Association between Pre-Hospital Antibiotic Exposure and Level of Bacterial Resistance (PHAE Study): A Matched Case Control Study at the Medical and Paediatric wards of Mbarara Regional Referral Hospital-South Western Uganda

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Abstract

Background

This study aimed to determine the association between pre-hospital antibiotic exposure and level of bacterial resistance among adult and paediatric patients.

Methods:

In the study, 79 antibiotic pre-exposed patients (cases) were compared with 79 non-pre-exposed patients (controls) hospitalized at medical and paediatric wards at Mbarara Regional Referral Hospital (MRRH) for various bacterial diagnoses. Data collected included participant demographics, previous medications and bacterial culture and sensitivity results. Data was analysed to determine the odds ratios for the occurrence of bacterial resistance between the cases and controls.

Results:

Results from the study showed that there was no statistically significant difference in terms of antibiotic resistance between pre-exposed and non-pre-exposed participants (OR: 0.5, 95%CI: 0.045 - 5.51, P = 0.571), whereby "no resistance" was defined as zero antibiotics resisted and "resistance" defined as 1 or more antibiotics resisted. However, when we adjusted the definition of "no resistance" and "resistance" to mean "one or less antibiotics resisted" and "two or more antibiotics resisted" respectively, there was a statistically significant more resistance in pre-exposed participants (cases) compared to non-pre-exposed participants (OR: 7, 95% CI: 1.59 - 30.8; p = 0.010). When the definition of resistance was further adjusted upwards to "three or more antibiotics resisted", the resistance in cases was still significantly higher compared to controls (OR: 5.4, 95%CI: 2.42 - 12.2, p = 0.000) and when the definition of resistance was further adjusted to "four or more antibiotics resisted", the OR increased even further (OR: 7.14, 95%CI: 3.24 - 15.8, p = 0.000). Ceftriaxone (17.6%) and amoxicillin (14.1%) were the commonest antibiotics to which participants were pre-exposed.

Conclusion:

The study showed that pre-hospital antibiotic exposure is strongly associated with resistance to one or more antibiotics. Strategies should be sought to reduce the level of such exposures and to enforce proper screening of patients during admission to facilitate rational prescription of antibiotics, improve quality of care, and slow the emergence of antimicrobial resistance in the management of infections.

Registration: This study was approved and registered by Mbarara University Research Ethics Committee (MUREC) and its number is 53/03-20

Background

Many patients are exposed to antibiotics before seeking medical care from referral hospitals. This pre-hospital exposure is a major contributor to excessive and irrational antibiotic use and has a potential to cause antibiotic resistance.[1] This is a global problem but it is more in developing countries with less facilitated public health services, weak and/or unimplemented regulations.[2] Infectious diseases for which antibiotics are prescribed are very common in the tropics because of the favorable conditions for the proliferation of many pathogenic bacteria. A study in Democratic Republic of Congo (DRC), India and Switzerland showed that transfer of antibiotic resistance by *Pseudomonas spp.* occurred more frequently under tropical temperatures (between 30⬚C and 37⬚C) than under temperatures (10⬚C).[3] According to WHO, the term "tropical diseases" is often taken to refer to infectious diseases that thrive in hot and humid conditions such as malaria, genital and urinary tract bacterial infections, respiratory system infections, soft tissue infections, central nervous system infections, leishmaniasis, schistosomiasis, onchocerciasis, lymphatic filariasis, African trypanosomiasis, and dengue.[4]

In order to successfully treat bacterial infections, antibiotics must be appropriately used whenever they are indicated. A study at Barnes-Jewish Hospital found out that inappropriate antibiotic use was responsible for a nearly 13% mortality increase in patients infected with *Pseudomonas aeruginosa*.[5] Yet in developing countries, studies show that inappropriate antibiotics use is common. A study carried out in five divisions of Uganda's Capital City- Kampala showed that many (53.5% of the households studied) patients with acute respiratory infections self-medicated and the treatments were inappropriate.[6]

Another study carried out in Kampala, Masaka and Jinja districts of Uganda showed that private health facilities were more likely to prescribe and dispense newer and more expensive antibiotics.[7] Many private health facilities commonly refer patients to advanced public hospitals.

