

EVALUATION OF CLINICAL USE OF CEFTRIAXONE AMONG INPATIENTS IN SELECTED HEALTH FACILITIES IN UGANDA

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Presentation outline

- ❖ Study Background
- ❖ Study Aim and Objectives
- ❖ Study Methods
- ❖ Key Study Finding
- ❖ Discussion
- ❖ Conclusions
- ❖ Recommendations



Study background (1)

- Ceftriaxone (3rd generation cephalosporin) critical in the treatment of many infections due to its high antibacterial potency, wide spectrum of activity, and low potential for toxicity (Lee et al., 2009).
- It is the most widely used drug for empiric treatment of inpatients with signs of systemic infection (Lee et al., 2009; Sileshi et al., 2016).
- In Uganda, reports indicate 80% exposure among in patients admitted in Mulago National Referral hospital (Kiguba, Karamagi, & Bird, 2016).
- There are emerging anecdotes about inefficacy of certain antibiotics including Ceftriaxone.



Study background (2)

- However, investigations by National Drug Authority on commercial brands of ceftriaxone on the Uganda market indicate their overall conformity to pharmacopeial standards
- Cephalosporins (like Ceftriaxone) have a high prevalence of inappropriate prescriptions (Lee et al., 2009; Saleh et al., 2015)
- A Cross sectional survey carried out in Mubende RRH on utilization of Ceftriaxone reported 81% inappropriate administration of ceftriaxone (Manirakiza et al., 2019).
- There was need to conducted a study involving a more facilities at different levels of care and ownership
- This Evaluation was conducted at 9 facilities with regional, level of care and affiliation representation so as to obtain a wider perspective on the utilization of Ceftriaxone in Uganda.



Study Aim and Objectives

Study Aim

To assess the appropriateness of ceftriaxone utilization at selected health facilities in Uganda.

Study Objectives

- i. To evaluate prescribing patterns of ceftriaxone among inpatients in selected Health facilities in Uganda
- ii. To assess compliance of ceftriaxone prescriptions to Uganda standard Treatment guidelines among in-patients in selected health facilities in Uganda
- iii. To document treatment outcomes for inpatients on ceftriaxone in selected facilities in Uganda



Study Methods (1)

Study design

- This was a quantitative retrospective study of prescribing practices of ceftriaxone.
- It was carried out over a period of three (3) months involving review of patient medical records. The documents reviewed included; patient prescriptions, in patient registers, treatment sheets and laboratory registers.

Study Sites

#	Level of Care	Number of Facilities	Ownership	Location
1	Regional Referral	1	Public (1)	Eastern (1)
2	General Hospital	5	Public (2) PNFP (2) PFP (1)	Kampala (1), Central (1) Kampala (1), Northern (1) Kampala (1)
3	Health Center IV	3	Public (3)	West Nile (1), Western (1), South western (1)



Study Methods (2)

Sample size and Sampling procedure

- A total of 885 patient medical records [about 100 medical records per health facility (MSH&WHO, 2007)] were reviewed retrospectively in November 2019- January 2020 using proportionate and systematic sampling techniques

Data collection tool used

- A standard structured data collection tool of World Health Organization (WHO) was adopted with modifications and pretested at Acute care unit of Mulago Hospital
- **The tool covered the following parameters;** patient demographics, prescriber qualification, indication for use, the dose, frequency, duration, contraindication, interactions and culture and sensitivity testing. In addition, the tool collected information on treatment outcomes which include; length of hospital stay, adverse drug reactions, treatment failure/switch to another antibiotic, cure or death of patients



Study Methods (3)

Data analysis

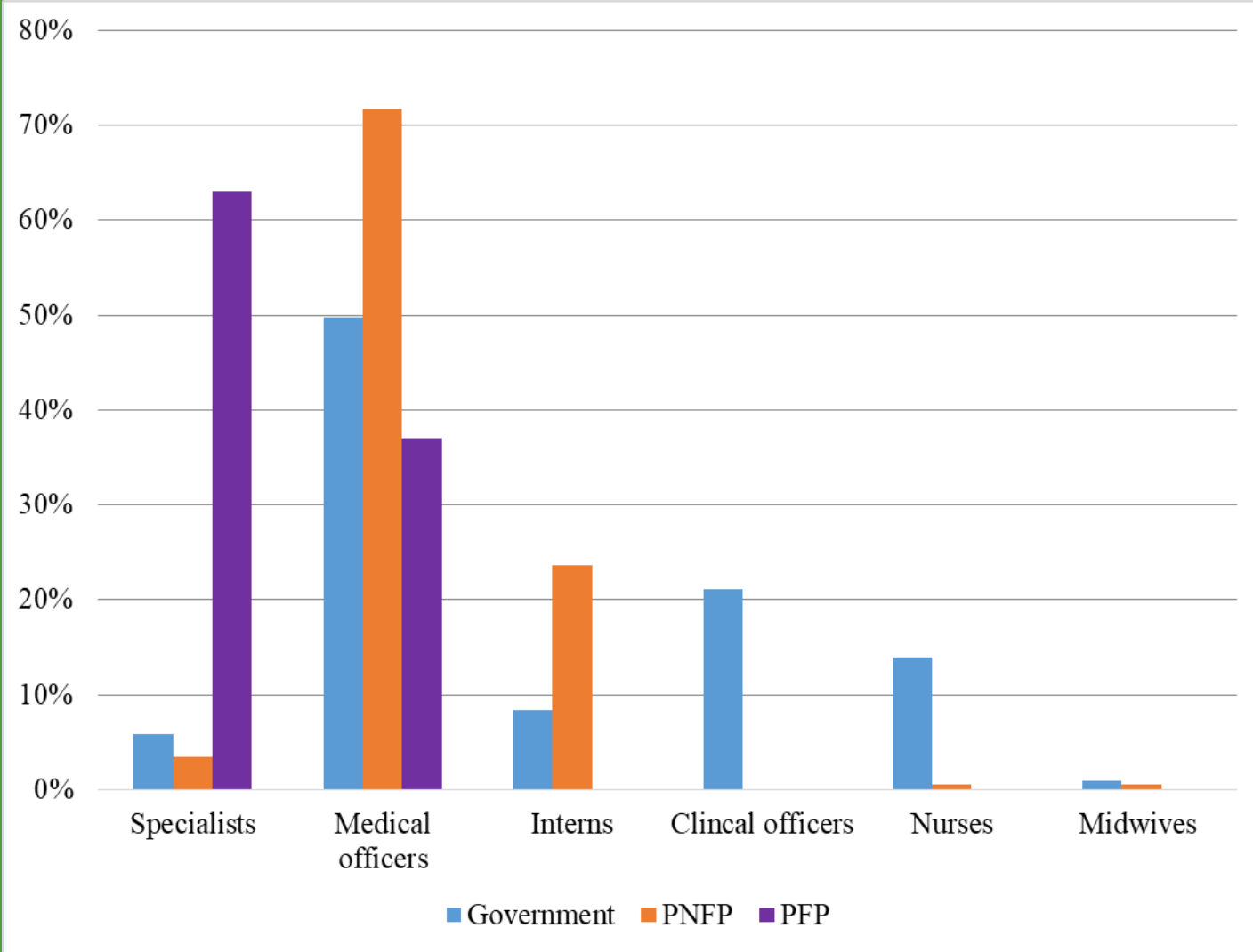
- The data was entered in Epi-Data and exported to STATA for analysis. Continuous variables like age and weight as means and ranges were summarized. For categorical variables like race and gender, percentages and proportions were used to summarize them.
- The prescriptions were evaluated against the Uganda Standard Treatment guidelines (UCG, 2016) and WHO STGs to assess compliance
- Analysis for appropriateness was done for seven (7) indicators using a WHO adapted Tool; i.e. Indication, dose, duration, laboratory investigations, accurate dispensing, drug interactions and treatment outcomes



