A review of clinical profile, complications and antibiotic susceptibility pattern of extensively drug-resistant (XDR) Salmonella Typhi isolates in children in Karachi.

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Abstract

Background: Enteric fever is a systemic infection, which can be caused by Salmonella enterica; Typhi and Paratyphi A. Over time, Salmonella Typhi has developed resistance to antibiotics resulting in the emergence of extensively drug-resistant (XDR) enteric fever. WHO estimated 5274 cases of XDR Enteric fever in Karachi from November 2016 to December 2019. This study aims to determine clinical course, complications and outcomes of XDR enteric fever among the pediatric population coming to Indus Hospital

Methods: A retrospective chart review of pediatric patients (aged one month to 15 years) seen in Indus Hospital between July 2017 to December 2018 was conducted. A pre-designed data abstraction form was used to record detailed information about seasonality and distribution of cases, demographic details, signs and symptoms, clinical course, treatment, complications and outcomes of the cases treated for XDR Enteric fever

Results: Six hundred and eighty children were included in the study. The median (IQR) age of the patients was 5 (2-8) years. More than half (n=391, 57.5%) of the patients were males. Most common clinical manifestations included fever, vomiting and diarrhea, noted in 680 (100%), 242 (35%) and 174 (25%) patients. Outcomes of 270 (39.7%) patients were recorded. Others were lost to follow up [351 (51.6%)], referred out [52 (7.6%)] or left against medical advice [7 (1%)]. 266 (39.1%) patients were cured, and four children (0.6%) expired. Seventy-eight patients (82%) and 15 patients (16.3%) got cured on Azithromycin and Meropenem alone while 157 on a combination of drugs.

Conclusion: Our review indicated that children under five years of age were affected more with XDR Enteric fever. Meropenem and Azithromycin, either alone or in combination were the most effective antibiotics for treating XDR Enteric fever in children coming to Indus hospital

Background

Enteric fever is a systemic infection, which can be caused by two serotypes of the gram-negative bacteria Salmonella enterica; Typhi and Paratyphi A (1). The disease is estimated to affect approximately 11 to 21 million individuals globally on an annual basis and has a high mortality rate (2). Recent data showed that globally 200,000 deaths result annually due to enteric fever (3). The burden of disease of enteric fever is the highest in Asia; 93% of the global cases are reported from within this region (3). Southeast Asia has the third-highest incidence within the region, with approximately 110 cases / 100 000 population. The estimated incidence of enteric fever in Pakistan was found to be 413 / 100 000 population in children aged 2-4 years and 573 / 100 000 population in children aged 5-15 years. (1)

Over time, Salmonella Typhi has developed resistance to many antibiotics which has resulted in the emergence of multi-drug resistant (MDR) Salmonella Typhi (S. Typhi) strains. These strains have shown resistance to both first and second-line antibiotics, namely Ampicillin, Chloramphenicol, Co-trimoxazole and fluoroquinolones (4). This strain of enteric fever has been endemic in countries like Pakistan, India,

Nepal and Bangladesh since the 1980s (5). A review of antimicrobial resistance of S. Typhi and Paratyphi A conducted in Pakistan from the year 2009 till 2011, showed an increased frequency of MDR S. Typhi (91.7%) as well as two cases of S.Typhi which were resistant to cephalosporin resistance (4).

In November 2016, a massive outbreak of ceftriaxone-resistant S. Typhi was reported among children residing in Hyderabad, Pakistan. Around 486 cases were reported, and the consumption of contaminated drinking water was linked with the infection. These strains were called extensively drug-resistant (XDR) S.Typhi as they showed resistance not only to first and second-line antibiotics but also to third-generation Cephalosporins. Drug sensitivity pattern of XDR Typhoid strain showed sensitivity to either Carbapenems or Azithromycin (6). Since the outbreak of XDR Enteric in Hyderabad, many other cases of XDR Enteric fever have been reported. WHO estimated 5274 cases of XDR Enteric fever in Karachi from November 2016 to December 2019 (7).

