Clinical presentations, diagnostics, treatments and treatment costs of children and adults with febrile illness in a tertiary referral hospital in south-eastern Guinea: a retrospective longitudinal cohort study.

Manuel Raab (manuel.j.raab@gmail.com)
Ludwig Maximilian University of Munich

Lisa M. Pfadenhauer
Ludwig Maximilian University of Munich

Dansira Doumbouya
Hôpital Régional de N'zérékoré

Guenter Froeschl
Ludwig Maximilian University of Munich

Research Article

Keywords: Febrile illness, Ebola, Viral haemorrhagic fevers, Malaria, Mortality, Guinea, West Africa

Posted Date: March 4th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-264789/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License

Version of Record: A version of this preprint was published at PLOS ONE on January 10th, 2022. See the published version at https://doi.org/10.1371/journal.pone.0262084.
Abstract

Background

Febrile illness is frequent among patients in the tropics. It is caused by a wide variety of common diseases such as malaria or gastrointestinal infections but also by less common but highly contagious pathogens with epidemic potential. This study describes the clinical features of adult and paediatric patients with febrile illness in in the largest tertiary referral hospital in south-eastern Guinea, a region at high risk for viral haemorrhagic fever outbreaks. The study further compares their diagnostic characteristics, treatments and outcomes with non-febrile patients in order to contribute to the local epidemiology of febrile illness.

Methods

We used retrospective data collection to record demographic and clinical data of all incoming patients during a study period of three months. For the follow-up study of inpatients, we retrospectively reviewed patient charts for diagnostic characteristics, diagnoses and outcomes.

Results

Of the 4317 patients admitted during the study period, 9.5% had a febrile illness. The majority of febrile adults (73.8%) and children (92.1%) were hospitalized after admission. By far, the most used diagnostic measures to identify causative agents in febrile patients were point-of-care tests. Treatments of febrile patients were mainly a combination of paracetamol and/or antibiotics. Most common discharge diagnoses for febrile inpatients were malaria (9.6% adults, 56.7% children), salmonella gastroenteritis/typhoid (10.6% adults, 7.8% children) and respiratory infection/pneumonia (5.3% adults, 18.7% children). Inpatient mortality for children was significantly higher in febrile than non-febrile children (18.5% vs. 5.1%, p < 0.001) and considerably higher in febrile than non-febrile adults (29.8% vs. 25.0%, p = 0.404).

Conclusions

The wide use of rapid diagnostic tests to identify causes of febrile illness highlights the low reliance on basic serological and advanced laboratory testing to research causative agents of febrile illness other than malaria or salmonella gastroenteritis/typhoid. This not only risks to over- or under-diagnose certain infectious diseases but also leaves the possibility of highly infectious diseases in febrile patients unexplored. Furthermore, healthcare facilities in south-eastern Guinea would benefit from antimicrobial stewardship due to their heavy reliance on antibiotics for treating febrile patients.

Background

Fever is a common reason for patients to seek healthcare in the tropics [1–3]. It is usually associated with non-specific gastrointestinal or respiratory symptoms but may also present itself as an isolated symptom. Fever is often used synonymously with the term “febrile illness”, which is defined as an illness with an elevated body temperature of at least 37.5°C or higher [4]. Possible causes of febrile illness include a wide spectrum of pathogens such as bacterial bloodstream infections (e.g. salmonella enterica subtypes), mycobacterial bloodstream infections (e.g. mycobacterium tuberculosis), bacterial zoonosis (e.g. brucellosis), protozoal infections (e.g. African trypanosomiasis), fungal infections (e.g. cryptococcus) and viral infections (e.g. rhinoviruses) [5]. In malaria endemic regions, malaria is often the default diagnosis for febrile illness, partly because of its high prevalence and partly because of the predominance of malaria eradication programs in the past decade which led to the over-diagnosing of malaria [6–8]. Especially in low-resource healthcare settings, identifying non-malarial febrile illness can be challenging due to impaired diagnostic capacities and few point-of care tests for most microorganisms [9]. While adequate treatment of febrile illness ideally depends on the identification of the causative agent, febrile illness in low-resource healthcare settings is usually treated with calculated antimicrobial and/or antimalarial medications, increasing the risk of drug resistance [10].

Next to more common causes of febrile illness in the tropics, certain pathogens with epidemic potential have emerged as equally important causes for febrile illness [11]. Notably, the 2014–2016 West African Ebola virus outbreak as well as the recent 2021 Ebola virus outbreak in south-eastern Guinea highlighted the importance of pathogen-specific screening and surveillance in West Africa for potentially infectious patients presenting with fever – fever being one of the most common symptoms amongst patients infected with Ebola virus [12, 13]. Guinea – one of the poorest African nations with a fragile healthcare system – was amongst the most affected countries by the Ebola virus epidemic [14]. Particularly its south-eastern region is now considered at high risk for outbreaks of viral haemorrhagic fevers such as Ebola virus disease, Marburg virus disease, Lassa fever and Crimean-Congo haemorrhagic fever [15–20]. All of these highly contagious diseases are known to
cause febrile illness in patients at an early stage of infection [21–24]. But also other potentially fatal infectious diseases causing febrile illness such as meningitis, leptospirosis or dengue have been reported in the region [25–29].

In this study we describe epidemiological, clinical and diagnostic characteristics, current treatment strategies, and outcomes of adult and paediatric patients with febrile illness treated at the largest referral hospital in south-eastern Guinea. We further compare these clinical features of febrile patients with non-febrile patients. Our study provides a profile of a typical Guinean provincial referral hospital by highlighting its procedures and capacities in regard to diagnosing and treating febrile illness. Thereby, we hope to contribute to a better understanding of the local epidemiology of febrile illness in a region at risk for infectious disease outbreaks. We point to further management needs in Guinean healthcare structures regarding febrile illness amongst patients.

### Methods

#### Study Setting

Our study was carried out at the Hôpital Régional de N’zérékoré (N’zérékoré Regional Hospital, HRNZ), a tertiary provincial referral hospital in south-eastern Guinea. N’zérékoré is Guinea’s second largest city with more than 300,000 inhabitants and is the capital of Guinea’s forested region, also known as Guinée Forestière with a population of over two million [30]. Bordering Sierra Leone, Liberia and Ivory Coast, the region has a tropical climate with a wet season lasting approximately from May until November and the dry season from December until April. Guinée Forestière is in south-eastern Guinea and is known as the region where the 2014–2016 West African Ebola outbreak most likely started [31]. A new Ebola outbreak close to N’zérékoré city was declared in early 2021 and several cases were hospitalized in the HRNZ prior to being laboratory confirmed [32].

With a capacity of approximately 175 beds and services in Internal Medicine, Surgery, Intensive Care, Gynaecology/Obstetrics, Ophthalmology and Dental Care, the HRNZ is amongst the three largest hospitals in the country. It is the largest referral hospital in Guinée Forestière receiving emergency patients as well as patients requiring specialized care from surrounding urban and rural areas. The hospital laboratory is equipped for basic serological, haematological, bacteriological and clinical biochemistry testing. Furthermore, an additional laboratory for viral haemorrhagic fevers was established in 2014. Supply shortages may, however, constrain laboratory diagnostic capacities. The only possibilities for imaging purposes are one X-ray and one ultrasound machine.

Upon hospital-entry, triage staff records main symptoms and body temperatures of all non-emergency patients in order to orient patients to the hospital’s different outpatient services. Severely ill patients are immediately directed to the emergency room. At the outpatient services, physicians may decide that patients require inpatient care and will send them to the emergency room for further examinations and inpatient admission. Patients requiring obstetric care or seeking access to the specialized HIV clinic located within the hospital compound may bypass hospital triage. Thus, all inpatients except HIV clinic and obstetric patients are handled at the level of the emergency room.

The emergency room separates paediatric, adult medical and surgical patients. Paediatric surgical patients are treated in the adult surgical ward. Physicians examine patients, administer malaria rapid antigen tests (mRDT) if necessary and initiate first treatments. They further decide whether patients require inpatient care or not.

Patient records are kept in various registers at hospital triage and the emergency room while patient charts are compiled only for inpatients at the level of the emergency room.