Study Findings (1)

- ❖ Over 885 patients' records were selected and assessed.
- ❖ The age of the patients whose files were reviewed ranged from < 1 to 98 years, mean age + SD (27.2 +/- 22.7 years).
- ❖ The weight ranged from 2.4 to 95kg; mean weight +SD (35.0 +/- 26.1).
- ❖ Overall Prescriptions reviewed were made mostly by Medical Officers (53.3%)
- ❖ About 63% of prescriptions made by specialists were in the PFP facility

Social demographic characteristics



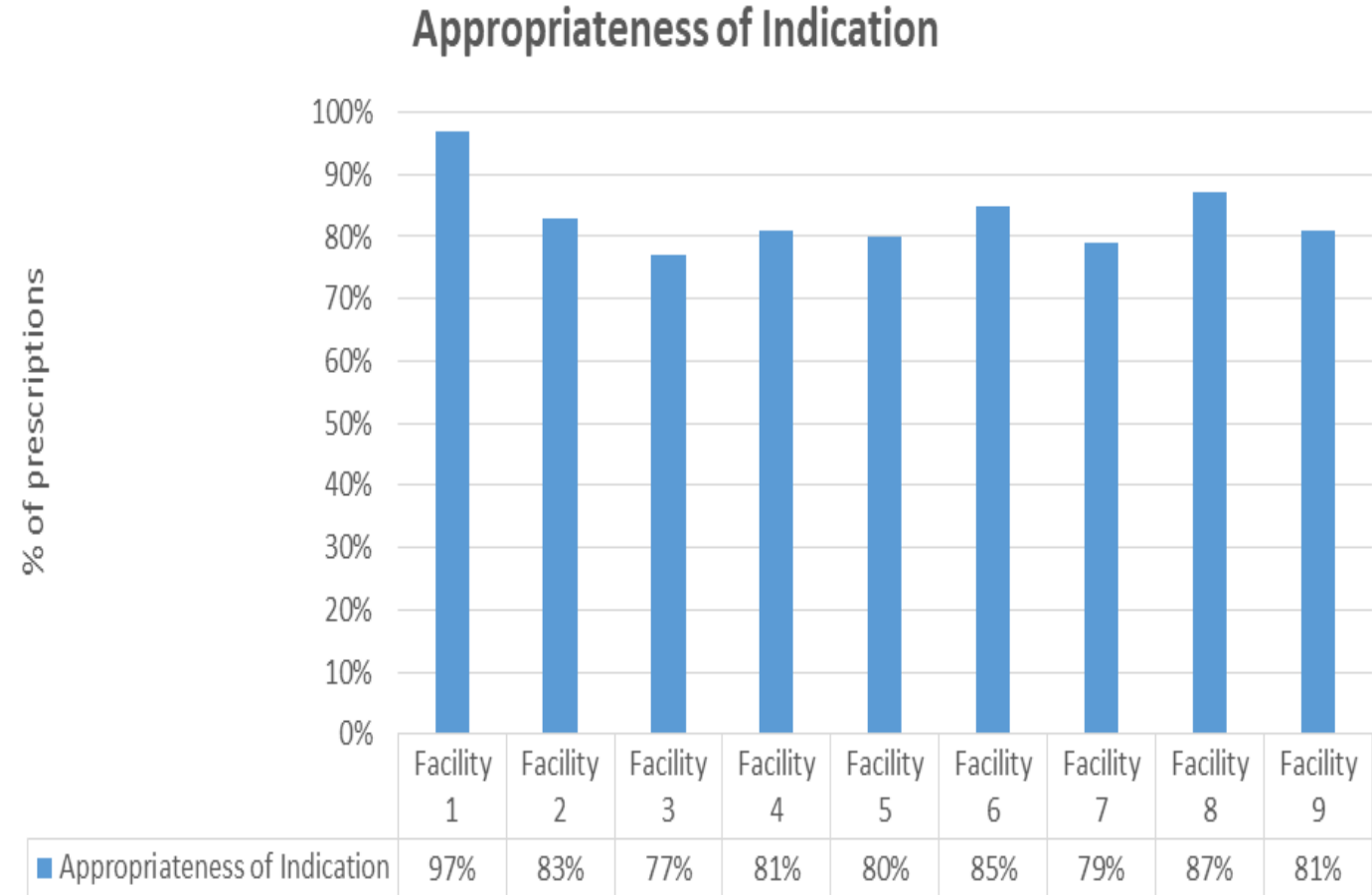
Study Findings (2)

- ❖ The average percentage for appropriateness of indication was 83%.
- ❖ Only the PFP facility scored above the WHO threshold of 90%

Ceftriaxone was mostly prescribed for;

