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# Beyond Malaria — Causes of Fever in Outpatient Tanzanian Children

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## ABSTRACT

### BACKGROUND

As the incidence of malaria diminishes, a better understanding of nonmalarial fever is important for effective management of illness in children. In this study, we explored the spectrum of causes of fever in African children.

### METHODS

We recruited children younger than 10 years of age with a temperature of 38°C or higher at two outpatient clinics — one rural and one urban — in Tanzania. Medical histories were obtained and clinical examinations conducted by means of systematic procedures. Blood and nasopharyngeal specimens were collected to perform rapid diagnostic tests, serologic tests, culture, and molecular tests for potential pathogens causing acute fever. Final diagnoses were determined with the use of algorithms and a set of prespecified criteria.

### RESULTS

Analyses of data derived from clinical presentation and from 25,743 laboratory investigations yielded 1232 diagnoses. Of 1005 children (22.6% of whom had multiple diagnoses), 62.2% had an acute respiratory infection; 5.0% of these infections were radiologically confirmed pneumonia. A systemic bacterial, viral, or parasitic infection other than malaria or typhoid fever was found in 13.3% of children, nasopharyngeal viral infection (without respiratory symptoms or signs) in 11.9%, malaria in 10.5%, gastroenteritis in 10.3%, urinary tract infection in 5.9%, typhoid fever in 3.7%, skin or mucosal infection in 1.5%, and meningitis in 0.2%. The cause of fever was undetermined in 3.2% of the children. A total of 70.5% of the children had viral disease, 22.0% had bacterial disease, and 10.9% had parasitic disease.

### CONCLUSIONS

These results provide a description of the numerous causes of fever in African children in two representative settings. Evidence of a viral process was found more commonly than evidence of a bacterial or parasitic process. (Funded by the Swiss National Science Foundation and others.)

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*A Quick Take animation is available at NEJM.org*

With malaria transmission declining in many parts of Africa,[1,2] there is increasing awareness that most acute febrile episodes are due to other infectious diseases — some of which are life-threatening — that must be identified and treated appropriately.[3,4] World Health Organization (WHO) guidelines recommend malaria testing for all patients with febrile illness in areas where malaria is endemic.[5] The advent of point-of-care rapid diagnostic tests for malaria presents health care providers with a new and daunting challenge: the need to determine the causes of febrile illness and the appropriate course of action when treating children who test negative for malaria. Studies have shown that the decrease in the use of antimalarial therapy has been accompanied by a commensurate increase in antibiotic use.[6-8] Stakeholders have thus recognized the need for an improved understanding of nonmalarial fever, both to optimize care and to reduce inappropriate antibiotic use.[9-12] Although several studies have examined nonmalarial fever in hospitalized patients, in particular those with bacteremia,[13-17] to our knowledge, none have included extensive algorithm-based screening to assess the relative distribution of bacterial, parasitic, and viral agents among acutely febrile sub-Saharan African children attending an outpatient clinic.

## Methods

### Study Sites and Populations

During the period from April through August 2008, we recruited children at the outpatient clinic of the Amana District Hospital in Dar es Salaam, an area of low endemicity for malaria, with infection rates in the community of roughly 1 to 4%[18] and only 6 to 12% of febrile patients found to have plasmodium parasitemia.[8] During the period from June through December 2008, we recruited patients at the outpatient clinic of the St. Francis Designated District Hospital in Ifakara, Kilombero District, Tanzania. Ifakara was once highly endemic for malaria, but at the time of the study, only about 7% of febrile patients had parasitemia. The Expanded Program on Immunization in Tanzania included bacille Calmette–Guérin, diphtheria–tetanus–pertussis, poliovirus, hepatitis B, and measles vaccines (but neither pneumococcal nor *Haemophilus influenzae* vaccine), and coverage was between 80% and 90%. A 3-day national integrated campaign of measles vaccination, vitamin A supplementation, and distribution of deworming tablets took place in August 2008. The mortality rate among children between 1 and 5 years of age in 2008 was 8.9 per 1000 person-years in the Kilombero and Ulanga districts.[19]