#### Data Sources and Study-Design

Using a retrospective study design, we analysed data of all patients who were admitted to the HRNZ between December 2, 2018 and March 1, 2019 (dry season), except obstetric and HIV clinic patients. Details on study design and data sources are well-explained elsewhere [33]. Data was extracted from hospital records and patient charts at three levels. First, triage data for all incoming patients comprised socio-demographic characteristics, symptoms, measured body temperatures and referral service. Second, we recorded diagnostic results, treatments, hospitalization status, suspected diagnoses (the most important three) and outcomes for all adult and paediatric emergency patients, except surgical patients, deceased patients during emergency treatment and patients whose body temperatures had not been recorded; these patients were excluded. Third, laboratory diagnostics, primary discharge diagnoses and outcomes of adult and paediatric medical inpatients were extracted from patient charts. When these charts were incomplete or unclear, we consulted the responsible healthcare worker for missing information.

For this study, we stratified patient data of all incoming patients by measured axillary body temperatures (cut-off 38.0°C). In our data, medical adult and paediatric emergency patients are subdivided into two groups (without fever: $< 38.0°C$ and with fever: $≥ 38.0°C$). They are described and compared by the variables age, symptoms, suspected diagnosis, diagnostics, initial treatment and admission status. Febrile and non-febrile patients requiring inpatient care are further compared to add more details regarding laboratory diagnostics, discharge diagnoses and outcomes.
Next to the above, we calculated an approximation for the average inpatient healthcare costs per adult and per paediatric inpatient based on laboratory costs, costs for medications and hospitalization costs per patient. Laboratory costs were calculated based on hospital price lists and all laboratory and imaging diagnostics performed on inpatients. Costs for medications were calculated based on the average amount of medications prescribed per inpatient and the average price per medication as indicated by the hospital pharmacy. We excluded the ten most expensive, yet rarely used medications from our approximation to reduce risk of skewed over-estimating inpatient medication costs. Hospitalization costs were calculated based on price lists as provided by the hospital administration.

Data Analysis

Data Analysis

Patient symptoms and diagnoses were coded according to the International Classification of Primary Care, 2nd edition (ICPC-2). All data was recorded and coded with Microsoft Excel 16 and analysed using IBM SPSS 25. Descriptive statistics were generated and proportions were compared using Pearson's Chi² Test and Exact Fisher Test. Statistical significance was determined at \( p \leq 0.05 \). Because of extreme outliers in age, we used non-parametric median and interquartile range (IQR) to describe the age of admitted patients.

Ethical Considerations

Ethical Considerations

Ethical approval for this study was granted by the Guinean Ethics Committee for Research in Health (opinion number 103/CNERS/18) and the Ethics Committee for Medical Research at the Ludwig-Maximilians-Universität (LMU), Munich, Germany (opinion number 18–834). Before its implementation, the study was presented to the regional health authorities and the HRNZ directorate who both consented to its implementation.

Since data was collected as part of routine clinical practice and for the purpose of this retrospective study extracted in an anonymized fashion, and in the further analysis presented in an aggregate manner, no informed consent was asked from patients.

All methods were carried out in accordance with relevant guidelines and regulations.

Results

General patient characteristics upon hospital admission

4317 patients were admitted during our study period. Of those patients, 2616 patients (60.6%) were handled by triage, 1178 patients (27.3%) by the adult emergency room and 523 patients (12.1%) by the paediatric emergency room (Table 1). In total, 67 patients (1.6%) deceased in the emergency room during treatment, of which 56 in the adult emergency room and 11 in the paediatric emergency room. Almost half of all the patients were male (2121/4317; 49.1%), the other half female (2193/4317; 50.8%). The majority of admitted patients (3375/4317; 78.2%) came from urban areas, the rest (795/4317; 18.4%) from rural areas. While patients reported fever as the most frequent primary reason for seeking care at the hospital, none of the 2616 patients handled by triage had a measured axillary body temperature \( \geq 38,0^\circ C \) (febrile). However, with regard to the emergency facilities, 15.4% (182/1178) of adult emergency patients and 43.8% (229/523) of paediatric emergency patients resulted to be febrile, amounting to a total 9.5% (411/4317) of all patients being febrile upon hospital admission. For 274 patients (6.3%) no body temperature was recorded. Of all admitted patient, most febrile patients were within the age group 0–4 years (4.3%; 174/4043; Fig. 1). The three most frequent referral services were internal medicine (35.4%), paediatrics (20.2%) and surgery (14.5%). Deceased patients, surgical patients and patients where body temperature was not recorded were excluded from the following analysis.

Table 1: Patient characteristics upon admission
|                          | Total     | Triage     | Adult emergency room | Paediatric emergency room |
|--------------------------|-----------|------------|----------------------|---------------------------|
| Total Number of Patients N | 4317      | 2616       | 1178                 | 523                       |
| **General Characteristics** |           |            |                      |                           |
| Median Age - years (IQR) | 27 (11-45) | 29 (16-45) | 35 (23-55)           | 1 (1-4)                   |
| Male Sex - n/N (%)        | 2121/4317 | 1134/2616 | 691/1178             | 296/523                   |
| Female Sex - n/N (%)      | 2193/4317 | 1482/2616 | 484/1178             | 227/523                   |
| Sex not registered - n/N (%) | 3/4317   | 0/2616     | 3/1178               | 0/523                     |
| Residence in urban area - n/N (%) | 3375/4317 | 2127/2616 | 863/1178             | 385/523                   |
| Residence in rural area - n/N (%) | 795/4317 | 487/2616  | 183/1178             | 125/523                   |
| Residence not registered - n/N (%) | 147/4317 | 2/2616     | 132/1178             | 13/523                    |
| **Referred Service**      |           |            |                      |                           |
| Internal Medicine - n/N (%) | 1527/4317 | 840/2616  | 687/1178             | 0/523                     |
| Paediatrics - n/N (%)     | 872/4317  | 360/2616  | 0/1178               | 512/523                   |
| Surgery - n/N (%)         | 625/4317  | 190/2616  | 435/1178             | 0/523                     |
| Ophthalmology - n/N (%)   | 446/4317  | 446/2616  | 0/1178               | 0/523                     |
| Gynaecology - n/N (%)     | 353/4317  | 353/2616  | 0/1178               | 0/523                     |
| Dental Clinic - n/N (%)   | 220/4317  | 220/2616  | 0/1178               | 0/523                     |
| Ear Nose Throat (ENT) Clinic - n/N (%) | 182/4317 | 182/2616 | 0/1178               | 0/523                     |
| Not recorded - n/N (%)    | 25/4317   | 25/2616   | 0/1178               | 0/523                     |
| Deceased during treatment - n/N (%) | 67/4317   | 0/2616    | 56/1178              | 11/523                    |
| **Body Temperature**      |           |            |                      |                           |
| <38°C - n/N (%)           | 3632/4317 | 2585/2616 | 781/1178             | 266/523                   |
| ≥38°C - n/N (%)           | 411/4317  | 0/2616    | 182/1178             | 229/523                   |
| Not recorded - n/N (%)    | 274/4317  | 31/2616   | 215/1178             | 28/523                    |
| **Most frequent primary reasons for consultation** | | | | |
| Fever, Musculoskeletal injury, Eye problems | | | | |
| Eye problems, Fever, Chest pain | | | | |
| Musculoskeletal injury, Abdominal pain, Head injury | | | | |
| Fever, Asthenia, Cough | | | | |

**Clinical features of medical adult and paediatric emergency patients: febrile vs. non-febrile patients**

Of 1119 medical adult and paediatric emergency patients whose body temperatures were recorded, 34.9% (391/1119) were febrile, with the larger proportion of febrile patients being paediatric patients (26.1% adults vs. 46.3% children; Table 2). Overall, asthenia (52.6%; 589/1119), loss of appetite (36.9%; 413/1119), vomiting (30.8%; 345/1119) and cough (30.3%; 339/1119) were the most frequently reported symptoms amongst medical emergency patients. Adult febrile patients were more likely than non-febrile patients to report asthenia (50.0% vs 36.1%, p = 0.002), diarrhoea (17.7% vs 10.1%, p = 0.020) and cough (25.6% vs. 11.0%, p < 0.001). They were also more likely to receive a mRDT upon admission (65.9% vs. 49.2%, p < 0.001). In total, 45 adult patients (7.2%; 45/629) had a positive mRDT result, of which 19 patients were febrile and 26 patients non-febrile (11.6% vs. 5.6%, p = 0.014). For children, none of the reported symptoms were more specific for febrile in comparison to non-febrile patients. MRDTs were performed on all but one paediatric patient with results being almost equally distributed between febrile
and non-febrile children: 50.0% of all children (47.1% febrile vs 52.5% non-febrile, p = 0.277) received a negative mRDT result and 49.8% (52.4% febrile vs. 47.5% non-febrile, p = 0.319) a positive result.