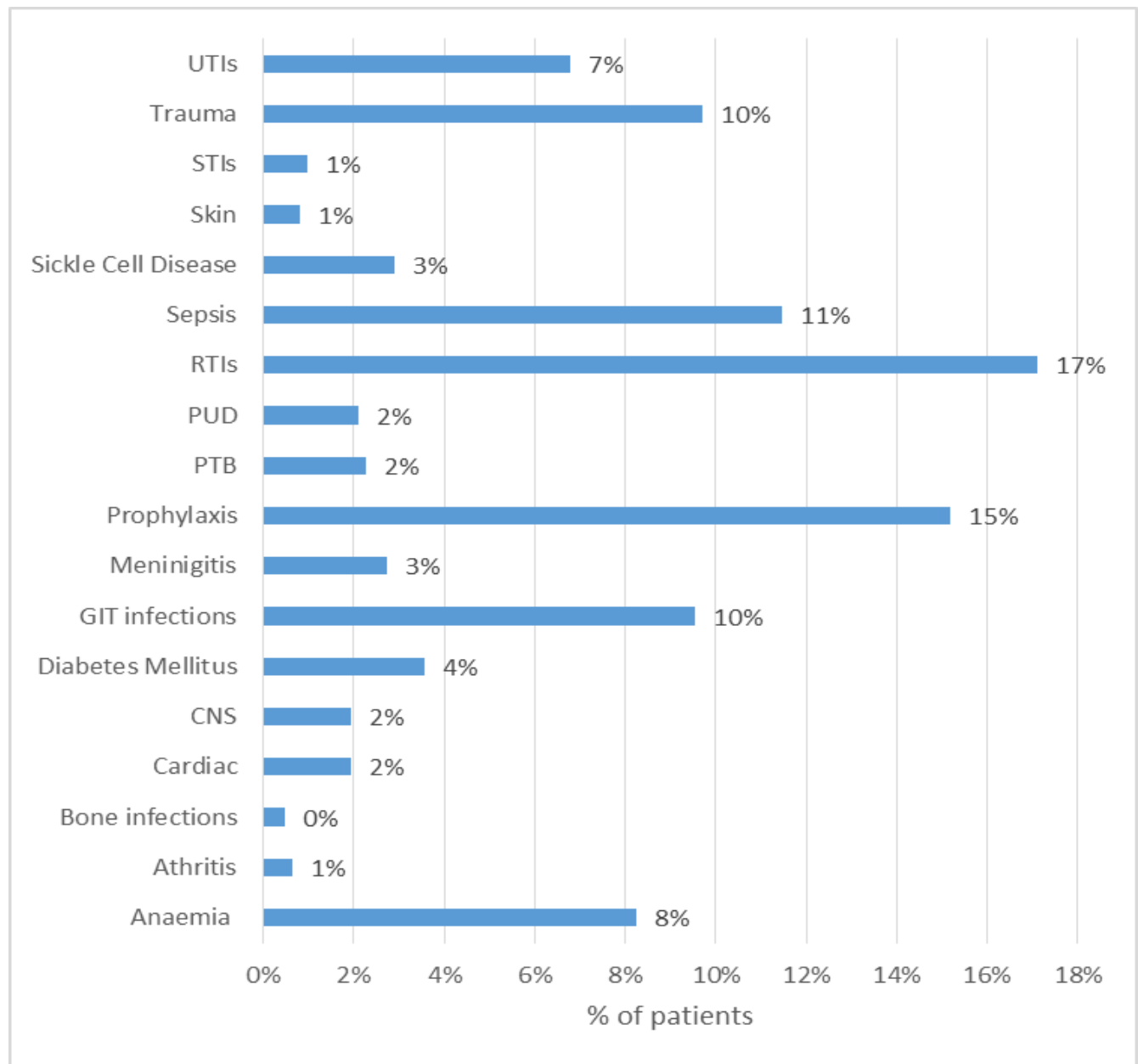
- Surgical prophylaxis- 25% (Trauma, labor and pregnancy complications)
- Respiratory Tract Infections (RTIs) (majorly pneumonia) - 17%,
- Sepsis (11%)
- GIT infections- 10%

1. Appropriateness of Indication



Study Findings (3)

- ❖ Ceftriaxone was found to be prescribed for conditions not listed under the Standard Treatment guidelines, e.g.
- ❖ Malaria- 7 %,
- ❖ Anemia- 8%,
- ❖ Hypertension- 0.5%
- ❖ 1.8% of the prescriptions had no indication for ceftriaxone prescription was given

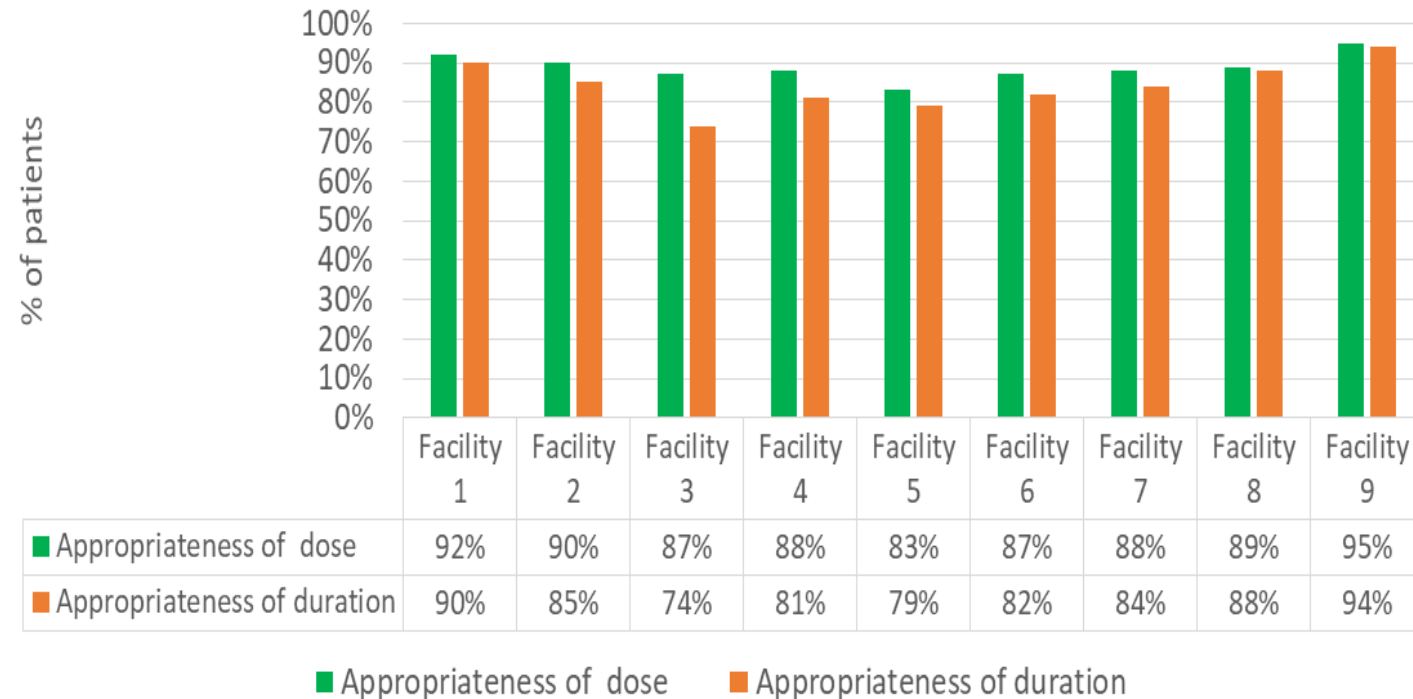


Study Findings (4)

