazole prophylaxis in HIV/AIDS patients. Thus, ongoing close monitoring and documentation of cotrimoxazole’s safety profile in our setting is critical. Metronidazole and ceftriaxone were mostly initiated during the current admission. The rare aa-ADRs linked to metronidazole use frequently involved the central nervous system: metronidazole is a small lipophilic molecule that can easily cross the blood–brain barrier and act centrally (Nau et al. 2010). The high incidence of metronidazole-associated rare aa-ADRs during hospital stay should be investigated further. Three percent (8/246; 95% CI: 1.4% to 6.4%) of patients who received metronidazole while in hospital developed a rare hospital-acquired metronidazole-associated aa-ADR. Metronidazole has a BNF list of 22 rare aa-ADRs (British National Formulary, 2014). If such aa-ADRs occur independently within-patient, the potential rate of occurrence of rare aa-ADRs among metronidazole users is 22*1/1000, or 2%. The observed occurrence rate of 3% for any rare aa-ADR is thus consistent with metronidazole being associated with a long list of 22 rare aa-ADRs.

We suggest that, periodically, Mulago Hospital and possibly other secondary care health facilities in resource-poor settings could set up ward-tailored ADR tracking logs, as used in our study, which are formally placed, by default, into patients’ hospital files to log and retrieve, for analysis, ADRs experienced by inpatients. The ADR tracking log has all the data fields of the full suspected ADR reporting form (Form S1) and is efficient for data collection with reduced paper burden. On patient-discharge, a copy of the log ought to be made for central analysis after every 200–500 such forms have been collected. For health facilities which admit 70–105 patients per week, a 6-week surveillance period once every 6 months, would suffice. This approach, if well-coordinated through a local hospital-based pharmacovigilance unit, will give facility-specific estimates of antibiotic safety and validate the findings of our study at a much lower cost.

This study had limitations. First, the demanding nature of data collection and high staff costs for high-quality data limited the number of inpatients studied to the range 600–800 rather than 1200–1500 as initially intended. However, higher than anticipated prevalence at admission and incidence during hospital stay of aa-ADRs meant that the achieved sample size was sufficient to describe the characteristics of these aa-ADRs. Second, variations from the planned systematic random sampling approach for recruiting inpatients were minor and unlikely to alter our findings. Third, refusal rates by omitted inpatients were not formally recorded but were low. Fourth, consensus – rather than individual assessments of aa-ADR causality and preventability followed by appraisal of interobserver agreement – was used. Fifth was the challenge of assessing ADR causality in acutely unwell patients.
with multiple comorbidities and on multiple medications. Hence, we screened patients using an ADR trigger tool to increase the probability to detect aa-ADRs; and subsequently applied the Naranjo ADR scale to the suspect clinical signs and symptoms to identify those that were at least possibly antibiotic-associated. We held extensive ward-team discussions and made consultations with the literature before reaching consensus on ADR causality. Sixth, we cannot claim generalizability of our findings to district hospitals, clinics, and other lower level health centers in Uganda. Similar studies conducted in lower level health facilities could elucidate the extent and characteristics of aa-ADRs in those settings.

Conclusion

Ceftriaxone showed the highest risk for hospital-acquired aa-ADRs (also of serious hospital-acquired aa-ADRs), even in HIV-negative/unknown serostatus patients, probably due to its high consumption. Levofloxacin signaled as high-risk for hospital-acquired aa-ADRs despite its low frequency of in-hospital use, thus, highlighting the utility of standardizing absolute aa-ADR counts by DDDs administered. Cotrimoxazole and antituberculous drugs were the most frequently implicated in community-acquired aa-ADRs (also in serious community-acquired aa-ADRs). Pharmaceutical quality testing of implicated antibiotics in Uganda could be worthwhile. In sentinel settings, periodic on-ward collection and analysis of antibiotic-safety-data standardized by DDDs, such as during a 6-week surveillance period once every 6 months, should be an efficient method of tracking antibiotics with 1%-risk for serious aa-ADRs.

Author Contribution

RK conceived of the study and drafted the manuscript and, in conjunction with SMB, participated in its design, implementation, statistical analysis, and drawing of inferences. CK participated in study design and, together with SMB, took part in the manuscript writing process. All authors approved the final manuscript. [3,901 words].

Disclosure

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). RK gratefully acknowledges funding support from 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 by the African Population and Health Research Centre (APHRC) in partnership with the International Development Research Centre (IDRC). In UK, SMB is funded by Medical Research Council program number MC_U105260794. SMB has GSK shares. The work here reported is solely the responsibility of the authors and does not necessarily represent the official views of the supporting offices. The funders had no role in the decisions on what and where to publish.

