UNIVERSITY VICTOR SEGALEN BORDEAUX 2

Impact of HIV on Malaria

A Systematic review of the literature

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Master's thesis submitted to the University Victor Segalen Bordeaux 2 in partial fulfilment of requirements for the award of the tropED-European Master of Science in International Health.

10th July, 2009

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DECLARATION

Where other people's work has been used from which ever source, this has been acknowledged and referenced in accordance to departmental requirements.

The thesis...Impact of HIV on Malaria- *A systematic review of the literature* is my own work.

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Total word count.....12,156.....

Date:.....2009/07/15

ACKNOWLEDGEMENTS

Writing acknowledgments is always a happy moment for me for the following reasons; firstly it signals the end of a long and gruesome journey sometimes with several twists, turns, ups and downs. Second and more importantly it is a moment of reflection, a time to turn back and give thanks to all those who in diverse ways have contributed to the success of this work.

First and foremost I wish to thank the Almighty God for giving me the life, the health, the strength, and for opening the window of opportunity for me to be able to undertake this course. Special thanks and appreciations to the architect and supervisor of this work, DR Pascal ***MILLET*** *of the University Victor Segalen, Bordeaux 2, France, for his constructive criticisms and steadfastness and constant support in ensuring this work come to its logical conclusion. Many thanks and appreciation also goes to the European Union and the Erasmus Mundus Programme without whose support, it would not have been possible for me to undertake this course.*

Special thanks and appreciations to my family for the tremendous amount of patience, love, and courage they showed during the periods I was away from them. Their love and support kept me going. I pray and hope that all the inconveniences they endured during my long absences from them will be a stepping stone for the salvation of us all. Amen.

CONTENTS

LIST OF ILLUSTRATIONS

Table 9 Summary of the main results/findings and conclusions/interpretations of studies that investigated the effect of HIV on malaria in adults and children

LIST OF ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
AOR	Adjusted Odds Ratio
CDC	Centre for Disease Control
CI	Confidence Interval
HDP	High density parasitemia
HIV	Human Immunodeficiency Syndrome
HR	Hazard Ratio
IUGR	Intra Uterine Growth Retardation
OR	Odds Ratio
P.*falciparum*	*Plasmodium falciparum*
P. *malariae*	*Plasmodium malariae*
P*. ovale*	*Plasmodium ovale*
P. *vivax*	*Plasmodium vivax*
Pyo	Person-years of observation
RR	Relative Risk
SMA	Severe Malaria Anaemia
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nations Children Emergency Fund
VSA	Variant Surface Antigen

WHO	World health Organisation

1.0. Executive Summary

Malaria and HIV are among the biggest medical challenges facing sub-Saharan Africa and large parts of the world where both infections are prevalent. The main objective of this study was to evaluate the evidence in support of or against an impact of HIV on the epidemiology of malaria through a carefully planned systematic review of the literature.

Twenty-four articles have been reviewed. The contents of all the articles reviewed were consistent with the theme; "**impact of HIV on epidemiology of malaria**". In 9 of the 24 articles selected for review, the study population was adults males and females. In 6 of the 24 articles, the study population was children. In another 4, the study population was pregnant women, and in 5 the study population was a mixture of adults and children. Of the 24 articles, 23 were from sub-Saharan Africa and 1 was from India. They were all in English. The publication dates ranged from 1977 to 2009. The study designs were diverse; In eleven articles, the study designs were cohorts, three were case-controls, 7 cross-sectional studies, and 3 utilizes secondary data. The quality varied from "high" through "intermediate" to "low". All the 24 articles were included in this review only in so far they met the inclusion criteria. However, for the purpose of answering the research question, and in other to provide a more focused answer to the research question, only the high quality ones papers were considered and to some extent , the intermediate quality ones.

Despite the limitations of this study which have been highlighted hitherto, this review has gathered sufficient information to form the basis of an informed decision with regards to the research question. Overall, information this research shows that there is sufficient evidence to support the theory that interactions existed between HIV and malaria. HIV alters the epidemiology of

malaria for the worse; increases parasitemia, lead to more frequent attacks of malaria, and more severe episodes. It is a significant risk factor for malaria. Emphasis on mosquito avoidance measures should form part of the education and counselling framework of HIV infected individuals in malaria endemic areas of the world. Where ever resources permit, due consideration should be given to integrating HIV control programmes with malaria control programmes.

2. Background

Malaria in humans is caused by infection with one of four protozoan parasites: *Plasmodium falciparum (P. falciparum), Plasmodium malariae (P. malariae), Plasmodium ovale (P. ovale), and Plasmodium vivax (P. vivax*). Although each of the above species of *plasmodium* is capable of causing a debilitating febrile illness, only infection with *P. falciparum* causes a substantial risk of death, and is responsible for most of the morbidity and mortality attributed to the disease (Idemyor, 2007). Human immunodeficiency virus (HIV) infection on the other hand is caused by infection with either Human Immunodeficiency Virus type-1 (HIV-1) or Human Immunodeficiency Virus type-2 (HIV-2). However HIV-1 is the most important as HIV-2 causes AIDS in only a minority of infected individuals and has a more restricted endemicity compared to HIV-1 (de Silva *et al*., 2008).

Malaria and Human Immunodeficiency Virus type-1 (HIV-1) infections are two of the most common infections in sub-Saharan Africa (Laufer *et al*., 2006) and to a lesser extent in other developing countries (Whitworth, 2006). An estimated 22 million Africans are infected with HIV-1 by 1998 (UNAIDS, 1998). This estimate rose to 38 million in 2003 (UNAIDS, 2004), and to 40.3 million in 2005 (UNAIDS, 2005). According to the up to date estimate, the number of people living with HIV/AIDS is 33 million (30 million-36 million) (UNAIDS/WHO, 2008). About 500 million suffer from malaria every year (CDC 1997). These two infections are among the greatest medical challenges facing Africa today (Chandramohan and Greenwood, 1998). Efforts directed at controlling them have not succeeded (UNAIDS/WHO 2005). There is a potential for interactions between these two infections. This will clearly be of public health significance not only for sub-Saharan Africa but also for other regions of

the world with high malaria endemicity and where HIV-epidemic continues to grow such as Southeast Asia (Rowland-Jones and Lohman, 2002). Moreover, because HIV and Malaria coexist in large populations in Africa, even a small interaction between the two infections may have important consequences (Laufer *et al.,* 2006).

An interaction between HIV and malaria could work in a bidirectional manner (Chandramohan and Greenwood, 1998). HIV predominantly affects the $CD4^+$ T lymphocytes (Stanley and Fauci, 1995). These cells play an important role in immunity against *Plasmodium falciparum* infection (Chandramohan and Grenwood, 1998; Butcher G.A., 1992; Brown *et al.,* 1986). HIV infection could impair immune response to malaria parasites, leading to a decrease ability to control parasitemia (Cohen et al., 2005), reduced immunity to clinical malaria, more frequent infections among the semi-immune and more severe disease among the semi-immune and non-immune (Chandramohan and Greenwood, 1998). Conversely, malaria could influence the natural course of HIV for the worse. The effect malaria may have on the natural history of HIV has been demonstrated by a number of in vitro studies (Poli *et al*., 1999, Xiao *et al.,* 1998, Freitag *et al*., 2001). Clinical in vivo studies to address this issue are however limited (Roland-Jones and Lohman, 2002). In a study in Malawi, Hoffmann *et al.* (19990 recruited two cohorts of HIV-1 positive individuals with and without acute malaria illness. They compared the blood HIV-1 RNA concentrations in the two groups at baseline and followed for four weeks after successful malaria therapy, or for 4 weeks after enrolment for the controls. They concluded that HIV-1 viral load was higher in the group with *P.falciparum* malaria than in controls. In another study conducted in Malawi (Kublin *et.al* 2005), they reported that HIV-infected individuals with malaria have a significantly increased viral load. Interpretation of CD4 cell count during

or just after a clinical malaria episode might introduce bias (Van Geertruyden *et al.* 2006). These findings if supported by more others and confirmed would strongly suggest that clinical malaria could contribute to higher plasma viraemia in HIV-infected patients, with implications for HIV progression and transmission (Rowland-Jones and Lohman, 2002) and diagnosis.

Using a mathematical model, Van geertruyden *et al.* estimated the additional Parasite biomass that could be ascribed to HIV-1 co-infection in sub-Saharan Africa. Their model showed that in 2005, HIV-1 increased the overall parasite biomass by 18.0% with the largest relative increase found in southern Africa which coincidentally has the highest HIV prevalence and unstable malaria transmission, and the largest absolute increase in Zambia, Malawi, Central African Republic and Mozambique, where both HIV and malaria are endemic. Korenromp *et al*. (2005) assessed the impact of HIV on malaria in the sub-Saharan African population. They used relative risks for malaria in HIV-infected people derived from literature sources and applied them to the HIV-infected population in each country , stratifying by age group, CD4 cell count, and urban as against rural residence. They reported limited HIV-1 impact though not with absolute certainty citing the contrasting geographic and epidemiologic features between the two diseases.