- ❖ The average scores for appropriateness of dose and dose duration across the 9 HFs were 89% and 84% respectively
- ❖ Only the Regional referral (Facility 9) met the WHO threshold of 95% for the two indicators

2. Appropriateness of dose and dose duration

Appropriateness of dose and duration of ceftriaxone prescribed

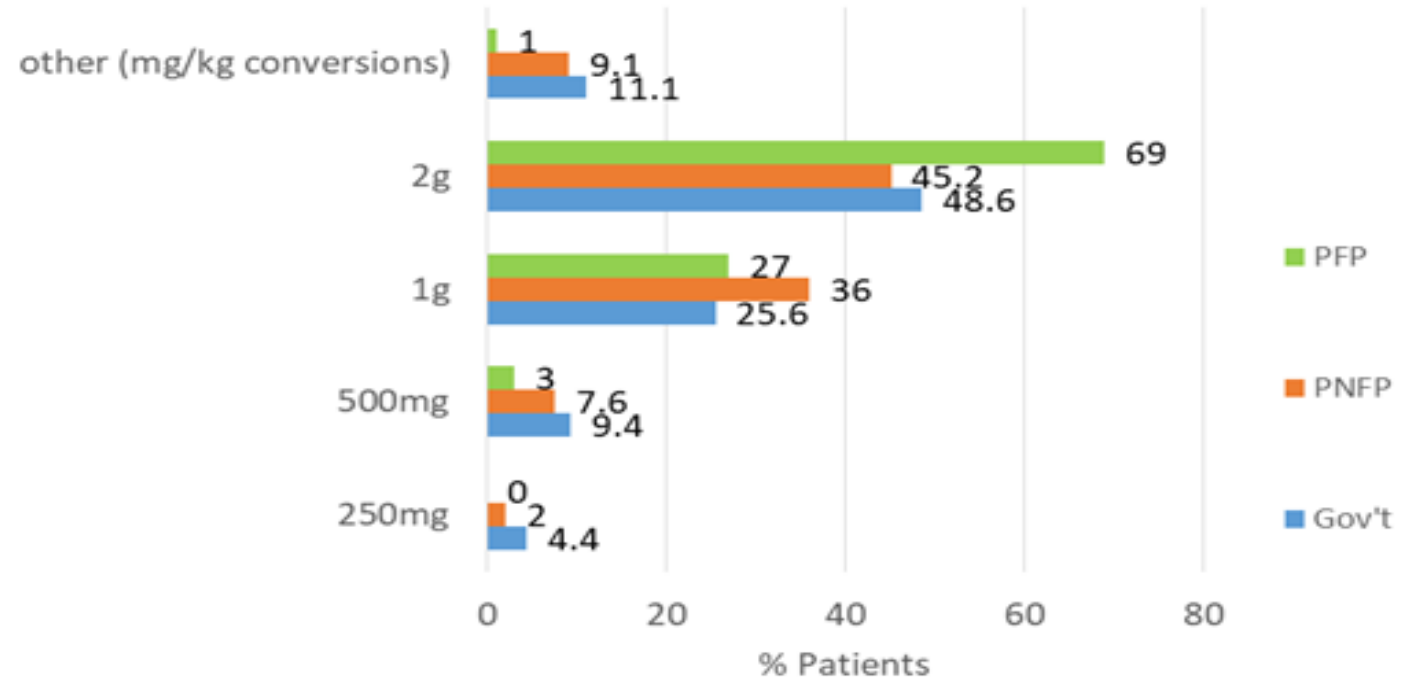


Study Findings (5)

- ❖ The most prescribed dose of ceftriaxone was 2g followed by 1g in all the nine HFIs with 50.1% and 28.8% of the patients receiving 2g and 1g respectively.
- ❖ 2g doses were most prescribed by GHs, while 1g doses were most prescribed by RH
- ❖ The PFP HFI prescribed most (69%) the 2g Ceftriaxone dose, while PNFP HFIs prescribed 1g dose most (36%)

2. Appropriateness of dose and dose duration

Doses of Ceftriaxone prescribed vs Facility ownership



Study Findings (6)

2. Appropriateness of dose and dose duration

- ❖ Medical officers and Specialists prescribed dose of 2g most (57.2% and 55.8% respectively), while the 1g dose was prescribed mostly by nurses and clinical officers (36.6%)
- ❖ The average duration that Ceftriaxone was prescribed was 3.87 (SD=2.28).
- ❖ The most prescribed duration for administration of Ceftriaxone was 5 days (41.0%)
- ❖ Over 5.31% of the patients were prescribed for Ceftriaxone without indicating the duration of administration/ use.
 - ❖ *Over 22.9% of prescriptions by medical interns didn't have duration of use specified.*
- ❖ The most frequency for administration prescribed being once daily (92.3%; 817/885)

Prescriber	Dose				
	250	500mg	1g	2g	other
Unspecified prescriber	0(0%)	0(0%)	0(0%)	1(100%)	0(0%)
Intern	1(1.0%)	6(6.3%)	26(27.1%)	50(52.1%)	13(13.5%)
Medical officer	12(2.6%)	36(7.7%)	118(25.1%)	269(57.2%)	35(7.5%)
Specialist	1(1.0%)	4(3.9%)	33(31.7%)	58(55.8%)	8(7.7%)
Clinical officer	6(4.9%)	6(4.9%)	45(36.6%)	54(43.9%)	12(9.8%)
Nurse	9(11.0%)	19(23.2%)	30(36.6%)	9(11.0%)	15(18.3%)
Midwife	0(0%)	2(33.3%)	1(16.7%)	2(33.3%)	1(16.9%)