In order to avoid excessive use of antibiotics, they should only be used when they are indicated. Inappropriate use leads to the development of resistance by the microbes through mutations. These mutations can lead to enzymatic degradation of the antibiotic, alteration of important target proteins in the bacteria, and changes in membrane permeability to the antibiotics.[8]

Many studies in developing countries have revealed the extent of antibiotic exposure and resistance separately.[9, 10] but little is known about the relationship between the exposure and resistance in hospitalized patients. Related studies have been done in developed countries and show statistically increased rates of antibiotic resistance in patients who used antibiotics before hospitalization.[11;12] A study done in expecting mothers in Denmark showed that babies born to mothers who used antibiotics had an increased risk of infection-related hospitalization.[13] But this study did not reveal whether the cause of hospitalization was related to antibiotic resistance.

Antibiotics are some of the most frequently prescribed medications globally and their consumption rate is on the increase.[14] An analysis showed a 35% global increase in consumption between 2000 and 2010.[15]

In Uganda, previous studies have shown that antibiotic prescriptions account for over 43% of all medicines prescribed.[16]

Before seeking health services from referral health facilities, many patients in Uganda are primarily managed with antibiotics from lower public and private health facilities such as private drug outlets, nursing homes, private clinics, and pharmacies either on self-medication basis or through prescription.[17]

According to the Ugandan National Drug Authority and Policy Act (NDP&A), 1993, antibiotics are classified under Group B, Class I drugs. Drugs in this group must only be dispensed upon presentation of a valid prescription. This is least followed and many patients who are referred or who seek advanced care by themselves are likely to have significant level of pre-hospital antibiotic exposure.[17] This pre-exposure may affect the results of the subsequent interventions because it is likely to be suboptimal.[16] Sub-optimally treated bacterial infections form a major part of the causes of antibiotic resistance.[16]

It is important to understand the nature and magnitude of the association between pre-hospital antibiotic exposure and antibiotic resistance. MRRH was selected for this study since it is the main referral center for Southwestern Uganda with many patients received after going through multiple layers of care.

It is important to have clear information about the magnitude and effects of pre-hospital exposure to antibiotics because it has implications on the effectiveness of subsequent interventions. Studies show that there is a relationship between general antibiotic exposure and antibiotic resistance.[1] and a relationship between use of antibiotics in primary health care (PHC) and resistance.[18]

Methods

The study was conducted at Mbarara Regional Referral Hospital located in Mbarara City. The hospital is the referral center for the Uganda's districts of Mbarara, Isingiro, Bushenyi, Kiruhura, Sheema, Rubirizi, Ntungamo, Kabale, Kanungu, Rukungiri and Mitooma. It also receives patients from some neighboring countries such as Rwanda, Tanzania and DRC. It is also the main referral hospital for many refugees in big camps such as Nakivale and Rwamwanja. These refugees come from countries such as DRC, Somalia, Rwanda and Burundi. With an official capacity of 350 beds, [19] the hospital serves a population of over 4 million patients, however, actual capacity is way above the official bed capacity which is the main reason why some patients sleep on the floor.

Study Design

We designed a matched case-control study at both medical and paediatric wards. In the study, a case was defined as patient due for admission with a diagnosis of a bacterial infection and had been pre-exposed to an antibiotic within the previous two months [20]. A control was defined as an admitted patient with a diagnosis of a bacterial infection who had not been exposed to an antibiotic within two months before coming to MRRH. A case and control were matched by diagnosis, age-bracket and gender. A

similar sample type was collected from the cases and controls, and care was taken to ensure that the samples taken from a matched pair were identical.

All study participants were required to have a confirmed diagnosis of bacterial infection at the medical and paediatric wards of MRRH. Evidence of antibiotic exposure /or non-exposure was determined by a verbal interview and review of medical documentation. A total of 158participants (79cases and 79controls) were included in the study by consecutive sampling from 3rd July 2020 to 29th January 2021.

Sample processing

Samples for culture and sensitivity testing were taken from all consented participants with clinical diagnosis of bacterial infection. But only samples which showed growth proceeded to analysis level.

