

**EVALUATION OF THE UTILITY OF THE INTEGRATED
MANAGEMENT OF CHILDHOOD ILLNESSES ALGORITHM FOR
HIV INFECTION IN CHILDREN LESS THAN FIVE YEARS OLD
AT THE MBAGATHI DISTRICT HOSPITAL, NAIROBI**

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REQUIREMENTS FOR THE DEGREE OF MASTERS OF MEDICINE IN
PAEDIATRICS AND CHILD HEALTH OF THE UNIVERSITY OF NAIROBI

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DECLARATION

This dissertation is original work and has not been presented for a degree in any other university.

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TABLE OF CONTENTS

List of Tables and Figures	vi
List of Abbreviations	vii
Acknowledgements	Viii
Dedication	ix
1 Abstract	1
2 Literature Review	3
• Introduction	3
• Paediatric HIV	4
• Overview of pathogenesis of HIV in Children	4
• Diagnosis and Treatment of HIV in Children	5
• The Integrated Management of Childhood Illnesses Strategy	6
• Clinical Presentation of Paediatric HIV	8
• Utility of Clinical Criteria	11
• IMCI algorithm for Paediatric HIV	14
3 Justification	18
4 Objectives	19
5 Methods and Participants	20
• Study Design	20
• Sample size estimation	21
• Data Collection	22
• Definitions of cases and terms	23
• Data Recording and Analysis	28
• Ethical considerations	29
6 Results	30
7 Discussion	43
9 Conclusions	49
10 Limitations and Recommendations	50
11 References	51
12 Appendices	57
• Annex 1	
• Annex 2	
• Annex 3	
• Annex 4	
• Annex 5	

LIST OF TABLES AND FIGURES

FIGURES		Page
1	Figure 1: Age and Sex Distribution of the Study Population	30
2	Figure 2: CD4+ T-lymphocyte percentage distribution by HIV status and IMCI Classification.	37
3	Figure 3: T-lymphocyte percentage distribution by HIV status and IMCI classification for children \leq 12 months of age.	40
4	Figure 4: CD4+ T-Lymphocyte percentage distribution by HIV status and IMCI classification for children aged 12 to 35 months.	40

TABLES

1	Table 1: Summary of Evaluation Studies on the Provisional WHO CCD for AIDS and IMCI HIV algorithm.	16
2	Table 2: WHO Grading of severity of immunosuppression in HIV infected children.	27
3	Table 3: Frequency of clinical symptoms in the study population.	31
4	Table 4: Frequency of clinical signs in the study population.	32
5	Table 5: Clustering of IMCI components in the study population	33
6	Table 6: HIV Status by age group of the study population based on laboratory test results.	33
7	Table 7: HIV Test Results and IMCI Classification of the Study Population.	34
8	Table 8: HIV Status and IMCI Classification of children aged 18 months and below.	35
9	Table 9: HIV status and IMCI classification of children aged over 18 months.	36
10	Table 10: Distribution of CD4+ T-lymphocyte percentages in relation to HIV status and IMCI classification.	37
11	Table 11: Classification of study population by HIV status, IMCI criteria and CD4+ T-lymphocyte percentages	38
12	Table 12: Median CD4+ T-lymphocyte distribution by HIV status and IMCI classification for different age categories.	39
13	Table 13: Severity of Immunosuppression of HIV infected children by IMCI classification.	42
14	Table 14: Prediction of Advanced and Severe immunosuppression by IMCI algorithm among HIV infected children.	43

LIST OF ABBREVIATIONS

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Disease Syndrome
WHO	World Health Organization
UNICEF	United Nations Children's Fund
IMCI	Integrated Management of Childhood Illnesses
CCD	Clinical Case Definition
PCP	Pneumocystis jiroveci pneumonia
LIP	Lymphocytic Interstitial Pneumonitis
DNA	Deoxyribonucleic acid
PCR	Polymerase chain reaction
TB	Tuberculosis
MTCT	Mother to child transmission
CTL	Cytotoxic T-lymphocytes
DCT	Diagnostic Counseling and Testing
ANC	Antenatal Clinic
KDHS	Kenya Demographic Health Survey
POPC	Paediatric Outpatient Clinic
MCH	Maternal and Child Health Clinic
ART	Antiretroviral Therapy
CCC	Comprehensive Care Centre
KNH	Kenyatta National Hospital
MDH	Mbagathi District Hospital

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DEDICATION

To my husband, Dr. J.O. Mecha, thankyou for walking the journey with me.

ABSTRACT

Background: Due to the growing importance of HIV/AIDS as a contributor to childhood mortality in high prevalence countries, an HIV component was added to the WHO/UNICEF strategy of Integrated Management of Childhood Illnesses (IMCI). Its objective was to enable primary-level health workers identify symptomatic HIV infected children in urgent need of referral for HIV testing and HIV-specific care. Validation studies of the IMCI HIV algorithm have reported variable performance due to regional differences in prevalent childhood diseases.

Objective: To assess the performance of the Kenyan adaptation of the IMCI HIV algorithm in identifying symptomatic HIV infected children and to determine its performance in identifying infected children with severe immunosuppression.

Methods: In this cross-sectional, descriptive study conducted at Mbagathi District Hospital, the sensitivity and specificity of the IMCI HIV algorithm to identify symptomatic HIV infection among hospitalized children was evaluated. After applying the IMCI HIV algorithm, the children were tested for HIV infection using antibody tests with confirmatory viral testing for those aged less than 18 months. CD4+ T-lymphocyte percentages were obtained to assess the immunological characteristics of the children

Findings: Of three hundred children recruited in the study 58 (19.3%) were HIV infected. The IMCI algorithm had a sensitivity of 77.8%, specificity of 80.9%, PPV of 49.4% and NPV of 93.7% for identifying HIV infection. Inclusion of CD4 percentage cut-off for severe immunosuppression improved the sensitivity and PPV of the algorithm for identifying severe immunosuppression in HIV infection to 89.6% and 57.8% respectively. Specificity and NPV however declined to 34.6% and 76.9% respectively.

Conclusion: The IMCI HIV algorithm was useful in prioritizing HIV infected children urgently in need of a HIV test as it identified 89.6% of HIV infected children with severe immunosuppression as symptomatic

Introduction

HIV infection is a viral infection caused by the Human Immunodeficiency Virus (HIV), a retrovirus of the lentiviridae sub-family. The first cluster of cases of HIV infection were described in 1981 in the United States of America among previously healthy homosexual males who were found to have cases of a rare neoplasm, Kaposi's sarcoma and Pneumocystis jiroveci pneumonia (P,P). In 1984 the association between Acquired Immunodeficiency Disease Syndrome (AIDS) and HIV was established [1]. A quarter of a century later, HIV infection and AIDS cases have increased in number to the point of constituting a global health crisis of unprecedented magnitude. In the year 2006, 40.3 million adults were living with HIV worldwide and of these 4.9 million were newly infected. The HIV epidemic is a problem in many countries but Africa which only contributes 10% of the world's population is the epicenter of the epidemic. More than 90% of HIV infected people live in the developing world and 70% of all cases worldwide are to be found in Africa [2]. Over half of the infected people are women aged less than twenty five years and HIV sero-prevalence among pregnant women in many sub-Saharan African countries is over 20% [2].

The first case of HIV infection in Kenya was diagnosed in 1984. In 1999 14% of antenatal clinic (ANC) mothers at Pumwani maternity hospital in Nairobi were reported to be HIV positive [3]. The Kenya Demographic Health Survey (KDHS) of 2003 however reported a decline in national prevalence to 7% in that year [4].

Paediatric HIV Infection

Approximately a quarter of a century since the first cases of paediatric HIV worldwide were described in 1982, the number of infected children has greatly increased. By the end of the year 2006, there were an estimated 2.3 million children less than fifteen years of age living with HIV infection worldwide. Of these, 700,000 were newly infected while 570,000 children died the same year from HIV. Currently 87% of HIV infected children live in Sub-Saharan Africa [2]. In Kenya in the year 2006 there were 150,000 children living with HIV, 30,000 of whom were newly infected

Over 95% of paediatric HIV infections are acquired vertically from mother to child.

Mother to Child transmission may occur during pregnancy, labor or breastfeeding [5].

Without treatment, when a mother has HIV infection and chooses to breastfeed, the risk of transmitting the virus to her child varies from 20-42% [6, 7]. Breastfeeding accounts for nearly one third of cases of mother to child transmission (MTCT) in Africa [8]. High HIV prevalence and rapid progression to death among many infected individuals have contributed, over the last two decades, to the reversal of previous gains in child survival and lowered life expectancy. In addition to morbidity and mortality caused by HIV infection, it is estimated that millions of Kenyan children have been orphaned by HIV and AIDS [3].

Overview of the pathogenesis of HIV in children

HIV is unique in that it specifically infects a subset of thymus-derived lymphocytes, as well as monocytes, macrophages and Langerhan's cells carrying the surface molecule CD4, which binds a glycoprotein on the envelope of HIV called gp120. The virus gains entry into host cells by binding to CD4 receptors found on the surfaces of these cells and

causes destruction of these cells with a resultant decrease in their number. CD4 cells play a central role in orchestrating the immune system, and their destruction renders an infected child vulnerable to a wide range of infections, both the usual and opportunistic infections. It is now also recognized that CD8 cytotoxic T lymphocytes (CTL) capable of killing HIV infected target cells develop at a slower rate in infants compared to adults due to the immaturity of their immune system [9] Clinical expression of HIV infection in children is also highly variable depending on their geographical location and differences in their genetic susceptibility. Some HIV positive children develop severe HIV-related signs and symptoms in their first year of life which are associated with high mortality. Other infected children who remain asymptomatic or mildly symptomatic for years are classified as slow progressors

Diagnosis and treatment of HIV infection in children

Early diagnosis of HIV infection is desirable because as indicated by various studies, in the absence of antiretroviral therapy or prophylaxis against opportunistic infections like P,P, disease progression in children is faster than in adults and as many as 40% of infected children progress to an AIDS defining illness by 12 months of age [10, 11]. Even in settings where antiretroviral therapy may not be readily available early diagnosis is still important because provision of supportive care alone decreases morbidity significantly and prolongs life. Kumwenda et al studied the effect of periodic vitamin A supplementation in HIV infected children in Malawi and found it to be associated with a decrease in mortality as well as in point prevalence of symptoms like persistent cough, chronic otitis media and chronic diarrhea among these children [12]. Chintu et al found that co-trimoxazole supplementation in Zambia decreased death and admission rates of

infected children by nearly half the initial rates. It also prevented gastroenteritis and septicemia among infected children [13].

The Integrated Management of Childhood Illnesses Strategy

Each year 12 million children worldwide die before their fifth birthday from treatable and preventable diseases. The majority of these deaths occur in resource-limited settings in developing countries with limited diagnostic facilities. In 1992 the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) developed the Integrated Management of Childhood Illnesses (IMCI) strategy aimed at reducing morbidity and mortality associated with the major causes of childhood illnesses in these countries. This strategy encompasses approaches at both the community and primary care (first-referral care) levels [14]. In Kenya, the IMCI programme has to date focused on formal, ambulatory (clinic/outpatient) care targeting health workers with limited training and limited access to diagnostic services. The approach is based on a set of country-adapted generic guidelines for the management of common serious childhood illnesses with diagnosis mainly relying on history and clinical examination.

