Changing etiologies in childhood acute febrile illness: implications for management in an era of declining malaria

Alastair Ian Matheson

A dissertation submitted in partial fulfillment of the requirements
for the degree of

Doctor of Philosophy

University of Washington
2016

Reading committee:
Judd Walson, Chair
Lisa Manhart
Jon Wakefield

Program authorized to offer degree:
Epidemiology

University of Washington

Abstract

Changing etiologies in childhood acute febrile illness:
implications for management in an era of declining malaria

Alastair Ian Matheson

Chair of the supervisory committee:
Judd Walson
Associate Professor
Global Health, Epidemiology, Allergy and Infectious Diseases, Pediatrics

Background: Acute febrile illness (AFI) is a common syndrome among children presenting to a healthcare facility in resource-limited settings and a substantial contributor to childhood mortality. In sub-Saharan Africa, malaria has historically been a leading cause of childhood AFI but malaria incidence and mortality have declined dramatically over the past decade. At the same time, other emerging infections may increasingly be replacing malaria as causes of AFI. For example, dengue virus has spread rapidly throughout the world and is now established in Africa. It is unclear how shifts in pathogen distribution and transmission impact AFI incidence and how these changes impact the management practices of healthcare workers (HCWs). This dissertation sought to describe recent time trends of malaria and non-malarial AFI (Aim 1), to evaluate the contribution of dengue to AFI in western Kenya (Aim 2), and determine whether seasonal variations in malaria incidence influence antibiotic prescribing for children with AFI (Aim 3).

Methods: All three aims were addressed using data from a large cohort in western Kenya that has been followed for over eight years. In particular, data from Lwak Mission Hospital formed the basis for these analyses. For Aim 1, quasi-Poisson regression was used to calculate the annual decline in visits from children with malaria, non-malarial AFI, and overall AFI. For Aim 2, serum specimens were obtained from patients of all ages with AFI who had either no known cause of their fever or a diagnosis for which dengue fever is often mistaken. Specimens were tested for the

presence of dengue virus using reverse-transcription polymerase chain reaction (PCR). In addition, specimens were also tested for evidence of a recent infection, indicated by the presence of IgM anti-dengue virus antibodies in an enzyme-linked immunosorbent assay. For Aim 3, we used logistic regression, adjusting for a child's malaria smear result, to assess whether seasonal variations in malaria were associated with HCWs' adherence to Integrated Management of Childhood Illness (IMCI) guidelines on antibiotic prescriptions among children with AFI.

Results: For Aims 1 and 3, approximately 11,400 childhood AFI visits to LMH between January 1, 2009 and December 31, 2014 informed the analyses. Visits from both non-malarial AFI and malaria declined substantially over this period (9.47% and 8.55% per year, respectively). Declines in malaria over this time were not statistically significant, likely due to a plateauing of malaria visits in the latter part of the study. However, among children with malaria there were opposing trends; visits where the child had malaria parasitemia alone declined significantly by 16.15% per year whereas the number of visits from children with malaria parasitemia and another clinical diagnosis of an AFI etiology remained largely the same. For Aim 2, 615 serum specimens were obtained from visits during two rainy periods (September–December 2011 and March–July 2013). There were no positive results for dengue infection using either PCR or IgM anti-dengue virus testing. For Aim 3, HCW management of AFI appeared to be associated with perceived risk of malaria. Overall, HCWs adhered to IMCI guidelines for antibiotics in 7,853 (69.0%) of included childhood AFI visits. However, periods of high malaria incidence were associated with fewer prescriptions of antibiotics in children who met criteria for antibiotic treatment and periods of low malaria incidence were associated with greater use of antibiotics in children who did not meet criteria for antibiotic treatment.

Conclusion: The clinical and epidemiological pictures of childhood AFI in sub-Saharan Africa are becoming more complicated, even as malaria and non-malarial AFI both decline. While malaria continues to be a major driver of AFI seen at this outpatient setting in rural western Kenya, an increasing proportion of febrile children with malaria receive additional diagnoses of

other causes of fever including upper respiratory tract infections and pneumonia. Dengue virus does not appear to be present in this part of western Kenya at this time but the risk of spread to the region from the coastal region remains. Seasonal variation in malaria was associated with non-adherence to IMCI guidelines for antibiotic prescriptions. Ongoing comprehensive surveillance of etiologies of AFI and investigations into the impact of changing patterns of disease burden on the management practices of HCWs' may lead to opportunities for improved prevention and management of childhood AFI.

TABLE OF CONTENTS

List of Tables

List of Figures

Acknowledgements

Behind the one name at the top of this dissertation are dozens of people who made it possible. First, I want to thank my committee mentors: Judd Walson, Lisa Manhart, Jon Wakefield, Joel Montgomery, and Matthew Thompson. They challenged me to think critically about my research and held me to high standards, all while enthusiastically supporting my ideas. Because of them, I am a better epidemiologist. I particularly want to acknowledge the support and mentorship of Judd, my chair, who opened doors and invested time and energy into my development.

I thank my colleagues and friends at the Kenya Medical Research Institute/CDC-Kenya, particularly Daniel Ondari, Godfrey Bigogo, Allen Audi, and the Lwak Mission Hospital clinic staff, for all their work on the PBIDS data. Thank you also to all the study participants of Asembo who gave their time and information. I am grateful for the support of Joshua Lacsina at UW and Petty Ahenda at the KEMRI/CDC lab in Nairobi, who performed the dengue testing.

Finally, I want to thank my friends and family for helping me on the journey. To my wife—thank you so much for your care and support. I could not have done it without you.

Chapter 1: Introduction

Acute febrile illness (AFI) is one of the most common syndromes among children presenting for health care in resource-limited settings.[1, 2] Although the mortality rate from infectious febrile causes among children aged 1–4 years was halved between 1990 and 2010 to 155 per 100,000 person-years, febrile illnesses, particularly malaria and respiratory infections, contribute to over 1.6 million deaths annually and account for nearly half of total global child mortality.[3] Declines in malaria transmission, increased coverage of pneumococcal vaccine, and the emergence of pathogens such as dengue virus in many previously non-endemic areas are resulting in dramatic shifts in the etiologies of fever in Africa.[4] An improved understanding of the distribution of causes of AFI over time, particularly in areas with declining incidence of malaria, is critical for optimizing program planning and policies for sustaining gains in childhood morbidity and mortality reduction.

An accurate assessment of fever etiologies in many resource-limited settings is often difficult due to limited diagnostic capacity to differentiate among causes of fever and the often narrow approach to research that results in many estimates of disease burden focusing on a single pathogen.[4, 5] In fact, there have been just two large studies aimed at comprehensively documenting causes of fever in Africa. One study reported that the majority of cases stemmed from viral respiratory infections, though 23% of children had multiple diagnoses,[6] and the other study identified substantial burden due to non-malarial zoonotic illnesses such as chikungunya and rickettsial diseases.[7]

In much of sub-Saharan Africa, malaria has historically been the primary suspected etiology of AFI.[5] However, the adoption of rapid diagnostic tests (RDTs) for malaria, the expanded availability and use of effective antimalarials, and the scale-up of long-lasting insecticide-treated bed nets have all contributed to declines in global malaria incidence (estimated at 3.27% per year

from 2000–2013).[8-10] Declining malaria incidence also appears to be associated with reduction in other causes of fever. As malaria incidence falls, host susceptibility to other infections, including non-typhoidal salmonella (NTS), HIV, and possibly pneumonia and other respiratory diseases, is likely to change due to the association between these diseases and malaria infection.[11-15]

In addition to the direct impact of declines in malaria, new and emerging infections are also affecting the landscape of AFI in many settings. For example, dengue virus has spread rapidly throughout the world, with more than half the world's population now at risk of acquiring dengue virus infection.[16] Recent outbreaks of dengue fever in Somali, Angola and on the Kenyan coast suggest that local transmission of dengue virus is occurring in Africa.[17-20]

As health care workers (HCWs) observe changes in the etiologies of AFI, their management practices may also shift. These variations in management occur despite the widespread adoption of guidelines such as the Integrated Management of Childhood Illness (IMCI), which offer a standard approach to treating children with fever and other common syndromes. For example, despite IMCI guidelines to the contrary, healthcare workers in malaria-endemic regions routinely disregard negative RDT results and prescribe antimalarials, particularly during seasons of high malaria incidence. In addition, seasonal increases in viral infections have been associated with increased antibiotic prescribing.[21-25] A change among HCWs in the perception of risk from malaria may influence antibiotic prescribing practices. Understanding the patterns and drivers of antibiotic prescribing, including any associations with seasonal changes in malaria incidence, may allow for targeted interventions to reduce the inappropriate prescribing of antibiotics and delay development of antibiotic resistance.[24, 26, 27] Given the increasing threat antibiotic resistance poses to global health, it is critical to understand how these shifts in management practices are affecting the use of antibiotics.

Examining childhood AFI as a complete syndrome, including observing incidence trends in areas with declining malaria, will allow health planners to better anticipate future healthcare needs. If decreasing malaria results in lower AFI overall, it may be possible to shift resources towards other syndromes associated with childhood morbidity and mortality. If, instead, other AFI etiologies replace malaria and overall AFI rates remain stable, greater emphasis will need to be placed on supporting HCW decision making for AFI management. HCWs in resource-limited settings primarily make treatment choices based on syndromic assessment and clinical judgement, which, for febrile children, may be influenced by perceptions of circulating AFI etiologies. While improved diagnostics may be useful, in many settings a syndrome-based approach to AFI may be better aligned with current assessment and management guidelines. Collecting accurate data on the rise of emerging pathogens and understanding the specific factors that influence antibiotic use for AFI are both important steps in developing tools and training for improved clinical management of febrile children.

This dissertation attempts to answer some pressing questions regarding childhood AFI in sub-Saharan Africa. The aims of the dissertation were as follows:

1. To determine whether the rate of presentation to a western Kenya facility for childhood AFI decreases in parallel with declines in malaria among the same population.
   Hypotheses: Total AFI will decline at a faster rate than would be expected given the rate of decline of fever due to malaria alone. This may be due to the fact that other causes of fever such as respiratory disease and NTS are partially driven by malaria and reducing malaria has an indirect benefit for these causes of fever.

2. To determine the proportion of AFI with an unclear etiology that is caused by dengue virus.
   Hypothesis: dengue virus will found in approximately 5% of AFI cases that have either no cause listed or a diagnosis for which dengue is often mistaken.

3. To determine whether clinician adherence to IMCI guidelines for antibiotic use in children with AFI is lower during periods of lower malaria transmission.
   Hypotheses: Clinical indications will not support antibiotic prescriptions for the majority of children in all seasons. However, healthcare workers will be more likely to prescribe antibiotics during the dry season, resulting in lower adherence to IMCI guidelines during periods of lower malaria transmission.

Chapter 2: Parallel declines in malaria and other acute febrile illnesses in Kenya: A time-series analysis

2.1 Introduction

Acute febrile illness (AFI) is one of the most common syndromes among children presenting to health care facilities in resource-limited settings. While AFI is non-specific and is associated with numerous infectious and non-infectious causes of morbidity, many major etiologies of AFI, including malaria and systemic bacterial infections, contribute substantially to childhood mortality.[1-3] Given the limited availability of diagnostic tools in resource-limited areas, where febrile illness is most common, current etiology-specific estimates of febrile illnesses may not accurately describe overall patterns and trends in AFI. As the distribution of specific etiologies of AFI, such as malaria, dengue, or typhoid, change over time, it is important to evaluate how overall rates of AFI and the proportion caused by each etiology shift in order to prioritize interventions to improve diagnosis and management of febrile illnesses.[4]

Malaria has historically been a significant driver of overall AFI and of severe AFI resulting in mortality in sub-Saharan Africa. As a result, children with AFI in many settings are often presumptively treated for malaria, especially in highly endemic regions.[5, 6, 8] The adoption of rapid diagnostic tests for malaria, the expanded availability and use of effective antimalarials, and the scale-up of long-lasting insecticide-treated bed nets (ITNs) have all contributed to declines in global malaria incidence (estimated at 3.27% per year from 2000–2013).[9, 10]

Given the substantial contribution of malaria to AFI in many settings, declines in malaria might be expected to be accompanied by a concomitant decrease in overall AFI. However, as malaria declines, other causes of fever may replace malaria, resulting in less-than-expected reductions in overall AFI. In addition, children with fever due to other causes may also have asymptomatic parasitemia, leading to the misclassification of malaria as the cause of their AFI.[12, 28, 29]

Finally, a substantial proportion of children with clinical malaria also have evidence of infection with other pathogens. [6, 30] These factors may all may continue to maintain a high incidence of AFI, even in the absence of malaria infection.

Understanding trends in overall AFI, particularly in areas with declining incidence of malaria is critical for optimizing program planning, policies, and treatment approaches for reducing childhood morbidity and mortality. If declines in malaria result in fewer cases of AFI overall, it may be possible to shift resources towards improving diagnostic and treatment capacity of other syndromes associated with morbidity and mortality. However, if non-malarial AFI increases while malaria declines, greater emphasis must be placed on improved diagnostic abilities at the point of care to better understand alternative etiologies of AFI. Using data from a large, multi-year, population-based prospective cohort of children in rural Kenya, we sought to describe trends in AFI over time, determine the relative contribution of malarial versus non-malarial fever to AFI, and evaluate whether the relative distribution of malarial and non-malarial fever changed over time.

2.2 Methods

2.2.1 Study setting

The Centers for Disease Control and Prevention and the Kenya Medical Research Institute (CDC/KEMRI) International Emerging Infections Program has been operating population-based infectious disease surveillance (PBIDS) in Asembo, western Kenya, since 2006. PBIDS covers approximately 25,000 people and takes place in a 100 km² sub-area of a larger health and demographic surveillance site (HDSS), where malaria remains holoendemic and adult HIV prevalence is high.[1, 31, 32]

The PBIDS catchment population includes individuals living within 5km of St. Elizabeth Lwak Mission Hospital (LMH) and those who are enrolled in PBIDS receive free treatment at LMH for syndromes under surveillance: AFI, respiratory disease, diarrhea, and jaundice. Patients visiting LMH are assessed using a standardized case report form that includes vital signs, symptoms, physical exam, and clinical diagnoses. These records are linked to a laboratory database, which includes malaria smear results. Demographic and socioeconomic information for the PBIDS population were abstracted from the HDSS data.

All participants provide written informed consent to participate. Parents or guardians provided informed written consent on behalf of minors. The protocol and consent forms were reviewed and approved by the Ethical Review Boards of the Kenya Medical Research Institute (KEMRI) and the Institutional Review Board of the U.S. Centers for Disease Control and Prevention (CDC).

2.2.2 Data sources and measures

We sought to describe temporal patterns in overall rates of AFI among children presenting to a health care facility (LHM) in an area experiencing general declines in malaria incidence. We included visits from children (aged 2–59 months) with AFI (temperature of ≥38.0°C) who presented to LMH between January 1, 2009 and December 31, 2014. We excluded repeat visits for the same AFI episode, defined as one or more additional clinic visits by the same child within 14 days of an initial visit and the same malaria status. Additional AFI visits that occurred within 14 days but had a missing malaria smear result were included.