Table 2: Clinical features of febrile vs. non-febrile medical adult and paediatric emergency patients
| Total | Adult medical patients | Paediatric medical patients |
|-------|------------------------|----------------------------|
|       | Total                  | Febrile N=164              | Non-febrile N=465 | p-value | Total | Febrile N=227 | Non-febrile N=263 | p-value |
| Total Number of Patients N - n/N (%) | 1119 | 629 | 164/629 (26.1) | 465/629 (73.9) | 490 | 227/490 (46.3) | 263/490 (53.7) | 0.281 |
| **Most frequent symptoms (besides fever)** |
| **General symptoms** |
| Asthenia - n/N (%) | 589/1119 (52.6) | 250/629 (39.7) | 82/164 (50.0) | 168/465 (36.1) | 0.002 | 339/490 (69.2) | 163/227 (71.8) | 176/263 (66.9) | 0.281 |
| Loss of appetite – n/N (%) | 413/1119 (36.9) | 158/629 (25.1) | 50/164 (30.5) | 108/465 (23.2) | 0.075 | 255/490 (52.0) | 123/227 (54.2) | 132/263 (50.2) | 0.415 |
| Headache – n/N (%) | 194/1119 (17.3) | 171/629 (27.2) | 46/164 (28.0) | 125/465 (26.9) | 0.761 | 23/490 (4.7) | 12/227 (5.3) | 11/263 (4.2) | 1.000 |
| Dizziness – n/N (%) | 113/1119 (10.1) | 112/629 (17.8) | 33/164 (20.1) | 79/465 (17.0) | 0.406 | 1/490 (0.2) | 0/227 (0.0) | 1/263 (0.4) | 1.000 |
| Digestive symptoms |
| Vomiting – n/N (%) | 345/1119 (30.8) | 116/629 (17.6) | 35/164 (21.3) | 76/465 (16.3) | 0.094 | 234/490 (47.8) | 98/227 (43.2) | 136/263 (62.0) | 0.070 |
| Diarrhoea – n/N (%) | 224/1119 (20.0) | 76/629 (12.4) | 29/164 (17.7) | 49/465 (10.5) | 0.020 | 146/490 (29.9) | 65/227 (28.6) | 81/263 (30.8) | 0.622 |
| Abdominal pain – n/N (%) | 221/1119 (19.7) | 176/629 (28.0) | 40/164 (24.4) | 136/465 (29.2) | 0.266 | 45/490 (9.2) | 21/227 (9.3) | 24/263 (9.1) | 1.000 |
| Respiratory symptoms |
| Cough – n/N (%) | 339/1119 (30.3) | 93/629 (14.8) | 42/164 (25.6) | 51/465 (11.0) | <0.001 | 246/490 (50.2) | 114/227 (50.2) | 132/263 (50.2) | 1.000 |
| Dyspnoea – n/N (%) | 104/1119 (9.3) | 72/629 (11.4) | 17/164 (10.4) | 54/465 (11.6) | 0.774 | 32/490 (6.5) | 14/227 (6.2) | 18/263 (6.8) | 0.855 |
| Malaria rapid diagnostic test (mRDT) |
| Negative – n/N (%) | 537/1119 (48.0) | 292/629 (46.4) | 89/164 (54.3) | 203/465 (43.7) | 0.023 | 245/490 (50.0) | 107/227 (47.1) | 138/263 (52.5) | 0.277 |
| Positive – n/N (%) | 289/1119 (25.8) | 45/629 (7.2) | 19/164 (11.6) | 26/465 (5.6) | 0.014 | 244/490 (49.8) | 119/227 (52.4) | 125/263 (47.5) | 0.319 |
| Not performed – n/N (%) | 293/1119 (26.2) | 292/629 (46.4) | 56/164 (34.1) | 236/465 (50.8) | <0.001 | 1/490 (0.2) | 1/227 (0.4) | 0/263 (0.0) | 0.463 |
| Most frequent suspected diagnosis |
| Malaria – n/N (%) | 632/1119 (56.5) | 163/629 (25.9) | 57/164 (34.8) | 106/465 (22.8) | 0.002 | 469/490 (95.7) | 221/227 (97.4) | 248/263 (94.3) | 0.118 |
| Gastroenteritis – n/N (%) | 376/1119 (33.6) | 285/629 (45.3) | 73/164 (44.5) | 212/465 (45.6) | 0.855 | 91/490 (18.6) | 42/227 (18.5) | 49/263 (18.6) | 1.000 |
| Pneumonia/Respiratory infection – n/N (%) | 356/1119 (31.8) | 51/629 (8.1) | 22/164 (13.4) | 29/465 (6.2) | 0.007 | 305/490 (62.2) | 140/227 (61.7) | 165/263 (62.7) | 0.852 |
| Gastrroduodenal Ulcer – n/N (%) | 106/1119 (9.5) | 106/629 (16.9) | 25/164 (15.2) | 81/465 (17.4) | 0.305 | 0/490 (0.0) | 0/227 (0.0) | 0/263 (0.0) | 0.000 |
| Stroke – n/N (%) | 54/1119 (4.8) | 54/629 (8.6) | 6/164 (3.7) | 48/465 (10.3) | 0.009 | 0/490 (0.0) | 0/227 (0.0) | 0/263 (0.0) | 0.000 |
| **Selected emergency medications** |
| **Antibiotics** |
| Ampicillin – n/N (%) | 650/1119 | 316/629 | 89/164 | 227/465 | 0.239 | 334/490 | 149/227 | 185/263 | 0.285 |
or without notifying hospital staff and 18.0% (128/710) deceased in inpatient care. The larger proportion of deceased inpatients was amongst adults: febrile vs. non-febrile patients (34.8% vs. 22.8%, p = 0.002). With regard to all diagnoses suspected in adult medical emergency patients combined, 58.5% (594/1016) belonged to the diagnosis group infectious diseases, 16.3% (166/1016) to non-infectious diseases of the gastrointestinal tract and 11.2% (114/1016) to non-infectious cardiovascular diseases (Fig. 2). In children, the three most frequently suspected diagnoses as per adult medical emergency patient were salmonella gastroenteritis/typhoid (45.3%; 286/629), malaria (25.9%; 163/629) and gastroduodenal ulcer (16.9%; 106/629). Only malaria was significantly more often diagnosed amongst children in the emergency room belonged to the diagnosis group infectious diseases, 12.2% (231/1919) to non-infectious diseases of the blood system and 6.4% (82/1275) to non-infectious diseases of the gastrointestinal tract (Fig. 3).

The three most frequently suspected diagnoses as per adult medical emergency patient were salmonella gastroenteritis/typhoid (45.3%; 286/629), malaria (25.9%; 163/629) and gastroduodenal ulcer (16.9%; 106/629). Only malaria was significantly more often diagnosed amongst febrile as compared to non-febrile adults (34.8% vs. 22.8%, p = 0.002). With regard to all diagnoses suspected in adult medical emergency patients combined, 58.5% (594/1016) belonged to the diagnosis group infectious diseases, 16.3% (166/1016) to non-infectious diseases of the gastrointestinal tract and 11.2% (114/1016) to non-infectious cardiovascular diseases (Fig. 2). In children, the three most frequently suspected diagnoses were malaria (95.7%; 469/490), respiratory infection/pneumonia (62.2%; 305/490) and gastroenteritis (18.6%; 91/490). There was no significant difference in the proportion of suspected diagnoses between febrile and non-febrile children. In total, 70.0% (892/1275) of all suspected diagnoses combined amongst children in the emergency room belonged to the diagnosis group infectious diseases, 12.2% (156/1275) to non-infectious diseases of the blood system and 6.4% (82/1275) to non-infectious diseases of the gastrointestinal tract (Fig. 3).

Treatments for medical emergency patients consisted mainly of antibiotic, analgesic/antipyretic and antimalarial treatment. For adult patients, ampicillin (50.2%; 316/629) and paracetamol (55.6%; 350/629) were by far the most commonly used medications. For children, ampicillin was given to 68.2% (334/490) of patients, artesunate to 42.7% (209/490) of patients and paracetamol to 33.5% (164/490) of patients. For both adults and children metronidazole was another frequently prescribed antibiotic (11.0% adults, 24.5% children). Furthermore, gentamycin was often used for paediatric patients (20.8%; 102/490). Altogether, only paracetamol was significantly more often used in the groups of febrile adult patients (72.6% vs. 49.8%, p < 0.001) and febrile paediatric patients (54.2% vs. 15.6%, p < 0.001) in comparison to non-febrile patients.