### Study Participants

Consecutive patients 2 months to 10 years of age presenting with an axillary temperature of 38°C or higher were screened for study inclusion; those who had severe malnutrition or were categorized as having emergency signs (requiring immediate livesaving procedures) according to the WHO Emergency Triage Assessment and Treatment criteria[20] were excluded. Infants younger than 2 months of age were also excluded, since infectious agents and thus therapeutic approaches can differ substantially between children in this age group and older children, as reflected in WHO Integrated Management of Childhood Illness guidelines. Four additional inclusion criteria were assessed: the patient's visit had to be the first for the present illness, the fever duration had to be 1 week or less, the chief reason for the clinic visit could not be injury or trauma, and the patient could not have received antimalarial agents or antibiotics during the preceding week. Details of the study were discussed with the parents or guardians of patients meeting the inclusion criteria; the parents or guardians provided written informed consent. The protocol and related documents were approved by the regional ethics committee in Basel, Switzerland, and by the national ethics committee in Tanzania. All authors vouch for the accuracy and completeness of the data and the fidelity of the study to the protocol. Patients were provided immediate supportive care and treatment for each treatable disease that was identified. The procedures followed were in accordance with the ethical standards set by the two ethics committees and with the Declaration of Helsinki.

### Study Procedures

#### *Clinical Assessment*

To record clinical findings, investigators used a standardized case-report form in which items relevant to a febrile presentation were listed, among



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them the chief reason for the visit, 23 symptoms and their respective durations, travel history, contact with sick persons, known chronic conditions, and 49 clinical signs. If the Integrated Management of Childhood Illness clinical criteria for a suspected human immunodeficiency virus (HIV) infection were met, voluntary HIV testing was recommended to the child's guardian. If a clinical or laboratory diagnosis could not be made at the initial visit, a follow-up visit was scheduled for day 7, when an identical, full clinical and laboratory assessment was performed again for patients who had a persistent fever or new symptoms.

*Microbiologic and Other Investigations*

In all cases, blood samples (5 ml) and pooled nasal and throat swabs were collected for microbiologic testing (cultures and rapid tests) on site and further serologic and molecular analysis in Switzerland and the United States. A systematic set of investigations was performed for all patients (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Additional tests and assessments were performed according to several non–mutually exclusive decision charts developed for the chief symptoms (Fig. S1 in the Supplementary Appendix). Methods for all laboratory analyses, as well as radiologic criteria for pneumonia, are reported in the Methods section in the Supplementary Appendix. For each pathogen, the most appropriate method of detection for the diagnosis of an acute episode of fever was selected.

*Definitive Diagnosis Based on Predefined Criteria*

For each patient, the final diagnosis (in some cases, more than one) was established on the basis of a set of predefined clinical and microbiologic criteria derived from WHO and Infectious Diseases Society of America guidelines as well as from systematic reviews (Table S1 in the Supplementary Appendix). To maximize consistency and to minimize subjectivity, the diagnosis was generated by means of a computer-based algorithm. A designation "severe" was added when the child's condition fulfilled WHO criteria for this state.[21] An acute respiratory infection was defined as any acute infection (≤1 week in duration) that was manifested as at least one respiratory sign or symptom and was localized to the upper or lower respiratory tract. Systemic infection was defined as a febrile illness, without localizing symptoms or signs, that was due to a parasite other than malaria, a bacterium other than *Salmonella enterica* serovar Typhi, or a virus and was documented by serologic testing or a polymerase-chain-reaction (PCR) assay performed on a blood specimen.

Because of the high rate of viral infection among asymptomatic children,[22,23] viruses detected by PCR assay performed on nasopharyngeal swab specimens were deemed the cause of the febrile illness only when the patient presented with concomitant respiratory symptoms or signs and no other infectious agent was identified. Patients who had virus detected in nasopharyngeal specimens and who had no overt respiratory symptoms or signs and no other identified disease were given a diagnosis of nasopharyngeal viral infection. Because of its high colonization rates among children,[24,25] *Streptococcus pneumoniae* identified by PCR assay of nasopharyngeal specimens was deemed the cause of illness only in cases of radiologically confirmed pneumonia or severe acute respiratory infection. For details of the study design, see the protocol, available at NEJM.org.