Different sample types were collected depending on the clinical diagnosis of the patient. They included blood, urine, high vaginal swab (HVS), wound swab, urethra swab, ear swab, stool, pus aspirate and sputum. The same sample type was collected from both the case and its corresponding control taking care that the collection procedures and the culturing processes were exactly the same for both the case and its corresponding control (Fig. 1).

Samples were initially cultured on appropriate culture media depending on the sample type and request. The following culture media were used in this study:

  a. Blood agar
  b. Chocolate agar
  c. MacConkey agar
  d. Cysteine-Lactose-Electrolyte-Deficient (CLED) agar
  e. Sabourud agar
  f. DNase agar

For blood cultures, commercially prepared blood culture bottles were used. Following incubation, positive samples were sub-cultured on solid media. Blood incubation took five days plus one of sensitivity testing. Urine and other samples incubation took an average of four days plus one day of sensitivity testing.

Identification of microorganisms was done using the specific identification test for each microorganism in the microbiology laboratory. Fully identified isolates were subjected to antimicrobial susceptibility testing following Clinical & Laboratory Standards Institute (CLSI) guidelines and results were recorded.

Data analysis

For each pair, the number of antibiotics resisted by the isolates from the case and their corresponding controls was entered in the dataset.

Stata13, (StataCorp), was used for this analysis. After declaring this as matched data, logistic regression was used to calculate the odds ratio of pre-hospital antibiotic exposure for antibiotic resistance. Pre-exposure status was labelled "0" for no pre-exposure (that is: control) and "1" for pre-exposure (that is: case)

For analysis purposes, antibiotic resistance was categorized as "no resistance = 0" or "resistance = 1" so as to make the outcome binary. For samples with number of antibiotics resisted equal to zero, this was named "0", while for number of antibiotics resisted equal to one and more, this was named "1".

We respectively adjusted the definitions of "resistance" and "no resistance" upwards with the intention of testing for multi-antibiotic resistance.

For the cases, the names of the antibiotics to which the participants had been pre-exposed were captured in the dataset. Analysis was done to reveal the frequencies of individual antibiotics.

Results

In total, we analysed data for 158participants (79cases and 79controls). Table 1 shows participants' demographics and characteristics

Table 1
Participants' demographics and characteristics

Variable	Study arm		
A) Participants' age/ Years	Control	Case	
Lower Quartile (Q1)	3	3	
Median (Q2)	**18**	**19**	
Upper quartile(Q3)	29	35	
Minimum	0 (below 1year)	0 (below 1year)	
Maximum	67	99	
Diagnosis	Percentage		
Septicemia	36.08		
Sepsis	33.54		
UTI	16.46		
Neonatal Sepsis	4.43		
Otitis Media	4.43		
Others	5.06		
C) Other Variables			Total
	Study arm		
	Control	Case	
i) Gender	Male	50 (63.29)	50 (63.29)	100
	Female	29 (36.71)	29 (36.71)	58
ii) Tribe	Munyankore	69 (87.34)	66 (83.54)	135 (85.44)
	Mukiga	3 (3.80)	5 (6.33)	8 (5.06)
	Muganda	1 (1.27)	4 (5.06)	5 (3.16)
	Mutooro	1 (1.27)	1 (1.27)	2 (1.27)
	Rwandese	1 (1.27)	1 (1.27)	3 (1.90)
	Other	4 (5.06)	1 (1.27)	5 (3.16)
iii) Occupation	Unemployed	40 (50.63)	48 (60.76)	88 (55.70)
	Student	10 (12.66)	6 (7.59)	16 (10.13)
	Civil servant	0 (0.00)	1 (1.27)	1 (0.63)

Variable	Study arm			
	Business	5 (6.33)	2 (2.59)	7 (4.43)
	Farmer	13 (16.46)	6 (7.59)	19 (12.03)
	Peasant	6 (7.59)	12 (15.19)	18 (11.39)
	Other	5 (6.33)	4 (5.06)	9 (5.70)