**Diagnostics, discharge diagnoses and outcomes of medical adult and paediatric inpatients: febrile vs. non-febrile patients**

Of the 1119 medical emergency patients, 418 adults and 447 children were hospitalized. 100 adult patients (23.9%; 100/418) and 55 paediatric patients (12.3%; 55/447) were lost to follow-up, leaving 94 febrile (29.6%; 94/318) and 224 non-febrile (70.4%; 224/318) adult inpatient charts and 178 febrile (45.4%; 178/392) and 214 non-febrile (54.6%; 214/392) paediatric inpatient charts for review (Fig. 4).

On average, adult febrile inpatients were hospitalized for almost one day longer than non-febrile inpatients (5.9 days vs. 5 days; Table 3). Paediatric inpatients stayed hospitalized less days than adults: 3.5 days on average for febrile children and 3.2 days for non-febrile children. Overall, 56.8% (403/710) of all inpatients were discharged with improved health, 24.3% (172/710) either self-discharged against medical advice or without notifying hospital staff and 18.0% (128/710) deceased in inpatient care. The larger proportion of deceased inpatients was amongst...
adults (26.4% adults vs. 11.2% children). However, febrile children were significantly more likely to die during hospitalization than non-febrile children (18.5% vs. 5.1%, p < 0.001), which only reached a level of a trend for adult inpatients (29.8% vs. 25.0%, p = 0.404).

The most frequent diagnostic tests performed amongst all inpatients were mRDT (78.6%; 558/710), thick blood smear (TBS, 38.3%; 272/710), Widal TO/TH test (23.7%; 168/719) and HIV antibody screening test (8.7%; 62/710), which was mainly used in adult inpatients. Overall, there were no significant differences in the proportion of positive malaria tests between febrile and non-febrile patients. MRDT were positive in 6.3% (20/318) of all adult inpatients (6.6% febrile vs. 8% non-febrile, p = 1.000) and in 48% (188/392) of all paediatric inpatients (50.6% febrile vs. 45.8% non-febrile, p = 0.416). TBS showed presence of *P. falciparum* in 4.4% (14/318) of adult inpatients (4.3% febrile vs. 4.5% non-febrile, p = 1.000) and in 8.7% (34/392) of paediatric inpatients (9.6% febrile vs. 7.9% non-febrile, p = 0.594).

Table 3: Diagnostics, diagnoses and outcomes of febrile vs. non-febrile medical adult and paediatric inpatients
|                                  | Total         | Adult medical inpatients | Paediatric inpatients | Comments                                                                 |
|----------------------------------|---------------|--------------------------|-----------------------|---------------------------------------------------------------------------|
|                                  |               | Total                    | Febrile N=94          | Non-febrile N=224             | p-value | Total | Febrile N=178 | Non-febrile N=214 | p-value |
| **Total Number of Patients** N – n/N (%) | 710           | 318                      | 94/318 (29.6)         | 224/318 (70.4) | 392 | 178/392 (45.4) | 214/392 (54.6) |  |
| **Days hospitalized** – Mean in days (SD) | 4.3 (3.0)     | 5.3 (4.0)                | 5.9 (4.1)             | 5.0 (3.9)       | 3.3 (2.0) | 3.5 (1.8) | 3.2 (2.1) |  |
| **Most frequently performed diagnostics** |               |                          |                       |                                                          |
| **Malaria rapid diagnostic test (mRDT)** |               |                          |                       |                                                          |
| Positive – n/N (%)               | 208/710 (29.3)| 20/318 (6.3)             | 6/94 (6.4)            | 14/224 (6.3)  | 1.000 | 188/392 (48.0) | 90/178 (50.6) | 98/214 (45.8) | 0.416 |
| Negative – n/N (%)               | 350/710 (49.3)| 148/318 (46.5)           | 59/94 (62.8)          | 89/224 (39.7) | <0.001 | 202/392 (51.5) | 87/178 (48.9) | 115/214 (53.7) | 0.361 |
| **Thick blood smear (TBS)**      |               |                          |                       |                                                          |
| Positive – n/N (%)               | 48/710 (6.8)  | 14/318 (4.4)             | 4/94 (4.3)            | 10/224 (4.5)  | 1.000 | 34/392 (8.7)  | 17/178 (9.7)  | 17/214 (7.9)  | 0.594 |
| Negative – n/N (%)               | 224/710 (31.5)| 85/318 (26.7)            | 38/94 (40.4)          | 47/224 (21.0) | 0.001 | 139/392 (35.5) | 59/178 (33.1) | 80/214 (37.4) | 0.397 |
| **Widal TO/TH**                  |               |                          |                       |                                                          |
| Positive – n/N (%)               | 129/710 (18.2)| 53/318 (16.7)            | 20/94 (21.3)          | 33/224 (14.7) | 0.187 | 76/392 (19.4) | 37/178 (20.8) | 39/214 (18.2) | 0.608 |
| Negative – n/N (%)               | 39/710 (5.5)  | 11/318 (3.5)             | 4/94 (4.3)            | 7/224 (3.1)   | 0.737 | 28/392 (7.1)  | 13/178 (7.3)  | 15/214 (6.5)  | 1.000 |
| **Cerebrospinal fluid**          |               |                          |                       |                                                          |
| Pathological (indicating bacterial) | 11/710 (1.5) | 2/318 (0.6)              | 2/94 (2.1)            | 0/224 (0.0)   | 0.087 | 9/392 (2.3)   | 5/178 (2.8)   | 4/214 (1.9)   | 0.737 |

Malaria in Guinea is assumed to be caused by *P. falciparum* only.

Malaria in Guinea is assumed to be caused by *P. falciparum* only.

Widal test plays a crucial role in diagnosing typhoid fever (which is recorded as a salmonella gastroenteritis).

Cerebrospinal fluid is used to diagnose bacterial meningitis only.
| Infection Type | Positive - n/N (%) | Negative - n/N (%) |
|----------------|-------------------|-------------------|
| Stool microscopy parasites | | |
| Normal | 3/710 (0.4) | 18/710 (2.5) |
| | 0/318 (0.0) | 10/318 (3.1) |
| | 0/94 (0.0) | 2/94 (2.1) |
| | 0/224 (0.0) | 8/224 (3.6) |
| | 3/392 (0.8) | 8/392 (2.0) |
| | 1/178 (0.6) | 4/178 (2.2) |
| | 2/214 (0.9) | 4/214 (1.9) |
| | 1.000 | 1.000 |
| HIV antibody test | | |
| Positive | 20/710 (2.8) | 8/710 (1.1) |
| | 20/318 (6.3) | 8/318 (2.5) |
| | 11/94 (11.7) | 9/94 (9.6) |
| | 9/224 (4.0) | 16/224 (7.1) |
| | 0.020 | 0.496 |
| | 0/392 (0.0) | 1/392 (0.3) |
| | 0/178 (0.0) | 1/178 (0.3) |
| | 0/214 (0.0) | 0/214 (0.0) |
| | 1.000 | 0.455 |
| Syphilis TPHA | | |
| Positive | 8/710 (1.1) | 5/710 (0.7) |
| | 8/318 (2.5) | 5/318 (1.6) |
| | 2/94 (2.1) | 2/94 (2.1) |
| | 6/224 (2.7) | 3/224 (1.3) |
| | 1.000 | 0.634 |
| | 0/392 (0.0) | 0/392 (0.0) |
| | 0/178 (0.0) | 0/178 (0.0) |
| | 0/214 (0.0) | 0/214 (0.0) |
| | 0.455 | |
| Toxoplasmosis IgG/IgM | | |
| Positive | 4/710 (0.6) | 5/710 (0.7) |
| | 4/318 (1.3) | 5/318 (1.6) |
| | 0/94 (0.0) | 2/94 (2.1) |
| | 4/224 (1.8) | 3/224 (1.3) |
| | 0.323 | 0.634 |
| | 0/392 (0.0) | 0/392 (0.0) |
| | 0/178 (0.0) | 0/178 (0.0) |
| | 0/214 (0.0) | 0/214 (0.0) |
| | 0.455 | |

There are no other diagnostic tests available for recognizing common parasitic infection.

HIV Antigen tests are used to diagnose HIV. If positive, patients are referred to the HIV clinic for further PCR testing.

Only TPHA screening test is used, confirmation test was unavailable during time of study.