The association between HIV-infection and malaria in pregnancy has been investigated by a number of researchers (Verhoeff *et al*., 1999; Van Eijk *et al.,* 2003; Steketee *et al.,* 1996). HIV-infection limits the pregnant woman's ability to control *P.falciparum* parasitemia as well as plancetal and newborn infection. This association was greatest in multigravidas (Steketee *et al.,* 1996). The presence of placental malaria in HIV-positive women may have implication for vertical transmission of HIV (Bloland *et al.,* 1995). HIV-infection is

associated with a significant increase in prevalence of malaria in pregnant women of all parities with the effect apparent from early in gestation (Verhoeff *et al.,* 1999). HIV-infection alters the patterns of malaria in pregnant women (van Eijk 2003) and in areas with both infections pregnant women should use malaria prophylaxis.

The association between HIV and malaria in children has also been studied (Colebunders *et al.,* 1990, Muller 2001, Nguyen-Dinh *et al.,* 1987, Kalyesubula *et al.,* 1997, Mermin, 2004,). The study of Colebunders *et al*. failed to show any direct interaction of major clinical importance between HIV infection and malaria. No association could be found between HIV-1 infection and malaria (Muller 2001, Nguyen-Dinh et al. 1987). Possibility of malaria offering some kind of protection against HIV have been suggested (Kalyesuba *et al.* 1997). Mermin *et al*., 2004 reported that children with HIV are almost two times as likely as children without HIV to have malaria.

Any consequence of HIV and malaria co-infection should also be looked at in the context of the certain features of malaria namely: the epidemiology and intensity of transmission. In some areas where malaria is stable, transmission is intense and perennial, although seasonal variations may occur. In these areas, immunity develops early in life, and young children and pregnant women are at greater risk of morbidity and mortality from severe malaria (Whitworth 2006). The accompanying HIV immunosuppression may increase both the rates of malaria infection and clinical malaria disease, but not the rates of severe or complicated malaria (Whitworth *et al* 2006, French *et al.,* 2001., Francesconi *et al.,* 2001., Patnaik *et al.,* 2005., Laufer *et al.,* 2006).

From a public health point of view, the Population level impact of HIV on malaria will depend on several factors; HIV prevalence, age distribution of both infections , and their geographic overlap (Korenromp *et al.,* 2005). Local distribution of CD4 cell counts and clinical stages of HIV-infected patients are also important because the effects of HIV multiply as imunosuppression progresses (Whitworth *et al.,* 2000, French *et al.,* 2001). The population attributable fraction of adult malaria due to HIV-1 would be expected to rise in parallel with HIV-1 prevalence (Whitworth, 2006). Almost half of malaria cases the world over occur in areas where the disease is holoendemic (Hay *et al.,* 2004). There is a call for HIV-1 programme managers working in areas where both diseases are prevalent to take cognisant of the fact that HIV-1 infection and HIV-1 related immunosuppression are important risk factors for severe malaria (Chalwe *et al* 2009). In further consideration of this fact, there is also a need for early detection of HIV-1 infection so that measures could be taken to prevent malaria and chemoprophylaxis with co-trimoxazole could be promptly implemented to protect against uncomplicated and severe malaria (Mermin *et al* 2004).

3. Study Objectives

3.1 Formulation of the Problem

Following the recognition of HIV-1 as a major infection in sub-Saharan Africa, a basic question that arose was how infection with this immunosuppressive virus would affect the natural history of other important infections afflicting the African population (Roland-Jones 2002). An association between HIV-1 and malaria is expected in theory but has not been convincingly shown in practice (Whitworth, 2000). It was against this backdrop that Chandramonmohan and Greenwood (1998) undertook a comprehensive review of clinical studies conducted at that time (1986-1992) that tried to address this issue. Their conclusion was that those studies failed to show any convincing and therefore indisputable evidence for an interaction between HIV-1 and Malaria, except for an increased rate of placental malaria in HIV–1 infected pregnant women. In addition, there were several limitations to those studies principal among them being the small sample sizes and the failure to take into consideration the wide variations in immunosuppresion found at different stages of HIV-1 infection (Whitworth, 2006). However, more research evidence has continued to emerge over the years and opinions remained divided. There is therefore still the need for more information to further our understanding of the interaction between HIV and malaria.

3.2 Study Objectives

The main objective of this study therefore is to conduct a systematic review of the Literature in the light of available information from empirical studies on the impact of HIV-1 on malaria. The findings from this study will have implications on the control of both HIV-1 and malaria.

4.0. Study Methods

4.1. Study Design

This study is a systematic review of the Literature. The Flow chart below shows the various processes undertaken in the conduct of this review. (Figure 1).

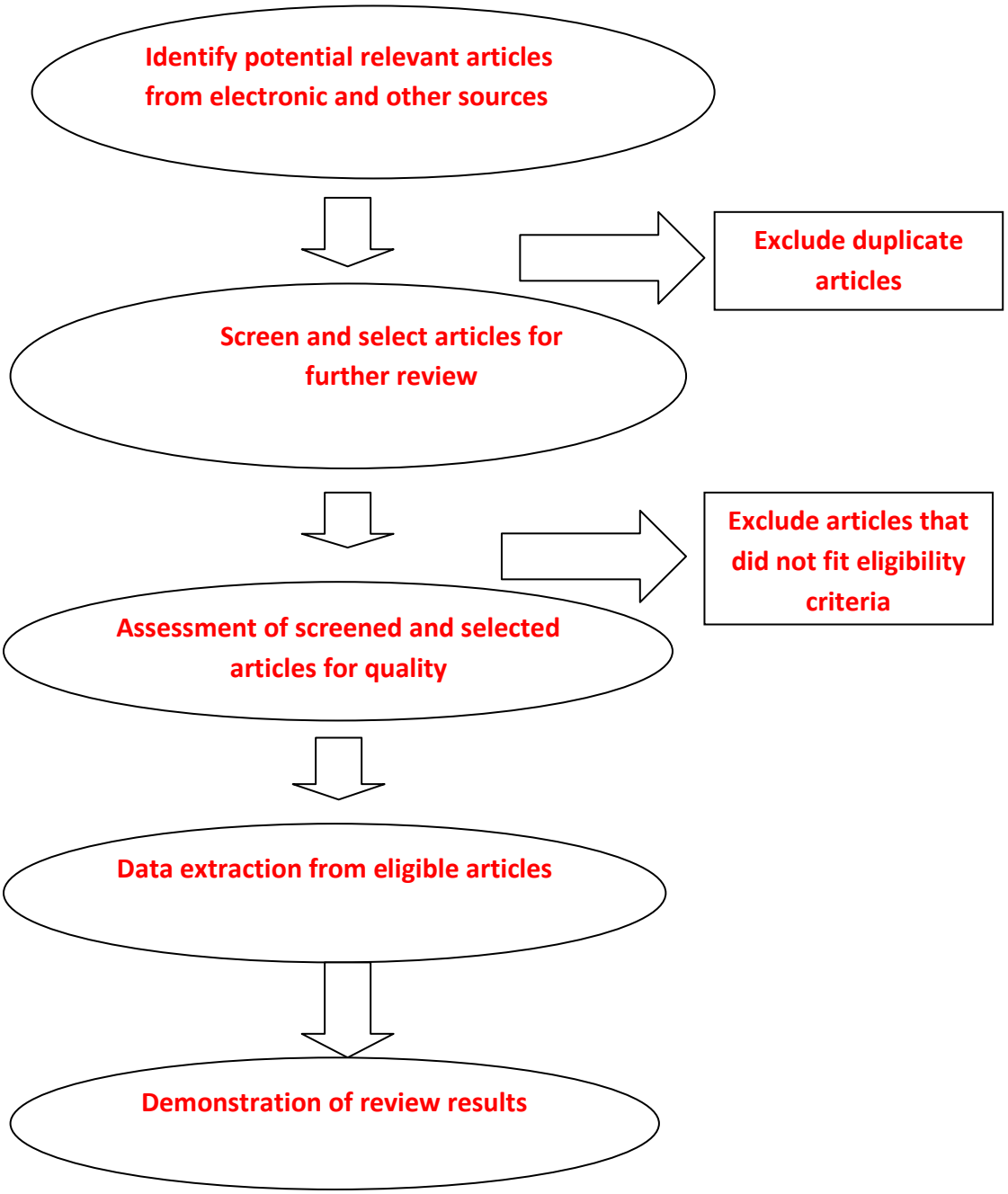

Figure 1: Flow diagram of article selection for review

4.2. Search and Selection Strategy

4.2.1. Literature Sources:

The following electronic databases were used; PUBMED (1950-2009), MEDLINE (1966-2009), EMBASE (1980-2009). Besides , in minimise the possibility of omitting other relevant literature that may not be contained in the above databases, use is also made extensively of other sources such as GOOGLE SCHOLAR, WHO, PAHO, LILAC, AIDSLINE etc. Hand search was also carried out.

4.2.2. Time of Publication of Literature:

No time restriction was imposed. Each database was therefore explored from the beginning up to May 2009.

4.2.3. Language of the Literature:

Studies published in English were selected.

4.2.4. Inclusion /Selection Criteria:

The theme of the publication must be in consonance with the following:

a. Investigation of the impact of HIV on malaria.

b. Objectively verifiable indicators of HIV status

c. Objectively verifiable indicators of infection with malaria

4.2.5. Search Terms:

The following terms were used as key words to identify the relevant articles:

HIV (OR: HIV/AIDS, Human immunodeficiency virus)

AND

Malaria.