IMCI guidelines initially did not include criteria for identifying symptomatic HIV infection in children. However with increasing numbers of HIV cases in the paediatric age group and emerging evidence for life-prolonging treatments, it became clear that guidance on the recognition and management of this disease within the scope of IMCI was required. Yet diagnosis and staging of paediatric HIV infection remains a challenge in developing countries due to the fact that definitive laboratory diagnostic methods are not easily accessible for both HIV and opportunistic infections. This difficulty in diagnosis and immunologic staging has resulted in inadequate treatment being availed to

the children that need it. The current IMCI strategy has therefore now included an algorithm aimed at early identification of children less than five years of age presenting with symptoms suggestive of HIV infection in resource-poor settings. Diagnosis of disease is made based on a set of clinical signs and symptoms that are highly suggestive of HIV infection. Diagnosis of presence of symptomatic HIV disease based on IMCI guidelines is made in the presence of three or more of the following:

1. Presence of tuberculosis in any parent in the last five years or confirmed HIV infection in parents.
2. Pneumonia (currently or previously).
3. Two or more episodes of persistent diarrhea (lasting more than fourteen days).
4. Growth faltering or weight less than the third centile for that age bracket.
5. Enlarged lymph nodes >1cm in two or more of following sites: the axilla, neck or groin regions.
6. Oral thrush at presentation (age >2months).

Health workers in resource limited settings may use this clinical algorithm to suspect presence of HIV infection in a child and send this child as a priority for HIV-specific laboratory tests to confirm the diagnosis. The rationale for developing the IMCI algorithm is therefore to improve the ability of the health worker to correctly identify the symptomatic HIV infected child in urgent need of HIV testing. Where laboratory tests like the polymerase chain reaction and enzyme linked immunosorbent assay do not seem feasible due to limited resources these guidelines may be used to prioritize who needs referral for HIV testing and further care.

Clinical criteria have been reported in previous studies to perform poorly as screening tools for identifying presence of infection but have been shown to perform well in identifying severe disease due to high specificity. The positive predictive value (PPV) of various signs and symptom also varies depending on disease prevalence. The IMCI HIV algorithm was developed in the year 2000 in South Africa based on disease patterns commonly seen among HIV infected children in southern Africa. However no immunologic assessment was carried out to determine the immune status of children identified by the algorithm as having signs and symptoms suggestive of HIV infection. The algorithm was then adapted for use in various African countries including Kenya. It is however not clear at what immunologic stage HIV infected children are identified by the algorithm as symptomatic and how many HIV infected children requiring antiretroviral treatment might be left out by adoption of the IMCI HIV algorithm as a tool for prioritizing on HIV testing.

Clinical presentation of paediatric HIV

Several studies have been carried out describing the clinical presentation of HIV infection in children, which has been found to vary considerably from that in adults. Shilpa et al studied the clinical profile of paediatric HIV in India and found that most of the HIV-infected children presented with protein-energy malnutrition and tuberculosis as well as gastrointestinal manifestations [15]. A similar study carried out earlier in Rwanda by Spira et al in 1988 reported different clinical features among HIV infected children which were chronic cough, persistent generalized lymphadenopathy and failure to thrive. These features were found to occur three to thirteen times more frequently among infected children [16]. Spira also reported that these clinical features tended to be more severe

among HIV-infected children compared to the general population. The clinical features with the greatest ability to discriminate between HIV infected and uninfected children were oral candidiasis and chronic parotitis that were found almost twenty times more frequently in infected compared to uninfected children. A study by Vetter et al of children hospitalized in Abidjan, Ivory Coast, indicated that the most common reasons for admission among HIV-infected children were respiratory infections and malnutrition [17]. Vetter also reported that although most pneumonia cases in paediatric AIDS were caused by the common bacterial pathogens, cases where there were severe respiratory symptoms with an interstitial pneumonitis and poor response to antibiotic treatment were most likely due to P,P. Lymphocytic interstitial pneumonitis (LIP) associated with minimal respiratory signs was usually missed all together in these children. Bakaki et al reported that in Uganda there was a higher incidence of marasmus, kwashiorkor, parotid enlargement, non-specific dermatitis and chronic diarrhoea among infected children older than 18 months compared to uninfected children [18]. Infants more commonly presented with candidiasis, ear discharge, dermatologic disorders, generalized lymphadenopathy, hepatosplenomegally and failure to thrive. Obimbo et al, in a study describing the predictors of early mortality among HIV infected children in Kenya reported that 44.5% of HIV infected children died by the age of one year while 63% had died by the age of two years [19]. Death in this cohort of children was due to infectious complications, the commonest of which were pneumonia (75%), diarrhoea (41%), sepsis (13%) and meningitis (13%). HIV infected children have been found through these studies to develop clinical manifestations early in life that are predictive of HIV infection and that can be used to identify sick children at risk of HIV infection. It is on the basis of these

findings that clinical criteria were developed to help identify children with symptomatic HIV infection to be used in resource poor settings to facilitate prioritization of children who may require counseling and testing to facilitate delivery of HIV-specific care including nutritional support, prophylactic therapy and initiation of antiretroviral therapy. Utility of clinical criteria has however been found through validation studies to vary considerably in different settings depending on the local prevalence of HIV infection and common childhood illnesses such as malnutrition, pneumonia, diarrhoeal diseases and malaria [20, 21] In Africa, signs and symptoms like persistent cough and poor weight gain, which are common in the general population, may not be very useful in discriminating between HIV-infected children and those with malnutrition or tuberculosis without HIV infection [22] This could lead to over-diagnosis of HIV-infection in this kind of setting using clinical criteria.

Children with AIDS have special diagnostic challenges. Many of the clinical signs and symptoms associated with AIDS are similar to those of other common childhood ailments such as pneumonia, malaria, failure to thrive, chronic cough and fever. These difficulties are exemplified by pneumonia which even in the absence of HIV infection has a high prevalence in the paediatric population and is responsible for approximately 30% of deaths in children below five years of age in developing countries [23]. The distinction between one child with bacterial pneumonia and another with tuberculosis, as well as deciding which of these two children might harbor HIV is a major diagnostic challenge, especially where diagnostic facilities are limited or non-existent. Where these facilities are available accurate recognition of signs and symptoms is still required of health personnel who should be well trained and experienced in recognizing these signs and

symptoms. English et al in a study assessing inpatient paediatric care in first referral level hospitals in Kenya reported that absence of standard case definitions for the identification of common illnesses as well as avoidance by health personnel to discuss HIV/AIDS have contributed significantly to childhood mortality in Kenya [24].

Utility of Clinical Criteria

Several studies have been carried out, both among adults and in children, to try to determine the validity of using clinical criteria to identify those most at risk of having HIV infection amongst groups of patients seen at various clinical care settings. Following various constraints and barriers to universal HIV testing in developing countries, the World Health Organization (WHO) in 1985 developed a provisional Clinical Case Definition (CCD) for AIDS in Bangui for use among adult patients in Africa. This case definition, based on five major and six minor clinical signs, was developed in an attempt to identify who might be HIV infected and therefore requiring urgent intervention in a resource poor setting with inadequate HIV diagnostic facilities. In 1987 WHO published a similar case definition for paediatric HIV also to be used in resource poor settings. Several validation studies were done of these two case definitions which reported several drawbacks associated with use of clinical criteria for diagnosis. An evaluation of the Bangui WHO CCD for AIDS among adult patients by Colebunders et al in 1986 in Kinshasa, Zaire reported a high specificity of 90%, a sensitivity of 59% and a PPV of 74% [25]. Amirali W et al in an evaluation of the same CCD in Dar-es-Salaam, Tanzania in 1995 reported a lower sensitivity of 36.6 % while specificity and PPV were high at 90.6% and 93.5% respectively [26]. The researchers however noted that a large number of HIV positive patients in the particular study population presented with signs and

symptoms different from those proposed by the CCD. Many of the infected patients presented with anorectal lesions that were not included in the CCD while P,P, which was one of the criteria in the CCD was a rare finding. With environmental pathogens varying from one geographical region to another and new ones appearing over time, the investigators felt that opportunistic infections could not reliably be used for diagnosis universally

Keou et al in an analysis of the evaluations of the WHO CCD by various researchers noted that though the provisional WHO CCD for adults was easy to use in resource poor settings it appeared to have low sensitivity in cases of full blown AIDS questioning the validity of its use in these cases [27]

Several studies have also been carried out evaluating utility of clinical criteria for HIV in children. Colebunders et al in an evaluation of the provisional paediatric WHO CCD for HIV in Kinshasa, Zaire reported a low sensitivity of 35%, a high specificity of 86% and a PPV of 26% [28]. The researcher in this study felt that the low sensitivity in this study population could be explained by the fact that frequency of major criteria like weight loss > 10 % was not significantly different between HIV infected and HIV negative children.

A study on the recognition of AIDS related signs and symptoms using the same paediatric WHO CCD by health personnel in rural south Rwanda by Hamms et al in 1994 also reported a low sensitivity of 13%, specificity was still high at 94% while PPV was 44% [29]. The researchers in this study felt that the low sensitivity and PPV indicated by the study could be improved by training the health personnel to recognize AIDS related signs and symptoms better especially where laboratory tests are not available. Van Gend et al also evaluating the paediatric WHO CCD in 2003 in Bloemfontein, South Africa had

similar results to the two other researchers with a low sensitivity of 14.5% and a high specificity of 98.6% but PPV was much higher at 81.8% compared to the previous studies [30]. The improved PPV was the result of higher HIV prevalence of 31.1%. The researchers in this study subsequently included certain clinical features like marasmus and splenomegally that were found to be present among many HIV infected children in the study population. This greatly improved the sensitivity of the CCD to 63.6% while specificity slightly decreased to 96.0%. Joubert in a letter validating the improved paediatric WHO CCD for paediatric HIV infection commented that though the CCD indeed had higher sensitivity than the previous CCD the slight decrease in specificity would lead to the inclusion of more false positive cases [31].

Similar studies have been done in Kenya evaluating the provisional paediatric WHO CCD. Mugo et al in a study at Kenyatta National Hospital (KNH) in 1992 on the proportion of HIV positive children identified by the WHO CCD criteria as HIV infected reported a sensitivity of 55.7% with specificity of 85.9% and PPV of 36.4% [32]. Othieno et al in a study evaluating the performance of the same CCD against a positive HIV test and a CD4/CD8 ratio < 0.6 corresponding to severe immunosuppression, reported a sensitivity of 60% with specificity, PPV and NPV were 94%, 94% and 60% respectively by the CCD to identify severe immunosuppression in a HIV infected child [33]. The researcher in this study recommended that further evaluations of clinical criteria should use a gold standard that included CD4/CD8 ratio to a HIV test which was a more objective measure for the presence of disease compared to a laboratory HIV test alone.

