CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

1.1  INTRODUCTION

1.1.1  BACKGROUND TO IMCI – (INTEGRATED MANAGEMENT OF CHILDHOOD ILLNESSES)

Every year approximately eleven million children under the age of five years die, mainly in the developing countries, from preventable or treatable diseases and from inadequate nutrition \(^1\). Many of those who survive are unable to grow and develop to their full potential \(^1\). In sub-Saharan Africa, about 1.2 million children under five years of age die every year of acute respiratory infections, especially pneumonia \(^2\). An estimated 800000 die of diarrhoeal diseases, about 500000 of measles and some 600000 of malaria \(^2\). Each of these diseases is associated with malnutrition in more than 50% of the cases where death occurs \(^2\). Most child deaths in developing countries occur at home without professional health care \(^2\).

In response to this, the World Health Organization (WHO) and United Nations Children’s Fund (UNICEF) developed a new strategy in 1992 called “Integrated Management of Childhood Illness” (IMCI) \(^3\). This was the work of a global team of child health experts who evaluated and tested the minimal number of signs and symptoms needed to safely assess and classify the severity of the most common life-threatening childhood illnesses.

At the end of 2004, a total of 100 countries reported having completed a national adaptation of the IMCI case management guidelines for first-level health facilities, and 65 of these countries were in the process of expanding training in clinical IMCI beyond
a few districts. The South African Government adopted the IMCI strategy as a national priority in 1996. Adaptations were made as necessary to deal with particular local problems such as paediatric HIV which has become a major threat to child survival.

1.1.2 TECHNICAL BASIS & REVIEW OF IMCI CRITERIA OF SUSPECTED SYMPTOMATIC HIV (SSHIV)

The IMCI guidelines for SSHIV used in this study are those given in the 2001 edition of the chart booklet. IMCI case management relies on case detection using simple clinical signs. Major features of HIV are shown in ‘The Structured Data Form’ set out in this study. (Appendix A) The selection of IMCI signs is based on expert opinion and research results (South African National Department of Health – Directorate of Mother and Child Health, together with UNICEF) and a careful balance is made between sensitivity and specificity. Such criteria should have high specificity to avoid false diagnoses, with sensitivity as high as possible, so as not to miss positive cases. 2001 IMCI guidelines for SSHIV (Appendix B) were modified in 2003 but the only related change made was an extension of the cut-off age for clearance of maternal HIV antibodies in the infant from 12 to 15 months.

1.1.3 SIGNIFICANCE & RATIONALE OF THIS STUDY

The HIV prevalence in South Africa continues to rise. In a study from Soweto, the prevalence of HIV infection in hospitalized children was 29.2%. That reached 26.5% among South African antenatal clinic attendees in 2002. These findings highlight the need for ongoing control and management. The progression has occurred despite the introduction of programmes to prevent the transmission of HIV from mother-to-child.
These programmes do not have 100% coverage and do not always eliminate mother-to-child transmission of HIV; hence there is still a need to improve early diagnosis of HIV infection in children. The aim of IMCI SSHIV is to facilitate early detection of the infection in children particularly at primary health care level especially where resources are limited.

The infections precipitated or aggravated by the declining immunity associated with HIV are the same infections from which otherwise healthy children may suffer. This has created the challenge as to when to suspect symptomatic HIV infection and how best to include this in a South African generic adaptation for IMCI case management guidelines. All proposed changes to IMCI are, as far as possible, evidence-based and are carefully evaluated to maintain acceptable IMCI standards so that the strategy will have the desired impact and not lose credibility.

IMCI practitioners, following clear guidelines for suspected symptomatic HIV (SSHIV) infection, refer children to the nearest hospital when necessary for further investigation and management. Understanding and co-operation between these different levels of health care is important. It thus was decided to compare the assessments made on children referred with SSHIV as the result of IMCI screening criteria, and the diagnosis of SSHIV infection on the same patients at the next referral level; namely, the regional hospital. IMCI guidelines for SSHIV are based on the Horwood study ⁹. The purpose of studying children from Edenvale Hospital was to determine how screening for SSHIV infection using IMCI guidelines compares to WHO criteria and other modifications of diagnostic guidelines for HIV in these children. However, the non-availability of antigen tests such as PCR and p24 especially in children under 15 months of age to reliably confirm the HIV diagnosis limits the validity of findings.
The significance of the study is the potential to apply acceptable screening methods for SSHIV where there are resource limitations.

1.2 LITERATURE REVIEW

1.2.1 DIAGNOSIS OF PAEDIATRIC HIV INFECTION

Paediatric HIV infection may be identified in one of two ways.

1. An infant exposed to HIV may be identified through HIV ELISA testing of maternal blood during pregnancy.

2. Infants and children may present with suggestive clinical presentations.

The gold standard for the diagnosis of HIV infection needs valid and specific laboratory tests. By definition a gold standard has a sensitivity of 100% and a specificity of 100% \(^{10}\). Sensitivity and specificity measure the diagnostic performance of a clinical sign compared with that of the gold standard. Sensitivity measures the proportion or percentage of those with the disease who are correctly identified by the sign. Specificity measures the proportion of those without disease who are correctly called free of the disease by using the sign \(^{10}\).

The ‘gold standard’ for diagnosis for HIV is a polymerase chain reaction (PCR) test \(^{11}\). In resource-limited countries, PCR tests may be unavailable in secondary and primary care health facilities because of the high cost.