4.3: Quality Assessment:

The quality of the included literature was assessed according to pre-determined quality assessment criteria. These criteria are listed below;

- Q.1 Did the study set out to answer a specific research question/or have a clear objective?
- Q.2 Were the settings and the study population clearly defined?
- Q.3 What was the study design?
- Q.4 Were the methods for diagnosing HIV and Malaria of acceptable standard?
- Q.5 Were the results presented in a logical and easy to understand format?
- Q.6 Were the results and conclusion comprehensively discussed?

Each of the above criterions was then assigned a score as follows:

- "**A^+**" if outright yes
- **"A^-"** if to a large extent yes
- **"B^+"** if to a large extent no
- **"B^-"** outright no

For the study design criteria: the following scores were assigned:

- **"A^+"** if the study was a cohort design
- **"A^-"** if the study was a case-control design and
- **"B"** if the study was a cross-sectional/other design.

After grading each paper on the above criteria, an overall quality score is assigned to the paper as follows: The quality was;

- **HIGH** if all the parameters attract an "A^{+}"
- **INTERMEDIATE** if the study has only one "A^{-}" the rest being A^{+}s
- **LOW** if the study has at least one "B" The researcher enlisted the help of a colleague and a senior researcher who independently carried out their own eligibility and quality assessment. Any disagreement was settled before inclusion.

4.4. Data Extraction:

- Data extraction was conducted by the researcher using a standardized data extraction form as shown below **(Table 1).**

1.0. Basic Information ID Title Journal Year of Publication Author	
2.0 Background Description Study Objective(s) Study Design	
3.0 Method Study Setting (Country/ Place) Study Population (Size) Study Period (Yeas/date)	

▪ Diagnosis of HIV ▪ Diagnosis of malaria ▪ Analytical methods	
4.0. Results ▪ Summary of main results/findings ▪ Any other results	
5.0. Conclusions: ▪ Main conclusions ▪ Limitations ▪ Recommendations	
6.0. Eligibility ▪ Eligibility for review confirmed ▪ Reason for exclusion	
7.0. Notes	

Table 1 Data extraction form

4.5. Data Analysis:

All the extracted information was entered into Microsoft office, and presented in the form of tables, and discussed didactically.

5.0. Results.

5.1. General description of reviewed articles.

After the initial search which took place in the month of May, a total of 1876 articles were identified as potential articles for inclusion. On further review of these articles, 1,012 were duplicate articles, and 840 did not meet the inclusion criteria. Finally 24 articles were selected. In 9 of the 24 articles selected for review, the study population was adult male and non pregnant women. In 6 of the 24 articles, the study population was children. In another 4, the study population were pregnant women, and in 5 the study population was a mixture of adults and children (Figure 2.0).Two of these five articles utilise secondary data to develop mathematical/projection models on the impact of HIV on malaria. Of the 24 articles, 23 were from sub-Saharan Africa and 1 was from India. They were all in English. The publication dates ranged from 1977 to 2009. The study designs were diverse; In eleven the study designs were cohorts, in 3 case-controls, in 7 cross-sectional, and in 3 secondary data. The quality varied from high through intermediate to low. The results of this research are more concisely presented in the following figures and tables (Figure 2) (Tables 2 – 9)

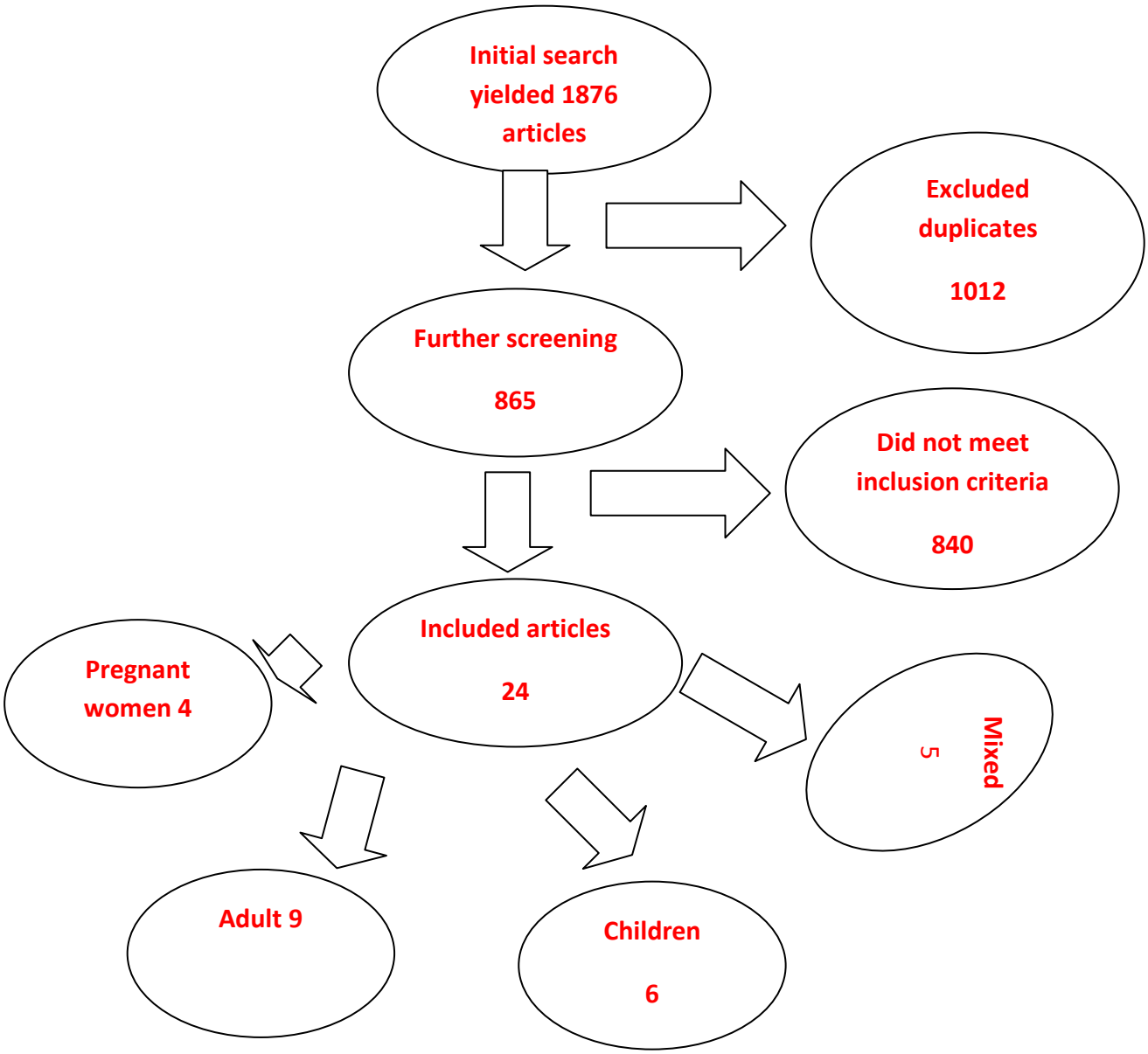

Figure 2.0. Flow chart of study selection results.

Year of Publication	First Author	Study Area	Study Population	Study Design	QUALITY ASSESSMENT						FINAL QUALITY SCORE
					Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	
2001	Francesconi	Uganda	Adults	Case-control	A^+	A^+	A^-	A^+	A^+	A^+	INTERMEDIATE
2009	Chalwe	Zambia	Adults	Case-control	A^+	A^+	A^-	A^+	A^+	A^+	INTERMEDIATE
2004	Grimwade	South Africa	Adults	Observational -cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2005	Cohen	South Africa	Adults	Prospective Cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2005	Patnaik	Malawi	Adults	Cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2006	Laufer	Malawi	Adults	Cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2001	French	Uganda	Adults	Cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2000	Whitworth	Uganda	Adults	Cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2003	Khasnis	India	Adults	cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH

Table 2 Summary of the studies that investigated the impact of HIV on Malaria in Adults and their Quality Assessment

Year of Publication	First Author	Study Area	Study Population	Study Design	QUALITY ASSESSMENT						FINAL QUALITY SCORE
					Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	
2003	Van Eijk	Kenya	Pregnant women	Cross-sectional	A^+	A^+	B	A^+	A^+	A^+	LOW
2004	Mount	Malawi	Pregnant Women	Cross-sectional	A^+	A^+	B	A^+	A^+	A^+	LOW
2009	Perrault	Kenya	Pregnant women	Cross-sectional	A^+	A^+	B	A^+	A^+	A^+	LOW
1999	Verhoeff	Malawi	Pregnant women	Cross-sectional	A^+	A^+	B	A^+	A^+	A^+	LOW

Table 3. Summary of studies that investigated the impact of HIV on Malaria in pregnant women and their Quality Assessment

Year of Publication	First Author	Study Area	Study Population	Study Design	QUALITY ASSESSMENT						FINAL QUALITY SCORE
					Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	
1991	Greenberg	Zaire	Children	Cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2007	Malamba	Uganda	Children	Prospective cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
1977	Kalyesubula	Uganda	Children	Prospective cohort	A^+	A^+	A^+	A^+	A^+	A^+	HIGH
2003	Villamor	Tanzania	Children	Cross-sectional	A^+	A^+	B	A^+	A^+	A^+	LOW
2006	Otieno	Kenya	Children	Cohort	A^+	A+	A^+	A^+	A^+	A^+	HIGH
1990	Colebunders	Zaire	Adults and Children	Case-Control	A^+	A^+	A^-	A^+	A^+	A^+	INTERMEDIATE