Pulmonary tuberculosis is usually diagnosed and treated by the external tuberculosis program.
clinic. Suspect cases are referred.

| Positive – n/N (%) | 1/710 (0.1) | 1/318 (0.3) | 0/94 (0.0) | 1/224 (0.4) | 1.000 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) |
| Negative – n/N (%) | 3/710 (0.4) | 3/318 (0.9) | 1/94 (1.1) | 2/224 (0.9) | 1.000 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) |

**Anti-streptolysin O**

| Positive – n/N (%) | 17/710 (2.4) | 12/318 (3.8) | 4/94 (4.3) | 8/224 (3.6) | 0.754 | 5/392 (1.3) | 3/178 (1.7) | 2/214 (0.1) |
| Negative – n/N (%) | 10/710 (1.4) | 9/318 (2.8) | 3/94 (3.2) | 6/224 (2.7) | 0.727 | 1/392 (0.3) | 1/178 (0.6) | 0/214 (0.0) |

**Hbs Antigen**

| Positive – n/N (%) | 7/710 (1.0) | 7/318 (2.2) | 1/94 (1.1) | 6/224 (2.7) | 0.678 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) |
| Negative – n/N (%) | 19/710 (2.7) | 19/318 (6.0) | 6/94 (6.4) | 13/224 (5.8) | 0.801 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) |

**Most frequent discharge diagnoses**

| Malaria – n/N (%) | 222/710 (31.3) | 24/318 (7.5) | 9/94 (9.6) | 15/224 (6.7) | 0.362 | 198/392 (50.5) | 101/178 (56.7) | 97/214 (45.3) | 0.025 |
| Respiratory infection – n/N (%) | 83/710 (11.7) | 10/318 (3.1) | 5/94 (5.3) | 5/224 (2.2) | 0.168 | 73/392 (18.6) | 33/178 (18.5) | 40/214 (18.7) | 1.000 |
| Gastroenteritis – n/N (%) | 69/710 (9.7) | 40/318 (12.6) | 10/94 (10.6) | 30/224 (13.4) | 0.581 | 29/392 (7.4) | 14/178 (7.8) | 15/214 (7.0) | 0.847 |

Hepatitis B surface antigen is used to diagnose active Hepatitis B. Other diagnostic tests are not available.

Diagnosis based on positive rapid test result and/or positive thick blood smear, or clinical presentation only.

Diagnosis based on clinical presentation and occasionally on radiological results; includes all respiratory infections other than tuberculosis.

Diagnosis based on clinical
| Diagnosis                  | n/N (%) | n/N (%) | n/N (%) | n/N (%) | p-value | n/N (%) | n/N (%) | n/N (%) | n/N (%) |
|----------------------------|---------|---------|---------|---------|---------|---------|---------|---------|---------|
| **Liver Disease (e.g. Hepatitis B)** - n/N (%) | 21/710 (3.0) | 19/318 (6.0) | 6/94 (6.4) | 13/224 (5.8) | 0.801 | 2/392 (0.5) | 2/178 (1.1) | 0/214 (0.0) | 0.207 |
| **Meningitis - n/N (%)** | 4/710 (0.6) | 2/318 (0.6) | 2/94 (2.1) | 0/224 (0.0) | 0.087 | 2/392 (0.5) | 2/178 (1.1) | 0/214 (0.0) | 0.207 |
| **HIV - n/N (%)**          | 21/710 (3.0) | 21/318 (6.6) | 10/94 (10.6) | 11/224 (4.9) | 0.081 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) | 0.081 |
| **Pulmonary Tuberculosis - n/N (%)** | 9/710 (1.7) | 9/318 (2.8) | 2/94 (2.1) | 7/224 (3.1) | 1.000 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) | 1.000 |
| **Gastroduodenal Ulcer - n/N (%)** | 14/710 (2.0) | 14/318 (4.4) | 1/94 (1.2) | 13/224 (5.8) | 0.073 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) | 0.073 |
| **Anaemia not specified - n/N (%)** | 22/710 (3.1) | 21/318 (6.6) | 2/94 (2.1) | 19/224 (8.5) | 0.046 | 1/392 (0.3) | 0/178 (0.0) | 1/214 (0.5) | 1.000 |
| **Stroke - n/N (%)**       | 43/710 (6.1) | 43/318 (13.5) | 14/94 (14.9) | 29/224 (12.9) | 0.720 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) | 0.720 |
| **Hypertension not specified** | 10/710 (1.4) | 10/318 (3.1) | 0/94 (0.0) | 10/224 (4.5) | 0.037 | 0/392 (0.0) | 0/178 (0.0) | 0/214 (0.0) | 0.037 |

Diagnosis based on clinical presentation and/or positive Anti Hbs results.

Diagnosis based on clinical presentation and/or cerebrospinal fluid results.

Diagnosis based on positive HIV Antigen test result, later confirmed through PCR at external HIV clinic.

Diagnosis based on clinical presentation and/or radiological findings and/or sputum analysis.

Diagnosis based on clinical presentation only.

Diagnosis based on Haemoglobin level without evidence of known cause.
Of all inpatients who were tested for malaria by means of mRDT, 67 adult inpatients and 172 paediatric inpatients were also tested for malaria through TBS (Table 4). For adult inpatients, a positive TBS was significantly more likely when the mRDT had been positive: 27.3% (3/11) of adult inpatients with a positive TBS were also tested positive by means of mRDT whereas only 3.6% (2/56) with a negative TBS were tested positive by means of mRDT (2/56, p = 0.006). In other words, 72.7% (8/11) of adult inpatients with a positive TBS received a negative mRDT while 96.4% (54/56) of adult inpatients with a negative TBS also received a negative mRDT result. For children, 5.9% (2/34) of inpatients with a positive TBS were also tested positive by means of mRDT and 4.3% (6/138) with a negative TBS were tested positive by means of mRDT. In other words, 94.1% (32/34) of paediatric inpatients with a positive TBS received a negative mRDT while 95.7% (132/138) of paediatric inpatients with a negative TBS received a negative mRDT result.

Table 4: Malaria RDT vs. TBS results of medical adult and paediatric inpatients where both mRDT and TBS were performed

|                        | Total          | Adult medical inpatients | Paediatric medical inpatients |
|------------------------|----------------|--------------------------|-----------------------------|
|                        | Total          | TBS positive N=11        | TBS negative N=56           | p-value | Total          | TBS positive N=34   | TBS negative N=138 | p-value |
| Total Number of Patients - n/N (%) | 239            | 67                       | 11/67 (16.4)                | 56/67 (83.6) | 172                | 34/172 (19.8)        | 138/172 (80.2)    | 0.704 |
| mRDT positive – n/N (%) | 13/239 (5.4)   | 5/67 (7.5)               | 3/11 (27.3)                 | 2/56 (3.6)  | 0.006               | 8/172 (4.7)          | 2/34 (5.9)        | 6/138 (4.3)  | 0.704 |
| mRDT negative – n/N (%) | 226/239 (94.6) | 62/67 (92.5)             | 8/11 (72.7)                 | 54/56 (96.4) | 0.006               | 164/172 (95.3)       | 32/34 (94.1)      | 132/138 (95.7) | 0.704 |

Overall, the most frequent discharge diagnoses of inpatients were malaria (31.3%; 222/710), respiratory infection/pneumonia (11.7%; 83/710) and salmonella gastroenteritis/typhoid (9.7%; 69/710). Within the diagnosis group infectious diseases, most common discharge diagnoses for adult inpatients were salmonella gastroenteritis/typhoid (34.2%; 40/117), malaria (20.5%; 24/117) and HIV (17.9%; 21/117). Particularly HIV was posed more frequently as discharge diagnosis than as suspected diagnosis (Fig. 5). For paediatric patients, the most frequent discharge diagnoses within the diagnosis group infectious diseases were malaria (65.3%; 198/303), respiratory infection/pneumonia (24.1%; 73/303) and salmonella gastroenteritis/typhoid (9.6%; 29/303). Within this group, particularly malaria was posed more frequently as discharge diagnosis than as suspected diagnosis (Fig. 6).

Altogether, malaria was diagnosed significantly more often compared to other diagnoses when mRDT or TBS showed positive test results (Table 5). However, 62 of 710 patients (8.6%) received a different discharge diagnosis than malaria even though positive mRDT or TBS
indicated infection with *P. falciparum*. Similarly, 91 of 710 patients (12.8%) received malaria as discharge diagnosis even though mRDT or TBS did not indicate infection with *P. falciparum*.