### STATISTICAL ANALYSES

Simple proportions were used for most analyses, and differences among groups were evaluated by means of a chi-square test. Data were entered into Epi Info, version 3.5.1 (Centers for Disease Control and Prevention). All statistical analyses were performed using Stata software, version 10 (StataCorp).

## RESULTS

### STUDY SAMPLE

A total of 1010 febrile children (510 in Dar es Salaam and 500 in Ifakara) were initially enrolled; 5 were subsequently excluded from the study (2 for whom consent was withdrawn, 1 who did not have blood drawn, and 2 who did not meet inclusion criteria). Demographic and clinical characteristics of the 1005 children included in the study are described in Table 1. For 63.0% of patients in Dar es Salaam and 71.5% of patients in Ifakara, fever was the main symptom cited by the parent or guardian. In total, 25,743 biologic tests were performed, and



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**Table 1. Demographic and Clinical Characteristics of the Children, According to Study Site.***

| Characteristic | Dar es Salaam (N=507) | Ifakara (N=498) |
|---|---|---|
| Female sex — no. (%) | 237 (46.7) | 250 (50.2) |
| Age — no. (%) | | |
| 2 to <12 mo | 150 (29.6) | 177 (35.5) |
| 12 to <36 mo | 228 (45.0) | 226 (45.4) |
| 36 to <60 mo | 75 (14.8) | 85 (17.1) |
| 5 to <8 yr | 36 (7.1) | 8 (1.6) |
| 8 to <11 yr | 18 (3.6) | 2 (0.4) |
| Weight for age — no./total no. (%) | | |
| Normal | 277/498 (55.6) | 292/497 (58.8) |
| 1 SD below mean | 150/498 (30.1) | 147/497 (29.6) |
| 2 SD below mean | 52/498 (10.4) | 48/497 (9.7) |
| 3 SD below mean | 16/498 (3.2) | 10/497 (2.0) |
| 4 SD below mean | 3/498 (0.6) | 0/497 (0) |
| Temperature at enrollment — no. (%) | | |
| 38 to <39°C | 382 (75.3) | 398 (79.9) |
| 39 to <40°C | 107 (21.1) | 81 (16.3) |
| ≥40°C | 18 (3.6) | 19 (3.8) |
| Chief symptom cited by parent or guardian — no./total no. (%) | | |
| Fever | 313/497 (63.0) | 354/495 (71.5) |
| Cough | 56/497 (11.3) | 47/495 (9.5) |
| Vomiting | 47/497 (9.5) | 28/495 (5.7) |
| Diarrhea | 33/497 (6.6) | 22/495 (4.4) |
| Abdominal pain | 15/497 (3.0) | 19/495 (3.8) |
| Other | 33/497 (6.6) | 25/495 (5.1) |

* Percentages may not sum to 100 because of rounding.

200 chest radiographs were obtained (Fig. S1 in the Supplementary Appendix).

### DIAGNOSES

Overall, 1232 distinct clinical or microbiologic diagnoses were made (Fig. 1). Acute respiratory infection was the most frequent diagnosis, made in 625 of 1005 patients (62.2%). Infections were localized to the upper respiratory tract in 439 patients (262 with tracheobronchitis, 141 with rhinitis, 24 with acute otitis media, 11 with nonstreptococcal tonsillitis, and 1 with pharyngitis) and to the lower respiratory tract in 186 patients (35 with bronchiolitis, 120 with non–radiologically confirmed pneumonia, and 31 with radiologically confirmed pneumonia). Other diagnoses were distributed as follows: 134 of 1005 (13.3%) children had a systemic infection, 120 (11.9%) had nasopharyngeal viral infection, 105 (10.5%) had malaria, 103 (10.3%) had gastroenteritis, 59 (5.9%) had urinary tract infection, 37 (3.7%) had typhoid fever, 15 (1.5%) had skin or mucosal infection, and 2 (0.2%) had meningitis. In 32 patients (3.2%), no potential infectious cause of illness was found.