XDR Enteric fever is a new strain and may have unique clinical manifestations and outcomes compared to MDR Enteric infection. There is a scarcity of data on clinical features and response to treatment in children suffering from XDR Enteric fever both nationally and in other parts of the world. Therefore, this study is done to determine clinical course, complications and outcomes of XDR enteric fever among the pediatric population coming to Indus Hospital. Primary endpoints include clinical manifestations, complications, response to treatment and the final outcome of the participants. Secondary endpoints included seasonality of the infection and geographic distribution of the cases.

Methods

Study design and data collection

A retrospective chart review was conducted of medical records of children who were treated for XDR Enteric fever at The Indus Hospital (TIH), Korangi campus from July 2017 to December 2018. All children, from 1 month to 15 years of age, were included in the study. TIH at the Korangi campus is a 330 bedded, multi-disciplinary tertiary care hospital. It is situated in the suburbs of Karachi and provides free of cost services to all patients. Pediatric services at Korangi campus include a total of 90 beds distributed in the general ward, oncology unit and critical care.

The data was extracted through the Health Management Informatics System (HMIS); data of all the children confirmed of having XDR Enteric fever, based on culture and sensitivity reports were included in the study. A pre-designed data abstraction form was used to record detailed information about seasonality and distribution of cases, patient demographics, signs and symptoms, clinical course, treatment, complications and outcomes. Investigations were also recorded to determine the severity and course of the disease. These included complete blood count (CBC), liver function test (LFTs), serum electrolytes, Prothrombin Time (PT), Activated Partial Thromboplastin Time (APTT), urine analysis, culture reports, urea and creatinine, cerebrospinal fluid analysis, ultrasound and CT scan reports. Data of complications retrieved from the medical record included electrolyte imbalances, hematological

complications like cytopenias, cholecystitis, hepatitis, ascites, pleural effusion, shock, renal dysfunction, neurological complications like fits, encephalitis, encephalopathy and aphasia

Microbiological culture of venous blood was performed using 5 ml of blood, drawn under aseptic measures. BacT/Aert culture bottles were used to collect blood samples (8). Antibiotic susceptibility for a group of antibiotics was tested using Kirby-Bauer disk disc diffusion method on Muller-Hinton agar with standard antimicrobial disks using Clinical Laboratory Standards Institute guidelines. The culture bottles and sensitivity tests are the frequently used standards in Pakistan.

Case definitions

Renal impairment: Increased creatinine > 1.5 times upper limit of normal or decreased in urine output <0.5ml/kg/ hour for 6 hours (9)

Hepatitis: Deranged Liver function tests with ALT more than twice the reference value with or without hyperbilirubinemia, impaired coagulation and hypoglycemia

Cholecystitis: Evidence of inflamed gall bladder sludge in gall bladder on ultrasound

Hematological complications: High or low level of hemoglobin, leucocyte or platelet count according to the given lab references

Encephalopathy: Changes in mental status, confusion or stupor with normal CSF findings

Encephalitis: Changes in mental status, confusion or stupor or signs of meningeal irritation with abnormal CSF findings

Diarrhea: Presence of loose or watery stools three times or more per day (10)

Statistical analysis

Data were analysed using SPSS version 24. Descriptive statistics were run for all continuous variables, exploring Skewness and Kurtosis. Mean with standard deviation was reported for normal distribution, while the median with interquartile range was reported for skewed distribution. For a normal distribution, normality was confirmed by applying T-test. For skewed distribution, the Mann-Whitney test was applied to determine significance. For categorical variables, frequencies were determined. Significance of correlations was determined by applying statistical tests; p-value < 0.05 was taken as significant

Results

A total of 1518 patients had blood culture positive for enteric fever during the study period. Out of these 1341 patients were children and 177 patients were adults. Out of 1341 pediatric patients, 680 met our inclusion criteria and were included in the final analysis. More than half (n=391, 57.5%) of the patients were males. The median (IQR) age of the patients was 5 (2-8) years, with minimum and maximum 0 days

to 14 years. Out of these patients, majority, 612 (90%), directly presented to the ER, followed by OPD, 65(9.6%). Around a hundred (n=101, 14.9%) patients were admitted in the hospital. Out of which 98 (97%) patients were admitted in the general ward, and the rest were admitted in ICU for treatment (Table1).