To further investigate the drivers of change in AFI incidence, we examined how the burden of malaria and non-malarial AFI changed over time. These analyses were limited to visits from febrile children (as defined above) to LMH between January 1, 2009 and December 31, 2014 with a recorded malaria smear result. Children were classified as having malaria if they had a positive

blood smear result, even if other diagnoses were made that could explain their fever. Children with a negative malaria smear were considered to have AFI due to a cause other than malaria (non-malarial AFI). Visits with no malaria smear result were treated as missing at random and were excluded from the analysis. Counts for a month were excluded from the time trend and proportion analyses if a third or more of the febrile visits had no malaria smear result. For the overall malaria and non-malarial AFI analyses, only February 2013 met this criterion (a shortage of supplies led to 91% of all febrile children not being tested for malaria that month).

We also investigated whether trends in overall and cause-specific (malaria or non-malarial) AFI visits varied by disease severity or age. Children with severe illness were defined as those with fever plus one or more of the World Health Organization Integrated Management of Childhood Illness (IMCI) danger signs (unable to breastfeed, vomiting everything, current or recent convulsions, lethargy, or unconscious).[33] Young children were defined as those aged 2–23 months. Among children with IMCI danger signs, there were four months where more than a third of visits had no malaria smear results available (November 2010, January 2011, February 2013, and September 2014), and these months were excluded from the cause-specific analyses of severe AFI time trends. Finally, because a substantial proportion of children diagnosed with malaria may have another cause of AFI, we explored whether rates of malaria changed differentially among children with malaria alone as compared to children with potential multiple etiologies of AFI. Children with malaria and a clinical diagnosis of one or more of the following causes of non-malarial AFI were classified as coinfected: meningitis, pneumonia, upper respiratory tract infection (URTI), urinary tract infection, or viral syndrome.

We adjusted for seasonal variations in incidence of malaria and other AFI etiologies by including rainfall data in our analyses. Using data from the U.S. National Centers for Environmental

Information's Global Summary of the Day, we aggregated daily precipitation records from a nearby weather station (Kisumu Airport) into a measurement of monthly rainfall.[34]

2.2.3 Statistical methods

We compared key demographics (age, gender, and socioeconomic status) of children at the time of their visit to LMH for AFI with the general childhood PBIDS population using two-sided t-tests and chi-squared tests. To understand the demographic and clinical profiles of children visiting LMH for each type of AFI (malaria and non-malarial), we used two-sided t-tests to compare age, gender, and presence of IMCI danger signs.

Given the absence of reliable data on person-time that would have been used to calculate incidence, we primarily aimed to explore how the number of visits to LMH for childhood AFI changed over the study period. We aggregated the number of AFI visits per month and fitted a quasi-Poisson regression model to assess the percent change in number of monthly visits over time. For the secondary analysis of etiologies that influenced changes in overall clinic AFI visits, we again used quasi-Poisson regression to examine trends in monthly counts of malaria and non-malarial AFI. We also used a quasi-binomial regression model to examine the monthly change in proportion of AFI that was associated with malaria (defined as a positive malaria smear result).

Estimates of the monthly change in counts from each time trend model were extrapolated to an annual change for a more intuitive interpretation. Standard errors in all models were calculated using the Newey and West heteroskedasticity and autocorrelation consistent covariance matrix (sandwich) estimators to account for the correlation from children with multiple visits during the study period.[35] In all models, we adjusted for seasonality using the previous month's cumulative rainfall and for age using the mean age of children that month appropriate to each model (overall AFI, malaria, and non-malarial AFI,). In order to better understand which specific groups of

children were experiencing the greatest changes in overall AFI, malaria, and non-malarial AFI, we conducted several subanalyses: children with severe vs. mild AFI, younger vs. older children, and, among children with malaria, those with malaria and additional causes of AFI vs. those with malaria alone.

RStudio v0.98.1091 (RStudio, Boston, MA) over R V3.1.0 (R Foundation for Statistical Computing, Vienna, Austria) and Stata v13.1 (StataCorp, College Station, TX) were used for all analyses.

2.3 Results

2.3.1 Study population and overall AFI visits

On January 1, 2009, the initial time point for this analysis, there were 4,594 children aged 2–59 months included in the PBIDS cohort. Over the six years of follow up, the total population of children followed decreased slightly to 4,367 by December 31, 2014. In total, 13,548 individual children were included in the population during the study period.

Between January 2009 and December 2014, there were 34,218 visits by children to LMH, 11,447 (33.5%) of which were unique cases of AFI from 4,151 individual children (30.6% of the total child population) (Figure 2.1). The mean age of children presenting to LMH with AFI was 2.43 years and 48.7% were female (Table 2.1). There were no significant differences between children who visited LMH with fever and the general child population in terms of age, gender, or socioeconomic status. Drinking water for most children presenting to LMH was drawn from unimproved public sources such as ponds or unprotected springs (44.2%) or unimproved private sources such as rainfall (18.8%); only 34.3% had access to an improved source (Table 2.1). Firewood was the primary source of cooking fuel in the households in which febrile children resided (96.8%) and most children had access only to unimproved sanitation such as a traditional pit latrine or no

facilities (89.6%) (Table 2.1). Nearly half (43.7%) of children who visited LMH with AFI did so only once, with a mean of 2.8 visits per child. There were 4,864 (42.5%) visits to LMH where the child was 2–23 months old (younger children group).

2.3.2 Causes of AFI visits to LMH

The most common clinical diagnosis made among all AFI visits was malaria (76.1%), followed by URTI (32.9%), pneumonia (6.1%) and fever of unknown origin (6.1%) (Table 2.2). Children presented with one or more IMCI danger signs (severe AFI) at 1,633 (14.3%) visits, with the most common danger signs being a reported inability to drink or breastfeed (60.1%), current or recent convulsions (24.6%), and vomiting everything with each feeding (17.8%).

Malaria smear results were available for 10,353 (90.4%) of all patient encounters for AFI at LMH and 7,803 (75.4%) of results were positive (Table 2.2). Patients seeking care at LMH with fever and a negative malaria smear (non-malarial AFI) were younger than febrile children with malaria (mean age of 1.99 vs. 2.55 years, $P<0.0001$) and less likely to present with an IMCI danger sign (12.8% vs. 14.4%, $P=0.036$) (Table 2.3).

Over one-third (36.0%) of children with a positive malaria smear also had a clinical diagnosis of at least one other AFI etiology of interest (meningitis, pneumonia, upper respiratory tract infection, urinary tract infection, or viral syndrome), a majority (91.5%) of which included a diagnosis of URTI (Table 2.2 and Table 2.3). There were no differences in age, gender, socioeconomic status, or proportion with an IMCI danger sign between children with malaria alone and those with malaria and another AFI etiology.

2.3.3 AFI time trends

Over the study period, there were consistent and significant declines in the number of childhood AFI visits to LMH (Figure 2.2 and Table 2.4). After adjusting for age and previous month's cumulative rainfall, overall childhood AFI visits to LMH decreased by 11.06% per year over the study period (95% CI: 4.10–17.43%, P=0.002) (Table 2.4).

Both non-malarial AFI and malaria visits declined over the six-year study period, although the decline in malarial AFI was not statistically significant. After adjustment for previous month's rainfall and mean age, the number of clinic visits for non-malarial AFI and malaria decreased by 9.47% per year (95% CI: 4.20–14.44%, P<0.001) and 8.55% per year (95%CI: -5.16–20.47%, P=0.201), respectively (Table 2.4 and Figure 2.2). The proportion of AFI patients who had malaria varied seasonally but this proportion did not decline significantly across years (adjusted decline in proportion of 2.91% per year, 95% CI: -1.87–7.47%, P=0.223).

When stratifying by severity of AFI, the decline in severe AFI was more pronounced. Among the 1,633 visits with one or more IMCI danger signs present, the adjusted decrease in number of visits was 14.69% per year (95% CI: 4.27–23.98%, P=0.007). Both non-malarial AFI and malaria contributed to the decline in severe AFI visits. After adjustment for rainfall and age, and excluding months where more than a third of AFI visits had missing malaria smear results, non-malarial severe AFI visits decreased by 15.90% per year (95% CI: 7.37–23.65%, P<0.001) and malaria-related severe AFI visits decreased by 16.50% per year (95% CI: 6.67–25.30%, P=0.001) (Table 2.5).

AFI declined more substantially among younger children. After adjustment for previous month's rainfall and mean age of children, overall AFI counts decreased significantly by 11.12% (95% CI: 2.55–18.93%, P=0.012) per year in the 2–23-month-group compared with a non-significant

decline of 7.40% (95% CI: -1.20–15.27%, P=0.090) per year among children aged 24–59 months. In the younger age group, both non-malarial AFI and malaria visits had magnitudes and patterns of change over time similar to overall AFI, whereas in the older age group, malaria visits declined at a greater rate (Supplemental Table 2.1).

The number of visits per month among children with malaria and another AFI diagnosis increased slightly from 2009–2014, though this change was not significant (adjusted increase of 3.86% per year, 95% CI: -16.23–7.19%, P=0.509) (Table 2.6). However, the counts of visits for children with malaria alone (i.e., no diagnosis of another AFI etiology) declined by 16.15% per year (95% CI: 4.89–26.09%, P=0.006).

2.4 Discussion

Among a large cohort of children in western Kenya followed for six years, visits to an outpatient facility for AFI declined substantially (11.06% per year). The decrease in observed AFI was driven by declines both in fevers attributed to malaria and to causes other than malaria (decreases of 8.55% and 9.47% per year, respectively). Visits from febrile children who were more severely ill (as determined by the presence of one or more IMCI danger signs) decreased faster than the overall rate (14.69% per year), with severe AFI due to malaria and to other causes both declining at a similar, significant rate. Younger children (2–23 months) also experienced greater declines in AFI visits than children overall. The fact that sicker and younger children had the greatest declines in visits from AFI suggests that fever-related mortality is also likely to decline, though this study was not designed to detect such a change.

The observed fall in non-malarial AFI during the study period suggests that declines in malaria are not being replaced by other causes of AFI. There are two likely main explanations for the reduced non-malarial AFI observed in this study. First, the introduction of interventions

specifically targeting non-malarial etiologies of AFI in the study population may have impacted rates of disease. For example, the 10-valent pneumococcal conjugate vaccine was introduced in Kenya in 2011, and may have reduced the burden of fevers due to pneumonia and otitis media.[36, 37] Secondly, infrastructure improvements in this region, such as more paved roads and piped water, along with gradually improving wealth, may also have contributed to an overall improvement in general health among children in the study region. From 2009–2014, children in the study region increasingly had access to safer drinking water sources, which is associated with better health and reduced risk from some etiologies of AFI such as dysentery and typhoid.[38]

Despite the finding that the number of visits from overall AFI reduced over time, we did not observe significant declines in visits for AFI due to malaria in this population, likely because the average monthly visit count associated with malaria decreased only incrementally in the later years of the study period. This finding is consistent with other reports from the region that have documented arrested declines in malaria transmission and rebounding parasitemia. [39, 40] This plateauing occurred despite several malaria control efforts being implemented in the region during that time. For example, mass distributions of ITNs were conducted in 2011–12 and malaria community case management activities were implemented in the study county.[41] Further investigation into the reasons for the stabilization of malaria visits is warranted.

Although the decline in visits for AFI due to malaria was not significant, our subanalysis revealed two opposing trends. Among patients with parasitemia but no clinical diagnosis of another AFI etiology, the rate of decline in visits was faster than almost any other group (16.15% per year), whereas visits from children with both malaria and a non-malarial AFI did not vary over time. The two groups of children were similar in terms of all demographics examined and severity at the time of presentation. The explanation for this result is unclear, especially given the decline in

non-malarial AFI in general, but may represent an increasing willingness of healthcare workers to consider multiple etiologies of AFI.

This study is one of few to simultaneously describe malaria and non-malarial AFI outpatient trends in sub-Saharan Africa and the first to make a direct comparison between the two. Previous studies that incidentally reported levels of non-malarial AFI over time found no change while malaria levels declined or stayed the same.[42, 43] However, data from these studies were only available to 2010 and one of the studies relied on suspected, rather than slide-confirmed, malaria. More recent data points from other parts of Africa are needed to determine whether our findings indicate a broader shift in the relationship between malaria and non-malarial AFI patterns or are specific to this setting.

This study benefited from the large cohort of children followed for multiple years in an area of changing malaria incidence. However, there are some limitations to our approach. We relied primarily on count data from clinic visits and changes in the size of the population or care seeking rates may explain the reduction in AFI. The former is unlikely as data from the HDSS suggest that the number of children aged 2–59 months remained relatively constant over the study period. For the latter, we found similar declines in fevers reported during active household surveillance that also occurs in the PBIDS study (Supplemental Figure 2.), which implies that care seeking rates also stayed constant. Another potential limitation of this analysis is the way in which children were classified as having malaria and other diagnoses. Defining malaria as a positive smear result may overestimate the true burden of disease due to high levels of asymptomatic parasitemia in the region.[40] However, our conclusions about time trends would remain valid if the proportion of asymptomatic parasitemia among febrile children does not vary over the study period. This assumption appears to be valid; data suggest that the proportion of parasitemic children who are symptomatic varies by season but there is no clear pattern across calendar years.[44] Finally, the

classification of causes of AFI may be subject to some reporting bias; it is possible that healthcare workers were more willing to make non-malarial AFI diagnoses among children with parasitemia if there was growing awareness among healthcare workers of the high levels of asymptomatic parasitemia in the region, though there is no evidence to either support or refute this possibility.

These data suggest that overall cases of AFI presenting to outpatient facilities in western Kenya are decreasing in frequency as part of a general trend of improving health. Despite the improvement, the number of malaria visits has plateaued and overall childhood AFI continues to be a substantial source of morbidity. Public health authorities should continue to seek ways to further reduce childhood AFI rather than reallocating resources to other health problems. Two important next steps are to investigate trends in specific non-malarial AFI etiologies to better understand the drivers of non-malarial AFI and to assess optimal treatment for coinfected children. Doing this will offer the opportunity to improve diagnostic and management strategies for febrile children at highest risk of poor outcomes.