Table 4. Summary of studies that investigated the impact of HIV on Malaria in Children and their Quality Assessment Scores

Year of Publication	First Author	Study Area	Study Population	Study Design	QUALITY ASSESSMENT						FINAL QUALITY SCORE
					Q 1	Q 2	Q 3	Q 4	Q 5	Q 6	
1990	Muller	Uganda	Adults and Children	Review of records	A^+	A^+	B	A^+	A^+	A^+	LOW
1998	Simooya	Zambia	Adults and Children	Cross-Sectional	A^+	A^+	B	A^+	A^+	A^+	LOW
2007	Onyenekwe	Nigeria	Adults and Children	Cross-sectional	A^+	A^+	B	A^+	A^+	A^+	LOW
2008	Van geertruyden	Sub-Saharan Africa	Adults and Children	Secondary data	A^+	A+	B	A^+	A^+	A^+	LOW
2005	Korenromp	Sub-Saharan Africa	Adults and Children	Secondary data	A^+	A^+	B	A^+	A^+	A^+	LOW

Table 5. Summary of studies that investigated the impact of HIV on Malaria in Adults and Children and their Quality Assessment

5.2. Impact of HIV on the epidemiology of malaria in Adults (n=9)

9 articles studied the impact of HIV on malaria in adults. Two were case-controls, and the remaining 7 were cohorts. They were published between 2000 and 2009. Two were from South Africa, 6 from east Africa and 1 from India. Francesconi *et al* reported an association between HIV infection and clinical malaria (AOR, 2.34; 95% CI, 0.89 – 6.17). This association attained statistical significant when they refined the definition of clinical malaria to include a cut-off point for parasite density (50^{th} percentile; ie 586 parasite/µL; 3.61; 95% CI, 1.04 – 12.52). Co-infection was associated with occurrence of acute episodes of fever (AOR 9.75, 95%CI = 1.19 – 80.00, P= 0.034) whereas, single infection with either HIV or malaria was not (AOR 1.01, 95%CI = 0.51-2.03, P 0.967 for HIV alone, AOR 1.75, 95% CI = 0.73 – 4.21, P = 0.209 for malaria alone). Chalwe et al (2009) in Zambia, concluded that HIV-1 infection was a significant risk factor for adults with severe malaria compared with controls with uncomplicated malaria and asymptomatic controls. Grimwade *et al* (2004) in South Africa suggested that underlying HIV infection is associated with a two-fold higher risk of severe malaria (OR 2.3; 95% Confidence interval 1.4 – 3.9) and six to eight fold increase in the risk of death (OR 7.5; 95% Confidence interval, 2.2 – 25.1).

In the study of Cohen *et al* (2005) in South Africa, among the risk factors for severe malaria as determined by multivariate analysis are, having a positive HIV serology, elevated parasite count, and non immunity. The risk of severe malaria was also increased in HIV infected patients with a $CD4^{+}$ T cell count <200 X 10^{6} cells/L. Similar observation was made by Chalwe *et al* (2008). The study of Patnaik *et al* in rural Malawi supported an association between HIV – infection and malaria. The incidence of first, second, and overall parasitemia is

significantly higher in HIV infected than in the non HIV infected. Respective adjusted hazard ratios (95%CIs) are 1.8 (1.2 – 2.7), 2.5 (1.5 – 2.7), and 1.9 (1.4 - 2.6). They however observed that HIV sero-positives did not have a significantly greater incidence of recrudescent parasitemia.

Laufer *et al* (2006) reported a higher incidence of clinical malaria episodes in participants with a CD4 cell count < 250 cells/mm^3 than in those with a CD 4 cell count of more than 500cells/mm^3 . This trend was preserved when they applied definitions of malaria that increased specificity. French *et al* (2001) reported a marked inverse relationship between incidence rates of *Plasmodium falciparum* malaria with CD4 cell counts; 140, 93 and 57 cases per 1000 pyo for CD4 T cell groups <200, 200-499, and > 500 respectively, P< 0.001. Their data thus support an interaction between symptomatic P. falciparum malaria and HIV.

The odds of having clinical malaria increased with deteriorating immune status as determined by by a falling CD4 T cell count (Whitworth *et al* 2000). The results of whitworth *et al* (2000) support an increase in prevalence of parasitemia in HIV-1-positive individuals. HIV-1 immunosuppression was also associated with increasing parasite density. There is now sufficient data to support the proposition that progressively impaired cell-mediated immunity as a result of HIV-1 infection leads to increased frequency and severity of malaria parasitemia. The result of Khasnis and Karnad (2003), from india support an HIV-1 associated increased risk of malaria severe malaria regardless of the CD4 T cell count. Disease severity and mortality are however not increased.

Table 6 Summary of the main results/findings and conclusions/interpretations of studies that investigated the effects of HIV on malaria in adults.

REFERENCE	STUDY PARTICIPANTS	MAIN RESULTS / FINDINGS	MAIN CONCLUSION/INTERPRETATION
Francesconi et al., 2001	Clinical malaria cases 36, Controls 134	An association was found between HIV infection and clinical malaria **(AOR, 2.34; 95%CI, 0.89 – 6.17)**; the association became statistically significant when the definition of clinical malaria included a cut-off for parasite density (50^{th} percentile; i.e, 586 parasites/µl; **AOR, 3.61; 95% CI, 1.04 -12.52**)	Despite the limited statistical power, the results of this study showed an association between HIV and clinical malaria.
Chalwe et al., 2009	Case-patients: patients with severe malaria	HIV-1 infection was present in 93% of case-patients, in 52% of controls with uncomplicated malaria, and in 45% of asymptomatic controls.	HIV-1 infection was a highly significant risk factor for adults with severe malaria

	29, Controls-1: patients with uncomplicated malaria 29 Controls-2: Asymptomatic 29	ODDS of HIV: Adults with severe malaria compared with controls with uncomplicated malaria **(OR=12.6, 95% CI 2.0 – 78.8, p=0.0005)** ODDS of HIV: Adults with severe malaria compared with asymptomatic controls **(OR= 16.6, 95% CI 2.5 – 111.5, p=0.0005)** Persons with severe malaria were more likely to have a CD4 count <350/µL than were asymptomatic controls **(OR=23.0, CI 3.35 – 158.00, P=0.0001)**	compare with controls with uncomplicated malaria and asymptomatic controls
Grimwade et al., 2004	613 adults with malaria	HIV prevalence was 29.9% (180/613); 110 (18%) had severe /complicated malaria and 28 (4.6%) died. HIV-infected patients were more likely to vomit or be confused and were more likely to be admitted to hospital (P= 0.05). In patients admitted to hospital, HIV infection was	HIV infection had an unexpectedly large association with the outcome of *falciparum* malaria in a region of unstable transmission.

		associated with severe/complicated malaria **(AOR 2.3; 95% CI, 1.4 -3.9) and with death (AOR 7.5; 95% CI, 2.2 – 25.1).**	
Cohen et al., 2005	336 patients with *P.falciparum* malaria	Risk factors for severe malaria determined by multivariate analysis included having a positive HIV sero-status. The risk of severe malaria was increased in HIV infected patients with a $CD4^+$ T cell count , 200 X 10^6 cells per litre **(P ≤ 0.001).**	HIV-infected nonimmune adults are at increased risk of severe malaria.
Patnaik .et al., 2005	HIV pos 224 HIV neg 125	HIV-1 seropositivity was associated with parasitemia **(adjusted HR, 1.8 [95% confidence interval , 1.2 – 2.7]** for a first parasitemia episode; adjusted HR, **2.5 [95% confidence interval 1.5 – 4.2]** for a second parasitemia episode [> 14 days after the first episode]; adjusted HR **1.9 [95% Confidence interval , 1.4**	HIV- infected adults in malaria endemic areas are at increased risk for malaria. Where possible, additional malaria prevention efforts should be targeted at this population.

		– 2.6] for parasitemia overall). HIV-1 RNA concentrations and CD4 cell counts were moderately but inconsistently associated with parasitemia. A high parasite density with fever was associated with HIV-1 seropositivity and a low CD4 cell count.	
Laufer. et al., 2006	632 HIV positives	The incidence of clinical malaria episodes was higher in participants with CD4 cell counts <200 cells/mm^3 than in those with CD4 cell counts > 500cells/mm^3. The trend was preserved when increasingly specific definitions of malaria disease were used. The prevalence of malaria infection was not associated with CD4 cell count. In per –visit analysis, lower CD4 cell counts were associated with higher incidences of pneumonia, sepsis, and tuberculosis but not of malaria. Severe malaria was rare, with only	Profoundly immunosuppressed adults with HIV infection require more frequent treatment for uncomplicated malaria, but malaria infection and disease are less strongly associated with HIV-associated immunosuppression than are other opportunistic infections. Where malaria is common, the high incidence of fever found among immunosuppressed adults may lead to misclassification of illness episode as