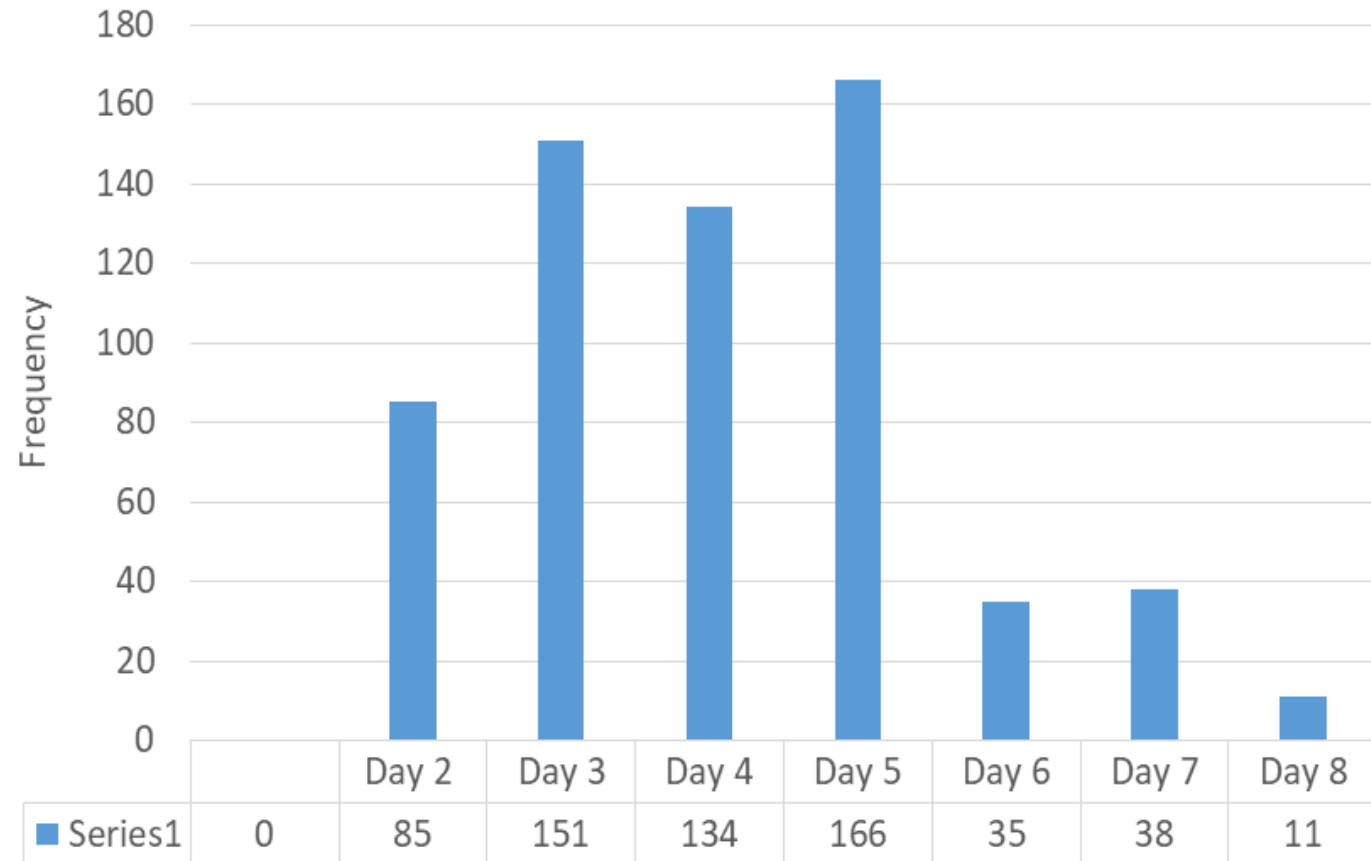


Study Findings (7)

- ❖ Only 58.3% of the Ceftriaxone doses prescribed were administered to completion
- ❖ On various occasions, doses were not administered on some days with the highest doses missed being on day 5 (166 doses) and Day 3 (151)
- ❖ Some patients were given ceftriaxone for a duration longer than prescribed.
- ❖ Some patients had the dosing frequency of ceftriaxone changed from once a day to twice a day contrary to the prescription.
- ❖ Furthermore, during sampling of prescription to select out those with ceftriaxone prescribed, over 15 patient treatment records (1.8%) were found having Ceftriaxone administered yet it wasn't prescribed

3. Appropriateness of dispensing of Ceftriaxone doses prescribed

Ceftriaxone doses prescribed not administered



Study Findings (8)

- ❖ Main reasons for the failure to have all the prescribed doses of ceftriaxone administered accordingly. These include;
- ✓ Ceftriaxone switched to another drug (20.1%)
- ✓ patient's condition having been improved and as such patient discharged (19.1%)
- ✓ Patient died (12.5%)
- ✓ Drug out of stock (8.9%)
- ✓ Self discharge (7.9%)

Over 24.4% of the patients who didn't complete the doses of ceftriaxone prescribed, had no reason provided to explain this



3. Appropriateness of dispensing of Ceftriaxone doses prescribed

Reason for missed doses	frequency	percentage
Can't buy/expensive	7	2.3%
Patient died	38	12.5%
drug changed	61	20.1%
Patient Improved and discharged	58	19.1%
no water for injection	1	0.3%
out of stock	27	8.9%
Self-discharge	24	7.9%
pharmacy closed	2	0.7%
Patient referred	11	3.6%
No reason given	74	24.4%