Association between pre-hospital exposure and antibiotic resistance: The odds ratio for existence of resistance between pre-exposed (cases) and non-pre-exposed (controls) was 0.5, 95%CI: 0.045–5.51, P-value = 0.571, whereby "no resistance" was defined as zero antibiotics resisted and "resistance" defined as 1 or more antibiotics resisted (Resistance 0). This showed that there was no statistically significant difference in terms of resistance between cases and controls using these cut-offs. However, when we adjusted the cut-offs to compare participants with "one or less antibiotics resisted" versus those with "two or more antibiotics resisted" (Resistance1), the results showed that resistance was significantly more in cases than in controls (OR: 7, 95% CI: 1.59–30.8; p = 0.010). When the definition of resistance was further adjusted upwards to "three or more antibiotics resisted" (Resistance 2), the comparison between cases and controls was still significant (OR: 5.4, 95%CI: 2.42–12.2, p = 0.000) and when the definition of resistance was further adjusted to "four or more antibiotics resisted" (Resistance3), the odds of resistance was still significantly higher in the cases versus controls (OR: 7.14, 95%CI: 3.24–15.8, p = 0.000).

Therefore, there was statistically significant strong association between pre-hospital antibiotic exposure and resistance to **one or more** antibiotics. This is summarized in Table 2

Table 2
Outcome0 "Resistance" and "no resistance" at different levels of definition

Outcome	Odds Ratio	SE	Z	P>|z|	95%CI
Resistance0	0.5	-0.57	2.67	0.571	0.045–5.51
Resistance1	7	5.29	2.57	0.010	1.59–30.8
Resistance2	5.43	2.23	4.11	0.000	2.42–12.2
Resistance3	7.14	2.88	4.87	0.000	3.24–15.8

Common antibiotics to which pre-hospital patients are exposed:

The antibiotics to which the hospitalized patients were pre-exposed to were as follows according to their frequencies. Ceftriaxone (17.61%) followed by amoxicillin (14.08%) were the antibiotics to which pre-

hospitalized patients are exposed most. Table 3 shows the different frequencies for the different antibiotics to which the participants were exposed.

Table 3
Common antibiotics involved in pre-exposure

S/N	Antibiotic Name	Frequency	Percentage
1	Ceftriaxone	25	17.61
2	Amoxicillin	20	14.08
3	Ampicillin	14	9.86
4	Ciprofloxacin	13	9.15
5	Azithromycin	9	6.34
6	Cloxacillin	9	6.34
7	Gentamicin	9	6.34
8	Cefixime	8	5.63
9	Metronidazole	7	4.93
10	Doxycycline	3	2.11
11	Flucamox	3	2.11
12	Cotrimoxazole	3	2.11
13	Cefalexin	2	1.41
14	Chloroamphenicol	2	1.41
15	Others		10.5

Discussion

Association between pre-hospital antibiotic exposure and the number of antibiotics to which the isolated bacteria are resistant:

In this study, a strong association was observed between pre-hospital antibiotic exposure and resistance to more than one antibiotic. With definitions of "no resistance" and "resistance" set at ""one or less" and "two or more" antibiotics resisted respectively, OR was 7, 95% CI: 1.59–30.8; p = 0.010. This means that the cases (pre-exposed) were **7times** as likely to carry a bacterial strain resistant to two or more antibiotics compared to the controls (with no pre-exposure). Therefore, there was significantly higher incidence of resistance in the pre-exposed participants than those without pre-exposure.

Antibiotics' effectiveness, which largely depends on their rational use is very important in management of infectious diseases in humans.[21] [22] [23] One of areas where irrational use of antibiotics is outside hospital settings as revealed by some studies.[6]

It is possible that pre-hospital antibiotic exposure is significantly irrational. A Study done in Kampala showed that most of acute respiratory infections (53.5%) were inappropriately managed [6] and hence potentially capable of breeding antibiotic resistance. There is a possibility of suboptimal dosing with antibiotics which is a clearly known factor for antibiotic resistance.

Another important revelation was that pre-exposed participants were more likely to have pathogens resistant to more antibiotics. Therefore, pre-exposed patients were significantly more likely to have multi-antibiotic resistance compared to non-pre-exposed participants..

It is therefore important that rational use of antibiotics is emphasized in lower health facilities. Their use should only be reserved for cases where they are really indicated.

It is therefore important that purposed assessment of antibiotic pre-exposure status while admitting patients at MRRH.

Culture and sensitivity testing should also be more emphasized for the pre-exposed patients since results of this study show that they strongly likely to carry resistant strains of bacteria.