For a symptomatic infant in the first year of life, a positive ELISA antibody test almost always suggests true HIV infection \(^{11}\). For certainty and reassurance a positive ELISA test first done before 15 months may be repeated at 18 months or later. This addresses
the possibility of previous technical error and also the unusual late persistence of maternal antibodies or acquired infection. Persistence of positive ELISA tests beyond 15 months or if older and breastfed, beyond 3 months after the cessation of breastfeeding, indicates a positive diagnosis \(^9\). A negative HIV ELISA test at any age excludes HIV infection. The third-generation ELISA tests for HIV antibody have a sensitivity approaching 100% and specificity more than 99% \(^{11}\).

As noted above local hospitals in developing countries are generally unable to use the PCR test. The ELISA is regarded as a feasible standard test for the children with SSHIV above 15 months of age but may not detect the true HIV status of younger children; Baragwanath researchers have found that the presence of clinical signs of HIV may predict infection in more than 80% of cases \(^6\).

Primary difficulties are faced in making a diagnosis of HIV in a clinical setting because the laboratory facilities required to do the blood test are often not easily available. Sometimes accessing experienced clinicians able to detect all the signs and symptoms of paediatric HIV infection might pose a problem. Because of this situation, IMCI and WHO criteria for paediatric SSHIV may be applied as a screening test for SSHIV infection, especially in children under 15 months of age.

Achieving a balance between sensitivity and specificity of AIDS screening tests is an ongoing difficulty. In most of the cases once sensitivity is very high, specificity becomes weak.

1.2.2 WHO CLINICAL CASE DEFINITION FOR AIDS IN CHILDREN

In 1986, WHO produced a clinical case definition for AIDS in children, to be used primarily in countries where other diagnostic resources were limited \(^{12}\). Both this WHO definition and IMCI criteria (Appendices B and C) refer to overt HIV infection in
children. The former consists of three major and six minor signs. The three major signs are weight loss, chronic diarrhoea and prolonged fever and the six minor signs are generalised lymphadenopathy, oropharyngeal candidiasis, repeated common infections, persistent cough, generalised dermatitis and confirmed maternal HIV infection (Appendix C). HIV infection which has progressed to overt clinical AIDS is suspected in an infant or child presenting with at least two of the major signs together with at least two minor signs (in the absence of known cases of immunosuppression of other recognised aetiologies) (see WHO definition, Appendix C).

WHO have noted the need for evaluation of the case definition in different settings. The frequency of presenting signs of AIDS used in diagnosis may be altered by other co-existing pathologies, such as malaria associated with splenomegaly, and malnutrition. This has resulted in some adaptations in IMCI guidelines. Studies from Ngwelezane, Bloemfontein, Congo, Rwanda, KwaZulu Natal and Ivory Coast evaluated the WHO clinical case definition for symptomatic paediatric HIV infection and some have developed their own adaptations.

1.2.3 PREVIOUS STUDIES RELATED TO IMCI SSVIH INFECTION

A. Horwood et al Study (Ngwelezane Hospital)

In 2001, a study by Horwood et al at Ngwelezane Hospital was undertaken with the assistance of WHO, to determine the validity of an algorithm used by IMCI primary health workers to identify children with paediatric SSVIH infection. It involved 690 children attending an outpatient department at the Ngwelezane district hospital in KwaZulu Natal. The children were assessed by experienced paediatricians and by IMCI practitioners following IMCI HIV algorithms. Viral loads were measured to
determine the true HIV status of the children. The IMCI practitioners’ and the paediatricians’ assessments were made separately, to assess the validity of the IMCI classification ⁹. The paediatrician correctly identified 71.7% of children with AIDS, whereas the old IMCI HIV algorithm (not the improved one) identified 56.1% ⁹.

The researchers recommended an improved HIV algorithm with signs and symptoms which were clinically relevant, widely applicable and practical to teach during IMCI training. This improvement consisted of four simple and sensitive screening questions and additional clinical features of HIV. Their study showed that primary level health workers, through the use of an algorithm, could (with some imperfections) identify children with symptomatic HIV infection.

WHO adopted a generic HIV algorithm based on the data from this study ⁹, which can be adapted and incorporated into IMCI in countries with a more than two percent prevalence of HIV ⁹. The Horwood study also showed that, in that study population, the WHO clinical case definition for paediatric AIDS (Appendix C) was specific (98.7%) but would identify relatively few AIDS cases because of low sensitivity (8.5%)

**B. van Gend et al ¹² Study (Bloemfontein)**

Paediatricians from the University of the Free State, working in Bloemfontein and collaborating with Netherlands researchers, have proposed a simplified case definition for paediatric symptomatic HIV infection ¹². This is based on the presence of 2 out of 4 clinical signs. This adaptation has also been used as one of the strategies for comparison in this study.
WHO algorithms were also evaluated in 2003 by van Gend et al.\textsuperscript{12} (Bloemfontein study), who applied the WHO clinical case definition for paediatric symptomatic HIV in Bloemfontein, South Africa. The purpose was to evaluate the usefulness of the WHO case definition as an instrument to diagnose AIDS in children. Additional clinical features not included in the WHO case definitions were recorded. The Bloemfontein study included 222 children, of whom 31.1% were HIV positive based on ELISA positive tests in all children and p24 antigen tests positive in those under 18 months of age. In the Bloemfontein study, the children were tested for the presence of HIV antibodies with the ELISA test, using both Vironostika HIV Uni-Form II Ag/Ab (Organon Teknika, Boxtel, Netherlands) and Enzygnost HIV Integral (Dade Beringh, Marburg, Germany). Therefore, those children with positive antibody tests were also tested for the presence of the p24 antigen using Innotest HIV antigen mAb (Inno-genetics, Ghent, Belgium)\textsuperscript{12} which is specific for HIV. With the exception of weight loss and generalised dermatitis, WHO case definition signs occurred more often in children with AIDS than in those not infected. In the Bloemfontein study, hepatosplenomegaly (Specificity 94.0% and PPV 75.7%) and marasmus (Specificity 92.7% and PPV 67.6%), which are not included in the WHO case definition, occurred more frequently in HIV positive than negative children. In this study, marasmus, hepatosplenomegaly, oropharyngeal candidiasis and generalised lymphadenopathy were found: 34.3%, 41.2%, 40.6% and 62.3% respectively, in SSHIV positive children. On the basis of these findings the study proposed new case definition guidelines for paediatric SSHIV. These consist of four signs:

1. marasmus,
2. hepatosplenomegaly,
3. oropharyngeal candidiasis and
4. generalised lymphadenopathy.

SSHIV infection was suspected in a child presenting with at least two of the above four signs. According to this case definition, the sensitivity of the new guideline to detect AIDS was 63.2% and the specificity 96.0%. Although the Bloemfontein adaptations proved to be much more diagnostically sensitive than the WHO case definition (63.2% vs 14.5%) in that setting, one out of three SSHIV positive children would still be missed. However, since the PPV (87.8%) was high, children who met the criteria were very likely to be HIV positive\textsuperscript{12}. This is important while stigma suffered by the HIV infected is still considerable and the negative consequences of a false diagnosis could be grave. This position should improve as people become better informed and more tolerant, particularly as there is now the prospect of effective suppressive therapy. A possible limitation of this study is that the findings may not apply in other countries because of differences in the occurrence of symptoms and signs between children in different communities. Examples of this occur in studies reported from the Congo\textsuperscript{14} Rwanda\textsuperscript{15} and Nigeria\textsuperscript{18} where there are different endemic diseases.

Hepatosplenomegaly may not be useful predictors of HIV infection where malaria is prevalent. In the Nigeria study, hepatosplenomegaly was found in 19% of HIV positive children and generalised lymphadenopathy occurred in 59% of these\textsuperscript{18}. In the Bloemfontein study, marasmus was seen in approximately one-third of the HIV positive children and in fewer HIV negative children (7.3%)\textsuperscript{12}. In a Sowetan study, malnutrition (underweight, kwashiorkor, marasmus, marasmic-kwashiorkor) was found in 65.8% of HIV infected children under the age of 5 years, compared to 33.1% in the non-HIV children\textsuperscript{6}. 
The strength of the “Proposed simplified case definition for paediatric symptomatic HIV infection” [van Gend et al] was that it was less subjective compared to the WHO clinical case definition for paediatric AIDS. [Appendix C] The Bloemfontein study [van Gend et al] also pointed out that in the WHO case definition, six of nine signs had to be obtained from the medical history and could not be objectively verified. In this study, the proposed definition consisted of four items [marasmus, hepatosplenomegaly, oropharyngeal candidiasis, generalised lymphadenopathy] which depended on simple physical examination. The medical history of the child was not required reducing the likelihood of data being incorrect or missing.

A possible weakness in this van Gend study was the need for clinical skills to elicit the above clinical signs. [hepatosplenomegaly, lymphadenopathy etc] This necessitated extra training for IMCI practitioners from primary care level because these clinical signs are not included in the basic IMCI training. The other weakness was not being generalisable to children in other developing countries for reasons noted above. The above study included children up to 13 years whereas IMCI is limited to the ages of 1 week to 59 months. The results may differ because of these age differences. The validation of the diagnosis of HIV infection in the van Gend study for those under 18 months of age was a p24 antigen positive result. It would have been preferable to base results on the PCR test since the sensitivity of the p24 antigen test is limited. A negative p24 antigen test result cannot be used to exclude HIV infection. For the children above 18 months of age the presence of antibodies against HIV were used to validate a positive diagnosis. Unfortunately because antigen tests like PCR are very expensive PCR could not be used for validation in this study 12.

The sensitivity and specificity of the WHO criteria for paediatric AIDS in the van Gend study was 14.5% and 98.6% respectively.
C. Jones et al\textsuperscript{19} (Coronation Hospital)

This study was done in the Prevention of Mother to Child Transmission (PMTCT) clinic at Coronation Women and Children’s Hospital in Johannesburg and involved a cohort of 301 infants attending the clinic. Each infant’s true HIV status was determined using PCR testing in conjunction with clinical assessments. At the visits at 6 weeks and at 7 and 12 months of age, 18 different doctors, experienced in local paediatric HIV care and blinded to the HIV test results, prospectively diagnosed the infants’ HIV infection status based on clinical findings. Structured data collection tools were used for recording. The data were concentrated on clinical features derived from CDC clinical guidelines. The performance of the IMCI algorithm in this study population was assessed retrospectively, by using the South African 2003 IMCI algorithm. The incomplete information about methodology and further aspects of the study is a considerable limitation. In a retrospective study measurement bias is of particular importance. This occurs when there is different availability of information referring to cases and controls; especially if it is widely known to be associated with the disease under study\textsuperscript{20}.

The study found IMCI detected 17\% of HIV infected infants at 6 weeks of age and improved to 50\% for infants aged 12 months. This was much lower than the rate of 70\% reported by Horwood \textit{et al}. The clinicians’ diagnoses clinically improved with age of the children, from 56\% at 6 weeks of age to 93\% at 12 months of age. This study showed that clinical diagnosis of HIV infection in infancy remains a challenge. It is suggested that a more pragmatic approach may be investment in assessment of affordable, simple methods of testing for early diagnosis in infants, rather than reliance on clinical skills alone.
D. **Factor *et al*\textsuperscript{21} study (Bangladesh)**

Factor *et al* study used aspects of methodology similar to those used by the researcher at Edenvale Hospital. Factor *et al* studied the diagnosis and management of febrile children using guidelines for IMCI and hospital diagnoses in Bangladesh\textsuperscript{21}.