IMCI Algorithm for Paediatric HIV

The IMCI algorithm, developed in the year 2000 in South Africa aims at identifying symptomatic HIV infection in children aged less than five years in the early disease stages before they progress to severe immunosuppression. The signs and symptoms that make up the criteria were identified based on disease patterns commonly seen among HIV infected children in southern Africa. Immunologic evaluation of HIV infected children identified by the algorithm as symptomatic for HIV was however not done. Two studies were subsequently carried out, one in South Africa and the other in Ethiopia, to validate the IMCI HIV algorithm. The study by Horwood et al in KwaZulu-Natal, South Africa in 2001, compared the performance of the IMCI HIV algorithm against a HIV laboratory test as well as the performance of a paediatrician [34]. The IMCI algorithm and the paediatrician had sensitivities of 56.1% and 71.7% respectively with specificity of 85% and 90.4% respectively for identifying HIV infection. The paediatrician had a higher PPV of 75.1% compared to 60% for the IMCI algorithm. The inclusion of clinical features found to have the highest predictive value for HIV infection within the study population improved the sensitivity of the algorithm to 67.2% with a specificity of 81.5% within that population. The improved algorithm was then adapted for use in several African countries including Kenya. A second validation study of the improved algorithm by Lulseged in Addis Ababa, Ethiopia in 2003, indicated a very low sensitivity of 16.3% with a specificity, PPV and NPV of 98.1%, 39.6% and 93.7% respectively [20]. The researchers in this particular study felt inclusion of signs like chronic parotid enlargement and persistent lymphadenopathy which were common in their study population would improve the sensitivity of the algorithm in the Ethiopian setting. The results of these

studies go to further strengthen the point that clinical criteria perform differently depending on varying disease prevalence and performance may be improved by taking into account the prevailing disease patterns in a region. Inwani et al evaluated performance of the IMCI algorithm in diagnosing HIV infection in children aged 18 months or less at Kenyatta National Hospital and also reported a low sensitivity of 19% [35]. Specificity was however high at 96% while PPV and NPV were 13% and 67% respectively. Inclusion of severe immune deficiency as determined by CD4 T lymphocyte percent to a positive HIV test, improved the sensitivity, PPV and NPV of the algorithm to 74%, 30% and 83% respectively while specificity declined to 83% for identifying severe immunosuppression. The researcher in this study concluded that the low sensitivity of the algorithm resulted in HIV infected children aged less than 18 months being identified late (Table 1).

The IMCI HIV algorithm was developed with the hope of identifying HIV infected children with suggestive symptoms to allow for prioritization in referral for HIV testing and further HIV treatment. The study by Inwani [35] is the only study on the IMCI algorithm that has included a CD4 T lymphocyte percent to a positive HIV test in evaluating the algorithm. Inclusion of severe immunosuppression as defined by CD4 percent greatly improved sensitivity of the algorithm from 19% to 74%. The patient population in this study was recruited from a tertiary hospital with many referral cases.

Table 1: Summary of Evaluation Studies on the Provisional WHO Clinical Case Definition for AIDS and the IMCI HIV Algorithm.

Author / Country	Sample Size	Gold standard	Sensitivity	Specificity	PPV ^(a)	NPV ^(b)
Evaluations of WHO Clinical Case Definition for adults						
Colebunders [25] / Zaire	174	ELISA ^(c)	59.0%	90.0%	74.0%	-
Amirali [26] / Tanzania	601	ELISA	36.6%	90.6%	93.5%	27.9%
Evaluations of WHO Clinical Case Definition for children						
Colebunders [28] / Zaire	159	ELISA	60.0%	90.0%	28.0%	-
Hamms [29] / Rwanda	472	ELISA	13.0%	94.0%	44.0%	-
Van Gend [30] / South Africa	300	ELISA	14.5%	98.6%	81.8%	-
Mugo [32] / Kenya	552	ELISA	55.7%	85.9%	36.4%	-
Othieno [33] / Kenya	156	ELISA with CD4/CD8 ratio <0.6	60.0%	94.0%	94.0%	60.0%
Evaluations of the IMCI HIV algorithm						
Horwood [34] / South Africa	690	HIV-RNA PCR	62.7%	81.5%	60.0%	82.2%
Lulseged [20] / Ethiopia	1,777	HIV-RNA PCR	16.3%	98.1%	39.6%	93.7%
Inwani [35] / Kenya	1,418	HIV-DNA PCR, CD4%	74.0%	83.0%	30.0%	83.0%

^(a) PPV – positive predictive value

^(b) NPV – negative predictive value

^(c) ELISA-Laboratory-based enzyme-linked immunosorbent assay

It was therefore necessary to still evaluate the performance of the IMCI HIV algorithm in the management of paediatric HIV at a first level referral health facility in Kenya where the algorithm is mainly intended for use. Possible uses of the clinical criteria in this setting would include:

1. Defining a high risk group in whom testing is essential, and by exclusion a group in whom testing is less essential if resources for testing are limited.

2. Defining a high risk group likely to require early antiretroviral treatment if it has a high sensitivity for severe immunosuppression.

STUDY JUSTIFICATION

In Sub-Saharan Africa, the HIV/AIDS epidemic remains a major cause of morbidity and mortality both among adults and children. There are currently 25.4 million adults and children living with HIV in Sub-Saharan Africa and 3.2 million people were newly infected in the year 2006 alone. Although recent statistics by the KDHS indicate a decline in HIV prevalence in Kenya to <7%, the disease still contributes significantly to disease burden in the country and has worsened the situation in the already fragile health care system in the country.

Care of HIV infected children living in resource poor settings poses enormous challenges to the already overburdened health care system in Kenya. Lack of clinical suspicion and adequate laboratory facilities for diagnosis and staging of HIV infection often result in delays in identifying infected children and initiation of prophylactic and specific treatment. The result is that the effective antiretroviral drugs that are becoming increasingly available fail to be of maximum benefit to the patients. Supportive treatment modalities that have been shown to decrease morbidity and prolong life even without use of antiretroviral drugs are also not availed early enough to patients that need them. The IMCI algorithm is intended to guide clinicians in the identification of HIV infected children aged less than five years presenting to health facilities with suggestive signs and symptoms who need to be referred for HIV testing, and to be started on prophylaxis and depending on their clinical and/or immunologic stage on antiretroviral therapy. Previous studies have indicated that clinical criteria are not highly effective when used as screening tools for infection, but are highly specific and perform well in identifying the more advanced stages of disease. The IMCI HIV algorithm is currently recommended by

the Division of Child Health, Ministry of Health, in Kenya for use at primary level health facilities for the prioritization for referral for HIV testing and further care as appropriate, of symptomatic HIV infected children aged less than five years. Due to lack of appropriate laboratory HIV test kits especially for children aged 18 months and less, as well as erratic supply of rapid test kits for older children the IMCI HIV algorithm is still used at primary health facilities for prioritizing children for referral for HIV testing. Based on the history of poor performance of clinical criteria as screening tools for infection and the fact that this particular algorithm has not been evaluated against the immunologic status of HIV infected children, an evaluation to define its utility in the management of paediatric HIV infection in Kenyan settings is justified

OBJECTIVES

The objectives of the study were:

1. To estimate the proportion of HIV infected children among children aged less than five years admitted at Mbagathi District Hospital.
2. To determine what proportion of HIV infected children identified by IMCI algorithm as having symptomatic HIV fulfill the immunologic criteria for initiation of antiretroviral therapy.

METHODS AND PARTICIPANTS

Study Design

This was a hospital-based descriptive cross-sectional study carried out among hospitalized children less than five years of age at the Mbagathi District Hospital paediatric ward. The Mbagathi District Hospital is a first referral level health facility within the city of Nairobi with a bed capacity of approximately 200 providing both in-patient and out-patient health services. The catchment area is largely the informal settlements to the south-east of Nairobi. It has one paediatric ward with a bed capacity of 40 but at any one time approximately 60 children are admitted. Patients are admitted from both the Paediatric Outpatient Clinic (POPC) and the Maternal and Child Health (MCH) Clinic. There are on average ten new admissions to the paediatric ward per day.

Study Population

Children aged between two and fifty nine months admitted to the paediatric ward of Mbagathi District Hospital.

Case selection

Inclusion criteria

Children aged between two and fifty nine months admitted to the paediatric ward of Mbagathi District Hospital whose parents/guardians gave consent for inclusion of the child in the study.

Exclusion Criteria

Children already on antiretroviral therapy.

Sample size estimation

The sample size calculation was primarily driven by a desire to specify the precision that could be obtained when calculating the sensitivity of the IMCI algorithm at detecting HIV infection. To make the calculations the following assumptions were made:

- 1) The IMCI criteria might have the same sensitivity, 70%, as observed in South Africa in the study by Horwood [34].
- 2) We would wish to specify 95% confidence limits of +/- 20% around this sensitivity of 70%.
- 3) Sensitivity is estimated as the proportion of HIV positive cases identified by the test, therefore we need to estimate the size of the population (the denominator) that would provide for a proportion of 70% to be estimated with precision +/- 20%.
- 4) The formula (below) for calculating sample size by controlling confidence intervals was used to obtain the minimum sample size for the study [36, 37]

$$n = Z\alpha_2^2 (p) (1 - p) / r^2$$

Where:

- n is the minimum number of HIV positive patients who were to be included in the study population = 21.
- $Z\alpha_2^2$ is the standard normal deviate corresponding to 95% confidence = 1.96.
- p is the estimated sensitivity of the diagnostic algorithm = 0.7 based on the validation study in South Africa by Horwood et al [34].
- r is the difference between the 95% confidence interval limits set for this study = 0.2 (with the 95% confidence interval set between 0.5 and 0.9).

5) To calculate the minimum sample size that is required to yield at least 21 HIV positive children an HIV prevalence rate of 13% among children admitted to the paediatric wards at Mbagathi District Hospital was assumed [based on data from Oyieko (38)].

A minimum sample size of 153 patients was therefore required so that at least 21 HIV infected children (sufficient to facilitate analysis) would be included the sample.

As many of the assumptions were based on limited data and in the hope of reporting the results with even greater precision the aim was to study a total of 300 patients.

Power of the study: The study did not have a null hypothesis and sample size was based on the study objectives and computed based on a level of precision. The levels of precision for prevalence, sensitivities and specificities are indicated.

Sampling technique

Consecutive sampling technique was used to select study subjects. All patients admitted the previous day, approximately ten patients per day, were recruited into the study excluding those that did not fit in the inclusion criteria.

Data Collection

The investigator visited the paediatric ward from Monday to Friday between 8 am and 5 pm. After obtaining informed consent from the legal guardians of the children, data was extracted using a pre-set questionnaire (Annex 1). All recruited children were classified as either having signs of symptomatic HIV infection (IMCI positive), or as NOT having signs suggestive of symptomatic HIV infection (IMCI HIV negative) according to the

IMCI HIV algorithm. The investigator was blinded to any previous HIV test results or the rapid test result until after the application of the IMCI HIV algorithm

Counseling and rapid HIV testing was conducted for all children in the Counseling Room by the investigator with the assistance of two trained counselors selected by the investigator. For children who already had a HIV test done the test result was sought from the file after history and physical examination.

Children found to be HIV positive using laboratory methods (HIV +ve) or classified as IMCI +ve had blood samples taken for CD4+ T-lymphocyte percentage evaluation

Definitions of Cases and Terms

The IMCI Algorithm for Identification of Symptomatic HIV Infection in Children Less Than Five Years.

Presence or absence of three or more of the following:

- Tuberculosis in any parent in the last five years or confirmed HIV infection in a parent.
- Features of pneumonia in the patient (currently or previously).
- History of two or more episodes of persistent diarrhoea, lasting more than fourteen days.
- Growth faltering or weight less than the third centile (below “very low weight curve” in the growth monitoring card), for the child’s age.
- Enlarged lymph nodes > one cm in two or more of the following sites: the neck, the axilla or the groin region.
- Oral thrush at presentation (age > two months).

Pneumonia

Pneumonia was defined as the presence of cough or difficulty in breathing and at least one of the following:

- a respiratory rate greater than 50 breathes per minute for children less than one year and greater than 40 breathes per minute for children between one and five years.
- presence of lower chest wall in-drawing.