2.5 Tables and figures

Table 2.1: Demographics of children who visited LMH for AFI

Demographic	**Clinic visits Jan 2009–Dec 2014 (N=11,447)**
Age—mean (SD)	2.43 (1.30)
Female	*(n=11,437)* 5,568 (48.7%)
Drinking water source	*(n=11,081)*
Unimproved public	4,904 (44.3%)
Improved public	2,246 (20.3%)
Unimproved private	2,073 (18.7%)
Improved private	1,443 (13%)
Other	415 (3.7%)
Cooking fuel	*(n=11,081)*
Firewood	10,801 (97.5%)
Charcoal	249 (2.2%)
Gas cooker	17 (0.2%)
Other	14 (0.1%)
Toilet type	*(n=11,054)*
Improved sanitation	1,072 (9.7%)
Unimproved sanitation	9949 (90%)
Other	33 (0.3%)

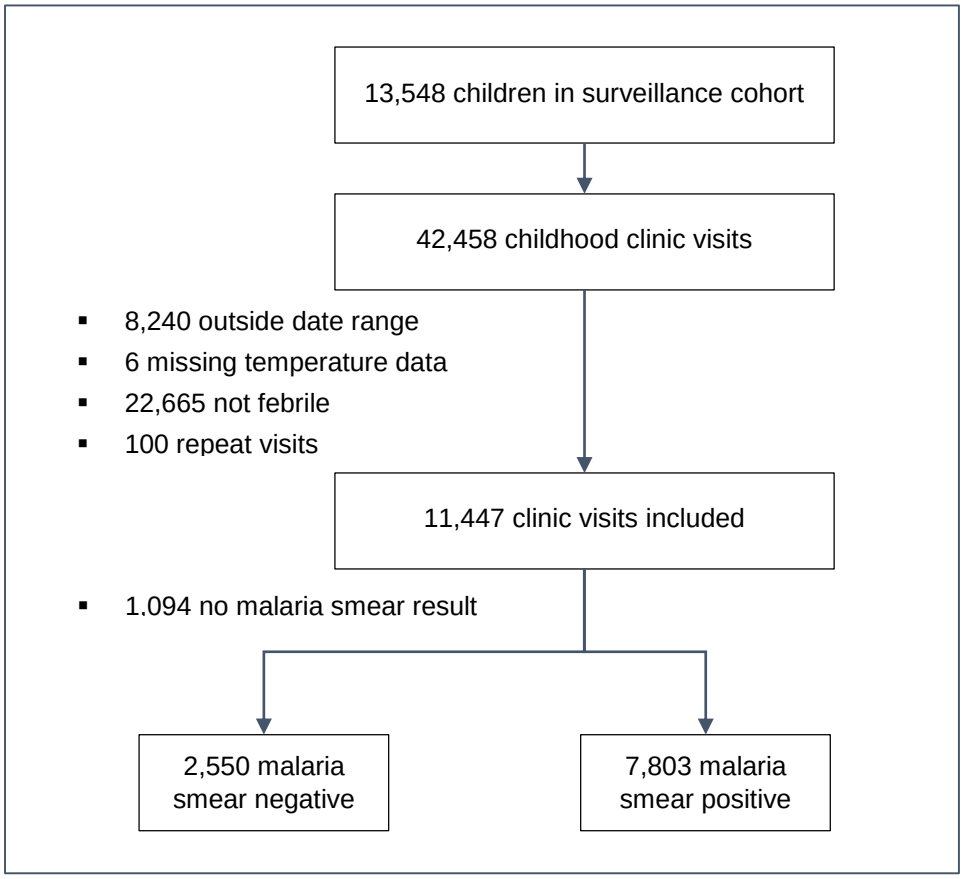


Figure 2.1: Flow chart of application of exclusion criteria to patients at LMH

Table 2.2: Clinical diagnoses among AFI patients at LMH (N=11,447)

Clinical diagnosis	All AFI visits (N=11,447)	Malaria smear positive (N=7,803)	Malaria smear positive + clinical diagnosis of another AFI etiology (N=2,810)
Fever of unknown origin	694 (6.1%)	1 (0%)	1 (0%)
Malaria	8,714 (76.1%)	7,754 (99.4%)	2,789 (99.3%)
Meningitis	9 (0.1%)	6 (0.1%)	6 (0.2%)
Pneumonia	699 (6.1%)	245 (3.1%)	245 (8.7%)
URIT	3,771 (32.9%)	2,571 (32.9%)	2,571 (91.5%)
UTI	22 (0.2%)	12 (0.2%)	12 (0.4%)
Viral syndrome	90 (0.8%)	6 (0.1%)	6 (0.2%)
Other diagnosis	2,414 (21.1%)	1,303 (16.7%)	366 (13%)

Table 2.3: Demographics of children who visited LMH for AFI (N=11,447)

Demographic	Non-malaria AFI (N=2,550)	Malaria (N=7,803)	Missing malaria smear result (N=1,094)
Age—mean (SD)	1.99 (1.30)	2.55 (1.27)	2.59 (1.29)
Female	1,250 (49.1%)*	3,787 (48.6%)*	531 (48.6%)*
IMCI danger sign	326 (12.8%)	1,124 (14.4%)	183 (16.7%)
Coinfected**	N/A	2,810 (36.0%)	N/A

* There were 3, 5, and 2 missing, respectively.
** Coinfected was defined as having a positive malaria smear and clinical diagnosis of a non-malarial cause of AFI.

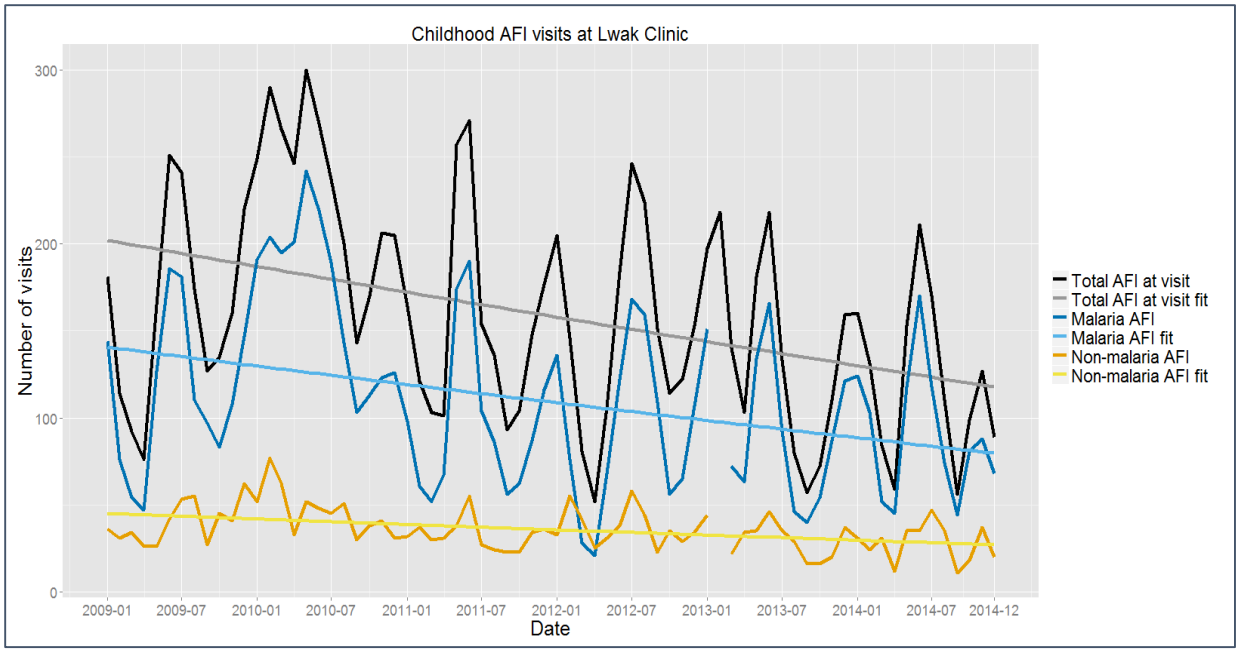


Figure 2.2: Time trends of overall AFI visits to LMH (N=11,447), malaria AFI visits (N=7,803), and non-malarial AFI visits (N=2,550)

Table 2.4: Monthly and annual percentage change in AFI cases seen at LMH (N=11,447)

Outcome	Adj. % decline in cases/mth (95% CI)*		Adj. % decline in cases/yr (95% CI)*		P-value
Overall AFI (N=11,447)†	0.97%	(0.35–1.58%)	11.06%	(4.10–17.43%)	0.002
Non-malarial AFI (N=2,550)	0.83%	(0.36–1.29%)	9.47%	(4.20–14.44%)	<0.001
Malaria (N=7,803)	0.74%	(-0.42–1.89%)	8.55%	(-5.16–20.47%)	0.210

* Adjusted for one-month lag cumulative rainfall and mean age of visitors
† Includes 1,094 children with no recorded malaria test

Table 2.5: Monthly and annual percentage change in AFI cases with IMCI danger signs seen at LMH (N=1,633)

Outcome	Adj. % decline in cases/mth (95% CI)*	Adj. % decline in cases/yr (95% CI)*	P-value
Overall AFI (N=1,633) †	1.31% (0.36–2.26%)	14.69% (4.27–23.98%)	0.007
Non-malarial AFI (N=326)	1.43% (0.64–2.22%)	15.90% (7.37–23.65%)	<0.001
Malaria (N=1,124)	1.49% (0.57–2.40%)	16.50% (6.67–25.30%)	0.001

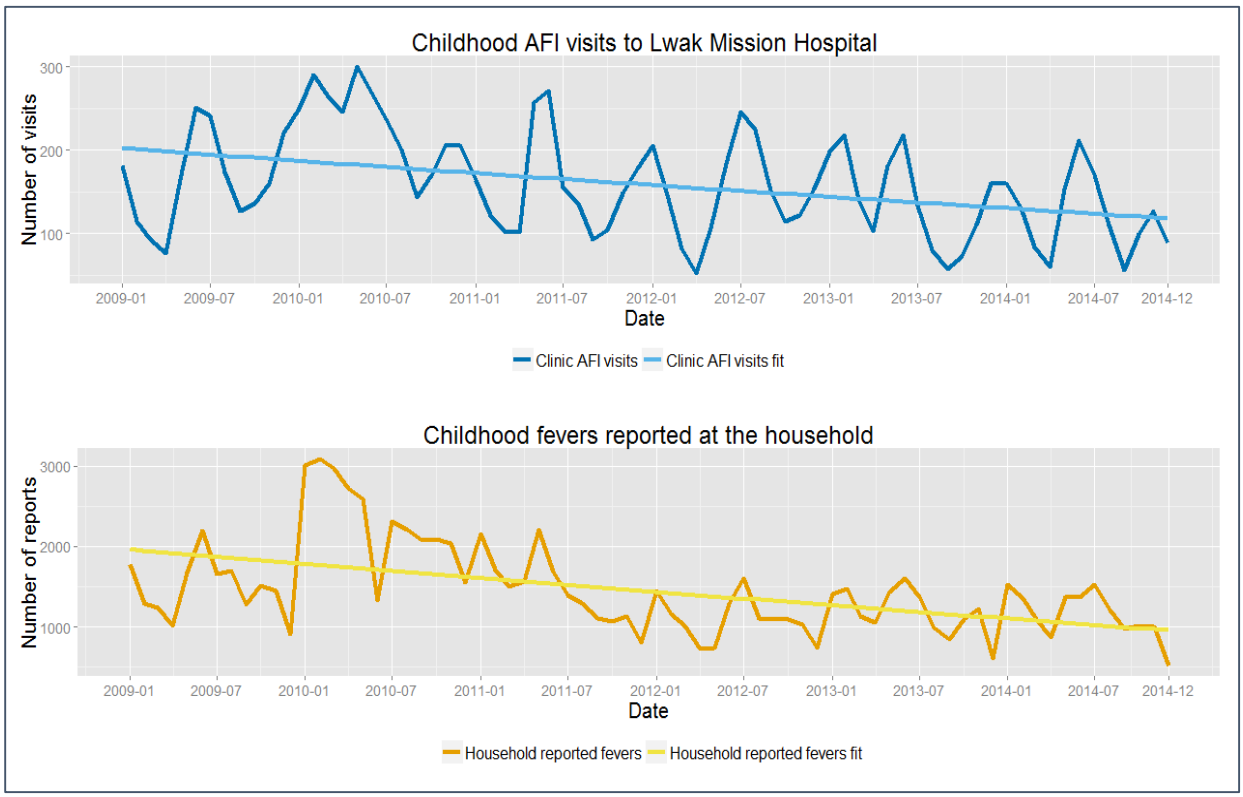
* Adjusted for one-month lag cumulative rainfall and mean age of visitors
† Includes 183 children with no recorded malaria test

Table 2.6: Monthly and annual percentage change in types of malaria cases among febrile children seen at LMH (N=7,803)

Outcome	Adj. % decline in cases/mth (95% CI)*	Adj. % decline in cases/yr (95% CI)*	P-value
Malaria only (no coinfection) (N=4,993)	1.45% (0.42–2.49%)	16.15% (4.89–26.09%)	0.006
Malaria + another AFI diagnosis (N=2,810)	-0.32% (-1.26–0.62%)	-3.86% (-16.23–7.19%)	0.509

* Adjusted for one-month lag cumulative rainfall and mean age of visitors

2.6 Supplemental figures and tables



Supplemental Figure 2.1: Comparison of AFI visits to LMH and reported household fevers over time

Supplemental Table 2.1: Percentage change in AFI cases per month and year by age group

Outcome	Group	Adj. % decline in cases/mth (95% CI)*	Adj. % decline in cases/yr (95% CI)*	P-value
Total AFI	2–23 months (N=4,864)	0.98% (0.22–1.73%)	11.12% (2.55–18.93%)	0.012
	24–59 months (N=6,583)	0.64% (-0.10–1.37%)	7.40% (-1.20–15.27%)	0.090
Non-malarial AFI	2–23 months (N=1,490)	0.97% (0.51–1.42%)	11.01% (5.95–15.80%)	<0.0001
	24–59 months (N=1,060)	0.52% (-0.08–1.11%)	6.05% (-0.92–12.54%)	0.087
Malaria	2–23 months (N=2,977)	0.92% (-0.06–1.89%)	10.50% (-0.72–20.47%)	0.066
	24–59 months (N=4,826)	0.74% (-0.31–1.77%)	8.52% (-3.73–19.32%)	0.165

* Adjusted for one-month lag cumulative rainfall and mean age of visitors

Chapter 3: No Evidence of Incident Dengue Virus Infections in Western Kenya, 2011–2013

3.1 Introduction

Over the past several decades, the incidence of dengue virus infections has increased rapidly to an estimated 390 million each year.[16] Originally thought to occur mainly in Southeast Asia and South America, dengue virus is now present in at least 128 countries, including those in Africa and the eastern Mediterranean, placing over half the world's population at risk of acquiring dengue infection.[45]

Dengue is caused by any of four types of a single-stranded RNA virus, which is primarily transmitted by the mosquitoes *Aedes aegypti* and *Aedes albopictus*. Dengue virus infections are usually self-limited and asymptomatic (over 80% according to a recent estimate),[16] but can cause symptoms ranging from mild illness (headaches and low fever) to high fevers, myalgia, and encephalitis. Recovery from dengue virus infection confers long-lasting immunity against the infecting dengue virus type.[46] However, subsequent infection with a different dengue virus type places a person at increased risk of severe dengue, which is associated with plasma leakage, hemorrhagic symptoms, and death.[47-49] There is currently no pharmacologic treatment for dengue, but skilled management of a patient with severe dengue can reduce mortality from as high as 20% to 1%.[50] Vaccine development is complicated by the need to confer protection against all four dengue virus types simultaneously so as to avoid increasing the risk of severe dengue, and vaccines are only now being tested in clinical trials.[51-53] Vector control efforts have shown potential but there are few high quality studies and only very weak evidence that they reduce dengue cases.[54] Although dengue is a major cause of acute febrile illness (AFI) worldwide, healthcare workers in settings with no history of dengue virus circulation are unlikely to consider dengue as a diagnosis, which may hinder appropriate care of febrile patients. Given

the spread of dengue virus, determining whether the virus is present in regions with high incidence of fever may lead to improved treatment outcomes.

Dengue is likely underreported in Africa due to limited availability of diagnostics and the routine presumption that fever is due to malaria.[55, 56] However, recent outbreaks in Angola, Kenya, Gabon, and Somalia, combined with serological studies that indicate ongoing endemic transmission, suggest that dengue is widespread on the continent.[18-20, 57] Entomological data and models support these findings by demonstrating the presence of *Ae. aegypti* in these settings.[58] As dengue incidence has increased in Africa over the past decade, malaria incidence has been decreasing and widespread deployment of the *Haemophilus influenzae* type b and pneumococcal vaccines promises to reduce the burden of fever caused by pneumonia.[10, 59] Healthcare workers and planners must adapt to the changing distribution of AFI etiologies. However, a lack of systematic, ongoing surveillance limits knowledge about the spatial reach of dengue and hinders disease control planning. We sought to determine the extent to which dengue virus contributes to AFI by testing for the virus among febrile patients in a western Kenya outpatient setting.