The study was conducted in a low malaria prevalence area to evaluate the management of febrile children using WHO/UNICEF IMCI fever guidelines for conditions other than malaria. Hospital physicians’ diagnoses, in these cases without recorded validation, were accepted to assess how well IMCI guidelines for the management of children with fever performed. The Bangladesh doctors concluded that IMCI guidelines were able to identify children requiring antibiotic therapy for supposed bacterial infections and that despite some misclassifications and overuse of antibiotics, the strategy was life saving. Both this and the Edenvale study lack a specific scientific gold standard and neither study is generalisable. In the Factor *et al* study the diagnosis was only based on the clinical features of the disease. Neither the Bangladesh nor Edenvale researchers (for infants under 15 months of age) were able to rely on gold standards for diagnostic confirmation in the cases studied and in both situations the opinions and decisions of the attending health workers were accepted without validation.

E. **CONCLUSION**

From the above studies, it can be seen that the IMCI algorithm is not currently an adequate diagnostic tool for HIV in young infants but may be potentially useful for screening where resources are limited.
CHAPTER 2: METHODS

2.1 AIM & OBJECTIVES OF THE STUDY

The study hypothesis: - IMCI assessment for “Suspected Symptomatic HIV” infection is a useful screening tool for AIDS.

The overall aim of this study was to determine the suitability of the IMCI SSHIV algorithm as a screening tool for paediatric AIDS.

The objectives of this study were:

**Objective one:** To look at the agreement between IMCI classification for SSHIV and WHO clinical case definition for AIDS using a retrospective record review of the same hospitalised children.

**Objective two:** Using HIV ELISA results in children older than 15 months to determine the sensitivity, specificity, positive predictive values and Likelihood ratios of the

- South African IMCI SSHIV criteria (Guidelines 2001),
- WHO clinical case definition for paediatric AIDS,
- Bloemfontein Proposed simplified case definition for paediatric SSHIV.

2.2 STUDY METHODS

2.2.1 Study site

Edenvale Hospital is a second level, 200 bed regional hospital situated in eastern Johannesburg and serving mainly the Edenvale area and Alexandra township.
The medical staff in the children’s ward consisted of one part-time specialist paediatrician and one full-time principal medical officer. The latter was the sole researcher responsible for reviewing all records and capturing and analyzing the data.

2.2.2 Study participants

The study population consisted of all medical patients in the age range covered by IMCI; namely, 1 week to 59 months, who were admitted to Edenvale Hospital during the study period of 1 January 2002 to 28 April 2003. Inclusion and exclusion criteria were then applied.

2.2.3 Selection criteria

The paediatric ward in Edenvale Hospital accommodated children less than 12 years of age. These included surgical, trauma, orthopaedic, medical and social cases. In this study only paediatric medical in-patient records were reviewed.

In comparing IMCI SSHIV and WHO clinical case definition for AIDS (objective 1) 304 children who met all the inclusion and exclusion criteria for objective 1 were included in selection criteria.

For objective 2, HIV ELISA test results were available for 219 children considered by the medical staff to have HIV-related symptoms and these formed the study population. This was a convenience sample, based on the need to have ELISA results and all patients who met all the inclusion and exclusion criteria for objective 2 then qualified and were included in the study.
2.2.4 Inclusion Criteria

**Inclusion Criteria for objective 1** (Total qualifying- 304 children)

a) Paediatric medical admissions within defined period.
b) Aged between 1 week and 59 months.

**Inclusion Criteria for objective 2** (Total qualifying- 50 children)

a) Paediatric medical admissions within defined period.
b) Aged between 15 and 59 months.
c) Available HIV ELISA results
2.2.5 Exclusion criteria

**Exclusion criteria for objective 1**

a) Unavailability of the hospital record.
b) Incompleteness of a record (i.e. insufficient clinical notes for assessment and classification)
c) Re-admissions (to avoid including children twice)

**Exclusion criteria for objective 2**

a) Unavailability of the hospital record.
b) Incompleteness of a record (i.e. insufficient clinical notes for assessment and classification)
c) Re-admissions (to avoid including children twice)
d) Unavailability (for various reasons) of a child’s HIV ELISA test results.

2.2.6 Study Measurements

The researcher alone reviewed each individual hospital record and completed a structured data form (Appendix A) which included the IMCI criteria case definition of SSHIV, the WHO clinical case definition criteria and the Bloemfontein Proposed simplified case definition criteria. The demographic data and all the HIV ELISA results were also recorded by the same researcher. HIV ELISA results were not blinded to the researcher because as a retrospective review all the data had already been recorded and would be objectively handled. From the recorded data a classification or diagnosis was made, based on each set of criteria (IMCI, WHO & Bloemfontein). Details of these are set out in Appendices B, C, and D.