Tuberculosis in a parent

Diagnosis of tuberculosis in a parent was established through history by asking the parent/guardian if either of the child's parents had received treatment for TB in the past or was currently being treated for TB

Growth assessment

During clinical examination the child's weight and height were taken and the investigator looked at the child's growth monitoring card where it was available.

For assessment of growth as a criteria item for IMCI classification the following were used.

- Weight for age less than the third centile at the time of examination, or
- Growth faltering defined as weight growth velocity $<5\%$ for more than two months [39].

These two measurements were used based on the weight criteria as indicated in the IMCI HIV algorithm at the time the study was conducted. Failure to include low weight for height (wasting) and low height for age (stunting) in the assessment criteria could have led to misclassification of children with acute malnutrition and chronic malnutrition.

Persistent diarrhea

Persistent diarrhea was defined as diarrhea that began acutely and lasted more than fourteen days.

Diarrhoea was defined as the presence of three or more motions of loose stool in twenty four hours.

Chronic fever

Chronic fever was defined as fever lasting for longer than one month, either intermittent or constant with reported lack of response to antibiotics or antimalarials [40].

HIV Case Definition by IMCI Criteria

A child was identified as symptomatic for HIV infection if three or more of the six clinical criteria were present.

Clinical findings and HIV classification based on the IMCI algorithm were clearly documented on a data sheet for every subject before blood was taken for HIV testing.

Laboratory testing for HIV

A HIV test was then carried out for every child as described below.

Counseling and Testing

Diagnostic counseling and testing (DCT) for HIV was carried out by the investigator with the assistance of two DCT counselors identified by the investigator. DCT is provided as part of the diagnostic workup of patients in the context of medical care. It is now national policy in Kenya that DCT should be offered to patients presenting at health care facilities for treatment. It includes the diagnosis of HIV infection in routine medical care in order to achieve better treatment outcomes for patients. It uses an opt-out approach in which it is assumed that presentation with signs and symptoms of disease to a health care facility

implies a desire by the patient for accurate diagnosis, therapy and care including testing for HIV. The HIV test is offered as part of the routine tests to be done for the patient but all patients are informed that the test will be done and that they have a right to decline having the test. The DCT strategy had been adopted by the Mbagathi District Hospital at the time the study was carried out and was offered for patients presenting with signs and symptoms suggestive of HIV.

Procedure:

Capillary blood samples were collected from the participants in the Counseling Room and were immediately tested using two different rapid HIV test kits.

Determine HIV1/2™ rapid test kit (Abbot Laboratories) was used as the screening test. The test has a sensitivity of 100% and a specificity of 99%.

Bioline HIV1/2™ rapid test kit (Standard Diagnostics, Kyonggi-Do, Korea) with a sensitivity of 100% and a specificity of 99.8% was used as the confirmatory test.

A positive sample was defined as one that gave positive results on both the screening and confirmatory tests.

A negative sample was defined as one that gave negative results on both the screening and confirmatory tests.

An indeterminate sample was defined as one that gave varying results on the screening and confirmatory tests.

Indeterminate samples were taken for the long ELISA test using Vironostika HIV Uni-Form II Ag/Ab™ (Organon Teknika, Boxtel, Netherlands).

Children aged less than eighteen months found to have positive results on either of the rapid tests had a DNA PCR test (Amplicor HIV-1 Monitor™ Roche Diagnostics, Basel,

Switzerland) carried out to confirm the actual presence of infection. Children aged over 18 months and still breastfeeding, with a positive test result on either of the rapid tests also had a DNA PCR test done one month after cessation of breastfeeding.

Doing two rapid antibody tests before doing viral PCR testing for a child aged less than 18 months is what is recommended in the national guidelines. This has however not been validated and was a weakness in the study that could have led to misclassification of HIV infected children with waning antibodies who do not yet have enough antibody response of their own

For DNA PCR testing, dried blood spots (DBTs) were collected and transported to the Kenya Medical Research Institute Laboratories, Kisumu

For all children identified by the IMCI HIV clinical algorithm as symptomatic for HIV and children confirmed by laboratory test to be HIV positive, venous blood samples were taken for evaluation of CD4+ T-lymphocyte percentages

Immunologic classification of children based on CD4 percentage was done based on the WHO 2006 guidelines for grading immunosuppression Table 2.

Table 2: WHO grading of severity of immunosuppression using CD4+ T lymphocyte percentage in HIV infected children.

Immunological category	Age of the child		
	< 12 months	12-35 months	36 – 60 months
	CD4%	CD4%	CD4%
No immunosuppression	>35%	>30%	>25%
Mild immunosuppression	31 – 35%	26 – 30%	21 – 25%
Advanced immunosuppression	26 – 30%	21 - 25%	16 - 20%
Severe immunosuppression	≤ 25%	≤ 20%	≤ 15%

Data Recording and Analysis

Data was first collected using precoded questionnaires then all clinical and laboratory results were entered into SPSS software (version 10.0) and cleaned for inconsistencies. Data on age distribution and clinical presentation of the study population was summarized into frequency tables. Comparative analysis of frequency of clinical signs and symptoms between HIV positive and HIV negative children was done using the Chi-square test (or the Fisher's Exact test where the numbers were small). p-values and odds ratios were calculated for the various signs and symptoms.

The children were then classified depending on their IMCI classification and HIV status by laboratory methods into 4 groups: Group A -HIV+ve, IMCI+ve; Group B -HIV+ ve, IMCI-ve; Group C -HIV-ve, IMCI+ve; and Group D -HIV-ve, IMCI-ve.

Median CD4+ T lymphocyte percentages were determined for the groups and Wilcoxon rank test for medians was used to assess for difference between these medians.

The HIV positive group was further classified into two immunologic categories. Children with severe immunosuppression were put in one group while the other group consisted of children with advanced, mild or no immunosuppression. Sensitivities, specificities, PPV and NPV for identifying HIV infection and severe immunosuppression were then calculated for the IMCI algorithm.

For comparative analysis between:

- i) categorical variables and HIV diagnosis, chi-square or Fischer's exact test were used.
- ii) continuous variables and HIV diagnosis non-parametric methods (Mann-Whitney) were used as most variables did not follow a normal distribution.

Statistical significance was defined as a p value < 0.05 .

Ethical Considerations

Permission to carry out the study was sought and obtained from the Kenyatta National Hospital Ethical Review Committee and the Mbagathi District Hospital Management Team, through the Medical Superintendent.

Voluntary written informed consent was obtained from parents/guardians for recruitment of their children into the study and for HIV-testing. Parents/guardians signed an attached consent form (see Annex 3).

Diagnostic counseling and testing was provided by trained counselors (including the investigator).

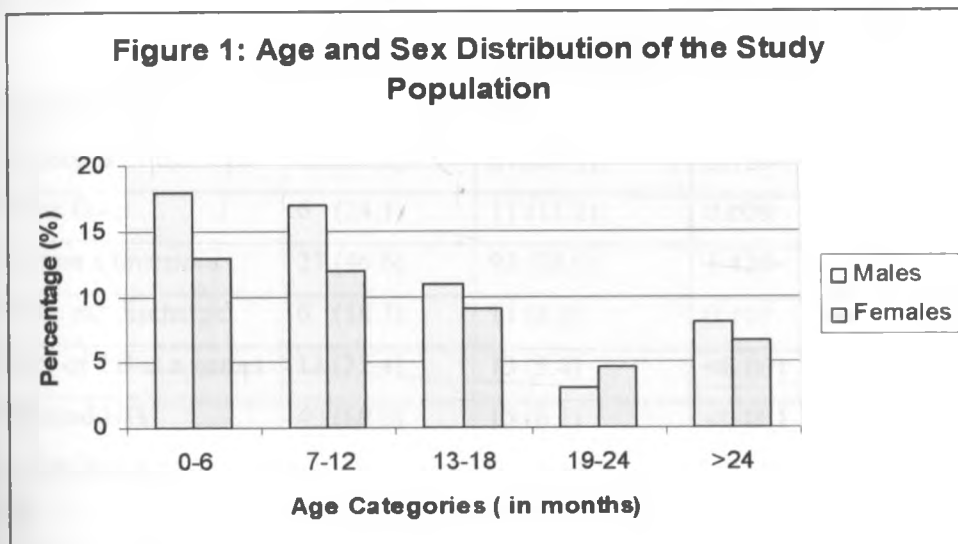
Test results informed immediate care of the child. Children identified as HIV positive were referred to the CCC in MDH through the ward doctor where supportive care and antiretroviral therapy are available.

HIV testing was also offered for parents of children recruited in the study by the investigator.

RESULTS.

Characteristics of study participants.

Recruitment of study participants was done between the months of January and June 2007. A total of 300 children were recruited into the study. Only 21(6.6%) of parents/guardians who were asked for permission for their children to be recruited into the study refused to give consent. Over one half of the children recruited (54.3%) were males and 137 (45.7%) were females. Males were more than females in all age categories except in the 19-24 months age category. The age range of the children was 2 months to 59 months with a median age of 11 months. Majority (77%) of the children were aged less than 18 months while 54.6% were aged less than 1 year, (Figure 1).



Clinical Presentation of the study population.

i) Clinical symptoms.

The commonest clinical symptom among both HIV positive and HIV negative patients was episodic diarrhea at 37.9% and 27.7% respectively. Persistent diarrhea was present in 31% of HIV infected and 11.6% of HIV negative children. History of recurrent

admissions though not a clinical symptom was present in 46% of HIV positive and 38% of HIV negative children. Persistent diarrhea, history of confirmed HIV infection in a parent and history of TB in a parent were significantly more common in HIV positive compared to HIV negative children (p-value < 0.001). Chronic fever was also significantly more common among HIV positive children (p-value 0.009). Eight children were accompanied by a non-parent caretaker. Data was collected on presence or absence of confirmed HIV infection in a parent. Parents who knew their status and were HIV negative and those who did not know their HIV status were grouped together and classified as no confirmed HIV infection in the parent. Table 3.

Table 3: Frequency of clinical symptoms in the study population.

Variable	Number of children (%)		P value	Odds ratio (95% CI)
	HIV positive	HIV negative		
Persistent diarrhea	18 (31.0)	28 (11.6)	<0.001	3.44 (1.65 – 7.17)
≥ 2 episodes of diarrhea	22 (37.9)	67 (27.7)	0.120	1.60 (0.84 – 3.03)
Chronic fever	6 (24.1)	11 (11.2)	0.009	2.53 (1.16 – 5.52)
Recurrent admissions	27 (46.6)	92 (38.0)	1.420	1.42 (0.77 – 2.63)
Chronic ear discharge	6 (10.3)	11 (4.5)	0.101	2.42 (0.76 – 7.51)
History of TB in a parent	13 (22.4)	13 (5.4)	<0.001	5.09 (2.05 – 12.63)
Confirmed HIV infection in parent	40 (69.0)	15 (6.2)	<0.001	33.63 (14.75 – 78.16)
Total	132	237	-	-

ii) Clinical signs.

The commonest clinical sign in the study population was pneumonia present in 87.9% of HIV positive and 76.9% of HIV negative children respectively. This was followed by chronic fever which was present in 81.0% of HIV positive and 70.7% of HIV negative children. Weight below 3rd centile for age, oral candidiasis and lymphadenopathy were

significantly more common among HIV positive children, all with p-values <0.001 (See table 4).

