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Original article

Aetiology of acute febrile illness in children in a high malaria transmission area in West Africa

B. Kaboré [1, 5, †], A. Post [1, †], P. Lompo [5], J.D. Bognini [5], S. Diallo [5], B.T.D. Kam [5], J. Rahamat-Langendoen [2, 3], H.F.L. Wertheim [2, 3], F. van Opzeeland [4], J.D. Langereis [3, 4], M.I. de Jonge [3, 4], H. Tinto [5, 6], J. Jacobs [7, 8], A.J. van der Ven [1, 3, §], Q. de Mast [1, 3, *, §]

[1] *Department of Internal Medicine, Radboud University Medical Center, Nijmegen, the Netherlands*
[2] *Department of Medical Microbiology, Radboud University Medical Center, Nijmegen, the Netherlands*
[3] *Radboudumc Center for Infectious Diseases (RCI), the Netherlands*
[4] *Section of Paediatric Infectious Diseases, Laboratory of Medical Immunology, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands*
[5] *IRSS/Clinical Research Unit of Nanoro (CRUN), Nanoro, Burkina Faso*
[6] *Centre Muraz, Bobo-Dioulasso, Burkina Faso*
[7] *Department of Clinical Sciences, Institute of Tropical Medicine (ITM), Antwerp, Belgium*
[8] *Department of Microbiology, Immunology and Transplantation, University of Leuven (KU Leuven), Leuven, Belgium*

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ABSTRACT

Objectives: Areas with declining malaria transmission in sub-Saharan Africa have recently witnessed important changes in the aetiology of childhood acute febrile illness (AFI). We describe the aetiology of AFI in a high malaria transmission area in rural Burkina Faso.

Methods: In a prospective hospital-based diagnostic study, children aged 3 months to 15 years with AFI were recruited and assessed using a systematic diagnostic protocol, including blood cultures, whole blood PCR on a selection of bacterial pathogens, malaria diagnostics and a multiplex PCR on nasopharyngeal swabs targeting 21 viral and 4 bacterial respiratory pathogens.

Results: A total of 589 children with AFI were enrolled from whom an infectious disease was considered in 575 cases. Acute respiratory tract infections, malaria and invasive bacterial infections (IBI) accounted for 179 (31.1%), 175 (30.4%) and 75 (13%) of AFI cases respectively; 16 (21.3%) of IBI cases also had malarial parasitaemia. A viral pathogen was demonstrated from the nasopharynx in 157 children (90.7%) with respiratory tract symptoms. Of all children with viral respiratory tract infections, 154 (92.4% received antibiotics, whereas no antibiotic was provided in 13 (17%) of IBI cases.

Conclusions: Viral respiratory infections are a common cause of childhood AFI in high malaria transmission areas, next to malaria and IBI. These findings highlight the importance of interventions to improve targeted treatment with antimicrobials. Most patients with viral infections received antibiotics unnecessarily, while a considerable number with IBI did not receive antibiotics. **B. Kaboré, Clin Microbiol Infect 2020;▪:1**

Introduction

Acute febrile illnesses (AFI) in children remain a major public health problem in sub-Saharan Africa (SSA). The past decade has seen major changes in infectious diseases patterns in many areas in SSA because of efforts in malaria control strategies as well as the introduction of new vaccines [1–3].

The management of children with AFI in SSA is complicated by the fact that history and physical examination are often not specific

* Corresponding author: Q. de Mast, Department of Internal Medicine, Radboudumc Centre for Infectious Diseases, Radboud University Medical Centre, Nijmegen, the Netherlands.
E-mail address: Quirijn.demast@radboudumc.nl (Q. de Mast).
† The first two authors contributed equally to this article and both should be considered first author.
§ The last two authors contributed equally to this article and both should be considered senior author.