Strategies should therefore be in place to reduce pre-hospital antibiotic exposure. This will significantly reduce the burden of antibiotic resistance.

Common antibiotics to which pre-hospital patients are exposed:

Ceftriaxone (17.61%) followed by amoxicillin (14.08%) are the antibiotics to which pre-hospitalized patients are exposed most. The others are ampicillin (9.86%), ciprofloxacin (9.15%), azithromycin (34%) and gentamicin (6.34%). Globally, these same antibiotics make the majority of the most frequently prescribed antibiotics to the extent of making it to the list of environmental pollutants as revealed by a study on waste waters.[24] Even in Europe, these same antibiotics make it to list of the most commonly administered antibiotics.[25] These antibiotics are still frequently used at MRRH for management and prophylaxis of a variety of infections. Another study done in Uganda also revealed that ceftriaxone, amoxicillin, azithromycin, ciprofloxacin, and metronidazole made the top five of the most frequently prescribed antibiotics in Kampala.[26] Yet this pre-exposure is a clear factor breeding resistance as revealed by another result of this study and even other studies.[27]

It is therefore likely that the use of these antibiotics in pre-hospitalized patients will affect the effectiveness of treatment of infectious conditions once these patients are admitted for treatment in a referral hospital. This is consistent with other studies carried out in different places. A systemic review

and meta-analysis (24studies) revealed that patients to whom an antibiotic was administered in PHC were likely to carry antibiotic-resistant bacterial strain than those to whom an antibiotic had not been administered.[28]

Conclusion

Pre-exposed patients are significantly more likely to carry antibiotic resistant strains of bacteria compared to non-exposed patients. This association was even strong with increased number of antibiotics used.

The commonest antibiotics to which participants were pre-exposed included: ceftriaxone (17.61%) followed by amoxicillin (14.08%). Ceftriaxone is at the same time among the commonest antibiotics used in the admitted patients to treat and prevent infections. It can therefore be possible that the same antibiotics or same class of antibiotics the patient is pre-exposed to can still be used at MRRH.

List Of Abbreviations

1. **ACE II:** Academic and Career Exploration II
2. **MRRH:** Mbarara Regional Referral Hospital
3. **OR:** Odds Ratio
4. **CI:** Confidence Interval
5. **MUREC:** Mbarara University Research and Ethics Committee
6. **DRC:** Democratic Republic of Congo
7. **WHO:** World Health   Organization
8. **NDP&A:** National Drug Policy and Authority
9. **PHC:** Primary Healthcare
10. **HVS:** High Vaginal Swab
11. **CLED:** Cysteine-Lactose-Electrolyte-Deficient
12. **CLSI:** Clinical & Laboratory Standards Institute

Declarations

Ethics approval and consent to participate

Approval from the following bodies and office was sought before starting the collection of data.

i. The Faculty Research Committee (FRC), Faculty of Medicine.
ii. The Research and Ethics Committee of MUST
iii. The Hospital Director, MRRH.

Informed consent was obtained from each adult participant before being included in the study. Informed consent was also obtained from parents and/or legal guardians of minor participants aged 16years or younger.

The data collected was treated with confidentiality. No unauthorized access was allowed in any way.

All the aspects of the methodology including data collection, analysis, storage and sharing were done in accordance with the ethical provisions as declared in the Declaration of Helsinki Ethical Principles for medical Research involving Human Subjects.

Consent for publication:

The manuscript does not contain any information or images that could lead to identification of any participant in the study. Therefore the participant consent for publication is not applicable.

Availability of data and materials:

The dataset generated for the study is available and can be accessed from the main author or the corresponding author on reasonable request

Competing Interests

All the authors of this work declare that none has conflict of interest.

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Authors' contributions:

BP is the main author and was involved in proposal and methodology designs, data collection, analysis and interpretation of results.

JT was involved in proposal review, review of methods, data collection and interpretation. CM was involved in proposal review, review of methods, data collection, analysis and interpretation. JN proposal review, review of methods and data collection

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BP is a male, Ugandan registered Pharmacist, and holds of a bachelor's degree in Pharmacy and master of Pharmacy in clinical pharmacy from Mbarara University of Science and Technology. Currently he works at Mbarara Regional Referral Hospital as a clinical pharmacist, head of Pharmacy Department and secretary to the Medicines and Therapeutics Committee.