Figure 2 shows the distribution of diseases according to age group. Urinary tract infection was predominantly diagnosed in the youngest children (<3 years of age in 95% of cases), whereas typhoid fever was diagnosed primarily in older children (≥1 year of age in 95% of cases), with a prevalence that increased with increasing age. The prevalence of malaria was highest among children older than 3 years of age, as expected in an area where malaria is moderately endemic. Infection with human herpesvirus 6 was mainly acquired in the first year of life. Acute respiratory infection was frequent in all age groups, but the frequency decreased slightly with increasing age. Diagnoses according to month and study site and differences in diagnoses between the urban and rural sites are provided in the Supplementary Appendix (Results section and Fig. S2).

### DIAGNOSES IN SEVERE CASES

Overall, the conditions of 133 of the 1005 patients (13.2%) fulfilled the criteria for severe disease. A total of 160 illnesses were diagnosed in these patients, as shown in Figure 3. Malaria, radiologically confirmed pneumonia, and typhoid fever were more common among patients with severe illness than among those with mild illness ($P<0.001$, $P=0.008$, and $P=0.01$, respectively). Of the 133 severely ill patients, 70 (52.6%) were subsequently hospitalized. Four children died: one from concurrent malaria and typhoid fever, one from sepsis due to *H. influenzae*, one from meningitis, and one from acute respiratory infection associated with coronavirus and pneumococcal infection.

### MULTIPLE DIAGNOSES

A total of 227 children (22.6%) had multiple conditions diagnosed. Of the 105 patients with malaria, 54 (51.4%) had a concomitant disease: 43 had acute respiratory infection (31 of whom had upper respiratory tract infection, 3 had bronchiolitis, 8 had non–radiologically confirmed pneumonia,



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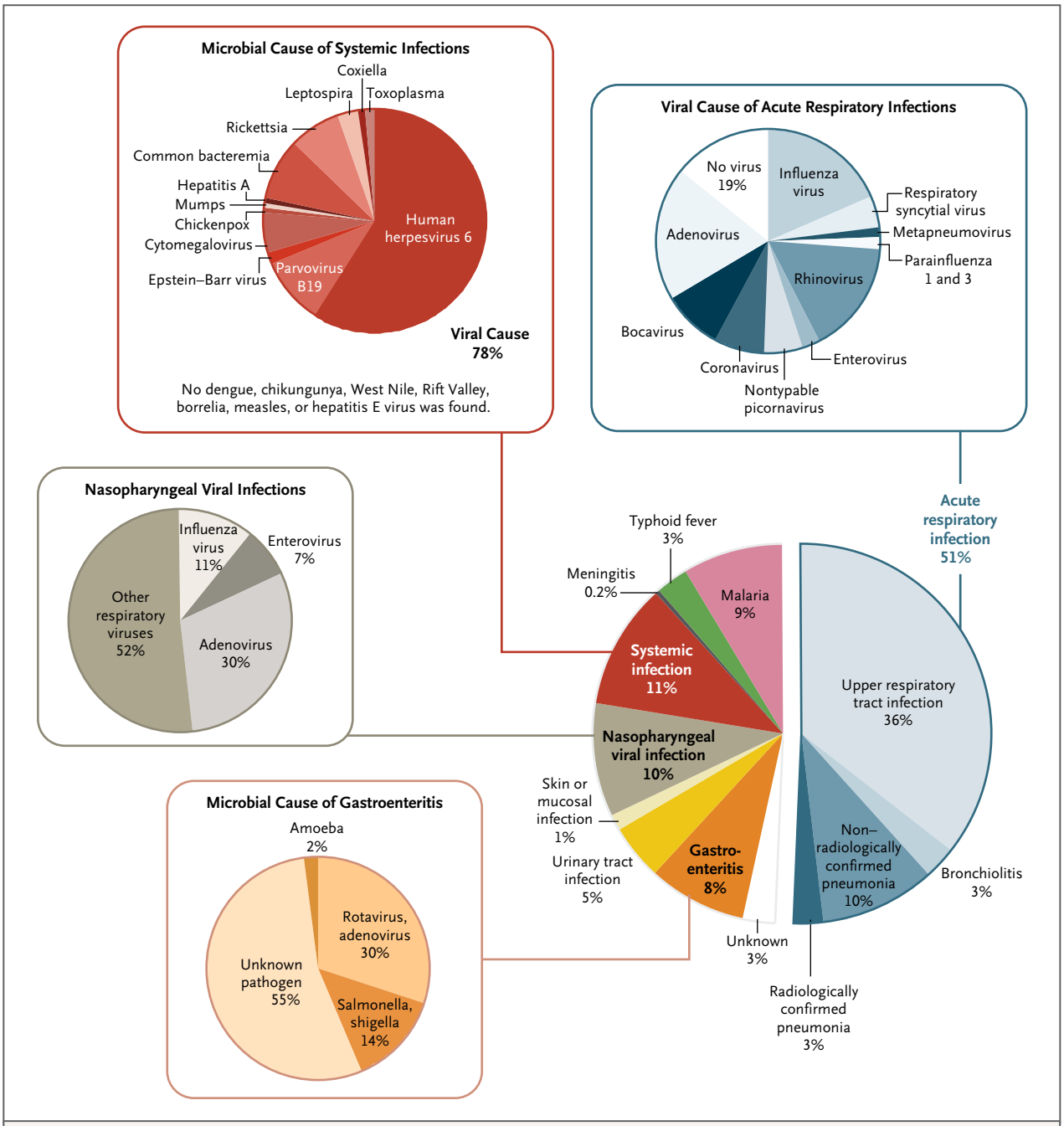