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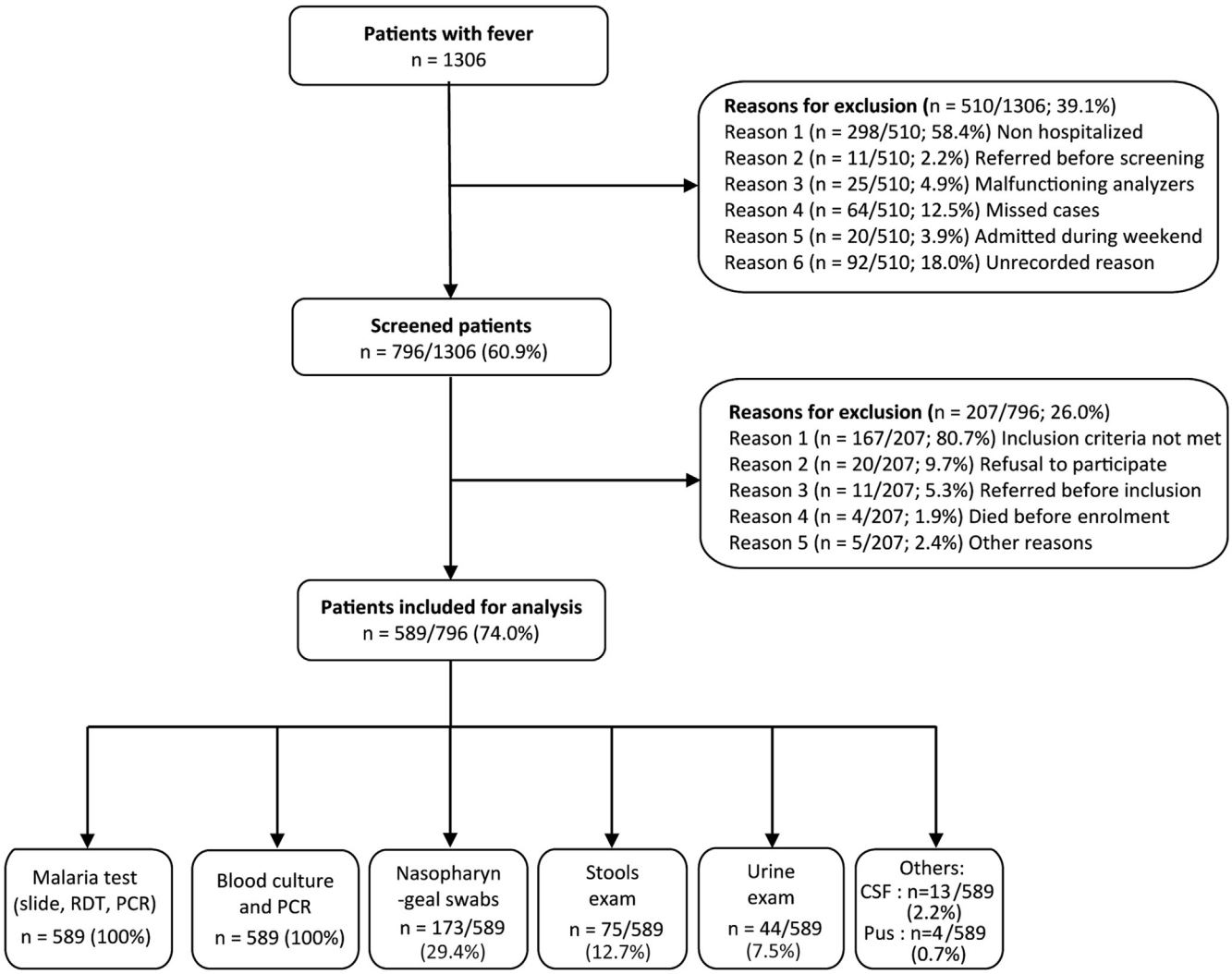

Fig. 1. Flow diagramme of study participant enrollment and laboratory analyses performed. CSF, cerebrospinal fluid; RDT, malaria rapid diagnostic test.

enough to determine the aetiology of infection. In addition, with the exception of malaria diagnostic tests, diagnostic tools are frequently not or only very limitedly available. AFI is therefore commonly treated empirically with antimalarials and/or antibiotics [4–6]. This practice has important disadvantages in view of the rapidly increasing burden of antimicrobial resistance. It is therefore important to gain insight into the epidemiology of nonmalarial febrile illness in SSA.

Recent studies from Eastern Africa have highlighted the importance of viral respiratory tract infections as causes of febrile illness in children [7,8]. Whether these data can be extrapolated to other areas in SSA is unclear. In Burkina Faso, a country in the semiarid Sahel and Savanna zones of West Africa, malaria transmission remains high, with marked seasonality in the rainy season [9–11]. Influenza virus has been reported to circulate in Burkina Faso [12,13], but its importance and that of other viral respiratory infections in the aetiology of nonmalaria fever remains unknown.