Table 5: Malaria as final diagnosis vs. malaria diagnostic test results

|                      | Total | Adult medical inpatients | Paediatric medical inpatients |
|----------------------|-------|--------------------------|-----------------------------|
|                      | Total | Diagnosis malaria N=24   | Other diagnosis N=294        | p-value   | Total | Diagnosis malaria N=198 | Other diagnosis N=194 | p-value |
| Total Number of Patients - n/N (%) | 710   | 318                      | 24/318 (7.5)               | 294/318 (92.5) | 392   | 198/392 (50.5)           | 194/392 (45.5)         | <0.001  |
| Patients with mRDT positive - n/N (%) | 208/710 (29.3) | 20/318 (6.3)             | 7/24 (29.2)                | 13/294 (4.4) | <0.001 | 188/392 (48.0)           | 152/198 (76.8)          | 36/194 (18.6) | <0.001 |
| Patients with mRDT negative - n/N (%) | 350/710 (49.3) | 148/318 (46.5)           | 16/24 (66.7)               | 132/294 (44.9) | <0.001 | 202/392 (51.5)           | 44/198 (22.2)           | 158/194 (81.4) | <0.001 |
| Patients with TBS positive - n/N (%) | 48/710 (6.8) | 14/318 (4.4)             | 6/24 (25.0)                | 8/294 (2.7)   | <0.001 | 34/392 (8.7)             | 29/198 (14.6)           | 5/194 (2.6)  | <0.001 |
| Patients with TBS negative - n/N (%) | 224/710 (31.5) | 85/318 (26.7)            | 8/24 (33.3)                | 77/294 (26.2) | <0.001 | 139/392 (35.5)           | 7/198 (3.5)            | 132/194 (68.0) | <0.001 |

**Inpatient expenses**

We calculated average inpatient healthcare expenses for all adult and paediatric inpatients based on laboratory expenses, expenses for medications and hospitalization costs (Table 6). Average laboratory expenses per adult inpatient were 51,700 Guinean Francs (GNF; 9000 GNF = approximately 1 USD), for medications GNF 35,900 and hospitalization costs GNF 85,000, amounting to average healthcare expenses per adult inpatient of GNF 49,570 or around 207 purchasing power parity (PPP) for actual health (2400 GNF = approximately 1 PPP actual health expenditure). Average laboratory expenses per paediatric inpatient were GNF 19,700, for medications GNF 229,000 and hospitalization costs GNF 80,000, amounting to average healthcare expenses per inpatient of GNF 328,700 or roughly 137 PPP for actual health.

Table 6: Inpatient healthcare expenses

|                      | Medical inpatients | adult Medical inpatients | paediatric Medical inpatients |
|----------------------|--------------------|--------------------------|-------------------------------|
| **Medications**      |                    |                          |                               |
| Average price per medication (excluding 10 most expensive drugs) | 51,700 GNF | 51,700 GNF |
| Total medications taken by patients | 2210 | 1735 |
| Total number of patients | 318 | 392 |
| Average medications per patient | 7 | 4 |
| Total cost for medications - in GNF | 114,257,000 GNF | 89,699,500 GNF |
| Average cost for medications per patient - in GNF | 359,000 GNF | 229,000 GNF |

| **Other**            |                    |                          |                               |
| Emergency room fee - in GNF | 15,000 GNF | 10,000 GNF |
| Hospitalization fee - in GNF | 70,000 GNF | 70,000 GNF |

| **Totals**           |                    |                          |                               |
| Laboratory costs per patient - in GNF | 51,700 GNF | 19,700 GNF |
| Medication costs per patient - in GNF | 359,000 GNF | 229,000 GNF |
| Hospitalization costs per patient - in GNF | 85,000 GNF | 80,000 GNF |
| Total costs per patient - in GNF | 495,700 GNF | 328,700 GNF |
| Total costs per patient - in PPP | 207 | 143 |
| Average GNI per capita in Guinea (2018) - in USD | $850 | $850 |
| Total inpatient cost per patient - in % of GNI | 6.5% | 4.4% |
| Average per capita spending on healthcare in Guinea (2017) - in USD | $34 | $34 |
| Average per capita spending on healthcare in Guinea (2017) - in % of GNI | 4.1% | 4.1% |
Discussion

With this study we hope to provide more insight into the local epidemiology of febrile illness in south-eastern Guinea, a region at high risk for outbreaks of diseases with epidemic potential such as Ebola virus disease. We described the clinical and diagnostic characteristics, treatments and outcomes of patients with febrile illness and compared them to non-febrile patients. Based on our findings, we can point to some management needs regarding diagnostic practices and treatments of febrile illness, side-lined by an estimation of the economic burden for patients seeking healthcare.

Febrile illness is a frequent reason for patients seeking healthcare in south-eastern Guinea. During our study period, 9.5% of all patients had a measured axillary body temperature ≥ 38°C upon hospital admission. During our study period, the typical febrile patient was admitted through the emergency room, mostly the medical service. His/her most common reported accompanying symptoms were asthenia, loss of appetite, headache, cough and abdominal pain. Together with fever, these symptoms guided clinicians towards suspecting the most common diseases in the region: malaria, diarrheal diseases/gastroenteritis and respiratory infection [34].

Malaria

Since malaria (P. falciparum) is endemic in south-eastern Guinea, it is evidently assumed to be the most common cause for febrile illness [35]. Ruling out malaria in febrile patients is a primary task for emergency medicine in the region [6, 10]. While mRDT are commonly used for this task, our study shows that mRDT test results do not necessarily correspond to malaria as suspected or discharge diagnoses. Furthermore, a large proportion of mRDT test results do not correspond to TBS results. In our study, 12.8% of all patients received malaria as discharge diagnosis despite negative diagnostic test results. Thus, point-of-care and laboratory diagnostic procedures seem to be only partly relevant when diagnosing malaria in south-eastern Guinea. Studies have indicated that mRDT and TBS in field settings miss roughly between 10–20% of malaria infections [36, 37]. This means that clinical experience is, at times, an important factor when diagnosing malaria. However, it has been pointed out that the practice of misdiagnosing malaria – due to malaria being the most ready-at-hand diagnosis for febrile illness – plays an equally important role in low-resource African healthcare settings and leads to an over-consumption of resources as well as more antimalarial drug resistance development [38, 39]. Since our study is only descriptive in regard to local diagnostic practices of febrile illness, we cannot ascertain true or false positive malaria cases. We can only emphasize that in malaria endemic regions at high risk for outbreaks of less common but highly infectious diseases with epidemic potential, investigation into the causes for febrile illness should at times go beyond the most probable entity, here malaria. This is in agreement with the Guinean national guidelines regarding malaria: when mRDT or TBS rule out malaria as the cause for febrile illness, other causes should be considered and investigated [40]. Furthermore, the assumed index case of the 2021 Ebola outbreak in south-eastern Guinea went unrecognized and was reportedly only treated against malaria by a number of different clinics as mRDT indicated infection with P. falciparum. Already the 2014–2016 West African Ebola virus epidemic has produced studies highlighting the relevance of malaria-sensitive screening tools for non-malarial illness such as Ebola virus disease and cases with coinfection [41, 42].

Salmonella gastroenteritis

Besides malaria, salmonella gastroenteritis/typhoid as diarrheal disease is another common diagnosis in south-eastern Guinea in patients with febrile illness, especially in adults. Widal TO/TH agglutination test is widely used and plays a major role in ascertaining this diagnosis. While this low-cost point-of-care test may be indicative of enteric fever in certain clinical situations and may be used according to Guinean national guidelines, its use is often discouraged due to its low specificity [43, 44]. In our study, 18.2% of all inpatients had a positive Widal TO/TH test result and a considerable proportion of patients was treated with antimicrobial drugs commonly used for gastroenteritis, namely ampicillin, metronidazole and ceftriaxone. A false diagnosis of enteric fever through Widal TO/TH agglutination test may result in the unnecessary use of antimicrobial drugs and provoke the development of drug-resistant bacteria [45, 46]. Moreover, it may lead to the non-consideration of diseases with epidemic potential as the cause for febrile illness [47]. Further strengthening of diagnostic capacities, particularly the possibility to perform blood cultures and antibiograms would undoubtedly improve identification and treatment of febrile illnesses caused by common gastrointestinal and systemic diseases.