2.3 DATA ANALYSIS

Epi-info version 6.04 software was used for data entry and analysis. The data was checked for consistency and all discrepancies were reviewed and corrected. All relevant data from the inpatient files were recorded on the Structured Data Form.
The following information was ascertained and calculated from the data entered in Epi-info:

- IMCI clinical features of SSHIV (Appendix B), WHO criteria (Appendix C) and Bloemfontein proposed simplified SSHIV infection (Appendix D) as previously set out in the text and in Appendices B, C and D;

- the number of children fulfilling the criteria of the WHO clinical case definition for paediatric AIDS, IMCI SSHIV classification and criteria for the Bloemfontein proposed simplified SSHIV infection;

- The agreement between IMCI SSHIV (SA IMCI criteria, Appendix B) and WHO clinical case definition for AIDS (Appendix C). The former included 8 features of which 3 must be present for classification as SSHIV infection. The WHO clinical case definition for paediatric AIDS requires at least two major and two minor signs (Appendix C). (Objective 1)

- sensitivity, specificity and positive predictive values and likelihood ratios were calculated for three sets of criteria; IMCI SSHIV infection (Appendix B), WHO clinical case definition (Appendix C) and Bloemfontein proposed adaptation (Appendix D) based on HIV ELISA results in children aged 15 months and older. These were compared. (Objective 2)

### 2.4 ETHICAL CONSIDERATION AND APPROVAL

Written informed consent was obtained from parents or guardians for HIV testing in selected inpatients suspected of having HIV infection. Requesting consent is routine practice used by attending clinicians. Pre and post testing counseling was provided by
social workers and trained professional nurses. Guidelines for counseling were used as set out by the Gauteng Health Department.

As the study involved a retrospective record review, gaining permission from the individual participants for their participation was not required by the Ethics Committee. Numbering data forms without noting identifying details ensured patients’ anonymity.

The research protocol was submitted to the University of the Witwatersrand Committee for Research on Human Subjects (medical) and approved unconditionally. The protocol clearance certificate number is M02-04-32.

Written permission to access records for this study was obtained from Dr. Kernes, Chief Executive Officer, Edenvale Hospital.

**FINANCIAL SUPPORT**

Financial support was not obtained from any outside source. The researcher was self-funded.
CHAPTER 3: RESULTS

During the study period (1 January 2002 to 28 April 2003) 1516 paediatric patients were admitted to Edenvale Hospital. There were a total of 916 paediatric medical patients in the IMCI age range after exclusion of others according to the set criteria, amongst these were patients admitted for surgical, orthopaedic, trauma and social reasons and those older than 59 months. Two hundred and nineteen (219) patients had HIV ELISA results but only 50 of these were above 15 months of age, a requirement for assessments in objective 2. One hundred and eighty four (184) children were ELISA reactive (84%) and 35 (16%) were non-reactive. (See Flow Diagram, on page 16) When criteria of IMCI SSHIV and WHO clinical case definition for AIDS were compared, ELISA results were not used and 304 children were included. (Objective 1)

3.1 AGREEMENT BETWEEN IMCI CLASSIFICATION FOR SSHIV AND WHO CLINICAL CASE DEFINITION FOR AIDS

(Objective 1)

Table 1 shows the agreement between IMCI SSHIV and WHO definition for AIDS using a retrospective record review of the same hospitalised children in the IMCI age range.

<table>
<thead>
<tr>
<th>IMCI SSHIV Classification</th>
<th>WHO clinical case definition for AIDS</th>
<th>Not WHO clinical case definition for AIDS</th>
<th>Total patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMCI SSHIV a</td>
<td>22</td>
<td>145</td>
<td>167</td>
</tr>
<tr>
<td>IMCI SSHIV unlikely b</td>
<td>1</td>
<td>136</td>
<td>137</td>
</tr>
<tr>
<td>Total patients</td>
<td>23</td>
<td>281</td>
<td>304</td>
</tr>
</tbody>
</table>

3 or more IMCI features

b 2 or less IMCI features
When assessing the IMCI classification for SSHIV infection in comparison to the WHO clinical case definition for AIDS, the same conclusion was reached for 158 (52%) of the 304 children. Of these, 22 children were considered as “paediatric AIDS” and 136 children were considered as “not paediatric AIDS” by IMCI as well as WHO. Only one infant meeting the WHO definition for AIDS was considered to be SSHIV unlikely according to IMCI. However, 145 of the 281 infants not meeting the WHO case definition for AIDS were considered to be SSHIV by the IMCI criteria. Since the HIV ELISA tests could not be verified by PCR in infants less than 15 months of age, it was not possible to analyse these differences further.
3.2 COMPARISONS BETWEEN IMCI SSHIV, WHO CLINICAL CASE DEFINITION AND BLOEMFONTEIN PROPOSED SIMPLIFIED CASE DEFINITION FOR SSHIV INFECTION

Table 2 compares the criteria of IMCI, the WHO AIDS clinical case diagnosis and the Bloemfontein proposed simplified case definition of paediatric SSHIV infection, using HIV ELISA as the gold standard, in the 50 children aged 15 months or more who met the study criteria. In this age group, the sensitivity of IMCI SSHIV infection was 85.7%, specificity 62.5% and PPV 92.3% (Table 2). The WHO clinical case definition for AIDS showed that sensitivity, specificity and PPV were 14.3%, 88% and 85.7% respectively. The Bloemfontein study, with a proposed simplified case definition for paediatric SSHIV infection, had a sensitivity of 54.8%, specificity of 75% and PPV of 92%. The positive
likelihood ratio of the IMCI criteria was 2.3, the Bloemfontein criteria had a positive likelihood ratio of 2.2 and WHO clinical case criteria had the lowest.