Given the importance of surveillance of causes of AFI for clinical management and design of diagnostic tools and public health strategies in high malaria transmission areas in West Africa, we investigated the aetiologies of AFI in children presenting to a referral hospital in rural Burkina Faso.

Materials and methods

Study area

The study was conducted at the district hospital, Centre Medical avec Antenne chirurgicale (CMA), Saint Camille de Nanoro, located in a rural area hyperendemic for *Plasmodium falciparum* malaria in Burkina Faso [15]. Seasonal malaria chemoprophylaxis against malaria in children younger than 5 was introduced in 2016. The national immunization programme includes vaccinations against diphtheria, tetanus, whooping cough, polio, measles and yellow fever. Vaccines against *Haemophilus influenzae* type b (Hib) and hepatitis B were introduced in 2006; against rotavirus (RV5, Rota-Teq) and *Streptococcus pneumoniae* (13-valent pneumococcal conjugate vaccine; PCV 13) in 2013; against rubella in 2015; and against *Neisseria meningitidis* group A (MenAficVac) in 2017.

Study design, population, procedures and diagnostic classification

Data used in this study were derived from a prospective hospital-based diagnostic accuracy study (PaluBac study) aiming to evaluate the accuracy of novel haematology analysers for the diagnosis of malaria and bacterial blood stream infection in adults

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Table 1
Patient demographics and clinical characteristics

Characteristic	Value
Sex	
Female	239 (40.6)
Age group	
<2 years	275 (46.7)
2–5 years	186 (31.6)
5–10 years	90 (15.3)
10–15 years	38 (6.4)
Nutritional status, median (IQR)[a]	
<5 years (WAZ)	−1.3 (−2.5 to 0.5)
5–15 years (BAZ)	−1.6 (−2.9 to 0.7)
Underweight[b]	
<5 years	319/451 (70.7%)
5–15 years	58/88 (65.9%)
Auricular temperature at enrollment	
<38°C	153 (26.0)
38 to <39°C	365 (62.1)
≥40°C	70 (11.9)
Duration of fever in days before admission, median (IQR)	2 (2–3)
No. of patients hospitalized	436 (74)
Duration of hospitalization in days, median (IQR)	4 (3–7)
Major symptoms at enrollment	
Runny nose	334 (56.7)
Cough	280 (47.5)
Headache	69 (11.7)
Vomiting	174 (29.5)
Diarrhoea	116 (19.7)
Abdominal pain	202 (34.3)
Dyspnea	77 (13.1)
Treatment before enrollment	
Antibiotics	109 (18.5)
Antimalarial	96 (16.3)
Antimalarial and antibiotic	140 (23.8)
Status at discharge	
Clinically recovered	501 (85.1)
Referred to other centres	54 (9.2)
Departed against medical advice	9 (1.5)
Deceased	25 (4.2)

Data are presented as *n* (%) unless otherwise indicated. BAZ, body mass index for age *z* score; IQR, interquartile range; WAZ, weight for age *z* score.
[a] Classification based on the World Health Organization (WHO) Child Growth Standards reference data.
[b] Underweight was defined as WAZ or BAZ below less than −1 standard deviation of WHO *z* score.

and children. Details and results of the PaluBac primary study objectives are reported elsewhere [16].

The primary objective of the current descriptive study was to describe the aetiology of AFI in enrolled children aged 3 months to 15 years. A secondary objective was to describe seasonal trends. There were no other prespecified objectives or group comparisons. From March until November 2016, only hospitalized children were enrolled. Thereafter, until the end of the study in June 2017, nonhospitalized children were also enrolled because of insufficient study recruitment. Comparison between hospitalized and nonhospitalized children was retrospectively included as an objective.