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Acknowledgments

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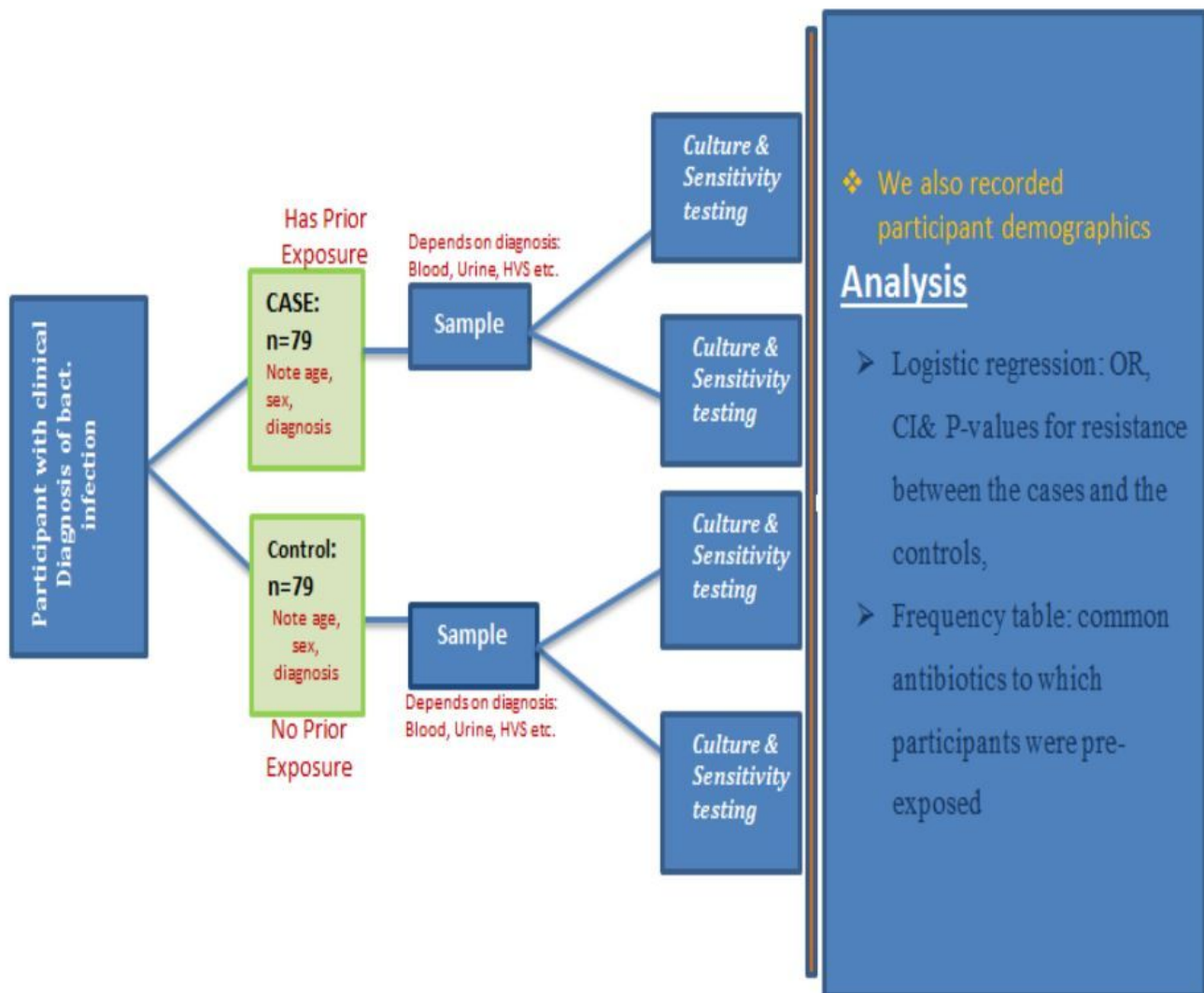
Figures

Figure 1

Data collection procedure

Methodology: diagrammatic