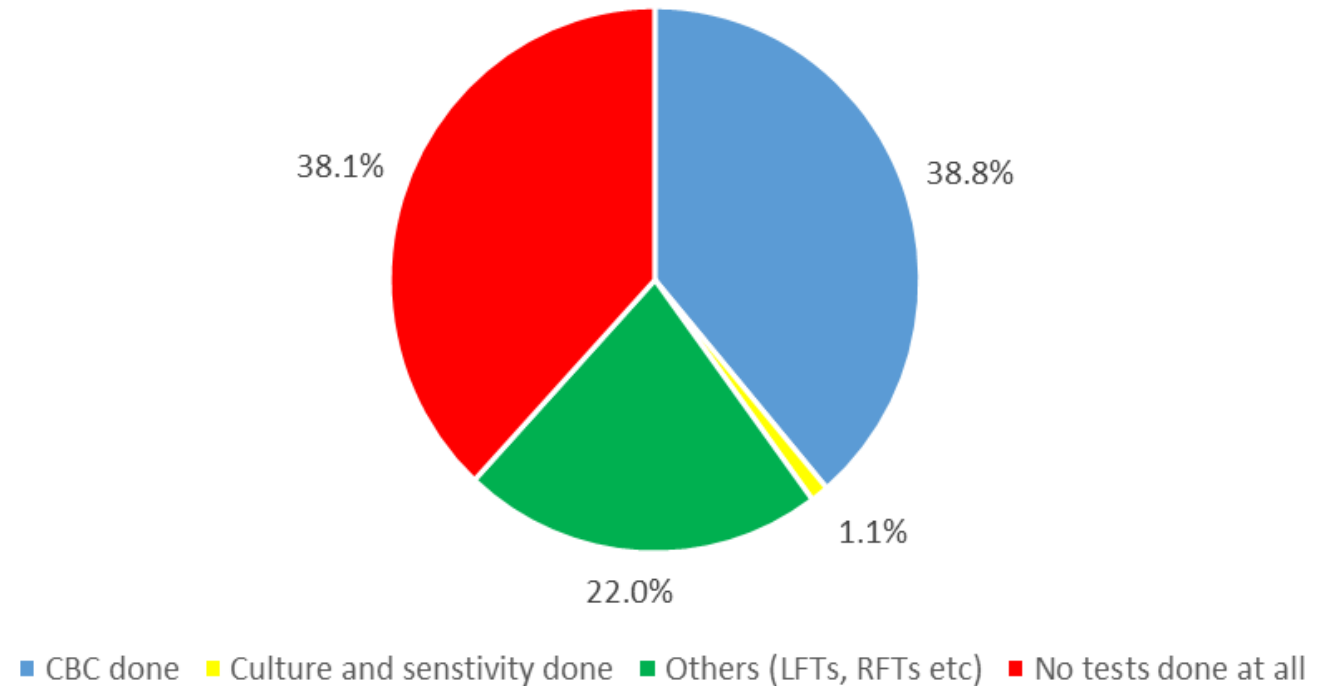


Study Findings (9)

- ❖ CBC and Culture and sensitivity Test were done in only 38.8% and 1.1% of the patients respectively.
- ❖ Other tests mostly done included Liver Functional Test (LFTs) and Renal Functional Test (RFTs), widal tests, TB test
- ❖ Over 38.1% of the patients were prescribed and treated with Ceftriaxone without any laboratory test done

4. Appropriate laboratory investigations done

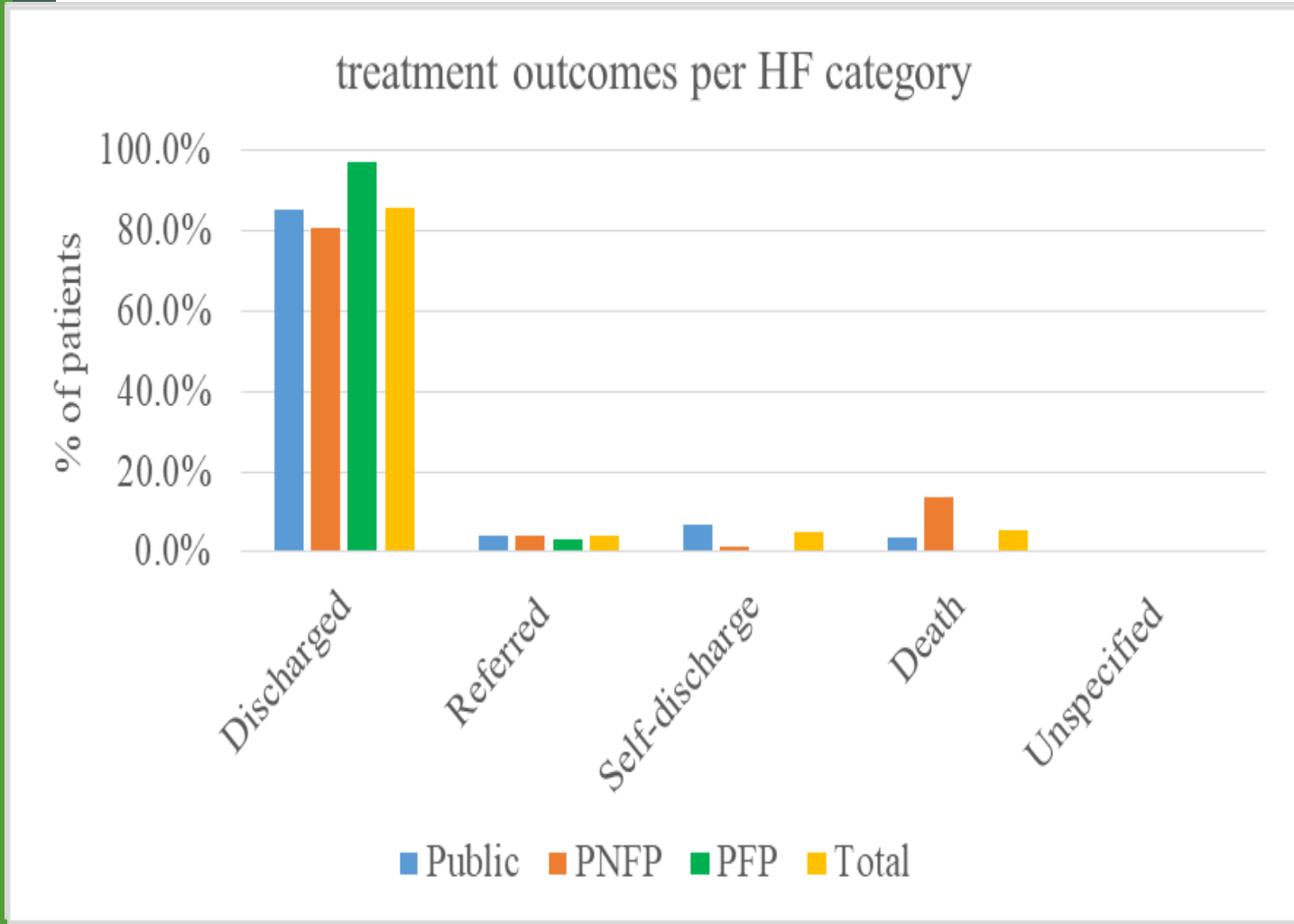
Laboratory investigations done



Study Findings (10)