3.2 Methods

3.2.1 Study setting

This research was conducted within the Centers for Disease Control and Prevention (CDC)/Kenya Medical Research Institute (KEMRI) population-based disease surveillance (PBIDS) program. PBIDS is located in Asembo, a rural site in Nyanza Province in western Kenya, and has been operating since late 2005. The area has holoendemic malaria transmission and a high prevalence of HIV (17% in adults aged ≥18 years).[1, 31, 32]

Participants in PBIDS are eligible for free treatment at the Lwak Mission Hospital outpatient clinic if they have one of the syndromes under surveillance, including acute respiratory disease, fever, diarrhea, and jaundice. All clinic patients with a history of fever or a presenting temperature of ≥38.0°C receive a malaria blood smear and a subset undergo a series of other diagnostic tests depending on other presenting symptoms, including blood culture, urine culture, naso- and oropharyngeal (NP/OP) swabs, and stool cultures. Sample collection and testing methods have been previously described.[60]

All participants provide written informed consent to participate. Parents or guardians provided informed written consent on behalf of minors. The protocol and consent forms were reviewed and approved by the Ethical Review Boards of the Kenya Medical Research Institute (KEMRI) and the Institutional Review Board of the U.S. Centers for Disease Control and Prevention (CDC).

3.2.2 Serum sample selection

In order to increase the likelihood of detecting acute dengue infections among febrile patients in Asembo, we applied the following inclusion criteria: patients of all ages with fever (≥38.0°C) at time of visit, a clinic visit during or shortly after a rainy season (September–December 2011 and March–July 2013), and a serum sample collected at the time of visit. Serum samples were collected from the first five patients aged five years or older and the first five patients aged less than five years who visits LMH with fever. We included patients with a positive malaria smear, a clinical diagnosis of a condition with symptoms that often overlap with dengue symptoms (measles, oral candidiasis, otitis media, rash, rubella, tonsillitis, upper respiratory tract infection, and viral syndrome), or a condition that is not likely to be the cause of fever (anemia, conjunctivitis, diarrhea, intestinal worms, scabies, and wheezing). We excluded patients with a clinical diagnosis of a condition for which symptoms do not largely overlap with dengue symptoms (amoebiasis, burn, dysentery, mumps, pneumonia, pulmonary tuberculosis, rotavirus, sexually

transmitted infections, and varicella), a positive result from lab diagnosis of other samples (bacteremia, urine culture, or NP/OP for influenza), and patients with serum that was collected more than five days after date of fever onset (the typical viremic period for dengue).

3.2.3 Dengue virus testing

Total RNA was extracted from 100 µl of each serum sample using the MagNA Pure 96 System with the DNA and Viral Nucleic Acid Small Volume Kit according to the manufacturer's instructions (Roche) and stored at -80°C for later processing. Dengue viral RNA was quantitated by real time RT-PCR using the AgPath-ID One-Step RT-PCR Kit (Life Technologies) and the CDC dengue virus-1–4 Real-Time RT-PCR Assay.[61] Real time RT-PCR reaction mixtures were formulated according to the manufacturer's instructions with 400 nM each of the forward and reverse primer and 120 nM of the TaqMan probe. Samples were run on an Applied Biosystems 7500 Fast Real-Time PCR System (Life Technologies) using the following reaction conditions: 45°C for 10 min, 95°C for 10 min, then 45 cycles of alternating between 95°C for 15 sec and 55°C for 1 min, with TaqMan probe fluorescence measured each cycle during the 55°C step. Data were analyzed using the Applied Biosystems 7500 SDS Software. RNA quality was validated using a human RNase P control, which ruled out inhibition of the PCR reaction. Purified dengue virus genomic RNA was used as a positive control.

3.2.4 IgM anti-dengue virus testing

Sera from the study subjects were tested using a sandwich type enzyme immunoassay for detection of IgM antibody to dengue virus. This was done according to the manufacturer's instructions using the InBios dengue virus Detect™ IgM Capture ELISA kit (InBios International, Inc Seattle, WA USA). The serum samples were incubated in micro-titer plates pre-coated by the manufacturer with anti-human IgM antibodies. After subsequent incubation with serum specimens and washing, the wells were treated with a specific conjugate and thereafter with

substrate. A stop solution was then added and the absorbance measurements read using the ELx800 absorbance microplate reader to determine the optical density.

3.2.5 Definition of dengue

We defined dengue infection as either a positive PCR result or a positive IgM anti-dengue virus.

3.3 Results

Clinic visit data were available from January 1, 2006 to August 31, 2013 and encompassed 127,827 unique visit records. The median patient age among all visits was 11.2 years and 58.3% were female (Table 3.1). Almost three-quarters (73.4%) of patients reported recent fever and 19.1% were febrile at the time of visit. The most common clinical diagnoses among all patients were malaria (38.3%) and upper respiratory tract infection (36.4%). Of those tested, 41.7% had a positive malaria smear result.

During the sampling period, there were 1,935 visits to the clinic where the patient had a current fever. A total of 693 febrile patients met the inclusion criteria, of whom 615 (88.7%) had samples available for testing (Figure 1). Patients included in the analysis were younger (median 4.8 years) and a smaller proportion were female (53.2%) than patients at all clinic visits (Table 3.1). The most common clinical diagnosis was malaria (77.2%) and 442 (77.1%) patients had a positive malaria smear result (Table 3.1).

There were no positive results for dengue using either PCR or IgM anti-dengue virus testing.

3.4 Discussion

In this study, no dengue virus infections were detected using molecular diagnostic testing, despite samples being collected during acute febrile episodes when patients would be expected to be viremic. In addition, there was no evidence of current or recent dengue virus infections when

using antibody-based testing. Dengue does not appear to be a cause of acute febrile illness among this rural population in western Kenya during the time period sampled.

The question of the actual etiology of the patients' fevers remains unanswered. It is possible that the malaria smear results and clinical diagnoses represent the true cause of disease, though relying on these methods alone is likely to result in significant misdiagnosis.[12, 62] The non-specific nature of AFI and the variety of etiologies found in similar settings highlight the need for more advanced molecular diagnostics available at the point of care that can direct clinicians towards an etiologic agent and appropriate treatment.[6]

There are several possible explanations for the absence of dengue reported here, the most straightforward being a true absence of dengue virus in western Kenya. This contrasts with several previous studies from adjacent or nearby districts that documented low levels of seroprevalence and seroincidence.[63-65] However, these studies all relied on IgG dengue virus antibody ELISA tests, which are known to have high crossreactivity with other flaviviruses and the yellow fever vaccine, and likely overestimate the amount of prior dengue virus infections.[66] Direct comparison between these papers and our findings is therefore challenging.

If the incidence of apparent dengue cases truly is low, rather than absent, we may have had an insufficient sample size to detect them. Assuming that the care-seeking rate for AFI caused by dengue was the same as previously reported for total AFI in this region (13.5%),[67] we would have needed an apparent dengue incidence rate of 226 per 100,000 person-years in order to have detected one case of symptomatic dengue virus infection. This incidence rate is similar to regions with high dengue incidence, such as Singapore and Brazil, and much higher than would be expected in the study setting.[68, 69] Despite designing inclusion criteria to enhance the probability of selecting patients with dengue, we may have missed isolated cases.

Another possible explanation for the results is the rural nature of the study site. The population density in Asembo is relatively low (325 persons/km^2) and the primary economic activity is agriculture.[1] The main dengue virus vectors, *Ae. aegypti* and *Ae. albopictus*, are predominantly urban and periurban in nature and therefore may be limited to nearby towns and cities. Though we were unable to identify any published entomologic data from the study region, *Ae. aegypti* has been found in nearby Kisumu.[70] Future studies should focus on febrile patients in these more urban settings.

This study was one of the first in Africa to use PCR to test for dengue virus rather than antibody-based methods alone. Of two previous instances where a combined testing regimen was used, one found moderate evidence of circulating dengue virus in Abidjan, Côte d'Ivoire, and the other took place during an outbreak on the Kenyan coast.[17, 71] Combining the two detection approaches allows for greater certainty that dengue virus is the etiologic agent of fever.

Besides what was probably too small a sample size to make a robust estimate of dengue incidence in this population, there were other limitations to this study. Our selection criteria may have systematically eliminated subjects with dengue virus infections. The most likely reason was restricting samples to those collected during the rainy season. While dengue incidence tends to increase with increasing rainfall, the effect typically lags by one to two months, or even longer in some models.[68, 72, 73] Although we included cases from the month following the traditional rainy periods, the lag between rainfall and dengue incidence has not been established in East Africa and a one-month lag period may have been too short.

In addition, most dengue virus infections are asymptomatic, though the proportion varies due to several factors including incidence in recent years.[74] Infected patients without fever are unlikely

to have presented to clinic and therefore will have remained undiagnosed. The proportion of dengue virus infections that are clinically silent is unclear in an area of emerging infections but may be higher than endemic areas, where secondary infections are more common.[74] The best estimate of the ratio of asymptomatic to symptomatic dengue virus infections in Kenya comes from a seroincidence survey conducted in Mombasa during the 2013 outbreak. There, investigators found that 44% of people with current or recent dengue virus infections reported having had recent fever.[17] The high prevalence of malaria in coastal Kenya makes it likely that some of the recent fevers would not have been caused by dengue virus,[75] but these data still suggest a substantial proportion of dengue virus infections in Asembo would present at the clinic with fever.

Though dengue is increasingly being recognized as a problem in Sub-Saharan Africa, our finding of no dengue in western Kenya suggests that dengue virus may not be well established in this area. Combined use of PCR and antibody detection methods can provide a more accurate picture of disease incidence than serology alone. This approach, combined with greater use of rapid diagnostic tests at the point of care, will be needed as part of a widespread surveillance system to accurately gauge the size and geographic spread of the dengue virus and dengue infections.

3.5 Figures and tables

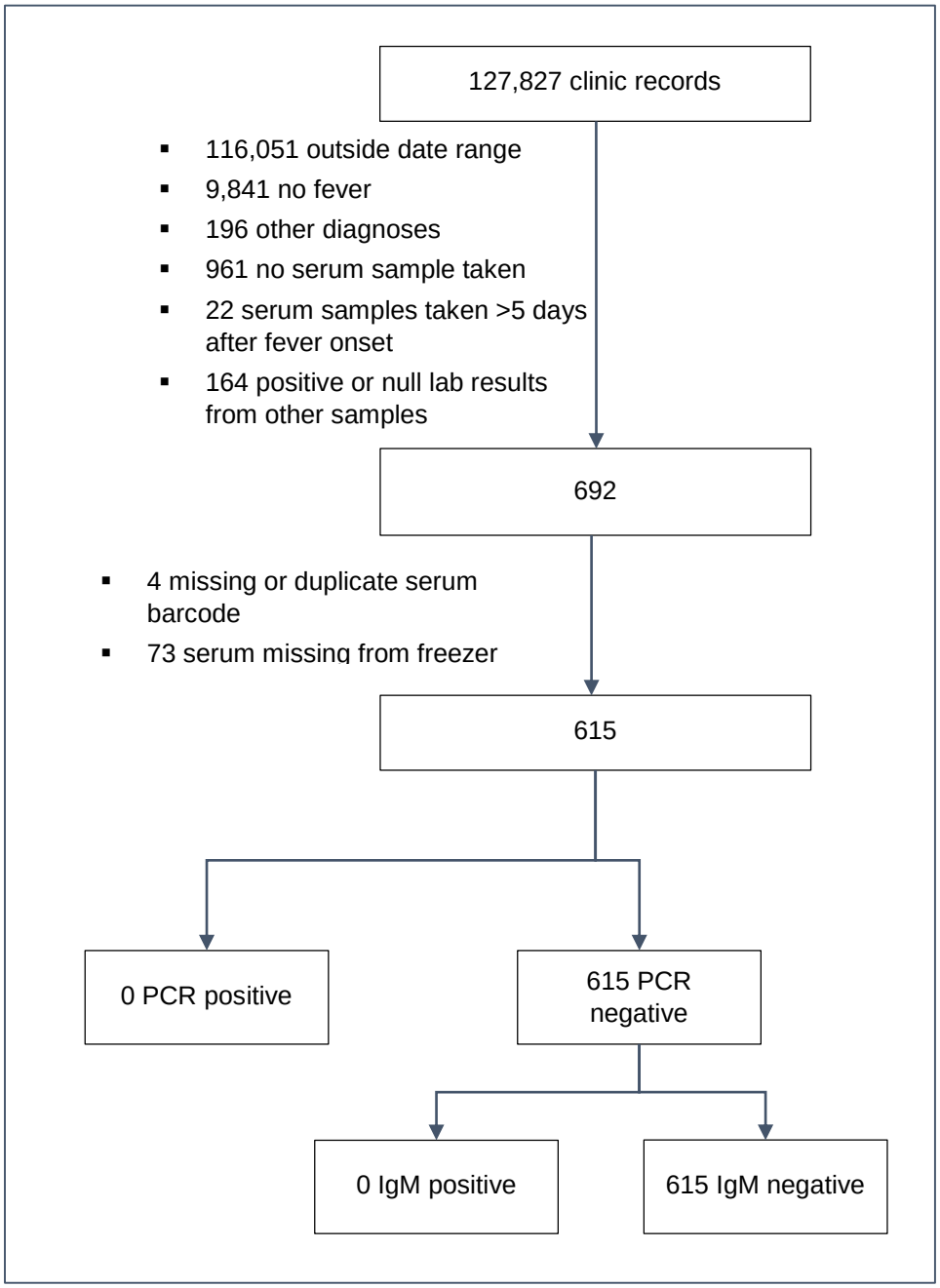


Figure 3.1: Selection of febrile patients for dengue testing

Table 3.1: Demographics of clinic visits to Lwak Mission Hospital

Demographic	All clinic visits (N=127,827)	Included patients (N=615)
Age—median (IQR)	11.2 years (22.8 years)	4.8 years (6.6 years)
Female	67,818 (58.3%) *(n = 116,340)*	327 (53.2%)
Febrile		
Reported	93,625 (73.4 %)	613 (99.7%)
At time of visit	24,313 (19.1%)	615 (100%)
Common diagnoses (>5% visits)		
Diarrhea	7,786 (6.1%)	29 (4.7%)
Malaria	48,943 (38.3%)	475 (77.2%)
Pharyngitis	6,448 (5.0%)	19 (3.1%)
Pneumonia	8,236 (6.4%)	0 (0%)
URTI	46,516 (36.4%)	4 (0.7%)
Malaria smear positive	42,737 (41.7%) *(n = 102,388)*	442 (77.1%) *(n = 573)*

Chapter 4: Changes in malaria season appear to affect IMCI guideline-directed antibiotic prescribing patterns for acute febrile illness

4.1 Introduction

Acute febrile illness (AFI) is one of the most common syndromes among children presenting to a healthcare facility in many resource limited settings.[1, 3] In much of sub-Saharan Africa, malaria has historically been the primary suspected etiology of AFI. As a result, guidelines have previously recommended presumptive malaria treatment in all children with AFI.[76] However, the incidence of malaria has declined in many settings over the past decade, with recent studies reporting that fewer than 10% of childhood fevers are now due to malaria.[6, 77] Other causes, including viral and bacterial infections, are now responsible for the majority of acute fevers in much of Africa.[6, 7, 78]

Limited laboratory capacity and the lack of available point-of-care rapid diagnostic tests for infections other than malaria often make it difficult to determine the true cause of AFI in resource-limited areas.[62, 79, 80] As a result, clinical guidelines are frequently based on syndromic management and empiric treatment.[7] The Integrated Management of Childhood Illness (IMCI) guidelines were developed by the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) to improve case management of sick children in outpatient settings and reduce childhood mortality.[81, 82] IMCI guidelines address the major syndromes associated with high mortality, including respiratory disease, diarrhea, AFI, and malnutrition. Multi-country evaluations of the IMCI guidelines have demonstrated improved assessment practices and treatment choices, but clear evidence of mortality benefit has only been demonstrated in some regions.[83-87] Given the declining incidence of malaria in many regions, the IMCI guidelines were updated in 2014 to recommend that febrile children in malaria-endemic regions be tested for malaria prior to treatment.[88] IMCI guidelines also now instruct health care workers (HCWs)

in malaria-endemic regions to consider alternative causes of fever and to treat potential bacterial etiologies with antibiotics.