		3 cases in 591 person-years of observation.	malaria.
French et al., 2001	1371 HIV-1 positives	Incidence rates of *Plasmodium falciparum* malaria fever showed a marked inverse relationship with CD4 T cell count; 140, 93 and 57 cases per 1000pyo for CD4 T cell groups <200, 200-499, and >500 respectively, P<0.001.	The data support an interaction between symptomatic *P. falciparum* and HIV. Emphasis on mosquito avoidance measures should be an important component of education and counselling of HIV/AIDS patients in malaria endemic areas, and suggests an additional HIV related public health problem in Africa.
Whitworth J.et al., 2000	No. Visits: HIV +, 3123, HIV-, 4097	Parasitemia was more common at visits by HIV-1 positive individuals **(328 of 2788 [11.8%] vs 231 of 3688 [6.3%] , p < 0.0001).** At HIV-1 positive visits, lower CD4 cell counts were associated with higher parasite densities, compared with HIV-1 negative visits	HIV infection is associated with an increased frequency of clinical malaria and parasitemia. This association tends to become more pronounced with advancing immunosuppression, and could have important public-health

		(**p<0.0076).** Clinical malaria was significantly more common at HIV-1 positive visit visits **(55 of 2788 [2.0%] vs 26 of 3688 [0.7%], p=0.0003**) and the odds of having clinical malaria increased with falling CD4 cell count **(p=0.0002)** and advancing clinical stage **(p=0.0024**). The risk of clinical malaria was significantly higher at visits by HIV-1-positive individuals than HIV-1-negative individuals **(4.0% vs 1.9%, p=0.009).** The risk of clinical malaria tend to increase with falling CD4 cell count **(p=0.052).**	implications for sub-Saharan Africa.
Khasnis and Karnad, 2003	Malaria patients, 43 Blood donors, 28749	Five (11.6%) of the 43 patients and 521 (1.8%) of 28749 blood donors had HIV infection **(OR 7.1, 95% CI= 2.8 to 18.2, p=0.001).**	HIV infection is associated with increased risk of severe malaria even with normal CD4 cell counts; severity of disease and mortality are not increased. However, prior HIV infection impairs protective immune response to

			Plasmodium falciparum in residents in hypoendemic areas.

5.3. Impact of HIV on Malaria in Pregnant women (n=4)

Four articles were located in this review that investigated the impact of HIV on malaria in pregnant women. They were published between 1999 and 2009. They were all from Eastern Africa. All 4 studies were cross-sectional.

Van Eijk et al., (2003) reported an association between HIV infection and clinical malaria. Compared with HIV-seronegative women, HIV sero positive women were more likely to be parasitemic, to have higher parasite densities, and to be febrile when parasitemic. Moreover, HIV seropositive women are more likely to harbour placental infection. Mount et al.,(2004) found that concentrations of IgG to placental type VSA were lower in HIV-infected women than in HIV-uninfected women. They were also lower among women infected with malaria than those not infected with malaria. Impairment was greatest in first pregnancy.

The results of Perrault et al.,(2009) show that HIV co-infection was associated with a significant increase in placental parasite density. Cord blood malaria prevalence was also higher in co-infected women and correlated with placental parasite density. The co-infected women have a significantly higher burden of placental malaria with increased risk of congenital infection. Verhoeff et al.,(1999) reported that the relative risk for parasitaemia in HIV-infected compared to HIV uninfected women was significantly increased in three of five parity groups, including the two highest ones (parity >3).

Table 7 Summary of the main results/findings and conclusions/interpretations of studies that investigated the effects of HIV on malaria in pregnant women.

Reference	Study participants	MAIN RESULTS / FINDINGS	MAIN CONCLUSION/INTERPRETATION
Van Eijk et al., 2003	5093 pregnant women.	Compared with HIV seronegative women, HIV seropositive women were more likely to be parasitemic, to hive higher parasite densities, and to be febrile when parasitemic. Placental infections in HIV serpositive women were more likely to be chronic.	HIV infection in pregnancy alters the pattern of malaria and that malaria preventive measures should be offered to pregnant women in areas where both infections areprevalent.
Mount et at., 2004	Malaria infected HIV+, 44 Malaria infected	Concentrations of IgG to placenta type VSA were lower in HIV-infected women that in HIV-uninfected women (median 8 units **[IQR 4-23] vs 20 [12-30]; p < 0.0001)**, among pregnant	HIV inection impairs antimalarial immunity, especially responses to placental typr VSA. The impairment is greatest in the most mmunosuppressed

	HIV-, 43 Malaria uninfected HIV +, 161 Malaria uninfected HIV -, 50	women with malaria (**p=0.009**) and those without malaria **(p=0.0062**). The impairment was greatest in the first pregnancy.	women and could explain the increased susceptibility to malaria seen in pregnant women with HIV infection.
Perrault et al., 2009	Total, 157 HIV +, 24.8% HIV -, 74.5%	HIV co-infection was associated with a significant increase in placental parasite density **(p<0.05).** Cord blood malaria prevalence was increased in co-infected women **(odds ration [OR]=5.42; 95% confidence interval [CI]=1.90 – 15.47)** and correlated with placental parasite density **(OR=2.57; 95% CI=1.80-3.67).**	The HIV co-infected women have a significantly increased burden of placental malaria that increases the risk of congenital infection.
Verhoeff et	621 ANC	Prevalence of HIV-1 infection was 25.6%. In	HIV infection is associated with a

al., 1999	attendees	primigravidae malaria prevalence at recruitment was 56.3% in HIV infected and 36.5 in HIV uninfected women **(P,0.04).** The corresponding figures for multigravidae were 23.8% and 11.1% ,respectively **(P,0.01**). HIV infected primigravidae had increased malaria prevalence at all gestational ages. Peak parasite prevalence occurred earlier in gestation in HIV infected primigravidae (16-19 weeks if HIV infected; 20-23 weeks if HIV uninfected).The relative risk for parasitemia in HIV-infected compared to HIV-uninfected women was significantly increased in three of five parity groups including the two highest ones (parity >3), indicating parity-specific immunity to malaria was impaired. Malaria prevalence at delivery remained high in HIV-infected women	significant increase in malaria prevalence in all parities with the effect apparent from early gestation.

		despite prior routine treatment with sulphadoxine-pyrimethamine in pregnancy. There was no significant difference in parasite prevalence at delivery between women who did or did not use sulphadoxine-pyrimethamine.	

5.4 The impact of HIV on Malaria in Children (n=5)

6 articles were located in this review that looked at the impact of HIV on malaria in the paediatric age group. 5 were cohort designs and 1 was a case-control. They were all from East Africa and were published between 1990 and 2007.

Malaria and infection with human immunodeficiency virus are among the leading causes of death in sub Saharan Africa (Malamba *et al.,* 2007). In Uganda for instance, malaria attributable mortality among under fives is 37 per 1000 person-years in high endemicity areas and 18 per 1000 person-years the low endemicity areas (Ugandan Ministry of Health, 2005, Nsungwa-Sabiiti *et al*., 2004). The estimated prevalence of HIV in adults is 7% (Ugandan ministry of health 2006) and in children 1.7% (Kengeya-Kayondo *et al.,* 1995).

In their study looking at the effect of HIV infection on morbidity and mortality in children with severe malaria, Malamba *et al.,* (2007) reported that HIV –infected children are more likely to die within 7 days and within 28 days of an episode of severe malaria anaemia compared to HIV negative children. HIV positive children also had more frequent re-admissions due to malaria within 28 days and within 6 months post-transfusion than HIV-uninfected children. A higher all -cause mortality and malaria-related mortality was observed among HIV infected children. In their multivariate analysis, Otieno *et al*., (2006) reported that the risk of severe malaria anaemia was elevated in HIV-1 exposed children and HIV-1 positive children compared to HIV-1 negative children. Both exposure to HIV-1 and infection were associated with increased prevalence of severe malarial anaemia (SMA). It is therefore suggested that in malaria endemic areas, HIV testing may be a good idea in paediatric populations.

The study of Colebunders *et al.,* (1990) in Zaire, Kinshasha was inconclusive in the sense that they stated that it was not possible for them to out rightly support or reject the notion of there being as interaction between HIV and malaria. However, they were of the opinion that there appears to be no apparent interaction of major clinical importance between HIV and malaria. Villamor *et al*., (2003) reported that they found some evidence of lower prevalence of parasitemia among HIV positive compared with HIV negative children after adjusting for factors such as season, anaemia, bed net use, maternal education, and other socioeconomic factors. No significant increase in malarial episode was observed in HIV –infected children compared to their uninfected controls (Kalyesubula *et al*., 1997). Similar observations were made by Greenberg and his colleagues from a study in Zaire, Kinshasha. In four well-defined groups of children; those with AIDS, those who where HIV-1 seropositive throughout the study period, those who were born to HIV-1 seropositive mothers but reverted to seronegativity, and those who were seronegative throughout the study, there was no statistically significant differences in the incidence, or severity of malaria. Their conclusion was that malaria was no more frequent or more severe in children with HIV infection. Furthermore, malaria does not seem to speed up the rate of progression of HIV.