**Figure 1. Distribution of All 1232 Diagnoses among 1005 Febrile Children at Two Sites in Tanzania.**
Numbers are percentages of all diagnoses. Percentages may not sum to 100 because of rounding.

and 1 had radiologically confirmed pneumonia), 4 had typhoid fever, 2 had gastroenteritis, 2 had urinary tract infection, 2 had purulent skin or mucosal infection, 4 had systemic viral disease, and 1 had bacteremia. The percentage of patients with multiple diagnoses was similar among those with a blood parasite density of less than 2000 parasites per cubic millimeter and those with a density of 2000 parasites per cubic millimeter or more (57.1% and 50.6%, respectively; P=0.65). Patients with malaria who had any parasite density were half as likely to have pneumo-



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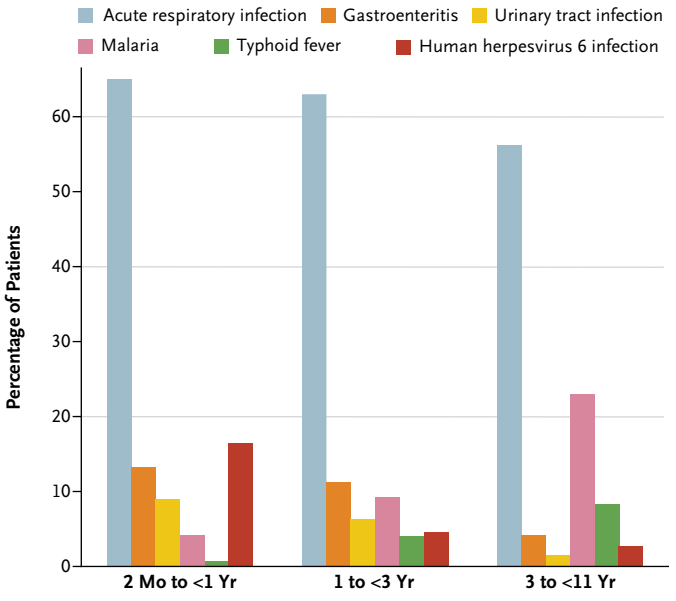