- ❖ The duration patients were admitted ranged from 1 to 49 days (mean 5, SD 4.8 days).
- ❖ Most of the patients (85.6%) treated with ceftriaxone were successfully discharged, while 3.8% were referred for further management.
- ❖ Over 10.6% of the patients didn't have the desired outcome, with 5.6% having died
- ❖ The PFP HF had the biggest proportion of patients discharged (97%)
- ❖ Public HFs had the largest proportion of self-discharge cases (6.8%), while PNFP HFs had most deaths registered (13.6%)

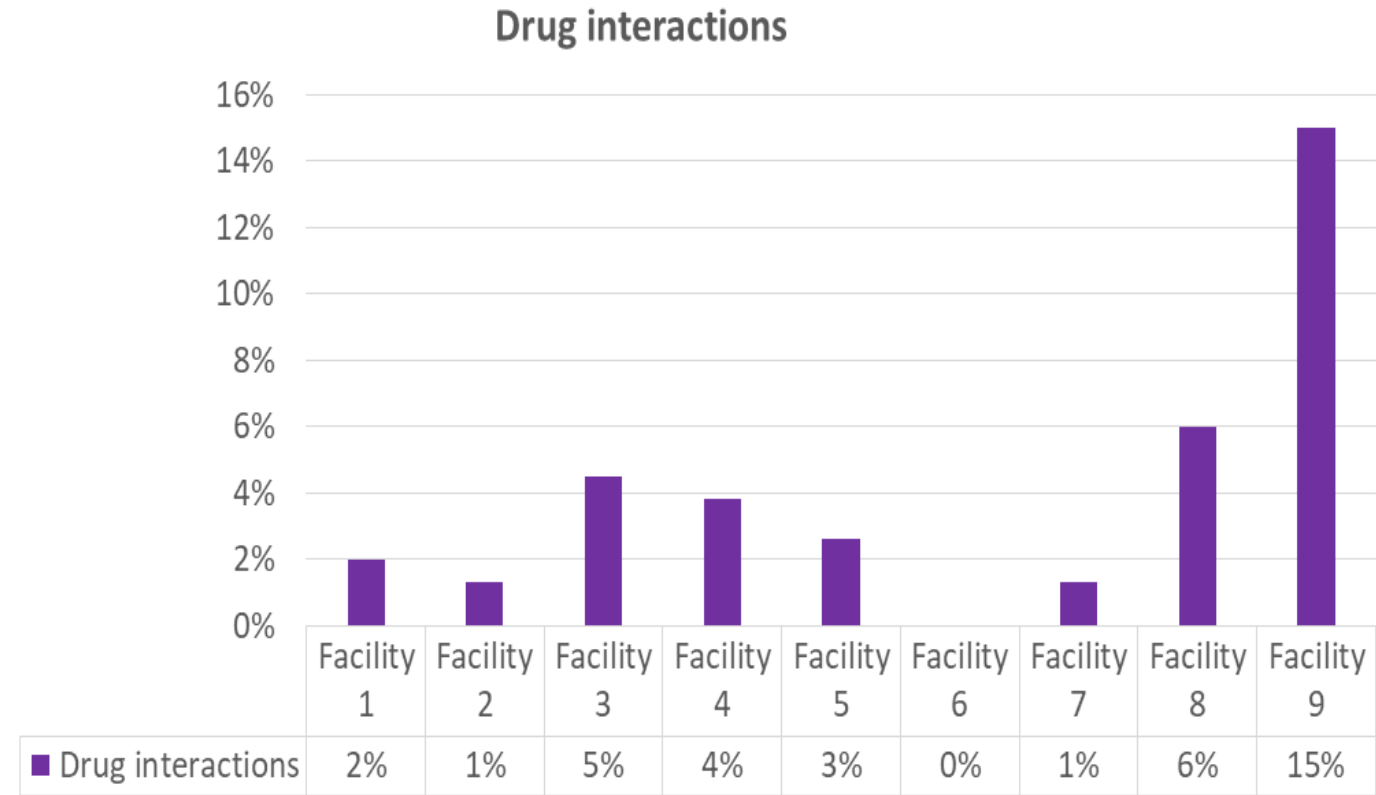
5. Treatment outcomes



Study Findings (11)

- ❖ One or more potential drug interactions with ceftriaxone were identified on the prescriptions reviewed for all the HFs except Facility 6 (HCIV-)
- ❖ . The overall average prevalence of possible drug interactions was 4%.
- ❖ The highest percentage of drug interactions was in facility 9 prescriptions (15%)
- ❖ The interacting drugs on the prescriptions containing ceftriaxone were furosemide and calcium containing products e.g. Calcivita® and Ringer's lactate

6. Drug interactions



Study Findings (12)

Generic prescribing

- In order to ensure access of patients to medicines, prescription by generic name is encouraged.
- In this study, 87.1% of the prescriptions had ceftriaxone prescribed by generic name.
- This was slightly below the set WHO threshold of 90% for generic prescribing.
- Public HFs had Ceftriaxone brand from CSPC Zhonguo Pharmaceuticals – China in stock at the time of review,
- The PNFPs and PFP had in stock; Epicephin®, Medaxonum®, Rocephin® and Powercef® during the review period



Discussion (1)

- Overall inappropriate use score (30%) was lower than that reported in related studies in other countries e.g.:
 - 46-87.9% in Ethiopia,
 - 62.4% in Eritrea,
 - 34.5% in Korea,
 - 53% in the USA and
 - 85.3% in Tehran

(Ayele et al., 2018; Berhe et al., 2019; Lee et al., 2009; Sewagegn et al., 2017; Sileshi et al., 2016).

- Inappropriate indication score (17%), was lower than reported in a similar study in Eritrea (44%) and higher than in one Ethiopia (4.7%)

(Berhe et al., 2019, Ayele et al., 2018; Sileshi et al., 2016)

- The differences in the score for inappropriate indication between countries may be attributed to differences in the Standard Treatment Guidelines (STGs), prescribers' qualifications and experiences, and extent of in-service training for Health Care workers on the use of STGs.



Discussion (2)

- Reasons for inappropriate indication could have been either diagnosis not being recorded on patient files or ceftriaxone being prescribed for non-recommended conditions.
- It was noted that the level of care and ownership of facility largely didn't impact the appropriateness of indication for prescribing ceftriaxone.
- Lack of diagnosis invalidates a prescription and logically such a prescription should not be dispensed and administered to the patient since that makes patient monitoring difficult
- The most common indications for prescribing ceftriaxone were, surgical prophylaxis (Trauma, labor and pregnancy complications), Respiratory Tract Infections (RTIs) majorly pneumonia, sepsis, and GIT infections. These are consistent with the most common causes of morbidity and mortality in Uganda as well as reported in other African Countries.