Table 8 Summary of the main results/findings and conclusions/interpretations of studies that investigated the effects of HIV on Malaria in Children

Reference	Study participants	MAIN RESULTS / FINDINGS	MAIN CONCLUSION/INTERPRETATION
Greenberg et al., 1991	Children born to HIV-1 seropositive mothers, 260 Children born to HIV-1 seronegative mothers, 327	No statistically significant differences were found in the incidence, severity, or response to therapy of malaria among four well-defined groups of children: those with acquired immunodeficiency syndrome (AIDS), those who were HIV -1-seropositive throughout the study, those who were born to HIV-1-seropositive mothers but reverted to seronegative , and those who were seronegative throughout the study. During the 13-month period the incidence of malaria in the 36 children with HIV infection in whom AIDS developed was lower,	Malaria was not more frequent or more severe in children with progressive HIV-1 infection and malaria did not appear to accelerate the rate of progression of HIV-1 disease.

		although not statististically so, than in the 37 in whom AIDS did not develop.	
Malamba et al., 2007	HIV-infected, 78 HIV-uninfected, 769	HIV-infected children were more likely to die within 7 days **(Hazard ratio [HR]=2.86, 95% confidence interval [CI] 1.3-6.29, p=0.009) and within 28 days (HR=3.70, 95% CI 1.91-7.17, p<0.001)** of an episode of severe malarial anaemia, and were more likely to die in 6 months post-transfusion **(HR= 5. 70, 95% CI 3.54-9.16, p<0.001)** compared to HIV-uninfected children. HIV-infected children had more frequent re-admission due to malaria within 28 days **(Incidence rate ration (IRR) = 3.74, 95% CI 1.41-9.90, p = 0.008) and within 6 months (IRR = 2.66, 95% CI 1.17 – 6.07, p=0.02)** post-transfusion than HIV-uninfected	HIV infected children with severe malarial anaemia suffered higher all-cause mortality and malaria –related mortality than HIV-uninfected children. Children with HIV and malaria should receive aggressive treatment and further evaluation of their HIV disease, particularly with regards to co-trimoxazole prophylaxis and antiretroviral therapy.

		children.	
Kalyesubula et al., 1977		HIV prevalence was 29.9% (180/613); 110 (18%) had severe /complicated malaria and 28 (4.6%) died. HIV-infected patients were more likely to vomit or be confused and were more likely to be admitted to hospital (P= 0.05). In patients admitted to hospital, HIV infection was associated with severe/complicated malaria **(AOR 2.3; 95% CI, 1.4 -3.9) and with death (AOR 7.5; 95% CI, 2.2 – 25.1).**	HIV infection had an unexpectedly large association with the outcome of falciparum malaria in a region of unstable transmission.
Villamor et al., 2003	560 children aged 6-60months	The prevalence of malaria parasitemia was 11.4% among HIV-infected children, compared with 27.6% among uninfected. After adjusting for season, anaemia, use of bed nets, maternal education and indication of socioeconomic status, they found some	HIV infection appears to be negatively correlated with parasitaemia in this group of children.

		evidence for lower prevalence of parasitaemia among HIV positive compared with HIV-negative children (prevalence ratio = 0.56; 95% CI=0.29-1.09; P=0.09)	
Otieno et al., 2006	HIV-1 (-), 194 HIV-1(exp), 100 HIV-1 (+), 23.	Relative to HIV-1 (-) group, the HIV-1 (exp) and HIV-1 (+) groups had lower haemoglobin concentrations (P , 0.001 and P <0.001 respectively), while parasitemia and HDP were equivalent between the three groups. Multivariate analysis demonstrated that the risk of SMA was elevated in HIV-1 (exp) children **(odds ratio, 2.17; 95% CI, 1.25-3.78; P <0.01) and HIV-1 (+) children (odds ratio ,8.71; 95% CI, 3.37-22.51; P<0.0001)**. HIV-1 exposure or infection were not significantly associated with HDP.	HIV-1 exposure and HIV-1 infection are associated with increased prevalence of SMA during acute *P.falciparum* infection, independent of parasite density.

Colebunders et al., 1990	HIV +, 59 HIV -, 83	HIV-1 seropositive patients patients presented more often with episodes of fever per person month observation than HIV-1 seronegative patients (P=0.003). The total number of positive thick film per person months observation was significantly higher among HIV-1 seropositive patients than HIV-1 seronegative ones , but percentages of positive thick film per episode of fever were the same in both groups .	This study suggests that there seems to be no direct interaction of major clinical importance between HIV infection and malaria.

5.5 The impact of HIV on the epidemiology of malaria in the general population.(n=5).

Several studies have investigated the relationship between Plasmodium falciparum malaria and HIV in paediatric and adult populations (Muller and Moser 1990., Simooya *et al*., 1988., Onyenekwe *et al.,* 2007.) Muller and Moser (1990), found no association between HIV-1 infection and malaria in either children or adults. *P.falciparum* malaria was present in approximately equal percentage of all patients. No differences in either the prevalence of malaria infection or in the parasite density could be demonstrated between HIV-1 positive and HIV-1 negative controls. HIV-1 positive patients showed the same response to treatment with anti-malarials as HIV-1 negative controls. Plasmodium falciparum infection does not appear to act as an opportunistic infection. Simooya *et al* (1988) similarly found no significant differences in antibody titre to *P.falciparum* in patients who where HIV antibody positive and those who were not. Onyenekwe *et al.,* (2007) demonstrated that the prevalence of malaria was tripled in symptomatic HIV seropositive individuals, a trend they argued could not be accounted for by malaria infection alone without any underlying immunosuppression. Van geertruyden *et al* (2008) applying a mathematical model were able to demonstrate that HIV increased the overall malaria parasite biomass by 18% (95%CI: 11.6-26.9). By increasing the parasite biomass, the HIV epidemic in sub-Saharan Africa also increase the emergence of antimalarial drug resistance. This is clearly a worrying signal as it will have serious public health implications.

Table 9.0. Summary of the main results/findings and conclusions/interpretations of studies that investigated the effects of HIV on Malaria in mixed population of Adults and Children.

Reference	**Study participants**	**MAIN RESULTS / FINDINGS**	**MAIN CONCLUSION/INTERPRETATION**
Muller and Mosser, 1990	HIV-1(+) children, 202 HIV-1(-) children, 216 HIV-1(+)adults, 737 HIV-1 (-) adults, 372	No association could be found between HIV-1 infection and malaria either in paediatrics or adults. *P.falciparum* malaria parasitaemia was present in 18% of all patients and no difference in prevalence of malaria infection , or in parasite density could be demonstrated between HIV-1 positive and HIV-1 negative patients. The comparision of clinical symptoms ahowed typical differences in AIDS related morbidity but no difference in malaria-specific morbidity.	*P.falciparum* malaria does not appear to act as an opportunistic agent in AIDS patients in Uganda.

		Also the response to malaria treatment was the same in HIV -1 positive and HIV-1 negative patients.	
Simooya et al., 1998	HIV (+), 28 HIV (-), 142	Parasitaemia was less common among those with with HIV antibodies than among those without (8 out of 28 929%) v 59 out of 142 (42%), respectively) but the difference was not statistically significant. The $\log_e$ mean parasite density in blood slides showing parasitaemia was higher in patients who were negative for HIV antibody than in those who were positive for HIV antibody, but the difference was not	No significant differences existed in antibody tire to P.falciparum in patients who were positive for HIV antibody and in those who were negative whether or not they had parasitaemia.

		statistically significant. (loge mean difference 2.43, SE 1.4113; $p<0.10$). Sixty three of the 67 (94%) patients with parasitaemia and 74 of the 103 (72%) without had considerable antibody titre to P.falciparum.	
Onyenekwe et al., 2007	Assymptomatic HIV seropositive, 101, Symptomatic HIV seropositive 47, HIV	Prevalence of P.falciparum malaria as a co-infection amongst the assymptomatic HIV seropositive group was 12 (11.8%) and among the symptomatic HIV seropositive group was 16 (33.3%). However the prevalence rate of P.falciparum malaria amongst the control HIV seronegative group was 5 (10.6%).	The study observed different prevalence rates of P.falciparum malaria amongst the three groups. The prevalence was tripled in symptomatic HIV seropositive group. This shows a clear departure from possible obtainable prevalence of malaria infection alone in this malaria endemic area.

	seronegative controls, 47.		
Van geertruyden et al., 2008	N/A	The model shows that in 2005 HIV-1 increased the overall malaria parasite biomass by 18.0% (95% CI: 11.6 – 26.9).The largest relative increase (134.9 – 243.9%) was found in southern Africa where HIV prevalence is the highest and malaria transmission unstable. The largest absolute increase was found in Zambia, Malawi, the Central African Republic and Mozambique, where both malaria and HIV are highly endemic.	The HIV epidemic by increasing the malaria parasite biomass in sub-Saharan Africa may also increase the emergence of antimalarial drug resistance, potentially affecting the health of the whole population in countries endemic for both HIV-1 and malaria.
Korenromp et al., 2005	N/A.	The impact of HIV was limited (although quantitatively uncertain) because of the different geographic distributions and contrasting age pattern of the diseases.	The impact of HIV was limited (although quantitatively uncertain) because of the different geographic distributions and contrasting age pattern of the diseases.