Height below 3rd centile for age, splenomegally and hepatomegally which are not included in the IMCI HIV algorithm were also significantly more common in HIV positive children (p value < 0.001).

Chronic parotitis and chronic otitis media were rare in the study population (1.0% and 0.3% respectively) and none of the children recruited in the study had herpes zoster.

Table 4: Frequency of clinical signs in the study population.

Variable	Number of children (%)		P value	Odds ratio (95% CI)
	HIV positive	HIV negative		
Pneumonia	51 (87.9)	186 (76.9)	0.060	2.19 (0.89 – 5.62)
Weight below 3 rd centile	30 (51.7)	52 (21.5)	<0.001	3.91 (2.06 – 7.45)
Height below 3 rd centile	23 (39.7)	28 (11.6)	<0.001	5.02 (2.48 – 10.21)
Abnormal temperature	47 (81.0)	173 (71.5)	0.140	1.70 (0.80 – 3.71)
Oral candidiasis	41 (70.7)	73 (30.2)	<0.001	5.58 (2.86 – 11.0)
Lymphadenopathy	15 (25.9)	8 (3.3)	<0.001	10.20 (3.77 – 28.25)
Splenomegally	15 (25.9)	10 (4.1)	<0.001	8.09 (3.17 – 20.95)
Hepatomegally	41 (70.7)	85 (35.1)	<0.001	4.45 (2.29 – 8.73)
Lower chest indrawing	46 (79.3)	79 (32.6)	<0.001	7.91 (3.80 – 16.77)
Total	309	694	-	-

Clustering of the IMCI Components in the study population.

The IMCI algorithm identified 91 (30%) of children in the study population as symptomatic for HIV infection. Of these, 45 children were confirmed by laboratory tests to be HIV positive while 46 were HIV negative. Majority (47.9%) of the HIV negative children had only one IMCI criteria item present while less than 20% had three or more

IMCI criteria items present. Majority of the HIV infected children had either three (37.9%) or four (27.6%) IMCI criteria items present. Table 5.

Table 5: Clustering of the IMCI Components in the study population.

Number of IMCI criteria items present	Number of children (%)		Total number of children
	HIV positive	HIV negative	
0	0 (0.0)	25 (10.3)	25
1	5 (8.6)	116 (47.9)	121
2	7 (12.1)	58 (24.0)	65
3	22 (37.9)	36 (14.9)	58
4	16 (27.6)	4 (1.65)	20
5	5 (8.6)	3 (1.25)	8
Total	58 (100)	242 (100)	300

HIV status of the study population based on laboratory test results.

The HIV prevalence in the study population was 19.3% (58/300) (95% CI 14.8 – 23.8).

The proportion of HIV infected children was 17.7% for children aged less than 12 months, 21.6% for children aged 12-35 months and 20.6% for children aged 36-59 months. See Table 6.

Table 6: HIV status by age group of the study population based on laboratory test results.

HIV Status	Age in months		
	0 – 11	12 – 35	36 – 59
Positive	29 (17.7%)	22 (21.6%)	7 (20.6%)
Negative	135 (82.3%)	80 (78.4%)	27 (79.4%)
Total	164 (100%)	102 (100%)	34 (100%)

Performance of the IMCI algorithm in identifying HIV infection in the study population.

Sensitivity and Specificity

The IMCI HIV algorithm correctly identified 45 out of 58 HIV infected children to be symptomatic for HIV infection giving a sensitivity of 77.6% (95% CI 66.9 - 88.3).

Of 242 children confirmed by laboratory methods to be HIV negative the IMCI algorithm classified 196 as asymptomatic for HIV infection giving a specificity of 81.0% (95% CI 75.9 – 85.9) by the algorithm to exclude presence of HIV infection.

Positive and Negative Predictive Values

Within the study population, 30% (91/300) of children were classified by the IMCI HIV algorithm as having symptoms suggestive of HIV infection. Approximately half of these children (45/91) were confirmed to be HIV positive by laboratory tests giving a PPV of 49.9% (95% CI 39.1 – 59.7). Of 209 children classified by the algorithm as asymptomatic for HIV infection 196 were confirmed by laboratory tests to HIV negative giving an NPV of 93.7%. (95% CI 90.5 – 97.1) See Table 7.

Table 7: HIV Test Results and IMCI classification of the study population.

		HIV test result by laboratory methods		Total
		Positive	Negative	
IMCI classification	Positive	45 (77.6%)	46 (19.1%)	91
	Negative	13(22.4%)	196 (80.9%)	209
Total		58 (100%)	242 (100%)	300

IMCI classification and HIV status of children aged 18 months and below.

Sensitivity and Specificity

Of 300 children recruited in the study, 77.0% (231/300) were aged 18 months or less. HIV prevalence in this age group was 18.2% (42/231). In this age category the algorithm identified 31/42 HIV infected children as symptomatic for HIV giving sensitivity of 73.8% (95% CI 60.5 – 87.1). Of the 189 children who were HIV negative the algorithm classified 154 as asymptomatic giving a specificity of 81.5% (95% CI 76.0 – 87.0).

Positive and Negative Predictive Values

PPV and NPV of the IMCI algorithm in this age category were 50.0% (95% CI 34.9 – 58.9%) and 93.3% (95% CI 89.5 – 97.1%) respectively. See Table 8.

Table 8: HIV status and IMCI Classification of children aged 18 months and below.

		HIV test results by laboratory methods		Total
		Positive	Negative	
IMCI class	Positive	31 (73.8%)	35 (18.5%)	66
	Negative	11 (26.2%)	154 (81.5%)	165
Total		42 (100%)	189 (100%)	231

IMCI Classification and HIV status of children over 18 months old.

Sensitivity and Specificity

Children aged over 18 months constituted 23.0% (69/300) of the study population. Of these children, 23.2% (16/69) were confirmed to be HIV positive using laboratory methods. The IMCI algorithm a sensitivity of 87.5% (95% CI 71.3 – 103.7) as it identified 14 of 16 HIV infected children and a specificity of 79.2% (95% CI 66.9 – 91.5) in this age category.

PPV and NPV

The PPV of the algorithm in this age group was 56.0% (95% CI 36.5 – 75.5) and NPV was 95.4% (95% CI 89.5 – 101.5). See Table 9.

Table 9: HIV status and IMCI Classification of children aged over 18 months.

		HIV test results by laboratory methods		Total
		Positive	Negative	
IMCI class	Positive	14 (87.5%)	11(20.8%)	25
	Negative	2 (12.5%)	42 (79.2%)	44
Total		16 (100%)	53(100%)	69

CD4+ T-lymphocyte percentage distribution.

CD4+ T-lymphocyte percentages were performed for 86 children in the study population.

These were children who were either classified by IMCI algorithm as symptomatic for HIV infection (IMCI +ve) or were confirmed to be HIV positive by laboratory methods (HIV +ve). The distribution of CD4+ T-cell percentages in relation to HIV status and IMCI classification is shown in Table 10.

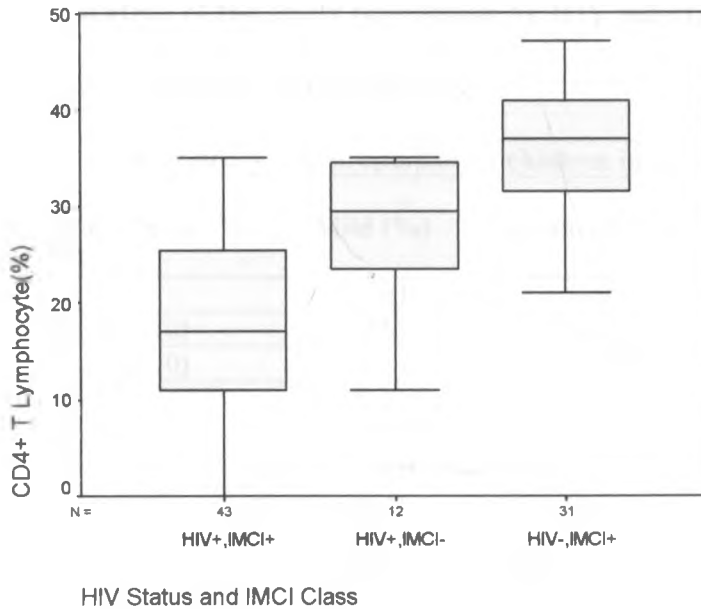
The CD4+ T lymphocyte percentages were lowest (median CD4% of 17.0%), among children who were **HIV +ve and IMCI+ve (Group A)**. The group classified as **HIV+ve, IMCI–ve (Group B)** had a median CD4% of 29.5% while the group classified as **HIV–ve, IMCI+ve (Group C)** had the highest median CD4% of 37.0%. The difference in median CD4 T lymphocyte percentages between Groups A and B and between Groups A and C, using Wilcoxon rank test were statistically significant (p-value 0.001). Table 10 and Figure 2.

Table 10: Distribution of CD4+ T-lymphocyte percentages in relation to HIV status and IMCI classification.

HIV status	IMCI classification	N	Median CD4% (Inter-quartile range)
HIV+ve	IMCI +ve (Group A)	43	17.0 (31.0 – 42.0)
	IMCI-ve (Group B)	12	37.0 (11.0 – 26.0)
HIV-ve	IMCI+ve (Group C)	31	29.5 (21.8 – 34.8)

Data in table 10 is graphically illustrated in Figure 2.

Figure 2: CD4+ T-lymphocyte percentages by HIV status and IMCI class.



The line at the centre of the each box represents the mean CD4% for that category while the upper and lower edges of the boxes represent the 95% confidence interval. The whiskers represent the 3rd and 97th percentiles for the CD4% counts within the particular category.

Immunological grading in relation to HIV status and IMCI classification for different age groups.

Majority (50%) of the children in group A across all the age categories had CD4 percent counts in the immune category of severe immunosuppression, and more than 70% had either advanced or severe immunosuppression. Children in Group B across all the age categories had comparable proportions of children with CD4 percent counts in the immune categories of mild, advanced and severe immunosuppression. The numbers of children aged 12 to 35 months and 36 to 59 months were low and did not allow for multiple sub-group analysis. Table 11.

Table 11: Classification of the study population by HIV infection status, IMCI criteria and CD4+ T lymphocyte percentages.

Degree of immunosuppression (based on CD4+ %)	Frequency and proportion of children in each immune category				
	None (%)	Mild (%)	Advanced (%)	Severe (%)	Total
HIV +ve					
< 12 months	0 (0)	7 (26.9)	6 (23.1)	13 (50.0)	26
12 – 35 months	0 (0)	4 (18.2)	6 (27.3)	12 (54.5)	22
≥ 36 months	3 (42.9)	0 (0)	0 (0)	4 (57.1)	7
Sub-total	3	11	12	29	55
HIV+ve, IMCI+ve Group A					
< 12 months	0(0)	4 (21.1)	4 (21.1)	11 (57.9)	19
12 – 35 months	0 (0)	2 (10.5)	6 (31.6)	11 (57.9)	19
≥ 36 months	1 (20.0)	0 (0)	0 (0)	4 (80.0)	5
Sub-total	1	6	10	26	43
HIV+ve, IMCI-ve Group B					
< 12 months	0 (0)	3 (42.9)	2 (28.6)	2 (28.6)	7
12 – 35 months	0 (0)	2 (66.7)	0 (0)	1 (33.3)	3
≥ 36 months	2 (100)	0 (0)	0 (0)	0(0)	2
Sub-total	2	5	2	3	12
HIV-ve, IMCI +ve Group C					
< 12 months	10 (55.6)	6 (33.3)	1 (5.6)	1 (5.6)	18
12 – 35 months	7 (87.5)	1 (12.5)	0 (0)	0 (0)	8
≥ 36 months	5 (100)	0 (0)	0 (0)	0(0)	5
Sub-total	22	7	1	1	31
Total	25	18	13	30	86

In group C, more than 50% of the children aged less than 12 months had CD4+ T lymphocyte percentage counts in the range of no immunosuppression. Numbers of children in the age groups 12 to 35 months and 36 to 59 months were again low. (Table 11).