The inclusion and exclusion criteria, study procedures, diagnostic classification and laboratory procedures are described in detail in Supplementary Table S1. In summary, children were eligible when they had fever (temperature ≥38.0°C) or hypothermia (≤35.5°C), or a reported history of fever with signs of severe clinical illness or a suspicion of severe infection. Children with fever for more than 7 days were excluded. At enrollment, medical history was taken and clinical examination was carried out. In all children, venous blood was collected for haemocytometry, malaria tests (microscopy, rapid diagnostic test [RDT] and PCR), blood culture, and plasma and whole blood bacterial PCR. A nasopharyngeal swab sample was taken from all children. PCR analysis was performed retrospectively on stored swabs from children with respiratory tract symptoms and negative results for malaria blood smear, blood cultures and bacterial PCR on blood. Diagnostic classification was retrospectively and independently done by two medical doctors (BK and AP) and by an infectious disease specialist (QdM) using prespecified case definitions (Supplementary Table S2).

Ethical aspects

The study protocol was approved by the national ethics committee of Burkina Faso (no. 2015-01-006), the institutional review board of IRSS (no. A03-2016/CEIRES), the ethical committee of the University of Antwerp (no. 15/47/492) and the internal review board of the Institute of Tropical Medicine Antwerp, Belgium (no. 1029/15). Written informed consent was obtained from all participants or their parents/legal guardians with additional assent from those aged 7 to 15 years. The trial was registered at ClinicalTrials.gov (NCT02669823).

Results

Study population and aetiology of fever

In total, 796 febrile children were screened, of whom 589 were enrolled (Fig. 1). Demographic and clinical characteristics of the enrolled participants are shown in Table 1. More than 75% of enrolled children were younger than 5 years old. The median (interquartile range (IQR)) duration of fever was 2 (2–3) days. Fig. 2 shows the distribution of diagnosed infections. An infectious disease was considered unlikely in 14 children (2.4%). From the remaining children, malaria and acute respiratory infections (ARI) were the principal causes of fever in respectively 175 (30.4%) and 179 (31.1%) cases. Median parasite density in febrile malaria (94% *falciparum* malaria) was 24<thinsp>738/μL (IQR 2321–84<thinsp>723). An invasive bacterial infection (IBI) was diagnosed in 75 children (13%), of whom 16 (21.3%) also had malaria parasitaemia. The remaining participants were classified as follows: gastroenteritis ($n = 23$, 4%), coinfections other than malaria-IBI ($n = 12$; 2.1%), localized bacterial infection ($n = 9$; 1.6%), newly diagnosed HIV infection ($n = 2$; 0.3%), acute hepatitis B ($n = 2$; 0.3%) and pulmonary tuberculosis ($n = 1$; 0.2%). Nine each (1.6%) had a suspected bacterial infection or suspected bacterial–malarial coinfection, whereas the infection remained unclassified in 79 children (13.7%). The distribution of diagnoses before and after protocol amendment is shown in Supplementary Table S3. The most common illnesses by age group is shown in Table 2. ARI was predominant in children younger than 2 years old, followed by malaria, whereas malaria was more common in those aged 2 to less than 10 years. In older children, IBI was more common.

Respiratory tract infections

A total of 179 children were clinically classified as having a upper ($n = 57$) or lower ($n = 122$) ARI. PCR was performed on 173 nasopharyngeal swab samples, yielding at least one virus in 157 samples (91%) and a total of 206 viruses. In four children a bacterial pathogen was detected (two *Mycoplasma pneumoniae,* one *Chlamydia pneumoniae* and one *Bordetella pertussis*). The distribution of viruses is shown in Fig. 2. Overall, rhinovirus/enterovirus were the most commonly detected viruses, followed by adenovirus, influenza A and B, and respiratory syncytial virus (RSV) B ($n = 18$, 9.0%). Adenovirus and rhinovirus/enterovirus were frequently detected together with other viruses (in 51% and 29% respectively) (Supplementary Fig. S1). A clear seasonal trend was observed (Fig. 3). Whereas the prevalence of rhinovirus/enterovirus was relatively stable over the months, adenovirus was most common during the dry season from December until June.