The maximum number of children, 540 (79%) came from district East (Figure 1). Two seasonal peaks were identified in the year 2018. One was in February-May 2018, and the second peak was observed in August-October 2018 (Figure 2).

Most common clinical manifestations included fever vomiting and diarrhea, which were noted in 680 (100%), 242 (35%) and 174 patients (25%) (Table1). Most frequent complications observed included hyponatremia (n=74, 11%), acidosis (n=75, 9%), hypokalemia (n=59, 9%) and bicytopenia (n=67, 10%) (Table2). One case of vertical transmission was observed, and the newborn died of XDR enteric infection. Four cases of encephalitis were identified, out of which three children had aphasia on presentation. All children with encephalitis had full recovery without any residual weakness or speech difficulty. One child developed multi-organ dysfunction and pulmonary hemorrhage.

Final outcomes of 270 (39.7%) patients were recorded; 351 (51.6%) were lost to follow up, 52 (7.6%) were referred out and 7 (1%) left without medical advice. 266 (39.1%) patients were cured and 4 children (0.6%) expired (Table1). Response to antibiotics was observed in 252 patients, 95 patients got cured on a single drug, while 157 patients got cured on a combination of drugs. Seventy-eight patients (82%) and 15 patients (16%) got cured on Azithromycin and Meropenem alone (Table 2). Azithromycin was the most common antibiotic used for the treatment of XDR. It was administered to 274 (61.2 %) patients, followed by Ceftriaxone and Meropenem, which were administered to 198 (44.2%) and 137 (30.6%) patients, respectively

Mortality was observed in 4 children, including a newborn. Out of those who died, two were on a single antibiotic, Meropenem, while the other two were on a combination of antibiotics (e.g. Meropenem and Ceftriaxone). Complications noted in them included bradycardia, respiratory distress, hypoglycemia, sepsis, electrolyte imbalance, encephalitis, and pulmonary hemorrhage.

Discussion

Enteric fever caused by S. Typhi continues to pose as a health burden globally, with the incidence being highest in low to middle-income countries (LMIC), due to poor infrastructure of public health (11). According to the World Health Organization (12), Pakistan faced the largest outbreak of XDR enteric fever, in Hyderabad in November 2016, followed by a similar outbreak in Karachi. XDR Enteric is a novel strain of S. Typhi which belongs to H58 lineage and has plasmid-encoded resistance and extended-spectrum β-lactamase (ESBL) gene which is responsible for resistance to both first and second-line antibiotics (13).

Out of 1518, total positive blood cultures for enteric fever, 1341 (88%) belonged to children. The median age of affected children was five years (IQR: 2-8 years). Literature from other parts of Pakistan have also reported a higher frequency of infection among children in comparison to adults and found children less

than five years of age to be affected more. An investigation of XDR enteric fever in Hyderabad (7) and in Islamabad (14) revealed that 56% and 33% affected children were under five years of age. This high burden of XDR Enteric fever among Pakistani children has resulted in government initiative in the form of efforts to improve water quality and sanitation and initiation of mass vaccination of children for Enteric fever in Hyderabad and Karachi (7). This higher incidence of XDR enteric fever amongst younger children could be explained by the fact that children have lower immunity and require lower bacterial dose for development of infection (15). Most of the participants in our study belonged to East district of Karachi, probably because Indus Hospital lies in the catchment area of this district. Many residential areas located in district East of Karachi, comprise of peri-urban slums, having unhygienic conditions, inadequate sewerage facilities and consumption of pipe-borne portable water supply by the people. The high burden of disease in these areas could be due to contaminated drinking water and mixing of drinking and sewage water, a finding which was also observed in Hyderabad (6).