**Figure 2. Most Common Diagnoses According to Age Group.**

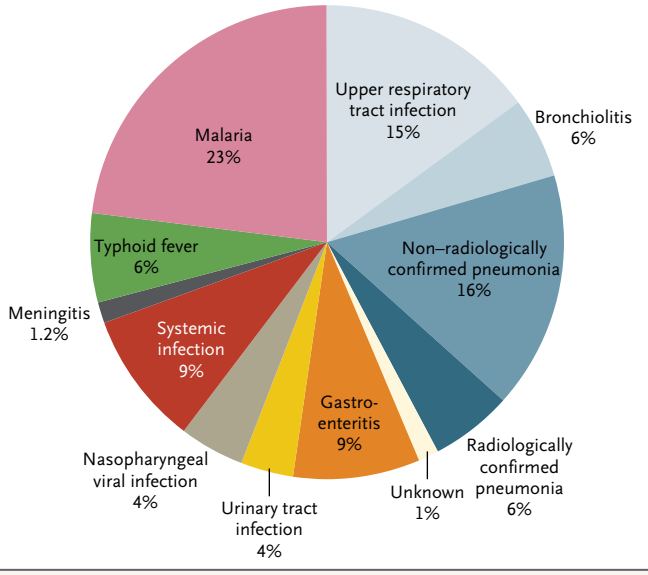


**Figure 3. Distribution of All 160 Diagnoses among 133 Febrile Children with Severe Illness.**

Numbers are percentages of all diagnoses. The distribution of features of severe illness was as follows: 42 cases of jaundice, 37 of respiratory distress, 27 of impaired consciousness, 19 of seizures, 14 of severe anemia (hemoglobin level, <5 g per deciliter), 9 of severe dehydration, 7 of marasmus, 5 of cardiovascular failure, 4 of plasmodium hyperparasitemia, 2 of renal failure, and 2 of meningismus. Percentages may not sum to 100 because of rounding.

nia (documented radiographically or not) as patients without malaria (P=0.05). The prevalence of typhoid fever was the same among patients with malaria and patients without malaria (4% in each group, P=0.94).

### DISEASES ACCORDING TO TYPE OF PATHOGEN

The distribution of illnesses by pathogen type (bacterial, viral, or parasitic) is presented in Figure 4A. Figure 4B shows the overlap among all pathogens identified, irrespective of the clinical and laboratory criteria used to determine final diagnoses. The numbers and proportions of children infected with each individual pathogen are presented in Table S2 in the Supplementary Appendix.

#### *Viral Diseases*

Among the 625 patients with clinical diagnoses of acute respiratory infection, PCR results were positive for at least one virus in 504 (81%): 344 of the 439 children with upper respiratory tract infection (78%), 29 of the 35 with bronchiolitis (83%), 107 of the 120 with non–radiologically confirmed pneumonia (89%), and 24 of the 31 with radiologically confirmed pneumonia (77%). A virus was documented in stool specimens from 31 of 103 patients with gastroenteritis (30.1%). Evidence of recent infection with human herpesvirus 6 and parvovirus B19 was found in 79 (7.9%) and 13 (1.3%) of the 1005 children, respectively. IgM antibodies for cytomegalovirus and Epstein–Barr virus were detected in 8 and 2 of the 199 tested children, respectively, and IgM for hepatitis A virus and hepatitis E virus was present in 1 and none of the 43 children with elevated liver enzyme levels. No dengue, chikungunya, West Nile, or Rift Valley fever virus was detected in the 199 children tested by means of PCR assay. Of the 120 patients with virus detected in nasopharyngeal specimens who had no clinical or laboratory findings beyond fever (i.e., those with nasopharyngeal viral infections), the virus was deemed to be possibly causal in at least 51%, because influenza, adenovirus, and enterovirus are known to produce fever without respiratory or other localized symptoms.[26-28]

#### *Bacterial Diseases*

Blood culture was performed with samples from 424 (83.6%) of the 507 children enrolled at the Dar es Salaam site only. Of these patients, 18 (4.2%) were positive for noncontaminant bacteria, 6 of whom had severe disease: 5 were positive for gram-



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positive cocci (3 for *Staphylococcus aureus*, 1 for *Streptococcus pneumoniae*, and 1 for an undetermined streptococcus species), and 13 were positive for gram-negative rods (4 for *Salmonella enterica* serovar Typhi, 2 for *Escherichia coli*, 1 for *Acinetobacter baumanii*, 1 for an undetermined acinetobacter species, 1 for *Aeromonas hydrophila*, 1 for *H. influenzae*, 1 for *Pseudomonas aeruginosa*, 1 for non-Typhi salmonella, and 1 for *Shigella flexneri*). Bacteremia originated in the gastrointestinal tract of 5 patients (including 4 with typhoid fever) and in the urinary tract of 2 patients, whereas originating sites in the other 11 cases of bacteremia could not be elucidated. Urinary tract infections were identified in 59 of 144 children (41.0%) tested by urine culture. Among the 54 children tested by stool culture, *Shigella flexneri* was identified in 11 (20%), and *Salmonella enterica* serovar Typhi was identified in 1 (2%). Of the 199 children for whom serologic testing for bacteria was indicated, 15 had evidence of an acute infection (6 with *Rickettsia typhi*, 4 with *R. conorii* or *R. africae*, 2 with *Leptospira interrogans* serovar *icterohaemorrhagiae*, 2 with *L. interrogans* serovar *hardjo*, and 1 with *Coxiella burnetii*). Of the 31 children with radiologically confirmed pneumonia and the 67 children with severe acute respiratory infection, 29 (94%) and 59 (88%), respectively, had PCR results that were positive for *Streptococcus pneumoniae*.