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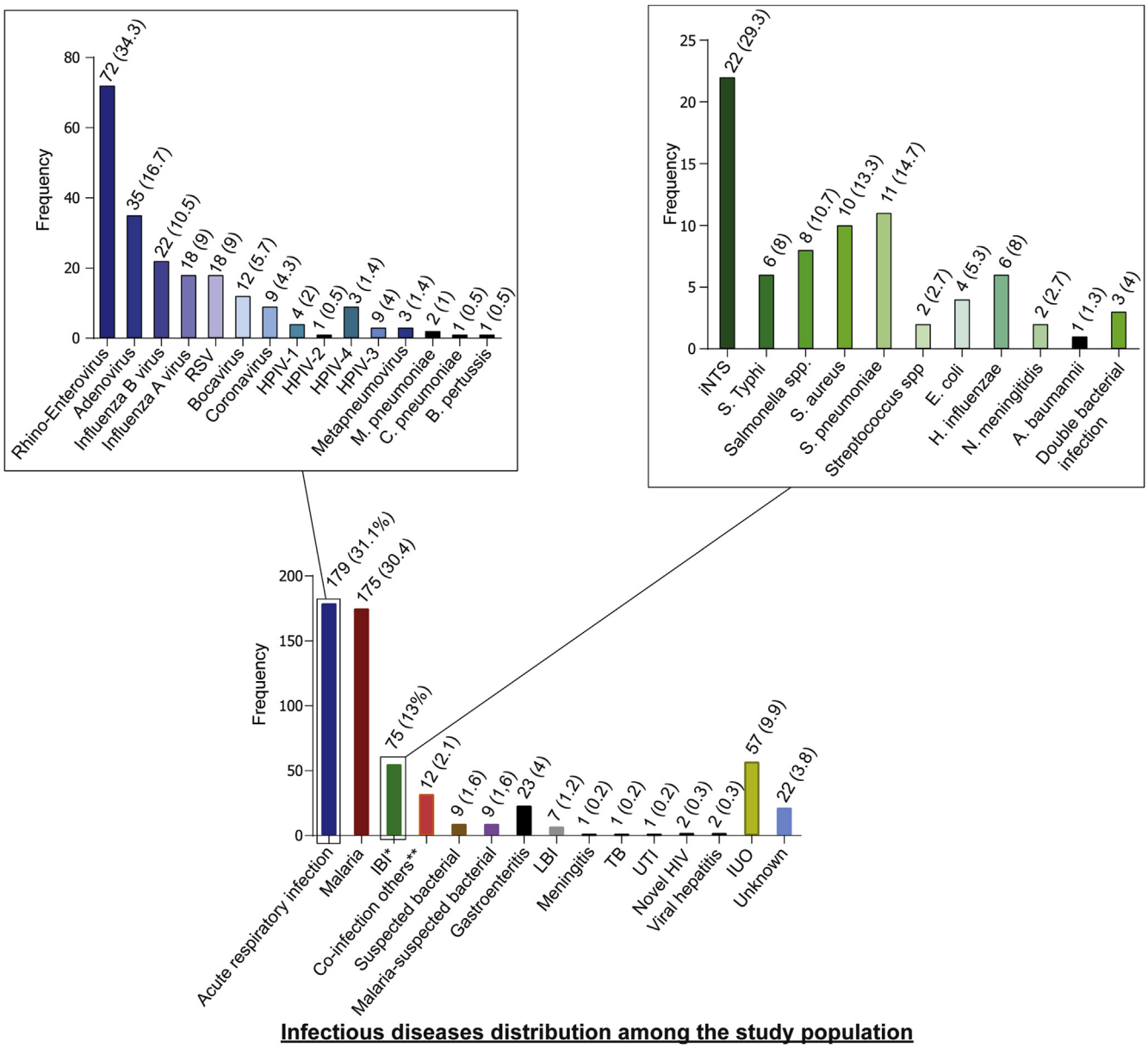

Fig. 2. Distribution of diagnoses and isolated pathogens among study population with acute febrile illnesses. *Including 16 cases of IBI-malaria coinfection. **'Coinfection others' represents malaria–viral ($n = 5$) or malaria-noninvasive bacterial ($n = 7$) coinfections. Data are presented as *n* (%); the percentage may not sum to 100 because of rounding. ARI, acute respiratory infection; HPIV, human parainfluenza virus; IBI, invasive bacterial infection; IUO, infection of unknown origin; LBI, localized bacterial infection; NTS, nontyphoidal *Salmonella;* RSV, respiratory syncytial virus; TB, pulmonary tuberculosis; UTI, urinary tract infection.

The peak of influenza B was observed from December until February and that of influenza A from March until May.