3.3 DEMOGRAPHIC DATA OF SAMPLE

a) Gender distribution

Table 3: Gender distribution of the children with ELISA results

<table>
<thead>
<tr>
<th>Gender</th>
<th>MALE</th>
<th>FEMALE</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA NON-REACTIVE</td>
<td>104 (56.5%)</td>
<td>80 (43.5%)</td>
<td>184 (100%)</td>
</tr>
<tr>
<td>ELISA REACTIVE</td>
<td>22 (62.9%)</td>
<td>13 (37.1%)</td>
<td>35 (100%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>126 (57.5%)</td>
<td>93 (42.5%)</td>
<td>219 (100%)</td>
</tr>
</tbody>
</table>

Of 219 children who had ELISA results, 126 were males (57.5%) and 93 were females (42.5%). Of those ELISA reactive 56.5% were male and 43.5% were female. The difference was not statistically significant (p= 0.422). (Table 3)

b) Age distribution

Table 4: ELISA status in age group divisions

<table>
<thead>
<tr>
<th>AGE (MONTHS)</th>
<th>&lt;15 MONTHS</th>
<th>≥15 MONTHS</th>
<th>TOTAL PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA REACTIVE</td>
<td>142 (84%)</td>
<td>42 (84%)</td>
<td>184 (84%)</td>
</tr>
<tr>
<td>ELISA NON-REACTIVE</td>
<td>27 (16%)</td>
<td>8 (16%)</td>
<td>35 (16%)</td>
</tr>
<tr>
<td>TOTAL</td>
<td>169 (100%)</td>
<td>50 (100%)</td>
<td>219 (100%)</td>
</tr>
</tbody>
</table>
For the diagnosis of paediatric SSHIV infection, important age groups are under 15 months and above 15 months. This, as noted previously, is the result of transplacental transfer of maternal antibodies found in younger children. In these younger children only antigen tests (p24 antigen, HIV PCR) can determine the true HIV-positive status. In this study, 169 (77.2%) children were under 15 months (142 were ELISA reactive) and 50 (22.9%) children were older than 15 months (42 were ELISA reactive). (Table 4)

3.4 CLINICAL FEATURES OF IMCI SSHIV & WHO CLINICAL CASE DEFINITION FOR AIDS IN THIS STUDY (Tables 5 & 6)

TABLE 5: Frequency of clinical features in all children classified as IMCI SSHIV infection

<table>
<thead>
<tr>
<th>IMCI SSHIV CLINICAL FEATURES</th>
<th>Classification as IMCI SSHIV infection</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
</tr>
<tr>
<td>Poor weight gain</td>
<td>132</td>
</tr>
<tr>
<td>Low weight for age</td>
<td>129</td>
</tr>
<tr>
<td>Generalised Lymphadenopathy</td>
<td>117</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>114</td>
</tr>
<tr>
<td>Oral Thrush</td>
<td>103</td>
</tr>
<tr>
<td>Persistent Gastroenteritis</td>
<td>34</td>
</tr>
<tr>
<td>Ear discharge</td>
<td>29</td>
</tr>
<tr>
<td>Parotid enlargement</td>
<td>5.0</td>
</tr>
</tbody>
</table>
IMCI defined criteria of SSHIV infection are shown in Appendix B. One hundred and sixty seven children were classified as having IMCI SSHIV infection. The clinical features of SSHIV infection are shown in Table 5. The most common feature, poor weight gain, was present in one hundred and thirty two children (79%) and the least common sign, parotid enlargement, was recorded in only 5 children (3%).

**TABLE 6: Frequency of clinical features in all children diagnosed as WHO paediatric AIDS (SSHIV infection)**

<table>
<thead>
<tr>
<th>SERIAL NO</th>
<th>Clinical features of WHO paediatric AIDS</th>
<th>WHO paediatric AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Chronic diarrhoea</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>Weight loss</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>Generalised Lymphadenopathy</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>Oral thrush</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Repeated common infections (i.e. ear, throat)</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Persistent cough</td>
<td>12</td>
</tr>
<tr>
<td>7</td>
<td>Generalised dermatitis</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>Prolonged fever &gt; 1 month</td>
<td>3.0</td>
</tr>
<tr>
<td>9</td>
<td>Confirmed maternal HIV status</td>
<td>3.0</td>
</tr>
</tbody>
</table>

In this study, 23 children were diagnosed as paediatric AIDS by WHO criteria. The commonest feature was chronic diarrhoea. All the children who were classified (diagnosed) as paediatric Aids had chronic diarrhoea. Other common features were weight loss (95%) and lymphadenopathy (78.3%).
CHAPTER 4: DISCUSSION, RECOMMENDATIONS & CONCLUSIONS

4.1 STRENGTHS & DEFICIENCIES OF THREE CRITERIA OF DIAGNOSIS OF HIV INFECTION IN CHILDREN

The most common clinical features of SSHIV infection in this study were poor weight gain (79%), lymphadenopathy (70%) and pneumonia (68.3%), which were higher than in the other studies. In a study in Nigeria the following were found: lymphadenopathy 59%, progressive weight loss 51% and persistent cough 32% \(^ {18}\). In Ngwelezane Hospital study: generalised lymphadenopathy 60.1%, weight loss 72.2% and pneumonia 47.4% were common \(^ {9}\). Thus while the percentages differ, these clinical features appear to be the most common in SSHIV.

As the HIV epidemic continues to escalate, it exerts an increasingly negative impact on childhood morbidity and mortality. A satisfactory strategy for screening at primary health care level is important to ensure optimal care and management. The impetus for improved diagnosis has been further enhanced by the greater availability of effective suppressive anti-viral therapy, which prolongs life and wellbeing.

Valid and specific laboratory tests provide a gold standard for the diagnosis of HIV infection. Unfortunately, many rural settings in Africa have a lack of laboratory facilities to validate the diagnosis of HIV infection.