Data suggest that HCW adherence to IMCI guidelines when making treatment recommendations remains suboptimal in many settings.[89, 90] Even among HCW who have been trained in the use of IMCI, treatment decisions appear strongly related to their individual perception of risk.[91] HCWs often continue to treat for malaria even in the presence of negative rapid diagnostic test (RDT) results, particularly during seasons of high malaria incidence.[92-95] HCWs may also be more likely to prescribe antibiotics when RDT testing for malaria is available, particularly among patients with negative malaria tests, although the appropriateness of these prescriptions has seldom been assessed.[92, 95-97] Finally, seasonal patterns of circulating viral infections have also been shown to be associated with increased use of antibiotics in many settings.[21-25, 98]

As malaria incidence declines in endemic regions, the perception of risk from malaria may be changing among HCWs, which could influence antibiotic prescribing practices. Understanding the patterns and drivers of antibiotic prescribing, including any association with seasonal changes in malaria incidence, may allow for targeted interventions to reduce the inappropriate prescribing of antibiotics and related consequences such as adverse events and the development of antibiotic resistance.[21, 24, 99] We sought to examine the relationship between seasonal patterns of malaria and HCWs' adherence to IMCI guidelines on antibiotic prescriptions in a large cohort of children in western Kenya.

4.2 Methods

4.2.1 Study setting

Data were obtained from the International Emerging Infections Program's (IEIP) population-based infectious disease surveillance (PBIDS), which is jointly operated by the Kenya Medical

Research Institute (KEMRI) and the Centers for Disease Control and Prevention (CDC). PBIDS has been operating in Asembo, western Kenya since 2006 and has been previously described in detail.[1] Study participants residing within 5 km of Lwak Mission Hospital (LMH) receive free care and treatment at LMH if they present with one of the syndromes under surveillance: AFI, respiratory disease, diarrhea, and jaundice. Most care at the LMH outpatient clinic is provided by clinical officers (equivalent to physician's assistants). Data on vital signs, history of and current symptoms, clinical diagnoses, and treatments given are collected using a standardized form. An onsite laboratory provides malaria smear results at the time of a patient's visit. Demographic data for the study come from a larger Health and Demographic Surveillance System (HDSS) that operates in the region.[31]

Parents or guardians provided informed written consent on behalf of minors. The protocol and consent forms were reviewed and approved by the Ethical Review Boards of the Kenya Medical Research Institute (KEMRI) and the Institutional Review Board of the U.S. Centers for Disease Control and Prevention (CDC).

4.2.2 Study population

We included children (aged 2–59 months) who presented to LMH with AFI (temperature of ≥38.0°C) between January 1, 2009 and December 31, 2014. We excluded visits where no symptom data were collected or where data on antibiotic prescriptions were missing. We also excluded repeat visits for the same AFI episode (one or more additional clinic visits by the same child within 14 days of an initial visit and the same malaria status).

4.2.3 Study measures

We classified each AFI visit by whether antibiotics were indicated for treatment or not under current (2014) WHO IMCI guidelines.[33] Though part of the study period predates the most

recent revision to the IMCI guidelines, there is substantial overlap between the two versions in the symptoms and diagnoses for an antibiotic indication (<1% of visits with an indication for antibiotics in our study may not have the same indication under the previous guidelines). Classifications were made using a two-stage approach. First, we considered whether antibiotic use was indicated for each presenting child's symptoms using current (2014) WHO IMCI guidelines. Second, if the symptoms alone did not merit antibiotic use under IMCI guidelines, we considered whether the final clinical diagnoses recorded by the HCW at that visit were for conditions in which IMCI guidelines suggest that antibiotics are indicated. Specifically, we assessed whether a diagnosis of pneumonia, otitis media, or another infection likely to be addressed by antibiotics. We based the conditions likely to benefit from antibiotics on lists generated in a similar study that divided diagnoses into those that should receive antibiotics and those that should not.[100] Diagnoses not included on this previously developed list were evaluated independently by two clinicians with training in pediatric infectious diseases (J.L.W. and M.J.T.), who determined if antibiotics were likely to be indicated for each diagnosis. A full list of diagnoses in each category can be found in Supplemental Table 4.1 and Supplemental Table 4.2. Children were grouped into one of four categories: antibiotic indicated and prescribed, antibiotic not indicated and not prescribed, antibiotic indicated but not prescribed, and antibiotic not indicated but prescribed.

The primary aim of this analysis was to determine whether HCW adherence to IMCI guidelines for antibiotic use varied by malaria season. There is no established definition of a malaria season, although several approaches have been proposed.[101, 102] Because of a secular trend of declining malaria and variable rainfall over the study period, it was not possible to define a malaria season by climate, an absolute threshold of malaria cases, or a given set of months. Instead, we defined a malaria season as any month where the number of malaria cases (as determined by smear microscopy) among febrile (temperature of ≥38.0°C) children 2–59 months exceeded the average monthly number of malaria cases over that month plus the previous five months (a right-aligned

six-month moving average). For February 2013, a shortage of malaria testing supplies meant that 91% of febrile children did not have a malaria smear result so it was not possible to categorize this month into a season. Therefore, visits in this month were excluded from analyses of the effect of season.

4.2.4 Statistical methods

We used using two-sided t-tests and chi-squared tests to compare demographics (age, gender, and socioeconomic status) between two sets of children: 1) among children for whom an antibiotic was indicated, those who were and those who were not prescribed antibiotics, and 2) among children for whom an antibiotic was not indicated, those who were and those who were not prescribed antibiotics.

We developed logistic regression models to examine the relationship between malaria season and adherence to IMCI guidelines on antibiotics, stratifying by whether or not antibiotics were indicated by IMCI guidelines. We were interested in the influence of malaria seasonality on antibiotic prescribing patterns, rather than the influence a child's specific malaria status might have. Therefore, we adjusted for malaria smear results (positive or negative), which were available to HCWs at the time of the visit. We excluded visits with missing malaria smear results. To account for correlation among children who visited the clinic multiple times, we calculated standard errors using Newey and West heteroskedasticity and autocorrelation consistent covariance matrix (sandwich) estimators.[35]

RStudio v0.98.1103 (RStudio, Boston, MA) over R V3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

4.3 Results

4.3.1 Study population

Between January 1, 2009 and December 31, 2014, 13,548 children aged 2–59 months were enrolled in PBIDS. Of these, 4,138 children made 11,375 visits to LMH that met the inclusion criteria of presenting to LMH with AFI and complete symptom and prescription records (Figure 4.1 and Table 4.1). The median age of children at included visits was 2.31 years (IQR: 1.32–3.49) and 48.7% of the visits were by females. There were no significant differences between included children and the general child population in terms of age, gender, or socioeconomic status. All visits had some symptom data recorded. Assessment of IMCI danger signs was generally complete, except for "a history of convulsions", where 24.9% of visits had no recorded data (Supplemental Table 4.3). There were 1,620 visits (14.2% of the total) in which the child had severe illness, defined as the presence of at least one IMCI danger sign.

4.3.2 Overall adherence to IMCI guidelines for antibiotics

Overall, 7,853 (69.0%) of childhood febrile visits adhered to IMCI guidelines for antibiotics.

4.3.3 Visits with an indication for antibiotics under IMCI guidelines

There were 2,544 visits (22.4% of the total) where the child's symptoms or diagnosis suggested an indication for antibiotic treatment, based on the 2014 IMCI guidelines. The most common syndromes for which an antibiotic was indicated were pneumonia (1,644 (64.6%)) and very severe febrile disease (1,629 (64.0%)) (Table 4.2). A majority (1,636 (64.3%)) of the indications for antibiotics were derived from the child's presenting symptoms rather than a clinical diagnosis (Table 4.2). Of the visits in which an antibiotic was indicated according to IMCI guidelines, antibiotics were not prescribed to the child approximately half of the time (1,242 (48.8%)) (Figure 4.1). Among visits where an antibiotic was indicated, children who were prescribed an antibiotic were younger than those who were not prescribed an antibiotic (mean 2.08 vs. 2.47 years,

P<0.001), but were not different in terms of gender or socioeconomic status (Table 4.1). Antibiotics were more likely to be indicated but not prescribed if the indication for an antibiotic was derived from symptoms assessed during the visit rather than from clinical diagnoses (60.1% vs. 7.0% of visits, respectively) (Table 4.2).

4.3.4 Visits with no indication for antibiotics under IMCI guidelines

Of the 8,831 visits at which there was no clear indication for antibiotic treatment according to IMCI guidelines, 2,280 (25.8%) resulted in an antibiotic prescription (Figure 4.1). Among visits where an antibiotic was not indicated, children who were prescribed an antibiotic were younger than those who were not prescribed an antibiotic (mean 2.23 vs. 2.56 years, P<0.001), but were not substantially different in gender distribution or socioeconomic status (Table 4.1). The most common diagnoses where an antibiotic was given but not indicated were malaria (819 (35.9%)), upper respiratory tract infections (704 (30.9%)), and pyrexia of unknown origin (595 (26.1%)) (Table 4.3).

4.3.5 Seasonality of AFI visits and adherence to IMCI guidelines

Among the 11,375 included visits, 6,046 (53.2%) occurred during a month of higher than average malaria activity (malaria season) and 5,115 (45.0%) occurred during a month of lower than average malaria activity (non-malaria season) (Figure 4.2). There were 214 (1.8%) visits during a month where there was not enough malaria testing to determine seasonality and these were excluded from our analyses. Of the 2,544 visits where an antibiotic was indicated, 1,390 (54.6%) occurred during a malaria season, compared with 4,656 (52.7%) of the visits where an antibiotic was not indicated (P=0.035) (Table 4.4).

Among visits where an antibiotic was indicated, presenting to clinic during a malaria season was associated with non-adherence to IMCI guidelines for antibiotic prescribing. After adjusting for

the child's malaria smear result, which can influence HCW decision making about prescribing antibiotics, a visit during malaria season at which antibiotic therapy was indicated by IMCI guidelines was 1.81 times (95% CI: 1.46–2.25, P<0.001) as likely to result in no antibiotic prescription as a similar visit in a non-malaria season (Table 4.5).

Among visits where an antibiotic was not indicated, presenting to clinic during non-malaria season was associated with non-adherence to IMCI guidelines for antibiotic prescribing. After adjustment, a visit during non-malaria season at which antibiotic therapy was not indicated by IMCI guidelines was 1.22 times (95% CI: 1.06–1.40, P<0.01) as likely to result in an antibiotic prescription as a visit during a malaria season (Table 4.5).

4.4 Discussion

In a large cohort of children in western Kenya, antibiotic prescriptions were not always made in accordance with IMCI guidelines. Children were not prescribed antibiotics at half (49%) of visits where their symptoms or clinical diagnosis indicated that an antibiotic prescription was warranted. Conversely, antibiotics were prescribed at 26% of visits where there was no clear indication for their use. The level of malaria seen at the clinic that month appeared to influence adherence to IMCI guidelines for antibiotic prescription. During a malaria season, children with an indication for antibiotics were nearly twice as likely to not receive an antibiotic prescription as similar children visiting during a non-malaria season. In contrast, children with no apparent indication for an antibiotic prescription were 22% more likely to receive one during a non-malaria season than during a malaria season.

As reported in other studies, children prescribed antibiotics at LMH were younger than those not receiving antibiotics, regardless of whether the antibiotic was appropriate.[103, 104] The reasons for this age gradient are unclear but could be driven by a combination of difficulty in clinical

assessment of younger children and a greater willingness to treat younger children empirically to avoid complications from their fever.

Nearly half of visits with an indication for antibiotics did not result in a prescription, which implies that either some febrile children are being undertreated or the IMCI guidelines err towards overtreatment. Similarly, the prescription of antibiotics at over a quarter of visits where there was no apparent need for antibiotics may reflect systematic overuse of antibiotics, which can contribute to increased antibiotic resistance,[99] or that the HCW was using additional data to inform their decision on antibiotic use that was not captured in the clinical record. High levels of non-adherence to antibiotic guidelines have been recorded in several resource-limited settings.[100, 105, 106] This phenomenon is also extremely common in high income countries, where the majority of antibiotic prescribing in children in ambulatory settings is considered unnecessary.[107-109] Our findings differed from a previous study in Uganda, which found a smaller proportion (11%) of febrile patients who presented with an indication for antibiotics did not receive them and a greater proportion (42%) of febrile patients who had no indication for an antibiotic did receive one.[100] Differences in the age of the study population (50% were aged over five years) and in the diagnoses made (all patients in the Uganda study had test-confirmed malaria) likely explain some of the variation between this study and ours.

The seasonal effect observed in adherence to IMCI guidelines for antibiotic use, even after accounting for individual malaria test results, suggests that perceptions of likely AFI etiologies can have a strong influence on clinical decision making. These data are consistent with findings from Burkina Faso where seasonal differences in the proportion of non-malarial diagnoses made among RDT-positive febrile patients were also observed.[98] Although we found a strong association between months of high malaria incidence and adherence to IMCI guidelines, it is unclear how HCWs arrived at a decision on whether or not to prescribe antibiotics. Possible

reasons include a lack of complete training in IMCI, drug shortages at the time of visit, a belief that clinical judgement of each patient was more appropriate than broad guidelines, perceived patient demand for antibiotics, or the presence of a condition or diagnosis that was not accurately captured in the clinic records.[91, 99, 105]

There are several strengths to this research. Our study is the first to examine the relationship between of the seasonality of malaria, a common cause of fever, and appropriateness of antibiotic prescriptions for treating febrile children. The study also benefited from a large sample of children, data collected over several seasons and well collected and managed clinical data. Some limitations are also apparent. We relied on recorded clinical diagnoses and had no means of determining the true etiology of a child's condition or whether a child truly did require antibiotics. However, the majority of visits in which antibiotics were indicated by IMCI guidelines met the criteria through presenting symptoms rather than clinical diagnosis. In addition, our data reflect the reality that IMCI guidelines are designed for use in settings with limited diagnostic capability and appropriateness of antibiotic use is defined, in part, on clinical judgement. We applied the most recent IMCI guidelines to determine whether or not an antibiotic was indicated, even though most included visits took place prior to 2014 when the newer guidelines were released. However, only 116 (4.6%) of the visits with an indication for antibiotics would not have had the same indication using the older guidelines, so this is unlikely to have influenced our results substantially. Though our primary hypothesis was that high levels of malaria influenced clinical decision making, we were not able to assess the HCW reasoning behind decisions on antibiotic prescribing. We also did not consider the type of antibiotic prescribed when assessing appropriateness so it is possible that an ineffective antibiotic was prescribed during a visit deemed to have adhered to IMCI guidelines. Finally, this study was not designed to detect negative health consequences that resulted from not prescribing antibiotics. Our findings suggest an urgent need to determine improved ways of targeting antibiotics among febrile children who present to

healthcare facilities in resource-limited countries, including investigating revisions to IMCI guidelines and use of additional diagnostic tools. Implementing practitioner behavior change for prescribing antibiotics has been difficult in most high-income countries, where risks of complications of AFI are far lower, and may be far harder in lower-income settings.[110, 111]

These data suggest that antibiotic prescribing for children with AFI in western Kenya is not in line with current IMCI guidelines. In addition, it appears as though the level of circulating malaria can influence adherence to IMCI guidelines for antibiotic prescriptions. However, additional research is required to identify optimal revisions to IMCI training programs and other interventions that can improve appropriate use of antibiotics in these settings. Such innovations are necessary for improving clinical outcomes and reducing antibiotic resistance.