Median CD4+ T-Lymphocyte Distribution by HIV Status and IMCI Classification.

For all the age categories, children in Group A had the lowest median CD4+ T-lymphocyte percentage compared to those in Group B and C. See Table 12 and Figures 3, and 4. Children in Group C had the highest median CD4+ T-lymphocyte percentages for the age categories less than 12 months and 12 to 35 months (median CD4% 37.0% and 33.5%). p-values were generated using the Wilcoxon rank test for medians.

Table 12: Median CD4+ T-Lymphocyte distribution by HIV status and IMCI classification for different age categories.

Age in months	True HIV status	IMCI Class	CD4+ T-lymphocyte percentage-n (%)	
			Median	P value with A as reference point
<12 months n = 44	HIV+ve	IMCI+ve (A)	20.0	
		IMCI -ve (B)	30.0	0.052
	HIV-ve	IMCI+ve (C)	37.0	0.012
Age 12-35 months n = 30	HIV+ve	IMCI+ve (A)	18.0	
		IMCI -ve (B)	27.0	0.452
	HIV-ve	IMCI+ve (C)	33.5	0.016

Figure 3: CD4+ T-Lymphocyte Percentage distribution by HIV status and IMCI classification for children ≤ 12 months of age.

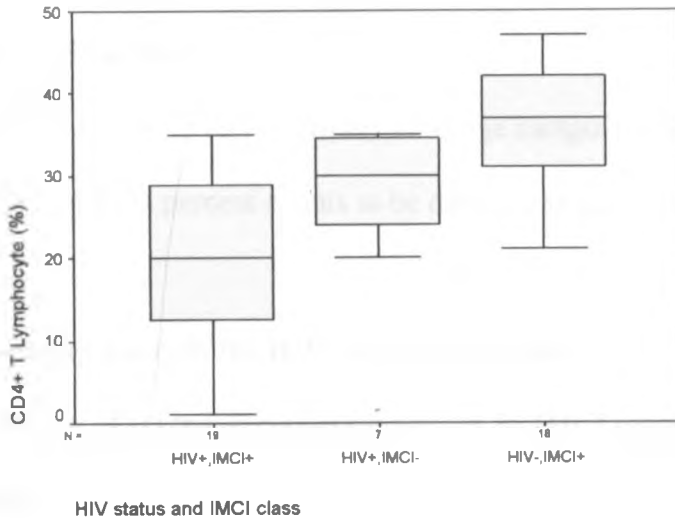
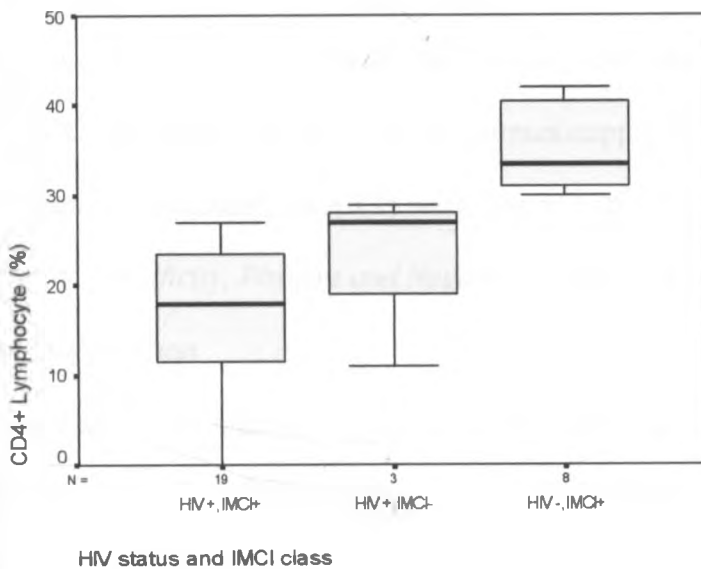


Figure 4: CD4+ T-Lymphocyte Percentage distribution by HIV status and IMCI classification for children aged 12 to 35 months.



The difference in the median CD4% for Group A (**HIV+ve, IMCI+ve**) children and Group B (**HIV+ve,IMCI-ve**) children was not statistically significant (p value 0.452).

The difference in median CD4% for Group C (HIV+ve, IMCI-ve) and Group A (HIV-ve, IMCI+ve) children was however statistically significant (p value 0.016).

CD4 T- lymphocyte Distribution by HIV status and IMCI classification for children aged > 35 months.

Children who were HIV positive in this age category were too few to allow for any sub-analysis of CD4 percent counts to be done in the age group.

Sub-group analysis for HIV Infected children.

Prediction of severe immunosuppression by IMCI algorithm among HIV infected children.

The following analysis was restricted to the subset of 58 HIV infected children.

HIV infected children were categorized into two groups based on their CD4 percentages: those with severe immunosuppression and those not severely immunosuppressed (those with advanced, mild and no immunosuppression). Sensitivity, specificity, NPV and PPV of the IMCI algorithm to identify severe immunosuppression in HIV infected children (those requiring beginning of ART) were determined.

Sensitivity, Specificity, Positive and Negative Predictive Values for Severe immunosuppression

The IMCI algorithm identified 26 out of 29 HIV infected children with severe immunosuppression giving a sensitivity of 89.6% (95% CI 78.5 – 100.7). Specificity was much lower at 34.5% (95% CI 17.2 – 51.8) while PPV and NPV were 57.8% (95% CI 43.4 – 72.2) and 76.9% (95% CI 54.0 – 99.8) respectively. See Table 13.

Table 13: Severity of immunosuppression of HIV infected children by IMCI classification.

IMCI Class	Degree of Immunosuppression, n (%) based on CD4%		N
	Severe	None, mild or advanced	
Positive	26 (89.6%)	19 (65.5 %)	45
Negative	3 (10.4%)	10 (34.5%)	13
Total	29(100%)	29 (100%)	58

χ^2 test, $p=0.028$

Prediction of Severe and Advanced Immunosuppression by IMCI Algorithm.

HIV infected children were also categorized into those with advanced and severe immunosuppression in one group and those with mild or no immunosuppression in another group. The term advanced immunosuppression is now used to refer to those children initially classified as having moderate immunosuppression as this immune category of children have been found to be at high risk of rapid progression to severe immunosuppression.

Sensitivity, Specificity, Positive and Negative Predictive Values

The IMCI algorithm identified 36 out of 41 HIV+ve children with advanced and severe immunosuppression giving a sensitivity of 87.8% (95% CI 77.8 – 97.8). It classified 8 out of 17 HIV+ve children with mild or no immunosuppression as asymptomatic for HIV infection giving a low specificity of 47.1% (95% CI 23.4 – 70.8). The PPV for advanced and severe immunosuppression was 80.0% (95% CI 68.3 – 91.7) and the NPV was 61.5% (95% CI 35.0 – 88.0). See Table 14.

Table 14: Prediction of Advanced and Severe immunosuppression by IMCI HIV algorithm among HIV infected children.

IMCI class	Degree of Immunosuppression based on CD4%		N
	Advanced and Severe	None and Mild	
Positive	36 (87.8%)	9 (52.9%)	45
Negative	5 (12.2%)	8 (47.1%)	13
Total	41(100%)	17 (100%)	58

χ² test, p=0.01

DISCUSSION

This study sought to assess the utility of the IMCI HIV algorithm in children aged between two and 59 months at a first level referral hospital in Kenya. Of the 300 children recruited in the study at MDH 77.8% were aged less than 18 months.

The HIV prevalence within this hospital based study population at MDH was 19.3%. This prevalence was higher than that reported in similar hospital-based study by Inwani [35] of 10.2%. The study by Inwani evaluated the performance of the IMCI HIV algorithm among children aged 18 months or less at KNH. A different study by Oyieko et al [38] assessing the acceptability of routine provider-initiated HIV-testing, reported a prevalence of 13.4% which included both HIV-infected and HIV-exposed children aged between three days and 12 years. A PCR-DNA test was not done to confirm HIV infection in exposed children aged less than 18 months; thus, the true HIV prevalence in this study may have been lower than 13.4%. Both these studies were done at KNH, whose patient population may be different from that at MDH for various reasons. With HIV care being implemented in primary care settings, KNH, which is a tertiary hospital, may be receiving a highly selected group of referral patients. User-fees for children aged less than five years are also much higher at KNH compared to MDH. This could result in parents of children from the lower socio-economic class opting to access health care at cheaper health facilities including MDH. Lower socioeconomic status has been found to be a risk factor associated with increased HIV prevalence [3]. This could explain why HIV prevalence was higher among children admitted at MDH whose patient population is generally of lower socioeconomic status compared to that found at KNH.

The clinical characteristics of children in the study population were also described. The morbidity patterns indicate pneumonia as the leading cause of admission both among HIV infected (87.9%) and HIV negative (76.9%) children. A significant number of HIV infected (37.9%) and HIV negative (27.7%) children had episodic diarrhoea. These findings are consistent with those reported by Obimbo [19] who evaluated predictors of early mortality among HIV infected children and found that pneumonia and diarrhoea contributed 75% and 41% respectively of deaths among infected children. Persistent diarrhoea, oral candidiasis, hepatomegally, splenomegally and lymphadenopathy occurred significantly more commonly among HIV infected compared to HIV negative children at MDH (p value < 0.05). Previous studies describing clinical features among HIV infected children have reported similar findings. Bakaki et al [18] in Uganda reported that oral candidiasis, lymphadenopathy, marasmus and hepatosplenomegally as important indicators of HIV infection. Ear discharge, previously found to be a significant indicator of HIV infection was however rare among HIV infected children at MDH [18]. Pneumonia was not a significant indicator of HIV infection among admitted children at MDH (p value 0.06) unlike the findings reported by Lucas et al in a necropsy study of HIV infected children in Abidjan [40]. History of TB in a parent and confirmed HIV infection in a parent were however significant indicators of HIV infection among children at MDH (p value < 0.001). The study by Horwood did not find these two to be significant indicators of HIV infection in children and did not include them in the improved algorithm developed from this study in South Africa [34].

Acceptance rate for HIV testing in the study population of 93.5% was similar to those reported by Horwood, Inwani and Oyieko of 96.8%, 95.1% and 97.0% respectively [34, 35, 38].