Respiratory infection/pneumonia

The third most important infectious disease entity frequently assumed in febrile patients is respiratory infection/pneumonia, especially in children. Due to the high fees and therefore low use of radiological imaging (x-ray), calculated antimicrobial treatment is the default option for suspected respiratory infection/pneumonia. Other diagnostic tests for respiratory infections such as sputum cultures are only used sporadically. Our study shows that a large majority of patients (58.1%) is treated with ampicillin and only rarely with amoxicillin. National guidelines recommend the use of amoxicillin for the treatment of respiratory infections. One reason for the observed preference of ampicillin over amoxicillin might be the fact that it can be administered intravenously, which is the case for its use at the HRNZ, as it is the case for the use of paracetamol at the HRNZ as well. Social scientific research on vaccination in Guinea has shown that Guineans favour intravenous application of therapeutic agents because local understandings of medical therapies attribute a higher power and efficacy to injections over orally...
administered medications [48]. However, excessive use of these antimicrobial agents against respiratory infections may lead to drug resistance [49, 50]. In addition, unnecessary parenteral application of antibiotics and other medications bears higher risks of complications such as venous catheter infections. We believe that Guinean healthcare structures could highly benefit from antimicrobial stewardship programs specifically designed for low-resource settings [51].

**Inpatient mortality and healthcare expenses**

During our study period, overall mortality of adult and paediatric medical inpatients was fairly high (18.0%) and even higher for febrile patients in comparison to non-febrile patients. Inpatient mortality in West African hospitals are roughly between 5–25% even though comparison of mortality rates is difficult due to different reporting practices and varying mortality rates in different services [52–55]. Nevertheless, our reported inpatient mortality rate is considerable and speaks to a wide array of interconnected issues such as patient morbidity, underlying factors regarding health-seeking behaviour and the quality of healthcare in some West African countries [56]. One particular reason for the delayed treatment of patients – a factor causing increased mortality for certain diseases – is economic constraint coupled with high out-of-pocket user fees in proportion to income [57–59]. We calculated that an adult inpatient spends roughly around 6.5% (in children 4.4%) of the per capita gross national income in Guinea as in 2018 [60]. This measures up to an enormous economic burden on inpatients and their families. Structural improvements in healthcare such as enhanced diagnostic capacities and advances in treatments for certain diseases as currently envisaged in post-Ebola Guinea must go hand in hand with propositions for better access [61].

**Limitations of the study**

The first limitation of our study is the fact that we only collected patient data at one particular hospital. This reduces generalizability of our findings. However, the epidemiology, the socio-economic conditions and healthcare provision in the little-accessible border region of south-eastern Guinea, Sierra Leone and Liberia are fairly similar and we thus believe that our findings are very important for this high-risk zone for outbreaks of diseases with epidemic potential [62].

Second, a study period of three months is relatively short. Our data does not capture seasonal disease patterns potentially causing a changing epidemiology of febrile illness. Data was collected during the dry season where transmission of malaria is usually lower than in the wet season, meaning that the average annual proportion of diagnosed malaria and positive malaria tests may actually be higher than reported in our study [63].

Third, our study was not designed to verify the aetiology of febrile illness in patients. Its aim was simply to describe the local epidemiology of febrile illness as it is produced in a low-resource setting.

Despite its disadvantages, we believe that the advantage of this approach is that it increases understanding of local clinical practices and highlights potential sites for improvement.

Fourth, our calculation regarding average inpatient expenses rely on a rough estimation on fees for medicines. We were only able to review the amount of medications each inpatient used but not the specific medications themselves. We adjusted average prices for medicines by eliminating the ten most expensive medications from our calculations to reduce skewing and hence risk of over-reporting medication fees. Nevertheless, our calculations remain rough estimates and should only be understood as a means to underscore the high economic burden of inpatient care.

**Conclusions**

Our study highlights the importance of malaria, salmonella gastroenteritis/typhoid and respiratory infection in patients with febrile illness in south-eastern Guinea. These diseases are mainly diagnosed on clinical grounds and rapid point-of-care diagnostic tests. Common serological and other diagnostic measures to ascertain aetiology of febrile illness are rarely used or only partially regarded. This practice risks to miss signal cases of highly infectious diseases such as Ebola virus disease. Diagnostic capacities in regions at risk for diseases with epidemic potential, such as south-eastern Guinea, should thus be enhanced. Furthermore, antimicrobial medications play a major role in treating febrile illness, increasing the possibility for drug resistance. Guinean hospitals would benefit from antimicrobial stewardship. Patients with febrile illness have a high inpatient mortality rate and the economic burden of inpatient care on patients and families is considerable. This underscores the importance of linking structural improvements in healthcare provision to increased access to healthcare.

**Abbreviations**

GNF: Guinean francs

HIV: Human immunodeficiency virus
Declarations

Ethics approval and consent to participate

Ethical approval for this study was granted by the Guinean Ethics Committee for Research in Health (opinion number 103/CNERS/18) and the Ethics Committee for Medical Research at the Ludwig-Maximilians-Universität (LMU), Munich (opinion number 18-834). Before its implementation, the study was presented to the regional health authorities and the HRNZ directorate who both consented to its implementation. As part of the hospital's routine aggregate data collection, no informed consent was asked from patients upon admission for the cross-sectional and retrospective data collection.

Consent for publication

Not applicable

Availability of data and material

Due to Guinean national regulations, patient-based datasets cannot be made freely accessible. Dataset can be provided, however, upon well-reasoned request and upon clearance by the involved Guinean authorities. Requests should be addressed to the corresponding author.

Competing interests

The authors declare to have no competing interests.

Funding

MR was supported financially through MeCuM International Scholarship by the Medical Department of the Ludwig-Maximilians-Universität (LMU), Munich. The scholarship covered travel and living expenses during the research period. The funding body played no role in study design, data collection, analysis, interpretation of findings or writing.

Authors' contributions

MR, LP, DD and GF were responsible for conceiving the study. MR and DD executed the data collection. MR and GF analysed the data. MR wrote the article. All authors read and reviewed the final submitted version of this manuscript.

Acknowledgements

The authors would like to thank the regional health authorities of N’Zérékoré and the HRNZ for their collaboration. We further wish to acknowledge all patients whose data was used for this study.

References

1. Prasad N, Murdoch DR, Reyburn H, Crump JA. Etiology of Severe Febrile Illness in Low- and Middle-Income Countries: A Systematic Review. PLOS ONE. 2015;10:e0127962.
2. Prasad N, Sharples KJ, Murdoch DR, Crump JA. Community prevalence of fever and relationship with malaria among infants and children in low-resource areas. Am J Trop Med Hyg. 2015;93:178–80.
3. Crump JA, Newton PN, Baird SJ, Lubell Y. Febrile Illness in Adolescents and Adults. In: Holmes KK, Bertozzi S, Bloom BR, Jha P, editors. Major Infectious Diseases. 3rd edition. Washington (DC): The International Bank for Reconstruction and Development / The World Bank; 2017. http://www.ncbi.nlm.nih.gov/books/NBK525177/. Accessed 21 Nov 2020.

4. Crump JA, Gove S, Parry CM. Management of adolescents and adults with febrile illness in resource limited areas. BMJ. 2011;343. doi:10.1136/bmj.d4847.

5. Maze MJ, Bassat Q, Feasey NA, Mandomando I, Musicha P, Crump JA. The epidemiology of febrile illness in sub-Saharan Africa: implications for diagnosis and management. Clin Microbiol Infect. 2018;24:808–14.

6. Guidelines for the treatment of malaria - Third edition. https://www.who.int/publications-detail-redirect/9789241549127. Accessed 31 Dec 2020.

7. Stoler J, Awandare GA. Febrile illness diagnostics and the malaria-industrial complex: a socio-environmental perspective. BMC Infect Dis. 2016;16:683.

8. Crump JA, Morrissey AB, Nicholson WL, Massung RF, Stoddard RA, Galloway RL, et al. Etiology of Severe Non-malaria Febrile Illness in Northern Tanzania: A Prospective Cohort Study. PLOS Negl Trop Dis. 2013;7:e2324.

9. Petti CA, Polage CR, Quinn TC, Ronald AR, Sande MA. Laboratory medicine in Africa: a barrier to effective health care. Clin Infect Dis. 2006;42:377–82.

10. WHO | IMAI district clinician manual: Hospital care for adolescents and adults. WHO. https://www.who.int/hiv/pub/imai/imai2011/en/. Accessed 31 Dec 2020.

11. Fichet-Calvet E, Rogers DJ. Risk Maps of Lassa Fever in West Africa. PLOS Negl Trop Dis. 2009;3:e388.

12. Rasmussen KM, Baas B, Veugelman MA, van der Ende J, van Boven AJ, de Groot R, et al. Simultaneous transmission of dengue fever and dengue haemorrhagic fever in reverse epidemics: a population-based study. Lancet. 2017;390:781–88.
30. N Zerekore - Guinea - Area Database - Global Data Lab. https://globaldatalab.org/profiles/region/GINr108/. Accessed 22 Nov 2020.