References

WHO (2006). Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach Available at http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf (accessed on 12 September 2015)

WHO-UMC (2011). Glossary of terms used in Pharmacovigilance. Available at http://who-umc.org/Graphics/24729.pdf (accessed 13 March 2015)

Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G, Faes C, et al. 2011. European surveillance of antimicrobial consumption (ESAC): Outpatient antibiotic use in Europe (1997–2009). J Antimicrob Chemother, 66(suppl 6):vi3–vi12.

Alexopoulou A, Dourakis SP, Mantzoukis D, Petsariotis T, Kandili A, Deutsch M, et al. (2008). Adverse drug reactions as a cause of hospital admissions: a 6-month experience in a single center in Greece. Eur J Intern Med 19: 505–510.

Almuzaini T, Choonara I, Sammons H (2013). Substandard and counterfeit medicines: a systematic review of the literature. BMJ Open 3: e002923.

Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) Index (2015). Available at: http://www.whocc.no/atc_ddd_index/(accessed 14 March 2015)

Breen RA, Miller RF, Gorsch T, Smith CJ, Schwenk A, Holmes W, et al. (2006). Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax 61: 791–794.

British National Formulary (2014) vol. 68. BMJ Group and Pharmaceutical Press, London.

Carrascogarrido P, de Andres LA, Barrera VH, de Miguel GA, Jimenez-Garcia R (2010). Trends of adverse drug reactions related-hospitalizations in Spain (2001–2006). BMC Health Serv Res 10: 287.

Courjon J, Pulcini C, Cua E, Risso K, Guillouet F, Bernard E, et al. (2013). Antibiotics-related adverse events in the infectious diseases department of a French teaching hospital: a prospective study. Eur J Clin Microbiol Infect Dis 32: 1611–1616.

WHO (2006). Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach Available at http://www.who.int/hiv/pub/guidelines/ctxguidelines.pdf (accessed on 12 September 2015)

WHO-UMC (2011). Glossary of terms used in Pharmacovigilance. Available at http://who-umc.org/Graphics/24729.pdf (accessed 13 March 2015)

Adriaenssens N, Coenen S, Versporten A, Muller A, Minalu G, Faes C, et al. 2011. European surveillance of antimicrobial consumption (ESAC): Outpatient antibiotic use in Europe (1997–2009). J Antimicrob Chemother, 66(suppl 6):vi3–vi12.

Alexopoulou A, Dourakis SP, Mantzoukis D, Petsariotis T, Kandili A, Deutsch M, et al. (2008). Adverse drug reactions as a cause of hospital admissions: a 6-month experience in a single center in Greece. Eur J Intern Med 19: 505–510.

Almuzaini T, Choonara I, Sammons H (2013). Substandard and counterfeit medicines: a systematic review of the literature. BMJ Open 3: e002923.

Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) Index (2015). Available at: http://www.whocc.no/atc_ddd_index/(accessed 14 March 2015)

Breen RA, Miller RF, Gorsch T, Smith CJ, Schwenk A, Holmes W, et al. (2006). Adverse events and treatment interruption in tuberculosis patients with and without HIV co-infection. Thorax 61: 791–794.

British National Formulary (2014) vol. 68. BMJ Group and Pharmaceutical Press, London.

Carrasco-Garrido P, de Andres LA, Barrera VH, de Miguel GA, Jimenez-Garcia R (2010). Trends of adverse drug reactions related-hospitalizations in Spain (2001–2006). BMC Health Serv Res 10: 287.

Courjon J, Pulcini C, Cua E, Risso K, Guillouet F, Bernard E, et al. (2013). Antibiotics-related adverse events in the infectious diseases department of a French teaching hospital: a prospective study. Eur J Clin Microbiol Infect Dis 32: 1611–1616.
Division of AIDS (DAID) (2004). Table for Grading the Severity of Adult and Paediatric Adverse Events Available at http://rsc.tech-res.com/safetyandpharmacovigilance/gradingtables.aspx (accessed 14 March 2015)

Hamad A, Cavell G, Wade P, Hinton J, Whittlesea C (2013). Risk of medication safety incidents with antibiotic use measured by defined daily doses. Int J Clin Pharmacy 35: 772–779.

van der Hooft CS, Dielemans JP, Siemes C, Aarnoudse AJ, Verhamme KM, Stricker BH, et al. (2008). Adverse drug reaction-related hospitalisations: a population-based cohort study. Pharmacoepidemiol Drug Saf 17: 365–371.