4.5 Figures and tables

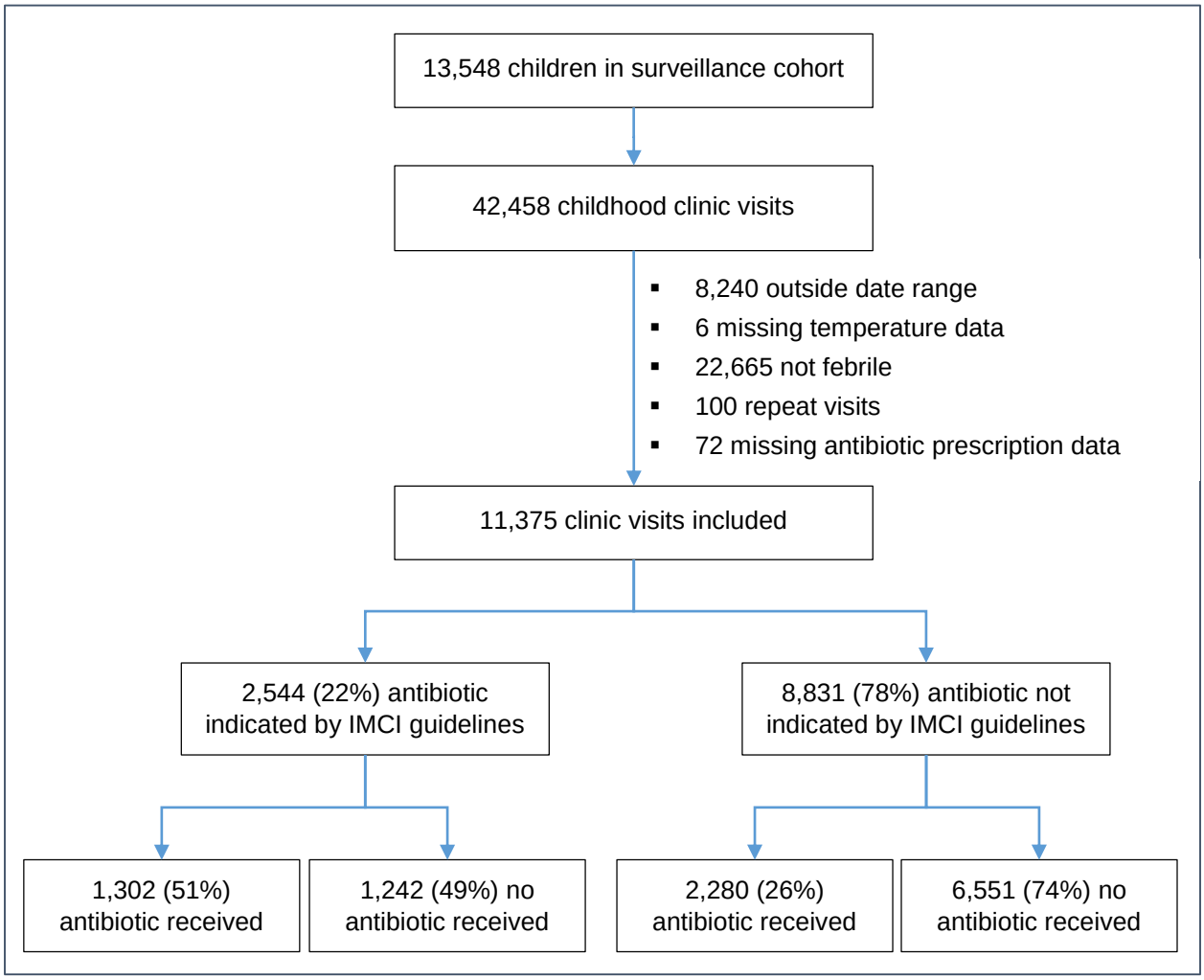


Figure 4.1: Study participants at LMH and antibiotic outcomes

Table 4.1: Demographics of children who visited LMH for AFI

Demographic	Total (N=11,375)	Indicated for antibiotic (N=2,544)			Not indicated for antibiotic (N = 8,831)		
		Received antibiotic (N=1,302)	Did not receive antibiotic (N=1,242)	P-value	Received antibiotic (N=2,280)	Did not receive antibiotic (N=6,551)	P-value
No. individual children	4,138	1,055	1,004		1,688	2,957	
Age—median (IQR)	2.31 (1.32–3.49)	1.76 (0.99–3.06)	2.34 (1.48–3.45)		2.00 (1.10–3.28)	2.50 (1.48–3.60)	
Female*	5,534 (48.7%)	626 (48.3%)	596 (48.2%)	0.951	1,123 (49.3%)	3,187 (48.7%)	0.623
Drinking water source**				0.279			0.314
Unimproved public	1737 (44.3%)	456 (45.1%)	446 (45.9%)		711 (44.2%)	1,249 (44.1%)	
Improved public	799 (20.4%)	184 (18.2%)	193 (19.9%)		323 (20.1%)	584 (20.6%)	
Unimproved private	737 (18.8%)	199 (19.7%)	180 (18.5%)		311 (19.3%)	519 (18.3%)	
Improved private	547 (13.9%)	140 (13.8%)	119 (12.2%)		220 (13.7%)	395 (14%)	
Other	104 (2.7%)	32 (3.2%)	34 (3.5%)		44 (2.7%)	82 (2.9%)	
Cooking fuel**				0.094			0.068
Firewood	3793 (96.7%)	979 (96.8%)	952 (97.9%)		1,553 (96.5%)	2,749 (97.2%)	
Charcoal	116 (3%)	30 (3%)	18 (1.9%)		49 (3%)	72 (2.5%)	
Gas cooker	10 (0.3%)	1 (0.1%)	0 (0%)		6 (0.4%)	5 (0.2%)	
Other	5 (0.1%)	1 (0.1%)	2 (0.2%)		1 (0.1%)	3 (0.1%)	
Toilet type***				0.924			0.044
Improved sanitation	393 (10.1%)	109 (10.8%)	94 (9.7%)		175 (10.9%)	277 (9.8%)	
Unimproved sanitation	3494 (89.5%)	893 (88.8%)	869 (89.8%)		1,425 (88.8%)	2,532 (89.8%)	
Other	19 (0.5%)	4 (0.4%)	5 (0.5%)		4 (0.2%)	10 (0.4%)	

* There were 10, 3, 2, 1, and 4 missing values, respectively
** Randomly selected one clinic visit per child. There were 214, 44, 32, 77, and 128 children with missing values, respectively
*** Randomly selected one clinic visit per child. There were 232, 49, 36, 82, and 138 children with missing values, respectively

Table 4.2: Syndromes and diagnoses associated with not prescribing antibiotics when indicated

Syndrome/diagnosis with indication for antibiotics	Total syndromes and diagnoses (N=11,375)		Antibiotic not prescribed (N=1,242)	
	n	% of total visits	n	% of visits for that syndrome/diagnosis
IMCI danger sign	1,620	(14.2%)	1,090	(67.3%)
Condition requiring antibiotics	2,544	(22.4%)	1,242	(48.8%)
From symptoms	2,003	(17.6%)	1,204	(60.1%)
From clinical diagnosis	908	(8.0%)	64	(7.0%)
Pneumonia	1,644	(14.5%)	692	(42.1%)
Severe symptoms	941	(8.3%)	579	(61.5%)
Non-severe symptoms	360	(3.2%)	97	(26.9%)
Diagnosed	699	(6.1%)	44	(6.3%)
Blood in stool	47	(0.4%)	13	(27.7%)
Fever	1,729	(15.2%)	1,107	(64.0%)
Very severe febrile disease	1,629	(14.3%)	1,096	(67.3%)
Suspected bacterial cause	130	(1.1%)	17	(13.1%)
Ear problem	129	(1.1%)	26	(20.2%)
Pus draining	57	(0.5%)	16	(28.1%)
Diagnosed	102	(0.9%)	10	(9.8%)
Severe acute malnutrition	27	(0.2%)	6	(22.2%)

Italics indicates need based on clinical diagnosis as opposed to symptoms

Table 4.3: Diagnoses made and prescribing of antibiotics among visits with no indication for antibiotics

Diagnosis	Total diagnoses made (N=8,831)		Antibiotic given (N=2,280)	
	n	% of visits with no abx indication	n	% of visits with no abx indication
Anemia	433	(4.9%)	107	(24.7%)
Conjunctivitis	53	(0.6%)	29	(54.7%)
Dehydration	37	(0.4%)	27	(73.0%)
Diarrhea	438	(5.0%)	292	(66.7%)
Influenza	9	(0.1%)	4	(44.4%)
Intestinal worms	68	(0.8%)	63	(92.6%)
Malaria	6,932	(78.5%)	819	(11.8%)
Oral candidiasis	47	(0.5%)	19	(40.4%)
Other diagnosis	97	(1.1%)	70	(72.2%)
Pharyngitis/tonsillitis	144	(1.6%)	144	(100%)
Pyrexia of unknown origin	606	(6.9%)	595	(98.2%)
Upper respiratory tract infection	3,248	(36.8%)	704	(21.7%)
Viral syndrome	81	(0.9%)	15	(18.5%)
Wheezing/bronchospasm	10	(0.1%)	10	(100%)

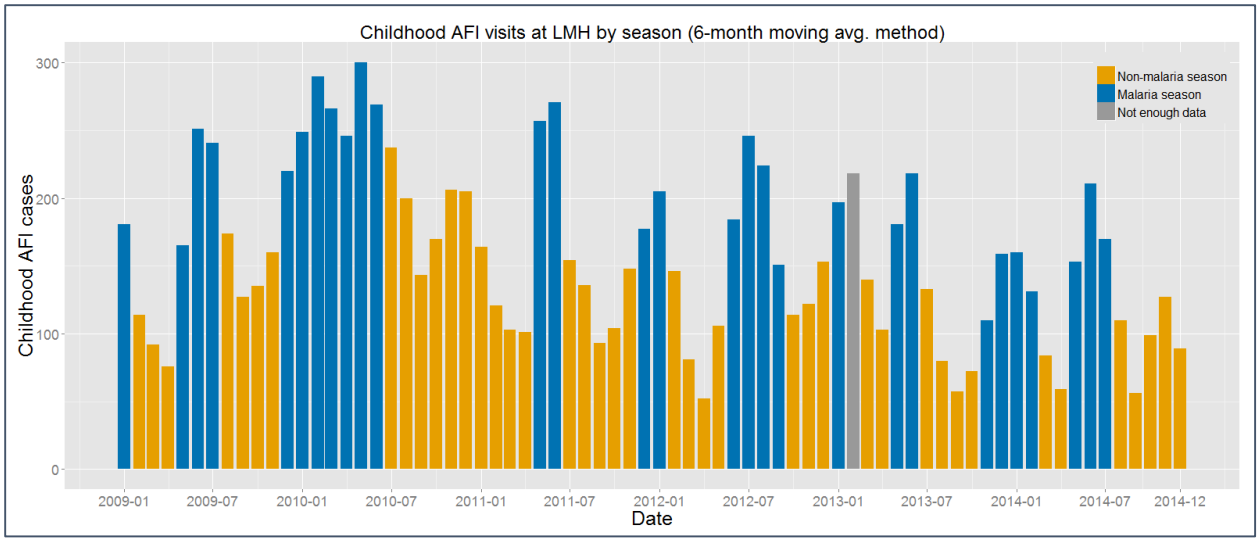


Figure 4.2: Malaria seasons throughout the study period

Table 4.4: Adherence to IMCI guidelines on antibiotic prescriptions by malaria season

	Malaria season		**Non-malaria season**	
All visits	6,046	(53.2%)	5,115	(45.0%)
Child indicated for antibiotics (N=2,544)				
Antibiotic indicated and provided (N=1,302)	589	(45.2%)	686	(52.7%)
Antibiotic indicated but not provided(N=1,242)	801	(64.5%)*	404	(32.5%)
Total visits	1,390	(54.6%)**	1,090	(42.8%)
Child not indicated for antibiotics (N=8,831)				
Antibiotic not indicated and not provided (N=6,551)	3,598	(54.9%)	2,827	(43.2%)
Antibiotic not indicated but given (N=2,280)	1,058	(46.4%)*	1,198	(52.5%)
Total visits	4,656	(52.7%)**	4,025	(45.6%)

* Among visits with non-adherence to IMCI guidelines on antibiotics, visits where antibiotics were inappropriately withheld were more likely to occur during malaria season than visits where antibiotics were inappropriately given (P<0.0001).
** P=0.035 when comparing the proportion of visits that occurred during malaria season between those with an indication for antibiotics and those without an indication.