The weakness with the WHO case definition is that of nine signs (three major and six minor), six are subjective and depend on the care takers. In the WHO case definition, confirmed maternal HIV infection is also included. This has limited applicability, particularly in remote areas where laboratory facilities are in reality seldom available, thus
not fulfilling WHO stated intentions to develop strategies for resource-poor settings. It is also not always easy to ascertain the mother’s HIV status: even if she knows her status she may be reluctant to disclose it. These factors influence the choice and use of different guidelines.

In IMCI one of the criteria is parotid enlargement, which is not commonly seen and might be difficult to detect at primary care level. It has not in the past been one of the clinical signs routinely taught during IMCI training. The IMCI assessment features for SSHIV classification has two overlapping features: low weight for age and poor weight gain. Generally speaking, mothers know whether their children are gaining weight. However, this evaluation is subjective unless shown on the child’s “Road to Health Card (RTHC)”. Moreover, the person accompanying the patient may be unable to provide an accurate detailed history of the child. Sometimes a language barrier makes getting a proper history more difficult. Out of eight IMCI features of SSHIV infection, four depend on the caretaker, as they are subjective in nature. If the caretaker of the child is unable to give adequate answers, classification for SSHIV and establishing a good screening test will not be easy. This point was made by Bloemfontein researchers when comparing their more objective assessments with those of the WHO criteria. It formed the basis for advocating their adaptation.

The major problem associated with the Bloemfontein proposed definition is the inclusion of hepatosplenomegaly as one of the criteria. This necessitates teaching the IMCI practitioners an additional clinical skill. Hepatosplenomegaly and marasmus may also not be useful predictors of HIV infection in populations in which malaria and malnutrition are prevalent. As opposed to the WHO case criteria, the features recommended in the Bloemfontein study are, however, not subjective.
4.2 DISCUSSION BASED ON RESULT OF EDENVALE STUDY

OBJECTIVE 1

It can be seen that there was poor correlation between the IMCI and WHO criteria, but it was not possible to assess which was more reliable since the ELISA was done less than 15 months of age. However, other studies have shown that signs and symptoms together with a positive ELISA are strongly predictive of HIV infection in infants less than 15 months of age. Since the Edenvale study only did an ELISA if there were suspicious signs and symptoms, it is likely that the majority of those who were ELISA positive were in fact HIV infected and therefore the IMCI criteria are probably more useful than WHO criteria for children less than 15 months.

OBJECTIVE 2

The finding of the Edenvale Hospital study supported previous studies that the WHO criteria had low sensitivity (14.3%), high specificity (88%) and PPV (85.7%) in children older than 15 months. The Edenvale Hospital study also found that in children older than 15 months age, the WHO criteria had the lowest likelihood ratio (LR) of 1.2 compared to other two criteria. High LR (for example, LR >10) indicates that the test, sign or symptom can be used to rule in the disease. If the WHO clinical case definition for AIDS is positive, it would be about 1.2 times more likely that the children would be ELISA reactive than non reactive.

It is noteworthy that relatively few children (n= 23) in the Edenvale study fulfilled WHO AIDS criteria. Poor quality of records might have accounted for this and the retrospective review of records excluded the possibilities of obtaining missing data. However, it would
still appear that the WHO criteria have a poor sensitivity and are therefore not particularly useful in the clinical setting.

According to the Edenvale hospital study, compared to the WHO and Bloemfontein criteria, IMCI criteria had the lowest specificity (62.5%) in children in the age group older than 15 months (Table 2). However, the sensitivity and PPV of IMCI SSHIV infection was highest (85.7%, 92.3%) when compared with the WHO and Bloemfontein criteria. The Bloemfontein criteria show results in between the IMCI and WHO criteria but still suffer from a low sensitivity.

In summary, the findings of this study are:

1. The IMCI approach for SSHIV has the disadvantages of low specificity. However, the IMCI classification for SSHIV infection has an important screening role in selecting cases for appropriate laboratory investigation. It should be made clear that IMCI is a screening test and it is not diagnostic, but should be used to screen children for definitive blood tests. However, IMCI fails to detect some children who are HIV infected. False positives, owing to the high sensitivity, remain a problem because of the associated social stigma but now that the disease is potentially manageable, attitudes should change. IMCI could serve as a screening tool for selecting cases needing referral for appropriate laboratory investigation for confirmation in a primary care setting.

2. The WHO criteria appear to miss too many HIV infected children while the Bloemfontein criteria are not as good as the IMCI criteria.
4.3 LIMITATIONS OF THE STUDY

A major limitation of this study was the inability to validate the clinical diagnosis by antigen tests such as the Polymerase Chain Reaction (PCR), and p 24 antigen tests, especially in children under 15 months of age. These investigations constitute the ultimate gold standard. They are, however, expensive. This resulted in a large number for less than 15 months of age having to be excluded from objective 2. The eventual number of 50 children who could be included in objective 2 may not have been sufficient for firm conclusions.

4.4 RECOMMENDATIONS

With reservations due to the limitations, the following suggested recommendations based on these research findings are made.

1) The IMCI criteria for SSHIV infection could be considered for use as a screening tool to select children to have appropriate laboratory investigation for confirmation and to avoid false labelling.

2) ELISA tests should be used for children more than 15 months for confirmation of HIV infection, but, given that antiretroviral therapy is now available, PCR tests should available to infants less than 15 months of age attending a regional hospital such as Edenvale.