(Ayele et al., 2018; Manirakiza et al., 2019; Sileshi et al., 2016).



Discussion (3)

- Whereas our study reported surgical prophylaxis has the most common indication for which Ceftriaxone was prescribed, another study by Manirakiza et al (2019) carried out Uganda reported for infections (57%) and respiratory disorders (20%).
- Manirakiza et al (2019) study was at one facility and such it lacked diversity
- Ceftriaxone was also found to be prescribed for none STG recommended conditions such as Malaria, Anemia, PUD, PTB, Hypertension among etc.



Discussion (4)

- Ceftriaxone dose recommended ranges from 1-2g in adults and 50-100mg/kg in children (UCG, 2016).
- In this study, the most prescribed dose of ceftriaxone was 2g as was also reported by previously studies in Uganda, Eritrea, and Ethiopia (*Berhe et al., 2019; Manirakiza et al., 2019; Sewagegn et al., 2017*).
- The mean duration over which Ceftriaxone was prescribed (3.87 days) was similar to that reported in a study by Manirakiza et al (2019) but relatively lower than that reported in various other related studies outside Uganda that reported means ranging from 5.6- 11.47 days

(Ayele et al., 2018; Berhe et al., 2019; Lee et al., 2009; Sewagegn et al., 2017)).

- However, these studies outside Uganda were at facilities of higher level of care (Regional referral and specialist hospitals)
 - *Facilities at higher levels of care usually manage referral patients and most of whom usually have conditions in more advanced stages that require longer treatment durations.*



Discussion (5)

- The most prescribed frequency for the administration in this study i.e. once daily (92.3%), was in agreement with a similar study in Uganda that reported 100% for a similar frequency (Manirakiza et al., 2019). However a study in Ethiopia reported twice-daily dosing as the most prescribed (*Sileshi et al., 2016*).
- Overall inappropriate utilization as regards prescribing correct doses and dose durations of 11% and 16% respectively.
 - *This Inappropriate dose score was lower than the 45 % reported in a related study in Eritrea (Berhe et al., 2019).*
- Unlike in our study in which inappropriate use was mostly due to inappropriate indication, studies elsewhere reported inappropriate use being due to inappropriate duration



Discussion (6)

- Ceftriaxone, like any other antibiotic, requires laboratory confirmation of the presence of a bacterial infection before prescribing it, save for situations that require prophylactic use.
 - *CBC and culture and sensitivity laboratory tests are always required*
- This wasn't the case in this study as 98.9% of patients files lacked record of laboratory tests
- In related studies, culture and sensitivity tests weren't done in 93% in Uganda (Manirakiza et al., 2019), 53.2% and 68.7% in Ethiopia (Ayele et al., 2018; Sileshi et al., 2016) and 33.5% in Korea (Lee et al., 2009)
- Such results are consistent reports that in Africa health workers prefer to treat suspected bacterial infections empirically to avoid extra costs to the patient and more so because the results take long to be returned (Ayele et al., 2018; Berhe et al., 2019).



Discussion (7)

- Lower facilities lack the requisite equipment and personnel to carry out the necessary tests indicative of inappropriate use of antibiotics and poor patient care management systems at these health facilities (Hafta et al., 2018).
- Over 85.6 % of the patients were discharged as having been successfully treated. This figure was comparable to a previous study carried out by Manirakiza et al (2019).
- However, in our study 5.6% of the patients were reported to have died and this could be attributed to treatment failure or improper diagnosis.
- Treatment failure could be due to of the incomplete or irregular drug administration (58%).
- A related study in Uganda reported only 18% of patients completed the prescribed doses of Ceftriaxone and had regular administration (Manirakiza et al., 2019).



Discussion (8)

- The overall mean score for possible interactions was 4% (Range: 0- 15%). Drug interaction identified involved Ringers lactate (contains calcium gluconate) in some cases yet co-administration of Ceftriaxone with calcium-containing products is reported to result in occasional occurrences of possible or probable embolic events (Steadman et al., 2010).
- Furthermore, Furosemide was also being co-administered with Ceftriaxone yet this is reported as having the potential to worsen kidney function (Bhagavathula et al., 2014).



Conclusion

- ❖ This study reveals that inappropriate use of Ceftriaxone is relatively high arising from inappropriate indication, dose and dosing duration of Ceftriaxone prescribed among facilities selected across Uganda.
- ❖ Ceftriaxone is being prescribed largely for surgical prophylaxis and is to a great extent being prescribed for conditions not provided for as per the Uganda Clinical Guidelines (2016).
- ❖ Furthermore, Culture and Sensitivity testing are rarely performed and there is high prevalence of doses missed during drug administration..
- ❖ Considering the above, it is possible that the increase in anecdotes of reduced efficacy of Ceftriaxone could probably be attributed to majorly its irrational use in clinical settings across Uganda



Recommendations (1)

Antimicrobial resistance is a natural, inevitable process, but this needs to be delayed to avoid/ prevent the negative consequences that come with it.

- There is need for retraining health workers at all levels and sectors, with emphasis the use of STGs to ensure that Ceftriaxone is used for the correct indication, in the correct dose and for the correct duration
- Restricting duration of Ceftriaxone use to the point in time the patient is able to take another drug especially an oral alternative
- Institute prescribing controls for Ceftriaxone to health workers at the level of medical officer and above and to only levels of care where laboratory services are available



Recommendations (2)

- Encourage proper recording by providing all facilities with the all necessary standard patients' record books (In patient registers, Treatment charts etc) and ensure they are used by the HF staffs especially in public HFs. The practice of asking patients to come with exercise books to be used for recording patient management information should be discouraged
- More studies need to be done, first look at a range of PFPs especially the low end and those located in rural areas. Furthermore, a prospective study needs to be undertaken to look at treatment outcomes so as to attribute such outcomes on Ceftriaxone use patterns.
- Need to invigorate MTC at the Health facilities, since these have a pivotal role of ensuing appropriate use of medicines at the primary level.
- Lastly, we need to monitor and develop routine susceptibility profiles of different bacteria (antibiograms) at national and regional health facilities for the available antimicrobial agents.



Appreciation

We wish to extend our gratitude and thanks the following;

- The management of the National Drug Authority, that funded this study
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- The Nine HFs that accepted to take part in this study and granted us all the required support
- The research Assistants (Records person and Nurse) at each of these HFs that worked with research team to extract information from the Patient files



Thanks for listening