Invasive bacterial infections

Blood cultures grew a pathogen in 52 cases; plasma and whole blood PCR identified 23 additional pathogens (Supplementary Table S4). As summarized in Fig. 2 and Table 2, the most commonly isolated pathogens in blood cultures were non-Typhoid *Salmonella* (NTS), *Salmonella* Typhi, *Streptococcus pneumoniae* and *Staphylococcus aureus.* Whole blood PCR identified another eight cases of *Salmonella* spp. (further typing not possible). Three children had bacteraemia with two different pathogens. Most NTS were seen in children younger than 5 years (21 NTS vs. three *S.* Typhi), whereas *Salmonella* Typhi was more common in children older than 5 (one NTS vs. three *S.* Typhi) (Table 2). *S. pneumoniae* and *H. influenzae* were also more common in young children.

Coinfections

A coinfection was identified in 32 patients (5.6%). Details of coinfections of malaria, IBI and viral ARI are summarized in Supplementary Fig. S2 and Supplementary Table S5. *Salmonella* was most commonly found in coinfection with malaria. Seven cases of malaria-NTS coinfection were diagnosed, all in children younger than 5, and two malaria–*Salmonella* Typhi coinfections. The remainder were malaria with other invasive ($n = 7$) or noninvasive bacterial infections ($n = 7$), malaria with a viral ARI ($n = 4$), IBI with a viral ARI ($n = 3$), one child with a new HIV infection together with malaria and one child with IBI, malaria

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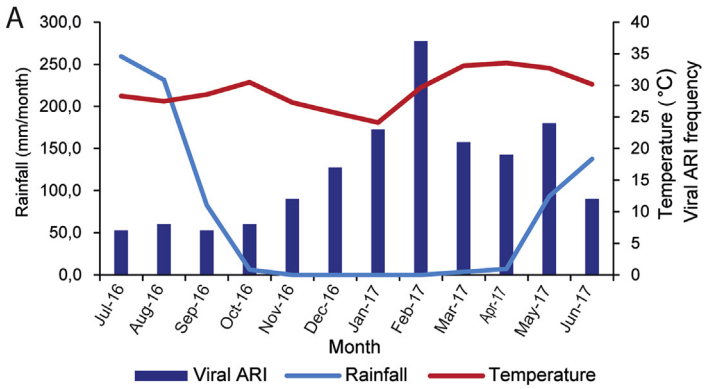
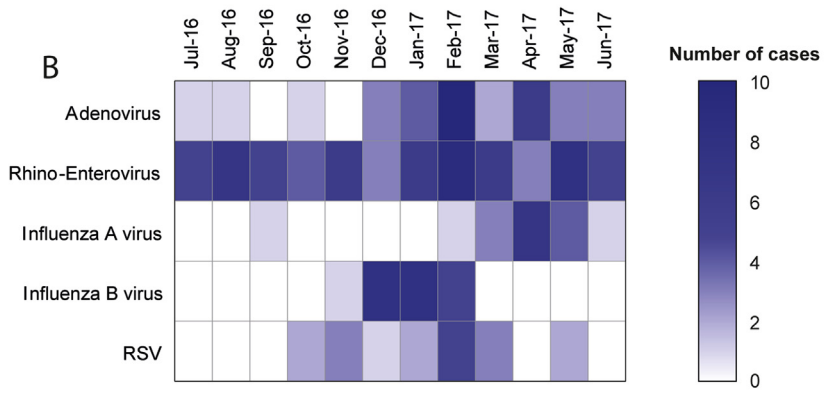
Table 2
Distribution of common diagnoses and isolated bacterial pathogens in bacteraemia cases per age group

Characteristic	Age group[a]			
	<2 years (n = 274)	2–5 years (n = 183)	5–10 years (n = 84)	10–15 years (n = 34)
Classification, n (%)				
ARI	111 (40.5)	50 (27.3)	15 (17.9)	3 (8.8)
Viral ARI	101 (36.9)	41 (22.4)	13 (15.5)	2 (5.9)
Malaria	78 (28.5)	69 (37.7)	26 (31.0)	2 (5.9)
IBI	22 (8.0)	15 (8.2)	10 (11.9)	8 (23.5)
IBI-malaria	6 (2.2)	7 (3.8)	2 (2.4)	1 (2.9)
IBI-viral ARI	2 (0.7)	1 (0.4)	0 (0.0)	1 (0.4)
Gastroenteritis	14 (5.1)	4 (2.2)	3 (3.6)	2 (5.9)
Other[b]	9 (3.3)	13 (7.1)	10 (11.9)	12 (35.3)
Unclassified/unknown	32 (11.7)	24 (13.1)	18 (21.4)	5 (14.7)
Bacterial pathogens, n				
Nontyphoidal *Salmonella*	13	8	0	1
Salmonella Typhi	0	3	3	0
Salmonella spp.[c]	2	1	5	0
Staphylococcus aureus	2	3	1	4
Streptococcus pneumoniae	4	3	0	4
Streptococcus spp.	1	0	1	0
Haemophilus influenzae	4	1	1	0
Escherichia coli	1	2	1	0
Neisseria meningitidis	1	1	0	0
Acinetobacter baumannii	0	1	0	0
Double infection[d]	2	0	0	1