### *Parasitic Diseases*

A total of 105 children had malaria, 2 children had toxoplasmosis, and 2 children had amoebic gastroenteritis.

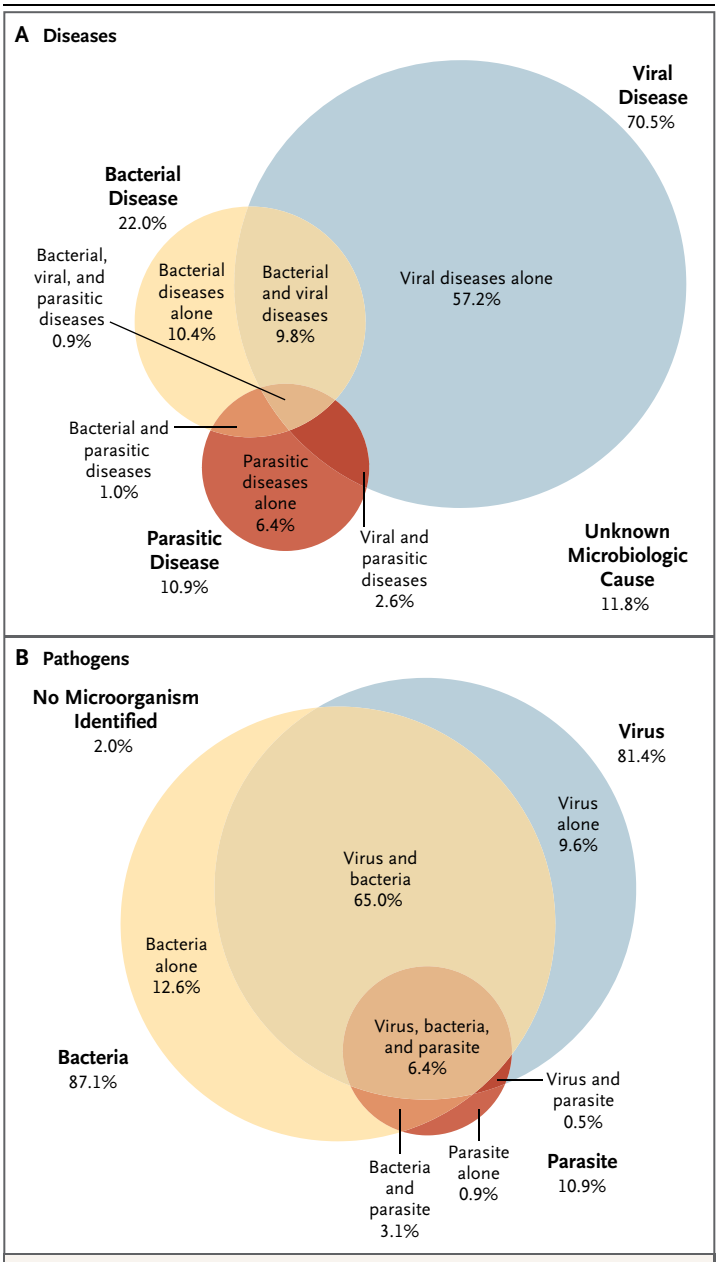


**Figure 4. Overlap among Disease Types and Pathogen Types in the 1005 Febrile Children.**

Panel A shows all diseases diagnosed in the present study; disease definitions are given in Table S1 in the Supplementary Appendix. Panel B shows types of pathogens identified, regardless of the clinical and laboratory criteria used to establish final diagnoses.