31. Baize S, Pannetier D, Oestereich L, Rieger T, Koivogui L, Magassouba N, et al. Emergence of Zaire Ebola Virus Disease in Guinea. N Engl J Med. 2014;371:1418–25.

32. Guinea: Information bulletin: Ebola Virus Disease Outbreak - Guinea. ReliefWeb. https://reliefweb.int/report/guinea/guinea-information-bulletin-ebola-virus-disease-outbreak. Accessed 21 Feb 2021.

33. Raab M, Pfadenhauer LM, Nguyen V-K, Doumouna D, Hoelscher M, Froeschl G. Period prevalence and identification challenges of viral haemorrhagic fever suspect cases in a tertiary referral hospital in Guinea: a cross-sectional, retrospective study of triage and emergency room patient profiles. BMC Infect Dis. 2020;20:838.

34. Mamady K, Hu G. A step forward for understanding the morbidity burden in Guinea: a national descriptive study. BMC Public Health. 2011;11:436.

35. World malaria report 2019. https://www.who.int/publications-detail-redirect/9789241565721. Accessed 23 Nov 2020.

36. Berzosa P, de Lucio A, Romay-Barja M, Herrador Z, González V, García L, et al. Comparison of three diagnostic methods (microscopy, RDT, and PCR) for the detection of malaria parasites in representative samples from Equatorial Guinea. Malar J. 2018;17. doi:10.1186/s12936-018-2481-4.

37. Mfuho KO, Achonduh-Atijegbe OA, Bekindaka ON, Esemu LF, Mbakop CD, Gandhi K, et al. A comparison of thick-film microscopy, rapid diagnostic test, and polymerase chain reaction for accurate diagnosis of Plasmodium falciparum malaria. Malar J. 2019;18:73.

38. Bisoffi Z, Buonfrate D. When fever is not malaria. Lancet Glob Health. 2013;1:e11–2.

39. Chandler CI, Jones C, Boniface G, Juma K, Reyburn H, Whitty CJ. Guidelines and mindlines: why do clinical staff over-diagnose malaria in Tanzania? A qualitative study. Malar J. 2008;7:53.

40. Ministry of Health, Guinea. Guide thérapeutique national. World Health Organization; 2013.

41. de Wit E, Falzarano D, Onyango C, Rosenke K, Marzi A, Ochieng M, et al. The Merits of Malaria Diagnostics during an Ebola Virus Disease Outbreak. Emerg Infect Dis. 2016;22:323–6.

42. Hartley MA, Young A, Tran A-M, Okoni-Williams HH, Suma M, Mancuso B, et al. Predicting Ebola infection: A malaria-sensitive triage score for Ebola virus disease. PLoS Negl Trop Dis. 2017;11. doi:10.1371/journal.pntd.0005356.

43. Mawazo A, Bwire GM, Matee MIN. Performance of Widal test and stool culture in the diagnosis of typhoid fever among suspected patients in Dar es Salaam, Tanzania. BMC Res Notes. 2019;12:316.

44. WHO | Sensitivity and specificity of typhoid fever rapid antibody tests for laboratory diagnosis at two sub-Saharan African sites. WHO. https://www.who.int/bulletin/volumes/91/12/15-11087627/en/. Accessed 30 Jan 2021.

45. Ohuru ME, Iroezindu MO, Maduakor U, Onodugo OD, Gugnani HC. Typhoid fever among febrile Nigerian patients: Prevalence, diagnostic performance of the Widal test and antibiotic multi-drug resistance. Malawi Med J. 2019;31:184–92.

46. Wasihun AG, Wlekidan LN, Gebremariam SA, Welderufael AL, Muthupandian S, Haile TD, et al. Diagnosis and Treatment of Typhoid Fever and Associated Prevailing Drug Resistance in Northern Ethiopia. Int J Infect Dis. 2015;35:96–102.

47. Raab M, Pfadenhauer LM, Millimouno TJ, Hoelscher M, Froeschl G. Knowledge, attitudes and practices towards viral haemorrhagic fevers amongst healthcare workers in urban and rural public healthcare facilities in the N’zérékoré prefecture, Guinea: a cross-sectional study. BMC Public Health. 2020;20:296.

48. Leach MA, Fairhead JR, Millimouno D, Diallo AA. New therapeutic landscapes in Africa: Parental categories and practices in seeking infant health in the Republic of Guinea. Soc Sci Med. 2008;66:2157–67.

49. Bernabé KJ, Langendorf C, Ford N, Ronat J-B, Murphy RA. Antimicrobial resistance in West Africa: a systematic review and meta-analysis. Int J Antimicrob Agents. 2019;54:330–6.

50. Tadesse BT, Ashley EA, Ongherello S, Havumaki J, Wijgoonewardena M, González IJ, et al. Antimicrobial resistance in Africa: a systematic review. BMC Infect Dis. 2017;17:616.

51. Pierce J, Apisarnthanarak A, Schellack N, Cornistein W, Maani AA, Adnan S, et al. Global Antimicrobial Stewardship with a Focus on Low- and Middle-Income Countries: A position statement for the international society for infectious diseases. Int J Infect Dis. 2020;96:621–9.

52. Abdulghanih-Iyoha BI, Okolo AA. Morbidity and mortality of childhood illnesses at the emergency paediatric unit of the University of Benin Teaching Hospital, Benin City. Niger J Paediatr. 2012;39:71-74.

53. Keita M, Koulilaly M, Soumah MM, Diané B, Tounkara TM, Camara AD, et al. Morbidité et mortalité hospitalières dans le service de dermatologie-MST du CHU de Conakry(Guinée). Ann Dermatol Vénér. 2014;141:S356–7.

54. Okoroiwu HU, Uchendu KI, Essien RA. Causes of morbidity and mortality among patients admitted in a tertiary hospital in southern Nigeria: A 6 year evaluation. PLOS ONE. 2020;15:e0237313.
Figures

Figure 1

Proportions of non-febrile and febrile patients by age group

55. Mortality Pattern at the Adult Medical Wards of a Teaching Hospital in Sub-Saharan Africa. https://medwelljournals.com/abstract/?doi=ijtmed.2009.27.31. Accessed 1 Jan 2021.

56. Sardan J-PO de. Une médecine inhospitalière: Les Difficiles Relations entre soignants et soignés dans cinq capitales d’Afrique de l’Ouest. Paris: Karthala; 2003.

57. Mhalu G, Weiss MG, Hella J, Mhimbira F, Mahongo E, Schindler C, et al. Explaining patient delay in healthcare seeking and loss to diagnostic follow-up among patients with presumptive tuberculosis in Tanzania: a mixed-methods study. BMC Health Serv Res. 2019;19:217.

58. Kansiime C, Kiwuwa SM, Levi M, Asiimwe BB, Katamba A. Health service delay among pulmonary tuberculosis patients presenting to a National Referral Hospital, Kampala, Uganda: a cross sectional study. Pan Afr Med J. 2013;15:84.

59. Gilson L, McIntyre D. Removing user fees for primary care in Africa: the need for careful action. BMJ. 2005;331:762–5.

60. GNI per capita, Atlas method (current US$) - Guinea | Data. https://data.worldbank.org/indicator/NY.GNP.PCAP.CD?locations=GN
Accessed 1 Jan 2021.

61. Kim JY, Farmer P, Porter ME. Redefining global health-care delivery. Lancet. 2013;382:1060–9.

62. Boozary AS, Farmer PE, Jha AK. The Ebola Outbreak, Fragile Health Systems, and Quality as a Cure. JAMA. 2014;312:1859–60.

63. Magombedze G, Ferguson NM, Ghani AC. A trade-off between dry season survival longevity and wet season high net reproduction can explain the persistence of Anopheles mosquitoes. Parasites Vectors. 2018;11:576.
Figure 2
Suspected diagnosis group in medical adult emergency patients

- Infectious diseases
- Non-infectious diseases of digestive system
- Non-infectious diseases of cardiovascular system
- Other non-infectious diseases: respiratory, urinary, neurological, blood system
- Diabetes

- Infectious disease
- Non-infectious disease blood system
- Other: non-infectious disease respiratory system, non-infectious disease neurological system
- Non-infectious disease gastrointestinal system
Figure 3
Suspected diagnosis group in medical paediatric emergency patients

Figure 4
Study flow chart

Figure 5
Proportions of diagnosed infectious diseases in medical adult patients
Figure 6

Proportions of diagnosed infectious diseases in medical paediatric patients