Performance of the IMCI HIV algorithm

The IMCI algorithm in this hospital-based population yielded a sensitivity of 77.6%, specificity of 80.9%, PPV of 49.4% and NPV of 93.7% for identifying HIV infection. This sensitivity was higher than 62.7% reported by Horwood [34] and much higher than 19.0% reported by Inwani [35]. The study by Horwood done in South Africa had a patient population with much lower prevalence of malnutrition compared to the patient population at MDH. The study by Inwani evaluated the original IMCI algorithm that includes parotid enlargement and ear discharge as criteria items. The study at MDH evaluated the Kenyan adaptation of the algorithm which does not include parotid enlargement and chronic ear discharge which could explain the difference in sensitivity. The children in the study at MDH were also slightly older (median age 11 months) compared to the children in the study by Inwani (median age 5.4 months). The IMCI algorithm has been reported to have higher sensitivity among older children which might be another explanation for the difference in sensitivity between the two studies [41]. The PPV of 49.4% for the algorithm at MDH was higher than that of 13% reported by Inwani at KNH [35]. This could be explained by the difference in HIV prevalence between the two studies as higher HIV prevalence increases PPV for clinical criteria. The PPV of 49.4% by the IMCI algorithm at MDH makes the algorithm an inadequate tool for diagnosis of HIV infection and a laboratory test would still be required to confirm presence of infection once a child is identified as symptomatic for HIV infection by the algorithm.

The algorithm performed better among children aged over 18 months (sensitivity 87.5%, PPV 56%) compared to children aged 18 months and less (sensitivity 73.8%, PPV 50%).

This goes to further indicate that clinical criteria appear to perform better among older children [41].

Although inclusion of severe immunosuppression using CD4 percent improved the sensitivity and PPV of the algorithm to 89.6% and 57.8% respectively there was a decline in specificity and NPV to 34.6% and 76.9% respectively for prediction of severe immunosuppression. This finding was similar to that reported by Inwani where inclusion of CD4 percent to the HIV test resulted in improved sensitivity and PPV of the algorithm with a decline in both specificity and NPV [35]. The studies by Horwood and Lulseged did not include CD4 percent as criteria for evaluating presence of disease [34, 20].

Inclusion of CD4 percent to a positive HIV test would be a more objective measure for presence of disease compared to evaluating the algorithm against a laboratory HIV test alone. Although sensitivity for identifying severe immunosuppression by the algorithm at MDH was high (89.6%), the low specificity (34.6%), makes this algorithm a poor screening tool for initiation of antiretroviral therapy as it also identifies many infected children who are not severely immunosuppressed as symptomatic. It would therefore result in initiation of antiretroviral therapy for HIV infected children who are not necessarily severely immunosuppressed. This would not be cost effective and is also associated with increased risk of drug toxicity among children who are not severely immunosuppressed.

The IMCI algorithm would however be useful in the study population in identifying children in need of urgent referral for HIV testing based on the fact that it identified 89.6% of HIV infected children with severe immunosuppression as symptomatic.

Children identified as symptomatic at primary health facilities without adequate or

appropriate HIV test kits (especially PCR test kits for children aged less than 18 months) can therefore be referred as a priority for HIV testing and further care.

The strengths of this study include the fact that the IMCI algorithm was evaluated against both a positive laboratory HIV test and a CD4 percent, which was felt to be a better measure for presence of disease compared to evaluating the algorithm against a laboratory HIV test alone. The study population was also recruited at a first level referral health facility which was felt to have a patient population similar to primary health facilities where the algorithm is intended for use.

The study however had several weaknesses. The sample size of 300 patients was small compared to previous studies evaluating the IMCI algorithm which had recruited 1,777, 690 and 1418 children [20, 34, 35]. Children aged 18 months and less had two antibody tests done to determine presence of exposure before being sent for a DNA-PCR test. This could have led to misclassification of HIV infected children with waning maternal antibodies who may not have formed antibodies of their own. The study population was also recruited from an in-patient population of children and a further study would be required to assess for the performance of the algorithm in an out-patient population.

CONCLUSIONS

1. HIV seroprevalence rate among children admitted to the paediatric ward at the Mbagathi District Hospital is high at 19.4%.
2. The IMCI HIV algorithm had a high sensitivity of 89.6% for identifying severe immunosuppression in a HIV infected children (requiring beginning of ART) but specificity was very low at 34.6%.

RECOMMENDATIONS

1. The IMCI HIV algorithm would be useful in the study population in prioritizing children in need of referral for urgent HIV testing as it would identify 89.6% of HIV infected children with severe immunosuppression.
2. The IMCI HIV algorithm would not be a useful screening tool in the study population for initiating ART due to the low specificity (34.6%) for severe immunosuppression.
3. Studies to validate the IMCI HIV algorithm in outpatient settings are required.

LIMITATIONS

1. This was an in-patient based study and its findings may not be reproducible in an outpatient setting.
2. Not all children aged 18 months or less had viral HIV tests done to confirm their HIV status due to financial constraints which could have led to misclassification of some HIV infected children.

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APPENDICES.

ANNEX 1.

QUESTIONNAIRE

Date _____ (dd / mm / yy)

Study Number _____

a) **Age** (months) _____

b) **Sex**

Male (1)	Female (2)

c) **Caretaker**

Father (1)

--

Mother (2)

--

Other (specify)

(3)

--

d) **History**

		Absent (1)	Present(2)
1	Pneumonia (currently or previously)		
2	Persistent diarrhea in the last three months		
3	Two or more episodes of diarrhea in the last three months		
4	Fever lasting more than 1 month		
5	Chronic ear discharge lasting > 14 days		
6	Previous or current herpes zoster		
7	Recurrent admissions (≥ 2 admissions in previous 1 year)		
8	History of TB in any parent		
9	Confirmed HIV infection in any parent		

f) Physical Examination

1. Weight	Actual weight (kg)	>p3 (1)	<p3 (2)
2. Height	Actual Height (cm)	>p3 (1)	<p3 (2)
3. Temperature	Actual Temp (°C)	Normal (1)	Abnormal (2)

p3= 3rd percentile

		Absent (1)	Present (2)
4.	Oral candidiasis		
5.	Lymphadenopathy > 1cm in two or more sites (axilla, neck or inguinal regions)		
6.	Ear discharge		
7.	Chronic parotitis		
8.	Splenomegaly (spleen palpable below the left costal margin)		
9.	Hepatomegaly		
10.	Lower chest in-drawing		
11.	Active zoster/ scarring from zoster		

HIV Diagnosis

IMCI Class	HIV Negative (1)	HIV Positive (2)

Final Laboratory HIV test			HIV Negative (1)	HIV Positive (2)
Rapid	ELISA	PCR-DNA		

ANNEX 2.

Counseling Information

What is HIV HIV is a virus that interferes with the immune function of the body and is quite prevalent in our society.

Transmission It is transmitted through sexual intercourse, through contact with blood and blood products and through mother to child transmission. In children it is mainly transmitted during pregnancy, labour and delivery and during breastfeeding.

How does HIV affect health In our bodies there is a cell type involved in protecting the body from infections. These cells are called CD4 cells. HIV makes copies of itself inside CD4 cells causing their destruction. Initially the body can replace these cells adequately but with time the body is unable to replace them fast enough and these cells begin to decline in number. As a result :

- Common infections occur more frequently e.g. Tuberculosis
- Uncommon and rare infections and conditions may also occur
- The amount of HIV in the body increases

One of the more severe infections in infancy is pneumocystis pneumonia, which is caused by the fungus pneumocystis jiroveci

The number of CD4 cells in children is expressed as a percentage. When the CD4 cell count is <15% of the normal for a child who one year or older and <20% for a child less than one year, this is

regarded as advanced severe disease. HIV at this time is in large amounts and the patient may lose weight and infections become frequent and more severe. This is called the AIDS stage.

CD4 cell count and the clinical signs and symptoms are used to determine the stages of HIV disease. If a laboratory is not available the clinical presentation is used to classify the patient. The stages are used to assess severity of the disease and to assist in making treatment decisions.

Diagnosis When the body is infected with HIV, the body produces substances to protect it called antibodies. Diagnosis is made when the virus itself or antibodies are found in blood. A child less than 18 of age months may have antibodies transmitted from his/her mother but still not have the virus.

This means a child less than 18 months of age found to have antibodies needs another test looking for the actual presence of the virus to confirm diagnosis or a repeat test looking for antibodies after the age of 18 months. Diagnosis can also be made using the clinical picture in advanced disease.

Treatment HIV infection has no cure yet. Drugs called antiretrovirals slow the process of HIV making copies of itself. When used in combination

these drugs are able to reduce the amount of HIV in the body often until it cannot be found in blood and also cause an increase in CD4 cell count.

The drugs are taken in combination because the HIV has the ability to change itself and become resistant to drugs and this resistant type of virus now starts to make copies of itself. The chance of this happening is much less when at least 3 antiretroviral drugs are used together. And should the virus become resistant to one drug, the other 2 will stop the resistant type from making copies of itself.

When to start
ARVs

They are started when a child is found to have a very low CD4% or or when he is found to be in stage 3 or 4 using clinical signs and symptoms.

When not to start
ARVs in a child

Some illnesses affecting the blood, liver or kidney do not allow for some patients who require antiretrovirals to be started on them. Blood tests are therefore done before starting patients on antiretroviral treatment to make sure these illnesses do not exist.

Who should not be
given ARVs

Drugs must be taken everyday and the patient who is unable or unwilling to take their drugs as prescribed should not be given antiretrovirals. This is because if the drugs are not taken as

prescribed they do not work well and the virus may become resistant to these drugs.

Other interventions Besides ARVs , a medicine called cotrimoxazole is given to the patient to prevent pneumocystis pneumonia and recurrent infections caused by bacteria. A balanced diet and micronutrients like vitamin A are necessary.

Pillars of comprehensive care in HIV/AIDS in children Confirmation of HIV infection, staging of disease, treatment of acute and other opportunistic infections, immunization, regular monitoring of growth and development, nutritional care, of infection (including TB and PCP) , counseling, providing ART, providing care for the mother and the family, and planning and providing for follow-up and community support.

ANNEX 3.

CONSENT FORM

Introduction

My name is Dr Mutai, I am a postgraduate student in the Department of Paediatrics and Child Health at the University of Nairobi. As part of my postgraduate studies I am required to carry out a research project. My research study is intended to find out how useful certain clinical signs and symptoms are in looking for HIV disease in children less than five years of age admitted at the Mbagathi District Hospital. These are clinical signs and symptoms currently recommended by the government of Kenya to be used by clinicians in identifying HIV infected children with disease but it is not known how well these signs identify these children

About the study

Who is invited to take part in this study:

All children aged less than five years admitted at the Mbagathi District Hospital are eligible for inclusion in the study unless their HIV status is already known.

What does the study involve?

Should you consent for your child to be recruited into the study I will ask you the parent/guardian certain questions concerning the child's and parents' medical history then I will examine the child for certain physical signs. I will use this information collected so far to decide whether the child is likely to have HIV disease or not.

I will then do a blood test that will tell us whether the child truly has HIV or not. Before I do the test I will take you through a counseling session where we will discuss about HIV, its transmission, its effects in the body, its diagnosis and treatment. I will then clean the

finger tip of the left ring finger 3 times using 3 different spirit swabs. I will then puncture the finger tip and draw a few drops of blood and test it using 2 different types of HIV test kits. Similar results on the two tests will indicate the child's true HIV status and this result will be communicated to you by me. You will be able to know the results of these two tests within 15 minutes. If the results on the two tests are different it will be necessary for me to take 2 mls of blood from your child's left arm vein after cleaning the area with a spirit swab for a third HIV test that will give us the child's true HIV status. It will take about two days for us to get the result from this third test which will again be communicated to you by me.

If your child is less than 18 months these first two tests I have told you about will only indicate whether he/she has been exposed to the virus or not, and not if he/she is truly infected. If the tests show that the child has been exposed it will be necessary for me to take blood for a different test that will look for actual presence of the virus in the blood. The results of this test will be ready in approximately two weeks and these results will again be communicated to you by me.