Enteric fever has been associated with considerable seasonal variations in different parts of the world (16) In Pakistan MDR Enteric peaks have been noted in May-June and in October. The seasonality was linked to increased consumption of contaminated local drinks and ice-cream during the hot season and post-monsoon contamination of drinking water with rainwater (17). We also observed two peak seasons of XDR Enteric cases, one in February-May 2018 and second in August-October 2018. This observation is contrary to previous epidemiological findings of Enteric fever in Karachi, which identified a clear relation of Enteric fever with monsoon rains. An epidemiological survey has shown that Sindh province, including Karachi, remained generally dry throughout 2018 (18), which makes post-monsoon contamination of water a less likely cause in our study. However, the timing of peak cases in our study was very similar to those observed in Lahore in 2018. In Lahore, increased numbers of cases of XDR Enteric fever were observed from January - April 2018 (19), while XDR peak in our study was from February-May 2018. The most probable explanation for the seasonal similarity of XDR cases between Karachi and Lahore is the intercity travelling of people.

Electrolyte imbalances were the most common complications observed. Hyponatremia was seen in 74 (11%) children and hypokalemia in 59 (9%). This electrolyte imbalance was one of the commonest reasons for hospital admission and can be attributed to vomiting and diarrhea seen in our patients. The hypovolemic shock was seen in 5 (0.7%) children. All children with shock responded to fluids and inotropes except for one child who expired. We observed neurological complications in 15 children. All of these children had seizures. Three children with fits had hyponatremia, 4 had encephalitis, and eight had encephalopathy. Daniel et al. (20) have reported 48 cases of enteric fever with encephalopathy. They found strong correlation of encephalopathy with dehydration and low white blood cell count (p-value <0.001). They postulated that in severe enteric infection immune response may be exaggerated leading to neurological complications. In our study, five children with encephalopathy had a severe clinical course. There is a possibility they had immunological mediated neuronal injury .

Four children developed aphasia, out of which 3 had encephalitis, and one had encephalopathy. All children recovered completely without any deficit. Few cases of aphasia caused by enteric fever have

been reported (21, 22) Literature reports multiple factors like electrolyte imbalance, cerebral injury and neurotoxins-associated injury in the Broca's speech as the cause of motor aphasia in Enteric fever (21).

We observed mortality in 4 children. Reasons for death were identified as encephalitis in one child and shock with multi-organ dysfunction in 3 children. Mortality in all children was observed in the third week of illness and could be due to delayed presentation, which may have delayed treatment. One case of vertical transmission was observed, and the newborn died of the infection in second-week life.

Any child who failed to show up for one month after the initial visit and could not be contacted over the phone was considered lost to follow up. Three hundred fifty-one children were lost to follow up in our study. The most probable explanation for this could be poverty; as most of our study participants belonged to low socio-economic strata. These patients may find it challenging to afford travelling expenses.

In our study, the most successful single drug was Azithromycin, which cured 78 cases (82%) followed by Meropenem, which cured 15 cases (16%). Tayyaba et al. studied antibiotic susceptibility of XDR Enteric in Karachi and found equal susceptibility of XDR strains to both Azithromycin (95%) and Meropenem (97%) (23). Other studies also reported equal cure rates with both the drugs (24, 25). We found Azithromycin superior to Meropenem probably because a majority of the patients were treated as out-patients and were given oral Azithromycin.

Seventy-six patients (48%) were successfully treated with a combination of Azithromycin and Meropenem. Children who received a combination of Azithromycin and Meropenem achieved fever defervescence two days earlier compared to children who received a single antibiotic. We can infer that these two antibiotics may have synergic action against XDR-Enteric fever. This synergism among various antibiotics has been observed in MDR Enteric fever also (26).

Eight children were cured on single drugs, although they were resistant to those antibiotics. Since we did not determine the minimum inhibitory concentration (MIC), therefore, there is a possibility that these strains were sensitive to antibiotics with a higher MIC breakpoint, and were falsely interpreted them as resistant strains.