Table 4.5: Relationship between malaria season and non-adherence to IMCI guidelines for antibiotics

		Non-adherence to IMCI guidelines	
		Crude OR (95% CI)	**Adj. OR (95% CI)†**
Among visits indicated for antibiotics (N=2,544)	**Antibiotics not prescribed**		
	Non-malaria season	Ref.	Ref.
	Malaria season	2.31 (1.97–2.71)*** (n=2,480)§	1.81 (1.46–2.25)** (n=2,193)‡
Among visits not indicated for antibiotics (N=8,831)	**Antibiotics prescribed**		
	Malaria season	Ref.	Ref.
	Non-malaria season	1.44 (1.31–1.59)*** (n=8,681)§	1.22 (1.06–1.40)* (n=8,123)‡

* P<0.01
** P<0.001
*** P<0.0001
§ There were 64 visits indicated for antibiotics and 151 visits not indicated for antibiotics during a month where seasonality was not determined
† Adjusted for malaria smear result of the child
‡ Malaria smear results were missing for 347 visits among visits indicated for antibiotics and 693 visits among visits not indicated for antibiotics

4.6 Supplemental tables and figures

Supplemental Table 4.1: Diagnoses that DO require an antibiotic prescription

Diagnosis	
Abscess*	Orchitis*
Amoebiasis	Otitis media
Arm abscess*	Otitis externa*
Boils*	Otitis media*
Burn, wound/injury, infected sores*, sores*	Parotitis*
Cellulitis*	Pneumocystis pneumonia*
Convulsions	Pneumonia/lower respiratory tract infection
Dysentery	Rash/skin problem, impetigo*
Ear infection*	Septic arthritis*
Enteric fever*; typhoid fever*	Septic dermatitis*
Klebsiela oxytoca*	Septic spots*
Ludwings angina*	Septicaemia*
Lymphadenitis*, adenitis*	Severe febrile illness*
Mastoiditis*	Sickle cell crisis*
Meningitis	Staphylococcus skin infection*
Neonatal sepsis*	Urinary tract infection

* Indicates a free-text diagnoses rather than a checked box

Supplemental Table 4.2: Diagnoses that DO NOT require an antibiotic prescription

Diagnosis	
Abdominal distension*	Malaria
Allergic reaction*, allergy*	Malnutrition, underweight*
Anemia	Measles*
Asthma	Mumps*
Bronchitis	Neutrophilia*
Chicken pox*	Oral candidiasis
Conjunctivitis	Protein energy malnutrition*
Dehydration	Pharyngitis/tonsillitis
Dental carries*, gingivitis*	Piriton*
Dermatitis*	Poor appetite*
Diarrhea	Peptic ulcer disorder*
Dyspepsia*	Pulmonary tuberculosis
Ear problem*	Pyrexia of unknown origin *
Eczema*	Rhinitis*
Epilepsy*	Ringworms*
Eye infection*	Salmonellosis*
Fungal infection*, fungal skin infection*	Scabies
Gastritis*	Septic scalp*
Giardiasis*	Splenomegaly*
Glomerulonephritis*	Stomatitis*
Glossitis*	Tinea capitis*
Herbal intoxication*	Tinea corporis*
Herpes zoster*	Upper respiratory tract infection
HIV	Uritcaria*
Influenza	Viral syndrome
Intestinal worms	Wheezing/bronchospasm
Jaundice*	

* Indicates a free-text diagnoses rather than a checked box

Supplemental Table 4.3: Completeness of assessment of each IMCI danger sign

IMCI danger sign	Yes		No		Number missing	
Inability to drink or breastfeed at all*	988	(8.7%)	10,359	(91.1%)	26	(0.2%)
Child vomiting everything*	289	(2.5%)	11,038	(97.0%)	48	(0.4%)
Lethargic	176	(1.5%)	11,194	(98.4%)	5	(0.04%)
Unconscious	20	(0.2%)	11,332	(99.6%)	23	(0.2%)
Had convulsions*	287	(2.5%)	8,259	(72.6%)	2,829	(24.9%)
Convulsing now	193	(1.7%)	11,156	(98.1%)	26	(0.2%)

* Indicates a symptom reported by the caregiver rather than seen by clinician
NB. There were no visits where all IMCI fields were missing

Supplemental Table 4.4: Appropriateness of antibiotic prescriptions by season and malaria smear result among children with indication for antibiotics under IMCI guidelines (N=2,544)

		Malaria season		Non-malaria season	
All visits (N=2,544)		1,390	(54.6%)	1,090	(42.8%)
Positive malaria smear (N=1,492)	Received antibiotics (followed IMCI guidelines) (N=403)	205	(50.9%)	197	(48.9%)
	Did not receive antibiotics (did not follow IMCI guidelines) (N=1,089)	743	(68.2%)	345	(31.7%)
	Total visits	948	(63.5%)*	542	(36.3%)
Negative malaria smear (N=705)	Received antibiotics (followed IMCI guidelines) (N=649)	310	(47.8%)	337	(51.9%)
	Did not receive antibiotics (did not follow IMCI guidelines) (N=56)	25	(44.6%)	31	(55.4%)
	Total visits	335	(47.5%)*	368	(52.2%)

* P<0.0001 when comparing the proportion of visits that occurred during malaria season between those with a positive malaria smear and a negative malaria smear.

Supplemental Table 4.5: Appropriateness of antibiotic prescriptions by season and malaria smear result among children with no indication for antibiotics under IMCI guidelines (N=8,831)

		Malaria season		Non-malaria season	
All visits (N=8,831)		4,656	(52.7%)	4,025	(45.6%)
Positive malaria smear (N=6,299)	Did not receive antibiotics (followed IMCI guidelines) (N=5,790)	3,280	(56.6%)	2,498	(43.1%)
	Received antibiotics (did not follow IMCI guidelines) (N=509)	271	(53.2%)	238	(46.8%)
	Total visits	3,551	(56.4%)*	2,736	(43.4%)
Negative malaria smear (N=1,839)	Did not receive antibiotics (followed IMCI guidelines) (N=441)	235	(53.3%)	205	(46.5%)
	Received antibiotics (did not follow IMCI guidelines) (N=1,398)	651	(46.6%)	745	(53.3%)
	Total visits	886	(48.2%)*	950	(51.7%)

* P<0.0001 when comparing the proportion of visits that occurred during malaria season between those with a positive malaria smear and a negative malaria smear.

Supplemental Table 4.6: Appropriateness of antimalarial prescriptions by malaria smear result and season among all children (N=11,375)

		Malaria season	Non-malaria season
All visits (N=11,375)		6,046 (53.2%)	5,107 (44.9%)
Positive malaria smear or diagnosis (N=8,747)	Receive antimalarials (followed IMCI guidelines) (N=8,679)	4,775 (55.0%)	3,737 (43.1%)
	Did not received antimalarials (did not follow IMCI guidelines) (N=66)	46 (69.7%)	20 (30.3%)
	Total visits	4,821 (55.1%)*	3,759 (43.0%)**
Negative malaria smear and diagnosis (N=2,628)	Did not receive antimalarials (followed IMCI guidelines) (N=2,593)	1,214 (46.8%)	1,332 (52.5%)
	Received antimalarials (did not follow IMCI guidelines) (N=29)	11 (37.9%)	18 (62.1%)
	Total visits	1,225 (46.6%)*	1,356 (51.6%)***

* P<0.0001 when comparing the proportion of visits that occurred during malaria season between those with a positive malaria smear/diagnosis and a negative malaria smear/diagnosis.
** There were 2 visits with missing antimalarial prescription data
*** There were 6 visits with missing antimalarial prescription data

Chapter 5: Conclusion

This study is consistent with other data demonstrating that the clinical and epidemiological pictures of childhood acute febrile illness (AFI) in sub-Saharan Africa are changing. As shown in Chapter 2, outpatient visits due to malaria have declined substantially in western Kenya in recent years, but this decrease appears to have plateaued. At the same time, visits from non-malarial AFI have been declining at a similar rate, for reasons that are unclear but which may relate to a general improvement in infrastructure and wealth in the region. While malaria continues to be identified in the majority of AFI seen at this Kenyan outpatient setting, a growing proportion of children presenting with parasitemia now also have alternative potential causes of fever identified at the same time. A more complete understanding of AFI etiology, including an improved understanding of specific diseases that contribute to non-malarial AFI and the role of coinfection with multiple pathogens, may yield additional insight into the declines in AFI, inform management guidelines, and potentially improve outcomes. For example, improved knowledge and understanding of changes in the etiology of AFI within a community may help healthcare workers (HCWs) make more accurate diagnoses and improve management decisions.

New and emerging pathogens also present a potential threat to the effectiveness of current treatment practices and guidelines. Although we found that dengue virus does not appear to be present in western Kenya, the risk of spread from the coastal region remains due to the likely presence of the vector, and it may already be circulating in nearby urban areas. If dengue virus arrives in western Kenya, it will be important to identify which populations are most affected and to understand patterns of dengue fever in this population. Ongoing disease surveillance to detect emerging pathogens will be crucial for identifying the presence of new causes of AFI (such as dengue virus) and to inform strategies to prevent infection and to manage disease.

As changes in the etiologies of AFI occur, there may be important implications for how AFI is managed. HCWs' pre-existing perceptions of what causes AFI may influence clinical judgement about a febrile child's specific condition and contribute to a failure to follow treatment guidelines. We demonstrated that seasonal variation in malaria was associated with non-adherence to Integrated Management of Childhood Illness (IMCI) guidelines for antibiotic prescriptions, regardless of a child's malaria test result. We found that children with an indication for an antibiotic were less likely to receive one during periods of high malaria transmission, and children with no indication for an antibiotic were more likely to receive one during periods of low malaria transmission. Investigations into decision making processes surrounding antibiotic use may lead to opportunities for improving IMCI guidelines and training.

Findings from this study provide several avenues for future research that could improve the knowledge and tools available to HCWs when seeing children with AFI in an outpatient setting:

1. There is an urgent need to develop cheap, accurate, and timely point-of-care diagnostics for non-malarial causes of childhood AFI. Access to a suite of diagnostic tools, particularly for detecting bacterial causes of fever, may allow HCWs to prescribe, or withhold, antibiotics more appropriately. In many resource-limited settings, HCWs typically have access only to a malaria rapid test for disease specific diagnosis. If the result of the malaria test is negative, uncertainty as to alternative causes of fever may lead to overprescription of antibiotics and failure to follow available treatment guidelines. Improved point-of-care diagnostics may improve treatment outcomes and help to stem the rise of antibiotic resistance.
2. Surveillance platforms must make regular use of diagnostic instruments that test for multiple etiologies of AFI simultaneously. Routine, comprehensive surveillance of AFI etiologies can serve two important functions. First, it can help prioritize the most common

AFI etiologies for the development of diagnostic tools. Second, the information can provide HCWs with accurate and real-time knowledge of currently circulating pathogens to inform clinical decision making. Data for these purposes have historically come from isolated studies of single pathogens that may overestimate the contribution to AFI from that particular disease. However, the Population-Based Infectious Disease Surveillance (PBIDS) platform, from which these study data came, is already introducing a diagnostic tool that will concurrently test specimens for 26 potential AFI etiologies. Its use could serve as a model for other surveillance platforms in the region.

3. The overall health impact of simultaneous treatment for multiple infections (such as malaria and bacterial respiratory infection) is currently not well understood. As diagnostic tools improve, febrile children with multiple potential etiologies, in particular those with malaria parasitemia and another fever-causing pathogen, will be identified more frequently. This creates an opportunity to efficiently tackle multiple diseases but additional research will be required to inform treatment guidelines for children with multiple potential causes of fever.
4. Finally, an improved understanding of the HCW decision making processes surrounding management of AFI has the potential to lead to interventions to reduce the inappropriate use of antibiotics in childhood febrile illness.

This study provides valuable data on childhood AFI in western Kenya. Some of the findings have already been shared with healthcare workers in the study region but additional engagement with health care workers and the community needs to continue in order to optimize opportunities to improve health care in the area. In addition, there is a need to develop improved diagnostic, surveillance, and reporting tools to better understand the distribution of pathogens causing AFI and to inform guidelines to mitigate risk from these infections in this area. The enormity of the burden of childhood AFI, and a tradition of focusing solely on particular etiologies, make this a

challenging task. This study, and the implications for future research it generates, can help the global health community shift to a more comprehensive discussion of this important contributor to childhood morbidity and mortality.

Chapter 6: Bibliography

1. Feikin, D.R., et al., *The burden of common infectious disease syndromes at the clinic and household level from population-based surveillance in rural and urban Kenya.* PLoS One, 2011. **6**(1): p. e16085.
2. Lubell, Y., et al., *Likely health outcomes for untreated acute febrile illness in the tropics in decision and economic models; a Delphi survey.* PLoS One, 2011. **6**(2): p. e17439.
3. Institute for Health Metrics and Evaluation. *GBD 2013*. 2015 March [cited 2015 November 2]; Available from: http://vizhub.healthdata.org/gbd-compare/.
4. Crump, J.A., *Time for a comprehensive approach to the syndrome of fever in the tropics.* Trans R Soc Trop Med Hyg, 2014. **108**(2): p. 61-2.
5. D'Acremont, V., C. Lengeler, and B. Genton, *Reduction in the proportion of fevers associated with Plasmodium falciparum parasitaemia in Africa: a systematic review.* Malar J, 2010. **9**: p. 240.
6. D'Acremont, V., et al., *Beyond malaria--causes of fever in outpatient Tanzanian children.* N Engl J Med, 2014. **370**(9): p. 809-17.
7. Crump, J.A., et al., *Etiology of severe non-malaria febrile illness in Northern Tanzania: a prospective cohort study.* PLoS Negl Trop Dis, 2013. **7**(7): p. e2324.
8. Global Burden of Disease Study Collaborators, *Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.* Lancet, 2015. **386**(9995): p. 743-800.
9. Murray, C.J., et al., *Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.* Lancet, 2014. **384**(9947): p. 1005-70.
10. O'Meara, W.P., et al., *Changes in the burden of malaria in sub-Saharan Africa.* Lancet Infect Dis, 2010. **10**(8): p. 545-55.
11. Alemu, A., et al., *Effect of malaria on HIV/AIDS transmission and progression.* Parasit Vectors, 2013. **6**: p. 18.
12. Gwer, S., C.R. Newton, and J.A. Berkley, *Over-diagnosis and co-morbidity of severe malaria in African children: a guide for clinicians.* Am J Trop Med Hyg, 2007. **77**(6 Suppl): p. 6-13.
13. Oppenheimer, S.J., *Iron and its relation to immunity and infectious disease.* J Nutr, 2001. **131**(2S-2): p. 616S-633S; discussion 633S-635S.
14. Scott, J.A., et al., *Relation between falciparum malaria and bacteraemia in Kenyan children: a population-based, case-control study and a longitudinal study.* Lancet, 2011. **378**(9799): p. 1316-23.
15. World Health Organization, *Malaria and HIV interactions and their implications for public health policy*. 2005, WHO: Geneva.
16. Bhatt, S., et al., *The global distribution and burden of dengue.* Nature, 2013.
17. Ellis, E.M., et al., *A household serosurvey to estimate the magnitude of a dengue outbreak in Mombasa, Kenya, 2013.* PLoS Negl Trop Dis, 2015. **9**(4): p. e0003733.
18. Centers for Disease Control and Prevention, *Ongoing dengue epidemic - Angola, June 2013.* MMWR Morb Mortal Wkly Rep, 2013. **62**(24): p. 504-7.
19. Caron, M., et al., *First evidence of simultaneous circulation of three different dengue virus serotypes in Africa.* PLoS One, 2013. **8**(10): p. e78030.
20. Kyobe Bosa, H., et al., *Dengue fever outbreak in Mogadishu, Somalia 2011: Co-circulation of three dengue virus serotypes*, in *16th International Congress on Infectious Diseases*. 2014: Cape Town, South Africa.
21. Goossens, H., et al., *Outpatient antibiotic use in Europe and association with resistance: a cross-national database study.* Lancet, 2005. **365**(9459): p. 579-87.
22. Polgreen, P.M., et al., *Respiratory fluoroquinolone use and influenza.* Infect Control Hosp Epidemiol, 2011. **32**(7): p. 706-9.
23. Safaeian, L., et al., *Seasonality and Physician-related Factors Associated with Antibiotic Prescribing: A Cross-sectional Study in Isfahan, Iran.* Int J Prev Med, 2015. **6**: p. 1.