Percentage may not sum to 100 because of rounding. ARI, acute respiratory infection.
[a] N represents the number per age group excluding cases for which infectious disease was considered unlikely.
[b] 'Other' refers to other diseases, as classified in Fig. 2.
[c] Detected by blood PCR and therefore not further typed.
[d] Double infection: *Shigella flexneri* and *Staphylococcus aureus; Escherichia coli* and *Streptococcus pneumoniae; H. influenzae* and *S. pneumoniae*.



Monthly distribution of viral acute respiratory infection and climate factors (rain and temperature)



Monthly distribution of main (Top 5) isolated viruses in acute respiratory infection cases

Fig. 3. (A) Monthly distribution of viral acute respiratory infections according to temperature (°C) and rainfall (mm/mo). (B) Monthly distribution of the five most frequently isolated viruses in acute respiratory infection cases. Data are restricted to 12 months (July 2016 to June 2017) to consider nonhospitalized patients and depict a year overview. Data on temperature and rainfall were collected from Zone d'Appui Technique in Nanoro.

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and HIV. Children with malaria-IBI coinfection had a lower malaria parasitaemia (median 3709/μL, IQR 101–81<thinsp>242) compared to monoinfected children (median 30<thinsp>099/μL, IQR 5161–90<thinsp>990; p 0.1).

Diagnosis according to admission status

Supplementary Figure S3 depicts the diseases distribution according to admission status. Most children with febrile malaria were hospitalized (140 of 175; 80%). Of all the children with IBI (including coinfections), 10 (13.3%) of 75 were not hospitalized. These patients had bacteraemia with *Salmonella* ($n = 6$), *S. aureus* ($n = 2$), *S. pneumoniae* ($n = 1$) and *H. influenzae* ($n = 1$). Among the children with ARI, 115 (64.2%) of 179 were hospitalized. A viral pathogen was detected in 102 (88.7%) of 115 hospitalized and in 55 (85.9%) of 64 nonhospitalized children.

Management and outcome

Thirteen patients (17.3%) with IBI did not receive antibiotics at admission; pathogens identified in these cases were *Salmonella* ($n = 6$), *S. aureus* ($n = 2$), *S. pneumoniae* ($n = 2$), *Escherichia coli* ($n = 1$), *Neisseria meningitidis* ($n = 1$) and *Acinetobacter baumannii* ($n = 1$). In contrast, 145 (92.4%) of 157 children classified as having a viral ARI received antibiotics. Among patients with negative malaria results, 111 (29%) still received antimalarials; 73 (65.8%) of those had a positive result of malaria RDT (HRP2- and/or pLDH-based RDT).

A total of 265 children (45%) reported at the week 2 control. All 25 children (4.2%) who died had been hospitalized. The proven or presumptive diagnosis in these children was malaria ($n = 11$), IBI ($n = 6$), malaria-IBI coinfection ($n = 2$), ARI ($n = 4$) and pulmonary tuberculosis ($n = 1$). In a single case, the cause was unknown. This included one child with *E. coli* IBI who had not received antibiotics at admission and one child with bacteraemia with an *E. coli*–producing extended-spectrum β-lactamase.