The strength of this study is that it is the only extensive study in our knowledge which examines the clinical course, outcomes and complications of XDR strain of S. Typhi amongst the pediatric population within Pakistan. The study also determined response to antibiotics in XDR Enteric fever. The limitations of this study include lack of use of minimum inhibitory concentration (MIC) for culture and sensitivity, along with an absence of molecular mapping, which would have provided a more comprehensive picture of the disease. We did not routinely perform stool cultures and hence could not identify carriers. Retrospective data had missing information on socio-demographics like drinking water quality, hygiene practices and the number of people in the household.

Conclusion

It can be concluded that children under five years of age were affected more with XDR Enteric fever. Meropenem and Azithromycin, either alone or in combination, were the most effective antibiotics for treating XDR Enteric fever. We advocate increasing nationwide awareness about the consumption of safe water, antibiotic stewardship and immunisation practices of children.

Declarations

Ethics approval and consent to participate: Ethical approval was taken from the Institutional Review Board (IRB) of Interactive Research & Development, registered with the US Department of Health and Human Services, Office for Human Research Protections at The Indus Hospital. As per the IRB, written informed consent was not required from the patients involved in this study.

Consent for publication: Not applicable

Availability of data and materials: The datasets used analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: SS and MM conceived the idea of the study and participated in study design and write up. SN and ND carried out data collection, MM and ND assisted with statistical analysis. All authors were involved in the coordination of the study, drafting the manuscript and approving the final version.

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Abbreviations

XDR: Extensively drug-resistant, MDR: multi-drug resistance, WHO: World health organisation, IQR: Interquartile range, S. Typhi: Salmonella Typhi, HMIS: Health Management Informatics System, CBC: complete blood count, LFT: liver function test, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time, ALT: alanine transaminase, CSF: cerebrospinal fluid

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Tables

Table 1: Demographic characteristics, clinical features, investigations, complications and outcome of the patients

Demographic features	Number (%)
Male	391 (57.5)
Female	289 (42.5)
Age in years Median (IQR)	5 (0-14)
Place of presentation	
E/R	612 (90)
OPD	65 (9.6)
Inpatient	3 (0.4)
Clinical features	Number (%)
Fever	680 (100)
Vomiting	242 (35.6)
Diarrhea	174 (25.6)
Anorexia	140 (20.6)
Cough	126 (18.5)
Abdominal pain	125 (18.4)
Bleeding per rectum	4 (0.6)
Rash	12 (1.8)
Urinary symptoms	14 (2.1)
Hepatomegaly	63 (9.3)
Splenomegaly	22 (3.2)
Duration of illness Median (IQR)	14 (8-26.3)
Lab investigations	Number (%)
Severe Anemia (Hb < 5gm/dl)	9(1)
Severe Thrombocytopenia (<50,000x10^9/L	24(3.5)
Raised CRP >5	395 (58.1)
Hyponatremia (severe+Moderate combined)	74 (10.9)
Hypokalemia (severe+Moderate combined)	59 (8.7)
Acidosis	75(9)
Raised serum creatinine	4 (0.6)
Complications	Number (%)
Bicytopenia	67(10)
Pancytopenia	16(2.4)
Hepatitis	11 (1.6)
Cholcystits (on abdominal ultrasound)	4 (0.5)
Mesenteric lymphadenopathy (on abdominal ultrasound)	11(2)
Pleural effusion (on abdominal ultrasound)	6 (1)
Peritoneal free fluid (on abdominal ultrasound)	8 (1)
Shock	5 (0.7)
Encephalopathy	16 (2.3)
Encephalitis	4 (0.6)
Aphasia	4(0.6)
Vertical transmission	1(0.1)
Outcome	
Cured	266 (39.1)
Died	4 (0.6)
Lost to follow up	351 (51.6)
LAMA/referred out	59 (8.6)