Further IMCI HIV research should aim to increase specificity, PPV values and sensitivity. It might be valuable to teach additional clinical skills that have high specificity, such as palpation for liver enlargement and consider inclusion of these in IMCI training for primary care IMCI practitioners.
4.5 CONCLUSION

Paediatric HIV care is an ongoing burden in South Africa and an increasing problem in primary care settings. HIV and AIDS is the largest cause of fatalities in children younger than five, accounting for 40 percent of deaths\textsuperscript{23}. This research contributes to providing further evidence for the screening potential of the IMCI algorithm as an effective identifier of children with SSHIV infection. This should then be followed by the appropriate blood tests.
### APPENDIX: A

#### STRUCTURED DATA FORM

<table>
<thead>
<tr>
<th>CODE NO</th>
<th>AGE</th>
<th>months</th>
<th>GENDER</th>
<th>RN</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>HIV ELISA test</td>
<td></td>
<td>( )</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td>Confirmed mother HIV infection</td>
<td></td>
<td>( )</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>Pneumonia&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>( )</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>Marasmus</td>
<td></td>
<td>( )</td>
<td></td>
</tr>
</tbody>
</table>

(Defined as a weight below 60% of the expected weight for age)

---

#### CLINICAL FEATURES OF SSHIV INFECTION

1. Chronic diarrhoea (> 1 month)  
2. Discharging ear at present or ever  
3. Poor weight gain  
4. Low weight for age (< 3<sup>rd</sup> percentile)  
5. Oral thrush  
6. Enlarged lymphadenopathy<sup>b</sup>  
7. Parotid gland enlargement  
8. Prolonged fever (> 1 month)  
9. Repeated common infections (otitis media, pharyngitis)  
10. Persistent cough (> 21 days)  
11. Generalised dermatitis  
12. Hepatosplenomegaly  

---

<sup>a</sup> Clinical diagnosis or/and radiological diagnosis  
<sup>b</sup> 0.5 cm or > size occurring bilaterally in 2 or > of the neck, armpit or groin
APPENDIX: B IMCI classification of symptomatic HIV

**Check HIV test status and consider Symptomatic HIV**

If the child has:

- Known HIV, or HIV positive mother OR
- PNEUMONIA or MALNUTRITION today OR
- Persistent Diarrhoea now or in the past 3 months OR
- Discharging ear now or ever

<table>
<thead>
<tr>
<th>ASSESS</th>
<th>If YES</th>
<th>Also</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ask:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has the child or mother had HIV test?</td>
<td>Classify HIV status</td>
<td>Classify Possible HIV symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If YES</th>
<th>Also</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive HIV test in child over 12 months</td>
<td>3 or more features present</td>
</tr>
<tr>
<td>Positive HIV test in child under 12 months OR positive HIV test in the mother</td>
<td>2 or less features present</td>
</tr>
<tr>
<td>Negative HIV test in child any age</td>
<td>SUSPECTED SYMPTOMATIC HIV</td>
</tr>
<tr>
<td>KNOWN HIV POSITIVE</td>
<td>SYMPTOMATIC HIV INFECTION UNLIKELY</td>
</tr>
<tr>
<td>POSSIBLE HIV POSITIVE</td>
<td></td>
</tr>
<tr>
<td>KNOWN HIV NEGATIVE</td>
<td></td>
</tr>
</tbody>
</table>

Ask LOOK and FEEL for features of symptomatic HIV infection:

- Pneumonia now?
- Ear discharge now OR in the past?
- Low weight for age?
- Poor weight gain?
- Persistent diarrhea now or in the past 3 months?
- Enlarged lymph glands in 2 or more of the following sites: neck, armpits, groin
- Oral thrush?
- Parotid enlargement?
APPENDIX: C

WHO CLINICAL CASE DEFINITION FOR PAEDIATRIC AIDS\textsuperscript{13} (PAEDIATRIC SSHIV)

HIV infection is suspected in an infant or child presenting with at least two of the following major signs associated with at least two minor signs in the absence of known cases of immunosuppression such as cancer.

**MAJOR SIGNS**

1. Weight loss or abnormally slow growth ($< 3^{\text{rd}}$ percentile of the expected weight for age)
2. Chronic diarrhoea $> 1$ month
3. Prolonged fever $> 1$ month

**MINOR SIGNS**

1. Generalised lymphadenopathy\textsuperscript{a}
2. Oropharyngeal Candidiasis
3. Repeated common infections (otitis media, pharyngitis)
4. Persistent cough\textsuperscript{b}
5. Generalised dermatitis
6. Confirmed maternal HIV infection

\textsuperscript{a} Generalised lymphadenopathy was defined as enlarged lymph nodes (0.5 cm or above) occurring bilaterally in two or more of the following sites: neck, axilla or groin

\textsuperscript{b} more than 21 days
APPENDIX: D

PROPOSED SIMPLIFIED CASE DEFINITION FOR PAEDIATRIC SYMPTOMATIC HIV INFECTION (Paediatric AIDS) (BLOEMFONTEIN STUDY)

HIV infection is suspected in a child presenting with at least two of the four following signs:

1. Marasmus *(Defined as a weight below 60% of the expected weight for age)*
2. Hepatosplenomegaly
3. Oropharyngeal Candidiasis
4. Generalised lymphadenopathy *a*

---

*a Generalised lymphadenopathy was defined as enlarged lymph nodes (0.5 cm or above) occurring bilaterally in two or more of the following sites: neck, axilla or groin.*
REFERENCES


22. Centre for Evidence-Based Medicine, University Health Network. University of Toronto <http://www.cebm.utoronto.ca/glossary/lrs.htm#top> (accessed date 19 May 2005)