Kiguba R, Karamagi C, Waako P, Ndagije HB, Bird SM (2015). Rare, serious, and comprehensively described suspected adverse drug reactions reported by surveyed healthcare professionals in Uganda: but with frequent missed-dose days. J Antimicrob Chemother 71: 1697–1706. doi:10.1093/jac/dkw025.

Kiguba R, Karamagi C, Bird SM (2016a). Extensive antibiotic prescription rate among hospitalized patients in Uganda: but with frequent missed-dose days. J Antimicrob Chemother 71: 1697–1706. doi:10.1093/jac/dkw025.

Kiguba R, Karamagi C, Bird SM (2016b). Incidence, risk factors and risk-prediction of hospital-acquired suspected adverse drug reactions: a prospective cohort of Ugandan inpatients. BMJ Open 7:e010568.

Lau PM, Stewart K, Dooley MJ (2003). Comment: hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 37: 303–304. author reply 304-305.

Lorent N, Sebatunzi O, Mukeshimana G, Van den Ende J, Clerinx J (2011). Incidence and risk factors of serious adverse drug events during antituberculous treatment in Rwanda: a prospective cohort study. PLoS ONE 6: e19566.

Marks DJR, Dheda K, Dawson R, Ainslie G, Miller RF (2009). Adverse events to antituberculosis therapy: influence of HIV and antiretroviral drugs. Int J STD AIDS 20: 339–345.

Mehta U, Durheim DN, Blockman M, Kredo T, Gounden R, Barnes KI (2008). Adverse drug reactions in adult medical inpatients in a South African hospital serving a community with a high HIV/AIDS prevalence: prospective observational study. Br J Clin Pharmacol 65: 396–406.

Mouton JP, Mehta U, Parrish AG, Wilson DP, Stewart A, Njuguna CW, et al. (2015). Mortality from adverse drug reactions in adult medical inpatients at four hospitals in South Africa: a cross-sectional survey. Br J Clin Pharmacol 80: 818–826.

Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. (1981). A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30: 239–245.

Nau R, Sörgel F, Eiffert H (2010). Penetration of drugs through the blood-cerebrospinal fluid/blood-brain barrier for treatment of central nervous system infections. Clin Microbiol Rev 23: 858–883.

Rozich JD, Haraden CR, Resar RK (2003). Adverse drug event trigger tool: a practical methodology for measuring medication related harm. Qual Saf Health Care 12: 194–200.

Safety monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre (2000). Available at: http://apps.who.int/medicinedocs/en/p/pdf/printed.html (accessed 15 January 2015)

Schumock GT, Thornton JP (1992). Focusing on the preventability of adverse drug reactions. Hospital Pharm 27: 538.

Shehab N, Patel PR, Srinivasan A, Budnitz DS (2008). Emergency department visits for antibiotic-associated adverse events. Clin Infect Dis 47: 735–743.

Sonal Sekhar M, Adheena Mary C, Anju PG, Hamsa NA. 2011. Study on drug related hospital admissions in a tertiary care hospital in South India. Saudi Pharm J 19:273–278.

StataCorp (2011). Stata Statistical Software: Release 12. In. College Station, StataCorp LP; TX.

Uganda AIDS Commission (2015). The HIV and AIDS Uganda Country Progress Report. Available at: http://www.unaids.org/sites/default/files/country/documents/UGA_narrative_report_2015.pdf (accessed 30 March 2016)

Van Boekel TP, Gandra S, Ashok A, Caudron Q, Grenfell BT, Levin SA, et al. (2014). Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 14: 742–750.

Weiss AJ, Elixhauser A, Bae J, Encinosa W. 2011. Origin of Adverse Drug Events in U.S. Hospitals. Statistical Brief #158. In: Healthcare Cost and Utilization Project (HCUP) Statistical Briefs. edn.Agency for Healthcare Research and Quality (USA), Rockville (MD) 2013.

WHO (2004). The World Medicines Situation. Available at: http://apps.who.int/medicinedocs/en/d/Js6160e/10.html (accessed 12 September 2015)

Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Form S1. Suspected ADR reporting form.

Table S1. (A) Incidence of hospital-acquired antibiotic-associated suspected ADRs per 100 Defined Daily Doses stratified by HIV-status.(B) Incidence of hospital-acquired antibiotic-associated suspected ADRs per 100 patients at risk stratified by HIV-status.

Table S2. Frequencies of individual antibiotic-associated ADRs in the Probable or Definite vs. Possible ADR causality categories, Uganda, 2014.
Table S3. Serious antibiotic-associated suspected adverse drug reactions, with preventability, experienced by hospitalized patients, Uganda, 2014.

Table S4. List of 24 rare antibiotic-associated suspected adverse drug reactions experienced by hospitalized patients, Uganda, 2014.