If we find your child to be HIV positive I will take another 2 mls of blood from the child's left arm vein that will be used to find out how advanced the disease is in the child's body.

What will the information obtained be used for?

We will be able to tell how useful the questions I asked you on the child's medical history and the signs I looked for in the physical examination are in looking for HIV disease in a child aged less than five years. Depending on the results of this study we will in future be able to know how well we can use these signs to tell which child infected

with HIV already has the disease and which one needs to be started on antiretroviral treatment

What will happen if your child is HIV positive?

I will ask for your permission to communicate this information to the child's primary doctor in the ward so that he/she can be started on certain preventive treatment which we will discuss during the counseling session. With your permission the doctor will then also be able to refer the child to a clinic within Mbagathi hospital that takes care of children who have been found to be HIV positive. The child will be registered in this clinic and if the CD4 blood test results indicate the child is in need of antiretroviral treatment this will be started at this clinic.

What will happen if the child is negative?

If your child is HIV negative he/she will continue to receive the routine medical care for whatever condition brought him/her to the hospital.

What if you want testing for yourself and the child's siblings?

Should you want to have HIV testing done for yourself or the child's siblings I will arrange to have this done within the Mbagathi hospital through the HIV Comprehensive Care Clinic (CCC).

What are the risks?

a) Blood removal: Removal of blood may be associated mild occasional discomfort such as bleeding, pain and infection. To minimize on the risk of this happening I will personally remove the blood for testing with extreme care using a sterile procedure after thorough cleaning. After removal I will apply gentle pressure to prevent/stop bleeding.

b) Confidentiality: HIV testing for your child may cause you some anxiety and some of the questions I will ask you might be personal. To protect the confidentiality of the all information you will divulge to me I will do the history taking, physical examination and HIV testing in a side room where only you, the child and myself will be present. Only the information that is useful for medical management of the child which will include HIV test results and CD4% results will be shared with the child's primary doctor with your permission to allow for the appropriate medical care to be given to the child.

Reassurance

Consent for your child to participate in this study is voluntary and should you feel uncomfortable with continuing you may withdraw at any time without explanation. This decision will not affect the medical care your child and he/she will continue to receive appropriate care.

What will you benefit from this study?

During the history taking and physical examination, any new information found will be relayed to the ward doctor with your permission so that he/she can give the appropriate treatment. Knowing your child's HIV status will allow for the child to be registered and followed up in the CCC where he/she can get the appropriate medical care.

Cost:

I will do the blood tests on your child at no cost but no money will be paid to you for taking part in this study.

To indicate that you have understood the conditions of this study and that you consent for your child to be recruited, please sign or put your left thumbprint in the space provided below.

I _____ the parent/guardian of
_____ confirms that the study has been explained to me
and give consent for my child to be recruited in it.

Parent's/guardian's Signature _____

I have adequately explained to the parent/guardian of the child all the issues touching on
this study and he/she has accepted for the child to be recruited into the study.

Dr Mutai

Investigator's signature _____ **Date** _____

For any issues you may contact

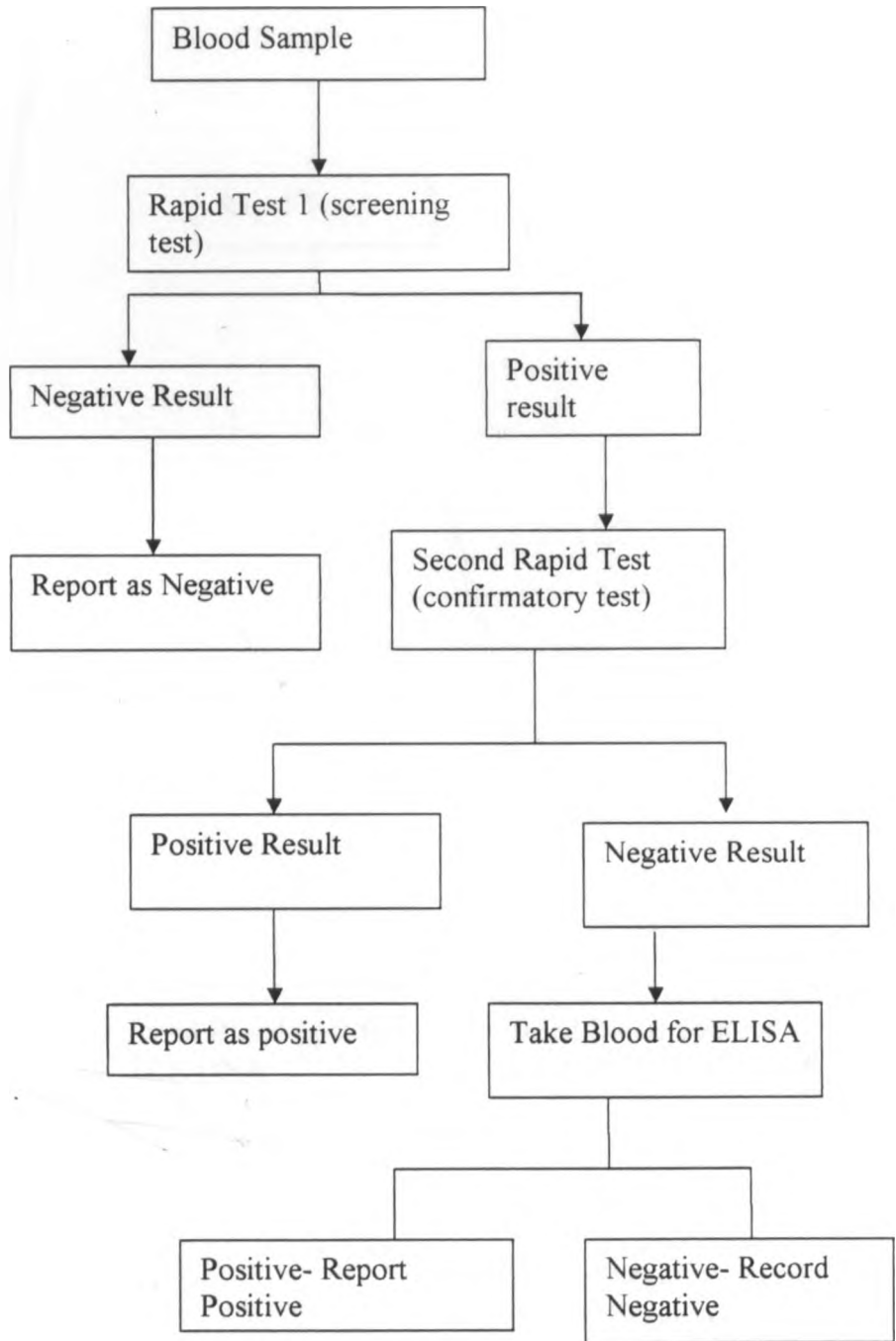
Dr Mutai Beatrice at 0733 250209

cc: Subject file

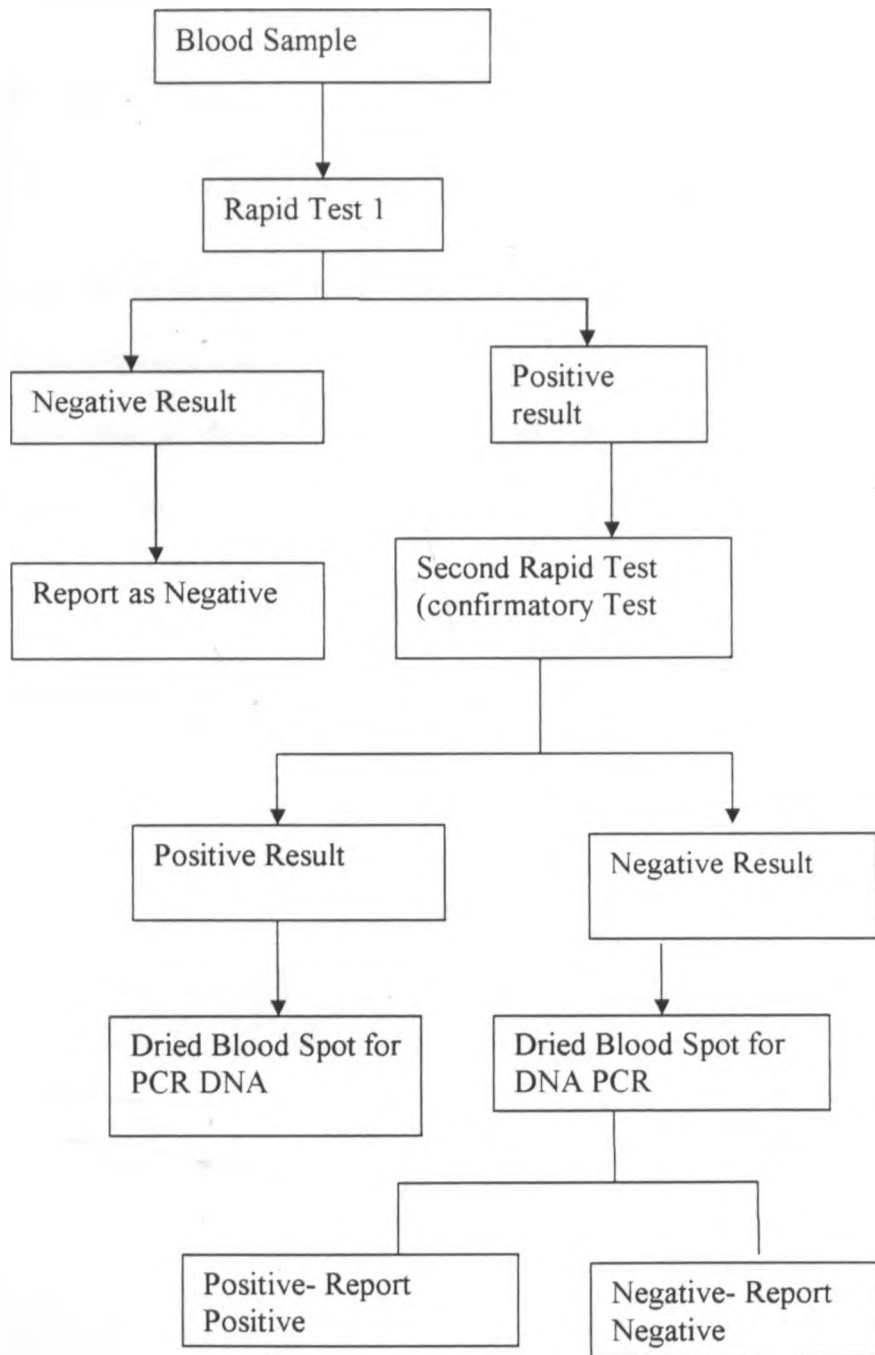
Investigator's file

ANNEX 4.

Protocol for HIV Testing in Children over 18 months:



Protocol for HIV Testing in Children below 18 months or > 18 months and breastfeeding:



ANNEX 5.

Computation of Sensitivity, Specificity, Positive and Negative Predictive Values.

		HIV Status by Laboratory Test	
		Positive	Negative
IMCI HIV Class	Positive	A	B
	Negative	C	D

Sensitivity will be calculated using: $a / (a + c)$

Specificity will be calculated using: $d / (b + d)$

Positive predictive value will be calculated using: $a / (a + b)$

Negative predictive value will be calculated using: $d / (d + c)$