24. Sun, L., E.Y. Klein, and R. Laxminarayan, *Seasonality and temporal correlation between community antibiotic use and resistance in the United States.* Clin Infect Dis, 2012. **55**(5): p. 687-94.
25. Van Boeckel, T.P., et al., *Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data.* Lancet Infect Dis, 2014. **14**(8): p. 742-50.
26. Njozi, M., et al., *Predictors of antibiotics co-prescription with antimalarials for patients presenting with fever in rural Tanzania.* BMC Public Health, 2013. **13**: p. 1097.
27. World Health Organization, *Antimicrobial resistance: global report on surveillance*. 2014, WHO: Geneva.
28. Koram, K.A. and M.E. Molyneux, *When is "malaria" malaria? The different burdens of malaria infection, malaria disease, and malaria-like illnesses.* Am J Trop Med Hyg, 2007. **77**(6 Suppl): p. 1-5.
29. Perkins, M.D. and D.R. Bell, *Working without a blindfold: the critical role of diagnostics in malaria control.* Malar J, 2008. **7 Suppl 1**: p. S5.
30. Berkley, J.A., et al., *HIV infection, malnutrition, and invasive bacterial infection among children with severe malaria.* Clin Infect Dis, 2009. **49**(3): p. 336-43.
31. Odhiambo, F.O., et al., *Profile: the KEMRI/CDC Health and Demographic Surveillance System--Western Kenya.* Int J Epidemiol, 2012. **41**(4): p. 977-87.
32. Dalal, W., et al., *Home-based HIV testing and counseling in rural and urban Kenyan communities.* J Acquir Immune Defic Syndr, 2013. **62**(2): p. e47-54.
33. World Health Organization, *Chart booklet : IMCI integrated management of childhood illness*. 2014, WHO: Geneva.
34. National Centers for Environmental Information. *Global Summary of the Day*. [cited 2015 August 7]; Available from: http://www7.ncdc.noaa.gov/CDO/cdoselect.cmd?datasetabbv=GSOD&countryabbv=&georegionabbv=.
35. Zeileis, A., *Object-oriented computation of sandwich estimators.* Journal of Statistical Software, 2006. **16**(9).
36. Ayieko, P., et al., *Assessment of health benefits and cost-effectiveness of 10-valent and 13-valent pneumococcal conjugate vaccination in Kenyan children.* PLoS One, 2013. **8**(6): p. e67324.
37. Fortanier, A.C., et al., *Pneumococcal conjugate vaccines for preventing otitis media.* Cochrane Database Syst Rev, 2014. **4**: p. CD001480.
38. World Health Organization. *Drinking-water*. Fact sheet No. 391 2015 June [cited 2015 October 19]; Available from: http://www.who.int/mediacentre/factsheets/fs391/en/.
39. Okiro, E.A., et al., *Changing malaria intervention coverage, transmission and hospitalization in Kenya.* Malar J, 2010. **9**: p. 285.
40. Zhou, G., et al., *Changing patterns of malaria epidemiology between 2002 and 2010 in Western Kenya: the fall and rise of malaria.* PLoS One, 2011. **6**(5): p. e20318.
41. President's Malaria Initiative, *Kenya — Malaria Operational Plan FY 2014*. USAID: Washington, D.C.
42. Roca-Feltrer, A., et al., *Lack of decline in childhood malaria, Malawi, 2001-2010.* Emerg Infect Dis, 2012. **18**(2): p. 272-8.
43. Rose-Wood, A., et al., *Trends in malaria morbidity among health care-seeking children under age five in Mopti and Sevare, Mali between 1998 and 2006.* Malar J, 2010. **9**: p. 319.
44. Geiger, C., et al., *Declining malaria parasite prevalence and trends of asymptomatic parasitaemia in a seasonal transmission setting in North-Western Burkina Faso between 2000 and 2009-2012.* Malar J, 2013. **12**: p. 27.
45. Brady, O.J., et al., *Refining the global spatial limits of dengue virus transmission by evidence-based consensus.* PLoS Negl Trop Dis, 2012. **6**(8): p. e1760.
46. Simmons, C.P., et al., *Dengue.* N Engl J Med, 2012. **366**(15): p. 1423-32.
47. Gubler, D.J., *The changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle?* Comp Immunol Microbiol Infect Dis, 2004. **27**(5): p. 319-30.
48. Huy, N.T., et al., *Factors associated with dengue shock syndrome: a systematic review and meta-analysis.* PLoS Negl Trop Dis, 2013. **7**(9): p. e2412.
49. Mizumoto, K., et al., *On the risk of severe dengue during secondary infection: a systematic review coupled with mathematical modeling.* J Vector Borne Dis, 2014. **51**(3): p. 153-64.

50. World Health Organization. *Dengue and severe dengue*. Fact Sheet 2012 January [cited 2012 November 18]; Available from: http://www.who.int/mediacentre/factsheets/fs117/en/index.html.
51. Capeding, M.R., et al., *Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial.* Lancet, 2014. **384**(9951): p. 1358-65.
52. Hadinegoro, S.R., et al., *Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease.* N Engl J Med, 2015. **373**(13): p. 1195-206.
53. Villar, L., et al., *Efficacy of a tetravalent dengue vaccine in children in Latin America.* N Engl J Med, 2015. **372**(2): p. 113-23.
54. Ballenger-Browning, K.K. and J.P. Elder, *Multi-modal Aedes aegypti mosquito reduction interventions and dengue fever prevention.* Trop Med Int Health, 2009. **14**(12): p. 1542-51.
55. Amarasinghe, A., et al., *Dengue virus infection in Africa.* Emerg Infect Dis, 2011. **17**(8): p. 1349-54.
56. Williams, H.A., et al., *Dispensary level pilot implementation of rapid diagnostic tests: an evaluation of RDT acceptance and usage by providers and patients--Tanzania, 2005.* Malar J, 2008. **7**: p. 239.
57. PROMED *Dengue/DHF update (33): Asia, Africa, Pacific - (2) Kenya (Mombasa)*. ProMED-mail 2013, 2013.
58. Attaway, D.F., et al., *Mosquito habitat and dengue risk potential in Kenya: alternative methods to traditional risk mapping techniques.* Geospat Health, 2014. **9**(1): p. 119-30.
59. Madhi, S.A., et al., *Vaccines to prevent pneumonia and improve child survival.* Bull World Health Organ, 2008. **86**(5): p. 365-72.
60. Feikin, D.R., et al., *Etiology and Incidence of viral and bacterial acute respiratory illness among older children and adults in rural western Kenya, 2007-2010.* PLoS One, 2012. **7**(8): p. e43656.
61. Santiago, G.A., et al., *Analytical and clinical performance of the CDC real time RT-PCR assay for detection and typing of dengue virus.* PLoS Negl Trop Dis, 2013. **7**(7): p. e2311.
62. Nkengasong, J.N., et al., *Laboratory systems and services are critical in global health: time to end the neglect?* Am J Clin Pathol, 2010. **134**(3): p. 368-73.
63. Blaylock, J.M., et al., *The seroprevalence and seroincidence of dengue virus infection in western Kenya.* Travel Med Infect Dis, 2011. **9**(5): p. 246-8.
64. Mease, L.E., et al., *Seroprevalence and distribution of arboviral infections among rural Kenyan adults: a cross-sectional study.* Virol J, 2011. **8**: p. 371.
65. Sutherland, L.J., et al., *Serologic evidence of arboviral infections among humans in Kenya.* Am J Trop Med Hyg, 2011. **85**(1): p. 158-61.
66. Peeling, R.W., et al., *Evaluation of diagnostic tests: dengue.* Nat Rev Microbiol, 2010. **8**(12 Suppl): p. S30-8.
67. Bigogo, G., et al., *Health-seeking patterns among participants of population-based morbidity surveillance in rural western Kenya: implications for calculating disease rates.* Int J Infect Dis, 2010. **14**(11): p. e967-73.
68. Hii, Y.L., et al., *Forecast of dengue incidence using temperature and rainfall.* PLoS Negl Trop Dis, 2012. **6**(11): p. e1908.
69. Teixeira, M.G., et al., *Epidemiological trends of dengue disease in Brazil (2000-2010): a systematic literature search and analysis.* PLoS Negl Trop Dis, 2013. **7**(12): p. e2520.
70. Mireji, P.O., et al., *Heavy metals in mosquito larval habitats in urban Kisumu and Malindi, Kenya, and their impact.* Ecotoxicol Environ Saf, 2008. **70**(1): p. 147-53.
71. L'Azou, M., et al., *Dengue: etiology of acute febrile illness in Abidjan, Cote d'Ivoire, in 2011-2012.* Trans R Soc Trop Med Hyg, 2015.
72. Gomes, A.F., A.A. Nobre, and O.G. Cruz, *Temporal analysis of the relationship between dengue and meteorological variables in the city of Rio de Janeiro, Brazil, 2001-2009.* Cad Saude Publica, 2012. **28**(11): p. 2189-97.
73. Karim, M.N., et al., *Climatic factors influencing dengue cases in Dhaka city: a model for dengue prediction.* Indian J Med Res, 2012. **136**(1): p. 32-9.
74. Grange, L., et al., *Epidemiological risk factors associated with high global frequency of inapparent dengue virus infections.* Front Immunol, 2014. **5**: p. 280.
75. Snow, R.W., et al., *Changing Malaria Prevalence on the Kenyan Coast since 1974: Climate, Drugs and Vector Control.* PLoS One, 2015. **10**(6): p. e0128792.

76. Child, W.H.O.D.o. and A. Health, *Handbook IMCI: Integrated management of childhood illness*. 2005: World Health Organization.
77. Mahende, C., et al., *Aetiology of acute febrile episodes in children attending korogwe district hospital in north-eastern Tanzania.* PLoS One, 2014. **9**(8): p. e104197.
78. O'Meara, W.P., et al., *Etiology of pediatric fever in western Kenya: a case-control study of falciparum malaria, respiratory viruses, and streptococcal pharyngitis.* Am J Trop Med Hyg, 2015. **92**(5): p. 1030-7.
79. Chappuis, F., et al., *Rapid diagnostic tests for non-malarial febrile illness in the tropics.* Clin Microbiol Infect, 2013. **19**(5): p. 422-31.
80. Petti, C.A., et al., *Laboratory medicine in Africa: a barrier to effective health care.* Clin Infect Dis, 2006. **42**(3): p. 377-82.
81. World Health Organization. *Integrated Management of Childhood Illness (IMCI)*. [cited 2015 November 2]; Available from: http://www.who.int/maternal_child_adolescent/topics/child/imci/en/.
82. Gove, S., *Integrated management of childhood illness by outpatient health workers: technical basis and overview. The WHO Working Group on Guidelines for Integrated Management of the Sick Child.* Bull World Health Organ, 1997. **75 Suppl 1**: p. 7-24.
83. Armstrong Schellenberg, J.R., et al., *Effectiveness and cost of facility-based Integrated Management of Childhood Illness (IMCI) in Tanzania.* Lancet, 2004. **364**(9445): p. 1583-94.
84. Gouws, E., et al., *Improving antimicrobial use among health workers in first-level facilities: results from the multi-country evaluation of the Integrated Management of Childhood Illness strategy.* Bull World Health Organ, 2004. **82**(7): p. 509-15.
85. Amaral, J., et al., *Effect of Integrated Management of Childhood Illness (IMCI) on health worker performance in Northeast-Brazil.* Cad Saude Publica, 2004. **20 Suppl 2**: p. S209-19.
86. El Arifeen, S., et al., *Integrated Management of Childhood Illness (IMCI) in Bangladesh: early findings from a cluster-randomised study.* Lancet, 2004. **364**(9445): p. 1595-602.
87. Bryce, J., et al., *Programmatic pathways to child survival: results of a multi-country evaluation of Integrated Management of Childhood Illness.* Health Policy Plan, 2005. **20 Suppl 1**: p. i5-i17.
88. Zarocostas, J., *Malaria treatment should begin with parasitological diagnosis where possible, says WHO.* BMJ, 2010. **340**: p. c1402.
89. Ahmed, H.M., M. Mitchell, and B. Hedt, *National implementation of Integrated Management of Childhood Illness (IMCI): policy constraints and strategies.* Health Policy, 2010. **96**(2): p. 128-33.
90. Rowe, A.K., et al., *Trends in health worker performance after implementing the Integrated Management of Childhood Illness strategy in Benin.* Trop Med Int Health, 2012. **17**(4): p. 438-46.
91. Lange, S., A. Mwisongo, and O. Maestad, *Why don't clinicians adhere more consistently to guidelines for the Integrated Management of Childhood Illness (IMCI)?* Soc Sci Med, 2014. **104**: p. 56-63.
92. Odaga, J., et al., *Rapid diagnostic tests versus clinical diagnosis for managing people with fever in malaria endemic settings.* Cochrane Database Syst Rev, 2014. **4**: p. CD008998.
93. Onchiri, F.M., et al., *Frequency and correlates of malaria over-treatment in areas of differing malaria transmission: a cross-sectional study in rural Western Kenya.* Malar J, 2015. **14**: p. 97.
94. Manyando, C., et al., *Rapid diagnostic tests for malaria and health workers' adherence to test results at health facilities in Zambia.* Malar J, 2014. **13**: p. 166.
95. Mubi, M., et al., *Malaria diagnosis and treatment practices following introduction of rapid diagnostic tests in Kibaha District, Coast Region, Tanzania.* Malar J, 2013. **12**(1): p. 293.
96. Msellem, M.I., et al., *Influence of rapid malaria diagnostic tests on treatment and health outcome in fever patients, Zanzibar: a crossover validation study.* PLoS Med, 2009. **6**(4): p. e1000070.
97. D'Acremont, V., et al., *Reduction of anti-malarial consumption after rapid diagnostic tests implementation in Dar es Salaam: a before-after and cluster randomized controlled study.* Malar J, 2011. **10**: p. 107.
98. Bisoffi, Z., et al., *Rapid malaria diagnostic tests vs. clinical management of malaria in rural Burkina Faso: safety and effect on clinical decisions. A randomized trial.* Trop Med Int Health, 2009. **14**(5): p. 491-8.
99. Radyowijati, A. and H. Haak, *Improving antibiotic use in low-income countries: an overview of evidence on determinants.* Soc Sci Med, 2003. **57**(4): p. 733-44.
100. Means, A.R., et al., *Correlates of inappropriate prescribing of antibiotics to patients with malaria in Uganda.* PLoS One, 2014. **9**(2): p. e90179.

101. Cairns, M., et al., *Estimating the potential public health impact of seasonal malaria chemoprevention in African children.* Nat Commun, 2012. **3**: p. 881.
102. Roca-Feltrer, A., et al., *A simple method for defining malaria seasonality.* Malar J, 2009. **8**: p. 276.
103. Clavenna, A. and M. Bonati, *Differences in antibiotic prescribing in paediatric outpatients.* Arch Dis Child, 2011. **96**(6): p. 590-5.
104. Resi, D., et al., *Antibiotic prescriptions in children.* J Antimicrob Chemother, 2003. **52**(2): p. 282-6.
105. Walter, N.D., et al., *Why first-level health workers fail to follow guidelines for managing severe disease in children in the Coast Region, the United Republic of Tanzania.* Bull World Health Organ, 2009. **87**(2): p. 99-107.
106. Senn, N., et al., *Use of antibiotics within the IMCI guidelines in outpatient settings in Papua New Guinean children: an observational and effectiveness study.* PLoS One, 2014. **9**(3): p. e90990.
107. Eckel, N., et al., *Pharmacoepidemiology of common colds and upper respiratory tract infections in children and adolescents in Germany.* BMC Pharmacol Toxicol, 2014. **15**: p. 44.
108. O'Brien, K., et al., *Clinical predictors of antibiotic prescribing for acutely ill children in primary care: an observational study.* Br J Gen Pract, 2015. **65**(638): p. e585-92.
109. Hersh, A.L., et al., *Antibiotic prescribing in ambulatory pediatrics in the United States.* Pediatrics, 2011. **128**(6): p. 1053-61.
110. Gerber, J.S., et al., *Durability of benefits of an outpatient antimicrobial stewardship intervention after discontinuation of audit and feedback.* JAMA, 2014. **312**(23): p. 2569-70.
111. Ranji, S.R., et al., *Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis.* Med Care, 2008. **46**(8): p. 847-62.

Vita

Alastair Matheson was born in Nelson, New Zealand and grew up in New Zealand and Wales. He received a BHSc from the University of Auckland in 2002. Alastair completed his MPH at the University of Auckland in 2005, with half of his studies spent on exchange at the University of California at Berkeley. Alastair worked in local public health for several years in New Zealand and the United States. In 2016, he completed his PhD in epidemiology at the University of Washington.