		However, in Botswana, Zimbabwe, Zwaiziland, South Africa and Namibia, the incidence of clinical malaria increased by ≤28% (95% CI 37% - 118%).	However, in Botswana, Zimbabwe, Zwaiziland, South Africa and Namibia, the incidence of clinical malaria increased by ≤28% (95% CI 37% - 118

6.0. Discussion

This research work was undertaken to assess the impact of HIV-1 infection on the epidemiology of malaria by means of a systematic review of the literature. The search took place in the month of May 2009. Twenty-four articles met the pre-set criteria for inclusion into the review process. In nine out of these 24 articles, the investigators assessed the impact of HIV-infection on malaria specifically in adults (Francesconi *et al.,* 2001; Chalwe *et al.,* 2009; Grimwade *et al*., 2004; Cohen *et al.,* 2005; Patnaik *et al.,* 2005; Laufer *et al.,* 2006; French *et al.,* 2001; Whitworth *et al*., 2000; Khasnis and Karnad, 2003). Four of the studies investigated the impact of HIV on malaria in pregnant women (van Eijk *et al.,* 2003; Mount *et al*., 2004; Perrault *et al.,* 2009; Verhoeff *et al*., 1999), Six were investigations into the effect HIV has on the epidemiology of malaria in children (Greenberg *et al.,* 1991, Malamba *et al.,* 2007., Kalyesubula et al., 1997; Villamor *et al*., 2003; Otieno *et al.,* 2006; Colebunders *et al.,* 1990) and Five studies included data from both paediatric and adolescents age groups and adults (Muller and Moser, 1990; Simooya *et al*., 1988; Onyenekwe *et al*., 2007; Van geertruyden *et al.,* 2008; Korenromp *et al*., 2005). The studies were published between 1977 and 2009. They were all published in English. The quality of the reviewed articles ranges from "high" through "intermediate" to "low". For the purpose of answering the research question which is "**whether or not HIV has an effect on malaria"** I have considered only the "high" and to some extent "intermediate" quality articles. The rationale behind this decision is that all of the "low" quality articles are observational (cross-sectional and reviews of records) and as such cannot be relied upon to draw firm conclusions of associations. On the other hand, all the "high" quality articles upon which this discussion is based are either prospective cohorts or at the very least cross-sectional. It is known that

prospective Cohort studies are more reliable in drawing conclusions regarding associations.

6.1. The Impact of HIV on Malaria

The 14 “high” and “intermediate” quality articles that investigated the impact of HIV on malaria showed a high level of concurrence at 78.6 percent. A concurrence of this magnitude is clearly pointing towards the fact that HIV indeed has an impact on the epidemiology of malaria. We are aware of the fact that a part of sub-Saharan Africa (West Africa) which is also endemic for Malaria although less so for HIV have not featured prominently among the reviewed articles. This is probably due to limited resources to carry out necessary research work from these countries. While we do not believe that this absence of articles from one region alone in itself is of sufficient magnitude to shift this percentage concordance to any appreciable margin on either side, we are cognisant of the fact that a few more articles would have added more value to this review.

Publication biases may have occurred at the levels of both the researchers and publishers and this cannot be entirely ruled out in this review. However, the reviewed articles are fairly recent in the sense that they were all published within the last three decades. During this time the issue of publication bias has been well publicised and authors and publishers are aware of the need to publish their findings whether they prove an association or not. This could therefore not be of a magnitude that is sufficient to change alter our findings.

Moreover, the field studies of the articles in this review were carried out in different geographic locations with different transmission intensities, and also at different times of the year. We know that transmission patterns for malaria

vary from country to country and even within the same country it can vary from one time of the year to the other (seasonal variations). The conclusion from this review however is that, this review has sufficient information to form the basis of an informed decision that there is an association between HIV and Malaria and that HIV is a risk factor for Malaria.

6.2. Immunity and semi-immunity to Malaria .

Central to any discussion on the interaction between HIV and malaria is an understanding of the fundamental immunological mechanisms that are involved in developing immunity and /or semi-immunity to malaria. This is because the centre point of any interaction between the two infections has to take cognisance of what is going on at the immunological stage. Immunological mechanisms can prevent the development of infection (Chandramohan and Greenwood, 1998). In the malarial endemic areas of the world, residents acquire two types of immunities; immunity against the clinical manifestations of the infection termed anti-toxic immunity, and immunity against infection with the parasite termed anti-parasite immunity (Francesconi *et al.,* 2001). This immunity confers a survival advantage to residents of endemic areas as they can tolerate a relatively high degree of parasitemia without any adverse consequences, thus giving rise to the so-called “Assymptomatic Parasitemia. The greatest beneficiaries of this protective immunity are adults in endemic areas. They however risk losing this benefit if they migrate to a non malaria endemic region for long periods i.e if the risk of exposure to infection is eliminated (Molineaux and Gramiccia, 1980). This is because this immunity is non-sterile and therefore repeated exposure to mosquito bites is necessary to maintain it. They can however ultimately regain their lost immunity after returning to the endemic zone but it may well be at a cost-(after one or several

bouts of severe and life-threatening malaria attacks). Because anti-malarial immunity takes years to develop, more than 10 years (Klein *et al.,* 2008) children in malaria endemic regions are therefore more susceptible to the morbidity and mortality associated with malaria. Non immune migrants from non endemic or low transmission areas do not have this protective immunity and are therefore always at risk of severe and life threatening malaria infection at any level of parasitaemia.

6.3. The immunological Basis of immunity and semi-immunity to Malaria.

Both T and B cells are believed to be essential to the acquisition of this immunity (Chandramohan and Greenwood, 1988). There are two main of $CD4^+$ helper T cell responses; one is the T_H 1 type and the other is the T_H 2 type (Langhorne *et al.,* 1989). When a person develops *falciparum* malaria for the first time, the T_H 1 response is the first to be set into motion. It leads to the destruction of the parasites through the release of toxic mediators by activated macrophages. (Chandramohan and Greenwood). If this protective mechanism fails, there is still room for further control of the infection through antibodies directed at the antigens in the blood (Nardin and Nussenzweig, 1993). This second protective mechanism is sub served by the T_H 2 response (follow 18 to 60 days later) and mediates the production of antibodies that prevent the proliferation of parasites (Langhorne *et al.,* 1989). These explanations sound plausible may well account to the anti-toxic and anti-parasite immunity to malaria exhibited by residents in high transmission areas.

6.4 HIV and immunity to Malaria

It is now known that HIV affects $CD4^+$ T lymphocytes (Stanley *et.al*., 1995). It is also now known that CD4 T cells, B cells, and antigen presenting cells are all integral to the immune response to malaria (Chandramohan and Greenwood, 1988). It has been reported that infection with HIV causes a switch to a predominantly T_H 2 response at the expense of the T_H 1 response, thus limiting the capacity of an individual to limit parasitemia and hence infection (Clerici and Shearer, 1994). On the basis of these findings, an immunological relationship between HIV and Malaria should therefore be expected at least in theory.

6.5 HIV and Parasitemia.

From the foregoing discussion, the stage is now set for further discussion of important aspects of the effects of HIV infection on malaria. HIV infection could impair immune responses to malaria parasites, leading to a reduced capability of the individual to limit parasitemia. Reports of HIV-1 infection as a risk factor for hyperparasitemia or severe malaria are however limited (Chalwe *et al* 2009). This fact is also reflected in this review. Form their multivariate analysis, an elevated parasite count is being cited as risk factor severe malaria by Cohen *et al* (2005). What level of parasitemia is regarded as “elevated” is however not clear. This is important for non immune and semi-immune individuals. However, Cohen et al (2005) did not observe an increase in parasite levels in HIV-infected patients as would be expected from an immunological point of view. Similar findings are in the literature (French et al., 2001). In my own opinion, a major limitation of these studies was that they failed to stratify HIV-1 positive patients according to their CD4 T cell levels and to specifically applying parasite quantitative techniques according to the CD4 T

cell levels. Whithworth *et al*., 2000 found that lower CD4 T cell counts were associated with higher parasite densities, compard with HIV-negative visits. The difference was statistically significant P = 0.0076. Failure to take into consideration CD4 T cell levels has been cited as a major limitation of earlier studies looking at an interaction between HIV and Malaria (Chandramohan and Greenwood, 1988). Persons with CD4 cell counts <400cells/mL experienced higher incidence rates of parasitemia, compared with those with CD4 cell counts ≥400 cells/mL (Patnaik et al., 2005). HIV-seropositivity was associated with parasitemia (adjusted HR, 1.8, 95% CI, 1.2 – 2.7) for a first parasitemia episode; adjusted HR, 1.9 (95% CI, 1.5 -4.2) for a second parasitemia episode (>14 days after the first episode); and adjusted HR 1.9 (95% CI, 1.4 -2.6) for parasitemia overall. (Patnaik et al., 2005).

6.6. HIV and the frequency, clinical presentations, and severity of malaria.

Other important aspects of the relationship between HIV and malaria worth discussing are the influence of HIV on the frequency, clinical presentation, and severity of malaria. Opinions have been and remained divided on the above issues. A number of articles have managed to throw light on these somehow controversial issues. The study of Francesconi and colleagues (2001) reported that there was no observed significant association with fever for single infection *ie* malaria or HIV. Interestingly, they observed a significant association between the occurrence of fever and co-infection with both HIV and malaria. This observation is suggestive of an important interaction between the two infections. (Francesconi *et al* 2001). There is a possibility that HIV suppresses the anti-toxic immunity which protects person with parasitemia from clinical manifestations of the disease of which fever is one. This hypothesis is further supported by the observation by Francesconi

and colleagues (2001) that non AIDS-infected individuals usually report prolonged fever lasting more than a month, whereas HIV-infected individuals report of more acute fever episodes. We found this information convincing, and a strong case to support the fact that an association do exist between HIV and malaria.