## DISCUSSION

Using a predefined algorithm applied to an extensive set of clinical, laboratory, and radiologic data, we were able to identify the possible cause of fever in 97% of the 1005 children included in our study. Of these children, 88% had evidence of infection with at least one microbe. More than half presented with acute respiratory infection; a virus was identified in 81% of these children.

Given the seasonal pattern of respiratory viral infections, malaria, and other vectorborne diseases, different results could have been obtained if the study had been conducted in another region or country or during another season or year. Because the two study sites are representative of urban and rural Tanzania, our findings can be generalized to the nation as a whole and, to an extent, to other countries in sub-Saharan Africa. Of course, if the rate of malaria transmission were higher in other regions, malaria would be expected to account for a higher pro-



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portion of all causes of fever. The same applies to potential epidemics of any type of disease, which would temporarily reduce the relative proportions of other diseases in that particular area. In the absence of any particular outbreak, common childhood viral diseases are as frequent in Africa as in any other continent. More studies with a similar comprehensive clinical, radiologic, and laboratory approach are required in different epidemiologic contexts to generate additional evidence.

The decision to perform diagnostic tests in predefined subsets of patients with a higher pretest probability of a given infection than in the overall study sample can be considered a potential limitation of our study. However, this increased the clinical relevance of our microbiologic investigations by increasing the probability that the identified infection was the cause of illness.

Our findings indicate that among preschool-age children, a high percentage of lower respiratory tract diseases are likely to be of viral origin[29,30]: 81% of patients with upper respiratory tract infection, bronchiolitis, or non–radiologically confirmed pneumonia had evidence of a virus in their nasopharyngeal samples, and this was also seen in 77% of patients with radiologically confirmed pneumonia. It is known that respiratory viruses, including rhinoviruses,[31] can cause lower respiratory tract disease, which may be severe, particularly in infants and young children with preexisting medical conditions. In fact, the presence of viral–bacterial coinfection may well be a major trigger for the development of severe pneumonia.[30,32] These findings indicate that less than 13% of the children with acute respiratory infection required treatment with antibiotics.

The substantial difference between Figure 4A (showing diseases diagnosed on the basis of predefined clinical and laboratory criteria) and Figure 4B (showing all pathogens identified in the children but not necessarily considered a cause of the febrile episode) underscores the limitations inherent in a diagnosis made on the basis of laboratory findings alone. It is essential to combine laboratory findings with detailed clinical information and, when available, quantitative pathogen loads in order to differentiate between colonization or infection and disease. This is especially important when new, highly sensitive molecular methods are used. However, these new tools provide the advantage of identifying agents with previously unrecognized pathogenic potential, revealing the complexity of infectious diseases in this particular clinical situation. Multiple diagnoses were made in almost a quarter of patients, and multiple infections were found in two thirds of the children, which reflects the difficulty in providing a simple diagnosis for a child's condition. The combination of multiple infections is likely to have led to pathogen interactions, which may have contributed to the clinical condition observed in many of these patients. Diagnostic tools should be considered in light of the clinical characteristics of the targeted population. A greater understanding is needed regarding the diagnostic value of different signs and tests, the disease course in patients presenting with multiple infections, and the potential diagnostic thresholds for new molecular tests, such as cutoffs for pathogen loads.

In Dar es Salaam and Ifakara, most of the febrile children probably had a viral illness and thus required neither an antimalarial agent nor an antibiotic. These findings support the suggestion that sending such children home without antimalarial treatment[33-35] or antibiotic treatment[35,36] is reasonable in the absence of severe clinical signs. The systematic provision of antibiotic treatment in children with nonmalarial fever is unlikely to provide a clinical benefit in most cases. Rather, it exposes the children to unnecessary adverse events and exposes the community to accelerated development of antimicrobial resistance. The diversity of the causes of fever, most of which cannot be diagnosed on clinical grounds alone, calls for the development of point-of-care tests.

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*S. pneumoniae* and providing advice regarding how to interpret the results; Olivier Peter for performing the serologic testing for rickettsia and coxiella; Katja Reitt for performing the serologic testing for leptospira; Leonor Alamo for reading the chest radiographs; Tom Smith for his useful comments on an earlier draft of the manuscript; and Angela Huttner for assistance with editing the text of an earlier version of the manuscript. Finally, we thank all patients and caregivers who participated in the study.

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