Table 2: Response to antibiotics

Cured with single drugs	N (%)
Ceftriaxone	6(6.3)
Cefixime	6(6.3)
Meropenem	15(15.8)
Azithromycin	78(82)
Ciprofloxacin	1(1.1)
Cured with multiple drugs	**N (%)**
Meropenem + Azithromycin	79(50)
Other drug combinations	81(51.6)

Figures

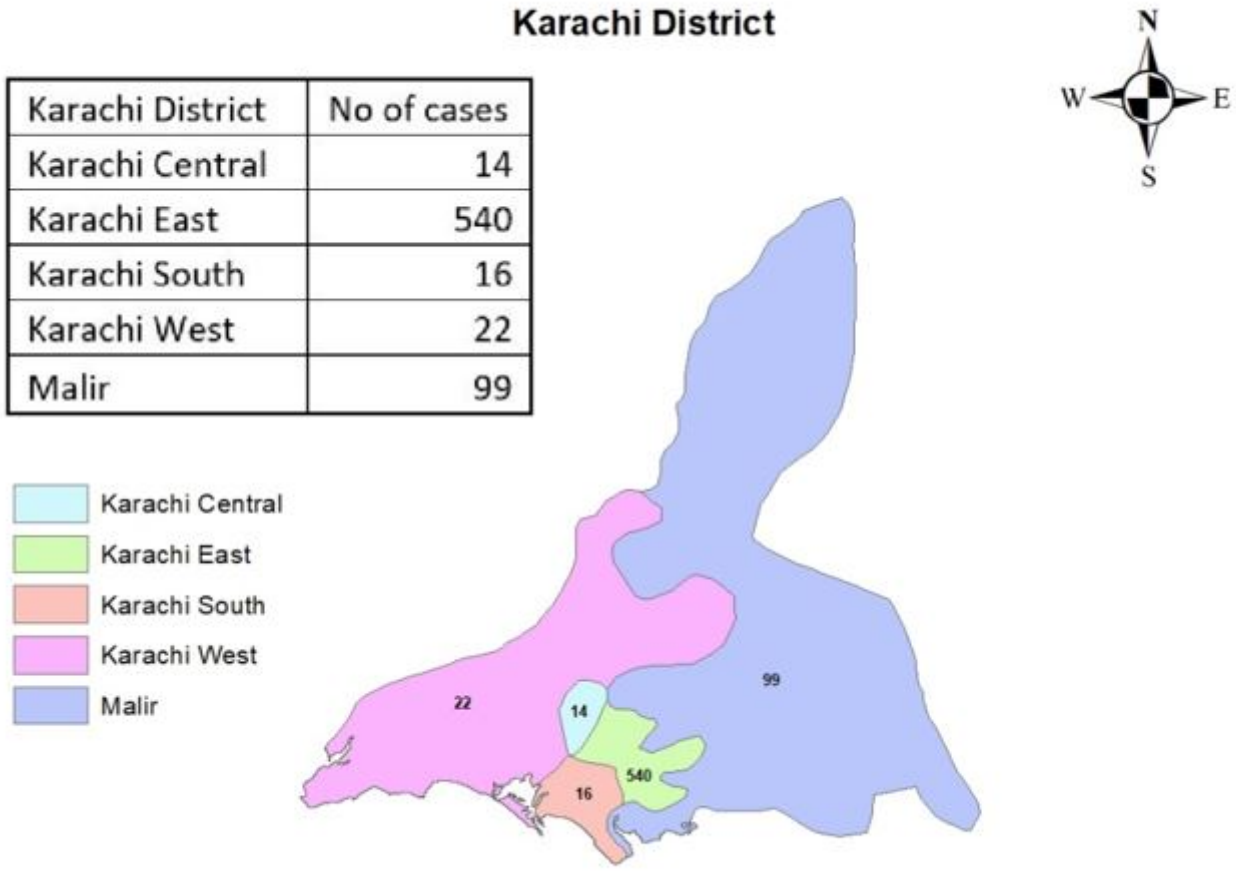

Figure 1

Geospatial map of XDR Enteric cases in Karachi

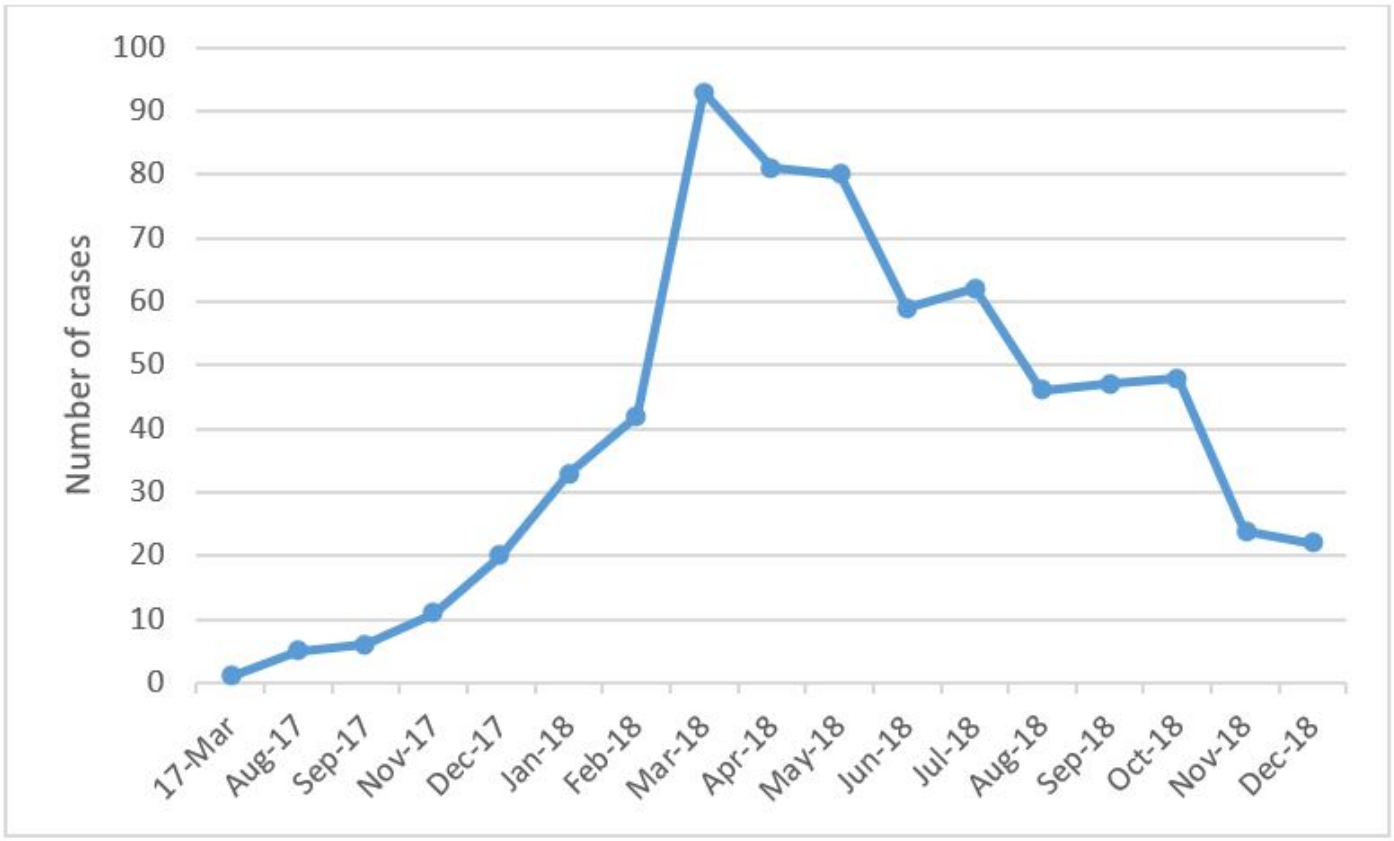

Figure 2

Seasonal pattern of XDR Enteric fever