Discussion

On the basis of this study, we conclude that next to malaria and IBI, common childhood viral respiratory infections are a leading cause of AFI in an area with intense malaria transmission in Burkina Faso. Using a comprehensive clinical and laboratory approach, we were able to attribute the cause (confirmed or suspected) of fever in more than 90% of enrolled children. In children younger than 2, viral ARIs were the most common cause of fever. Recent studies from other SSA countries where malaria incidence has declined sharply have highlighted the importance of common childhood viral infections as a leading cause of febrile illness [7,8,17–19]. Our study confirms these findings in a different epidemiologic context in a different region in SSA. Of course, malaria accounted for a much higher proportion of fever cases in this high malaria transmission area compared to these earlier studies. This epidemiologic pattern may also change in the coming years in our study area as a consequence of ongoing efforts to curb the burden of malaria, including the introduction of seasonal malaria prophylaxis in children [20].

Both malaria and viral ARI had a clear seasonal pattern, with malaria being the most common in the rainy season (June to October); RSV and influenza respectively peaked during the dry and cold months from December to May, whereas rhinovirus/enteroviruses were common throughout the year. Data on influenza seasonality from SSA are limited; our data show that our study area follows the pattern from Northern and Saharan Africa, in contrast to African countries situated nearer to the equator, which experience year-round influenza activity [21].

More than 75% of children with respiratory tract symptoms in our study had at least one virus, a proportion that decreased with age. PCR on nasopharyngeal swabs was only performed in children with respiratory complaints; these children were classified as having a viral ARI when PCR results were positive together with a negative result of malarial and bacterial tests. We used a multiplex (ePlex) PCR system which has previously been shown to have good performance [22], although data on its performance in SSA are limited. Multiplex PCR systems on upper respiratory tract samples have the potential to reduce unnecessary antibiotic use, especially when viruses such as influenza or RSV are detected. However, their impact on antibiotic prescription practices remains debatable, and the high cost of this diagnostic platform currently limits its use in resource-limited countries. In addition, a major limitation was the difficulty in differentiating colonization from infection, which may have led to overestimation of the contribution of viruses in ARI. This is a general limitation of aetiologic studies for pneumonia using upper respiratory tract samples, including in SSA [23,24].

Thirteen per cent of children with AFI had an IBI, and coinfection with malaria was common. NTS and *Salmonella* Typhi were the most frequently isolated bacteria, similar to what was previously reported in other studies from the same study area [9,10]. The proportion of invasive pneumococcal infections in our study was lower than reported in 2010 in the same area, which is likely the result of the introduction of the conjugated pneumococcal vaccine in 2013 in Burkina Faso [10]. NTS infections were most common in children younger than 5 and were associated with malaria, as previously reported [25–27]. We also confirm the findings of Hogan et al. [28] that in children with malaria, the frequency of IBI increases with decreasing parasite densities. This finding should be considered in light of the widespread use of malaria RDTs, which do not provide parasite densities.

It is challenging to differentiate bacterial infections from malaria or viral infections on merely clinical grounds. Over 90% of children classified as having a viral ARI received antibiotics during their participation in the study. Empiric treatment with antimalarials was also common, despite the rapid availability of malaria test results. In contrast, 13.3% of children with IBI were not hospitalized, and nearly 18% did not receive antibiotics. This emphasizes the need for easy-to-use and accessible clinical algorithms, biomarkers and pathogens-specific diagnosis to identify those in need of hospitalization and antibacterial treatment.

Some limitations of our study need to be addressed. Firstly, as mentioned above, children frequently harbour respiratory tract viruses, and we cannot exclude misclassification of some children with a bacterial infection on the basis of a positive result in the multiplex PCR. The same holds true for malaria, as asymptomatic malarial parasitaemia is highly prevalent in our study area. Secondly, selection bias occurred because recruitment took place in a referral hospital, so only hospitalized children were initially eligible for enrollment. In addition, a high proportion of children had already received treatment with antibiotics and/or antimalarials before referral, which may have negatively affected the diagnostic performance of microbiologic tests. Thirdly, our diagnostic approach did neither include a standard chest X-ray, routine urine culture, or standard stool culture in those with diarrhoea.

In conclusion, common childhood viral ARIs and IBI are important causes of nonmalaria AFI in children in a high malaria transmission area in Burkina Faso. These findings highlight the importance of interventions aiming to improve targeting antimicrobials to those who need them.

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Transparency Declaration

Financial support was received from Sysmex Europe GmbH. The funding sources were involved in the study design but not in data collection, analysis and interpretation or in the preparation of the report. All authors report no conflicts of interest relevant to this article.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2020.05.029.

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