Francesconi *et al* set to further prove their case for an interaction between the two infections by refining the definition of malaria through the introduction of a cut off level for malaria parasite density. Refining the definition of malaria to include cut off levels for parasite density has been reported to increase the reliability of microscopy by Kilian *et al* (2000), as well as to increase the specificity of the case definition of malaria (Armstrong Schellenberg *et a*l 1994) by effectively reducing false positive cases and addressing the issue of assymptomatic parasitemia. A marked inverse relationship was observed between the incidence of Plasmodium falciparum malaria and CD4 T cell count (French *et al* 2001). This observation is supportive of an association between symptomatic *P.falciparum* and HIV. French *et al* (2001) on the basis of this observation suggested that emphasis on mosquito measures should form part of HIV education and counselling. HIV–infectd patients are more likely to vomit or be confused and were also more likely to be admitted to hospital according to research by Grimwade et al (2004). Among hospitalized patients, HIV co-infected infected patients had more severe and complicated malaria and are at approximately 7 times more likely to die (Grimwade *et al* 2004).

Clinical malaria was significantly more common at visits made by HIV-infected patients compared with visits made by non HIV-infected patients ($p=0.0003$). The odds of having clinical malaria increased with falling CD4 cell

count (p=0002) and advancing clinical stage (p=0.0024) (Whitworth *et al* 2000). The association between the two infections tend to become more pronounced as immunosuppression advances. These findings further underscore the point made earlier on the importance of taking into account CD4 cell count in investigation any association between HIV and malaria. Most of the earlier articles failed to take this point into account. This may explain in part why previous reviews failed to show any convincing and consistent link between the two infections (Chandramohan and Greenwood 1998).

HIV infected adults in malaria –endemic areas are at increased risk for malaria (Patnaik *et al* 2005, Cohen *et al* 2005). HIV-infected patients with a $CD4^+$ T cell count of $< 200 \times 10^6$ cells per Litre are at increased risk of severe malaria ($P \leq 0.001$). Non-immune HIV-infected patients are significantly more likely to have severe malaria than were their non-immune counterparts but who are HIV negative, thus supporting the argument that HIV increases the risk of clinical malaria in the non-immune (Cohen *et al* 2005). The incidence of clinical malaria episodes was higher in participants with CD4 cell counts < 200 cells/mm^3 than in those with cell counts >500 cells/mm^3. Again this trend persisted when the definitions of malaria were refined to increase to reduce false positives and increase specificity. (Laufer *et al* 2006). The findings of Chalwe *et al* (2009) are in agreement with those of Cohen *et al* (2005) above. The risk of clinical malaria was more likely among people with CD4 cell count , 350 /µL. The study of Khasnis and Karnad (2003) also concluded that HIV is associated with an increased risk of severe malaria even with normal CD4 cell counts.

Malaria and infection with human immunodeficiency virus are among the leading causes of death in sub Saharan Africa (Malamba *et al.,* 2007). In

Uganda for instance, malaria attributable mortality among under fives is 37 per 1000 person-years in high endemicity areas and 18 per 1000 person-years the low endemicity areas (Ugandan Ministry of Health, 2005, Nsungwa-Sabiiti *et al*., 2004). The estimated prevalence of HIV in adults is 7% (Ugandan ministry of health 2006) and in children 1.7% (Kengeya-Kayondo *et al.,* 1995).

In their study looking at the effect of HIV infection on morbidity and mortality in children with severe malaria, Malamba *et al.,* (2007) reported that HIV –infected children are more likely to die within 7 days and within 28 days of an episode of severe malaria anaemia compared to HIV negative children. HIV positive children also had more frequent re-admissions due to malaria within 28 days and within 6 months post-transfusion than HIV-uninfected children. A higher all -cause mortality and malaria-related mortality was observed among HIV infected children. In their multivariate analysis, Otieno *et al*., (2006) reported that the risk of severe malaria anaemia was elevated in HIV-1 exposed children and HIV-1 positive children compared to HIV-1 negative children. Both exposure to HIV-1 and infection were associated with increased prevalence of severe malarial anaemia (SMA). It is therefore suggested that in malaria endemic areas, HIV testing may be a good idea in paediatric populations.

The study of Colebunders *et al.,* (1990) in Zaire, Kinshasha was inconclusive in the sense that they stated that it was not possible for them to out rightly support or reject the notion of there being as interaction between HIV and malaria. However, they were of the opinion that there appears to be no apparent interaction of major clinical importance between HIV and malaria. Villamor *et al*., (2003) reported that they found some evidence of lower prevalence of parasitemia among HIV positive compared with HIV negative

children after adjusting for factors such as season, anaemia, bed net use, maternal education, and other socioeconomic factors. No significant increase in malarial episode was observed in HIV –infected children compared to their uninfected controls (Kalyesubula *et al*., 1997). Similar observations were made by Greenberg and his colleagues from a study in Zaire, Kinshasha. In four well-defined groups of children; those with AIDS, those who where HIV-1 seropositive throughout the study period, those who were born to HIV-1 seropositive mothers but reverted to seronegativity, and those who were seronegative throughout the study, there was no statistically significant differences in the incidence, or severity of malaria. Their conclusion was that malaria was no more frequent or more severe in children with HIV infection. Furthermore, malaria does not seem to speed up the rate of progression of HIV. So the argument is more polarized in the case of children.

6.7. HIV and Malaria Transmission.

Through HIV mediated immune suppression, it is reasonable to speculate that the Plasmodium parasite reservoir in HIV infected individuals will rise. In further consideration of this fact, it is also reasonable to suppose that HIV will lead to an increase in malaria transmission. (van geertruyden and D'Alessandro 2007). If this were the case, then we would expect people living in the same household as an HIV-infected individual to have higher rates of malaria among HIV-negative people than do families without an HIV-infected individual. This has been found to be the case in a study by Mermin *et a*l (2005). The work of Mermin et al (2005) though innovative and interesting, should taken with caution. This is because as Whithworth and Hewit (2005) put it "Apart from this observation, there is currently no firm evidence that HIV modifies malaria transmission or that malaria modifies HIV transmission".

Other considerations worth taking on board in further consideration of this issue include the use of insecticide-treated bed-nets and cotrimoxazole prophylaxis as both reduces the incidence of malaria in HIV infected persons (Mermin et al., 2006).

6.8 Limitations of this study

One of the major limitations of this study was that the search was limited to articles published in English. There is the possibility that the researcher might have missed out articles published in other languages especially French and Portuguese. However, as most French articles are also published in English, and there are only a few Portuguese speaking countries in Africa south of the Saharan, it is the opinion of the researcher that this limitation will not be of sufficient magnitude to alter the findings of this study in any significant way.

We are aware of the fact that publication biases might have also affected the findings of this study if researchers and publishers were more inclined to publish studies that show an association as against those that did not. The upside of this limitation is the fact that the issue of publication bias has received wide publication in recent times. It is expected that both researchers and publishers are aware of the need to publish both positive and negative findings.

This review is tilted towards southern and eastern Africa. This bias has to do with the fact that HIV is more of a problem in these parts of Africa than in west Africa. Research on HIV and malaria is therefore more active in southern and eastern Africa than in western Africa. Although in my opinion this limitation should not influence the findings of this review in any significant form, it would

have definitely added to our understanding of the issue if articles were forthcoming from western Africa on this topic. Moreover any limitation of the individual studies that have been included in this research work will invariable be a limitation to this work. All of the articles on pregnant women are cross-sectional and are therefore not regarded as “high” enough quality for the result they contain to be incorporated in this review, so also the articles on the general population.

Some of the criticisms levied by earlier reviewers on some of the earlier articles still persist to date, namely: the issue of small sample sizes and failure to take into consideration CD4 cell counts. One of the major drawback of traditional literature reviews is their highly subjective nature. In as much as systematic reviews are aimed at addressing this limitation and improve the quality of the evidence, it is worth pointing out that systematic reviews still encompass a subjective component in them as they are not quantitative. In this review the quality assessment has some element of subjectivity. However I have tried to minimise any effect this may have on this work by engaging the services of colleagues and a senior researcher as well as input from my supervisor.

7.0 Conclusions and Recommendations

Malaria and HIV are among the biggest contemporary medical challenges facing sub-Saharan Africa and large parts of the world where both infections are prevalent. Since HIV came to the lime light in the early 1980s, the big question that occupied the minds of medical professional was the impact it will have on other infections in the world's most affected areas. An association between HIV and malaria is expected, at least in theory. This is because cellular immunity is central to the protection against malaria and HIV affects this component of the immune system. However, this association largely remain to be shown in practice as earlier reviews failed to show an association.

The main objective of this study was to assess the evidence for or against an impact of HIV on the epidemiology of malaria through a carefully planned systematic review of the literature. Despite the limitations of this study, this review has sufficient information to form the basis of an informed decision with regards to the research question. Overall, this research shows that there is sufficient evidence to support the theory that interactions existed between HIV and malaria. HIV alters the epidemiology of malaria significantly and it is a significant risk factor for malaria. Although the current evidence stop short of declaring malaria as an opportunistic infection, nevertheless emphasis on mosquito avoidance measures should form part of the education and counselling framework of HIV infected individuals in malaria endemic areas of the world, in the light of the clear association between the two infections. Moreover, consideration should be given to the integration of malaria control programmes with HIV programmes.

Despite the fact that the nature of the association between the two infections is becoming more and clearer, it is still recommended that future studies should pay greater emphasis on sample sizes, serial CD4-T cell counts, distinction between HIV-infections and associated immunodeficiency. More emphasis should also be put on longitudinal-based / cohort studies as despite their limitations; expertise, cost, and time consuming. They have greater power to asses associations.

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